				1			0	10						
	Asp T	yr Ala	Met	Selr 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45
5	Glu T	rp Val	Ala	Va1 50	Ile	Ser	Glu	Asn	Gly 55	Gly	Tyr	Thr	Arg	Tyr 60
	Ala A	sp Ser	Val	Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Ala	Asp	Thr	Ser 75
10	Lys A	sn Thr	Ala	Tyr 80	Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90
	Thr A	la Val	Tyr	Tyr 95	Cys	Ser	Arg	Trp	Gly 100	Gly	Asp	Gly	Phe	Tyr 105
15	Ala M	let Asp	Val	Trp 110	Gly	Gln	Gly	Thr	Leu 115	Val	Thr	Val	Ser	Ser 120
20	(2) IN	NFORMAT	ION I	FOR :	EQ :	ID NO	0:5:							
25	(1)	(A) L (B) T (D) T	ENGTI YPE:	d: 10	09 a	mino cid		ds						
()	(xi)	SEQUE					SEQ	ID	NO:5					
30	Asp 1	Ile Val	Met	Thr 5	Gln	Ser	His	Lys	Phe 10	Met	Ser	Thr	Ser	Val 15
	Gly A	Asp Arg	Val	Ser 20	tle	Thr	Cys	Lys	Ala 25	Ser	Gln	Asp	Val	Asn 30
35	Thr A	Ala Val	Ala	Trp 35	tyr	Gln	Gln	Lys	Pro 40	Gly	His	Ser	Pro	Lys 45
	Leu l	Leu Ile	Tyr	Ser 50	1	Ser	Phe	Arg	Tyr 55	Thr	Gly	Val	Pro	Asp 60
40	Arg I	Phe Thr	Gly	Asn 65	Arg	Ser	Gly	Thr	Asp 70	Phe	Thr	Phe	Thr	Ile 75
45	Ser S	Ser Val	Gln	Ala 80	Glu	Asp	Leu	Ala	Val 85	Tyr	Tyr	Cys	Gln	Gln 90
	His :	Tyr Thr	Thr	Pro 95		Thr	Phe	Gly	Gly 100	Gly	Thr	Lys	Leu	Glu 105
50	Ile 1	Lys Arg	Ala 109		1									

	(2) INFORMATION FOR SEQ ID NO:6:
5	(1) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 120 amino acids  (B) TYPE: amino acid  (D) TOPOLOGY: linear
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:
10	Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly 1 10 15
	Ala Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys 20 25 30
15	Asp Thr Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu 35 40 45
20	Glu Trp Ile Gly Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr
	Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser
25	Ser Asn Thr Ala Tyr Leu Gln Val Ser Arg Leu Thr Ser Glu Asp 80 85 90
80	Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
30	Ala Met Asp Tyr Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser 110 115 120
35	(2) INFORMATION FOR SEQ ID NO:7:
40	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 27 bases  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear
	(x1) SEQUENCE DESCRIPTION: SEQ ID NO:7:
45	TCCGATATCC AGCTGACCCA GTCTCCA 27
50	(2) INFORMATION FOR SEQ ID NO:8:
	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 31 bases  (B) TYPE: nucleic acid

	45
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:
	GTTTGATCTC CAGCTTGGTA CCXXCXCCGA A 31
10 .	(2) INFORMATION FOR SEQ ID NO:9:
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 bases
15	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:
	AGGTXXAXCT GCAGXAGTCX GG 22
25	(2) INFORMATION FOR SEQ ID NO:10:
1	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 34 bases
30	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:
	TGAGGAGACG GTGACCGTGG TCCCTTGGCC CCAG 34
40	(2) INFORMATION FOR SEQ ID NO:11:
45	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 bases  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear
50	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:
	GTAGATAAAT CCTCTAACAC AGCCTATCTG CAAATG 36

	(2)	INFORMATION FOR SEQ ID NO:12:
5		(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 bases  (B) TYPE: nucleic acid
		(C) STRANDEDNESS: single (D) TOPOLOGY: linear
10		x1) SEQUENCE DESCRIPTION: SEQ ID NO:12:
15		GTAGATAAAT CCAAATCTAC AGCCTATCTG CAAATG 36
15	(2)	INFORMATION FOR SEQ ID NO:13:
		(i) SEQUENCE CHARACTERISTICS: (A) LENGTH 36 bases
20	*	(B) TYPE: pucleic acid
		(C) STRANDEDNESS: single
		(D) TOPOLOGY: linear
25		(x1) SEQUENCE DESCRIPTION: SEQ ID NO:13:
	1	
	1	GTAGATAAAT CCTCTTCTAC AGCCTATCTG CAAATG 36
30	(2)	INFORMATION FOR SEQ ID NO:14:
		(i) SEQUENCE CHARACTERISTICS:
		(A) LENGTH: 68 bases
35		(B) TYPE: nucleic acid
		(C) STRANDEDNESS: single (D) TOPOLOGY: linear
		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:
40		(XI) SEQUENCE DESCRIPTION. SEQ ID NO.14.
		CTTATAAAGG TGTTTCCACC TATAACCAGA AATTCAAGGA TCGTTTCACG 50
45		ATATCCGTAG ATAAATCC 68
	(2)	) INFORMATION FOR SEQ ID NO:15:
50		(i) SEQUENCE CHARACTERISTICS:
00		(A) LENGTH: 30 bases
		(B) TYPE: nucleic acid
		(C) STRANDEDNESS: single
		(D) TOPOLOGY: linear

(x1) SEQUENCE DESCRIPTION: SEQ ID NO:15:

# CTATACCTCC CGTCTGCATT CTGGAGTCCC 30 5 (2) INFORMATION FOR SEQ ID NO:16: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 107 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:16: Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu 20 Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Arg Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys 35 25 Leu Leu Ile Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Lys Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile 30 Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Ala Gly Gly Thr Lys Leu Glu Ile Lys 107 40 (2) INFORMATION FOR SEQ ID NO:17: (1) SEQUENCE CHARACTERISTICS: (A) LENGTH: 107 amino acids 45 (B) TYPE: amino acid (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17: 50 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg

Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Arg Leu Glu Ser Gly Val Pro Ser 5 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile 10 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu 15 Ile Lys 107 (2) INFORMATION FOR SEQ ID NO:18: 20 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 107 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear 25 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18: Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val 30 Gly Asp Arg Val Thr | Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys 35 Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser 40 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln 45 Tyr Asn Ser Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu 100 105 Ile Lys 50 107

	(2) INFORMATION FOR SEQ ID NO:19:
5	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 129 amino acids  (B) TYPE: amino acid  (D) TOPOLOGY: linear
	(x1) SEQUENCE DESCRIPTION: SEQ ID NO:19:
10	Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly 1 5 10 15
15	Ala Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr 20 25 30
15	Gly Tyr Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu 35 40 45
20	Glu Trp Met Gly Leu Ile Asn Pro Tyr Lys Gly Val Ser Thr Tyr 50 55 60
	Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Lys Ala Thr Leu 65 70 75
25	Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Leu Met Glu Leu Leu 80 85 90
30	Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
SO (1)	Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp Gly 110 115 120
35	Ala Gly Thr Thr Val Thr Val Ser Ser 125 129
	(2) INFORMATION FOR SEQ ID NO: 20:
40	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 122 amino acids  (B) TYPE: amino acid  (D) TOPOLOGY: linear
45	(x1) SEQUENCE DESCRIPTION: SEQ ID NO:20:
	Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly 1 10 15
50	Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Tyr Ser Phe Thr 20 25 30
	Gly Tyr Thr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu 35 40 45

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		Glu	Trp	Val	Ala	Leu 50	Ile	Asn	Pro	Tyr	Lys 55	Gly	Val	Ser	Thr	Tyr 60	
5		Åsn	Gln	Lys	Phe	Lys 65	Asp	Arg	Phe	Thr	11e 70	Ser	Val	Asp	Lys	Ser 75	
		Lys	Asn	Thr	Ala	Tyr 80	Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	
10		Thr	Ala	Val	Tyr	Tyr 95	Cys	Ala	Arg	Ser	Gly 100	Tyr	Tyr	Gly	Asp	Ser 105	
16		Asp	Trp	Tyr	Phe	Asp 110	Val	Trp	Gly	Gln	Gly 115	Thr	Leu	Val	Thr	Val 120	
15		Ser	Ser 122														
		(2)	INFO	RMAT	ION	FOR :	EQ :	ID N	0:21	:			141				
20 25		(	(	EQUE A) L B) T D) T	ENGT	H: 1:	22 au	mino cid		ds							
		(x	i) S	EQUE	NCE	DESC	RIPT	ION:	SEQ	ID 1	NO: 2	1:					
30		Glu 1	Val	Gln	Leu	Val 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Va1	Gln	Pro	Gly 15	
(	1	Gly	Ser	Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ser 30	
35		Ser	Tyr	Ala	Met	Ser 35	Trp	Val	Arg	Gln	A1a 40	Pro	Gly	Lys	Gly	Leu 45	
		Glu	Trp	Val	Ser	Val 50	Ile	Ser	Gly	Asp	Gly 55	G1y	Ser	Thr	Tyr	Tyr 60	
40		Ala	Asp	Ser	Val	Lys 65	Gly	Arg	Phe	Thr	11e 70	Ser	Arg	Asp	Asn	Ser 75	
45		Lys	Asn	Thr	Leu	Tyr 80	Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90	
45		Thr	Ala	Val	Tyr	Tyr 95	Cys	Ala	Arg	Gly	Arg 100	Val	Gly	Tyr	Ser	Leu 105	
50		Ser	Gly	Leu	Tyr	Asp 110	Tyr	Trp	Gly	Gln	Gly 115	Thr	Leu	Val	Thr	Val 120	
		Ser	Ser 122														

# (2) INFORMATION FOR SEQ ID NO:22:

## (1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 454 amino acids
- (B) TYPE: amino acid

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(D) TOPOLOGY: linear

#### (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

	(x	1) 5	EQUE	NCE	DESCI	KIPI.	LON:	SEQ	ID I	NO: 2.	4:				
10	Gln 1	Val	Gln	Leu	Gln 5	Gln	Ser	Gly	Pro	Glu 10	Leu	Val	Lys	Pro	Gly 15
15	Ala	Ser	Val	Lys	11e 20	Ser	Cys	Lys	Thr	Ser 25	Gly	Tyr	Thr	Phe	Thr 30
15	Glu	Tyr	Thr	Met	His 35	Trp	Met	Lys	Gln	Ser 40	His	Gly	Lys	Ser	Leu 45
~~	Glu	Trp	Ile	G1y	Gly 50	Phe	Asn	Pro	Lys	Asn 55	Gly	Gly	Ser	Ser	His 60
	Asn	Gln	Arg	Phe	Met 65	Asp	Lys	Ala	Thr	Leu 70	Ala	Val	Asp	Lys	Ser 75
25	Thr	Ser	Thr	Ala	Tyr 80	Met	Glu	Leu	Arg	Ser 85	Leu	Thr	Ser	Glu	Asp 90
20	Ser	G1y	Ile	Tyr	Tyr 95	Cys	Ala	Arg	Trp	Arg 100	Gly	Leu	Asn	Tyr	Gly 105
30	Phe	Asp	Val	Arg	Tyr 110	Phe	Asp	Val	Trp	Gly 115	Ala	Gly	Thr	Thr	Val 120
35	Thr	Val	Ser	Ser	Ala 125	Ser	Thr	Lys	G1y	Pro 130	Ser	Val	Phe	Pro	Leu 135
	Ala	Pro	Ser	Ser	Lys 140	Ser	Thr	Ser	Gly	G1y 145	Thr	Ala	Ala	Leu	Gly 150
40	Cys	Leu	Val	Lys	Asp 155	Tyr	Phe	Pro	Glu	Pro 160	Val	Thr	Val	Ser	Trp 165
45	Asn	Ser	Gly	Ala	Leu 170	Thr	Ser	Gly	Val	His 175	Thr	Phe	Pro	Ala	Val 180
45	Leu	Gln	Ser	Ser	Gly 185	Leu	Tyr	Ser	Leu	Ser 190	Ser	Val	Val	Thr	Val 195
50	Pro	Ser	Ser	Ser	Leu 200	Gly	Thr	Gln	Thr	Tyr 205	Ile	Cys	Asn	Val	Asn 210
			4			15		F-100 22							

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys

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		Ser	Cys	Asp	Lys	Th: 230	His	Thr	Cys	Pro	Pro 235	Cys	Pro	Ala	Pro	Glu 240
5		Leu	Leu	Gly	Gly	Pro 245	Ser	Val	Phe	Leu	Phe 250	Pro	Pro	Lys	Pro	Lys 255
		Asp	Thr	Leu	Met	11e 260	Ser	Arg	Thr	Pro	Glu 265	Va1	Thr	Cys	Va1	Val 270
10		Val	Asp	Val	Ser	His 275	Glu	Asp	Pro	Glu	Val 280	Lys	Phe	Asn	Trp	Tyr 285
22		Val	Asp	Gly	Val	G1u 290	Val	His	Asn	Ala	Lys 295	Thr	Lys	Pro	Arg	Glu 300
15		Glu	Gln	Tyr	Asn	Ser 305	Thr	Tyr	Arg	Val	Val 310	Ser	Val	Leu	Thr	Val 315
20		Leu	His	Gln	Asp	Trp 320	Leu	Asn	Gly	Lys	Glu 325	Tyr	Lys	Cys	Lys	Val 330
		Ser	Asn	Lys	Ala	Leu 335	Pro	Ala	Pro	Ile	Glu 340	Lys	Thr	Ile	Ser	Lys 345
25		Ala	Lys	Gly	Gln	Pro 350	Arg	Glu	Pro	Gln	Val 355	Tyr	Thr	Leu	Pro	Pro 360
		Ser	Arg	Glu	G1u	Met 365	Thr	Lys	Asn	Gln	Va1 370	Ser	Leu	Thr	Cys	Leu 375
30	61	Val	Lys	Gly	Phe	Ty:	Pro	Ser	Asp	Ile	Ala 385	Val	G1u	Trp	G1u	Ser 390
35	j	Asn	Gly	Gln	Pro	G1u 395	Asn	Asn	Tyr	Lys	Thr 400	Thr	Pro	Pro	Val	Leu 405
		Asp	Ser	Asp	Gly	Ser 410	Phe	Phe	Leu	Tyr	Ser 415	Lys	Leu	Thr	Val	Asp 420
40		Lys	Ser	Arg	Trp	Gin 425		Gly	Asn	Val	Phe 430	Ser	Cys	Ser	Val	Met 435
		His	Glu	Ala	Leu	His 440		His	Tyr	Thr	Gln 445	Lys	Ser	Leu	Ser	Leu 450
45		Ser	Pro	Gly	Lys 454											
50		(2)	INFO	RMAT	ION	FOR	SEQ	ID N	0:23	1						
		(	(	A) L B) T	ENGT YPE:	H: 5	ACTE 57 a no a lin	mino cid		ds						

		(x:	L) SI	EQUEN	NCE I	ESCE	RIPTI	ON:	SEQ	ID I	NO:23	3:				
_		His 1	His	Gln	Val	Gln 5	Leu	Gln	Gln	Ser	Gly 10	Pro	Glu	Leu	Val	Lys 15
5		Pro	Gly	Ala	Ser	Val 20	Lys	Ile	Ser	Cys	Lys 25	Thr	Ser	Gly	Tyr	Thr 30
10		Phe	Thr	Glu	Met	Gly 35	Trp	Ser	Cys	Ile	Ile 40	Leu	Phe	Leu	Val	Ala 45
		Thr	Ala	Thr	Gly	Val 50	His	Ser	Glu	Val	Gln 55	Leu	Val	Glu	Ser	Gly 60
15		Gly	Gly	Leu	Val	Gln 65	Pro	Gly	Gly	Ser	Leu 70	Arg	Leu	Ser	Cys	Ala 75
		Thr	Ser	Gly	Tyr	Thr 80	Phe	Thr	Glu	Tyr	Thr 85	Met	His	Trp	Met	Arg 90
.0		Gln	Ala	Pro	Gly	Lys 95	Gly	Leu	Glu	Trp	Val 100	Ala	Gly	Ile	Asn	Pro 105
25		Lys	Asn	Gly	Gly	Thr 110	Ser	His	Asn	Gln	Arg 115	Phe	Met	Asp	Arg	Phe 120
		Thr	Ile	Ser	Val	Asp 125	Lys	Ser	Thr	Ser	Thr 130	Ala	Tyr	Met	Gln	Met 135
30	(1	Asn	Ser	Leu	Arg	Ala 140	¢1u	Asp	Thr	Ala	Val 145	Tyr	Tyr	Cys	Ala	Arg 150
25	1	Trp	Arg	Gly	Leu	Asn 155	Tyr	Gly	Phe	Asp	Val 160	Arg	Tyr	Phe	Asp	Val 165
35		Trp	Gly	Gln	Gly	Thr 170	Leu	Val	Thr	Val	Ser 175	Ser	Ala	Ser	Thr	Lys 180
40		Gly	Pro	Ser	Val	Phe 185	Pro	Leu	Ala	Pro	Cys 190	Ser	Arg	Ser	Thr	Ser 195
		Glu	Ser	Thr	Ala	Ala 200	Leu	Gly	Cys	Leu	Val 205	Lys	Asp	Tyr	Phe	Pro 210
45		Glu	Pro	Val	Thr	Val 215	Ser	Trp	Asn	Ser	Gly 220	Ala	Leu	Thr	Ser	Gly 225
E0		Val	His	Thr	Phe	Pro 230	Ala	Val	Leu	Gln	Ser 235		Gly	Leu	Tyr	Ser 240
50		Leu	Ser	Ser	Val	Va1 245		Val	Thr	Ser	Ser 250		Phe	Gly	Thr	Gln 255
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	Thr	Tyr	Thr	Cys	Asn 260	Val	Asp	His	Lys	Pro 265	Ser	Asn	Thr	Lys	Val 270
5	Asp	Lys	Thr	Val	Glu 275	Arg	Lys	Cys	Cys	Val 280	Thr	Cys	Pro	Pro	Cys 285
	Pro	Ala	Pro	Glu	Leu 290	Leu	Gly	Gly	Pro	Ser 295	Val	Phe	Leu	Phe	Pro 300
10	Pro	Lys	Pro	Lys	Asp 305	Thr	Leu	Met	Ile	Ser 310	Arg	Thr	Pro	Glu	Val 315
46	Thr	Cys	Val	Val	Val 320	Asp	Val	Ser	His	Glu 325	Asp	Pro	Glu	Val	Lys 330
15	Glu	Cys	Pro	Pro	Cys 335	Pro	Ala	Pro	Pro	Val 340	Ala	Gly	Pro	Ser	Val 345
7	Phe	Leu	Phe	Pro	Pro 350	Lys	Pro	Lys	Asp	Thr 355	Leu	Met	Ile	Ser	Arg 360
	Thr	Pro	Glu	Val	Thr 365	Cys	Val	Val	Val	Asp 370	Val	Ser	His	Glu	Asp 375
25	Pro	Glu	Val	Gln	Phe 380	Asn	Trp	Tyr	Val	Asp 385	Gly	Met	Glu	Val	His 390
20 ( )	Asn	Ala	Lys	Thr	Lys 395	Pro	Arg	Glu	Glu	Gln 400	Phe	Asn	Ser	Thr	Phe 405
30	Arg	Val	Val	Ser	Val 410	Leu	Thr	Val	Val	His 415	Gln	Asp	Trp	Leu	Asn 420
35	Gly	Lys	Glu	Tyr	Lys 425	Cys	Lys	Val	Ser	Asn 430	Lys	Gly	Leu	Pro	Ala 435
	Pro	Ile	Glu	Lys	Thr 440	Ile	Ser	Lys	Thr	Lys 445	Gly	Gln	Pro	Arg	Glu 450
40	Pro	Gln	Val	Tyr	Thr 455	Leu	Pro	Pro	Ser	Arg 460	Glu	Glu	Met	Thr	Lys 465
AE.	Asn	Gln	Val	Ser	Leu 470	Thr	Cys	Leu	Val	Lys 475	Gly	Phe	Tyr	Pro	Ser 480
45	Asp	Ile	Ala	Val	Glu 485	Trp	Glu	Ser	Asn	Gly 490	Gln	Pro	Glu	Asn	Asn 495
50	Tyr	Lys	Thr	Thr	Pro 500	Pro	Met	Leu	Asp	Ser 505	Asp	Gly	Ser	Phe	Phe 510
	Leu	Tyr	Ser	Lys	Leu 515	Thr	Val	Asp	Lys	Ser 520		Trp	Gln	Gln	Gly 525

		,								103						
		Asn	Val	Phe	Ser	Cys 530	Ser	Val	Met	His	Glu 535	Ala	Leu	His	Asn	His 540
5		Tyr	Thr	Gln	Lys	Ser 545	Leu	Ser	Leu	Ser	Pro 550	Gly	Lys			555
		(2) I	NFOF	TAM	ON I	FOR	EQ 1	D NO	0:24							
10		(i	(A	A) LE	ENGTH	CHAR H: 21 amir OGY:	l4 an	nino cid		is						
15		(xi	) SI	EQUE	NCE I	DESCE	RIPTI	ON:	SEQ	ID t	NO: 24	4:				
		Asp 1	Val	Gln	Met	Thr	Gln	Thr	Thr	Ser	Ser 10	Leu	Ser	Ala	Ser	Leu 15
20		Gly	Asp	Arg	Val	Th:	Ile	Asn	Cys	Arg	Ala 25	Ser	Gln	Asp	Ile	Asn 30
		Asn	Tyr	Leu	Asn	Tro 35	Tyr	Gln	Gln	Lys	Pro 40	Asn	Gly	Thr	Val	Lys 45
25		Leu	Leu	Ile	Tyr	Ty	Thr	Ser	Thr	Leu	His 55	Ser	Gly	Val	Pro	Ser 60
30		Arg	Phe	Ser	Gly	Ser 55	Gly	Ser	Gly	Thr	Asp 70	Tyr	Ser	Leu	Thr	Ile 75
30	FI	Ser	Asn	Leu	Asp	Gln 80	Glu	Asp	Ile	Ala	Thr 85	Tyr	Phe	Cys	Gln	Gln 90
35		Gly	Asn	Thr	Leu	Pro 95	Pro	Thr	Phe	Gly	Gly 100	G1y	Thr	Lys	Val	Glu 105
		Ile	Lys	Arg	Thr	Val 110	Ala	Ala	Pro	Ser	Val 115	Phe	Ile	Phe	Pro	Pro 120
40		Ser	Asp	Glu	Gln	Leu 125	Lys	Ser	Gly	Thr	Ala 130	Ser	Val	Val	Cys	Leu 135
45		Leu	Asn	Asn	Phe	Tyr 140	Pro	Arg	Glu	Ala	Lys 145	Val	Gln	Trp	Lys	Val 150
+		Asp	Asn	Ala	Lev	Gln 155	Ser	Gly	Asn	Ser	Gln 160	Glu	Ser	Val	Thr	Glu 165
50		Gln	Asp	Ser	Lys	Asp 170	Ser	Thr	Tyr	Ser	Leu 175	Ser	Ser	Thr	Leu	Thr 180
		Leu	Ser	Lys	Ala	Asp 185		Glu	Lys	His	Lys 190	Val	Tyr	Ala	Cys	Glu 195
					1											

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Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn 200 205 210

Arg Gly Glu Cys 214

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## (2) INFORMATION FOR SEQ ID NO:25:

(1) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 233 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr 1 5 10 15

Gly Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu 20 25 30

Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Asp Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
50 55 60

Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser
65 70 75

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr 80 85 90

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
95 100 105

Tyr Cys Gln Gln Gly Asn Thr Leu Pro Pro Thr Phe Gly Gln Gly

Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe 125 130 135

Ile Phe Pro Pro Set 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 155 160 165

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu 170 175 180

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser 185 190 195

129 of 1033

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 215 220 225

Lys Ser Phe Asn Arg Gly Glu Cys 230 233

Ind >

#### DO/EO BIBLIOGRAPHIC DATA ENTRY

SERIAL NUMBER: US / 146206
IA NUMBER: PCT/ US92 / 05126
FAMILY NAME: CARTER
GIVEN NAME: PAUL J.
PRIORITY CLAIMED (Y/N): Y
NO BASIC FEE (Y/N): N
ATTORNEY DOCKET NUMBER: 70991
CORRESPONDENTS NAME/ADDRESS:
CAROLYN R. ADLER
GENENTECH. INC.
460 POINT SAN BRUND BOULEVARD
SOUTH SAN FRANCISCO, CALIFORNIA 94080

RECEIPT DATE: 11 / 17 / 93
TA FILING DATE: 06 / 15 / 92
DELAY WAIVED (Y/N): Y
DEMAND RECEIVED (Y/N): Y
PRIORITY DATE: 06 / 14 / 91
US DESIGNATED ONLY (Y/N): N
COUNTRY: USX

APPLICATION TITLES: METHOD FOR MAKING HUMANIZED ANTIBODIES

OK TO UPDATE? (Y OR N)

BAR CODE LABEL



# U.S. PATENT APPLICATION

SERIAL NUMBER

FILING DATE

CLASS

**GROUP ART UNIT** 

08/146,206

11/17/93

435

1804

APPLICANT

PAUL J. CARTER, SAN FRANCISCO, CA; LEONARD G. PRESTA, SAN FRANCISCO, CA.

\*\*CONTINUING DATA\*\*\*\*\*\*\*\*\*\*\*\*

VERIFIED

THIS APPLN IS A 371 OF

/US92/05126 06/15/92

\*\*FOREIGN/PCT APPLICATIONS\*\*\*\*\*\*\*\*\*

VERIFIED

PCT

PCT/US92/05126

06/15/92

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS	FILING FEE RECEIVED	ATTORNEY DOCKET NO.	*
CA	9	18	9	\$1,592.00	709P1	

JANET E. HASAK GENENTECH, INC.

460 POINT SAN BRUNO BOULEVARD

SOUTH SAN FRANCISCO, CA 94080-4990

IMMUNOGLOBULIN VARIANTS

TILE

This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application which is identified above.

By authority of the COMMISSIONER OF PATENTS AND TRADEMARKS

Date

Certifying Officer

PATENT APPLICATION SERIAL NO. 18746206

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE FEE RECORD SHEET

DS20071 11272,793 (41,57)

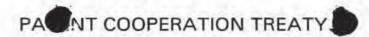
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PTO-1556 (5/87)

	STATE		7.7	- VVI 17		1.1		Application o	r Dock	et Number	
1	PATENT A	PPLICATIO Effecti		<b>DETERN</b> er 1, 1992		ION RECO	RD	08/	146	206	
			AS FILED Column 1)	- PART I	(Col	lumn 2)	SMAL	L ENTITY	OR	OTHER T	
OR		NUMBE	RATI	FEE 475		RATE	FEE 950				
BASIC	FEE							\$3 <del>55:00</del>	OR		\$710.00
OTA	L CLAIMS		24 mir	nus 20 = *	4		x\$11:	=	OR	x\$22=	-
NDE	PENDENT CLA	IMS	9 mi	inus 3 =   *	6		x 37=		OR	x 74=	
MU	LTIPLE DEPEN	DENT CLAIM PR	ESENT				+115	=	OR	+230=	P
If the	difference in colu	mn 1 is less then zer	ro, enter "0" ir	n column 2			TOTA	L	OR	TOTAL	1
		CLAIM (Column 1)	S AS AM	IENDED - (Colum		(Column 3)	SMAL	L ENTITY	OR	OTHER T	
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHE NUME PREVIO PAID	BER	PRESENT EXTRA	RATE	ADDI- TIONAL FEE		RATE	ADDI- TIONAL FEE
20	Total		Minus	**		=	x\$11:		OR	x\$22=	
ME	Independent		***	***		x 37:		OR	x 74=		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM						+ 115	=	OR	+230=	
	(Column 1) (Column 2) (Column 3)						TOTA ADDIT. FE		OR	TOTAL DDIT. FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHI NUMI PREVIO PAID	BER	PRESENT EXTRA	RATI	ADDI- TIONAL FEE		RATE	ADDI- TIONAL FEE
DE	Total	1	Minus	**		=	x\$11		OR	x\$22=	
MEN	Independent	7-21	Minus'	***		=	x 37	-	OR	x 74=	
•	FIRST PRE	SENTATION OF	MULTIPLE I	DEPENDEN	T CLAIM		+ 115:		OR	+ 230=	
		(Column 1)		(Colum	in 2)	(Column 3)	TOT ADDIT. F		OR	TOTAL DDIT. FEE	
AMENDMENT C		CLAIMS REMAINING AFTER AMENDMENT		HIGH NUM PREVIO PAID	BER	PRESENT EXTRA	RAT	ADDI- TIONAL FEE		RATE	ADDI- TIONAL FEE
ZDZ	Total	. 41	Minus	**		=	x\$11=		OR	x\$22=	
ME	Independent	12:	Minus	***		=	x 37		OR	x 74=	
4	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM								OR	+230=	
* 16	he entry in colu	mn 1 is less than t mber Previously P	he entry in	column 2, wr	ite "0" in d	column 3,	TO	TAL	OR	TOTAL	

FORM PTO-875 (Rev.10-92)



To:

13	Rec'd	PCT/FT.	17FEB	1993
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#### From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

United States Patent and Trademark Office

Washington, D.C.

Date of mailing:

09 February 1993 (09.02.93)

in its capacity as elected Office

International application No.:

PCT/US92/05126

Applicant's or agent's file reference:

709P1

International filing date:

15 June 1992 (15.06.92)

Priority date:

14 June 1991 (14.06.91)

Applicant:

CARTER, Paul, J. et al

	ed with the International preliminary Examining Authority on:  07 January 1993 (07.01.93)	
in a notice effection	ng later election filed with the International Bureau on:	
The election X w	as not	
	tion of 19 months from the priority date.	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorized officer:

J. Leitao

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 730.91.11





# **PCT**

REC'D 23 SEP. 1993

INTERNATIONAL PRELIMINARY EXAMINATION REPORT POT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 709P1	FOR FURTHER ACTION See Preli	Notification of Transmittal of International minary Examination Report (Form PCT/IPEA/416)
International application No.	International filing date (day/month/y	rear) Priority date (day/month/year)
PCT/US 92/05126	15/06/1992	14/06/1991
International Patent Classification (IPC)		1,700,2002
	C12N15/13	
Applicant		
GENENTECH, INC. et al.		
1. This international preliminary e	examination report has been prepared by th	nis International Preliminary Examining
Authority and is transmitted to	the applicant according to Article 36.	
2. This REPORT consists of a t	otal of 8 sheets.	
This report is also accome	panied by ANNEXES, i.e. sheets of the c	description, claims and/or drawings amended
during international prelim	ninary examination and/or containing rectif	fications made before this Authority.
These annexes consists of a tot	al of 3 sheets.	
3. This report contains indications	and corresponding pages relating to the fo	ollowing items:
IX Basis of the report		*
II Priority		
	of opinion with regard to novelty, inventive	step and industrial applicability
IV Lack of unity of inv		*
	with regard to novelty, inventive step or in	ndustrial applicability;
citations and explan	ations supporting such statement	1981 000 1991 100 100 PM MARKEY 72 000 100 PM
VI Certain documents	cited .	
VII Certain defects in th	e international application	
VIII Certain observation	s on the international application	
	945	
Date of submission of the demand	Date of com	pletion of this report
07/01/1993	- C	2 0. 09. 93
Name and mailing address of the IPEA/	The second second	officer
W-8000 Munich 2	- 6	2- Jemma
Tel. (+49-89) 2399-0, Tx: 5 Fax: (+49-89) 2399-4465	23656 epmu d	C. Germinario

I. Basis of the report	
1. This report has been drawn up on the basis of:	
[ ] the international application as originally filed.	
[x] the description, pages 1-107_	, as originally filed,
pages	
	, filed with the letter of,
	, filed with the letter of,
[x] the claims, No. 10-17	_, as originally filed,
No	_, as amended under Article 19,
No.	
No. 1-9, 18, 19	_, filed with the letter of 12.06.93,
Но.	_, filed with the letter of,
[x] the drawings, sheets/fig 1/9 - 9/9	, as originally filed,
sheets/fig	, filed with the demand,
sheets/fig	, filed with the letter of,
sheets/fig	, filed with the letter of
2. The amendments have resulted in the cancellation of: pages:	
sheets of drawings/figures No.:	· ·
3. [ ] This report has been established as if (some of) the amend	dments had not been made, since they have been
considered to go beyond the disclosure as filed:	
4. Additional observations, if necessary:	

Intern. application No. PCT/US92/05126

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

[ ] the entire international application,

[x] claims Nos. 17, 18

#### because:

[x] the said international application, or the said claims Nos. 17, 18 relate to the following subject matter which does not require an international preliminary examination (specify):

Claims 17 is directed to a mere presentation of information, namely the translation of the information inherent in an amino acid sequence into a message or a language readable by the computer.

Claim 18 would appear to be directed to a method of preparing a computer program.

According to Rule 67.1 (V) and (VI) no International Preliminary Examination (thus no preliminary Written Opinion) can be carried out for such a subject matter.

[x] the description, claims or drawings (indicate particular elements below) or said claims Nos. 16 are so unclear that no meaningful opinion could be formed (specify):

Claim 16 represents a novel claim-category; its subject matter is in fact a machine or an apparatus i.e. a computer.

Now an independent claim directed to a machine must cite all the essential technical features necessary to define said machine; the information saved in memory of a computer are not considered a characterizing part of the same. Therefore the subject matter of claim 16 is definitely not at all characterized as requested by Art.

[ ] the claims, or said claims Nos are so inadequately supported the description that no meaningful opinion could be formed.  [ ] no international search report has been established for said claims		6 PCT (see PCT Guidelines C III 4.4).	
the description that no meaningful opinion could be formed.			
	[ ] the	e claims, or said claims Nos	are so inadequately supported by
no international search report has been established for said claims	th	e description that no meaningful opinion could be formed.	
one international search report has been established for said claims			
The state of the contract of the contract of the state of the contract of the	[ ] no	international search report has been established for said claims	5 14 mg
Nos	No	s	

V. Reasoned statement under Article 35 citations and explanations supporti	(2) with regard to novelty, inventive step and industrial a ing such statement	applicability;
1. STATEMENT		
	and the second s	
Novelty (N)	Claims 1-9, 12-15, 19	YES
	Claims 10,11	NO
5.00 4.7.000	the second the special transfer and the	9
Inventive Step (IS)	Claims 2, 6-9, 13, 14, 19	YES
	Claims 1, 3-5, 12, 15	ио
Industrial Applicability (IA)	Claims 1-19	YES

-- 70000150 (505.54)

#### 2. CITATIONS AND EXPLANATIONS

The following document is referred to in the present IPER as the closest prior art:

WO-A-90/07861;

2. This earlier application describes a method for designing humanized antibodies which consists of all the steps a) to g) of the present claim 1.

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More precisely the features under item a) that the amino acid sequences of both donor (import) and acceptor (consensus) antibody are from the variable domain and that the human sequence (acceptor) is a consensus sequence are disclosed at page 10, last two lines and page 11 first lines and page 12 "criterion I.

Steps under b) and c) are disclosed at page 5 line 8 to 31 and claim 18.

Steps under items d) to g) are disclosed in claims 19 to 21 and at page 5 line 32 to page 6 line 20 and more in details at page 11 line 19 to page 15 line 2.

Among the three criteria for selecting FR-residues convenient for substitution (item f), criterion 2. is disclosed at page 14 under "criterion IV" and criterion 1. is disclosed at page 14 lines 7 and 8.

2.1 Under "criterion I" at page 12 of the earlier WO application two different options are contemplated for the selection of the acceptor antibody; the first option is based on the homology with the framework of the donor immunoglobulin, the second on the use of a consensus framework from many human antibodies.

The IPEA recognizes that the latter possibility, which corresponds to the present invention, is not further disclosed with details or exemplified.

Therefore the use of a "consensus sequence" as acceptor is not actually an embodiment of the WO-A-90/07861 invention.

For this reason claims 1 to 9, 13 to 15 and 19 are regarded as novel.

2.2. Claims 10 to 12 do not comprise any reference to a consensus sequence as acceptor of the non-human CDR. Therefore the unique feature discriminating between the present invention and the subject matter of the earlier WO application is missing.

It should moreover be noted that the WO-A-90/07861 discloses in details the humanized Eu antibody light chain where the CDRs are replaced by the corresponding CDRs from anti-Tac light chain and where additionally other amino acids in the FR are replace by the corresponding anti-Tac amino acids (see Experimental, page 26, 27; Fig. 2 and explanation of the same at page 7).

From Fig. 2 and explanation of the same at page 7).

From Fig. 2 and explanation of the same is evident that the site 63L of the Eu light chain, which is one of those contemplated by the present claim 10, is replaced by the corresponding amino acid from the anti-Tac light chain (see \*).

For this reason claims 10 and 11 are not regarded as novel (Art. 33.2 PCT).

3. Though the WO-A-90/07861 does not discloses in details a consensus sequence, it nevertheless unambiguously suggests the use of a consensus framework from many human antibodies as acceptor sequence (criterion I, page 12). The existence of different criteria (thus not only that based on the homology) for selecting the acceptor sequence is moreover stressed on page 13, line 12, by the sentence ""Regardless of how the acceptor immunoglobulin is chosen..."

Since the reduction to practice of this suggesting is carried out merely by comparing known sequences taken from available collection and designing on paper the requested consensus sequence, the production of said sequence falls within the competence of the skilled person and therefore does not involve per se an inventive merit.

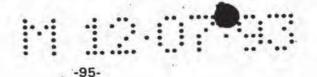
For this reason claims 1 and 15 are not regarded as inventive (Art. 33.3 PCT).

- 3.1 The ability of the glycosylation sites on the variable domain to influence antigen binding has been known since long time as recognized in the description (see page 3 last paragraph).
  Claims 3 and 4 are therefore not regarded as involving an inventive step (Art.33.3 PCT).
- 3.2 The earlier WO application under "criterion II" at page 13 teaches that "rare residues" in the framework of human acceptor should be replaced by residues from the donor (import) sequence, should said residues (from the donor) be "common" for human sequences at that site.

The interpretation of this teaching by the skilled reader should be that "residues which are highly conserved across all different human antibody types should be conserved".

Therefore also the selecting criterion according to claim 5 is suggested in the earlier WO application. Hence the subject matter of claim 5 is not regarded as involving an inventive step (Art. 33.3 EPC).

- 4. Claims 2 and claim 19 identify an additional not previously suggested criterion for the selection of the FR-residues suitable for substitution; the subject matter of the two claims is therefore recognized as involving an inventive step.
- 4.1 Claims 6 to 9 and 13 and 14 are directed to specific embodiments of the invention. Such embodiments do not appear to be disclosed or suggested in the prior art. Said claims are thus recognized as novel and as involving an inventive step.



#### CLAIMS

#### WE CLAIM:

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- A method for making a humanized antibody comprising amino acid sequence of a non-human, import antibody and a human antibody, comprising the steps of:
  - a. obtaining the amino acid sequences of at least a portion of an import variable domain and of a consensus human variable domain;
  - identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human amino variable domain sequences;
  - substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
  - aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
  - identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
  - f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:
    - non-covalently binds antigen directly,
    - interacts with a CDR; or
    - participates in the V<sub>L</sub> V<sub>H</sub> interface; and
  - g. for any non-homologous import antibody amino acid residue which is reasonably expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence.
- The method of claim 1, having an additional step of determining if any such non-homologous residues are exposed on the surface of the domain or buried within it, and if the residue is exposed, retaining the consensus residue.
- 3. The method of claim 1) having the additional steps of searching the import variable domain sequence for glycosylation sites, determining if any such glycosylation site is reasonably expected to affect the antigen binding or affinity of the antibody, and if so, substituting the glycosylation site into the consensus sequence.
  - 4. The method of claim 1) having the additional steps of searching the consensus variable domain sequence for glycosylation sites which are not present at the

## SUBSTITUTE SHEET

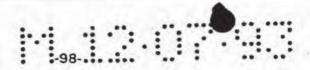
corresponding amino acid in the import sequence, and if the glycosylation site is not present in the import sequence, substituting the import amino acid residues for the amino acid residues comprising the consensus glycosylation site.

- 5 5. The method of claim 1) having an additional step which comprises aligning import antibody and consensus antibody FR sequences, identifying import antibody FR residues which are non-homologous with the aligned consensus FR sequence, and for each such non-homologous import antibody FR residue, determining if the corresponding consensus antibody residue represents a residue which is highly conserved across all species at that site, and if it is so conserved, preparing a humanized antibody which comprises the consensus antibody amino acid residue at that site.
  - The method of claim 1, wherein the corresponding consensus antibody residues are selected from the group consisting of 4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 67H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.

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- 7. A method comprising providing at least a portion of an import, non-human antibody variable domain amino acid sequence having a CDR and a FR, obtaining the amino acid sequence of at least a portion of a consensus human antibody variable domain having a CDR and a FR, substituting the non-human CDR for the human CDR in the consensus human antibody variable domain, and then substituting an amino acid residue for the consensus amino acid residue at at least one of the following sites:
- 25 4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 67H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.
  - 8. The method of claim 7, wherein the substituted residue is the residue found at the corresponding location of the non-human antibody.
  - The method of claim 1 or 7, wherein the consensus human variable domain is a consensus based on human variable domains and additionally variable domains from species other than human.
- A humanized antibody variable domain having a non-human CDR incorporated
   into a human antibody variable domain, wherein the improvement comprises



# AVISENGGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCS RWGGDGFYAMDVWGQGTLVTVSS

- 18. A method comprising storing a computer representation of the following amino acid sequence:
  - a. DIQMTQSPSSLSASVGDRVTITCRASQDVSSYLAWYQQKPGKAPKLLIY
    AASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSLPYTFG
    QGTKVEIKRT, or
  - b. EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVRQAPGKGLEWV AVISENGGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCS RWGGDGFYAMDVWGQGTLVTVSS
- 19. A method for making a humanized antibody comprising amino acid sequence of a non-human, import antibody and a human antibody, comprising the steps of:
  - a. obtaining the amino acid sequences of at least a portion of an import variable domain and of a consensus human variable domain;
  - identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human amino variable domain sequences;
  - c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
  - aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
  - identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
  - f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:
    - non-covalently binds antigen directly,
    - 2. interacts with a CDR; or
    - participates in the V<sub>L</sub> V<sub>H</sub> interface;
  - g. for any non-homologous import antibody amino acid residue which is reasonably expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence; and
  - h. for any non-homologous import antibody amino acid residue, determining if any such non-homologous residue is exposed on the surface of the domain or buried within it, and if the residue is exposed, retaining the consensus residue.

München 2 1. 09. 93

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

BARZ, Peter P. BARZ & P. WEINHOLD Siegfriedstrasse 8 D-80803 MÜNCHEN ALLEMAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year) 2 0, 09, 93

Applicant's or agent's file reference

709P1

IMPORTANT NOTIFICATION

International application No.

International filing date (day/month/year)

Priority date (day/month/year)

PCT/US 92/05126

15/06/1992

14/06/1991

Applicant

GENENTECH, INC. et al.

- The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international 1. preliminary examination report and its annexes, if any, established on the international application.
- A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but 3. not of any annexes) and will transmit such translation to those Offices.
- 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office

D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d

Fax: (+49-89) 2399-4465

Authorized officer

H.-P. Dietenhofer



# **PCT**

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 709P1	FOR FURTHER ACTION		tion of Transmittal of International Examination Report (Form PCT/IPEA/416)		
nternational application No.	International filing date (day/me	onth/year)	Priority date (day/month/year)		
PCT/US 92/05126	15/06/1992		14/06/1991		
nternational Patent Classification (IPC	c) or national classification and IPC				
	C12N15/13				
GENENTECH, INC. et al.	*				
Authority and is transmitted t	examination report has been prepared to the applicant according to Article 36		national Preliminary Examining		
This report is also accon	npanied by ANNEXES, i.e., sheets of iminary examination and/or containing	f the descripti rectifications	ion, claims and/or drawings amended s made before this Authority.		
These annexes consists of a to	otal of 3 sheets.				
I X Basis of the report Priority III Non-establishment IV Lack of unity of in V Reasoned statemer citations and expla  VI Certain documents VII Certain defects in the	of opinion with regard to novelty, involvention of with regard to novelty, inventive step nations supporting such statement	enlive step ar	nd industrial applicability		
Date of submission of the demand	Date o	f completion	of this report		
07/01/1993		2 0. 09, 93			
Buropean Patent Office, E W-8000 Munich 2 Tel. (+49-89) 2399-0, Tx: Fax: (+49-89) 2399-4465	rhardistrasse 27	ized officer	C. Germinario		

Form PCT/IPEA/409 (cover sheet) (July 1992) P20476

(14/06/1993)

his report has been drawn up on the basis of:	
[ ] the international application as originally filed.	
[x] the description, pages 1-107	, as originally filed,
pages	, filed with the demand,
	, filed with the letter of
pages	, filed with the letter of
[x] the claims, No. 10-17	, as originally filed,
No.	
No. q	, filed with the demand,
No. 1-9, 18, 19	, filed with the letter of 12.06.93,
No.	, filed with the letter of,
[x] the drawings, sheets/fig 1/9 - 9/9	, as originally filed,
sheets/fig	
sheets/fig	, filed with the letter of
chasta/fic	, filed with the letter of

III.	Non-establishment	of	opinion	with	regard	to	novelty,	inventive	step	and	industrial	applicability	
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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

the entire international application,

IX	claims	Nos.	17.	18	

#### because:

[x] the said international application, or the said claims Nos. 17, 18 relate to the following subject matter which does not require an international preliminary examination (specify):

Claims 17 is directed to a mere presentation of information, namely the translation of the information inherent in an amino acid sequence into a message or a language readable by the computer.

Claim 18 would appear to be directed to a method of preparing a computer program.

According to Rule 67.1 (V) and (VI) no International Preliminary Examination (thus no preliminary Written Opinion) can be carried out for such a subject matter.

(x)	the description, claims or drawing			s (indicate	particu	ılar elem	ments	below) or said claims					
	Nos. 16				are so	unclear	that	no	meaningful	opinion	could	be	formed
	(specify):												

Claim 16 represents a novel claim-category; its subject matter is in fact a machine or an apparatus i.e. a computer.

Now an independent claim directed to a machine must cite all the essential technical features necessary to define said machine; the information saved in memory of a computer are not considered a characterizing part of the same. Therefore the subject matter of claim 16 is definitely not at all characterized as requested by Art.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

6 PCT (see PCT Guidelines C III 4.4).	
[ ] the claims, or said claims Nos the description that no meaningful opinion could be formed.	are so inadequately supported by
[ ] no international search report has been established for said claims Nos.	

Form PCT/IPEA/409 (sheet 3) (July 1992)

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

V.	Reasoned states	ent under	Article	35(2)	with regard	to novelty,	inventive	step	and	industrial	applicabili	ity;
	citations and e	xplanatio	ns suppor	rting	such stateme	nt						

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Novelty (N)	Claims 1-9, 12-15, 19	YES
noverty (n)	Claims 10, 11	NO NO
	Claims 10, 11	
Inventive Step (IS)	Claims 2, 6-9, 13, 14, 19	YES
	Claims 1, 3-5, 12, 15	NO NO
Industrial Applicability (IA)	Claims 1-19	YES
	Claims	NO NO

#### 2. CITATIONS AND EXPLANATIONS

The following document is referred to in the present IPER as the closest prior art:

WO-A-90/07861;

2. This earlier application describes a method for designing humanized antibodies which consists of all the steps a) to g) of the present claim 1.

More precisely the features under item a) that the amino acid sequences of both donor (import) and acceptor (consensus) antibody are from the variable domain and that the human sequence (acceptor) is a consensus sequence are disclosed at page 10, last two lines and page 11 first lines and page 12 "criterion I.

Steps under b) and c) are disclosed at page 5 line 8 to 31 and claim 18.

Steps under items d) to g) are disclosed in claims 19 to 21 and at page 5 line 32 to page 6 line 20 and more in details at page 11 line 19 to page 15 line 2.

garded as novel.

Among the three criteria for selecting FR-residues convenient for substitution (item f), criterion 2. is disclosed at page 14 under "criterion IV" and criterion 1. is disclosed at page 14 lines 7 and 8.

- 2.1 Under "criterion I" at page 12 of the earlier WO application two different options are contemplated for the selection of the acceptor antibody; the first option is based on the homology with the framework of the donor immunoglobulin, the second on the use of a consensus framework from many human antibodies.
  The IPEA recognizes that the latter possibility, which corresponds to the present invention, is not further disclosed with details or exemplified.
  Therefore the use of a "consensus sequence" as acceptor is not actually an embodiment of the WO-A-90/07861 invention.
  For this reason claims 1 to 9, 13 to 15 and 19 are re-
- 2.2. Claims 10 to 12 do not comprise any reference to a consensus sequence as acceptor of the non-human CDR. Therefore the unique feature discriminating between the present invention and the subject matter of the earlier WO application is missing. It should moreover be noted that the WO-A-90/07861 discloses in details the humanized Eu antibody light chain where the CDRs are replaced by the corresponding CDRs from anti-Tac light chain and where additionally other amino acids in the FR are replace by the corresponding anti-Tac amino acids (see Experimental, page 26, 27; Fig. 2 and explanation of the same at page 7). From Fig. 2 and explanation of the same is evident that the site 63L of the Eu light chain, which is one of those contemplated by the present claim 10, is replaced by the corresponding amino acid from the anti-Tac light

chain (see \*).

For this reason claims 10 and 11 are not regarded as novel (Art. 33.2 PCT).

3. Though the WO-A-90/07861 does not discloses in details a consensus sequence, it nevertheless unambiguously suggests the use of a consensus framework from many human antibodies as acceptor sequence (criterion I, page 12). The existence of different criteria (thus not only that based on the homology) for selecting the acceptor sequence is moreover stressed on page 13, line 12, by the sentence ""Regardless of how the acceptor immunoglobulin is chosen..."

Since the reduction to practice of this suggesting is carried out merely by comparing known sequences taken from available collection and designing on paper the requested consensus sequence, the production of said sequence falls within the competence of the skilled person and therefore does not involve per se an inventive merit.

For this reason claims 1 and 15 are not regarded as inventive (Art. 33.3 PCT).

- 3.1 The ability of the glycosylation sites on the variable domain to influence antigen binding has been known since long time as recognized in the description (see page 3 last paragraph).

  Claims 3 and 4 are therefore not regarded as involving
  - Claims 3 and 4 are therefore not regarded as involving an inventive step (Art.33.3 PCT).
- 3.2 The earlier WO application under "criterion II" at page 13 teaches that "rare residues" in the framework of human acceptor should be replaced by residues from the donor (import) sequence, should said residues (from the donor) be "common" for human sequences at that site.

The interpretation of this teaching by the skilled reader should be that "residues which are highly conserved across all different human antibody types should be conserved".

Therefore also the selecting criterion according to claim 5 is suggested in the earlier WO application. Hence the subject matter of claim 5 is not regarded as involving an inventive step (Art. 33.3 EPC).

- 4. Claims 2 and claim 19 identify an additional not previously suggested criterion for the selection of the FR-residues suitable for substitution; the subject matter of the two claims is therefore recognized as involving an inventive step.
- 4.1 Claims 6 to 9 and 13 and 14 are directed to specific embodiments of the invention. Such embodiments do not appear to be disclosed or suggested in the prior art. Said claims are thus recognized as novel and as involving an inventive step.

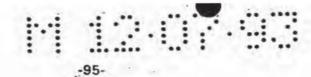
PRTICLE 34

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# CLAIMS

### WE CLAIM:

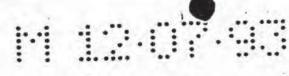
- A method for making a humanized antibody comprising amino acid sequence of a non-human, import antibody and a human antibody, comprising the steps of:
  - a. obtaining the amino acid sequences of at least a portion of an import variable domain and of a consensus human variable domain;
  - identifying Complementarity Determining Region (CDR) amino acid
     sequences in the import and the human amino variable domain sequences;
  - substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
  - aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
  - identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
  - f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:
    - 1. non-covalently binds antigen directly,
    - 2. interacts with a CDR; or
    - 3. participates in the V<sub>L</sub> V<sub>H</sub> interface; and
  - g. for any non-homologous import antibody amino acid residue which is reasonably expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence.
- The method of claim 1, having an additional step of determining if any such non-homologous residues are exposed on the surface of the domain or buried within it, and if the residue is exposed, retaining the consensus residue.
- The method of claim 1) having the additional steps of searching the import
  variable domain sequence for glycosylation sites, determining if any such
  glycosylation site is reasonably expected to affect the antigen binding or
  affinity of the antibody, and if so, substituting the glycosylation site into the
  consensus sequence.
- The method of claim 1) having the additional steps of searching the consensus
   variable domain sequence for glycosylation sites which are not present at the

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corresponding amino acid in the import sequence, and if the glycosylation site is not present in the import sequence, substituting the import amino acid residues for the amino acid residues comprising the consensus glycosylation site.

- 5 5. The method of claim 1) having an additional step which comprises aligning import antibody and consensus antibody FR sequences, identifying import antibody FR residues which are non-homologous with the aligned consensus FR sequence, and for each such non-homologous import antibody FR residue, determining if the corresponding consensus antibody residue represents a residue which is highly conserved across all species at that site, and if it is so conserved, preparing a humanized antibody which comprises the consensus antibody amino acid residue at that site.
  - The method of claim 1, wherein the corresponding consensus antibody residues are selected from the group consisting of 4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 67H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.
  - 7. A method comprising providing at least a portion of an import, non-human antibody variable domain amino acid sequence having a CDR and a FR, obtaining the amino acid sequence of at least a portion of a consensus human antibody variable domain having a CDR and a FR, substituting the non-human CDR for the human CDR in the consensus human antibody variable domain, and then substituting an amino acid residue for the consensus amino acid residue at at least one of the following sites:
- 25 4L, 35L, 36L, 38L, 43L, 44L, 46L, 58L, 62L, 63L, 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 58H, 60H, 67H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.
- The method of claim 7, wherein the substituted residue is the residue found at
   the corresponding location of the non-human antibody.
  - The method of claim 1 or 7, wherein the consensus human variable domain is a consensus based on human variable domains and additionally variable domains from species other than human.
  - A humanized antibody variable domain having a non-human CDR incorporated into a human antibody variable domain, wherein the improvement comprises

# AVISENGGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCS RWGGDGFYAMDVWGQGTLVTVSS

- 18. A method comprising storing a computer representation of the following amino acid sequence:
  - a. DIQMTQSPSSLSASVGDRVTITCRASQDVSSYLAWYQQKPGKAPKLLIY
    AASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYNSLPYTFG
    QGTKVEIKRT, or
  - b. EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVRQAPGKGLEWV AVISENGGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCS RWGGDGFYAMDVWGQGTLVTVSS
- 19. A method for making a humanized antibody comprising amino acid sequence of a non-human, import antibody and a human antibody, comprising the steps of:
  - a. obtaining the amino acid sequences of at least a portion of an import variable domain and of a consensus human variable domain;
  - identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human amino variable domain sequences;
  - substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
  - d. aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
  - identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
  - f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:
    - non-covalently binds antigen directly,
    - interacts with a CDR; or
    - participates in the V<sub>L</sub> V<sub>H</sub> interface;
  - g. for any non-homologous import antibody amino acid residue which is reasonably expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus antibody FR sequence; and
  - h. for any non-homologous import antibody amino acid residue, determining if any such non-homologous residue is exposed on the surface of the domain or buried within it, and if the residue is exposed, retaining the consensus residue.



# INTERNATIONAL AP UNDER THE PATENT COOPERATION TREATY

### REQUEST

THE UNDERSIGNED REQUESTS THAT THE PRESENT INTERNATIONAL APPLICATION BE PROCESSED ACCORDING TO THE PATENT COOPERATION TREATY

(The following is to be filled in by the receiving Office) INTERNATIONAL PCT 8 92/05

INTERNATIONAL FILING DATE:

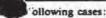
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		Applicant's or agent's file (indicated by applicant if	desired)	709P	1
Box No. 1 TITLE OF INVENTION					
IMMUNOGLOBULIN VARIAN	ITS				
Box No. II APPLICANT (WHETHER OF IS APPLICANT. Use this box for indication includes, where applicable, a legal entity) is the person identified in this box is (mark of Name and address: **  GENENTECH, INC.  460 Point San Bruno Boule South San Francisco, Califunited States of America	ng the applicant or, if involved, continue in ne check-box only):	Box No. III.  applicant inventor	ants, one of th		
Telephone number (including area code):	Telegraphic address:		Teleprinter	address:	
415-225-1000			FAX: 415	-952-98	81
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ame and address, including postal code and country:	national Authorities:	en appointed as agent or common representative to ac
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Carolyn R. ADLER		
GENENTECH, INC.		
460 Point San Bruno Boulevard		
South San Francisco, California	a 94080	
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elephone number (including area code): Telegra	phic address:	Teleprinter address:
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OA OAPI Patent: Benin, Burkina Faso.	Cameroon Central	African Republic, Chad, Congo, Côte d'Ivoire
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HU Hungary	X Us	United States of America(3)
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KP Democratic People's Republic of Kore	201	

Form PCT/RO/101 (second sheet) (January 1992)

#### Supplemental Box. Use this box



- (i) if more than three persons are involved as applicants and/or inventors: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III;
- (ii) if, in Box No. II or any of the sub-boxes of Box No. III, the indication "the States indicated in the 'Supplemental Box," is checked; in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State or States (or EP or OA, if applicable) for the purposes of which he/she/it is applicant;
- (iii) if, in Box No. II or any of the sub-boxes of Box No. III, a person indicated as "applicant and inventor" or "inventor only" is not inventor for the purposes of all designated States or for the purposes of the United States of America; in such case, write "Continuation of Box No. II" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor and, next to such name, the State or States (or EP or OA, if applicable) for the purposes of which the named person is inventor;
- (iv) if there is more than one agent and their addresses are not the same; in such case, write "Continuation of Box No. IV" and indicate for each additional agent the same type of information as required in Box No. IV;
- (v) if, in Box No. V, the name of any country (or OAPI) is accompanied by the indication "patent of addition," "certificate of addition," or "inventor's certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "Continuation" or "Continuation-in-part"; in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of parent title or filing of parent application;
- (vi) if there are more than three earlier applications whose priority is claimed; in such case, indicate "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) if, in any of the Boxes, the space is insufficient to furnish all the information; in such case, write "Continuation of Box No..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient;
- (viii) if the applicant intends to claim, in respect of any designated Office, the benefit of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty; in such case, write "Statement Concerning Non-prejudicial Disclosures or Exceptions to Lack of Novelty" and furnish that statement below.

### Continuation Box IV

Also: BUTING, Walter E., DREGER, Ginger R., FITTS, Renee A.,

HASAK, Janet E., HENSLEY, Max D., GLAISTER, Debra J.,

RAINES, Stephen, WINTER, Daryl B.

All of: GENENTECH, INC.

460 Point San Bruno Boulevard

South San Francisco, California 94080

United States of America

### Continuation Box V

United States of America Application Serial Number 715,272 filed

(14.06.91)

	Sheet nu	imber4	
Box No. VI PRIORITY CL	AIM (IF ANY). The priority of t	the following earlier application(s) is	hereby claimed:
Country (country in which it was filed if national application; one of the countries for which it was filed if regional or international application)  (1) US	Filing Date (day, month, year)  14 June 1991 (14.06.91)	Application No.	Office of filing (fill in only if the earlier application is an international applica- tion or a regional applica- tion)
			+
(2)			
(3)			
When the earlier application was Office, the applicant may, again	us paymens of the required fee, ask why requested to prepare and tran	the purposes of the present internation	ertified copy of the above-men-
Searching Authority has already to the extent possible, on the res	been requested (or completed) and	search (international, international-typed the said Authority is now requested this such search or request either by rest.	o base the international search.
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Date of request for search:		Number (if available) given to search request:	
signed by the applicant is requir	erty, signed on behalf of any applicant red. If in such case it is desired to i	(Carolyn R. ADLER Paul J. CARTER, I by an agent, a separate power of attornate use of a general power of attorna	, Agent for eonard G. PRESTA)
Box No. IX CHECK LIST	attached to this form. (To be filled in by the Applicant)	This international application items marked below:	as filed is accompanied by the
of sheets: 1. request 2. description	on contains the following number  4 sheets 107 sheets 5	X separate signed power of     copy of general power of     X priority document(s) (see	f attorney
3. claims	1 sheets	4. receipt of the fees paid of	
4. abstract		5. Cheque for the payment	of fees
5. drawings			
	Total 126 sheets	6. X request to charge deposit	
	of the drawings (if any) the abstract for publication.	7. X other document (specify) Fee Calculation Sheet	Transmittal Sheet,
	(The following is to be fill	ed in by the receiving Office)	
1. Date of actual receipt of the	e purported international application	on: 13 Rec'd PCT/PC	15 JUN 1992
	ceipt due to later but timely receive purported international application	d papers	TO COLL INC.
3. Date of timely receipt of the	e required corrections under Article	e 11 of the PCT:	
4. Drawings Received	No Drawings		

THIS SHEET IS NOT PART OF AND DOES NOT COUNT AS A SHEET OF THE INTERNATIONAL APPLICATION APPLICANT This column for use hy receiving Office GENENTECH, INC. et al. INTERNATIONAL APPLICATION NUMBER DATE STAMP OF RECEIVING OFFICE (to be filled in by the receiving Office) TEE CALCULATION SHEET FEES SUBMITTED OR TO BE CHARGED TO DEPOSIT ACCOUNT T 1. TRANSMITTAL FEE<sup>2</sup>..... 190 S 1320 II. SEARCH FEE3 ..... more International Searching Authorities, the name of the Authority to which the international application is to be transmitted. Note that the amount of the search fee depends on the identity of the International Searching Authority.) III. INTERNATIONAL FEE<sup>4</sup> BASIC FEES 126 Indicate the number of SHEETS contained in the international application bi 525 first 30 sheets .... 960 62 sheets × 10 remaining Add amounts entered in boxes b, and b, and enter total in box B. This figure is the amount of the BASIC FEE ..... B 1485 **DESIGNATION FEES**<sup>5</sup> Indicate the number of NATIONAL PA-TENTS which have been sought and multiply by the amount of di 508 127 the designation fee. Indicate the number of REGIONAL PA-TENTS which have been sought and multiply by the amount of d<sub>2</sub> 127 127 the designation fee. Add amounts entered in boxes d1 and d2 and enter total in box D (if that total exceeds the figure which corresponds to the amount of the D 635 Add amounts entered in boxes B and D, and enter total in box I. This figure is the total amount of the INTERNATIONAL FEE . . . 1 IV. TOTAL OF PRESCRIBED FEES SUBMITTED OR TO BE CHARGED TO DEPOSIT ACCOUNT Add amounts entered in boxes T, S and I, and enter total in the TOTAL box. This figure is the amount of the PRESCRIBED FEES SUBMITTED OR TO BE CHARGED TO DEPOSIT ACCOUNT ... TOTAL THE APPLICANT MAY PAY THE PRESCRIBED FEES BY [CHEQUE, POSTAL MONEY ORDER, BANK DRAFT, CASH, REVENUE STAMPS, COUPONS, ETC.]. PAYMENT SHOULD BE MADE IN THE PRE-SCRIBED CURRENCY TO THE [ACCOUNT OF, ACCOUNT INDICATED BELOW OF, ORDER OF] THE RECEIVING OFFICE. PAYMENT MAY ALSO BE MADE BY AUTHORIZATION TO CHARGE A DEPOSIT ACCOUNT AT THE RECEIVING OFFICE IF THE LATTER HAS A DEPOSIT ACCOUNT SYSTEM.

ACCOUNT AT THE	RECEIVING OFFICE IF THE LATTER HAS A DEPOSIT ACCOUNT STSTEM.	
DEPOSIT ACCOUN	NT AUTHORIZATION?	
The RO/ US	is hereby authorized to charge the total fees indicated above to my deposit account.	
The RO/ US	is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.	
The RO/ US	is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.	
07-0630	12 June 1992 Cawor R. All	

Form PCT/RO/101 (Annex) (January 1991)

Deposit Account Number

Signature

Date

# PATENT COOPERATION TREATY

**PCT** 

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

pplicant's or agent's file reference 09P1	FOR FURTHER see Notification of (Form PCT/ISA)  ACTION	of Transmittal of International Search Report (220) as well as, where applicable, item 5 below.
nternational application No.	International filing date( day/month/year)	(Earliest) Priority Date (day/month/year)
CT/US 92/05126	15/06/92	14/06/91
ENENTECH, INC. et al.		
according to Article 18. A copy is being This international search report consi-	een prepared by this International Searching Auting transmitted to the International Bureau.  sts of a total of sheets.  copy of each prior art document cited in this rep	
I. X Certain claims were found u	nsearchable (see Box I).	
2. Unity of invention is lacking	(see Box II).	
	n contains disclosure of a nucleotide and/or amin	o acid sequence listing and the
international search was car	ried out on the basis of the sequence listing	
	filed with the international application. furnished by the applicant separately from the in	nternational application
<u> </u>	but not accompanied by a statement to matter going beyond the disclosure in the	the effect that it did not include
	Transcribed by this Authority	
4. With regard to the title,	the text is approved as submitted by the applica	int
X	the text has been established by this Authority	to read as follows:
METHOD FOR MAKING H	HUMANIZED ANTIBODIES.	
5. With regard to the abstract,		
<u> X</u>	the text is approved as submitted by the applica	Carried and the second and the secon
4	the text has been established, according to Rule Box III. The applicant may, within one month search report, submit comments to this Author	from the date of mailing of this international
6. The figure of the drawings to b	e published with the abstract is:	
Figure No. 2	as suggested by the applicant.	None of the figures.
- DT	The state of the s	
	because the applicant failed to suggest a figure.	

Form PCT/ISA/210 (first sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

PCT/US 92/05126

POT MATTER (If several designation	International Application No	
		C12N5/10
Minimum Docur	nentation Searched?	
	Classification Symbols	
CO7K ; C12N ;	G06F	
	[1] 전 12로 7대 (2) 전 12 전	
RED TO BE RELEVANT		
Document, 11 with indication, where approp	riate, of the relevant passages 12	Relevant to Claim No.13
175 - 182 tano, Anna; Chothia, Cy M. 'Framework residue inant of the position a mation of the second hy in the VH domains of globulins' in the application e whole document, especaph 7	vrus; Lesk, 71 is a major and vpervariable	1-12,15
documents: 10 general state of the art which is not ficular relevance ablished on or after the international forw doubts on priority claim(s) or sh the publication date of another reason (as specified) an oral disclosure, use, exhibition or or to the international filing date but late claimed  of the International Search OBER 1992	"T" later document published after the or priority date and not in conflicited to understand the principle invention  "X" document of particular relevance; cannot be considered novel or car involve an inventive step  "Y" document of particular relevance; cannot be considered to involve a document is combined with one o ments, such combination being of in the art.  "&" document member of the same particular relevance of Mailing of this Internation.  Date of Mailing of this Internation.  O 2. 11.	the claimed invention in inventive step when the remore other such docubivious to a person skilled atent family
	Minimum Documents:  CO7K; C12N;  Documentation Searched other to the Extent that such Documents to the Extent that such Documents.  TOF MOLECULAR BIOLOGY 15, 1990, ACADEMIC PRESIDENTS  LOF MOLECULAR BIOLOGY 15, 1990, ACADEMIC PRESIDENTS  To 182  tano, Anna; Chothia, Cym. 'Framework residue in ant of the position at mation of the second hy in the VH domains of globulins' in the application e whole document, especially in the application of the second hy in the VH domains of globulins' in the application ewhole document, especially 1990  General state of the art which is not dicular relevance while the publication date of another increased as specific the publication date of another in reason (as specified) and or a specified of the international filing date but late claimed of the International Search OBER 1992	And the properties of the art which is not incitate relevance who less on or a feer the international row doubts on priority claim(s) or to the international filing date but late claimed or to the international filing date but late claimed or to the international filing date but late claimed or to the international filing date but late claimed or to the international filing date but late claimed or the international search of the internat

Category o	NTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)	
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	NATURE. vol. 342, December 1989, LONDON GB pages 877 - 883 Chothia, Cyrus; Lesk, Arthur M.; Tramontano, Anna; Levitt, Michael; Smith-Gill, Sandra J.; Air, Gillian; Sheriff, Steven; Padlan, 'Conformations of immunoglobulin hypervariable region' cited in the application See the whole document, especially 'Discussion'	1-12,15
P,X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA. vol. 89, May 1992, WASHINGTON US pages 4285 - 4289 Carter, Paul et al. 'Humanization of an anti-p185HER2 antibody for human cancer therapy.' see the whole document	1-15
		11.50

Form PCT/ISA/210 (extra sheet) (January 1985)

See notes on accompanying

Box,1	x,I Observations where certain claims were found un-	searchable (Continuation of item 1 of first sheet)
This int	is international search report has not been established in resp	ect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: 17-18 because they relate to subject matter not required to be see PCT-Rule 39.1(1v)	searched by this Authority, namely:
2.	Claims Nos.: because they relate to parts of the international applica an extent that no meaningful international search can	ation that do not comply with the prescribed requirements to such be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted	in accordance with the second and third sentences of Rule 6.4(a).
Box I	ox II Observations where unity of invention is lacking	(Continuation of item 2 of first sheet)
1.	. As all required additional search fees were timely paid searchable claims.	d by the applicant, this international search report covers all
2.	As all searchable claims could be searches without effort of any additional fee.	Fort justifying an additional fee, this Authority did not invite payment
3.	As only some of the required additional search fees to covers only those claims for which fees were paid, sp	were timely paid by the applicant, this international search report secifically claims Nos.:
₩.		
4.	No required additional search fees were timely paid restricted to the invention first mentioned in the claim	by the applicant. Consequently, this international search report is ms; it is covered by claims Nos.:
Rem	Remark on Protest	The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)



9205126 61838

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 07/10/92

Patent document cited in search report	Publication date		Publication date	
/0-A-9007861	26-07-90	AU-A- CA-A- EP-A-	5153290 2006865 0451216	13-08-90 28-06-90 16-10-91

Office, No. 12/82

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82



# From the INTERNATIONAL BUREAU PCT NOTIFICATION CONCERNING United States Patent and Trademark DOCUMENT TRANSMITTED Office Washington, D.C. Date of mailing: in its capacity as elected Office 24 September 1993 (24.09.93) International filing date: International application No.: PCT/US92/05126 15 June 1992 (15.06.92) Applicant: GENENTECH, INC. et al The International Bureau transmits herewith the following documents and number thereof: copy of the international preliminary examination report and annexes (Article 36(3)(a))

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorised officer:

B. Fitzgerald

Telephone No.: (41-22) 730.91.11

Form PCT/IB/310 (July 1992)

Facsimile No.: (41-22) 740.14.35

000274361

pplication filed by: 20 months 30 months	s
INTERNATIONAL APPLICATION PAPERS IN THE A International application (RECORD COPY) Article 19 amendments PCT/IB/331 PCT/IPEA/409 IPER (PCT/IPEA/416 on front) Annexes to 409 Priority document(s) No. INTERNATIONAL APPLICATION ON DOUBLE	Request form PCT/RO/101 PCT/IB/302 PCT/ISA/210-Search Report Search Report references Other 3/0
RECEIPTS FROM THE APPLICANT: (other than check  Basic National Fee (paid or authorized to charge)  Translation of international application as filed:  Description Claims Words in the drawing figure(s) Article 19 amendments Annexes to 409  Oath / Declaration DNA diskette	Preliminary amendment(s) filed  17 NON 1993  Information Disclosure Statement Assignment document Power of attorney/Change of address Substitute specification Verified small status claim Other
Notes: Onesas / 211	
Notes: ARTICLE 34 NOT ENTITY CLAIMS GRE INCOMPLET.	
35 U.S.C. 371 - Receipt of Request (PTO-1390)  Date acceptable path / declaration received	WIPO Publication Publ.ication No.
25 U.S.C. 371 - Receipt of Request (PTO-1390)  Date acceptable oath / declaration received  17 NO  Date complete 35 U.S.C. 371 requirements met	WIPO Publication
22 CLAIMS GRE INCOMPLE.  35 U.S.C. 371 - Receipt of Request (PTO-1390)  Date acceptable oath / declaration received  17 NO  Date complete 35 U.S.C 371 requirements met  17 NO  102(e) Date	WIPO Publication Publ.ication No. WO/ Publication No. WO/ Publication Date Publication Language
CLAIMS GRE INCOMPLE.  35 U.S.C. 371 - Receipt of Request (PTO-1390)  Date acceptable oath / declaration received  17 NO  Date complete 35 U.S.C 371 requirements met  17 NO  102(e) Date  17 NO  Date of completion of DO/EO 906 - Notification of Missing	WIPO Publication Publ.ication No. WO/ Publication No. WO/ Publication Date  Publication Date  Publication Language
Date acceptable oath / declaration received  Date complete 35 U.S.C 371 requirements met  17 NO  Date of completion of DO/EO 906 - Notification of Missing  Date of completion of DO/EO 907 - Notification of Acceptant	WIPO Publication Publ.ication No. WO/ Publication No. WO/ Publication Date  Publication Date  Publication Language  Not Published U.S. only Designated EP request
22AIMS GRE INCOMPLE.  35 U.S.C. 371 - Receipt of Request (PTO-1390)  Date acceptable oath / declaration received  17 NO  Date complete 35 U.S.C 371 requirements met  17 NO  102(e) Date  17 NO  Date of completion of DO/EO 906 - Notification of Missing  Date of completion of DO/EO 907 - Notification of Acceptant	WIPO Publication Publ.ication No. WO/ Publication Date  Publication Date  Publication Language  Publication Language  Publication Language  Not Published U.S. only Designated EP request

Date of completion of DO/EO 909 - Notification of Abandonment

# COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office and citizenship are as stated below next to my name,

I believe I am the original and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

invention entitle	ed:		Hamilton is a complete to the
METHOD FOR	MAKING HUMANIZED ANTIBODIES		
the specification	n of which (check only one item below):		
3-0	is attached hereto.		
-	was filed as United States application Serial No and was amended on	on	
the state of the s	was filed as PCT international application Num PCT Article 19 on (if applicable).	nber PCT/US92/05126 o	on 15 JUNE 1992 and wa
	hat I have reviewed and understand the conten- nded by any amendment referred to above.	ts of the above-identified	specification, including the
	the duty to disclose information which is material code of Federal Regulations, §1.56(a).	I to the examination of th	is application in accordance
the United Stat inventor's certi-	foreign priority benefits under Title 35, United tor's certificate or of any PCT international applites of America listed below and have also iden ficate or any PCT international application(s) derica filed by me on the same subject matter has s claimed.	cation(s) designating at le tified below any foreign signating at least one co	east one country other that application(s) for patent ountry other than the United
PRIOR FOREIGI	N/PCT APPLICATION(S) AND ANY PRIORITY C	LAIMS UNDER 35 U.S.C	. 119:
COUNTRY	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of such of the claims of this application is not disclosed in that/those priori application(s) in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose material information a defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

# Attorney's Docket No. 709P1

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

The state of the s		STATUS (Check one)					
U.S. Application Number	U.S. Filing Date	Patented	Pending	Abandoned			
07/715,272	14 June 1991		) x	IABN			
			1				
PCT APPLICATIONS DESIGNATING T							
PCT Application No.   PCT	Filing Date   U.S. Serial Number	s	1				
l l			1	1			
	The state of the s		1				

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

Carolyn R. Adler - Reg. No. 32,324
Renee A. Fitts - Reg. No. 35,136
Walter E. Buting - Reg. No. 23,092
Ginger R. Dreger - Reg. No. 33,055
Daryl B. Winter - Reg. No. 32,637

Sean A. Johnston - Reg. No. 35,910
Dennis G. Kleid - Reg. No. 32,037
Janet E. Hasak - Reg. No. 28,616
Stephen Raines - Reg. No. 25,912

Send correspondence to

Genentech, Inc.

Attn: Janet E. Hasak

460 Point San Bruno Boulevard

South San Francisco, CA 94080-4990

Telephone: (415) 225-1896

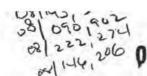
I hereby declare that all statements made herein of my own knowledge and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that willful false statements may jeopardize the validity of the application or any patent issue thereon.

The undersigned hereby authorizes the U.S. attorney or agent named herein at accept and follow instructions from his foreign patent agent as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

Inventor's signature	Mul J. Cote.	LD /14/93
Residence 2074 18th Avenue, San_Erancisco, CA	94116 CA	10.4.2
Citizenship United Kingdom		
Post Office Address 2074 18th Avenue, San Francisco, CA	94116	
Full name of second or joint inventor, if Leonard G. Presta	any	
Second Inventor's signature A. F.	resta	10/14/93
Residence 1900 Gough Street, #206, San Francisc	o, CA 94109	743
Citizenship U.S.A.		
Post Office Address 1900 Gough Street, #206, San Francisc	o, CA 94109	



Paul J. Carter et al PPLICATION DIVISION





W/146206

PATENT DOCKET 709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Art Unit: To Be Assigned

Examiner: To Be Assigned

Serial No. To Be Assigned

Filed: 17 November 1993

METHOD OF MAKING HUMANIZED ANTIBODIES)

460 Point San Bruno Boulevard South San Francisco, CA 94080-4990

(415) 225-1896

### PRELIMINARY AMENDMENT

Honorable Commissioner of Patents and Trademarks Washington, D.C. 20231

Sir:

In the Specification:

RECEIVED JUN 1 0 1994

Please amend the specification by inserting after page 76 the attached GRAND Listing 800 pages 77-92.

Please further amend the specification by renumbering pages 95-99 to be pages 93-97.

#### Remarks

This amendment is prepared for the purposes of introducing a substitute sequence listing into the application. In accordance with 37 C.F.R. § 1.821(f), I hereby state that this Sequence Listing is submitted in paper copy and in computer-readable copy, and that the content of these copies are the same, without adding any new matter.

Early entry of these amendments is requested. The inventors submit that this application is now in compliance with the requirement of 37 C.F.R. §1.821-1.825.

Respectfully submitted,

and E. Haark

GENENTECH, INC.

Janet E. Hasak Reg. No. 28,616

Date: November 17, 1993

-77-SEQUENCE LISTING (1) GENERAL INFORMATION: (i) APPLICANT: Paul J. Carter Leonard G. Presta (ii) TITLE OF INVENTION: Method for Making Humanized Antibodies 10 (iii) NUMBER OF SEQUENCES: 25 (iv) CORRESPONDENCE ADDRESS: (A) ADDRESSEE: Genentech, Inc. 15 (B) STREET:\460 Point San Bruno Blvd (C) CITY: South San Francisco STATE: California (E) COUNTRY: USA (F) ZIP: 94080 20 (v) COMPUTER READABLE FORM: (A) MEDIUM TYPE: \5.25 inch, 360 Kb floppy disk (B) COMPUTER: IBM PC compatible (C) OPERATING SYSTEM: PC-DOS/MS-DOS 25 (D) SOFTWARE: patin (Genentech) CURRENT APPLICATION DATA: (A) APPLICATION NUMBER: (B) FILING DATE 30 (C) CLASSIFICATION: (vii) PRIOR APPLICATION DATA: (A) APPLICATION NUMBER: 07/715272 (B) FILING DATE: 14-JUN-1991 35 (viii) ATTORNEY/AGENT INFORMATION: (A) NAME: Hasak, Janet E. (B) REGISTRATION NUMBER: 28,616 (C) REFERENCE/DOCKET NUMBER: 40 (ix) TELECOMMUNICATION INFORMATION: (A) TELEPHONE: 415/225-1896 (B) TELEFAX: 415/952-9881 (C) TELEX: 910/371-7168 45 (2) INFORMATION FOR SEQ ID NO:1: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 109 amino acids 50 (B) TYPE: amino acid (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1: Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val 5 10

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Asn

20 25 30 Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys 5 Leu Leu Ile Tyr Ser Ala Ser Phe Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Arg Ser Gly Thr Asp Phe Thr Leu Thr Ile 10 Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Ser Leu Gln His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu 15 100 Ile Lys Arg Thr 109 20 (2) INFORMATION FOR SEQ ID NO:2: (i) SEQUENCE CHARACTERISTICS (A) LENGTH 1/20 amino acids 25 (B) TYPE: aming acid (D) TOPOLOGX: linear (xi) SEQUENCE DESCRIPTION. SEQ ID NO:2: Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser\Cys Ala Ala Ser Gly Phe Asn Ile Lys 35 Asp Thr Tyr Ile His Trp Wal Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr 40 Ala Asp Ser Val Lys Gly Arg\Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp 85 Thr Ala Val Tyr Tyr Cys Ser Ard Trp Gly Gly Asp Gly Phe Tyr 100 50 Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser 110 115 55 (2) INFORMATION FOR SEQ ID NO:3: (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 109 amino acids

(B) TYPE: amino acid TOPOLOGY: linear (D) (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3: 5 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser Gly Asp Arg Val 10 Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys 15 Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile 20 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln 80 Tyr Asn Ser Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu 25 95 100 Ile Lys Arg Thr 109 (2) INFORMATION FOR SEQ ID (i) SEQUENCE CHARACTERISTICS LENGTH: 120 amino acids TYPE: amino acid (B) 35 (D) TOPOLOGY: lihear (xi) SEQUENCE DESCRIPTION:\ SEQ ID NO:4: Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly 40 Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr Ala Met Ser Trp Val Art Gln Ala Pro Gly Lys Gly Leu 45 Glu Trp Val Ala Val Ile Ser Glu\Asn Gly Gly Tyr Thr Arg Tyr 50 Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser Lys Asn Thr Ala Tyr Leu Gln Met Abn Ser Leu Arg Ala Glu Asp 55

95

Thr Ala Val Tyr Tyr Cys Ser Arg Tro Gly Gly Asp Gly Phe Tyr

-80-Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser 110 115 5 (2) INFORMATION FOR SEQ ID NO:5: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 109 amino acids (B) TYPE amino acid 10 (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5: Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val 15 Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn 20 Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly His Ser Pro Lys Leu Leu Ile Tyr Ser\Ala Ser Phe Arg Tyr Thr Gly Val Pro Asp 50 25 Arg Phe Thr Gly Asn Arg Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln 30 250 Thr Phe Gly Gly Gly Thr Lys Leu Glu His Tyr Thr Thr Pro 100 35 Ile Lys Arg Ala 109 (2) INFORMATION FOR SEQ ID NO:6: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 120 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6: Glu Val Gln Leu Gln Gln Ser\Gly Pro Glu Leu Val Lys Pro Gly Ala Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Thr Tyr Ile His Trp Val Ly's Gln Arg Pro Glu Gln Gly Leu 35 Glu Trp Ile Gly Arg Ile Tyr Pro\Thr Asn Gly Tyr Thr Arg Tyr

55

55

-81-Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser 65 Ser Asn Thr Ala Tyr Leu Gln Val Ser Arg Leu Thr Ser Glu Asp 5 Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr 100 10 Ala Met Asp Ty Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser 110 115 (2) INFORMATION FOR SEQ ID NO:7: 15 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH 27 bases (B) TYPE: nucleic acid (C) STRANDEDNESS: single 20 (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7: TCCGATATCC AGCTGA.CCCA GTCTCCA 27 (2) INFORMATION FOR SEQ ID 30 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 bases (B) TYPE: nucleic acid (C) STRANDEDNESS; single 35 (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8: 40 GTTTGATCTC CAGCTTGGTA CCHSCDCCGA A 31 (2) INFORMATION FOR SEQ ID NO:9: 45 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 bases (B) TYPE: nucleic acid (C) STRANDEDNESS: single 50 (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9: AGGTSMARCT GCAGSAGTCW GG 22

		V
		(2) INFORMATION FOR SEQ ID NO:10:
	5	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 34 bases  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear
	10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:
		TGAGGAGACG GTGACCGTGG TCCCTTGGCC CCAG 34
	15	(2) INFORMATION FOR SEQ ID NO:11:
1	20	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 bases  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear
	25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:
	30	GTAGATAAAT CCTCTAACAC AGCCTATCTG CAAATG 36 (2) INFORMATION FOR SEQ ID NO:12:
	35	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 bases  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear
	40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:
		GTAGATAAAT CCAAATCTAC AGCCTATCTG CAAATG 36
	45	(2) INFORMATION FOR SEQ ID NO: 13:
	50	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 36 bases  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear
	55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:
		GTAGATAAAT CCTCTTCTAC AGCCTATCTG CAAATG 36

		(2) INFORMATION FOR SEQ ID NO:14:
	5	(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 68 bases  (B) TYPE: nucleic acid  (C) STRANDEDNESS: single  (D) TOPOLOGY: linear
	10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:
		CTTATAAAGG TGTTTCCACC TATAACCAGA AATTCAAGGA TCGTTTCACG 50
	15	ATATCCGTAG ATAAATCC 68
	20	(2) INFORMATION FOR SEQ ID NO:15:
\		(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 30 bases  (B) TYPE: nycleic acid
/	25	(C) STRANDEDNESS single (D) TOPOLOGY: linear
	30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:
	30	CTATACCTCC CGTCTGCATT CTGCAGTCCC 30
	35	(2) INFORMATION FOR SEQ ID NO:16:
		(i) SEQUENCE CHARACTERISTICS:  (A) LENGTH: 107 amino acids  (B) TYPE: amino acid
	40	(D) TOPOLOGY: linear
		(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:
	45	Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu 1 10 15
		Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Arg
	50	Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys
		Leu Leu Ile Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser
	55	Iva Dhe Ser Cly Ser Cly Ser Cly The Ass Two Ser Isu The Ile

-84-Ser Asn Leu Glt Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln 80 Gly Asn Thr Leu\Pro Trp Thr Phe Ala Gly Gly Thr Lys Leu Glu 5 95 100 Ile Lys 107 10 (2) INFORMATION FOR SEQ ID NO:17: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1\07 amino acids (B) TYPE: amino acid 15 (D) TOPOLOGY: \linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17: Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val 20 10 Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg 25 Asn Tyr Leu Asn Trp Tyr\Gln Gln Lys Pro Gly Lys Ala Pro Lys 35 Leu Leu Ile Tyr Tyr Thr Sex Arg Leu Glu Ser Gly Val Pro Ser 30 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile 65 Ser Ser Leu Gln Pro Glu\Asp Phe Ala Thr Tyr Tyr Cys Gln Gln 35 Gly Asn Thr Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu 100

40 Ile Lys 107

### (2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 107 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

# 50 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val

55 Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser 20 25 30
Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys

0/

35 40 45 Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser 50 5 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln 10 Tyr Asn Ser Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu 95 100 15 Ile Lys 107 (2) INFORMATION FOR SEQ ID NO:19: 20 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 129 amino acids (B) TYPE: amino ac\id (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19: 25 Glu Val Gln Leu Gln Gln Set Gly Rro Glu Leu Val Lys Pro Gly 10 Ala Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr 20 Gly Tyr Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu 35 Glu Trp Met Gly Leu Ile Asn Pro Tyr Lys Gly Val Ser Thr Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Lys Ala Thr Leu 40 Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Leu Met Glu Leu Leu Asn Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg 95 100 Ser Gly Tyr Tyr Gly Asp Ser Asp Trp Tyr Phe Asp Val Trp Gly 110 50 Ala Gly Thr Thr Val Thr Val Ser Ser 125 129 (2) INFORMATION FOR SEQ ID NO:20: 55 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 122 amino acids

(B) TYPE: amino acid

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		(1	) TO	OPPLO	OGY:	line	ear								
	(xi	i) si	EQUE	1CE/I	DESCR	RIPTI	ON:	SEQ	ID I	10:20	):				
5	Glu 1	Val	Gln	Leu	Val 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15
10	Gly	Ser	Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Tyr	Ser	Phe	Thr 30
10	Gly	Tyr	Thr	Met	Asn 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45
15	Glu	Trp	Val	Ala	Leu 50	Tle	Asn	Pro	Tyr	Lys 55	Gly	Val	Ser	Thr	Tyr 60
	Asn	Gln	Lys	Phe	Lys 65	Asp	Arg	Phe	Thr	Ile 70	Ser	Val	Asp	Lys	Ser 75
20	Lys	Asn	Thr	Ala	Tyr 80	Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90
25	Thr	Ala	Val	Tyr	Tyr 95	Cys	Ala	Arg	Ser	Gly 100	Tyr	Tyr	Gly	Asp	Ser 105
23	Asp	Trp	Tyr	Phe	Asp 110	ya1	Trp	Gly	Gln	Gly 115	Thr	Leu	Val	Thr	Val 120
30	Ser	Ser 122					7								
	(2)	INFO	RMAT	ION I	FOR S	SEQ (	D N	2.21	:						
35	(:	(1	B) T		H: 12 amin	22 ar	mino		ds						
	(x:	i) Si	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID I	NO:2	1:				
40	Glu 1	Val	Gln	Leu	Val 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15
45	Gly	Ser	Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ser 30
	Ser	Tyr	Ala	Met	Ser 35	Trp	Val	Arg	Giln	Ala 40	Pro	Gly	Lys	Gly	Leu 45
50	Glu	Trp	Val	Ser	Val 50	Ile	Ser	Gly	Asp	Gly 55	Gly	Ser	Thr	Tyr	Tyr 60
55	Ala	Asp	Ser	Val	Lys 65	Gly	Arg	Phe	Thr	11e	Ser	Arg	Asp	Asn	Ser 75
23	Lys	Asn	Thr	Leu	Tyr 80	Leu	Gln	Met	Asn	ser 85	Leu	Arg	Ala	Glu	Asp 90

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Val Gly Tyr Ser Leu 100

Ser Gly Leu Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val 110

Ser Ser 122

## 10 (2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 454 amino acids
  - (B) TYPE: amino acid
- 15 (D) TOPOLOGY: linear

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly 20 Ala Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu Tyr Thr Met His Trp Met Lys Gln Ser His Gly Lys Ser Leu 25 35 40 Glu Trp Ile Gly Gly Phe Ash Tro bys Asn Gly Gly Ser Ser His 55 30 Asn Gln Arg Phe Met Asp Lys Ala Thr Leu Ala Val Asp Lys Ser 70 Thr Ser Thr Ala Tyr Met Glu Leu\ Arg Ser Leu Thr Ser Glu Asp 35 85 Ser Gly Ile Tyr Tyr Cys Ala Arg Trp Arg Gly Leu Asn Tyr Gly 100 Phe Asp Val Arg Tyr Phe Asp Val Top Gly Ala Gly Thr Thr Val 115 120 Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu 130 45 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly 140 150 Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp 50 155 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val 185 190 195

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr \Ile Cys Asn Val Asn

			1			-00								
			1	200					205					210
His	Lys	Pro	Ser	Asn 215	Thr	Lys	Val	Asp	Lys 220	Lys	Val	Glu	Pro	Lys 225
Ser	Cys	Asp	Lys	Thr 230	His	Thr	Cys	Pro	Pro 235	Cys	Pro	Ala	Pro	Glu 240
Leu	Leu	Gly	Gly	Pro 245	Ser	Val	Phe	Leu	Phe 250	Pro	Pro	Lys	Pro	Lys 255
Asp	Thr	Leu	Met	110	Ser	Arg	Thr	Pro	Glu 265	Val	Thr	Cys	Val	Val 270
Val	Asp	Val	Ser	His 275	Glu	Asp	Pro	Glu	Val 280	Lys	Phe	Asn	Trp	Tyr 285
Val	Asp	Gly	Val	Glu 290	Val	His	Asn	Ala	Lys 295	Thr	Lys	Pro	Arg	Glu 300
Glu	Gln	Tyr	Asn	Ser 305	Thr	Tyr	Arg	Val	Val 310	Ser	Val	Leu	Thr	Val 315
Leu	His	Gln	Asp	Trp 320	Leu	Asn	Gly	Lys	Glu 325	Tyr	Lys	Cys	Lys	Val 330
Ser	Asn	Lys	Ala	Leu 335	Pro	Ala	Pro	Ile	Glu 340	Lys	Thr	Ile	Ser	Lys 345
Ala	Lys	Gly	Gln	Pro 350	AAG	Glu	pro	Gln	Val 355	Tyr	Thr	Leu	Pro	Pro 360
Ser	Arg	Glu	Glu	Met 365	Thr	Lys	Asn	Gln	Val 370	Ser	Leu	Thr	Cys	Leu 375
Val	Lys	Gly	Phe	Tyr 380	Pro	ser	Asp	Ile	Ala 385	Val	Glu	Trp	Glu	Ser 390
Asn	Gly	Gln	Pro	Glu 395	Asn	Asn	Tyr	Lys	Thr 400	Thr	Pro	Pro	Val	Leu 405
Asp	Ser	Asp	Gly	Ser 410	Phe	Phe	Leu	Tyr	Ser 415	Lys	Leu	Thr	Val	Asp 420
Lys	Ser	Arg	Trp	Gln 425	Gln	Gly	Asn	Val	Phe 430	Ser	Cys	Ser	Val	Met 435
His	Glu	Ala	Leu	His 440	Asn	His	Tyr	Thr		Lys	Ser	Leu	Ser	Leu 450
Ser	Pro	Gly	Lys 454											
	Ser Leu Asp Val Glu Leu Ser Ala Ser Val Asn Asp Lys His	Ser Cys Leu Leu Asp Thr Val Asp Glu Gln Leu His Ser Asn Ala Lys Ser Arg Val Lys Asn Gly Asp Ser Lys Ser His Glu	Ser Cys Asp Leu Leu Gly Asp Thr Leu Val Asp Val Val Asp Gly Glu Gln Tyr Leu His Gln Ser Asn Lys Ala Lys Gly Ser Arg Glu Val Lys Gly Asn Gly Gln Asp Ser Asp Lys Ser Arg	Ser Cys Asp Lys Leu Leu Gly Gly Asp Thr Leu Met Val Asp Val Ser Val Asp Gly Val Glu Gln Tyr Asn Leu His Gln Asp Ser Asn Lys Ala Ala Lys Gly Gln Ser Arg Glu Glu Val Lys Gly Phe Asn Gly Gln Pro Asp Ser Asp Gly Lys Ser Arg Trp His Glu Ala Leu Ser Pro Gly Lys	His Lys Pro Ser Asn 215  Ser Cys Asp Lys Thr 230  Leu Leu Gly Gly Pro 245  Asp Thr Leu Met Ile 260  Val Asp Val Ser His 275  Val Asp Gly Val Glu 290  Glu Gln Tyr Asn Ser 305  Leu His Gln Asp Trp 320  Ser Asn Lys Ala Leu 335  Ala Lys Gly Gln Pro 350  Ser Arg Glu Glu Met 365  Val Lys Gly Phe Tyr 380  Asn Gly Gln Pro Glu 395  Asp Ser Asp Gly Ser 410  Lys Ser Arg Trp Gln 425  His Glu Ala Leu His 440  Ser Pro Gly Lys	His Lys Pro Ser Asn Thr 215  Ser Cys Asp Lys Thr His 230  Leu Leu Gly Gly Pro Ser 245  Asp Thr Leu Met Ile Ser 260  Val Asp Val Ser His Glu 275  Val Asp Gly Val Glu Val 290  Glu Gln Tyr Asn Ser Thr 305  Leu His Gln Asp Trp Leu 320  Ser Asn Lys Ala Leu Pro 335  Ala Lys Gly Gln Pro Arg 350  Ser Arg Glu Glu Met Thr 365  Val Lys Gly Phe Tyr Pro 380  Asn Gly Gln Pro Glu Asn 395  Asp Ser Asp Gly Ser Phe 410  Lys Ser Arg Trp Gln Gln His Glu Ala Leu His Asn 440  Ser Pro Gly Lys	His Lys Pro Ser Asn Thr Lys 215  Ser Cys Asp Lys Thr His Thr 230  Leu Leu Gly Gly Pro Ser Val 245  Asp Thr Leu Met Ile Ser Arg 260  Val Asp Val Ser His Glu Asp 275  Val Asp Gly Val Glu Val His 290  Glu Gln Tyr Asn Ser Thr Tyr 305  Leu His Gln Asp Trp Leu Asn 320  Ser Asn Lys Ala Leu Pro Ala 335  Ala Lys Gly Gln Pro Axg Glu 350  Ser Arg Glu Glu Met Thr Lys 365  Val Lys Gly Phe Tyr Pro Ser 380  Asn Gly Gln Pro Glu Asn Asn 395  Asp Ser Asp Gly Ser Phe Phe 410  Lys Ser Arg Trp Gln Gln Gly 425  His Glu Ala Leu His Asn His 440	His Lys Pro Ser Asn Thr Lys Val Ser Cys Asp Lys Thr His Thr Cys 330 Leu Leu Gly Gly Pro Ser Val Phe 245 Asp Thr Leu Met Ile Ser Arg Thr 260 Val Asp Val Ser His Glu Asp Pro 275 Val Asp Gly Val Glu Val His Asn 290 Glu Gln Tyr Asn Ser Thr Tyr Arg 305 Leu His Gln Asp Trp Leu Asn Gly 320 Ser Asn Lys Ala Leu Pro Ala Pro 335 Ala Lys Gly Gln Pro Arg Glu Pro 350 Ser Arg Glu Glu Met Thr Lys Asn 365 Val Lys Gly Phe Tyr Pro Ser Asp 380 Asn Gly Gln Pro Glu Asn Asn Tyr 395 Asp Ser Asp Gly Ser Phe Phe Leu Lys Ser Arg Trp Gln Gln Gly Asn 425 His Glu Ala Leu His Asn His Tyr	His Lys Pro Ser Asn Thr Lys Val Asp 215  Ser Cys Asp Lys Thr His Thr Cys Pro 230  Leu Leu Gly Gly Pro Ser Val Phe Leu 245  Asp Thr Leu Met Ile Ser Arg Thr Pro 260  Val Asp Val Ser His Glu Asp Pro Glu 275  Val Asp Gly Val Glu Val His Asn Ala 290  Glu Gln Tyr Asn Ser Thr Tyr Arg Val 305  Leu His Gln Asp Trp Leu Asn Gly Lys 320  Ser Asn Lys Ala Leu Pro Ala Pro Ile 335  Ala Lys Gly Gln Pro Axg Glu Pro Gln 365  Val Lys Gly Phe Tyr Pro Ser Asp Ile 380  Asn Gly Gln Pro Glu Asn Asn Tyr Lys 395  Asp Ser Asp Gly Ser Phe Phe Leu Tyr Lys Ser Arg Trp Gln Gln Gly Asn Val Lys Glu Ala Leu His Asn His Tyr Thr 440  Ser Pro Gly Lys	### Bush Pro Ser Asn Thr Lys Val Asp Lys 220  Ser Cys Asp Lys Thr His Thr Cys Pro Pro 235  Leu Leu Gly Gly Pro Ser Val Phe Leu Phe 245  Asp Thr Leu Met Ile Ser Arg Thr Pro Glu 265  Val Asp Val Ser His 275  Glu Asp Pro Glu Val 290  Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val 325  Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu 325  Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu 335  Ser Arg Glu Glu Met Thr Lys Asn Gln Val 355  Ser Arg Glu Glu Met Thr Lys Asn Gln Val 365  Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr 380  Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr 385  Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr 385  Lys Ser Asp Gly Ser Phe Phe Leu Tyr Ser 415  Lys Ser Arg Trp Gln Gln Gly Asn Val Phe 425  His Glu Ala Leu His Asn His Tyr Thr Gln 445  Ser Pro Gly Lys	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys 2215  Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys 235  Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro 250  Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val 265  Val Asp Val Ser His Glu Asp Pro Glu Val Lys 275  Val Asp Gly Val Glu Val His Asn Ala Lys Thr 295  Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser 305  Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr 325  Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys 335  Ala Lys Gly Gln Pro Axg Glu Pro Gln Val Tyr 355  Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser 370  Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val 385  Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr 395  Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys 410  Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser 430  His Glu Ala Leu His Asn His Tyr Thr Gln Lys 445  Ser Pro Gly Lys	### Box   Pro   Ser   Asn   Thr   Lys   Val   Asp   Lys   Lys   Val   Lys   Lys   Lys   Lys   Val   Lys   Lys   Lys   Lys   Val   Lys   Ly	His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu 215  Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala 230  Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys 260  Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys 260  Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn 280  Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro 295  Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu 305  Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys 325  Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile 335  Ala Lys Gly Gln Pro Akg Glu Pro Gln Val Tyr Thr Leu 355  Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr 365  Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp 380  Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr 410  Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser 425  His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Pro Gly Lys	200 205  His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro 215  Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro 230  Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro 245  Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val 265  Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp 280  Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg 290  Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr 305  Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser 325  Ser Arg Glu Glu Met Thr Lys Asn Gln Val Tyr Thr Leu Pro 355  Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys 361  Asp Gly Gln Pro Ser Asp Ile Ala Val Glu Trp Glu 385  Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val 395  Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val 415  Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser 440  Ser Pro Gly Lys

(2) INFORMATION FOR SEQ ID NO:23: 55

- (i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 557 amino acids
  (B) TYPE: amino acid

# (D) TOROLOGY: linear

### (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

His His Gln Vall Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys 5 Pro Gly Ala Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr 10 Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Phe Thr Glu Met Thr Ala Thr Gly Wal His Ser Glu Val Gln Leu Val Glu Ser Gly 15 Gly Gly Leu Val Gin Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly Tyr Thr Phe Thr Glu Tyr Thr Met His Trp Met Arg 20 80 Gly Leu Glu Trp Val Ala Gly Ile Asn Pro Gln Ala Pro Gly Lys 100 25 Lys Asn Gly Gly Thr Ser His Asn Gln Arg Phe Met Asp Arg Phe Thr Ser Thr Ala Tyr Met Gln Met Thr Ile Ser Val Asp Lys ser 30 Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Asn Ser Leu Arg Ala 145 Trp Arg Gly Leu Asn Tyr Gly Phe Asp Val Arg Tyr Phe Asp Val 35 155 160 Trp Gly Gln Gly Thr Leu Val\ Thr Val Ser Ser Ala Ser Thr Lys 170 175 40 Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser 185 Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro 45 200 Glu Pro Val Thr Val Ser Trp Asn\Ser Gly Ala Leu Thr Ser Gly 215 220 Val His Thr Phe Pro Ala Val Leu Qln Ser Ser Gly Leu Tyr Ser 235 Leu Ser Ser Val Val Thr Val Thr Ser Ser Asn Phe Gly Thr Gln 245 250 255 55 Thr Tyr Thr Cys Asn Val Asp His Lys\Pro Ser Asn Thr Lys Val 260

265

270

-90-

Asp Lys Thr Val Glu Arg Lys Cys Cys Val Thr Cys Pro Pro Cys Pro Ala Pro Glu\Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro 5 295 Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val 310 315 Asp Val Ser His Glu Asp Pro Glu Val Lys 10 Thr Cys Val Val Val 320 325 Glu Cys Pro Pro Cys Pto Ala Pro Pro Val Ala Gly Pro Ser Val 335 340 15 Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg 350 355 Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp 20 365 370 Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Met Glu Val His 385 380 Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe 25 395 400 Arg Val Val Ser Val Leu Thr Val Wal His Gln Asp Trp Leu Asn 410 415 30 Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ala 430 425 435 Pro Ile Glu Lys Thr Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu 35 445 Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys 455 460 Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro 40 Ser 475 Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn 45 Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp Gly Ser Phe Phe 500 505 510 Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser\Arg Trp Gln Gln Gly 50 515 520 525 Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His 535 Gly Lys Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro 555 545 550

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(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 214 amino acids
(B) TYRE: amino acid

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Asp Val Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu 10 Gly Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Asp Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asn Gly Thr Val Lys 15 Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Arg Phe Ser Gly Ser Ser Asn Leu Asp Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln 80 25 Gly Asn Thr Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu 95 Ile Lys Arg Thr Val Ala \Ala Pro Ser Val Phe Ile Phe Pro Pro 30 120 Ser Asp Glu Gln Leu/Lys/Ser Gly Thr Ala Ser Val Val Cys Leu 125 130 35 Leu Asn Asn Phe Tyr Pko Ard Glu Ala Lys Val Gln Trp Lys Val 140 145 Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu 155 160 165 40 Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr 175 Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu 45 190 Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn 200 205

50 Arg Gly Glu Cys 214

#### (2) INFORMATION FOR SEQ ID NO:25:

- 55 (i) SEQUENCE CHARACTERISTICS:
  (A) LENGTH: 233 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

	1.22.	- /	-2024							17.12					
-	Met 1	Gly	Trp	Ser	Cys 5	Ile	Ile	Leu	Phe	Leu 10	Val	Ala	Thr	Ala	Thr 15
5	Gly	Val	His	Ser	Asp 20	Ile	Gln	Met	Thr	Gln 25	Ser	Pro	Ser	Ser	Leu 30
10	Ser	Ala	Ser	Val	Gly 35	Asp	Arg	Val	Thr	Ile 40	Thr	Cys	Arg	Ala	Ser 45
	Gln	Asp	Ile	Asn	Asn 50	Tyr	Leu	Asn	Trp	Tyr 55	Gln	Gln	Lys	Pro	Gly 60
15	Lys	Ala	Pro	Lys	Leu 5	Leu	Ile	Tyr	Tyr	Thr 70	Ser	Thr	Leu	His	Ser 75
	Gly	Val	Pro	Ser	Arg 80	Phe	Ser	Gly	Ser	Gly 85	Ser	Gly	Thr	Asp	Tyr 90
20	Thr	Leu	Thr	Ile	Ser 95	Ser	Leu	Gln	Pro	Glu 100	Asp	Phe	Ala	Thr	Tyr 105
25	Tyr	Cys	Gln	Gln	Gly 110	Asn	Thr	Leu	Pro	Pro 115	Thr	Phe	Gly	Gln	Gly 120
	Thr	Lys	Val	Glu	11e 125	Lys	Arg	Thr	Val	Ala 130	Ala	Pro	Ser	Val	Phe 135
30	Ile	Phe	Pro	Pro	Ser 140	Asp	Glu	Gln	Leu	Lys 145	Ser	Gly	Thr	Ala	Ser 150
25	Val	Val	Cys	Leu	Leu 155	Asn	Ash	Phe	Tyr	Pro 160	Arg	Glu	Ala	Lys	Val 165
35	Gln	Trp	Lys	Val	Asp 170	Asn	Ala	Leu	Gln	Ser 175	Gly	Asn	Ser	Gln	Glu 180
40	Ser	Val	Thr	Glu	Gln 185	Asp	Ser	Lys	Asp	Ser 190	Thr	Tyr	Ser	Leu	Ser 195
	Ser	Thr	Leu	Thr	Leu 200	Ser	Lys	Ala	Asp	Tyr 205	Glu	Lys	His	Lys	Val 210
45	Tyr	Ala	Cys	Glu	Val 215	Thr	His	din	Gly	Leu 220	Ser	Ser	Pro	Val	Thr 225
50	Lys	Ser	Phe	Asn	Arg 230	Gly	Glu	Cys 233							

CONT

Patent and Trademark C Address: COMMISSIONER OF THE ATTS AND TRADEMARKS

LS APPLICATION NO.	FORST NAMED APPLICANT	ATTY, DOCKET NO.
087146,206	CARTER	P 703P1
CAROLYN R. ADLER	5611	PCT/US92/US126 4
GENENTECH, INC. 460 POINT SAN BRUN SOUTH SAN FRANCISC		06/15/92 06/14/9
		04/04/94
NOTIFICATION	OF ACCEPTANCE OF APPLICATE AND 37 CFR 1.494 OR 1.495	
2. The United States Applic	tentability examination in the United Streets Number assigned to the application	
17 NO√ 1993 35 U.S.C. 102(e) D.	17 NOV 1993	
17 NOV 1993 35 U.S.C. 102(e) DA	ATE DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMEN	nts
17 NOV 1993 35 U.S.C. 102(e) DA	ATE DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMEN	nts
35 U.S.C. 102(e) D.  3. A request for immed and the application will be ex	DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMENT Under 35 U.S.C. 371 Requirement turn.	nts
35 U.S.C. 102(e) D.  3. A request for immed and the application will be established.  4. The following items have by U.S. Basic National Fellowing of the internation	DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMENT Interest of the samination under 35 U.S.C. 371(f) transited in turn.	nts
35 U.S.C. 102(e) D.  3. A request for immed and the application will be established.  4. The following items have be Copy of the internation of the internation of the internation of the internation of the internation.	DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMENT Interest of the comment of the comme	nts
35 U.S.C. 102(e) D.  3. A request for immed and the application will be ended and the application will be ended as a second of the internation of the internation of the internation of the internation of Copy of Article 19 am	DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMENT Interest of the common state of the commo	was received on 19 NOV 1993

Other ARTICLE 34 AMENDMENTS NOT ENTITY, CLAIMS ARE INCOMPLETE. A Filing Receipt (PTO-103X) will be issued for the present application in due course. Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

Copy of the Search Report and copies of the references cited therein.

Preliminary amendment(s) filed 17 NOV 1993 a

Information Disclosure Statement(s) filed

Power of Attorney and /or Change of Address.

Verified Statement Claiming Small Entity Status.

Assignment document.

Substitute specification filed

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

FORM PCT/DO/EO/903 (May 1993)

	REQUEST FOR PATENT FE	E REFUND	,	
1 Da	te of Request: 29 MAR 94 2 Seri	al/Patent	# 08/144	206
3 Pl	ase refund the following fee(s):	4 PAPER NUMBER	5 DATE FILED	6 AMOUNT
/	Filing	1	17/10/13	\$ 172.00
	Amendment		T. H.	\$
	Extension of Time			\$
	Notice of Appeal/Appeal			\$
	Petition			\$
	Issue			\$
	Cert of Correction/Terminal Disc.			\$
;	Maintenance			\$
	Assignment			\$
	Other			\$
11 10 11 11 11 11 11 11		7 TOTAL 7 OF REF		\$ 172.00
		8 TO BE	REFUNDED B	Υ:
10 RB	Ason:	Т	reasury Ch	neck
/	Overpayment	1 0	redit Depo	sit A/C #:
-	Duplicate Payment	9 6	7 0	630
	No Fee Due (Explanation):			
	EPO SEARC	4		
	FUND REQUESTED BY:		0	1 10 -1.
	ED/PRINTED NAME: MPERSON			legal Specialis
SIG	NATURE:	F	PHONE: 302	53/21
OFF	ICE:	******	*****	********
THI	S SPACE RESERVED FOR FINANCE USE ONI	Y:	/	, /
APP	ROVED: Mach . ( Jan	DATE:	4/6/	154
			1 1	

Instructions for completion of this form appear on the back. After completion, attach white and yellow copies to the official file and mail or hand-carry to:

Office of Finance Refund Branch Crystal Park One, Room 802B

# RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206

DATE: 04/15/94 TIME: 12:13:19

INPUT SET: S2658.raw

1		SEQUENCE LISTING
2	1-1	ALCOHOL TURNS AND
3	(1)	General Information:
5	(i)	APPLICANT: Paul J. Carter
6	702.5	Leonard G. Presta
7		
8	(ii)	TITLE OF INVENTION: Method for Making Humanized Antibodies
9	12221	NUMBER OF CROUDINGES. OF
11	(111)	NUMBER OF SEQUENCES: 25
12	(iv)	CORRESPONDENCE ADDRESS:
13	15.4	(A) ADDRESSEE: Genentech, Inc.
14		(B) STREET: 460 Point San Bruno Blvd
15		(C) CITY: South San Francisco
16		(D) STATE: California
17		(E) COUNTRY: USA
18		(F) ZIP: 94080
19		
20	(v)	COMPUTER READABLE FORM:
21		(A) MEDIUM TYPE: 5.25 inch, 360 Kb floppy disk
22		(B) COMPUTER: IBM PC compatible
23		(C) OPERATING SYSTEM: PC-DOS/MS-DOS
24		(D) SOFTWARE: patin (Genentech)
25	7.04	
26	(V1)	CURRENT APPLICATION DATA:
27		(A) APPLICATION NUMBER:
28		(B) FILING DATE:
30		(C) CLASSIFICATION:
31	(vii)	PRIOR APPLICATION DATA:
32	1.11	(A) APPLICATION NUMBER: 07/715272
33		(B) FILING DATE: 14-JUN-1991
34		
35	(viii)	ATTORNEY/AGENT INFORMATION:
36		(A) NAME: Hasak, Janet E.
37		(B) REGISTRATION NUMBER: 28,616
38		(C) REFERENCE/DOCKET NUMBER: 709P1
39		
40	(ix)	TELECOMMUNICATION INFORMATION:
41		(A) TELEPHONE: 415/225-1896
42		(B) TELEFAX: 415/952-9881
43		(C) TELEX: 910/371-7168
693	(2) TN	FORMATION FOR SEQ ID NO:23:
694	(2) 114	TOWNSTON FOR DEG ID NO.25.
695	(i)	SEQUENCE CHARACTERISTICS:
696		(A) LENGTH: (557 amino acids) ONY SSL are Shown,
697		(B) TYPE: amino acid
698		SEQUENCE CHARACTERISTICS:  (A) LENGTH: 557 amino acids  (B) TYPE: amino acid  (D) TOPOLOGY: linear  SEQUENCE DESCRIPTION: SEQ ID NO:23: Liscopancy
699		dieceman
700	(xi)	SEQUENCE DESCRIPTION: SEQ ID NO:23:
701		

### RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206

DATE: 04/15/94 TIME: 12:13:25

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														INI	UISE
702 703	His 1	His	Gln	Val	Gln 5	Leu	Gln	Gln	Ser	Gly 10	Pro	Glu	Leu	Val	Lys 15
704	-														
705	Pro	Gly	Ala	Ser	Val	Lva	TIE	Ser	Cvs	Lva	Thr	Ser	Glv	Tvr	Thr
706		011	*****	002	20	-7-		001	Cyo	25		201	011	-1-	30
707					20					2.5					30
708	Dhe	Thr	Glu	Mat	G111	Trn	Sor	Cure	TIA	TIO	LOW	Dhe	Lou	Tral	712
709	FILE	TILL	GIU	Mec	14.4	IID	Ser	Cys	TIE	40	Leu	File	neu	val	45
					35					40					45
710	mlana	77-	mlass	a1	17-1	***		a3	77-7	a1-	T	37-7	a1		01
711	Int	Ala	Int	GLY		HIS	ser	GIU	val		Leu	val	GIU	Ser	WWW.
712					50					55					60
713		~7			-	-	~7				-		-	_	
714	GIA	Gly	Leu	Val		Pro	GLY	GLY	Ser		Arg	Leu	Ser	Cys	
715					65					70					75
716	100021-01		112		WCUSEON S	10.2	2.4		100				Vancous et al.		
717	Thr	Ser	Gly	Tyr	Thr	Phe	Thr	Glu	Tyr	Thr	Met	His	Trp	Met	
718					80					85					90
719															
720	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val	Ala	Gly	Ile	Asn	Pro
721					95					100					105
722															
723	Lys	Asn	Gly	Gly	Thr	Ser	His	Asn	Gln	Arg	Phe	Met	Asp	Arg	Phe
724				-	110					115					120
725															
726	Thr	Ile	Ser	Val	Asp	Lvs	Ser	Thr	Ser	Thr	Ala	Tvr	Met	Gln	Met
727	(	1000			125	-3-				130					135
728															
729	Agn	Ser	T.011	Ara	77-	G111	Acn	The	77.	1701	Tierr	Tree	Cva	112	Arm
730	ASII	Ser	пец	Arg	140	GIU	Asp	1111	nra		TAT	TAT	Cys	MIG	The state of the s
					140					145					150
731	Massa	7	<b>a</b> 1	*	7	m	a1	nh -		11-1		m	nl-		**- 7
732	Trp	Arg	GIA	Leu		TAL	GTA	Pne	Asp		Arg	TYT	Phe	Asp	Val
733					155					160					165
734	en		07	-		. 500		mi		-				mi	-
735	Trp	Gly	GIn	GIY		ren	val	Thr	val		ser	Ala	Ser	Thr	1000
736					170					175					180
737			A Second		-			-							
738	Gly	Pro	Ser	Val			Leu	Ala	Pro	-	Ser	Arg	Ser	Thr	
739					185					190					195
740															
741	Glu	Ser	Thr	Ala	Ala	Leu	Gly	Cys	Leu	Val	Lys	Asp	Tyr	Phe	Pro
742					200					205					210
743															
744	Glu	Pro	Val	Thr	Val	Ser	Trp	Asn	Ser	Gly	Ala	Leu	Thr	Ser	Gly
745					215					220					225
746															
747	Val	His	Thr	Phe	Pro	Ala	Val	Leu	Gln	Ser	Ser	Gly	Leu	Tyr	Ser
748			1-2-		230				1000	235					240
749					77.7					1					
750	Leu	Ser	Ser	Val	Val	Thr	Val	Thr	Ser	Ser	Asn	Phe	Glv	Thr	Gln
751				-	245	2000			-	250	A			-	255
752															
753	Thr	Tyr	Thr	Cve	Asn	Val	Agn	Hie	Live	Pro	Ser	Agn	Thr	Lave	Val
754	****	- 1 -	****	CYS	260	val	nap	****	LYS	265	DOL	11011	****	Lys	270
154					200					200					2/0

## RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206

DATE: 04/15/94

### INPUT SET: S2658.raw

755														115 125	
756	Agn	Tare	Thr	TEV	Glas	Ara	Tare	Cys	Cva	Val	Thr	Cve	Dro	Dro	Cve
757	ASP	пуз	1111	val	275	rig	цуз	cys	cys	280	1111	cla	FIG	rio	285
758					213					200					203
759	Pro	ATa	Pro	Glu	Len	T.011	Gly	Gly	Dro	Sor	Val	Dhe	Len	Dho	Pro
760	FIG	ALG	FIO	GIU	290	Leu	GLY	GLY	110	295	var	THE	nea	1110	300
761					250					233					300
762	Dro	Tarm	Dro	Tare	Acn	Thr	Ton	Met	T10	Cor	Arm	Thr	Dro	G7.11	17-1
763	PLO	Був	PIO	Буз	305		neu	Mer	TIE	310	ALG	THE	PIG	GIU	315
					203					310					212
764 765	mlo	a	77-7	37-1	17-7	7	17-7	Ser	***	<i>α</i> 1	7.00	Time	C7.	11-1	Tire
766	THE	Cys	Val	val	320	ASD	val	ser	nis	325	Asp	PIO	GIU	val	330
					320					323					330
767	07		D	D	a	D-4-0	*1-	D	D	****		01	D		17-7
768	GIU	Cys	PIO	PIO	1 m 10 m 10 m	PIO	ALA	Pro	PIO			GIA	PIO	ser	
769					335					340					345
770	Dha	*	nh-	Desa	D		-	T	Non	mh sa	T	Mak	T1 -	Com	B
771	Phe	Leu	Pne	PIO		гуя	Pro	Lys	Asp		Leu	Met	TTE	Ser	
772					350					355					360
773	mi	D	a1	**- 1	ml	~	11-1	17-1	17- 7		11-1		***	G7	
774	Thr	Pro	GIU	val		Cys	val	Val	val			ser	HIS	GIU	and the second
775					365					370					375
776	D	<b>~</b> 1		a) -	D1-		m	m	**-1		01		01	17-7	***
777	Pro	GIU	val	Gin		Asn	Trp	Tyr	val			Met	GIU	val	
778					380					385					390
779		27-		ml		Dava	7	G7	G1	a1-	Dha			role es	Dha
780	ASII	Ala	Lys	IIII		PIO	Arg	Glu	GIU		Pne	Asn	Ser	THE	
781					395					400					405
782 783	7~~	17-1	17-1	Cox	17-7	Tou	The	1701	17-1	Uin	C1=	Ann	Ten	Tou	Acn
	Arg	val	Val	ser	410		int	Val	Val	415		Азр	irb	Leu	420
784 785					410	13.				413					420
786	01.,	Tara	01.	There	Tara	Cara	Tarm	Val	Cor	Agn	Tara	C1.	Tou	Dro	717
787	GLY	гур	GIU	TAT	425		Lys	val	ser	430		GIA	Leu	PIO	435
788					423					430					422
789	Dro	TIO	010	Two	The	TIO	Cor	Lys	The	Tare	Cly	aln.	Dro	Ara	GIN
790	PIO	TTE	GIU	Буз	440		ser	Lys	1111	445		GTII	PLO	arg	450
791					440					447					450
792	Dro	Gln	Val	There	Thr	Len	Pro	Pro	Cor	Arm	Glin	G111	Met	Thr	Lys
793	FLO	GIII	val	TAT	455		FIG	PLO	261	460		GLU	ricc	1111	465
794					433					400					403
795	Acn	G1n	Wal	Car	T.011	Thr	Cve	Leu	Wal	Tara	Gly	Dhe	Tyr	Pro	Ser
796	ASII	GIII	val	Der	470		cys	Lieu		475		FIIC	TAT	220	480
797					470					413					400
798	Nan	TIO	772	Tral	7711	Trn	Clu	Cor	Aen	Clar	Cin	Dro	CIT	Aen	Asn
	Asp	Tre	ALA	Val			GIU	ser	Maii	490		FIO	GIU	Aoii	495
799					485					450					493
800	Mazar	T	The	The	Dro	Dro	Mot	Leu	Acn	Car	Acn	G111	Car	Dhe	Dho
801	TAT	цув	IIIL	1111	500		Met	Leu	мар	505	A	GLY	Ser	FILE	510
802					300					505					310
803 804	Torr	The	Sar	Tare	Lou	The	1701	Aan	Lare	Sar	Ann	Trn	Gla	Gla	Gly
805	neu	TAT	per	пуз	515		val	vah	пув	520		TTP	GIII	GIII	525
806					213					320					525
807	Aen	Val	Pho	Ser	Cve	Ser	Val	Met	His	Glu	Ala	Leu	His	Asn	His
007	Hom	var	£ 11C	Der	CYO	CCL	v Ca.L		****			204			******

808

# RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206

535

DATE: 04/15/94 TIME: 12:13:36

INPUT SET: S2658.raw

809													
810	Tyr	Thr	Gln	Lys	Ser	Leu	Ser	Leu	Ser	Pro	Gly	Lys	
911					545							Δ	

530

540

8 811 812 555

# SEQUENCE VERIFICATION REPORT PATENT APPLICATION US/08/146,206

DATE: 04/15/94 TIME: 12:13:37

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Line

Error

Original Text

696

Entered (557) and Calc. Seq. Length (552) differ

(A) LENGTH: 557 amino acids



APPLICATION NUMBER	FILING DATE	FIRST	NAMED APPLICANT		ATTY, DOCKET NO/TITLE
08/146,206	11/17/93	CARTER		Р	70901
CARULYN R. GENENTECH, 460 POINT	TV CAN THE PART IN	03A1/05	502		3
		ALIFORNIA S	94080	0000	
			DA	TE MAILED:	05/02/94
	n Number and Filin	g Date have been as	FE GRANTED signed to this appl	ication. Howev	er, the items indicated
below are mis THE PAYMI	n Number and Filin sing, The required ENT OF A SURC for small entities wh	FILING DA' g Date have been as items and fees iden CHARGE for items	FE GRANTED signed to this appl stified below must a 1 and 3-6 only	ication. Howev be timely subn of \$	er, the items indicated
below are mis THE PAYMI \$ 37 CFR 1.16(e) If all required it	n Number and Filin sing. The required ENT OF A SURC for small entities wh	FILING DA' g Date have been as items and fees ider HARGE for items to have filed a verified lited within the period	FE GRANTED signed to this applitified below musts 1 and 3-6 only d statement claiming	ication. However, be timely submof \$such status. The	er, the items indicated attendited ALONG WITE
below are mis THE PAYMI \$ 37 CFR 1.16(e)  If all required it entity,  small  Applicant is g FILING DAT required above	n Number and Filin sing. The required ENT OF A SURC. for small entities where the entity (verified states iven ONE MONTH E of this application,	FILING DA'  g Date have been as items and fees ider HARGE for items to have filed a verified ited within the period tent filed), is: FROM THE DATE WHICHEVER IS L. ent. Extensions of tire	signed to this appletified below musts 1 and 3-6 only d statement claiming set below, the total a OF THIS LETTER ATER, within which	ication. However, be timely submof \$ such status. The mount owed by a \$ OR TWO MO to file all required.	er, the items indicated nitted ALONG WITE for large entities of surcharge is set forth in

An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above

4. The oath or declaration does not identify the application to which it applies. An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and

Number and Filing Date, is required. 6. ☐ The signature of the following joint inventor(s) is missing from the oath or declaration:

An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Filing Date, is required.

7. 

The application was filed in a language other than English. Applicant must file a verified English translation of the application and a fee of \$\_ under 37 CFR 1.17(k), unless this fee has already been paid.

processing fee is required for returned checks. (37 CFR 1.21(m)).

9. D Your filing receipt was mailed in error because check was returned without payment.

The application does not comply with the Sequence Rules. See attached Notice to Comply with Sequence Rules 37 CFR 1.821-1.825.

11. Other.

Direct the response and any questions about this notice to Application Processing Division, Special Processing and Correspondence Branch (703) 308-1202.

A copy of this notice <u>MUST</u> be returned with the response.

PORM PTO-1533 (REV. 5-98)

3. 

The oath or declaration: ☐ is missing.

☐ does not cover items omitted at time of execution.

Application Number and Filing Date is required.

OFFICE COPY

# REQUIREMENTS FOR PATENT AS NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

#1500 #151010 151010 100 # 211010 1410	
1. This application clearly fails to comply with the requirements of 37 CFR 1.8	21
- 1.825. Applicant's attention is directed to these regulations, published at 1114 OG May 15, 1990 and at 55 FR 18230, May 1, 1990.	29,
2. This application does not contain, as a separate part of the disclosure on	
paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).	
3. A copy of the "Sequence Listing" in computer readable form has not been	
submitted as required by 37 CFR 1.821(e).	
4. A copy of the "Sequence Listing" in computer readable form has been submitted	
However, the content of the computer readable form does not comply with the requiremen of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."	ts
5. The computer readable form that has been filed with this application has been	n
found to be damaged and/or unreadable as indicated on the attached CRF Diskette Proble	
Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).	
6. The paper copy of the "Sequence Listing" is not the same as the computer	
readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).	
Other:	
Applicant must provide:	
An initial or substitute computer readable form (CRF) copy of the "Sequence	
Listing"	
An initial or substitute paper copy of the "Sequence Listing", as well as an	
amendment directing its entry into the specification	
A statement that the content of the paper and computer readable copies are the s	ame
and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)	
For questions regarding compliance with these requirements, please conta	ct:

For Rules Interpretation, call (703) 308-1123

For CRF submission help, call (703) 308-4212

For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.





# UNITED STATES DEPARTMENT OF COMMERCE Patent and Trademark Office Address: COMMISSIONER OF PATENTS AND TRADEMARKS Washington, D.C. 20231

APPLICATION IC MINES FILING DATE FIRST NAMED APPLICANT

ATTY. DOCKET NO./TITLE

08/146,206

11/17/93

CARTER

709P1

03A1/0502

GENEMIECH, INC.

460 POINT SAN BRUNG BOULEVARD

SOUTH SAN FRANCISCO, CALIFORNIA 94080

0000

P

05/02/94

NOTICE TO FILE MISSING PARTS OF APPLICATION FILING DATE GRANTED
An Application Number and Filing Date have been assigned to this application. However, the items indicate below are missing. The required items and fees identified below must be timely submitted ALONG WITH PAYMENT OF A SURCHARGE for items 1 and 3-6 only of \$ for large entities of \$ for small entities who have filed a verified statement claiming such status. The surcharge is set forth i 37 CFR 1.16(e).
If all required items on this form are filed within the period set below, the total amount owed by applicant as a large entity, small entity (verified statement filed), is \$
Applicant is given ONE MONTH FROM THE DATE OF THIS LETTER, OR TWO MONTHS FROM THE FILING DATE of this application, WHICHEVER IS LATER, within which to file all required items and pay any fees required above to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).
<ol> <li>□ The statutory basic filing fee is: □ missing □ insufficient. Applicant as a □ large entity □ small entity, must submit \$to complete the basic filing fee.</li> </ol>
2. □ Additional claim fees of \$as a □ large entity, □ small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
3.   The oath or declaration:
☐ is missing. ☐ does not cover items omitted at time of execution.
An oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date is required.
4.  The oath or declaration does not identify the application to which it applies. An oath or declaratio in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
5.  The signature to the oath or declaration is:  missing;  a reproduction;  by a person other that the inventor or a person qualified under 37 CFR 1.42, 1.43, or 1.47. A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
6. □ The signature of the following joint inventor(s) is missing from the oath or declaration:
An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Filing Date, is required.
7.  The application was filed in a language other than English. Applicant must file a verified English translation of the application and a fee of \$under 37 CFR 1.17(k), unless this fee has already been paid.
8. A \$ processing fee is required for returned checks. (37 CFR 1.21(m)).
9. User filing receipt was mailed in error because check was returned without payment.
10. C The application does not comply with the Sequence Rules. See attached Notice to Comply with Sequence Rules 37 CFR 1.821-1.825.
11, □ Other,
Direct the response and any questions about this notice to, Application Processin Division, Special Processing and Correspondence Branch (703) 308-1202.
A same of this motion V

H RESPONSE

200 of 1033

PORM PTO-1533 (REV. 5-65)

BI Exhibit 1002

NUCLEOTIDE BEQUENCE AND OR ANINO ACID SEQUENCE DISCLOSURES
The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the for the formula teason(s):
1. This application clearly fails to comply with the requirements of 37 CFR 1.821
- 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29 May 15, 1990 and at 55 FR 18230, May 1, 1990.
2. This application does not contain, as a separate part of the disclosure on
paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).
3. A copy of the "Sequence Listing" in computer readable form has not been
submitted as required by 37 CFR 1.821(e).
4. A copy of the "Sequence Listing" in computer readable form has been submitted.
However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."
5. The computer readable form that has been filed with this application has been
found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).
6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).
7. Other:
Applicant must provide:
An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"
An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification
A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)
For questions regarding compliance with these requirements, please contact:
For Rules Interpretation, call (703) 308-1123 For CRF submission help, call (703) 308-4212 For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.

PATENT DOCKET 709P1

#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PAUL J. CARTER et al.

Application of

Serial No. 08/146,206

Filed: 17 November 1993

For: METHOD FOR MAKING HUMANIZED)

ANTIBODIES

Group Art Unit: Unknown

Examiner: Unassigned

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an anvelops addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on

Tune 2 1994

(Date of Deposit)

Elisa R. Hamby

Name of Depositing Party

Signature of Depositing Party

Jate of Eignature

CERTIFICATE RE: SEQUENCE LISTING

BOX SEQUENCE
Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I hereby state that the Sequence Listing submitted with this application is submitted in paper copy and a computer-readable diskette, and that the content of the paper and computer readable copies are the same.

A copy of a document pursuant to 37 C.F.R. § 10.9(b) is attached as proof of the authorization of the undersigned to prosecute the above-mentioned application. The original of this document is on file in the Office of Enrollment and Discipline.

Respectfully submitted,

School Services

Wendy M. Lee

Date: 02 14

460 Pt. San Bruno Blvd.

So. San Francisco, CA 94080-4990

Phone: (415) 225-1994 Fax: (415) 952-9881



180



#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

PAUL J. CARTER et al.

Serial No. 08/146,206

Filed: 17 November 1993

For: METHOD FOR MAKING HUMANIZED)

**ANTIBODIES** 

Group Art Unit: Unknown

Examiner: Unassigned

CERTIFICATE OF MAILING
I hereby cartify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on

June 2 1994

[Date of Deposit]

EVSAR Hamby

Name of Depositing Party

Signature of Depositing Party

Pate of Signature

9/2°

#### **AMENDMENT**

BOX SEQUENCE
Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

This is responsive to the Notice to File Missing Parts of Application - Filing Date Granted and Notice to Comply with Sequence Rules Pursuant to 37 CFR 1.821-1.825, mailed 2 May 1994. The due date for this response is 2 June 1994. This response is timely filed.

Please amend the application as follows:

#### IN THE SPECIFICATION

Please amend the specification by replacing the original Sequence Listing pages 77-94 with the attached corrected Sequence Listing as pages 77-94.

### REMARKS

An error in the original Sequence Listing filed 11/17/93 was found in SEQ ID NO:23 in that there claimed to be 557 amino acids, and only 552 residues are shown. This error has been corrected and now corresponds to Figure 6A and the sequence entitled "pH52-8.0". Another error was found

08/146,206 Page No. 2

in SEQ ID NO:19 which has also been corrected and now corresponds to Figure 5 (lower panel) and the sequence entitled "muxCD3".

The inventors submit that this application is now in compliance with the requirements of 37 CFR 1.821-1.825, and respectfully request further processing of this application.

A copy of a document pursuant to 37 C.F.R. § 10.9(b) is attached as proof of the authorization of the undersigned to prosecute the above-mentioned application. The original of this document is on file in the Office of Enrollment and Discipline.

Respectfully submitted,

GENENTECH, INC.

Date: 62 94

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460 Pt. San Bruno Blvd. So. San Francisco, CA 94080-4990

Phone: (415) 225-1994 Fax: (415) 952-9881



#### SEQUENCE LISTING

- 5 (i) APPLICANT: Carter, Paul J. Presta, Leonard G.
  - (ii) TITLE OF INVENTION: Method for Making Humanized Antibodies
- 10 (iii) NUMBER OF SEQUENCES: 25
  - (iv) CORRESPONDENCE ADDRESS:
    - (A) ADDRESSEE: Genentech, Inc.
    - (B) STREET: 460 Point San Bruno Blvd
    - (C) CITY: South San Francisco
    - (D) STATE: California
    - (E) COUNTRY: USA
    - (F) ZIP: 94080
    - (v) COMPUTER READABLE FORM:
      - (A) MEDIUM TYPE: 5.25 inch, \$60 Kb floppy disk
      - (B) COMPUTER: IBM PC compatible
      - (C) OPERATING SYSTEM: PC-DOS/MS-DOS
      - (D) SOFTWARE: patin (Genentech)
  - (vi) CURRENT APPLICATION DATA:
    - (A) APPLICATION NUMBER: 08/146206
    - (B) FILING DATE: 17-NOV-1993
    - (C) CLASSIFICATION:
  - (vii) PRIOR APPLICATION DATA:
    - (A) APPLICATION NUMBER: 07/715272
    - (B) FILING DATE: 14-JUN-1991
- 35 (viii) ATTORNEY/AGENT INFORMATION:
  - (A) NAME: Hasak, Janet E.
  - (B) REGISTRATION NUMBER: 28,616
  - (C) REFERENCE/DOCKET NUMBER: 709P1
  - 0 (ix) TELECOMMUNICATION INFORMATION:
    - (A) TELEPHONE: 415/225-1896
    - (B) TELEFAX: 415/952-9881
    - (C)/TELEX: 910/371-7168
  - 45 (2) INFORMATION FOR SEQ ID NO:1:
    - (i) SEQUENCE CHARACTERISTICS:
      - (A) LENGTH: 109 amino acids
      - (B) TYPE: amino acid
    - / (D) TOPOLOGY: linear

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	(x:	i) SI	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID I	NO:1	:				
	Asp 1	Ile	Gln	Met	Thr 5	Gln	Ser	Pro	Ser	Ser 10	Leu	Ser	Ala	Ser	Val
5	Gly	Asp	Arg	Val	Thr 20	Ile	Thr	Cys	Arg	Ala 25	Ser	Gln	Asp	Val	Asr 30
10	Thr	Ala	Val	Ala	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	Lys	Ala	Pro	Lys 45
	Leu	Leu	Ile	Tyr	Ser 50	Ala	Ser	Phe	Leu	Glu 55	Ser	Gly	Val	Pro	Ser 60
15	Arg	Phe	Ser	Gly	Ser 65	Arg	Ser	Gly	Thr	Asp 70	Phe	Thr	Leu	Thr	116
1	Ser	Ser	Leu	Gln	Pro 80	Glu	Asp	Phe	Ala	Thr 85	Tyr	Tyr	Cys	Gln	Glr 90
20	His	Tyr	Thr	Thr	Pro 95	Pro	Thr	Phe	Gly	Gln 100	Gly	Thr	Lys	Val	Glu 105
25	Ile	Lys	Arg	Thr 109											
	(2)	INFO	RMAT	ION I	FOR .	SEQ	ID N	0:2:							
30	(	()	A) Li B) T	ENGT	H: 1	ACTE 20 au no a 1in	mino cid		ds						
25	(x	i) S	EQUE	NCE I	DESC	RIPT	ION:	SEQ	ID 1	NO:2	:				
35	Glu 1	Val	Gln	Leu	Val 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15
40	Gly	Ser	Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Phe	Asn	Ile	Lys 30
	Asp	Thr	Tyr	Ile	His 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Lei
45	Glu	Trp	Val	Ala	Arg 50	Ile	Tyr	Pro	Thr	Asn 55	Gly	Tyr	Thr	Arg	Ty:
	Ala	Asp	Ser	Val	Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Ala	Asp	Thr	Se:

Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp 80 85 90

	Thr	Ala	Val	Tyr	Tyr 95	Cys	Ser	Arg	Trp	Gly 100	Gly	Asp	Gly	Phe	Tyr 105
5	Ala	Met	Asp	Val	Trp 110	Gly	Gln	Gly	Thr	Leu 115		Thr	Val	Ser	Ser 120
	(2)	INFO	RMAT	ION 1	FOR :	SEQ	ID NO	0:3:							
10	(	()		ENGTI YPE :		09 at	mino cid		ds						
15	(x	i) s	EQUEI	NCE I	DESC	RIPT	ION:	SEQ	ID 1	10:3	:				
A	Asp 1	Ile	Gln	Met	Thr 5	Gln	Ser	Pro	Ser	Ser 10	Leu	Ser	Ala	Ser	Val 15
20	Gly	Asp	Arg	Val	Thr 20	Ile	Thr	Cys	Arg	Ala 25	Ser	Gln	Asp	Val	Ser 30
25	Ser	Tyr	Leu	Ala	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	Lys	Ala	Pro	Lys 45
25	Leu	Leu	Ile	Tyr	Ala 50	Ala	Ser	Ser	Leu	Glu 55	Ser	Gly	Val	Pro	Ser 60
30	Arg	Phe	Ser	Gly	Ser 65	Gly	Ser	Gly	Thr	Asp 70	Phe	Thr	Leu	Thr	Ile 75
	Ser	Ser	Leu	Gln	Pro 80	Glu	Asp	Phe	Ala	Thr 85	Tyr	Tyr	Cys	Gln	Gln 90
35	Tyr	Asn	Ser	Leu	Pro 95	Tyr	Thr	Phe	Gly	Gln 100		Thr	Lys	Val	Glu 105
	Ile	Lys	Arg	Thr 109											
40	(2)	INFO	RMAT	ION :	FOR :	SEQ	ID N	0:4:							
45	(	(.	, 전, M. 프라틴	ENGT:		20 an	mino cid		ds						
	(x	i) s	EQUEI	NCE I	DESC	RIPT	ION:	SEQ	ID I	NO:4	:				
50	Glu 1		Gln	Leu	Val	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15

	Gly	Ser	Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ser 30
5	Asp	Tyr	Ala	Met	Ser 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45
	Glu	Trp	Val	Ala	Val 50	Ile	Ser	Glu	Asn	Gly 55	Gly	Tyr	Thr	Arg	Tyr 60
10	Ala	Asp	Ser	Val	Lys 65	Gly	Arg	Phe	Thr	Ile 70	Ser	Ala	Asp	Thr	Ser 75
15	Lys	Asn	Thr	Ala	Tyr 80	Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90
15	Thr	Ala	Val	Tyr	Tyr 95	Cys	Ser	Arg	Trp	Gly 100	Gly	Asp	Gly	Phe	Tyr 105
20	Ala	Met	Asp	Val	Trp 110	Gly	Gln	Gly	Thr	Leu 115	Val	Thr	Val	Ser	Ser 120
	(2)	INFO	RMAT	ION	FOR A	SEQ :	ID N	0:5:							
25	(:	(1	A) L B) T	NCE ( ENGT) YPE:	H: 1	09 at	mino cid								
30	(x	i) si	EQUE	NCE :	DESC	RIPT	ION:	SEQ	ID I	NO:5	:				
	Asp 1	Ile	Val	Met	Thr 5	Gln	Ser	His	Lys	Phe 10	Met	Ser	Thr	Ser	Val
35	Gly	Asp	Arg	Val	Ser 20	Ile	Thr	Cys	Lys	Ala 25	Ser	Gln	Asp	Val	Asr 30
	Thr	Ala	Val	Ala	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	His	Ser	Pro	Lys 45
40	Leu	Leu	Ile	Tyr	Ser 50	Ala	Ser	Phe	Arg	Tyr 55	Thr	Gly	Val	Pro	Asp 60
45	Arg	Phe	Thr	Gly	Asn 65	Arg	Ser	Gly	Thr	Asp 70	Phe	Thr	Phe	Thr	Ile 75
	Ser	Ser	Val	Gln	Ala 80	Glu	Asp	Leu	Ala	Val 85	Tyr	Tyr	Cys	Gln	Glr 90
50	His	Tyr	Thr	Thr	Pro 95	Pro	Thr	Phe	Gly	Gly 100	Gly	Thr	Lys	Leu	Glu 105

Ile	Lys	Arg	Ala
	-		109

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(2)	INFORMATION	FOR	SEQ	ID	NO:6:
-----	-------------	-----	-----	----	-------

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 120 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
1 5 10 15

Ala Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys 20 25 30

Asp Thr Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
35 40 45

Glu Trp Ile Gly Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr
50 55 60

25 Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser 65 70 75

> Ser Asn Thr Ala Tyr Leu Gln Val Ser Arg Leu Thr Ser Glu Asp 80 85 90

> Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr 95 100 105

Ala Met Asp Tyr Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser

#### (2) INFORMATION FOR SEQ ID NO:7;

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 27 bases
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

TCCGATATCC AGCTGACCCA GTCTCCA 27

50

	(2) INFORMATION FOR SEQ ID NO:8:
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 bases
5	<ul><li>(B) TYPE: nucleic acid</li><li>(C) STRANDEDNESS: single</li></ul>
	(D) TOPOLOGY: linear
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:
	GTTTGATCTC CAGCTTGGTA CCHSCDCCGA A 31
15	(2) INFORMATION FOR SEQ ID NO:9:
- 1	
),	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 22 bases
2/	(B) TYPE: nucleic acid
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:
	AGGTSMARCT GCAGSAGTCW GG 22
30	
	(2) INFORMATION FOR SEQ ID NO:10:
	(i) SEQUENCE CHARACTERISTICS:
35	(A) LENGTH: 34 bases (B) TYPE: nucleic acid
33	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10
	TGAGGAGACG GTGACCGTGG TCCCTTGGCC CCAG 34
45	(2) INFORMATION FOR SEQ ID NO:11:
	(i) SEQUENCE CHARACTERISTICS:
50	(A) LENGTH: 36 bases (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:	
5	GTAGATAAAT CCTCTAACAC AGCCTATCTG CAAATG 36	
	(2) INFORMATION FOR SEQ ID NO:12:	
10 15	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 36 bases</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
13	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:	
20	GTAGATAAAT CCAAATCTAC AGCCTATCTG CAAATG 36	
	(2) INFORMATION FOR SEQ ID NO:13:	
30	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 36 bases</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:	
35	GTAGATAAAT CCTCTTCTAC AGCCTATCTG CAAATG 36	
	(2) INFORMATION FOR SEQ ID NO:14:	
40	<ul> <li>(i) SEQUENCE CHARACTERISTICS:</li> <li>(A) LENGTH: 68 bases</li> <li>(B) TYPE: nucleic acid</li> <li>(C) STRANDEDNESS: single</li> <li>(D) TOPOLOGY: linear</li> </ul>	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:	
50	CTTATAAAGG TGTTTCCACC TATAACCAGA AATTCAAGGA TCGTTTCACG	50

(2) INFORMATION FOR SEQ ID NO:15:

5 10	(:	(1	A) LI 3) T' C) S'	ENGTI YPE : FRANI	CHARA H: 30 nucl DEDNI DGY:	bas leic ESS:	ses acid	d								
10	(x:	i) sı	EQUE	NCE 1	DESCI	RIPT	ION:	SEQ	ID I	NO:15	5:					
15	CTA	racc'	rcc (	CGTC'	rgca:	rt c	rgga(	GTCC	30							
- 1	(2)	INFO	RMAT	ION I	FOR S	SEQ :	ID NO	0:16	:							
20	(:	(1	A) LI B) T	ENGT:	CHARA H: 10 amin OGY:	07 ar	mino cid		ds							
25	(x:	i) SI	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID I	NO:1	5:					
	Asp 1	Ile	Gln	Met	Thr 5	Gln	Thr	Thr	Ser	Ser 10	Leu	Ser	Ala	Ser	Leu 15	
30	Gly	Asp	Arg	Val	Thr 20	Ile	Ser	Cys	Arg	Ala 25	Ser	Gln	Asp	Ile	Arg 30	
	Asn	Tyr	Leu	Asn	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Asp	Gly	Thr	Val	Lys 45	
35	Leu	Leu	Ile	Tyr	Tyr 50	Thr	Ser	Arg	Leu	His 55	Ser	Gly	Val	Pro	Ser 60	
40	Lys	Phe	Ser	Gly	Ser 65	Gly	Ser	Gly	Thr	Asp 70	Tyr	Ser	Leu	Thr	Ile 75	
	Ser	Asn	Leu	Glu	Gln 80	Glu	Asp	Ile	Ala	Thr 85	Tyr	Phe	Cys	Gln	Gln 90	
45	Gly	Asn	Thr	Leu	Pro 95	Trp	Thr	Phe	Ala	Gly 100	Gly	Thr	Lys	Leu	Glu 105	
	Ile	Lys														

	(2)	INFO	RMAT	ION I	FOR S	SEQ :	ID NO	0:17	:						
5	(:	(1	A) LI B) T	ENGTI YPE:	CHARA H: 10 amin OGY:	07 ar	mino cid		ds						
	(x:	i) SI	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID I	NO:1	7:				
10	Asp 1	Ile	Gln	Met	Thr 5	Gln	Ser	Pro	Ser	Ser 10	Leu	Ser	Ala	Ser	Val 15
15	Gly	Asp	Arg	Val	Thr 20	Ile	Thr	Cys	Arg	Ala 25	Ser	Gln	Asp	Ile	Arg 30
15	Asn	Tyr	Leu	Asn	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	Lys	Ala	Pro	Lys 45
(20/	Leu	Leu	Ile	Tyr	Tyr 50	Thr	Ser	Arg	Leu	Glu 55	Ser	Gly	Val	Pro	Ser 60
1	Arg	Phe	Ser	Gly	Ser 65	Gly	Ser	Gly	Thr	Asp 70	Tyr	Thr	Leu	Thr	Ile 75
25	Ser	Ser	Leu	Gln	Pro 80	Glu	Asp	Phe	Ala	Thr 85	Tyr	Tyr	Cys	Gln	Gln 90
2.0	Gly	Asn	Thr	Leu	Pro 95	Trp	Thr	Phe	Gly	Gln 100	Gly	Thr	Lys	Val	Glu 105
30	Ile	Lys 107													
35	7 - 2	i) s:	EQUE	NCE (	FOR SCHARMENT OF THE CHARMENT	ACTE	RIST mino	ICS:							
40	(x:				OGY: DESC			SEQ	ID 1	NO:1	В:				
45	Asp 1	Ile	Gln	Met	Thr 5	Gln	Ser	Pro	Ser	Ser 10	Leu	Ser	Ala	Ser	Val 15
45	Gly	Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser

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

Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile 5 65 Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln 10 Tyr Asn Ser Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu 95 Ile Lys 107

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#### (2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 122 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly 25 10 Ala Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr 30 Gly Tyr Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu Glu Trp Met Gly Leu Ile Asn Pro Tyr Lys Gly Val Ser Thr Tyr 35 Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser 40 Ser Ser Thr Ala Tyr Met Glu Leu Leu Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Tyr Gly Asp Ser 95 45 Asp Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val

Ser Ser 50 122

(2) INFORMATION FOR SEQ ID NO:20:

5	(	(1	A) LI B) T	ENGTI YPE:	CHARI H: 12 amin OGY:	22 ar	mino cid		ds						
	(x	i) S	EQUE	NCE 1	DESC	RIPT	ION:	SEQ	ID I	NO:2	2 :				
10	Glu 1	Val	Gln	Leu	Val 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15
	Gly	Ser	Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Tyr	Ser	Phe	Thr 30
15	Gly	Tyr	Thr	Met	Asn 35	Trp	Val	Arg	Gln	Ala 40	Pro	Gly	Lys	Gly	Leu 45
30/	Glu	Trp	Val	Ala	Leu 50	Ile	Asn	Pro	Tyr	Lys 55	Gly	Val	Ser	Thr	Tyr 60
	Asn	Gln	Lys	Phe	Lys 65	Asp	Arg	Phe	Thr	Ile 70	Ser	Val	Asp	Lys	Ser 75
25	Lys	Asn	Thr	Ala	Tyr 80	Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90
	Thr	Ala	Val	Tyr	Tyr 95	Cys	Ala	Arg	Ser	Gly 100	Tyr	Tyr	Gly	Asp	Ser 105
30	Asp	Trp	Tyr	Phe	Asp	Val	Trp	Gly	Gln	Gly 115	Thr	Leu	Val	Thr	Val
35	Ser	Ser 122													
	(2)	INFO	RMAT	ION I	FOR :	SEQ :	ID N	0:21	:						
40	(	(	A) Li B) T	ENGT	CHAR H: 1: amin OGY:	22 at	mino cid		ds						
45	(x	i) s	EQUE	NCE I	DESC	RIPT	ION:	SEQ	ID I	NO:2	1:				
13	Glu 1	Val	Gln	Leu	Val 5	Glu	Ser	Gly	Gly	Gly 10	Leu	Val	Gln	Pro	Gly 15
50	Gly	Ser	Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	Ser 25	Gly	Phe	Thr	Phe	Ser 30

Ser Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu 35 Glu Trp Val Ser Val Ile Ser Gly Asp Gly Gly Ser Thr Tyr Tyr 5 50 Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser 10 Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Val Gly Tyr Ser Leu 95 15 Ser Gly Leu Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val 115 110 Ser Ser 122 (2) INFORMATION FOR SEQ ID NO:22: (i) SEQUENCE CHARACTERISTICS: 25 (A) LENGTH: 454 amino acids (B) TYPE: amino acid (D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22: 30 Gln Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly 10 Ala Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr 35 Glu Tyr Thr Met His Trp Met Lys Gln Ser His Gly Lys Ser Leu 40 Glu Trp Ile Gly Gly Phe Asn Pro Lys Asn Gly Gly Ser Ser His 55 Asn Gln Arg Phe Met Asp Lys Ala Thr Leu Ala Val Asp Lys Ser 45 Thr Ser Thr Ala Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp

Ser Gly Ile Tyr Tyr Cys Ala Arg Trp Arg Gly Leu Asn Tyr Gly

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	Phe	Asp	Val	Arg	Tyr 110	Phe	Asp	Val	Trp	Gly 115	Ala	Gly	Thr	Thr	Val 120
5	Thr	Val	Ser	Ser	Ala 125	Ser	Thr	Lys	Gly	Pro 130	Ser	Val	Phe	Pro	Leu 135
	Ala	Pro	Ser	Ser	Lys 140	Ser	Thr	Ser	Gly	Gly 145	Thr	Ala	Ala	Leu	Gly 150
10	Cys	Leu	Val	Lys	Asp 155	Tyr	Phe	Pro	Glu	Pro 160	Val	Thr	Val	Ser	Trp 165
20.	Asn	Ser	Gly	Ala	Leu 170	Thr	Ser	Gly	Val	His 175	Thr	Phe	Pro	Ala	Val 180
15	Leu	Gln	Ser	Ser	Gly 185	Leu	Tyr	Ser	Leu	Ser 190	Ser	Val	Val	Thr	Val 195
29/	Pro	Ser	Ser	Ser	Leu 200	Gly	Thr	Gln	Thr	Tyr 205	Ile	Cys	Asn	Val	Asn 210
KI	His	Lys	Pro	Ser	Asn 215	Thr	Lys	Val	Asp	Lys 220	Lys	Val	Glu	Pro	Lys 225
25	Ser	Cys	Asp	Lys	Thr 230	His	Thr	Cys	Pro	Pro 235	Cys	Pro	Ala	Pro	Glu 240
	Leu	Leu	Gly	Gly	Pro 245	Ser	Val	Phe	Leu	Phe 250	Pro	Pro	Lys	Pro	Lys 255
30	Asp	Thr	Leu	Met	Ile 260	Ser	Arg	Thr	Pro	Glu 265	Val	Thr	Cys	Val	Val 270
35	Val	Asp	Val	Ser	His 275	Glu	Asp	Pro	Glu	Val 280	Lys	Phe	Asn	Trp	Tyr 285
	Val	Asp	Gly	Val	Glu 290	Val	His	Asn	Ala	Lys 295		Lys	Pro	Arg	Glu 300
40	Glu	Gln	Tyr	Asn	Ser 305	Thr	Tyr	Arg	Val	Val 310	Ser	Val	Leu	Thr	Val 315
45	Leu	His	Gln	Asp	Trp 320	Leu	Asn	Gly	Lys	Glu 325	Tyr	Lys	Cys	Lys	Val 330
45	Ser	Asn	Lys	Ala	Leu 335	Pro	Ala	Pro	Ile	Glu 340	Lys	Thr	Ile	Ser	Lys 345
50	Ala	Lys	Gly	Gln	Pro 350	Arg	Glu	Pro	Gln	Val 355	Tyr	Thr	Leu	Pro	Pro 360

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu 370 375 365 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser 5 385 Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu 395 400 10 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp 410 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met 15 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 440 Ser Pro Gly Lys 454

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### (2) INFORMATION FOR SEQ ID NO:23:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 469 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:
- Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr 1 5 10 15

  Gly Val His Ser Glu Val Gln Leu Val Glu Ser Gly Gly Leu
- Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly
- 40 Tyr Thr Phe Thr Glu Tyr Thr Met His Trp Met Arg Gln Ala Pro 50 55 60
  - Gly Lys Gly Leu Glu Trp Val Ala Gly Ile Asn Pro Lys Asn Gly
    65 70 75
  - Gly Thr Ser His Asn Gln Arg Phe Met Asp Arg Phe Thr Ile Ser 80 85 90
- Val Asp Lys Ser Thr Ser Thr Ala Tyr Met Gln Met Asn Ser Leu 50 95 100 105

	Arg	Ala	Glu	Asp	Thr 110	Ala	Val	Tyr	Tyr	Cys 115	Ala	Arg	Trp	Arg	Gly 120	
5	Leu	Asn	Tyr	Gly	Phe 125	Asp	Val	Arg	Tyr	Phe 130	Asp	Val	Trp	Gly	Gln 135	
	Gly	Thr	Leu	Val	Thr 140	Val	Ser	Ser	Ala	Ser 145	Thr	Lys	Gly	Pro	Ser 150	
10	Val	Phe	Pro	Leu	Ala 155	Pro	Cys	Ser	Arg	Ser 160	Thr	Ser	Glu	Ser	Thr 165	
15	Ala	Ala	Leu	Gly	Cys 170	Leu	Val	Lys	Asp	Tyr 175	Phe	Pro	Glu	Pro	Val 180	
15	Thr	Val	Ser	Trp	Asn 185	Ser	Gly	Ala	Leu	Thr 190	Ser	Gly	Val	His	Thr 195	
29	Phe	Pro	Ala	Val	Leu 200	Gln	Ser	Ser	Gly	Leu 205	Tyr	Ser	Leu	Ser	Ser 210	
1	Val	Val	Thr	Val	Thr 215	Ser	Ser	Asn	Phe	Gly 220	Thr	Gln	Thr	Tyr	Thr 225	
25	Cys	Asn	Val	Asp	His 230	Lys	Pro	Ser	Asn	Thr 235	Lys	Val	Asp	Lys	Thr 240	
	Val	Glu	Arg	Lys	Cys 245	Cys	Val	Glu	Cys	Pro 250	Pro	Cys	Pro	Ala	Pro 255	
30	Pro	Val	Ala	Gly	Pro 260	Ser	Val	Phe	Leu	Phe 265	Pro	Pro	Lys	Pro	Lys 270	
35	Asp	Thr	Leu	Met	Ile 275	Ser	Arg	Thr	Pro	Glu 280	Val	Thr	Cys	Val	Val 285	
	Val	Asp	Val	Ser	His 290	Glu	Asp	Pro	Glu	Val 295	Gln	Phe	Asn	Trp	Tyr 300	
40	Val	Asp	Gly	Met	Glu 305	Val	His	Asn	Ala	Lys 310	Thr	Lys	Pro	Arg	Glu 315	
	Glu	Gln	Phe	Asn	Ser 320	Thr	Phe	Arg	Val	Val 325	Ser	Val	Leu	Thr	Val 330	
45	Val	His	Gln	Asp	Trp 335	Leu	Asn	Gly	Lys	Glu 340	Tyr	Lys	Cys	Lys	Val 345	
50	Ser	Asn	Lys	Gly	Leu 350	Pro	Ala	Pro	Ile	Glu 355	Lys	Thr	Ile	Ser	Lys 360	

Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro 370 375 Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu 5 385 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu 10 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp 430 15 Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met 440 445 His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu 455 460 Ser Pro Gly Lys 469

#### 25 (2) INFORMATION FOR SEQ ID NO:24:

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50

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 214 amino acids
    - (B) TYPE: amino acid
    - (D) TOPOLOGY: linear
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:
- Asp Val Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu 35 Gly Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Asp Ile Asn 40 Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asn Gly Thr Val Lys 40 Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser 50 45 Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Asp Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln

				95					100					Glu 105	
5	Lys	Arg	Thr	Val 110	Ala	Ala	Pro	Ser	Val 115	Phe	Ile	Phe	Pro	Pro 120	
Ser	Asp	Glu	Gln	Leu 125	Lys	Ser	Gly	Thr	Ala 130	Ser	Val	Val	Cys	Leu 135	
10 Leu	Asn	Asn	Phe	Tyr 140	Pro	Arg	Glu	Ala	Lys 145	Val	Gln	Trp	Lys	Val 150	
Asp	Asn	Ala	Leu	Gln 155	Ser	Gly	Asn	Ser	Gln 160	Glu	Ser	Val	Thr	Glu 165	
	Asp	Ser	Lys	Asp 170	Ser	Thr	Tyr	Ser	Leu 175	Ser	Ser	Thr	Leu	Thr 180	
Leu	Ser	Lys	Ala	Asp 185	Tyr	Glu	Lys	His	Lys 190	Val	Tyr	Ala	Cys	Glu 195	
Val	Thr	His	Gln	Gly 200	Leu	Ser	Ser	Pro	Val 205	Thr	Lys	Ser	Phe	Asn 210	
25 Arg	Gly	Glu	Cys 214												
(2) I	NFO	TAMS	ON I	FOR S	SEQ :	ID NO	0:25	:							
30 (i	(I		ENGTI		33 ar	mino cid		ds							
35 (xi	) SI	EQUE	ICE I	DESC	RIPT	ION:	SEQ	ID 1	NO:25	5:					
Met 1	Gly	Trp	Ser	Cys 5	Ile	Ile	Leu	Phe	Leu 10	Val	Ala	Thr	Ala	Thr 15	
40 Gly	Val	His	Ser	Asp 20	Ile	Gln	Met	Thr	Gln 25	Ser	Pro	Ser	Ser	Leu 30	
	Ala	Ser	Val	Gly 35	Asp	Arg	Val	Thr	Ile 40		Cys	Arg	Ala	Ser 45	
45 Gln	Asp	Ile	Asn	Asn 50	Tyr	Leu	Asn	Trp	Tyr 55	Gln	Gln	Lys	Pro	Gly 60	
Lys	Ala	Pro	Lys	Leu 65	Leu	Ile	Tyr	Tyr	Thr 70	Ser	Thr	Leu	His	Ser 75	

		Gly	Val	Pro	Ser	Arg 80	Phe	Ser	Gly	Ser	Gly 85	Ser	Gly	Thr	Asp	Tyr 90	
	5	Thr	Leu	Thr	Ile	Ser 95	Ser	Leu	Gln	Pro	Glu 100	Asp	Phe	Ala	Thr	Tyr 105	
		Tyr	Cys	Gln	Gln	Gly 110	Asn	Thr	Leu	Pro	Pro 115	Thr	Phe	Gly	Gln	Gly 120	
	10	Thr	Lys	Val	Glu	Ile 125	Lys	Arg	Thr	Val	Ala 130	Ala	Pro	Ser	Val	Phe 135	
7	1	Ile	Phe	Pro	Pro	Ser 140	Asp	Glu	Gln	Leu	Lys 145	Ser	Gly	Thr	Ala	Ser 150	
7	15	Val	Val	Cys	Leu	Leu 155	Asn	Asn	Phe	Tyr	Pro 160	Arg	Glu	Ala	Lys	Val 165	
7	20	Gln	Trp	Lys	Val	Asp 170	Asn	Ala	Leu	Gln	Ser 175	Gly	Asn	Ser	Gln	Glu 180	
		Ser	Val	Thr	Glu	Gln 185	Asp	Ser	Lys	Asp	Ser 190	Thr	Tyr	Ser	Leu	Ser 195	
	25	Ser	Thr	Leu	Thr	Leu 200	Ser	Lys	Ala	Asp	Tyr 205	Glu	Lys	His	Lys	Val 210	
	20	Tyr	Ala	Cys	Glu	Val 215	Thr	His	Gln	Gly	Leu 220	Ser	Ser	Pro	Val	Thr 225	
	30	Lys	Ser	Phe	Asn	Arg 230	Gly	Glu	Cys 233								

# RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206A

DATE: 06/14/94 TIME: 17:05:48

INPUT SET: S8112.raw

This Raw Listing contains the General Information Section and up to the first 5 pages.



	SEQUENCE LISTING	CMTC
(1)	General Information:	ENTER
(i)	APPLICANT: Carter, Paul J. Presta, Leonard G.	
(ii)	TITLE OF INVENTION: Method for Making Humanize	d Antibodies
(iii)	NUMBER OF SEQUENCES: 25	
	CORRESPONDENCE ADDRESS:  (A) ADDRESSEE: Genentech, Inc.  (B) STREET: 460 Point San Bruno Blvd  (C) CITY: South San Francisco  (D) STATE: California  (E) COUNTRY: USA  (F) ZIP: 94080	
	COMPUTER READABLE FORM:  (A) MEDIUM TYPE: 5.25 inch, 360 Kb floppy disk  (B) COMPUTER: IBM PC compatible  (C) OPERATING SYSTEM: PC-DOS/MS-DOS  (D) SOFTWARE: patin (Genentech)	
. 15/0-075	CURRENT APPLICATION DATA:  (A) APPLICATION NUMBER: 08/146206  (B) FILING DATE: 17-NOV-1993  (C) CLASSIFICATION:	
(vii)	PRIOR APPLICATION DATA:  (A) APPLICATION NUMBER: 07/715272  (B) FILING DATE: 14-JUN-1991	
viii)	ATTORNEY/AGENT INFORMATION:  (A) NAME: Hasak, Janet E.  (B) REGISTRATION NUMBER: 28,616  (C) REFERENCE/DOCKET NUMBER: 709P1	
(ix)	TELECOMMUNICATION INFORMATION: (A) TELEPHONE: 415/225-1896 (B) TELEFAX: 415/952-9881 (C) TELEX: 910/371-7168	
(2) IN	FORMATION FOR SEQ ID NO:1:	

# RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206A

DATE: 06/14/94 TIME: 17:06:00

(3	4	A) LI	NCE ( ENGTI YPE:	H: 10	09 ar	nino		ds					21,12	01 5
	(1	) T	OPOL	OGY:	line	ear								
(x:	i) SI	EQUE	NCE I	DESCI	RIPT	ION:	SEQ	ID I	NO:1	:				
7.7	Ile	G1n	Met	Thr 5	Gln	Ser	Pro	Ser	Ser 10		Ser	Ala	Ser	Val 15
Gly	Asp	Arg	Val	Thr 20	Ile	Thr	Cys	Arg	Ala 25	Ser	Gln	Asp	Val	Asn 30
Thr	Ala	Val	Ala	Trp 35		Gln	Gln	Lys	Pro 40		Lys	Ala	Pro	Lys 45
Leu	Leu	Ile	Tyr	Ser 50	Ala	Ser	Phe	Leu	Glu 55	Ser	Gly	Val	Pro	Ser 60
Arg	Phe	Ser	Gly	Ser 65	Arg	Ser	Gly	Thr	Asp 70		Thr	Leu	Thr	Ile 75
Ser	Ser	Leu	Gln	Pro 80	Glu	Asp	Phe	Ala	Thr 85		Tyr	Cys	Gln	Gln 90
His	Tyr	Thr	Thr	Pro 95	Pro	Thr	Phe	Gly	Gln 100		Thr	Lys	Val	Glu 105
Ile	Lys	Arg	Thr 109											
(:	(1	EQUE A) L: B) T	NCE ( ENGT) YPE:	CHAR H: 1: amin DGY:	ACTE 20 at no ac 1ine	RIST mino cid ear	ICS: acio		NO:2	:				
124														
	Val	Gln	Leu	Val 5	Glu	Ser	Gly		Gly 10		Val	Gln	Pro	Gly 15
Glu 1	Val Ser			5	Ser		-		10	Gly				15
Glu 1 Gly		Leu	Arg	Leu 20	Ser	Cys	Ala	Ala	10 Ser 25	Gly	Phe	Asn	Ile	15 Lys 30
Glu 1 Gly Asp	Ser	Leu	Arg	Leu 20 His 35	Ser	Cys	Ala	Ala	Ser 25 Ala 40	Gly Pro	Phe	Asn	Ile	Lys 30 Leu 45

# RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206A

DATE: 06/14/94 TIME: 17:06:13

				65					70				100	75
Lys	Asn	Thr	Ala	Tyr 80	Leu	Gln	Met	Asn	Ser 85	Leu	Arg	Ala	Glu	Asp 90
Thr	Ala	Val	Tyr	Tyr 95	Сув	Ser	Arg	Trp	Gly 100		Asp	Gly	Phe	Tyr 105
Ala	Met	Asp	Val	Trp 110	Gly	Gln	Gly	Thr	Leu 115	Val	Thr	Val	Ser	Ser 120
2)	INFO	RMAT	ION	FOR :	SEQ :	ID N	0:3:							
(	(	EQUE A) L B) T D) T	ENGT	H: 10	09 an	mino cid		ds						
(x	i) s	EQUE	NCE I	DESC	RIPT	ION:	SEQ	ID 1	NO:3	;				
Asp 1	Ile	Gln	Met	Thr 5	Gln	Ser	Pro	Ser	Ser 10	Leu	Ser	Ala	Ser	Val
Gly	Asp	Arg	Val	Thr 20	Ile	Thr	Cys	Arg	Ala 25	Ser	Gln	Asp	Val	Ser 30
Ser	Tyr	Leu	Ala	Trp 35	Tyr	Gln	Gln	Lys	Pro 40	Gly	Lys	Ala	Pro	Lys 45
Leu	Leu	Ile	Tyr	Ala 50	Ala	Ser	Ser	Leu	Glu 55	Ser	Gly	Val	Pro	Ser 60
Arg	Phe	Ser	Gly	Ser 65		Ser	Gly	Thr	Asp 70	Phe	Thr	Leu	Thr	Ile 75
Ser	Ser	Leu	Gln	Pro 80	Glu	Asp	Phe	Ala	Thr 85	Tyr	Tyr	Cys	Gln	Gln 90
Tyr	Asn	Ser	Leu	Pro 95		Thr	Phe	Gly	Gln 100	Gly	Thr	Lys	Val	Glu 105
Ile	Lys	Arg	Thr 109											
(2)	INFO	RMAT	ION	FOR	SEQ	ID N	0:4:							
(	(	EQUE A) L B) T D) T	ENGT:	H: 1 ami	20 a	mino cid	aci	ds						
(2	i) s	EQUE	NCE	DESC	RIPT	ION.	SEO	ID	NO : 4					

# RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206A

DATE: 06/14/94 TIME: 17:06:26

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1					5					10					15
Gly	S	er	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser
					20		-			25					30
	m	***	77-	Mob	Cox	Marin	17-1	7/ ><~	01-	77-	Duc	01	Tara	d1	T
sp	1	A.T.	ALA	Mer	35	rrb	val	Arg	GIII	40	PIO	GIY	пув	Gly	45
Glu	T	rp	Val	Ala	11.000	Ile	Ser	Glu	Asn	Mark Street	Gly	Tyr	Thr	Arg	31.000
					50					55					60
Ala	A	sp	Ser	Val	Lys	Gly	Arg	Phe	Thr	Ile	Ser	Ala	Asp	Thr	Ser
					65					70					75
are	Δ.	an	Thr	Δla	Tier	T.011	Gln	Met	Acn	Car	T.011	Ara	212	Glu	Acn
Lys		344		1124	80	нец	0411	rice	ri511	85	LCL	ura	ALG	Olu	90
										6.4				34.3	
Thr	· A.	la	Val	Tyr	Tyr 95	Cys	Ser	Arg	Trp	Gly 100	Gly	Asp	Gly	Phe	Tyr 105
					23					100					105
Ala	Me	et	Asp	Val	Trp	Gly	Gln	Gly	Thr	Leu	Val	Thr	Val	Ser	
					110					115					120
	IN	SE	EQUE	NCE (	CHAR	SEQ :	RIST	ics:	i a						
		SE (Z	EQUE A) Li B) T	NCE ( ENGTI YPE:	CHAR H: 1		RIST: mino cid	ics:	is						
(	i)	SE (F (E	EQUE A) Li B) T	NCE ( ENGTI YPE:	CHAR H: 1 amin OGY:	ACTE	RIST: mino cid ear	ICS: acid		NO:5	:				
(x	i)	SE (F (E (I	EQUE A) Li B) TO D) TO	NCE ( ENGTI YPE: OPOLO	CHAR H: 1 amin DGY:	ACTE 09 and no ac line	RIST: mino cid ear	ICS: acid	ID 1			Ser	Thr	Ser	Val
(x	i) :i)	SE (F (E (I	EQUE A) Li B) TO D) TO	NCE ( ENGTI YPE: OPOLO	CHAR H: 1 amin DGY:	ACTE 09 and no ac line	RIST: mino cid ear	ICS: acid	ID 1			Ser	Thr	Ser	Val
(x Asp	i) :i)	SH (F (I SH	EQUED  A) Li  B) T  C) T  C  EQUED  Val	NCE ( ENGTI YPE: OPOLO NCE I	CHARMAN Amin DGY:  DESCRIPTION Thr  5	ACTE 09 and no ac line RIPT	RIST: mino cid ear ION:	ICS: acid SEQ His	ID I	Phe 10	Met				15
(x Asp	i) :i)	SH (F (I SH	EQUED  A) Li  B) T  C) T  C  EQUED  Val	NCE ( ENGTI YPE: OPOLO NCE I	CHARMAN Amin DGY:  DESCRIPTION Thr  5	ACTE 09 and no ac line RIPT	RIST: mino cid ear ION:	ICS: acid SEQ His	ID I	Phe 10	Met			Ser Val	15
(x Asp 1 Gly	i) :i) · I:	SF (F) (F) (F) (F) (F) (F) (F) (F) (F) (F	EQUED A) Li B) TO EQUED Val	NCE ( ENGTH YPE: OPOLO NCE H Met	CHAR H: 10 amin DGY: DESCI Thr 5 Ser 20	ACTEN 09 an no ao line RIPT: Gln	RIST: mino cid ear ION: Ser	SEQ His	ID 1	Phe 10 Ala 25	Met	Gln	Asp	Val	15 Asn 30
(x (x 1 Gly	i) :i) · I:	SF (F) (F) (F) (F) (F) (F) (F) (F) (F) (F	EQUED A) Li B) TO EQUED Val	NCE ( ENGTH YPE: OPOLO NCE H Met	CHARACHER 10 amin DGY: DESCRIPTION 5 Ser 20 Trp	ACTEN 09 an no ao line RIPT: Gln	RIST: mino cid ear ION: Ser	SEQ His	ID 1	Phe 10 Ala 25 Pro	Met	Gln	Asp		Asn 30 Lys
(x Asp 1 Gly	i) :i) · I:	SF (F) (F) (F) (F) (F) (F) (F) (F) (F) (F	EQUED A) Li B) TO EQUED Val	NCE ( ENGTH YPE: OPOLO NCE H Met	CHAR H: 10 amin DGY: DESCI Thr 5 Ser 20	ACTEN 09 an no ao line RIPT: Gln	RIST: mino cid ear ION: Ser	SEQ His	ID 1	Phe 10 Ala 25	Met	Gln	Asp	Val	Asn 30
(xAsp 1 Gly	i) ii) ii) A:	SH (F)	EQUED A) Li B) TO C) TO EQUED Val Arg Val	NCE (ENGTHENDED) NCE I Met Val	CHARACH: 10 amin DGY: DESCION Thr 5 Ser 20 Trp 35	ACTED 09 and no according RIPT: Gln Ile	RIST: mino cid ear ION: Ser Thr	SEQ His Cys	ID I	Phe 10 Ala 25 Pro 40	Met Ser Gly	Gln	Asp	Val Pro	Asn 30 Lys 45
(xAsp 1 Gly	i) ii) ii) A:	SH (F)	EQUED A) Li B) TO C) TO EQUED Val Arg Val	NCE (ENGTHENDED) NCE I Met Val	CHARACH: 10 amin DGY: DESCION Thr 5 Ser 20 Trp 35	ACTED 09 and no according RIPT: Gln Ile	RIST: mino cid ear ION: Ser Thr	SEQ His Cys	ID I	Phe 10 Ala 25 Pro 40	Met Ser Gly	Gln	Asp	Val Pro	Asn 30 Lys 45
(xAsp 1Gly Thr	i)	SF (F	EQUED A) Li B) TO C) TO CQUED Val Arg Val	NCE (ENGTHENDED) NCE I Met Val Ala	CHARACH: 10 amin DGY: DESC! Thr 5 Ser 20 Trp 35 Ser 50	ACTED 09 and and aline RIPT: Gln Ile Tyr	RIST: mino cid ear HON: Ser Thr Gln Ser	SEQ His Cys	ID I	Phe 10 Ala 25 Pro 40 Tyr 55	Met Ser Gly Thr	Gln His	Asp Ser Val	Val Pro	15 Asn 30 Lys 45 Asp 60
(xAsp 1 Gly Thr	i)	SF (F	EQUED A) Li B) TO C) TO CQUED Val Arg Val	NCE (ENGTHENDED) NCE I Met Val Ala	CHARACH: 10 amin DGY: DESC! Thr 5 Ser 20 Trp 35 Ser 50	ACTED 09 and and aline RIPT: Gln Ile Tyr	RIST: mino cid ear HON: Ser Thr Gln Ser	SEQ His Cys	ID I	Phe 10 Ala 25 Pro 40 Tyr 55	Met Ser Gly Thr	Gln His	Asp Ser Val	Val Pro	Asn 30 Lys 45 Asp 60
(x Asp 1 Gly Thr	i) ii) iii) iii) A: A: (P)	SF (F) (F) (F) (F) (F) (F) (F) (F) (F) (F	EQUED A) Li B) TO C) TO C) TO Val Arg Val Ile Thr	NCE (ENGTHENDED) NCE I Met Val Ala Tyr	CHARACHER 1 amin DGY: DESCION Thr 5 Ser 20 Trp 35 Ser 50 Asn 65	ACTED 19 ar no ac line RIPT: Gln Ile Tyr Ala Arg	RIST: mino cid ear HON: Ser Thr Gln ser Ser	SEQ His Cys Gln Phe	ID ILys Lys Lys Arg	Phe 10 Ala 25 Pro 40 Tyr 55 Asp 70	Met Ser Gly Thr	Gln His Gly Thr	Asp Ser Val	Val Pro Pro Thr	15 Asn 30 Lys 45 Asp 60 Ile 75
(xAspp 1 Gly Thr	i) ii) iii) iii) A: A: (P)	SF (F) (F) (F) (F) (F) (F) (F) (F) (F) (F	EQUED A) Li B) TO C) TO C) TO Val Arg Val Ile Thr	NCE (ENGTHENDED) NCE I Met Val Ala Tyr	CHARACHER 1 amin DGY: DESCION Thr 5 Ser 20 Trp 35 Ser 50 Asn 65	ACTED 19 ar no ac line RIPT: Gln Ile Tyr Ala Arg	RIST: mino cid ear HON: Ser Thr Gln ser Ser	SEQ His Cys Gln Phe	ID ILys Lys Lys Arg	Phe 10 Ala 25 Pro 40 Tyr 55 Asp 70	Met Ser Gly Thr	Gln His Gly Thr	Asp Ser Val	Val Pro	15 Asn 30 Lys 45 Asp 60 Ile 75
(x Asp 1 Gly Thr	i) ii) iii) iii) A: A: (P)	SF (F) (F) (F) (F) (F) (F) (F) (F) (F) (F	EQUED A) Li B) TO C) TO C) TO Val Arg Val Ile Thr	NCE (ENGTHENDED) NCE I Met Val Ala Tyr	CHARLES CHARLE	ACTED 19 ar no ac line RIPT: Gln Ile Tyr Ala Arg	RIST: mino cid ear HON: Ser Thr Gln ser Ser	SEQ His Cys Gln Phe	ID ILys Lys Lys Arg	Phe 10 Ala 25 Pro 40 Tyr 55 Asp 70 Val	Met Ser Gly Thr	Gln His Gly Thr	Asp Ser Val	Val Pro Pro Thr	Asn 30 Lys 45 Asp 60 Ile 75

### RAW SEQUENCE LISTING PATENT APPLICATION US/08/146,206A

DATE: 06/14/94 TIME: 17:06:39

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206 His Tyr Thr Thr Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu
207
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208
209 Ile Lys Arg Ala
210
                  109
211
     (2) INFORMATION FOR SEQ ID NO:6:
212
213
214
        (i) SEQUENCE CHARACTERISTICS:
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             (A) LENGTH: 120 amino acids
             (B) TYPE: amino acid
216
217
            (D) TOPOLOGY: linear
218
      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:
219
220
221
    Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
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223
224
      Ala Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys
225
226
227
    Asp Thr Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
228
                       35
229
     Glu Trp Ile Gly Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr
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231
232
233
      Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser
234
                       65
235
     Ser Asn Thr Ala Tyr Leu Gln Val Ser Arg Leu Thr Ser Glu Asp
236
237
                       80
238
239
      Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
                       95
240
241
242
     Ala Met Asp Tyr Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
243
                      110
                                           115
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245
246
      (2) INFORMATION FOR SEQ ID NO:7:
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248
         (i) SEQUENCE CHARACTERISTICS:
249
             (A) LENGTH: 27 bases
             (B) TYPE: nucleic acid
250
             (C) STRANDEDNESS: single
251
252
            (D) TOPOLOGY: linear
253
      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:
254
255
256
    TCCGATATCC AGCTGACCCA GTCTCCA 27
257
258
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# SEQUENCE VERIFICATION REPORT PATENT APPLICATION US/08/146,206A

DATE: 06/14/94 TIME: 17:06:53

INPUT SET: S8112.raw

Line Error

Original Text

27

Wrong application Serial Number

(A) APPLICATION NUMBER: 08/146206

H9 11/



#### PATENT DOCKET 709P1

#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

PAUL J. CARTER et al.

Serial No. 08/146,206

Filed: 17 November 1993

For: METHOD FOR MAKING HUMANIZED)

**ANTIBODIES** 

HIL 1 1 1994

CARCLIE 1800

Group Art Unit: 1804

Examiner: Unassigned

CERTIFICATE OF MAILING

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June 24 1994

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RECENT

JUL 06 1994

#### REQUEST FOR A CORRECTED FILING RECEIPT

Honorable Commissioner of Patents and Trademarks Washington, D.C. 20231

APPLICATION TO 162

Sir:

Attached is a copy of the Official Filing Receipt received from the PTO in the above application for which issuance of a corrected filing receipt is respectfully requested. Please make the correction as follows: Under "CONTINUING DATA..." please add --WHICH IS A CIP OF 07/715,272 06/14/91--; and please correct the title to read --METHOD FOR MAKING HUMANIZED ANTIBODIES--.

The correction is not due to any error by applicant and no fee is believed to be due. However, in the event that the Patent Office determines that fees are due in connection with the filing of this document, we hereby authorize the Commissioner to charge such fees to our Deposit Account No. 07-0630.

A copy of a document pursuant to 37 C.F.R. § 10.9(b) is attached as proof of the authorization of the undersigned to prosecute the above-mentioned application. The original of this document is on file in the Office of Enrollment and Discipline.

Date

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GENENTECH, INC.

Wendy M. Lee



UNITED STATES DEPARTMENT OF COMMERCE
Pateint and Trademark Office
ASSISTANT SCRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

### LIMITED RECOGNITION UNDER 37 CFR § 10.9(b)

Wendy M. Lee is hereby given limited recognition under 37 CFR § 10.9(b) as an employee of Genentech, Inc. to prepare and prosecute patent applications and to represent patent applicants wherein Genentech, Inc. is the assignee of record of the entire interest. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to December 9, 1994: (i) Wendy M. Lee ceases to iawfully reside in the United States, (ii) Wendy M. Lee's employment with Genentech, Inc. ceases or is terminated, or (iii) Wendy M. Lee ceases to remain or reside in the United States on an H-1 visa.

This document constitutes proof of such recognition. The original of this document is on file in the Office of Enrollment and Discipline of the U.S. Patent and Trademark Office.

Expires: December 9, 1994

Cameron Weifferbach, Director
Office of Enrollment and Discipline