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(54) ANTICANCER AGENT

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(51) Int. Cl.

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

- (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

FIG. 1			
	VARIABLE REGION	CDR1	CDR2
#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) 23D4-1 (A3/A19)	DVVMTQTPLSLSVTPGOPASIS DVVMTQSPLSLPVTPGEPASIS DVVMTQSPLSLPVTPGEPASIS DVVMTQSPLSLPVTPGEPASIS DVVMTQSPLSLPVTPGEPASIS DVVMTQTPLSLSVTPGOPASIS DVVMTQSPLSLPVTPGEPASIS DIVMTQSPLSLPVTPGEPASIS DIVMTQSPLSLPVTPGEPASIS DIVMTQSPLSLPVTPGEPASIS DIVMTQSPLSLPVTPGEPASIS DIVMTQSPLSLPVTPGEPASIS	GRSSQSLLYGNGNN-YLDWYL GRSSQSLLHSNGYN-YLDWYL GRSSQSLLHSDGKT-YLYWYL GRSSQSLLHSDGKT-YLYWYL GRSSQSLLHSDGKT-YLYWYL GRSSQSLLHSNGYN-YLDWYL GRSSQSLLHSNGYN-YLDWYL GRSSQSLLHSNGYN-YLDWYL	OKPGOSPOLLIYLGSI 58 /OKPGOSPOLLIHRGFY 59 OKPGOSPOLLIYLGSN 58 OKPGOSPOLLIYEVSS 58 OKPGOSPOLLIYEVSS 58 OKPGOSPOLLIYLGSN 58 OKPGOSPOLLIYLGSN 58 OKPGOSPOLLIYLGSN 58 OKPGOSPOLLIYEGST 58 OKPGOSPOLLIYEGSN 58
		CDR3	CONSTANT REGION
#1-4 (A18b) #2-3 (A3/A19) #4-1 (02/01) #7-2 (A3/A19) #3-2 (A18b) #3-2 (A18b) #11-1 (A18b) #13-1 (A3/A19) #14-1 (A3/A19) 23D4-1 (A3/A19)	RFSGVPDRFSGSGSGTDFTLKI RASGVPDRFSGSGSGTDFOLKI RASGVPDRFSGSGSGTDFTLKI RASGVPDRFSGSGSGTDFTLKI RFSGVPDRFSGSGSGTDFTLKI RFSGVPDRFSGSGSGTDFTLKI RSGVPDRFSGSGSGTDFTLKI RASGVPDRFSGSGSGTDFTLKI RASGVPDRFSGSGSGTDFTLKI RASGVPDRFSGSGSGTDFTLKI * ******* ** ** **	SRVEADDVG I YYQMQAQOGP- SRVEAEDVGVYYQMQALQTP- SRVEAEDVGVYYQMGALQTP- SRVEAEDVGVYYQMQG I HLP- SRVEAEDVGVYYQMQG I HLP- SRVEAEDVGVYYQMQALQTP- SRVEAEDVGVYYQMQALQTP- SRVEAEDVGVYYQMQALQTP-	PTFGGGTKVEIKRTVAA 118 -LTFGGGTKVEIKRTVAA 118 -RTFGQGTKVEIKRTVAA 117 -WTFGQGTKVEIKRTVAA 117 -YTFGQGTKLEIKRTVAA 117 -YTFGQGTKLEIKRTVAA 117 -WTFGQGTKLEIKRTVAA 118 -RTFGQGTKLEIKRTVAA 118 -FTFGQGTRLDIKRTVAA 118
#1-4 (A18b)	PSVF1FPPSDEQLKSGTASVVC		SANSAESVIEADSKDSI 178
#1-4 (A18b) #2-3 (A3/A19) #4-1 (02/01) #7-2 (A3/A19) #8-2 (A18b) #19a-2 (A18b) #11-1 (A18b) #11-1 (A18b) #13-1 (A3/A19) #14-1 (A3/A19) 23D4-1 (A3/A19)	PSVF1FPPSDEQLKSGTASVVG PSVF1FPPSDEQLKSGTASVVG PSVF1FPPSDEQLKSGTASVVG PSVF1FPPSDEQLKSGTASVVG PSVF1FPPSDEQLKSGTASVVC PSVF1FPPSDEQLKSGTASVVC PSVF1FPPSDEQLKSGTASVVC PSVF1FPPSDEQLKSGTASVVC PSVF1FPPSDEQLKSGTASVVC	LLINNFYPREAKVOWKVDNALC LLINNFYPREAKVOWKVDNALC LLINNFYPREAKVOWKVDNALC LLINNFYPREAKVOWKVDNALC LLINNFYPREAKVOWKVDNALC LLINNFYPREAKVOWKVDNALC LLINNFYPREAKVOWKVDNALC LLINNFYPREAKVOWKVDNALC LLINNFYPREAKVOWKVDNALC	DISGNSQESVTEQDSKDST 177 DISGNSQESVTEQDSKDST 178 DISGNSQESVTEQDSKDST 177 DISGNSQESVTEQDSKDST 177 DISGNSQESVTEQDSKDST 177 DISGNSQESVTEQDSKDST 178 DISGNSQESVTEQDSKDST 177 DISGNSQESVTEQDSKDST 177 DISGNSQESVTEQDSKDST 177
#1-4 (A18b)	YSLSSTLTLSKADYEKHKLYAC		
#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)	YSLSSTLTLSKADYEKHKLYAC YSLSSTLTLSKADYEKHKLYAC YSLSSTLTLSKADYEKHKLYAC YSLSSTLTLSKADYEKHKLYAC YSLSSTLTLSKADYEKHKLYAC YSLSSTLTLSKADYEKHKLYAC YSLSSTLTLSKADYEKHKLYAC YSLSSTLTLSKADYEKHKLYAC YSLSSTLTLSKADYEKHKVYAC YSLSSTLTLSKADYEKHKVYAC	EVTHQGLSSPVTKSFNRGEC EVTHQGLSSPVTKSFNRGEC EVTHQGLSSPVTKSFNRGEC EVTHQGLSSPVTKSFNRGEC EVTHQGLSSPVTKSFNRGEC EVTHQGLSSPVTKSFNRGEC EVTHQGLSSPVTKSFNRGEC EVTHQGLSSPVTKSFNRGEC	220 219 219 219 219 219 220 219 219





C;

1.0

8,0

0.2

0.0

30

PROTEIN

(µg)

650

3600

FIG. 3C

20

Volume (mi)

Buffer: 50mM Na acetate, pH 5.4, 0.005% Tween20

CONCENTRATION VOLUME

(m)

5.0

5.0

(µm/ml)

130

710

091209_1000(#1 clone)

10

Column: SPSPW (TOSOR)

Flow rate: 1.0ml/min

SAMPLE

8

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300

Absorbance 100 0

Conditions

0



Fraction number 8 29 30 31 32 33 35 37 39





FIG. 5



FIG. 6A

A549

		 20	-		40	+ 50	
#1H31YC220A.pro	DVVMTQTPLSLS	VTPGQPASI	SCKSSQSLL	YSDGKTYLY	NYLQKPGHSPI	ł	50
#7VL(I).pro	EIVMTQSPLSLP		-				50
#7RLI.pro	EIVMTQSPLSLP						50
C51.pro	EIVLTQSPATLS	LSPGERATL	SCRASQSV-	SSYLA	NYQQKPGQAPI	х ~	45 45
C87.pro	EIVLTQSPATLS	LSPGERAIT	SCKASUSE~	351 VAI	ntukkpulapi	ĸ	43
	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~					4	
	60	70				100	
#1H31YC220A.pro							99
#7VL(I).pro	LLIYLGSNRASG						99
#7RLI.pro	LLIYLGSNRASG						99 -94
C51.pro C87.pro	LLIYDASNRATG						93
car.pro	LLIVISIKAAU	LPART 5000	Saincirit	SSLEFEDER	V CLYMAN N		22
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	110	12	0 1	30	1.40	150	
#1H31YCZ20A.pro							149
#7VL(I).pro	PI-TFGQGTKVE			•			148
#7RLI.pro	PI-TEGQGTRLE						148 143
C51.pro C87.pro	PL-TFGGGTKVE PY-TFGQGTRLE						145
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	160					200	
	**********						
#1H31YC220A.pro							199
#7VL(I).pro	AKVQWKVDNALQ						198 198
#7RLI.pro C51.pro	AKVQWKVDNALQ AKVQWKVDNALQ	-					193
C87.pro	AKVQWKVDNALQ						192
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	210	22	0				
		-					222
#1H31YC220A.pro							220
#7VL(I).pro	CEVTHQGLSSPV						219 219
#7RLI.pro C51.pro	CEVTHQGLSSPV CEVTHQGLSSPV						214
C31.pro C87.pro	CEVTHOGLSSPV						213
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FIG. 6B

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MOLT-4
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MOLT-4							
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			20			50	
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#1H31YC220A.pro	DVVMTQTPL	SLSVTPGQP	ASISCKSSQS	LLYSDG-KT	nl ywylokpg-	ISP	49
#4.pro	OVYMTQTPL	SLSVTPGEP	ASISCRSTQS	LLDSDGVNP	SFDWYVQKPGC	)SP	50
#7EI.pro	ETVMTQSPL	SLPVTPGEP	ASISCRSSQS	LLHSNG-YN	rlowylqkpgg	)SP	49
\$7TR.pro	DVMTQSPL	SLPVTPGEP	ASISCRSSQS	LLHSNT-RN	rlowylokpgo	2SP	49
#7RL1.pro	EIVMTQSPL	SI. PVTPGEP	ASISCRSSQS	LLHSNT-RN	/LDWYLQKPGC	SP	49
#7VL.pro	EIVMTOSPL	SLPVTPGEP	ASISCRSSQS	LLHSNT-RN	n dwyl Qkpgg	SP	49
\$13. <i>p</i> ro	DIVMTOSPL	SLPVTPGEP	ASISCRESOS	LLHSNG-YN'	rlowylókpgo	SP	49
S21.pro					<b>YLDWYLQKPGC</b>		49
538.pro			the second s		n.DWYLQKPGC	779. S.	49
CS1.pro					rlawyqqkpgg	5	44
						<b>.</b>	
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		68	78	88	98	122	
#1H31YC220A.pro							99
#4.pro		han a the second second	enantre remainae resourcemente	والمتراكبة مراكبتهم للمتحمد ومراجب	WGVYYCMORI	- Ander and a	100
#7EI.pro					OVGVYYCMQAL		99
#7TR.pro					WGVYYOMQAL		99
#7RLI.pro					XGVYYCMQGL	See.	99
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#7VL.pro	· · · · · · · · · · · · · · · · · · ·				JVGVYYCMQAL		99
513.pro					WGVYYCMQAL		99
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#1H31YC220A.pro	*****					••• \$	149
#1H31YC220A.pro #4.pro	PQYTEGQGT	+ KLEIKRTVA	APSVFIFPPS	DEQLKSGTA	SVVCLLNNFYP	··· ·RE	1000
#4.pro	PQYTFGQGT PL-TFGGGT	+ KLEIKRTVA KVEIKRTVA	APSVFIFPPS APSVFIFPPS	DEQLKSGTA DEQLKSGTA	SVVCLLNNFYF SVVCLLNNFYF	+ 'RE 'RE	149 149 148
#4.pro #7EI.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT	+ KLEIKRTVA KVEIKRTVA KVEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA DEQLKSGTA DEQLKSGTA	SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF	rre Pre Pre Pre	149
#4.pro #7EI.pro #7TR.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT	+ KLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA	SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF	rre Re Re Re Re	149 148 148
#4.pro #7EI.pro #7TR.pro #7RLI.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PI-TFGQGT	+ KLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA	SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF	+ YRE YRE YRE YRE YRE	149 148 148 148
#4.pro #7EL.pro #7TR.pro #7RLL.pro #7VL.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PI-TFGQGT PR-TFGQGT	+ KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA	SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF	-+ YRE YRE YRE YRE YRE YRE YRE	149 148 148 148 148
#4.pro #7EL.pro #7TR.pro #7RLI.pro #7VL.pro \$13.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PP-TFGQGT	+ KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KLEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA DEQLKSGTA	SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF	-+ RE RE RE RE RE RE RE	149 148 148 148 148 148
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#4.pro #7EI.pro #7TR.pro #7RL.pro #7VL.pro \$13.pro \$21.pro \$38.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT -Y-TFGQGT	* KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KLEIKRTVA KLEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA:	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF	* RE RE RE RE RE RE RE RE	149 148 148 148 148 148 148 148 147
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#4.pro #7EI.pro #7TR.pro #7RL.pro #7VL.pro \$13.pro \$21.pro \$38.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGGGT PL-TFGGGT	* KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KLEIKRTVA KLEIKRTVA KVEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA:	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF	* RE RE RE RE RE RE RE RE 200	149 148 148 148 148 148 148 148 147
#4.pro #7EL.pro #7TR.pro #7RL1.pro #7VL.pro \$13.pro \$21.pro \$38.pro C\$1.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGGGT PL-TFGGGT	* KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA:	SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF	- + RE RE RE RE RE RE RE RE + 2000	149 148 148 148 148 148 148 148 147 143
#4.pro #7EL.pro #7TR.pro #7RL1.pro #7VL.pro \$13.pro \$21.pro \$38.pro C\$1.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA KLEIKRTVA KLEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: 180 TYSLSSTLTI	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF	- + RE RE RE RE RE RE RE RE RE YA	149 148 148 148 148 148 148 148 147 143
#4.pro #7EL.pro #7TR.pro #7RL1.pro #7VL.pro \$13.pro \$21.pro \$38.pro (\$1.pro \$38.pro (\$1.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT PL-TFGGGT AKVQWKVCM AKVQWKVCM	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KLEIKRTVA KVEIKRTVA KLEIKRTVA KLEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: 180 TYSLSSTLTI	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF L 190 LSKADYEKHKL	-+ RE RE RE RE RE RE RE RE RE YA YA	149 148 148 148 148 148 148 148 147 143
#4.pro #7EL.pro #7TR.pro #7VL.pro \$13.pro \$21.pro \$38.pro (\$1.pro \$38.pro (\$1.pro #1H31Y(22@A.pro #4.pro #7EL.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT PL-TFGGGT AKVQWKVDN AKVQWKVDN	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA KLEIKRTVA KLEIKRTVA LEIKRTVA LEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS SVFEQDSKDS SVTEQDSKDS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: 180 TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF L LSKADYEKHKL SKADYEKHKL	-+ RE RE RE RE RE RE RE RE YA YA YA	149 148 148 148 148 148 148 147 143 199 199
#4.pro #7EL.pro #7TR.pro #7VL.pro \$13.pro \$21.pro \$38.pro (51.pro \$38.pro (51.pro #1H31Y(22@A.pro #4.pro #7EL.pro #7TR.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT PL-TFGGGT AKVQWKVDN AKVQWKVDN AKVQWKVDN	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA KLEIKRTVA KVEIKRTVA LEIKRTVA KVEIKRTVA LOSGNSQE IALQSGNSQE IALQSGNSQE	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS SVFEQDSKDS SVTEQDSKDS SVTEQDSKDS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: TSLSSTLTI TSLSSTLTI TSLSSTLTI	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF	-+ RE RE RE RE RE RE RE RE YA YA YA YA	149 148 148 148 148 148 148 148 147 143 199
#4.pro #7EL.pro #7TR.pro #7VL.pro \$13.pro \$21.pro \$38.pro (\$1.pro \$38.pro (\$1.pro #1H31Y(22@A.pro #4.pro #7EL.pro #7TR.pro #7RL1.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT PL-TFGGGT AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA KLEIKRTVA KLEIKRTVA LOSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS SVFEQDSKDS SVTEQDSKDS SVTEQDSKDS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: TSLSSTLTI TSLSSTLTI TSLSSTLTI TSLSSTLTI	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF	-+ RE RE RE RE RE RE RE RE YA YA YA YA YA YA	149 148 148 148 148 148 148 147 143 199 199 198 198
#4.pro #7EL.pro #7TR.pro #7TR.pro #7VL.pro \$13.pro \$21.pro \$38.pro (\$1.pro \$38.pro (\$1.pro #1H31Y(22@A.pro #4.pro #7EL.pro #7TR.pro #7TR.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT PL-TFGGGT AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA KLEIKRTVA KVEIKRTVA LOSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS SVFEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: TSLSSTLTI TSLSSTLTI TSLSSTLTI TSLSSTLTI TSLSSTLTI	SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF L SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL	-+ RE RE RE RE RE RE RE RE YA YA YA YA YA YA YA	149 148 148 148 148 148 148 147 143 199 199 198 198 198 198
#4.pro #7EL.pro #7TR.pro #7TR.pro #7VL.pro \$13.pro \$21.pro \$38.pro (\$1.pro \$38.pro (\$1.pro #1H31Y(22@A.pro #4.pro #7EL.pro #7TR.pro #7TR.pro \$7RL1.pro \$13.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT PL-TFGGGT AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KLEIKRTVA KVEIKRTVA KLEIKRTVA KLEIKRTVA KLEIKRTVA KLEIKRTVA KLEIKRTVA KLEIKRTVA KLEIKRTVA KLEIKRTVA KLEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS SVFEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: TSLSSTLTI TSLSSTLTI TSLSSTLTI TSLSSTLTI TSLSSTLTI	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF	-+ RE RE RE RE RE RE RE RE YA YA YA YA YA YA YA YA	149 148 148 148 148 148 147 143 199 199 198 198 198 198 198
#4.pro #7EL.pro #7TR.pro #7TR.pro #7VL.pro \$13.pro \$21.pro \$38.pro (51.pro \$38.pro (51.pro #1H31Y(22@A.pro #4.pro #7EL.pro #7TR.pro #7TR.pro \$13.pro \$21.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT PL-TFGGGT AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA LOSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS SVFEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI	SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SVVCLLNNFYF SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL	-+ RE RE RE RE RE RE RE RE YA YA YA YA YA YA YA YA YA	149 148 148 148 148 148 147 143 199 199 198 198 198 198 198 198
#4.pro #7EL.pro #7TR.pro #7TR.pro #7VL.pro \$13.pro \$21.pro \$38.pro (\$1.pro \$38.pro (\$1.pro #1H31Y(22@A.pro #4.pro #7EL.pro #7TR.pro #7TR.pro \$7RL1.pro \$13.pro	PQYTFGQGT PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PL-TFGGGT PL-TFGGGT AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN AKVQWKVDN	KLEIKRTVA KVEIKRTVA KVEIKRTVA RLEIKRTVA KVEIKRTVA KLEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA KVEIKRTVA LOSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE IALQSGNSQE	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS SVFEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS	DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: DEQLKSGTA: TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI TYSLSSTLTI	SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF SVVCLENNFYF	-+ RE RE RE RE RE RE RE RE YA YA YA YA YA YA YA YA YA YA	149 148 148 148 148 148 147 143 199 199 198 198 198 198 198

## *FIG.* 6*C*

		210	220
		****	
#1H31YC220A.pro	CEVTHQ	GLSSPVTKSI	FNRGEA
#4.pro	CEVTHQ	GLSSPVTKSI	FNRGEC
#7EI.pro	CEVTHQ	GLSSPVTKSI	FNRGEC
#7TR.pro	CEVTHO	GLSSPVTKSI	INRGEC
#7RLI.pro	CEVTHQ	GLSSPVTKSF	NRGEC
#7VL.pro	CEVTHO	GLSSPVTKSP	PNRGEC
S13.pro	CEVTHQ	GLSSPVTKSI	INRGEC
SZ1.pro	CEVTHO	GLSSPVTKSP	NRGEC
S38.pro	CEVTHQ	GLSSPVTKSI	NRGEC
C51.pro	CEVTHQ	GLSSPVTKSF	NRGEC

## FIG. 6D

ES-2

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		10	20	30	40	50
#1H31YC220A.pro			ASISCKSSQSI			
#4.pro	· · · · ·		ASISCRSTOSI		~	
#7.pro	•		ASISCRSSQSI			
#7RLI.pro			ASISCRSSQSI			-
#10.pro			ASISCKSSQSI			
#11.pro	•	-	ASISCKSSQSI			
22F6.pro	DIVMTQSPI	SLPVTPGEP	ASISCRSSQSI	LLHSNG-FN-	YLDWYLQKPG	QS
22F6C220A.pro	DIVMTQSPI	LSLPVTPGEP	ASISCRSSQSI	LLHSNG-FN-	YLDWYLQKPG	QS
C51.pro	EIVLTQSPA	ATLSLSPGER	ATLSCRASQS	VSS-'	YLAWYQQKPG	QA
C67.pro	EIVLTOSPO	<b>STLSLSPGER</b>	ATLSCRASOS	VSSSI	NLAWYQQKPG	QA
C82.pro	EIVLTQSP	ATLSLSPGER/	ATLSCRASQS	VGP-1	FLAWYQQKPG	QA
000	CTU TOCO		and crostere		O ADDODOUDC	<b>0</b> . x
C88.pro	ETALIÓSHY	ATLSLSPGER	AILSURASES		TLANTQUEEG	QA
C88.pro		-+ 60	70	80	-+ 90	-+ 100
(88.pro #1H31YC220A.pro		-+ 60 -+	- <del>f</del>	-+ 80 -+	-+ 90 -+	-+ 100 -+
	PHLLIYEVS	60 SSRFSGVPDRI	-+ 70 -+	80 FLKISRVEAEI	90 90 9VGVYYCMQ-	-+ 100 -+ -G
#1H31YC220A.pro	PHLLIYEVS	60 SSRFSGVPDRI	70 FSGSGSGTDF	80 FLKISRVEAEI	90 	-+ 100 -+ -G -R
#1H31YC220A.pro #4.pro	PHLLIYEV PQLLIHRGP PQLLIYLGS	60 SSRFSGVPDRI FYRASGVPDRI SNRASGVPDRI	70 FSGSGSGTDF FSGSGSGTDF	80 FLKISRVEAEI FLRISRVEAEI	90 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ-	-+ -6 -R -A
#1H31YC220A.pro #4.pro #7.pro	PHLLIYEVS PQLLIHRGI PQLLIYLGS PQLLIYLGS	60 SSRFSGVPDRI YRASGVPDRI SNRASGVPDRI SNRASGVPDRI	70 FSGSGSGTDF FSGSGSGTDF FSGSGSGTDF	80 FLKISRVEAEI FLRISRVEAEI FLKISRVEAEI FLKISRVEAEI	90 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ-	-+ -G -R -A -G
#1H31YC220A.pro #4.pro #7.pro #7RLI.pro	PHLLIYEVS PQLLIHRGP PQLLIYLGS PQLLIYLGS PQLLIQEVS	60 SSRFSGVPDRI TYRASGVPDRI SNRASGVPDRI SNRASGVPDRI SRRFSGVPDRI	70 FSGSGSGTDF FSGSGSGTDF FSGSGSGTDF FSGSGSGTDF	80 FLKISRVEAEI FLRISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI	90 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ-	-+ -G -R -A -G -G
#1H31YC220A.pro #4.pro #7.pro #7RLI.pro #10.pro	PHLLIYEVS PQLLIHRGI PQLLIYLGS PQLLIYLGS PQLLIYEVS	60 SSRFSGVPDRI TYRASGVPDRI SNRASGVPDRI SNRASGVPDRI SRRFSGVPDRI SSRFSGVPDRI	70 FSGSGSGTDF FSGSGSGTDF FSGSGSGTDF FSGSGSGSGTDF FSGSGSGSGSDF	80 FLKISRVEAEI FLRISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI	90 DVGVYYCMQ- DVGVYYCMQ- DVGVYYCMQ- DVGVYYCMQ- DVGVYYCMQ- DVGVYYCMQ-	-+ -G -R -G -G -G
#1H31YC220A.pro #4.pro #7.pro #7RLI.pro #10.pro #11.pro	PHLLIYEVS PQLLIHRGP PQLLIYLGS PQLLIYLGS PQLLIYEVS PQLLIYES	60 SSRFSGVPDRI FYRASGVPDRI SNRASGVPDRI SNRASGVPDRI SRRFSGVPDRI SSRFSGVPDRI STRASGVPDRI	70 FSGSGSGTDF FSGSGSGTDF FSGSGSGSGTDF FSGSGSGSGTDF FSGSGSGSGTDF	80 FLKISRVEAEI FLRISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI	90 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYFCMQ-	-+ -G -R -G -G -G -G
#1H31YC220A.pro #4.pro #7.pro #7RLI.pro #10.pro #11.pro 22F6.pro	PHLLIYEVS PQLLIHRGI PQLLIYLGS PQLLIYLGS PQLLIYEVS PQLLIYLGS PQLLIYLGS	60 SSRFSGVPDRI FYRASGVPDRI SNRASGVPDRI SNRASGVPDRI SRFSGVPDRI SSRFSGVPDRI STRASGVPDRI	70 FSGSGSGTDF FSGSGSGTDF FSGSGSGSGTDF FSGSGSGSGTDF FSGSGSGSGTDF FSGSGSGSGTDF	80 FLKISRVEAEI FLRISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI	90 90 90 90 90 90 90 90 90 90 90 90 90 9	-+ -G -R -G -G -G -A
#1H31YC220A.pro #4.pro #7.pro #7RLI.pro #10.pro #11.pro 22F6.pro 22F6C220A.pro	PHLLIYEVS PQLLIHRGP PQLLIYLGS PQLLIYLGS PQLLIYEVS PQLLIYEVS PQLLIYLGS PRLLIYDAS	60 SSRFSGVPDRI SSRFSGVPDRI SNRASGVPDRI SNRASGVPDRI SSRFSGVPDRI SSRFSGVPDRI STRASGVPDRI STRASGVPDRI STRASGVPDRI	70 FSGSGSGTDF FSGSGSGTDF FSGSGSGTDF FSGSGSGSGTDF FSGSGSGSGTDF FSGSGSGTDF FSGSGSGTDF	80 FLKISRVEAEI FLRISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI FLRISRVEAEI FLRISRVEAEI	90 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYFCMQ- 2VGVYFCMQ- 2VGVYFCMQ- 2VGVYFCMQ-	-+ -G -R -G -G -G -A -A -R
#1H31YC220A.pro #4.pro #7.pro #7RLI.pro #10.pro #11.pro 22F6.pro 22F6C220A.pro C51.pro	PHLLIYEVS PQLLIYLGS PQLLIYLGS PQLLIYLGS PQLLIYEVS PQLLIYES PQLLIYLGS PRLLIYDAS PRLLIYGAS	60 SSRFSGVPDRI SSRFSGVPDRI SNRASGVPDRI SNRASGVPDRI SSRFSGVPDRI SSRFSGVPDRI STRASGVPDRI STRASGVPDRI SNRATGIPARI	70 FSGSGSGTDF FSGSGSGTDF FSGSGSGTDF FSGSGSGSGTDF FSGSGSGSGTDF FSGSGSGTDF FSGSGSGTDF FSGSGSGTDF	80 FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI FLKISRVEAEI FLRISRVEAEI FLRISRVEAEI FLRISRVEAEI FLRISRVEAEI FLTISRLEPEI	90 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYYCMQ- 2VGVYFCMQ- 2VGVYFCMQ- 2VGVYFCMQ- 2FAVYYCQQ- 2FALYYCQQY	-+ -G -R -G -G -G -G -A -R GS

## FIG. 6E

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					140	
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#1H31YC220A.pro	LHLPQ	TFGQGTKLI	EIKRTVAAPS	VFIFPPSDEQ	LKSGTASVVC	LN
#4.pro	IEFPl	TFGGGTKVI	EIKRTVAAPS	VFIFPPSDEQ	LKSGTASVVC	LN
#7.pro	LQTPF	RTFGQGTKVI	EIKRTVAAPS	VFIFPPSDEQ	LKSGTASVVC	LLN
#7RLI.pro	LQTP1	TFGQGTRLI	EIKRTVAAPS	VFIFPPSDEQ	ILKSGTASVVCI	LN
#10.pro	TYVPH	ITFGQGTKVI	EIKRTVAAPS	VFIFPPSDEQ	LKSGTASVVC	LN
#11.pro	IHLPY	TFGQGTKLI	EIKRTVAAPS	VFIFPPSDEQ	LKSGTASVVC	LLN
22F6.pro	VQTPF	TFGPGTRL	DIKRTVAAPS	VFIFPPSDEQ	ILKSGTASVVC	LN
22F6C220A.pro	VQTPF	TFGPGTRL	DIKRTVAAPS	VFIFPPSDEQ	LKSGTASVVC	LN
C51.pro	SDWPL	TFGGGTKVI	EIKRTVAAPS	VFIFPPSDEQ	LKSGTASVVC	LN
C67.pro	SLW	TFGQGTKVI	EIKRTVAAPS	VFIFPPSDEQ	ILKSGTASVVC	LN
C82.pro	YTWPG-N	ISFGGGAKVI	EIKRTVAAPS	VFIFPPSDEQ	LKSGTASVVCI	LN
C88.pro	SNWPPRS	STEGQGTRLI	EMKRTVAAPS	VFIFPPSDEQ	LKSGTASVVC	LN
	~~~~~~~					
					190	
#1H31YC220A.pro					LSSTLTLSKA	
#4.pro		-	• •	-	LSSTLTLSKA	
#7.pro		-			LSSTLTLSKA	
#7RLI.pro		-	* *	•	LSSTLTLSKA	
#10.pro					LSSTLTLSKA	
#11.pro		*	• •	•		
11 22 1 21 2				15403803113	IL NATEL HEARAN	
22F6 pro			and the state of t		LSSTLTLSKA	
22F6.pro 22F6C220A.pro	NFYPREAK	QWKVDNAL	QSGNSQESVT	EQDSKDSTYS	LSSTLTLSKA	DYE
22F6C220A.pro	NFYPREAK	QWKVDNALO	QSGNSQESVT QSGNSQESVT	EQDSKDSTYS EQDSKDSTYS	LSSTLTLSKAI	DYE DYE
22F6C220A.pro C51.pro	NFYPREAK NFYPREAK NFYPREAK	/QWKVDNAL( /QWKVDNAL( /QWKVDNAL(	QSGNSQESVT QSGNSQESVT QSGNSQESVT	EQDSKDSTYS EQDSKDSTYS EQDSKDSTYS	LSSTLTLSKAI LSSTLTLSKAI LSSTLTLSKAI	DYE DYE DYE
22F6C220A.pro C51.pro C67.pro	NFYPREAKN NFYPREAKN NFYPREAKN NFYPREAKN	/QWKVDNAL( /QWKVDNAL( /QWKVDNAL( /QWKVDNAL(	QSGNSQESVT QSGNSQESVT QSGNSQESVT QSGNSQESVT	EQDSKDSTYS EQDSKDSTYS EQDSKDSTYS EQDSKDSTYS	LSSTLTLSKA LSSTLTLSKA LSSTLTLSKA LSSTLTLSKA	DYE DYE DYE DYE
22F6C220A.pro C51.pro	NFYPREAK NFYPREAK NFYPREAK NFYPREAK NFYPREAK	/QWKVDNAL( /QWKVDNAL( /QWKVDNAL( /QWKVDNAL( /QWKVDNAL(	2SGNSQESVT 2SGNSQESVT 2SGNSQESVT 2SGNSQESVT 2SGNSQESVT	EQDSKDSTYS EQDSKDSTYS EQDSKDSTYS EQDSKDSTYS EQDSKDSTYS	LSSTLTLSKAI LSSTLTLSKAI LSSTLTLSKAI	DYE DYE DYE DYE DYE DYE

# FIG. 6F

		********	
		210	
		-+	-+
#1H31YC220A.pro	KHKLYACE	VTHQGLSSPV	TKSFNRGEA
#4.pro	KHKLYACE	<b>/THQGLSSPV</b>	TKSFNRGEC
#7.pro	KHKLYACE	VTHQGLSSPV	TKSFNRGEC
#7RLI.pro	KHKLYACE	/THQGLSSPV	TKSFNRGEC
#10.pro	KHKLYACE	/THQGLSSPV	TKSFNRGEC
#11.pro	KHKLYACE	/THQGLSSPV	TKSFNRGEC
22F6.pro	KHKVYACE	/THQGLSSPV	TKSFNRGEC
22F6C220A.pro	KHKVYACE	/THQGL SSPV	TKSFNRGEA
C51.pro	KHKVYACE	/THQGLSSPV	TKSFNRGEC
C67.pro	KHKVYACEV	/THQGLSSPV	TKSFNRGEC
C82.pro	KHKVYACEN	/THQGLSSPV	TKSFNRGEC
C88.pro	KHKVYACE	/THQGLSSPV	TKSFNRGEC

FIG. 6G

BxPC-3

		+	-+			•• •	
			20				
the seas			ASISCRSTQS				50
#4.pro #7G.pro	-		ASISCRSSQSI				49
#78.pro #7EI.pro			ASISCRSSQS				49
#7RLI.pro			ASISCRSSQS				49
#7VL.pro			ASISCRSSQS				49
#13.pro	-		ASISCRSSQS				49
#19.pro #14.pro	-		ASISCRSSQSI				49
Z2F6.pro	•		ASISCRSSQSI				49
			70				
#4.pro			SGSGSGTDFT				100
#7G.pro	-		SGSGSGTDFTI				99
#7EL.pro	•		SGSGSGTDFTI				99
#7RLI.pro	•		SGSGSGTDFTI				9 <u>9</u>
#7VL.pro	•		SGSGSGTDFTI				99
#13.pro	-		SGSGSGTDFT				99
#14.pro	-		SGSGSGTDFT				99
22F6.pro	• • •		SGSGSGTDFT				99
	~						
			120				
	~~~~~~~~						149
#4 nra		rkvftkrtva	APSVETEPPS	DEOLKSGTAS	VVCLENNFYP	RE	
#4.pro #76.pro	PL~TFGGGT		APSVFIFPPS APSVFIFPPS				148
#7G.pro	PL-TFGGGT PR-TFGQGT	FKVEIKRTVA	APSVFIFPPS	DEQLKSGTAS	VVCLLNNFYP	RE	148 148
#7G.pro #7EI.pro	PL-TFGGGT PR-TFGQGT PR-TFGQGT	TKVEIKRTVA FKVEIKRTVA	APSVFIFPPS APSVFIFPPS	DEQLKSGTAS ¹ DEQLKSGTAS ¹	VVCLLNNFYP VVCLLNNFYP	RE RE	
#7G.pro #7EI.pro #7RLI.pro	PL-TFGGGT PR-TFGQGT PR-TFGQGT PI-TFGQGT	TKVEIKRTVA TKVEIKRTVA TRLEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP	RE RE RE	148
#7G.pro #7EI.pro #7RLI.pro #7VL.pro	PL~TFGGGT PR~TFGQGT PR~TFGQGT PI~TFGQGT PR~TFGQGT	TKVEIKRTVA TKVEIKRTVA TRLEIKRTVA TKVEIKRTVA	APSVFIFPPS APSVFIFPPS	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS'	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP	RE RE RE RE	148 148
#7G.pro #7EI.pro #7RLI.pro	PL-TFGGGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT	TKVEIKRTVA TKVEIKRTVA TRLEIKRTVA TKVEIKRTVA TKVEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS'	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP	RE RE RE RE	148 148 148
#7G.pro #7EI.pro #7RLI.pro #7VL.pro #13.pro	PL~TFGGGT PR~TFGQGT PI~TFGQGT PR~TFGQGT PPWTFGQGT PR~TFGQGT	IKVEIKRTVA IKVEIKRTVA IRLEIKRTVA IKVEIKRTVA IKVEIKRTVA IKLEIKRTVA	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS'	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP	RE RE RE RE RE	148 148 148 149
#7G.pro #7EI.pro #7RLI.pro #7VL.pro #13.pro #14.pro	PL-TFGGGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGPGT	IKVEIKRTVA IKVEIKRTVA IRLEIKRTVA IKVEIKRTVA IKVEIKRTVA IKLEIKRTVA IRLDIKRTVA	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI	DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP	RE RE RE RE RE RE	148 148 148 149 148
#7G.pro #7EI.pro #7RLI.pro #7VL.pro #13.pro #14.pro	PL-TFGGGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGPGT	IKVEIKRTVA IKVEIKRTVA IRLEIKRTVA IKVEIKRTVA IKLEIKRTVA IRLEIKRTVA	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS'	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP	RE RE RE RE RE RE	148 148 148 149 148
#7G.pro #7EI.pro #7RLI.pro #7VL.pro #13.pro #14.pro	PL-TFGGGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT	IKVEIKRTVA IKVEIKRTVA IKVEIKRTVA IKVEIKRTVA IKLEIKRTVA IRLDIKRTVA 160	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' 180	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP	RE RE RE RE RE RE -+ 200	148 148 148 149 148
#7G.pro #7EI.pro #7RLI.pro #7VL.pro #13.pro #14.pro 22F6.pro	PL-TFGGGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PPWTFGQGT PR-TFGQGT	IKVEIKRTVA IKVEIKRTVA IKVEIKRTVA IKVEIKRTVA IKLEIKRTVA IRLDIKRTVA 160	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS DEQLKSGTAS	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP 190	RE RE RE RE RE RE -+ 200 -+	148 148 148 149 148
#7G.pro #7EI.pro #7RLI.pro #13.pro #14.pro 22F6.pro	PL-TFGQGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGQGT	IKVEIKRTVA IRLEIKRTVA IRLEIKRTVA IKVEIKRTVA IKLEIKRTVA IRLDIKRTVA 160 	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI 170 -+	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' 180 ++	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP 190 SKADYEKHKL	RE RE RE RE RE RE -+ 200 -+ YA	148 148 148 149 148 148
#7G.pro #7EI.pro #7RLI.pro #13.pro #14.pro 22F6.pro #4.pro #7G.pro	PL-TFGQGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGPGT AKVQWKVDP AKVQWKVDP	IKVEIKRTVA IRLEIKRTVA IRLEIKRTVA IKVEIKRTVA IKLEIKRTVA IRLDIKRTVA 160 +	APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS APSVFIFPPS	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' 180 ++	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP 190 SKADYEKHKL SKADYEKHKL	RE RE RE RE RE RE -+ 2000 -+ YA YA	148 148 148 149 148 148
#7G.pro #7EI.pro #7RLI.pro #13.pro #14.pro 22F6.pro	PL-TFGQGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGPGT	IKVEIKRTVA IRLEIKRTVA IRLEIKRTVA IKVEIKRTVA IKLEIKRTVA IRLDIKRTVA 160 VALQSGNSQE VALQSGNSQE	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI -+	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' 180 ++	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP 190 SKADYEKHKL SKADYEKHKL	RE RE RE RE RE -+ 200 -+ YA YA YA	148 148 148 149 148 148 148 199
#7G.pro #7EI.pro #7RLI.pro #13.pro #14.pro 22F6.pro #4.pro #7G.pro #7EI.pro	PL-TFGGGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGPGT AKVQWKVDI AKVQWKVDI AKVQWKVDI AKVQWKVDI	REVEIKRTVA REVEIKRTVA REVEIKRTVA REVEIKRTVA REVEIKRTVA RELEIKRTVA RELEIKRTVA 160 VALQSGNSQE VALQSGNSQE VALQSGNSQE	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI 170 5VTEQDSKDS SVTEQDSKDS SVTEQDSKDS	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' 180 	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL	RE RE RE RE RE -+ 200 -+ YA YA YA YA	148 148 148 149 148 148 148 199 199 198
#7G.pro #7EI.pro #7RLI.pro #13.pro #14.pro 22F6.pro #4.pro #7G.pro #7EI.pro #7RLI.pro	PL-TFGGGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGPGT AKVQWKVDI AKVQWKVDI AKVQWKVDI AKVQWKVDI	IKVEIKRTVA IRLEIKRTVA IRLEIKRTVA IKVEIKRTVA IKLEIKRTVA IRLDIKRTVA IRLDIKRTVA IGØ VALQSGNSQE VALQSGNSQE VALQSGNSQE VALQSGNSQE	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI -+	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' 180 -+	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL	RE RE RE RE RE -+ 200 -+ YA YA YA YA YA	148 148 148 149 148 148 148 199 198 198 198
#7G.pro #7EI.pro #7RLI.pro #13.pro #14.pro 22F6.pro 22F6.pro #7G.pro #7FI.pro #7RLI.pro #13.pro #14.pro	PL-TFGGGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGQGT PF-TFGPGT AKVQWKVDI AKVQWKVDI AKVQWKVDI AKVQWKVDI AKVQWKVDI AKVQWKVDI	REVEIKRTVA REVEIKRTVA REVEIKRTVA REVEIKRTVA REVEIKRTVA RELEIKRTVA RELEIKRTVA ALQSGNSQE VALQSGNSQE VALQSGNSQE VALQSGNSQE VALQSGNSQE VALQSGNSQE	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI 5VTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS SVTEQDSKDS	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' TSLSSTLTL' TYSLSSTLTL' TYSLSSTLTL' TYSLSSTLTL' TYSLSSTLTL'	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL	RE RE RE RE RE RE -+ 200 -+ YA YA YA YA YA YA YA YA YA YA	148 148 148 149 148 148 148 199 198 198 198 198 198
#7G.pro #7EI.pro #7RLI.pro #13.pro #14.pro 22F6.pro 22F6.pro #7G.pro #7FI.pro #7RLI.pro #7VL.pro #13.pro	PL-TFGGGT PR-TFGQGT PI-TFGQGT PR-TFGQGT PR-TFGQGT PF-TFGQGT PF-TFGPGT AKVQWKVDI AKVQWKVDI AKVQWKVDI AKVQWKVDI AKVQWKVDI AKVQWKVDI	REVEIKRTVA REVEIKRTVA REVEIKRTVA REVEIKRTVA REVEIKRTVA RELEIKRTVA RELEIKRTVA 160 VALQSGNSQE VALQSGNSQE VALQSGNSQE VALQSGNSQE VALQSGNSQE VALQSGNSQE	APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI APSVFIFPPSI 170 5VTEQDSKDS' SVTEQDSKDS' SVTEQDSKDS' SVTEQDSKDS' SVTEQDSKDS' SVTEQDSKDS'	DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' DEQLKSGTAS' TSLSSTLTL' TYSLSSTLTL' TYSLSSTLTL' TYSLSSTLTL' TYSLSSTLTL'	VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP VVCLLNNFYP SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL SKADYEKHKL	RE RE RE RE RE RE -+ 200 -+ YA YA YA YA YA YA YA YA YA YA	148 148 149 148 148 148 199 198 198 198 198 198

FIG. 6H

		· • • • • •
	210	220
	****	,
#4.pro	CEVTHQGLSSPVTKSF	IRGEC
#76.pro	CEVTHQGLSSPVTKSF	IRGEC
#7EI.pro	CEVTHQGLSSPVTKSF	IRGEC
#7RLI.pro	CEVTHQGLSSPVTKSF	IRGEC
#7VL.pro	CEVTHQGLSSPVTKSF	IRGEC
#13.pro	CEVTHQGLSSPVTKSF	IRGEC
#14.pro	CEVTHQGLSSPVTKSF	IRGEC
Z2F6.pro	CEVTHQGLSSPVTKSF	IRGEC

FIG. 61

8-16

10	20	30	40	50
QSPLSLPVTP				
	70	80	90	10
GSNRASGVPDI	•			
	120	130	140	15
GTKVEIKRTV				
	170	180	190	20
DNALQSGNSQ				
210				
LSSPVTKSFNF				





FIG. 7.4

In vivo assay(via oral)

Sheet 13 of 14



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 ¹⁰ 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 2015/¹⁵ 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 ³⁵ 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 45 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 50 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 55 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. 60

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 65 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

20 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 5 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 25 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 poly-30 peptide 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% 35 or more with that amino acid sequence.

Effects of the Invention

According to the present invention, an anticancer agent 40 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 45 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. 50

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 55 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. 2A schematically indicates a cDNA design for obtaining a monomer human antibody light chain. The nucleotide sequences appearing in FIG. 2A 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. 2B 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. 3A 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. 3B is a diagram indicating the results of newly 20 carrying out primary purification of a polypeptide of clone #1, and more particularly, is a stained image of SDS-PAGE analysis.

FIG. 3C 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. 3D 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. 6A is a diagram indicating the amino acid sequences of wild type human antibody κ -type light chains. The amino acid sequences appearing in FIG. 6A 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. 6B is a diagram indicating the amino acid sequences of wild type human antibody κ -type light chains.

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

The amino acid sequences appearing in FIG. 6B and FIG. 6C 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.

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S38.pro is SEQ ID NO: 48.

C51.pro is SEQ ID NO: 41.

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

FIG. 6E is a diagram indicating the amino acid sequences 65 of wild type human antibody k-type light chains continuing from FIG. 6D.

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

The amino acid sequences appearing in FIG. 6D, FIG. 6E, and FIG. 6F correspond to the sequence ID numbers 5 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. 6G is a diagram indicating the amino acid sequences of wild type human antibody κ -type light chains.

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

The amino acid sequences appearing in FIG. 6G and FIG. 6H correspond to the sequence ID numbers assigned in the 25 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. 6I is a diagram indicating the amino acid sequence 35 of a wild type human antibody κ -type light chain. The amino acid sequence ("#7.pro") appearing in FIG. 6I corresponds to SEQ ID NO: 14 assigned in the sequence listing.

FIG. 7A is a diagram indicating the results of an in vivo assay, and more particularly, indicating the condition of a 40 single-dose oral administration study in animals.

FIG. 7B 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. 7C 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. 8A is a diagram indicating the results of safety 50 studies (toxicity studies), and more particularly, indicating the toxicity studies conducted in order to confirm the safety to human.

FIG. 8B is a diagram indicating the results of safety studies (toxicity studies), and more particularly, indicating 55 the body weight change in mice in the 7-day repeat-dose toxicity study (caudal vein).

FIG. 8C 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 tox- 60 icity study (caudal vein).

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention provides an anticancer agent containing a human antibody k-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 k-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 10 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 15 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 SEO 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 30 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% 5 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 10 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 15 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 20 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, 25 dimer in which the variable region is composed of a poly-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 30 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 35 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 40 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 45 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 50 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 55 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. 60

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 65 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 k-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 peptide 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 ĸ-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 10 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 15 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 SEO ID NO: 13 and SEO ID NO: 20 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 25 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 cyto- 30 toxicity 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 35 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 $\,$ 40 $\,$ 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 45 other than the cysteine at position 219 in the amino acid sequence of SEO 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) 50 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 55 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 60 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 65 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 SEO 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 epitopetagged 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 5 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 10 may or may not be glycosylated depending on the host used in the recombinant production procedure. Moreover, the human antibody k-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 k-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 20 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 25 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 intro- 35 ducing 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 40 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 45 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- 50 free protein synthesis system), a polynucleotide encoding the human antibody ĸ-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 55 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 60 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 synthe- 65 sis system is selected in consideration of such factors as the origin of the gene to be translated (prokaryotic or eukary-

otic) 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 k-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 5 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. 10 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 20 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 25 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 30 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 35 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 intra- 40 muscular 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 45 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 50 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 55 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 inven- 60 tion 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 65 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 3.0×107 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 V κ gene belonging to subgroup II to obtain roughly 750 bp PCR products (k-type light chain genes belonging to subgroup II). These PCR products were cloned and subjected to sequence analysis, and the V κ 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/ol), 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 LEH-HHHHH (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 20 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 Vk gene belonging to subgroup II to obtain roughly 660 bp PCR ²⁵ 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 V κ 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) 35 on the N-terminal and LEHHHHHHH (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 40 sequence indicated in SEO 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 45 light chain (#9_WT)) was the base sequence indicated in SEO 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 50 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 55 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 60 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 anti-65 body light chain (22F6_WT)) was the base sequence indicated in SEQ ID NO: 36, and the total length of the human

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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 10 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 LEHHHHHHH (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. 2A and 2B. As shown in FIG. 2A, 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. 2B, 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 GCTCTCGAGCACCACCACC CACCACCACTGA (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 5 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 10 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 15 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 20 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 25 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). 30

(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 35 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 40 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. 45 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 50 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 55 (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 60 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 65 (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

	Concentration in	Cell viab	ility (%)
Clone	well (µM)	After 24 hr	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

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	-	/	
	TABLE 1	-continued	
	Concentration in	Cell viab	ility (%)
Clone	well (µM)	After 24 hr	After 48 hr
#4 WT #4 C220A	20 44	50 96	54 93
	TAB	LE 2	
	Concentration in	Cell viab	ility (%)
Clone	well (μM)	After 24 hr	After 48 hr
#2 WT	27	81	86

#2 #7 #7 #1 #1 #1 #1• 22 22 23 23

WT	27	81	86	15
C220A	40	94	95	
WT	35	49	53	
C220A	40	92	93	
3 WT	40	101	101	
3 C220A	56	97	81	
4 WT	32	100	94	20
4 C220A	40	89	88	20
F6 WT	62	80	92	
F6 C220A	32	65	64	
D4 WT	28	83	85	
D4 C220A	44	96	92	
				25

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 30 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 viat	oility (%)	
Cell type	Clone	24 hr after 4 ne addition		5
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	6
	#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	6
	S21	78.2	91.3	

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TABLE	3-continued

		Cell viat	oility (%)
Cell type	Clone	24 hr after addition	48 hr after addition
	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 50 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 ⁵ 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. 7A shows a condition of a single-dose oral administration study in animals. FIG. 7B shows the body weight change in animals in the single-dose oral administration study. FIG. 7C shows the macroscopic findings in animals in the single-dose oral administration study. FIG. 8A 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 repeatdose toxicity study (caudal vein). FIG. **8**C shows the autopsy findings in mice in the 7-day repeat-dose toxicity study (caudal vein).

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INDUSTRIAL APPLICABILITY

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

SEQUENCE LISTING

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p Tyr Leu Gln Lys Pro Gly His Ser 35 40
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<pre>click for the site of the set of the se</pre>	agc	agca	ccc ·	tgac	gctg	ag ca	aaago	caga	c tao	cgaga	aaac	aca	aagt	cta	egeet	gcgaa	600			
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Ser Gly Ser Gly	Thr Asp Phe Thr Leu Thr Ile Thr Ser Leu Glu Pro
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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
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Pro Ser Val Phe	Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
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Thr Ala Ser Val	Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
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Lys Val Gln Trp	Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
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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
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Tyr Asp Thr Ser	Thr Arg Ala Ala Gly Ile Pro Ala Arg Phe Ser Gly
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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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Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Arg Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys <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 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala Leu Gln Thr Pro Arg Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys <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 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser

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Pro Gln 50	Leu	Leu	Ile	Tyr	Leu 55		Ser	Asn	Arg	Ala 60		Gly	Val	Pro
Asp Arg 65		Ser	Gly	Ser 70		Ser	Gly	Thr	Asp 75		Thr	Leu	Lys	Ile 80
Ser Arg	Val	Glu	Ala 85		Asp	Val	Gly	Val 90		Tyr	Суз	Met	Gln 95	
Leu Gln	Thr			Thr	Phe	Gly			Thr	Lys	Val			Lys
Arg Thr		100 Ala	Ala	Pro	Ser		105 Phe	Ile	Phe	Pro		110 Ser	Asp	Glu
Gln Leu	-	Ser	Gly	Thr		120 Ser	Val	Val	Сүз		125 Leu	Asn	Asn	Phe
130 Tyr Pro		Glu	Ala	-	135 Val	Gln	Trp	Lys		140 Asp	Asn	Ala	Leu	
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Thr Tyr	Ser	Leu	165 Ser	Ser	Thr	Leu	Thr	170 Leu	Ser	Lys	Ala	Asp	175 Tyr	Glu
Lys His	Lys	180 Leu	Tyr	Ala	Суз	Glu	185 Val	Thr	His	Gln	Gly	190 Leu	Ser	Ser
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		20					25					30		
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Pro Gln 50		Leu	Ile	Tyr	Leu 55	Gly	Ser	Asn	Arg	Ala 60	Ser	Gly	Val	Pro
Asp Arg 65	Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80
Ser Arg	Val	Glu	Ala 85	Glu	Asp	Val	Gly	Val 90	Tyr	Tyr	Суз	Met	Gln 95	Gly
Leu Gln	Thr	Pro 100	Arg	Thr	Phe	Gly	Gln 105	Gly	Thr	Lys	Val	Glu 110	Ile	Lys
Arg Thr	Val 115	Ala	Ala	Pro	Ser	Val 120	Phe	Ile	Phe	Pro	Pro 125	Ser	Asp	Glu
Gln Leu 130		Ser	Gly	Thr	Ala 135	Ser	Val	Val	Суз	Leu 140	Leu	Asn	Asn	Phe
Tyr Pro 145	Arg	Glu	Ala	Lys 150	Val	Gln	Trp	Гла	Val 155	Asp	Asn	Ala	Leu	Gln 160
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Lys	His	Lys 195	Leu	Tyr	Ala	Суз	Glu 200	Val	Thr	His	Gln	Gly 205	Leu	Ser	Ser
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Asn	Gly	Tyr 35	Asn	Tyr	Leu	Asp	Trp 40	Tyr	Leu	Gln	Lys	Pro 45	Gly	Gln	Ser
Pro	Gln 50	Leu	Leu	Ile	Tyr	Leu 55	Gly	Ser	Asn	Arg	Asp 60	Ser	Gly	Val	Pro
Asp 65	Arg	Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80
Ser	Ser	Val	Glu	Ala 85	Glu	Asp	Val	Gly	Val 90	Tyr	Tyr	СЛа	Met	Gln 95	Ala
Leu	Glu	Thr	Pro 100	Pro	Thr	Phe	Gly	Gln 105	Gly	Thr	Lys	Leu	Glu 110	Ile	Lys
Arg	Thr	Val 115	Ala	Ala	Pro	Ser	Val 120	Phe	Ile	Phe	Pro	Pro 125	Ser	Asp	Glu
Gln	Leu 130	Lys	Ser	Gly	Thr	Ala 135	Ser	Val	Val	Суз	Leu 140	Leu	Asn	Asn	Phe
Tyr 145	Pro	Arg	Glu	Ala	Lys 150	Val	Gln	Trp	Гла	Val 155	Asp	Asn	Ala	Leu	Gln 160
Ser	Gly	Asn	Ser	Gln 165	Glu	Ser	Val	Thr	Glu 170	Gln	Asp	Ser	Lys	Asp 175	Ser
Thr	Tyr	Ser	Leu 180	Ser	Ser	Thr	Leu	Thr 185	Leu	Ser	Lys	Ala	Asp 190	Tyr	Glu
Lys	His	Lys 195	Val	Tyr	Ala	Суз	Glu 200	Val	Thr	His	Gln	Gly 205	Leu	Ser	Ser
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Asp 65	Arg	Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80
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Leu	Gln	Thr	Pro 100	Arg	Thr	Phe	Gly	Pro 105	Gly	Thr	Lys	Val	Asp 110	Ile	Lys
Arg	Thr	Val 115	Ala	Ala	Pro	Ser	Val 120	Phe	Ile	Phe	Pro	Pro 125	Ser	Asp	Glu
Gln	Leu 130	Lys	Ser	Gly	Thr	Ala 135	Ser	Val	Val	Суз	Leu 140	Leu	Asn	Asn	Phe
Tyr 145	Pro	Arg	Glu	Ala	Lys 150	Val	Gln	Trp	Lys	Val 155	Asp	Asn	Ala	Leu	Gln 160
Ser	Gly	Asn	Ser	Gln 165	Glu	Ser	Val	Thr	Glu 170	Gln	Asp	Ser	Lys	Asp 175	Ser
Thr	Tyr	Ser	Leu 180	Ser	Ser	Thr	Leu	Thr 185	Leu	Ser	Lys	Ala	Asp 190	Tyr	Glu
ГЛа	His	Lys 195	Val	Tyr	Ala	Суа	Glu 200	Val	Thr	His	Gln	Gly 205	Leu	Ser	Ser
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	Pro	Ala	Ser 20		Ser	Сүз	Arg	Ser 25		Gln	Ser	Leu	Leu 30		Ser
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Pro	Gln 50	Leu	Leu	Ile	Tyr	Leu 55	Gly	Ser	Asn	Arg	Ala 60	Ser	Gly	Val	Pro
Asp 65	Arg	Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80
Ser	Arg	Val	Glu	Ala 85	Glu	Asp	Val	Gly	Val 90	Tyr	Tyr	Суз	Met	Gln 95	Ala
Leu	Gln	Thr	Tyr 100	Thr	Phe	Gly	Gln	Gly 105	Thr	Lys	Leu	Glu	Ile 110	Гла	Arg
Thr	Val	Ala 115	Ala	Pro	Ser	Val	Phe 120	Ile	Phe	Pro	Pro	Ser 125	Asp	Glu	Gln
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Pro 145	Arg	Glu	Ala	ГÀа	Val 150	Gln	Trp	Lys	Val	Asp 155	Asn	Ala	Leu	Gln	Ser 160
Gly	Asn	Ser	Gln	Glu 165	Ser	Val	Thr	Glu	Gln 170	Asp	Ser	ГЛа	Asp	Ser 175	Thr
Tyr	Ser	Leu	Ser 180	Ser	Thr	Leu	Thr	Leu 185	Ser	Lys	Ala	Asp	Tyr 190	Glu	Гла
His	Lys	Val 195	Tyr	Ala	Суз	Glu	Val 200	Thr	His	Gln	Gly	Leu 205	Ser	Ser	Pro
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Asp	Gly	Lуз 35	Thr	Tyr	Phe	Tyr	Trp 40	Tyr	Leu	Gln	Arg	Pro 45	Gly	Arg	Ser
Pro	Gln 50	Leu	Leu	Ile	Gln	Glu 55	Val	Ser	Arg	Arg	Phe 60	Ser	Gly	Val	Pro
Asp 65	Arg	Phe	Ser	Gly	Ser 70	Gly	Ser	Gly	Ser	Asp 75	Phe	Thr	Leu	Гла	Ile 80
Ser	Arg	Val	Glu	Ala 85	Glu	Asp	Val	Gly	Val 90	Tyr	Tyr	Суа	Met	Gln 95	Gly
Thr	Tyr	Val	Pro 100	His	Thr	Phe	Gly	Gln 105	Gly	Thr	Lys	Val	Glu 110	Ile	Lys
Arg	Thr	Val 115	Ala	Ala	Pro	Ser	Val 120	Phe	Ile	Phe	Pro	Pro 125	Ser	Asp	Glu
Gln	Leu 130	Lys	Ser	Gly	Thr	Ala 135	Ser	Val	Val	Сүз	Leu 140	Leu	Asn	Asn	Phe
Tyr 145	Pro	Arg	Glu	Ala	Lys 150	Val	Gln	Trp	Lys	Val 155	Asp	Asn	Ala	Leu	Gln 160
Ser	Gly	Asn	Ser	Gln 165	Glu	Ser	Val	Thr	Glu 170	Gln	Asp	Ser	Lys	Asp 175	Ser
Thr	Tyr	Ser	Leu 180	Ser	Ser	Thr	Leu	Thr 185	Leu	Ser	ГЛа	Ala	Asp 190	Tyr	Glu
Lys	His	Lys 195	Leu	Tyr	Ala	Сүз	Glu 200	Val	Thr	His	Gln	Gly 205	Leu	Ser	Ser
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Asn	Leu	Ala 35	Trp	Tyr	Gln	Gln	Lys 40	Pro	Gly	Gln	Ala	Pro 45	Arg	Leu	Leu
Ile	Tyr 50	Gly	Ala	Ser	Ser	Arg 55	Ala	Thr	Gly	Ile	Pro 60	Asp	Arg	Phe	Ser
Gly 65	Ser	Gly	Ser	Gly	Thr 70	Asp	Tyr	Thr	Leu	Thr 75	Ile	Ser	Arg	Leu	Glu 80
Pro	Glu	Asp	Phe	Ala 85	Leu	Tyr	Tyr	Суз	Gln 90	Gln	Tyr	Gly	Ser	Ser 95	Leu
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Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys <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 Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Gly Pro Phe 3.0 Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Thr Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gl
n Gln Arg Tyr Thr Tr
p \mbox{Pro} Gly Asn Ser Phe Gly Gly Gly Ala Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys <210> SEQ ID NO 52 <211> LENGTH: 216 <212> TYPE: PRT <213> ORGANISM: human

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Leu Ala Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	Gln	Ala	Pro	Arg 45	Leu	Leu	Ile
Tyr Glu Ala 50	Ser	Asn	Arg	Ala 55	Thr	Gly	Ile	Pro	Ala 60	Arg	Phe	Ser	Gly
Ser Gly Ser 65	Gly	Pro	Asp 70	Phe	Thr	Leu	Thr	Ile 75	Ser	Ser	Leu	Glu	Pro 80
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Arg Ser Thr	Phe 100	Gly	Gln	Gly	Thr	Arg 105	Leu	Glu	Met	ГЛа	Arg 110	Thr	Val
Ala Ala Pro 115	Ser	Val	Phe	Ile	Phe 120	Pro	Pro	Ser	Asp	Glu 125	Gln	Leu	Lys
Ser Gly Thr 130	Ala	Ser	Val	Val 135	Суз	Leu	Leu	Asn	Asn 140	Phe	Tyr	Pro	Arg
Glu Ala Lys 145	Val	Gln	Trp 150	Lys	Val	Asp	Asn	Ala 155	Leu	Gln	Ser	Gly	Asn 160
Ser Gln Glu	Ser	Val 165	Thr	Glu	Gln	Asb	Ser 170	Lys	Asp	Ser	Thr	Tyr 175	Ser
Leu Ser Ser	Thr 180	Leu	Thr	Leu	Ser	Lys 185	Ala	Asp	Tyr	Glu	Lys 190	His	Lys
Val Tyr Ala 195	Сүз	Glu	Val	Thr	His 200	Gln	Gly	Leu	Ser	Ser 205	Pro	Val	Thr
Lys Ser Phe	7 a m	7	a1	a1	<i>a</i>								
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Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Leu Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys <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 Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Phe Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile Tyr Leu Gly Ser Thr Arg Ala Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Phe Cys Met Gln Ala Val Gln Thr Pro Phe Thr Phe Gly Pro Gly Thr Arg Leu Asp Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Ala <210> SEQ ID NO 55 <211> LENGTH: 66 <212> TYPE: DNA <213> ORGANISM: Artificial Sequence <220> FEATURE: <223> OTHER INFORMATION: Description: Artificially Synthesized Sequnce <400> SEQUENCE: 55 gtcacaaaga gcttcaacag gggagagtgt ctcgagcacc accaccacca ccactgagat ccggct

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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 20 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 30 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 $_{35}$ 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.