#.3 (CP 10/7 OFFICIAL PLEASE ENTER P.N. 10-7-9

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1816 Examiner: P. Nolan CERTIFICATE OF HAND DELIVERY I hereby certify that this correspondence is being delivered to Receptionist, Group 1800 of the United States Patent and Trademark Office, Washington, D.C. 20231 on October 7, 1997 R. H. Mitchell Printed Name R. H. Mitchell

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicants submit herewith patents, publications or other information (attached hereto and listed on the attached Form PTO-1449) of which they are aware, which they believe may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR §1.56.

This Information Disclosure Statement:

(a) [ ] accompanies the new patent application submitted herewith. 37 CFR §1.97(a).

(b) [ ] is filed within three months after the filing date of the application or within three months after the date of entry of the national stage of a PCT application as set forth in 37 CFR§1.491.

(c) [ ] as far as is known to the undersigned, is filed before the mailing date of a first Office action on the merits.

(d) [X] is filed after the first Office Action and more than three months after the application's filing date or PCT national stage date of entry filing but, as far as is known to the undersigned, prior to the mailing date of either a final rejection or a notice of allowance, whichever occurs first, and is accompanied by either the fee ($230) set forth in 37 CFR §1.17(p) **or** a certification as specified in 37 CFR §1.97(e), as checked below. Should any fee be due, the U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $220.00 to cover the cost of this Information Disclosure Statement. Any deficiency or overpayment should be charged or credited to this deposit account. **A duplicate of this sheet is enclosed.**

(e) [ ] is filed after the mailing date of either a final rejection or a notice of allowance, whichever occurred first, and is accompanied by the fee ($130) set forth in 37 CFR §1.17(i)(1) **and** a certification as specified in 37 CFR §1.97(e), as checked below. **This document is to be considered as a petition requesting consideration of the information disclosure statement**. The U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $130.00 to cover the cost of this Information Disclosure Statement. Any deficiency or overpayment should be charged or credited to this deposit account. **A duplicate of this sheet is enclosed.**

[If either of boxes (d) or (e) is checked above, the following "certification" under 37 CFR §1.97(e) may need to be completed.] The undersigned certifies that:

[ ] Each item of information contained in the information disclosure statement was cited in a communication mailed from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

[ ] No item of information contained in this information disclosure statement was cited in a communication mailed from a foreign patent office in a counterpart foreign application or, to the knowledge of the undersigned after making reasonable inquiry, was known to any individual designated in 37 CFR §1.56(c) more than three months prior to the filing of this information disclosure statement.

A list of the patent(s) or publication(s) is set forth on the attached Form PTO-1449 (Modified).

A copy of the items on PTO-1449 is supplied herewith:

[x] each [ ] none [ ] only those listed below:

Those patent(s) or publication(s) which are marked with an asterisk (*) in the attached PTO-1449 form are not supplied because they were previously cited by or submitted to the Office in a prior application Serial No. ___, filed _____and relied upon in this application for an earlier filing date under 35 USC §120.

A concise explanation of relevance of the items listed on PTO-1449 is:

[x] not given

[ ] given for each listed item

[ ] given for only non-English language listed item(s) [Required]

[ ] in the form of an English language copy of a Search Report from a foreign patent office, issued in a counterpart application, which refers to the relevant portions of the references.

The Examiner is reminded that a "concise explanation of the relevance" of the submitted prior art "may be nothing more than identification of the particular figure or paragraph of the patent or publication which has some relation to the claimed invention," MPEP §609.

While the information and references disclosed in this Information Disclosure Statement may be "material" pursuant to 37 CFR §1.56, it is not intended to constitute an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

In accordance with 37 CFR §1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR §1.56(a) exists. It is submitted that the Information Disclosure Statement is in compliance with 37 CFR §1.98 and MPEP §609 and the Examiner is respectfully requested to consider the listed references.

Respectfully submitted,

GENENTECH, INC.

Date: October 6, 1997

By: _____

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Duplicate of DS received 04/17/95

Sheet 1 of 4

FORM PTO-1449 — U.S. Dept. of Commerce, Patent and Trademark Office

Atty Docket No.	Serial No.
P0709P1	08/146,206
Applicant: Carter and Presta	
Filing Date: 17 Nov 1993	Group: ~~1806~~ 1816

LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

U.S. PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Name	Class	Subclass	Filing Date
PN	1	4,816,567	~~28.03.89~~ 3-28-89	Cabilly et al.			

FOREIGN PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
PN	2	0 239 400	~~9-30-87~~ ~~30.09.87~~	EPO				
	3	0 620 276	~~10-19-94~~ ~~19.10.94~~	EPO				
	4	WO 89/01783	~~3-9-89~~ ~~09.03.89~~	PCT				
	5	WO 89/06692	~~7-25-89~~ ~~27.07.89~~	PCT				
	6	WO 90/07861	~~7-26-90~~ ~~26.07.90~~	PCT				
	7	WO 91/09967	~~7-11-91~~ ~~11.07.91~~	PCT				
	8	WO 92/22653	~~12-23-92~~ ~~23.12.92~~	PCT				
PN	9	WO 93/02191	~~2-4-93~~ ~~04.02.93~~	PCT				

MAILED DEC 26 1995

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Examiner: Patrick Nolan — Date Considered: 12/16/96

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

M. T. DAVIS 12/05-/01

USCOMM-DC 80-398.

FORM PTO-1449

U.S. Dept. of Commerce
Patent and Trademark Office

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Atty Docket No.	Serial No.
P0709P1	08/146,206
Applicant: Carter and Presta	
Filing Date: 17 Nov 1993	Group: 1806

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Examiner	Date Considered
Adams	10/25/95

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

M.T. DAVIS 12/05/01

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LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

Atty Docket No.	Serial No.
P0709P1	08/146,206
Applicant: Carter and Presta	MAILED
Filing Date: 17 Nov 1993	Group: ~~1806~~ 1818 DEC 26 1995

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Examiner: Patrick J. Nolan | Date Considered: 12/16/96

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

USCOMM-DC 80-398.

FORM PTO-1449

U.S. Dept. of Commerce
Patent and Trademark Office

Atty Docket No.	Serial No.
P0709P1	08/146,206
Applicant: Carter and Presta	
Filing Date: 17 Nov 1993	Group: 1806

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Examiner: Adams

Date Considered: 10/25/95

*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

M. T. DAVIS 12/05/01

USCOMM-DC 80-398.

Patent Docket P0709P1 #32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1816 Examiner: P. Nolan **CERTIFICATE OF HAND DELIVERY** I hereby certify that this correspondence is being delivered to Receptionist, Group 1800 of the United States Patent and Trademark Office, Washington, D.C. 20231 on October 7, 1997 R. H. Mitchell Printed Name: R. H. Mitchell

AMENDMENT TRANSMITTAL

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Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated as shown below.

	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Rate	Additional Fees
Total	35	-	31	4	x 88 =	$88.00
Independent	8	-	10	0	x 80 =	$0.00
__ First Presentation of Multiple Dependent Claims					+ 260 =	
					Total Fee Calculation	$88.00

_____
X
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No additional fee is required.
The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $88.00. **A duplicate copy of this transmittal is enclosed.**
Petition for Extension of Time is enclosed.

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 07-0630. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,
GENENTECH, INC.

Date: October 6, 1997

By: _____
Wendy M. Lee
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#32

Patent Docket P0709P1

10/7/97

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: 1816 Examiner: P. Nolan **CERTIFICATE OF HAND DELIVERY** I hereby certify that this correspondence is being delivered to Receptionist, Group 1800 of the United States Patent and Trademark Office, Washington, D.C. 20231 on October ___, 1997 Printed Name:

SUPPLEMENTAL AMENDMENT UNDER 37 C.F.R. §1.111

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicants respectfully request reconsideration of the above-identified application in view of the following amendments and remarks.

IN THE SPECIFICATION:

On page 8, lines 25-27 and page 15, lines 23-24, please replace the sequence in its entirety with the following sequence --

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVRQAPGKGLEWVAVISENGSDTYYADS
VKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARDRGGAVSYFDVWGQGTLVTVSS--

On page 9, line 30, please replace "huκI" with --huIII--.

IN THE CLAIMS:

10. (Three times amended) A humanized antibody variable domain having a non-human Complementarity Determining Region (CDR) incorporated into a human antibody variable domain, wherein an amino acid residue has been substituted for the human amino acid residue at a site selected from the group consisting of:

4L, [36L], 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, [70L,] 73L, 85L, [87L,] 98L, 2H,

4H, [24H,] 36H, [37H,] 39H, 43H, 45H, [49H, 68H,] 69H, 70H, [73H,] 74H, 75H, 76H, 78H and 92H.

Please add the following claims:

--39. A humanized heavy chain variable domain comprising FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, wherein FR1-4 comprise the four framework regions of a consensus human variable domain of a human heavy chain immunoglobulin subgroup and CDR1-3 comprise the three complementarity determining regions (CDRs) of a nonhuman import antibody, and further wherein consensus human framework region (FR) residues have been replaced by nonhuman import residues where the FR residue (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) comprises a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L - V_H interface.

40. The humanized heavy chain variable domain of claim 39 wherein the human heavy chain immunoglobulin subgroup is V_H subgroup III.

41. The humanized heavy chain variable domain of claim 40 wherein:
FR1 of the consensus human variable domain comprises the amino acid sequence:
EVQLVESGGGLVQPGGSLRLSCAAS (SEQ ID NO:27);
FR2 of the consensus human variable domain comprises the amino acid sequence:
WVRQAPGKGLEWVA (SEQ ID NO:28);
FR3 of the consensus human variable domain comprises the amino acid sequence:
RFTISRDDSKNTLYLQMNSLRAEDTAVYYCAR (SEQ ID NO:29); and
FR4 of the consensus human variable domain comprises the amino acid sequence:
WGQGTLVTVSS (SEQ ID NO:30).

42. The humanized antibody of claim 22 which lacks immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient.--

REMARKS

A. Amendments

The undersigned confirms having met with Examiners Nolan and Eisenschenk in the interview 7/23/97 and takes this opportunity to thank the Examiners for the courtesies extended in the interview. Claims 39-41 have been added herein which use language as proposed by Examiner Nolan in the interview. Independent claim 39 is similar to a combination of presently pending claims 22 and 23. Basis for the language "FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, wherein FR1-4 comprise the four framework regions of a consensus human variable domain of a human heavy chain immunoglobulin subgroup and CDR1-3 comprise the three complementarity determining regions (CDRs) of a nonhuman import antibody" in claim 39 is found on page 1, lines 28-30 and page 25, lines 28-29, for example. Claim 40 finds specification basis on at least page 15, line 18. Claim 41 finds specification support in Figure 1B with respect to the framework regions of the HUV_HIII consensus sequence therein. Claim 42 has also been added and finds specification basis on at least page 60, lines 25-32 and page 70, lines 6-8. With respect to the amendments to the specification, the sequence on pages 8 and 15 has been corrected (see Section B of this amendment) and the typographical error with respect to the Fig. 5 sequence has been corrected herein. In that the amendments do not introduce new matter, their entry is respectfully requested.

B. Substitute Sequence Listing

A further substitute sequence listing is submitted herewith. Applicants have found that SEQ ID NO:4 in the previous sequence listings did not correspond to the HUV_HIII consensus sequence of Fig. 1B (see page 9, lines 1-2) and hence SEQ ID NO:4 in the attached substitute sequence listing has been corrected accordingly. Furthermore, SEQ ID NO:4 is hereby corrected on pages 8 and 15 of the application. In addition, separate sequence identifiers (SEQ ID NO's 27-30) have been given to the FR1-4 sequences in claim 41 added herein. In accordance with 37 C.F.R. §§1.821(f) and (g), the undersigned hereby states that the content of the paper and the computer readable sequence listings is the same. I further state that this submission includes no new matter.

C. Antibodies humanized according to the teachings of the instant application

As discussed in the interview, the consensus human variable domain of the instant claims has been used to humanize a number of antibodies, including:

1. *Anti-p185^{HER2} antibodies*. See Example 1 of the application, including Table 3 on page 72 (which describes humanized variants huMAb4D5-1-8) and page 65, lines 1-4 (concerning the use of a consensus human variable domain as recited in the claims herein). huMAb4D5-6 and huMAb4D5-8 had binding affinities which were suprisingly *superior* to that of the nonhuman antibody (muMAb4D5); see second to last column of Table 3. Repeated administration of the humanized anti-p185^{HER2} antibody huMAb4D5-8 has not lead to an immunogenic response in cancer patients treated therewith. See abstract of Baselga *et al.*, *J. Clin. Oncol.* 14(3):737-744 (1996), of record.

2. *Anti-CD3 antibodies*. See Example 3 on pages 79-88 of the application; and Fig. 5 as well as page 9, lines 25-31 concerning the use of a consensus human variable domain as claimed herein. [Note: In the Fig. 5 V_H consensus sequence (huIII), the last residue of FR2 is S, *i.e.* A→S, and eighth residue of FR3 is N, *i.e.* D→N, because of changes in 1987 to 1991 consensus sequence of Kabat *et al.*; such an equivalent consensus sequence and other changes in consensus sequences that result from the addition of further human antibody sequences to subsequent antibody compilations by Kabat *et al.* are clearly encompassed by the claims herein]. Humanized anti-CD3 variant (v1) was found to enhance the cytotoxic effects of activated human cytotoxic T lymphocytes (CTL) 4-fold against SK-BR-3 tumor cells overexpressing p185^{HER2} (page 81, lines 1-4). Variants of the humanized v1 antibody were made (v6 to v12; see page 82, line 22 and page 84, line 17 through to page 85, line 2 and page 86, lines 17-31), including the most potent variant, v9, which bound Jurkat cells almost as efficiently as the chimeric BsF(ab')$_2$ (page 86, lines 20-22).

3. *Anti-CD18 antibody*. See Example 4 on page 89 of the application and Figs. 6A and 6B with respect to a consensus human variable domain as claimed in the instant application. The binding affinity of the humanized anti-CD18 antibody (pH52-8.0/pH52-9.0; see Figs. 6A and 6B of

the application) was similar to the nonhuman H52 antibody; *i.e.* the humanized antibody has an affinity of 3.9 ± 0.9nM and murine H52 antibody has an affinity of 1.5 ± 0.3nM.

4. *Anti-IgE antibodies.* See Presta *et al. J. Immunol.* 151(5)2623-2632 (1993), of record. Use of a consensus human variable domain of the claims of the instant application is disclosed on page 2624 (column 1, first and third full paragraphs) and in Fig. 1. A number of humanized variants were made (see full paragraph 2 in column 1 on page 2624), including F(ab)-12 with only five framework region substitutions which exhibited binding comparable to the murine antibody (paragraph 2 on page 2631). Multidose administrations of full length anti-IgE variant 12 did not induce a human antihuman antibody response in allergic patients treated therewith (see column 1, last paragraph on page 311 of Shields *et al.*, *Int. Arch. Allergy Immunol.* 107:308-312 (1995), of record).

5. *Anti-CD11a antibodies.* See Werther *et al. J. Immnol.* 157:4986-4995 (1996), of record. Use of a consensus human variable domain as taught and claimed in the instant application is discussed in the first sentence of the Results section on page 4988 and in Fig. 1 (see note in paragraph 2 above, with respect to changes in 1987 to 1991 consensus sequences. Eight humanized variants were made (see Table 1 on page 4989), including HuIgG1 which had an apparent Kd similar to the parent murine antibody and comparable activity to the murine antibody in the cell adhesion and mixed leukocyte reaction (MLR) assays (see paragraph briging columns 1-2 on page 4993).

6. *Anti-VEGF antibodies.* See Presta *et al.* "Humanization of an anti-VEGF monoclonal antibody for the therapy of solid tumors and other disorders" *Cancer Research*, in press, pps. 1-32 of the manuscript, of record. The first paragraph on page 12 refers to the use of a consensus human variable domain as in the claims of this application. With respect to the consensus sequence in the figure on page 32 of the manuscript, see note in paragraph 2 above concerning change in 1987 to 1991 consensus sequences. As shown in Table 1 on page 29, twelve humanized anti-VEGF antibodies were made. The humanized antibody 12-IgG1 acquired the binding properties and biological activities of a high-affinity murine anti-VEGF MAb (see page 16,

last paragraph of this reference).

D. FR substitutions by Queen *et al.*

With respect to pending claim 10 herein reciting substitutions at specified sites in the V_H and V_L framework regions, as discussed at the interview, Queen *et al. PNAS, USA* 86:10029-10033 (1989) and US Patent 5,530,101 (the "101 patent") (cited by the office in the previous office action) use sequential numbering for the variable domain residues of the antibodies described in these references, whereas the claims of the instant application use Kabat numbering for the framework region residues (see page 14, lines 6-22 of the instant application). As requested by the Examiner in the interview, alignments of heavy chain variable domain (Exhibit A) and light chain variable domain (Exhibit B) sequences of the 101 patent (including the sequences for the murine and humanized anti-Tac antibody of Queen *et al.*) with sequential and Kabat residue numbering are attached. "murx" refers to the murine antibody sequence; "hzx" refers to the humanized antibody sequence; "H" is used for heavy chain variable domain sequences and "L" for light chain variable domain sequences. The sites at which the 101 patent refers to FR substitutions are:

Anti-Tac antibody (Figs. 1A and 1B of 101 patent)			
V_H FR substitions		**V_L FR substitutions**	
Sequential numbering	**Kabat numbering**	**Sequential numbering**	**Kabat numbering**
27H	27H	48L	48L
30H	30H	60L	60L
48H	48H	63L	63L
67H	66H		
68H	67H		
93H	89H		
95H	91H		
98H	94H		

107H	103H		
108H	104H		
109H	105H		
111H	107H		
Fd79 antibody (Figs. 2A and 2B of 101 patent)			
V_H FR substitions		**V_L FR substitutions**	
Sequential numbering	**Kabat numbering**	**Sequential numbering**	**Kabat numbering**
82H	81H	9L	9L
97H	93H	45L	41L
112H	103H	46L	42L
		53L	49L
		81L	77L
		83L	79L
Fd138-80 antibody (Figs. 3A and 3B of 101 patent)			
V_H FR substitions		**V_L FR substitutions**	
Sequential numbering	**Kabat numbering**	**Sequential numbering**	**Kabat numbering**
27H	27H	36L	36L
30H	30H	48L	48L
37H	37H	63L	63L
48H	48H	87L	87L
67H	66H		
68H	67H		
93H	89H		
98H	94H		

111H	103H		
112H	104H		
113H	105H		
115H	107H		
M195 antibody (Figs. 4A and 4B of the 101 patent)			
V_H FR substitions		**V_L FR substitutions**	
Sequential numbering	**Kabat numbering**	**Sequential numbering**	**Kabat numbering**
27H	27H	10L	10L
30H	30H	40L	36L
48H	48H	52L	48L
67H	66H	67L	63L
68H	67H	74L	70L
93H	89H	110L	106L
95H	91H		
98H	94H		
106H	103H		
107H	104H		
108H	105H		
110H	107H		
mik-β1 antibody (Figs. 5A and 5B of the 101 patent)			
V_H FR substitions		**V_L FR substitutions**	
Sequential numbering	**Kabat numbering**	**Sequential numbering**	**Kabat numbering**
1H	1H	13L	13L
29H	29H	41L	42L

30H	30H	70L	71L
49H	49H		
72H	72H		
73H	73H		
84H	82bH		
89H	86H		
90H	87H		
CMV5 antibody (Figs. 6A and 6B of the 101 patent)			
V_H FR substitions		**V_L FR substitutions**	
Sequential numbering	**Kabat numbering**	**Sequential numbering**	**Kabat numbering**
5H	5H	49L	49L
24H	24H		
27H	27H		
28H	28H		
30H	30H		
69H	68H		
80H	79H		
97H	93H		
AF2 antibody (Figs. 44A and 44B of the 101 patent)			
V_H FR substitions		**V_L FR substitutions**	
Sequential numbering	**Kabat numbering**	**Sequential numbering**	**Kabat numbering**
27H	27H	48L	48L
28H	28H	63L	63L
30H	30H	70L	70L

93H	89H		
95H	91H		
98H	94H		
107H	103H		
108H	104H		
109H	105H		
111H	107H		

Should the Examiner have any comments or questions concerning this amendment, he is invited to call Wendy Lee at (650) 225-1994 concerning these.

Respectfully submitted,
GENENTECH, INC.

Date: October 6, 1997

By: _____
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EXHIBIT A

Alignment of heavy chains from '101 patent

```
sequential 1        10        20        30        40        50
Kabat      1        10        20        30        40        50
           .        .         .         .         .         .
murxTacH   QVQLQQSGAELAKPGASVKWSCKASGYTFTSYRMHWVKQRPGQGLEWIGY
hzxTacH    QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYTMHWVRQAPGQGLEWIGY
EuH       QVQLVQSGAEVKKPGSSVKVSCKASGGTFSRSAIIWVRQAPGQGLEWMGG
murxMikH   QVQLKQSGPGLVQPSQSLSITCTVSGFSVTSYGVHWIRQSPGKGLEWLGV
hzxMikH    EVQLLESGGGLVQPGQSLRLSCAASGFTVTSYGVHWVRQAPGKGLEWVGV
LayH       AVQLLESGGGLVQPGGSLRLSCAASGFTFSASAMSWVRQAPGKGLEWVAW
murxAF2H   QVQLQQPGADLVMPGAPVKLSCLASGYIFTSSWINWVKQRPGRGLEWIGR
hzxAF2H    QVQLVQSGAEVKKPGSSVKVSCKASGYIFTSSWINWVRQAPGQGLEWMGR
murxCMV5H  EVQLQQSGPELVKPGASMKISCKASVYSFTGYTMNWVKQSHGQNLEWIGL
hzxCMV5H   QVQLVQSGAEVKKPGSSVRVSCKASGYSFTGYTMNWVRQAPGKGLEWVGL
murxFd138H QVQLQQSDAELVKPGASVKISCKVSGYTFTDHTIHWMKQRPEQGLEWFGY
hzxFd138H  QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHTIHWMRQAPGQGLEWFGY
murxFd79H  EMILVESGGGLVKPGASLKLSCAASGFTFSNYGLSWVRQTSDRRLEWVAS
hzxFd79H   EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGLSWVRQAPGKGLEWVAS
murxM195H  EVQLQQSGPELVKPGASVKISCKASGYTFTDYNMHWVKQSHGKSLEWIGY
hzxM195H   QVQLVQSGAEVKKPGSSVKVSCKASGYTFTDYNMHWVRQAPGQGLEWIGY

sequential          60        70        80        90
Kabat         a     60        70        80  abc   90
                    .         .         .         .
murxTacH   INPSTGYTEYNQKFKDKATLTADKSSSTAYMQLSSLTFEDSAVYYCARG
hzxTacH    INPSTGYTEYNQKFKDKATITADESTNTAYMELSSLRSEDTAVYYCARG
EuH        IVPMFGPPNYAQKFQGRVTITADESTNTAYMELSSLRSEDTAFYFCAGG
murxMikH   IW-SGGSTDYNAAFISRLTISKDNSKSQVFFKVNSLQPADTAIYYCARA
hzxMikH    IW-SGGSTDYNAAFISRFTISRDNSKNTLYLQMNSLQAEDTAIYYCARA
LayH       KYENGNDKHYADSVNGRFTISRNDSKNTLYLQMNGLQAEVSAIYYCARD
murxAF2H   IDPSDGEVHYNQDFKDKATLTVDKSSSTAYIQLNSLTSEDSAVYYCARG
hzxAF2H    IDPSDGEVHYNQDFKDRVTITADESTNTAYMELSSLRSEDTAVYYCARG
murxCMV5H  INPYNGGTSYNQKFKGKATLYVDKSSNTAYMELLSLTSADSAVYYCTRR
hzxCMV5H   INPYNGGTSYNQKFKGRVTVSLKPSFNQAYMELSSLFSEDTAVYYCTRR
murxFd138H IYPRDGHTRYSEKFKGKATLTADKSASTAYMHLNSLTSEDSAVYFCARG
hzxFd138H  IYPRDGHTRYAEKFKGKATITADESTNTAYMELSSLRSEDTAVYFCARG
murxFd79H  ISRGGGRIYSPDNLKGRFTISREDAKNTLYLQMSSLKSEDTALYYCLRE
hzxFd79H   ISRGGGRIYSPDNLKGRFTISRNDSKNTLYLQMNSLQAEDTALYYCLRE
murxM195H  IYPYNGGTGYNQKFKSKATLTVDNSSSTAYMDVRSLTSEDSAVYYCARG
hzxM195H   IYPYNGGTGYNQKFKSKATITADESTNTAYMELSSLRSEDTAVYYCARG
```

EXHIBIT A
(cont.)

```
sequential                    110
Kabat                  103     110
                        •       •
murxTacH    GGV------FDYWGQGTTLTVSS
hzxTacH     GGV------FDYWGQGTLVTVSS
EuH         YGIYS----PEEYNGGLVTVSS
murxMikH    GDYNYDG--FAYWGQGTLVTVSA
hzxMikH     GDYNYDG--FAYWGQGTLVTVSS
LayH        AGPYVSPTFFAHWGQGTLVTVSS
murxAF2H    FLPW-----FADWGQGTLVTVSA
hzxAF2H     FLPW-----FADWGQGTLVTVSS
murxCMV5H   GFRDYS---MDYWGQGTSVTVSS
hzxCMV5H    GFRDYS---MDYWGQGTSVTVSS
murxFd138H  RDSRERNG-FAYWGQGTLVTVS-
hzxFd138H   RDSRERNG-FAYWGQGTLVTVSS
murxFd79H   GIYYADYGFFDVWGTGTTVIVSS
hzxFd79H    GIYYADYGFFDVWGQGTLVTVSS
murxM195H   RPA------MDYWGQGTSVTVSS
hzxM195H    RPA------MDYWGQGTLVTVSS
```

EXHIBIT B

Alignment of light chains from '101 patent

```
sequential 1        10        20        30              40
Kabat      1        10        20        30             40
           .        .         .         .              .
murxTacL   QIVLTQSPAIMSASPGEKVTITCSASSSIS-----YMHWFQQKPGTSPKL
hzxTacL    DIQMTQSPSTLSASVGDRVTITCSASSSIS-----YMHWYQQKPGKAPKL
EuL        DIQMTQSPSTLSASVGDRVTITCRASQSINT----WLAWYQQKPGKAPKL
murxMikL   QIVLTQSPAIMSASPGEKVTMTCSGSSSVS-----FMYWYQQRPGSSPRL
hzxMikL    DIQMTQSPSSLSASVGDRVTITCSGSSSVS-----FMYWYQQKPGKAPKL
LayL       DIQMTQSPSSLSVSVGDRVTITCQASQNVNA----YLNWYQQKPGLAPKL
murxAF2L   NIVMTQSPKSMYVSIGERVTLSCKASENVDT----YVSWYQQKPEQSPKL
hzxAF2L    DIQMTQSPSTLSASVGDRVTITCKASENVDT----YVSWYQQKPGKAPKL
murxCMV5L  DIVLTQSPATLSVTPGDSVSLSCRASQSISN----NLHWYQQKSHESPRL
hzxCMV5L   EIVLTQSPGTLSLSPGERATLSCRASQSISN----NLHWYQQKPGQAPRL
murxFd138L DIVMTQSHKFMSTSVGDRVSITCKASQDVGS----AVVWHQQKSGQSPKL
hzxFd138L  DIQMTQSPSTLSASVGDRVTITCKASQDVGS----AVVWHQQKPGKAPKL
murxFd79L  DIVLTQSPASLAVSLGQRATISCRASQSVSTSTYNYMHWYQQKPGQPPKL
hzxFd79L   EIVMTQSPATLSVSPGERATLSCRASQSVSTSTYNYMHWYQQKPGQSPRL
murxM195L  DIVLTQSPASLAVSLGQRATISCRASESVDNYGISFMNWFQQKPGQPPKL
hzxM195L   DIQMTQSPSSLSASVGDRVTITCRASESVDNYGISFMNWFQQKPGKAPKL

sequential    50        60        70        80        90
Kabat         50        60        70        80        90
              .         .         .         .         .
murxTacL   WIYTTSNLASGVPARFSGSGSGTSYSLTISRMEAEDAATYYCHQRSTYPL
hzxTacL    LIYTTSNLASGVPARFSGSGSGTEFTLTISSLQPDDFATYYCHQRSTYPL
EuL        LMYKASSLESGVPSRFIGSGSGTEFTLTISSLQPDDFATYYCQQYNSDSK
murxMikL   LIYDTSNLASGVPVRFSGSGSGTSYSLTISRMEAEDAATYYCQQWSTYPL
hzxMikL    LIYDTSNLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSTYPL
LayL       LIYGASTREAGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQYNNWPP
murxAF2L   LIYGASNRYTGVHDRFTGSGSATDFTLTISSVQAEDLADYHCGQSYNYPF
hzxAF2L    LIYGASNRYTGVPSRFSGSGSGTDFTLTISSLQPDDFATYYCGQSYNYPF
murxCMV5L  LIKYASQSISGIPSRFSGSGSGTDFTLSVNGVETEDFGMYFCQQSNSWPH
hzxCMV5L   LIKYASQSISGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQSNSWPH
murxFd138L LIYWASTRHTGVPDRFTGSGSGTDFTLTITNVQSEDLADYFCQQYSIFPL
hzxFd138L  LIYWASTRHTGVPSRFTGSGSGTEFTLTISSLQPDDFATYFCQQYSIFPL
murxFd79L  LIKYASNLESGVPARFSGSGFGTDFTLNIHPVEEEDTVTYYCQHSWEIPY
hzxFd79L   LIKYASNLESGIPARFSGSGSGTEFTLTISRLESEDFAVYYCQHSWEIPY
murxM195L  LIYAASNQGSGVPARFSGSGSGTDFSLNIHPMEEDDTAMYFCQQSKEVPW
hzxM195L   LIYAASNQGSGVPSRFSGSGSGTDFTLNISSLQPDDFATYYCQQSKEVPW
```

EXHIBIT B
(cont.)

```
sequential    100
Kabat         100
               *
murxTacL    TFGSGTKLELK
hzxTacL     TFGQGTKVEVK
EuL         MFGQGTKVEVK
murxMikL    TFGAGTKLELK
hzxMikL     TFGQSTKVEVK
LayL        TFGQGTKVEVK
murxAF2L    TFGSGTKLEIK
hzxAF2L     TFGQGTKVEVK
murxCMV5L   TFGGGTKLEIK
hzxCMV5L    TFGQGTKVEIK
murxFd138L  TFGAGTRLELK
hzxFd138L   TFGQGTKVEVK
murxFd79L   TFGGGTKLEIK
hzxFd79L    TFGQGTRVEIK
murxM195L   TFGGGTKLEIK
hzxM195L    TFGQGTKVEIK
```

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Carter, Paul J.
Presta, Leonard G.

(ii) TITLE OF INVENTION: Method for Making Humanized Antibodies

(iii) NUMBER OF SEQUENCES: 30

(iv) CORRESPONDENCE ADDRESS:
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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: WinPatin (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
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(viii) ATTORNEY/AGENT INFORMATION:
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(B) REGISTRATION NUMBER: 40,378
(C) REFERENCE/DOCKET NUMBER: P0709P1

(ix) TELECOMMUNICATION INFORMATION:
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(B) TELEFAX: 650/952-9881

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(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
 1               5                  10                  15

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
            35                  40                  45
```

```
Leu Leu Ile Tyr Ser Ala Ser Phe Leu Glu Ser Gly Val Pro Ser
                50                  55                  60

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

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                80                  85                  90

His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
                95                 100                 105

Ile Lys Arg Thr
            109
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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

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

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

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

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser
                65                  70                  75

Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala 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 Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
               110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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

```
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser
                20                  25                  30

Ser 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
                50                  55                  60

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

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                80                  85                  90

Tyr Asn Ser Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu
                95                  100                 105

Ile Lys Arg Thr
            109
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

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

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
                20                  25                  30

Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
                35                  40                  45

Glu Trp Val Ala Val Ile Ser Glu Asn Gly Ser Asp Thr Tyr Tyr
                50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser
                65                  70                  75

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

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

Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
               110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids
(B) TYPE: Amino Acid
(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
 1               5                  10                  15

Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn
            20                  25                  30

Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly His Ser Pro Lys
            35                  40                  45

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

Arg Phe Thr Gly Asn Arg Ser Gly Thr Asp Phe Thr Phe Thr Ile
            65                  70                  75

Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
            80                  85                  90

His Tyr Thr Thr Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu
            95                 100                 105

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
 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

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
           110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 27 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

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

TCCGATATCC AGCTGACCCA GTCTCCA 27

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GTTTGATCTC CAGCTTGGTA CCHSCDCCGA A 31

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AGGTSMARCT GCAGSAGTCW GG 22

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TGAGGAGACG GTGACCGTGG TCCCTTGGCC CCAG 34

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu
 1               5                  10                  15

Gly Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Arg
            20                  25                  30

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

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

Lys Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile
65                  70                  75

Ser Asn Leu Glu Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
                80                  85                  90

Gly Asn Thr Leu Pro Trp Thr Phe Ala Gly Gly Thr Lys Leu Glu
            95                  100                 105

Ile Lys
    107
```

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: Amino Acid
(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
 1               5                  10                  15

Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg
            20                  25                  30

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

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

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

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                80                  85                  90

Gly Asn Thr Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu
            95                  100                 105
```

GTAGATAAAT CCTCTAACAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GTAGATAAAT CCAAATCTAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

GTAGATAAAT CCTCTTCTAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 68 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CTTATAAAGG TGTTTCCACC TATAACCAGA AATTCAAGGA TCGTTTCACG 50

ATATCCGTAG ATAAATCC 68

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: Nucleic Acid
(C) STRANDEDNESS: Single
(D) TOPOLOGY: Linear

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

CTATACCTCC CGTCTGCATT CTGGAGTCCC 30

(2) INFORMATION FOR SEQ ID NO:16:

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

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

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

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
            35                  40                  45

Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser
            50                  55                  60

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

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
            80                  85                  90

Tyr Asn Ser Leu Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu
            95                 100                 105

Ile Lys
107
```

(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
 1               5                  10                  15

Ala Ser Met Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr
            20                  25                  30

Gly Tyr Thr Met Asn Trp Val Lys Gln Ser His Gly Lys Asn Leu
            35                  40                  45

Glu Trp Met Gly Leu Ile Asn Pro Tyr Lys Gly Val Ser Thr Tyr
            50                  55                  60

Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Val Asp Lys Ser
            65                  70                  75
```

```
Ser Ser Thr Ala Tyr Met Glu Leu Leu Ser Leu Thr Ser Glu Asp
                80                  85                  90

Ser Ala Val Tyr Tyr Cys Ala Arg Ser Gly Tyr Tyr Gly Asp Ser
                95                 100                 105

Asp Trp Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val Thr Val
               110                 115                 120

Ser Ser
   122
```

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 122 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

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

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

Glu Trp Val Ala 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 Val Asp Lys Ser
            65                  70                  75

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

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

Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val
           110                 115                 120

Ser Ser
   122
```

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 122 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

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

```
Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
                20                  25                  30

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

Glu Trp Val Ser Val Ile Ser Gly Asp Gly Gly Ser Thr Tyr Tyr
                50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser
                65                  70                  75

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

Thr Ala Val Tyr Tyr Cys Ala Arg Gly Arg Val Gly Tyr Ser Leu
                95                  100                 105

Ser Gly Leu Tyr Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val
                110                 115                 120

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 454 amino acids
(B) TYPE: Amino Acid
(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
  1                 5                  10                  15

Ala Ser Val Lys Ile Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr
                20                  25                  30

Glu Tyr Thr Met His Trp Met Lys Gln Ser His Gly Lys Ser Leu
                35                  40                  45

Glu Trp Ile Gly Gly Phe Asn Pro Lys Asn Gly Gly Ser Ser His
                50                  55                  60

Asn Gln Arg Phe Met Asp Lys Ala Thr Leu Ala Val Asp Lys Ser
                65                  70                  75

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

Ser Gly Ile Tyr Tyr Cys Ala Arg Trp Arg Gly Leu Asn Tyr Gly
                95                  100                 105

Phe Asp Val Arg Tyr Phe Asp Val Trp Gly Ala Gly Thr Thr Val
                110                 115                 120

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
                125                 130                 135
```

```
Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
                140                 145                 150

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
            155                 160                 165

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
        170                 175                 180

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
200                 205                 210

His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
215                 220                 225

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
230                 235                 240

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
245                 250                 255

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
260                 265                 270

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
275                 280                 285

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
290                 295                 300

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305                 310                 315

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
320                 325                 330

Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
335                 340                 345

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
350                 355                 360

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
365                 370                 375

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
380                 385                 390

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
395                 400                 405

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
410                 415                 420

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
425                 430                 435
```

```
His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                440                 445                 450

Ser Pro Gly Lys
            454
```

(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 Gly Leu
                20                  25                  30

Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Thr Ser Gly
                35                  40                  45

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
                95                 100                 105

Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Trp Arg Gly
               110                 115                 120

Leu Asn Tyr Gly Phe Asp Val Arg Tyr Phe Asp Val Trp Gly Gln
               125                 130                 135

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser
               140                 145                 150

Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
               155                 160                 165

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
               170                 175                 180

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
               185                 190                 195

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
               200                 205                 210

Val Val Thr Val Thr Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr
               215                 220                 225
```

```
Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr
                230                 235                 240

Val Glu Arg Lys Cys Cys Val Glu Cys Pro Pro Cys Pro Ala Pro
                245                 250                 255

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
                260                 265                 270

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
                275                 280                 285

Val Asp Val Ser His Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr
                290                 295                 300

Val Asp Gly Met Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                305                 310                 315

Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val Leu Thr Val
                320                 325                 330

Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val
                335                 340                 345

Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
                350                 355                 360

Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
                365                 370                 375

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
                380                 385                 390

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
                395                 400                 405

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu
                410                 415                 420

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                425                 430                 435

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
                440                 445                 450

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
                455                 460                 465

Ser Pro Gly Lys
            469
```

(2) INFORMATION FOR SEQ ID NO:24:

(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
 1               5                  10                  15

Gly Asp Arg Val Thr Ile Asn Cys Arg Ala Ser Gln Asp Ile Asn
            20                  25                  30

Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Asn Gly Thr Val Lys
            35                  40                  45

Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser Gly Val Pro Ser
            50                  55                  60

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

Ser Asn Leu Asp Gln Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln
            80                  85                  90

Gly Asn Thr Leu Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu
            95                  100                 105

Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro
            110                 115                 120

Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu
            125                 130                 135

Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
            140                 145                 150

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu
            155                 160                 165

Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
            170                 175                 180

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
            185                 190                 195

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

Arg Gly Glu Cys
            214
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) 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
               110                 115                 120

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

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
               140                 145                 150

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

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
               200                 205                 210

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
```

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 122 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

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

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
```

```
Glu Trp Val Ala Leu Ile Asn Pro Tyr Lys Gly Val Thr Thr Tyr
                50                  55                  60

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Val Asp Lys Ser
                65                  70                  75

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

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

Asp Trp Tyr Phe Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val
               110                 115                 120

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

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

Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser
                20                  25
```

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
 1               5                  10                  14
```

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

```
Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr Leu Tyr Leu
 1               5                  10                  15

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                20                  25                  30
```

Ala Arg
32

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
1 5 10 11

1816 #34

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

ENTERED

SEQUENCE LISTING

(1) General Information:

(i) APPLICANT: Carter, Paul J.
Presta, Leonard G.

(ii) TITLE OF INVENTION: Method for Making Humanized Antibodies

(iii) NUMBER OF SEQUENCES: 26

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genentech, Inc.
(B) STREET: 1 DNA Way
(C) CITY: South San Francisco
(D) STATE: California
(E) COUNTRY: USA
(F) ZIP: 94080

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: 3.5 inch, 1.44 Mb floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: WinPatin (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

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Lee, Wendy M.
(B) REGISTRATION NUMBER: 40,378
(C) REFERENCE/DOCKET NUMBER: P0709P1

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 650/225-1994
(B) TELEFAX: 650/952-9881

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 109 amino acids

(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
 1               5                  10                  15

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
        35                  40                  45

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

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

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
                80                  85                  90

His Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu
            95                  100                 105

Ile Lys Arg Thr
        109
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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

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

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

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

Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser
65                  70                  75
```

```
100   Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
101                    80                  85                  90
102
103   Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
104                    95                 100                 105
105
106   Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
107                   110                 115                 120
108
109   (2) INFORMATION FOR SEQ ID NO:3:
110
111      (i) SEQUENCE CHARACTERISTICS:
112          (A) LENGTH: 109 amino acids
113          (B) TYPE: Amino Acid
114          (D) TOPOLOGY: Linear
115
116     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:
117
118   Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val
119     1               5                  10                  15
120
121   Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Val Ser
122                    20                  25                  30
123
124   Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys
125                    35                  40                  45
126
127   Leu Leu Ile Tyr Ala Ala Ser Ser Leu Glu Ser Gly Val Pro Ser
128                    50                  55                  60
129
130   Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
131                    65                  70                  75
132
133   Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
134                    80                  85                  90
135
136   Tyr Asn Ser Leu Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu
137                    95                 100                 105
138
139   Ile Lys Arg Thr
140                109
141
142   (2) INFORMATION FOR SEQ ID NO:4:
143
144      (i) SEQUENCE CHARACTERISTICS:
145          (A) LENGTH: 120 amino acids
146          (B) TYPE: Amino Acid
147          (D) TOPOLOGY: Linear
148
149     (xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:
150
151   Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly
152     1               5                  10                  15
```

```
153
154   Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser
155                   20                  25                  30
156
157   Asp Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
158                   35                  40                  45
159
160   Glu Trp Val Ala Val Ile Ser Glu Asn Gly Gly Tyr Thr Arg Tyr
161                   50                  55                  60
162
163   Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Ala Asp Thr Ser
164                   65                  70                  75
165
166   Lys Asn Thr Ala Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp
167                   80                  85                  90
168
169   Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
170                   95                 100                 105
171
172   Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
173                  110                 115                 120
174
175  (2) INFORMATION FOR SEQ ID NO:5:
176
177     (i) SEQUENCE CHARACTERISTICS:
178         (A) LENGTH: 109 amino acids
179         (B) TYPE: Amino Acid
180         (D) TOPOLOGY: Linear
181
182      (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:
183
184   Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val
185     1               5                  10                  15
186
187   Gly Asp Arg Val Ser Ile Thr Cys Lys Ala Ser Gln Asp Val Asn
188                   20                  25                  30
189
190   Thr Ala Val Ala Trp Tyr Gln Gln Lys Pro Gly His Ser Pro Lys
191                   35                  40                  45
192
193   Leu Leu Ile Tyr Ser Ala Ser Phe Arg Tyr Thr Gly Val Pro Asp
194                   50                  55                  60
195
196   Arg Phe Thr Gly Asn Arg Ser Gly Thr Asp Phe Thr Phe Thr Ile
197                   65                  70                  75
198
199   Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Gln
200                   80                  85                  90
201
202   His Tyr Thr Thr Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu
203                   95                 100                 105
204
205   Ile Lys Arg Ala
```

206 109

207

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

209

210 (i) SEQUENCE CHARACTERISTICS:
211 (A) LENGTH: 120 amino acids
212 (B) TYPE: Amino Acid
213 (D) TOPOLOGY: Linear

214

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

216

217 Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
218 1 5 10 15
219
220 Ala Ser Leu Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys
221 20 25 30
222
223 Asp Thr Tyr Ile His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu
224 35 40 45
225
226 Glu Trp Ile Gly Arg Ile Tyr Pro Thr Asn Gly Tyr Thr Arg Tyr
227 50 55 60
228
229 Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser
230 65 70 75
231
232 Ser Asn Thr Ala Tyr Leu Gln Val Ser Arg Leu Thr Ser Glu Asp
233 80 85 90
234
235 Thr Ala Val Tyr Tyr Cys Ser Arg Trp Gly Gly Asp Gly Phe Tyr
236 95 100 105
237
238 Ala Met Asp Tyr Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
239 110 115 120
240

241 (2) INFORMATION FOR SEQ ID NO:7:

242

243 (i) SEQUENCE CHARACTERISTICS:
244 (A) LENGTH: 27 base pairs
245 (B) TYPE: Nucleic Acid
246 (C) STRANDEDNESS: Single
247 (D) TOPOLOGY: Linear

248

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

250

251

252 TCCGATATCC AGCTGACCCA GTCTCCA 27

253

254 (2) INFORMATION FOR SEQ ID NO:8:

255

256 (i) SEQUENCE CHARACTERISTICS:
257 (A) LENGTH: 31 base pairs
258 (B) TYPE: Nucleic Acid

SEQUENCE VERIFICATION REPORT
PATENT APPLICATION *US/08/146,206B*

DATE: 10/08/97
TIME: 13:19:59

INPUT SET: S20851.raw

Line	Error	Original Text
27	Wrong application Serial Number	(A) APPLICATION NUMBER: 08/146206

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/146,206	11/17/93	CARTER P	789P1

18M1/1223

JANET E. HASAK
GENENTECH, INC.
460 POINT SAN BRUNO BOULEVARD
SOUTH SAN FRANCISCO CA 94080-4990

EXAMINER	
NOLAN, P	33
ART UNIT	PAPER NUMBER
1816	

DATE MAILED: 12/23/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/146,206	Applicant(s) Carter et al.
	Examiner Patrick J. Nolan	Group Art Unit 1816

☒ Responsive to communication(s) filed on *6-27-97, 9-1-97 and 10-7-97*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-8, 10-12, 15, and 22-42* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8, 10-12, 15, and 22-41* is/are rejected.

☒ Claim(s) *42* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Serial No. 08/146,206

Art Unit 1816

1. Claims 1-8, 10-12, 15 and 22-42 are pending.

Double Patenting

2. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-12, 15 stand 19-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12, 15 and 19 of copending application Serial No. 08/439,004.

Applicant's request these rejection be held in abeyance until the prosecution of the two pending cases are completed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section

371(c) of this title before the invention thereof by the applicant for patent.

5. Claims 1-8, 10-12, 15 and 22-24 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 5,530,101 (82).

Applicant's arguments filed 6-23-97 have been fully considered but are not found persuasive.

6. Applicant argues that the '101 patent does not teach the determination of residues which will disrupt the V_L-V_H interface as part of their method to make a humanized antibody.

However, Applicant's claims are drawn to using <u>one</u> of the following effects recited in claim 1 and 23, part (f), not all three.

7. Applicant argues that the determination of residues being exposed to the CDR region is not the same as the '101 teaching of whether the residue "interacts with a CDR".

Protein chemistry dictates that for an amino acid residue to interact with another amino acid residues it needs to be exposed to it.

8. Applicant argues that since the '101 patent does not specifically teach glycosylation of the residue being a factor for selection it cannot be used as a prior art reference.

The teaching of glycosylation effects on amino acid residues, is of record, as taught by Roitt et al., submitted in the last office action. Roitt is an educational textbook demonstrating concepts well known to those in the art.

9. Applicant argues that claims drawn to specific residue changes have been amended to distinguish the claims from the '101 patent. Applicant has also demonstrated the numbering difference between the '101 patent and the current application.

If applicant wishes to distinguish over the prior art, they <u>may</u> do so by claiming the actual numbering system used in the actual claim.

The following new grounds of rejections are necessitated by the amendments filed 6-27-97, 9-1-97 and 10-7-97.

10. Claims 22-25, 38, and 39 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 5,693,762 (A).

The '762 patent teaches the aligning of heavy chain immunoglobulin regions for the creation of a consensus sequence to be used in making a humanized antibody (column 13, lines 4-26 and claims 7-9 and 20, in particular). The '762 patent also teaches that in selecting which consensus framework sequence to be used, the acceptor immunoglobulin most likely should be as homologous to the donor sequence as possible (i.e. same isotype) (column 13).

The prior art teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 26-36 and 40-41 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent 5,693,762 (A), in view of Kabat et al.

The '762 patent has been discussed supra. The claimed

invention differs from the prior art teachings only by the recitation the Ig gamma isotype sequences used to make a consensus heavy chain framework region.

However, Kabat et al., teach the sequences of all known Ig gamma subtypes.

Therefore it would have been prima facie obvious to one of skill in the art at the time the invention was made to use the teachings of the '762 patent and align all of the known Ig gamma heavy chains for the creation of a consensus sequence with the expectation that said consensus sequence immunoglobulin would have a smaller chance of changing the an amino acid near the CDR's that distorts their conformation, as taught by the '762 patent (column 13).

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

13. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (703) 305-3973. The FAX number for our group, 1816, is (703) 305-7939. Any inquiry of a general nature relating to the status of this application or proceeding should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Patrick J. Nolan, Ph.D.
December 19, 1997

F.C. Eisenschenk
Primary Examiner
December 19, 1997

Notice of References Cited

Application No.	Applicant(s)		
08/146,206	Carter et al.		
Examiner	Group Art Unit	Page 1 of 1	
Patrick J. Nolan	1816		

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A	5,693,762	12-2-97	Queen et al.	530	387.2
B					
C					
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N						
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
U		
V		
W		
X		

TDoi 12/05/01

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: P. Nolan RECEIVED APR 16 1998 CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on April 8, 1998 Nicole Kehoe

NOTICE OF CHANGE OF ADDRESS AND AREA CODE

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Please direct all future communications in connection with the above referenced patent application to:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Please also note the change in area code from 415 to 650 (see below).

Respectfully submitted,
GENENTECH, INC.

Date: April 8, 1998

By: _____
Wendy M. Lee
Reg. No. 40,378

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

GP1644

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: P. Nolan CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on June 23, 1998 Yvonne E. Carter

NOTICE OF APPEAL

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicant hereby appeals to the Board of Appeals and Interferences from the decision dated 23 December 1997, of the Primary Examiner finally rejecting claims 1-8, 10-12, 15, and 22-41 and objecting to claim 42.

The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $310 to cover the fees for this appeal and to charge the deposit account for any further fees in regard to this patent application. **A duplicate copy of this Notice is enclosed for this purpose.**

07/01/1998 SSANDARA 00000105 070630 08146206
01 FC:119 310.00 CH

Respectfully submitted,
GENENTECH, INC.

Date: June 23, 1998

By: _____
Richard B. Love
Reg. No. 34,659

RECEIVED
JUL 6 1998
GROUP 1600

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: P. Nolan CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on June 23, 1998 Yvonne E. Carter

PETITION AND FEE FOR THREE MONTH EXTENSION OF TIME
(37 CFR 1.136(a))

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicant petitions the Commissioner of Patents and Trademarks to extend the time for response to the FINAL OFFICE ACTION dated 23 December 1997 for three month(s) from 23 March 1998 to 23 June 1998. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $950.00 to cover the cost of the extension. Any deficiency or overpayment should be charged or credited to this deposit account. A duplicate of this sheet is enclosed.

07/01/1998 SSAMDAR9 00000105 070630 08146206
02 FC:117 950.00 CH

Respectfully submitted,
GENENTECH, INC.

Date: June 23, 1998

By: _____
Richard B. Love
Reg. No. 34,659

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

#37

In re Application of Paul J. Carter et al.
Serial No.: 08/146,206
Filed On: November 17, 1993
Mailed On: 23 June 1998

Docket No.: P0709P1
By: Richard B. Love
Reg. No.: 34,659

LS

The following has been received in the U.S. Patent Office on the date stamped:

X Petition to Extent Time for Three Months
X Notice of Appeal Transmittal
X Fees $ 1,260.00
X Postcard

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE

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 the date appearing below: (i) Wendy M. Lee ceases to lawfully reside in the United States, (ii) Wendy M. Lee's employment with Genentech, Inc. ceases or is terminated, or (iii) if Wendy M. Lee ceases to remain or reside in the United States on a 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, 1995

Cameron Weiffenbach, Director
Office of Enrollment and Discipline

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: P. Nolan CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on June 23, 1998 Yvonne E. Carter

#28 Sup 8-17-

FORMAL PLEASE ENTER P.N. 8-13-98

PETITION AND FEE FOR THREE MONTH EXTENSION OF TIME
(37 CFR 1.136(a))

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicant petitions the Commissioner of Patents and Trademarks to extend the time for response to the FINAL OFFICE ACTION dated 23 December 1997 for three month(s) from 23 March 1998 to 23 June 1998. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $950.00 to cover the cost of the extension. Any deficiency or overpayment should be charged or credited to this deposit account. A duplicate of this sheet is enclosed.

08/19/1998 DLYONS 00000007 070630 08146206

01 FC:117 950.00 CH
02 FC:119 310.00 CH

Respectfully submitted,

GENENTECH, INC.

Date: June 23, 1998

By: Richard B. Love
Richard B. Love
Reg. No. 34,659

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: P. Nolan CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on June 23, 1998 Yvonne E. Carter

NOTICE OF APPEAL

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicant hereby appeals to the Board of Appeals and Interferences from the decision dated 23 December 1997, of the Primary Examiner finally rejecting claims 1-8, 10-12, 15, and 22-41 and objecting to claim 42.

The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $310 to cover the fees for this appeal and to charge the deposit account for any further fees in regard to this patent application. A duplicate copy of this Notice is enclosed for this purpose.

Respectfully submitted,
GENENTECH, INC.

Date: June 23, 1998

By: _____
Richard B. Love
Reg. No. 34,659

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

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

08/146,206

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKETT NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	37

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) Wendy Lee (3) _____

(2) Patrick Nolan (4) _____

Date of Interview 8-13-98

Type: ☒ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☒ Yes ☐ No. If yes, brief description: Wall street Journal article

Agreement ☐ was reached with respect to some or all of the claims in question. ☒ was not reached.

Claims discussed: Newly Proposed Claims Faxed 8-10-98

Identification of prior art discussed: Green Patent 5,693,762

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Discussed unexpected results to overcome 103 rejections

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☒ 1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

Patrick J. Nolan
Examiner's Signature

Patent Docket P0709P10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: P. Nolan RECEIVED SEP 0 1 1999 GROUP 1800 **CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on August 24, 1996 Wendy M. Lee

AMENDMENT TRANSMITTAL

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an Amendment under 37 C.F.R. §1.129(a) in the above-identified application.

The fee has been calculated as shown below.

	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Rate	Additional Fees
Total	72	-	35	37	x 22 =	$814.00
Independent	7	-	10	0	x 78 =	$0.00
__ First Presentation of Multiple Dependent Claims					+ 250 =	
					Total Fee Calculation	$814.00

X Amendment under 37 C.F.R. §1.129(a) submitted with fee of $750.00 pursuant to 37 C.F.R. §1.17(r)

X The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $1,564.00 pursuant to 37 C.F.R. §1.17(r). **A duplicate copy of this transmittal is enclosed.**

X A Declaration of Steven Shak with Exhibits A-F is enclosed.

X A Supplemental Information Disclosure Statement, PTO-1449 Form, and copies of Refs. 218-224 are enclosed.

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 07-0630. **A duplicate copy of this sheet is enclosed.**

Respectfully submitted,
GENENTECH, INC.

Date: August 24, 1998

By: _____
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Revised (10/13/95)

Claims 08/23/98

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: P. Nolan CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on August 24, 1998 Wendy M. Lee

AMENDMENT UNDER 37 C.F.R. §1.129(a)

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

This paper is being filed in response to the Office Action mailed December 23, 1997. In the Office Action, the Examiner issued a final rejection of claims 1-8, 10-12, 15 and 22-41 and objected to claim 42. Applicants filed a Notice of Appeal on June 23, 1998. Applicants have not yet filed an Appeal Brief. Accordingly, the present response is being submitted under Section 1.129(a) along with the fee set forth in Section 1.17(r). In that August 23, 1998 fell on a Sunday, this amendment is timely filed.

Entry of the following amendment is respectfully requested:

IN THE CLAIMS:

Please cancel claims 1-8, 10-12, 15 and 22-42 without prejudice or disclaimer of the subject matter claimed therein.

Please add the following claims:

--43. (New) A humanized antibody variable domain comprising a non-human Complementarity Determining Region (CDR) incorporated into a human antibody variable domain, and further comprising an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H and 92H, utilizing the numbering system set forth in Kabat.

44. (New) The humanized variable domain of claim 43 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR was obtained.

45. (New) The humanized variable domain of claim 43 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.

46. (New) The humanized variable domain of claim 43 wherein the human antibody variable domain is a consensus human variable domain.

47. (New) The humanized variable domain of claim 43 wherein the residue at site 4L has been substituted.

48. (New) The humanized variable domain of claim 43 wherein the residue at site 38L has been substituted.

49. (New) The humanized variable domain of claim 43 wherein the residue at site 43L has been substituted.

50. (New) The humanized variable domain of claim 43 wherein the

residue at site 44L has been substituted.

51. (New) The humanized variable domain of claim 43 wherein the residue at site 58L has been substituted.

52. (New) The humanized variable domain of claim 43 wherein the residue at site 62L has been substituted.

53. (New) The humanized variable domain of claim 43 wherein the residue at site 65L has been substituted.

54. (New) The humanized variable domain of claim 43 wherein the residue at site 66L has been substituted.

55. (New) The humanized variable domain of claim 43 wherein the residue at site 67L has been substituted.

56. (New) The humanized variable domain of claim 43 wherein the residue at site 68L has been substituted.

57. (New) The humanized variable domain of claim 43 wherein the residue at site 69L has been substituted.

58. (New) The humanized variable domain of claim 43 wherein the residue at site 73L has been substituted.

59. (New) The humanized variable domain of claim 43 wherein the residue at site 85L has been substituted.

60. (New) The humanized variable domain of claim 43 wherein the residue at site 98L has been substituted.

61. (New) The humanized variable domain of claim 43 wherein the

residue at site 2H has been substituted.

62. (New) The humanized variable domain of claim 43 wherein the residue at site 4H has been substituted.

63. (New) The humanized variable domain of claim 43 wherein the residue at site 36H has been substituted.

64. (New) The humanized variable domain of claim 43 wherein the residue at site 39H has been substituted.

65. (New) The humanized variable domain of claim 43 wherein the residue at site 43H has been substituted.

66. (New) The humanized variable domain of claim 43 wherein the residue at site 45H has been substituted.

67. (New) The humanized variable domain of claim 43 wherein the residue at site 69H has been substituted.

68. (New) The humanized variable domain of claim 43 wherein the residue at site 70H has been substituted.

69. (New) The humanized variable domain of claim 43 wherein the residue at site 74H has been substituted.

70. (New) The humanized variable domain of claim 43 wherein the residue at site 92H has been substituted.

71. (New) An antibody comprising the humanized variable domain of claim 43.

72. (New) An antibody which binds p185^{HER2} and comprises a

humanized antibody variable domain comprising a non-human Complementarity Determining Region (CDR) incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

73. (New) The antibody of claim 72 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR was obtained.

74. (New) The antibody of claim 72 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.

75. (New) The antibody of claim 72 wherein the human antibody variable domain is a consensus human variable domain.

76. (New) The antibody of claim 72 wherein the residue at site 4L has been substituted.

77. (New) The antibody of claim 72 wherein the residue at site 38L has been substituted.

78. (New) The antibody of claim 72 wherein the residue at site 43L has been substituted.

79. (New) The antibody of claim 72 wherein the residue at site 44L has been substituted.

80. (New) The antibody of claim 72 wherein the residue at site 46L has been substituted.

39 40
81. (New) The antibody of claim 72 wherein the residue at site 58L has been substituted.

40 50
82. (New) The antibody of claim 72 wherein the residue at site 62L has been substituted.

41 30
83. (New) The antibody of claim 72 wherein the residue at site 65L has been substituted.

42 50
84. (New) The antibody of claim 72 wherein the residue at site 66L has been substituted.

43 30
85. (New) The antibody of claim 72 wherein the residue at site 67L has been substituted.

44 30
86. (New) The antibody of claim 72 wherein the residue at site 68L has been substituted.

45 30
87. (New) The antibody of claim 72 wherein the residue at site 69L has been substituted.

A cont'd

46 30
88. (New) The antibody of claim 72 wherein the residue at site 73L has been substituted.

47 30
89. (New) The antibody of claim 72 wherein the residue at site 85L has been substituted.

48 30
90. (New) The antibody of claim 72 wherein the residue at site 98L has been substituted.

49 30
91. (New) The antibody of claim 72 wherein the residue at site 2H has been substituted.

92. (New) The antibody of claim 72 wherein the residue at site 4H has been substituted.

93. (New) The antibody of claim 72 wherein the residue at site 36H has been substituted.

94. (New) The antibody of claim 72 wherein the residue at site 39H has been substituted.

95. (New) The antibody of claim 72 wherein the residue at site 43H has been substituted.

96. (New) The antibody of claim 72 wherein the residue at site 45H has been substituted.

97. (New) The antibody of claim 72 wherein the residue at site 69H has been substituted.

98. (New) The antibody of claim 72 wherein the residue at site 70H has been substituted.

99. (New) The antibody of claim 72 wherein the residue at site 74H has been substituted.

100. (New) The antibody of claim 72 wherein the residue at site 75H has been substituted.

101. (New) The antibody of claim 72 wherein the residue at site 76H has been substituted.

102. (New) The antibody of claim 72 wherein the residue at site 78H has been substituted.

61 30

103. (New) The antibody of claim 72 wherein the residue at site 92H has been substituted.

104. (New) A humanized antibody variable domain comprising a non-human Complementarity Determining Region (CDR) incorporated into a consensus human variable domain, and further comprising an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

SUB I3

105. (New) An antibody which lacks significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient and comprises (a) non-human Complementarity Determining Region (CDR) incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

SUB I4

+1 cont'd

106. (New) An antibody which lacks significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient and comprises a consensus human variable domain of a human heavy chain immunoglobulin subgroup, wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprising a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) comprises a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by

SUB I5

affecting the proximity or orientation of the V_L and V_H regions with respect to one another.

107. (New) The antibody of claim 106 comprising a non-human FR residue which noncovalently binds antigen directly.

108. (New) The antibody of claim 106 comprising a non-human FR residue which interacts with a CDR.

109. (New) The antibody of claim 106 comprising a non-human FR residue which comprises a glycosylation site which affects the antigen binding or affinity of the antibody.

110. (New) The antibody of claim 106 comprising a non-human FR residue which participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another.

111. (New) A humanized antibody comprising a consensus human variable domain of human V_H subgroup III, wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprising a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) comprises a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another.

112. (New) The humanized antibody of claim 111 which lacks significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient.

113. (New) A humanized variant of a non-human parent antibody which binds an antigen with better affinity than the parent antibody and comprises a consensus human variable domain of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprising a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) comprises a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another.

114. (New) The humanized variant of claim 113 which binds the antigen at least about 3-fold more tightly than the parent antibody.--

REMARKS

The undersigned confirms having met with Examiner Nolan in the personal interview on August 13, 1998 and thanks the Examiner for the courtesies extended in the interview. In the interview, the undersigned pointed out that claim 42 was not rejected, but was objected-to in the above-noted final Office Action. However, the basis for the objection was not elaborated in the body of the Office Action. The Examiner indicated that claim 42 was objected to for depending on a rejected claim (*i.e.* claim 22). Other issues discussed in the interview will be mentioned herein-below where appropriate.

Amendments

The previously pending claims are cancelled herein without prejudice and without disclaimer of the subject matter claimed

therein and without acquiescing in any rejection or objection raised by the Office. Applicants reserve the right to pursue continuing application(s) directed to cancelled claims. The claims herein correspond to those discussed in the interview and are believed to be allowable.

Former claim/specification basis for each of the claims added herein can be found at least as follows:

Claims 43 and 47-70 - claim 10 as amended 10-7-97; and page 6, lines 21-22 for "utilizing the numbering system set forth in Kabat"
Claim 44 - original claim 11
Claim 45 - original claim 12
Claim 46 - language from claim 1
Claim 71 - page 11, lines 3-4
Claims 72 and 76-103 - claim 10 as amended 10-7-97; page 63, line 21 for "antibody which binds $p185^{HER2}$"; and page 6, lines 21-22 for "utilizing the numbering system set forth in Kabat"
Claim 73 - original claim 11
Claim 74 - original claim 12
Claim 75 - language from claim 1
Claim 104 - claim 10 as amended 10-7-97; claim 1 for "consensus human variable domain"; and page 6, lines 21-22 for "utilizing the numbering system set forth in Kabat"
Claim 105 - claims 10 and 42 from the amendment 10-7-97; and page 6, lines 21-22 for "utilizing the numbering system set forth in Kabat"
Claim 106 - combination of claims 22, 23 and 42
Claims 107-110 - claim 23
Claim 111 - combination of claims 22, 23 and 26
Claim 112 - claim 42
Claim 113 - claims 22 and 23; page 71, lines 1-2 and Table 3 on

page 72 showing humanized variants with improved binding affinity compared to the murine parent antibody.
Claim 114 - page 71, lines 1-2

In that the claims do not introduce new matter, their entry is respectfully requested.

Information Disclosure

1. In the above-mentioned interview, the undersigned inquired as to the status of the IDS carried to the PTO September 1997 citing references 100-207. The Examiner indicated he had this IDS and the references and would consider them with respect to the above application. Applicants await receipt of a copy of the initialed PTO-1449 form indicating consideration of the cited art.

2. A further supplemental IDS is submitted herewith. Applicants respectfully request consideration of the art cited in this supplemental IDS with respect to the instant application.

Provisional Double Patenting Rejection

Claims 1-12, 15 and 19-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12, 15 and 19 of copending application Serial No. 08/439,004. This rejection is moot as USSN 08/439,004 is now abandoned.

Section 102(e) - US Patent 5,530,101

Claims 1-8, 10-12, 15 and 22-24 are rejected under 35 USC §102(e) as being anticipated by US Patent 5,530,101 ("the '101 patent")

With respect to claim 10, the Examiner states in item 9 of the Office Action that the claim may be distinguished over the prior art by claiming the actual numbering system used in the actual

claim. In order to expedite prosecution, Applicants have followed the Examiner's suggestion and recite the numbering system of Kabat in independent claims 43, 72, 104 and 105 herein for claim precision.

Further patentable features in these claims and the claims which depend thereon include, without limitation: the target antigen $p185^{HER2}$ in claim 72 (which is not taught in the '101 patent); a consensus human variable domain which, as will be explained below, is not taught or enabled by the '101 patent; and the antibody which lacks significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient (see comments below).

Applicants submit that independent claims 43, 72, 104 and 105 herein as well as the claims which depend thereon are patentable over the cited art.

Reconsideration and withdrawal of the Section 102 rejection is respectfully requested.

Section 102(e) - US Patent 5,693,762

Claims 22-25, 38 and 39 are rejected under 35 USC §102(e) as being anticipated by US Patent 5,693,762 ("the '762 patent").

The Examiner asserts that the '762 patent taught the aligning of heavy chain immunoglobulin regions for the creation of a consensus sequence to be used in making a humanized antibody and that the acceptor immunoglobulin most likely should be as homologous to the donor sequence as possible (*i.e.* same isotype).

Applicants submit that the '762 patent does not anticipate the instant invention.

Importantly, the '762 patent did not in fact teach a consensus human variable domain as the term is used in the present application.

Applicants contend that the phrase "consensus framework from many human antibodies" in line 7 of column 13 in the '762 patent which is cited by the Office, was not intended to refer to a "consensus human variable domain" as in the present application (*i.e.* a sequence representing the most frequently occurring amino acid residues at each location in all immunoglobulins of any particular subclass; see page 14, lines 29-31 of the instant application). Applicants submit that the '762 patent was using the phrase "consensus framework from many human antibodies" synonymously with a framework "from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized". If one reads lines 4-26 in column 13 of the '762 patent and, indeed, the entire patent, it becomes clear that the method for humanizing advocated therein involved selecting an immunoglobulin framework sequence from a single human immunoglobulin which was unusually homologous to the donor immunoglobulin to be humanized and this is what was actually done in the working examples. It is apparent then that the phrase "consensus framework from many human antibodies" was used in the '762 patent as another way of saying "a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized", *i.e.*, a framework from a particular human immunoglobulin which "agrees" with the donor immunoglobulin when the sequences are aligned.

Thus, Applicants submit that the '762 patent did not teach or enable a consensus human variable domain as described in the present application, much less a "consensus human variable domain of a human heavy chain immunoglobulin subgroup." Accordingly,

reconsideration and withdrawal of the rejection is respectfully requested.

As to rejected claim 38, this relates to the method of "veneering" or "resurfacing" an antibody. As discussed in the above-mentioned interview, this approach was not taught in the '762 patent.

Applicants respectfully request reconsideration and withdrawal of the Section 102(e) rejection in view of the above.

Section 103

Claims 26-36 and 40-41 are rejected under 35 USC §103 as being unpatentable over the '762 patent in view of Kabat *et al*.

The Examiner asserts that the claimed invention differs from the prior art teachings only by recitation of Ig gamma isotype sequences used to make a consensus heavy chain framework region. The Examiner cites Kabat as teaching the sequences of all known Ig gamma subtypes and contends that it would have been *prima facie* obvious at the time the invention was made to use the teachings of the '762 patent and align all of the known Ig gamma heavy chains for the creation of a consensus sequence with the expectation that such consensus sequence immunoglobulin would have a smaller chance of changing an amino acid near the CDRs that distorts their conformation as allegedly taught in column 13 of the '762 patent.

Applicants submit that the instant invention is patentable over the cited art.

With respect to the Examiner's combining of the '762 patent and Kabat, Applicants submit that the rejection is made impermissibly using hindsight reconstruction of the present invention. "One cannot use hindsight reconstruction to pick and choose among

isolated disclosures in the prior art to depreciate the claimed invention." *In re Fine* 837 F2d 1071, 1075 (Fed. Cir. 1988).

In particular, as noted above, the term "consensus framework from many human antibodies" in the '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acid residues at each location in all immunoglobulins of any particular subclass as in the present application. Thus, Applicants submit that the '762 patent would not have provided any motivation to make a consensus human variable domain as in the present application.

With respect to the Examiner's assertion that "the claimed invention differs from the prior art teachings only by recitation of Ig gamma isotype sequences used to make a consensus heavy chain framework region", Applicants believe that the Examiner has misunderstood the selection invention involving a "V_H subgroup III" consensus sequence. As opposed to a collection of antibodies with the same "isotype" due to the amino acid sequence of their heavy chain constant region (page 11 of the application), V_H subgroup III represents a subclass of antibodies grouped together because of their heavy chain variable domain sequences. For this reason alone, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Moreover, Applicants submit that there was nothing in the cited art to suggest combining Kabat with the '762 patent. In particular, the term "consensus" is not used in Kabat. Kabat refers to "occurrences of most common amino acid" for various heavy or light chain immunoglobulin subgroups. Without knowing about the invention of the present application, Applicants contend that those skilled in the art would not have been motivated to combine the mention of "consensus framework from many human antibodies" in the '762 patent with Kabat's disclosure of "occurrences of most common

amino acid", especially since, as elaborated above, the '762 patent did not intend the term "consensus framework" to refer to "occurrences of most common amino acid".

This further illustrates that the Examiner is using impermissible hindsight to combine the references.

Moreover, Applicants are able to show that the '762 patent would have taught away from the instantly claimed invention. In particular, the '762 patent states that one must select a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin in order to reduce the chance of distorting the conformation of the CDR's (see column 13 of the '762 patent). This has been termed the "best-fit" method of humanization.

On the contrary, the instant invention does not rely on selection of an unusually homologous framework from a single human antibody; a consensus human variable domain comprising the most frequently occurring amino acid residues at each location in human immunoglobulins is used as the framework region.

Whereas the '762 patent requires at least 65% homology between the human "acceptor" framework region (FR) sequence and murine "donor" FR sequence (see column 13, lines 33-36) to avoid distorting the conformation of the CDRs, Applicants have generated humanized antibodies using the V_H subgroup III consensus sequence having low FR homology to murine donor antibody FR sequences.

For example, in contrast to the teachings of the '762 patent, Applicants have shown that FR homologies as low as 53% for an anti-CD18 antibody (Example 4 on page 89 of the present application); 57% for an anti-IgE antibody [Presta *et al. J. Immunol.*

151(5):2623-2632 (1993) (of record)]; 57% for an anti-CD11a antibody [Werther *et al. J. Immunol.* 157:4986-4995 (1996) (of record)]; 61% for an anti-VEGF antibody [Presta *et al. Cancer Research* 57(20):4593-4599(1997)(copy attached)] and 63% for an anti-HER2 antibody1 (Example 1 herein) have resulted in humanized antibodies with strong binding affinities.

Applicants submit that the '762 patent would have lead those skilled in the art away from the instantly claimed invention because they would have feared that this would result in "distortions in the CDR's" of the humanized antibody so produced.

In further support of the patentability of the instant claims, Applicants will now show that the claimed invention can produce humanized antibodies with at least three unexpected and useful properties. Unexpected results provide objective evidence of non-obviousness. *Specialty Composites v. Cabot Corp.*, 845 F. 2d 981, 6 USPQ 2d 1601 (Fed. Cir. 1988).

The unexpected properties to be demonstrated include: lack of significant immunogenicity of the claimed humanized antibodies upon repeated administration to a human patient, *e.g.*, to treat a chronic disease in the patient; binding affinities superior to those of the non-human parent antibody; and the ability to use the same consensus human variable domain to make many strong affinity antibodies, thus avoiding tailoring each human FR to each non-human antibody to be humanized.

In order to demonstrate that lack of significant immunogenicity upon repeated administration of the humanized antibody to a human

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1 In the case of the anti-HER2 antibody, surprisingly, the humanized antibody had <u>improved</u> binding affinity relative to the murine parent antibody. This unexpected result will be discussed in more detail below.

patient could not have been predicted for the instantly claimed humanized antibodies, Applicants refer to Isaacs *et al. The Lancet* 340:748-752 (1992) (of record). Isaacs *et al.* demonstrate that three out of four patients treated with humanized CAMPATH-1H antibody (*i.e.* the antibody humanized in Riechmann) developed antiglobulins that were able to inhibit the binding of CAMPATH-1H to its antigen (see first paragraph of the discussion on page 751 of this reference).

On the contrary, the instant application describes humanized antibodies which lack significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient. Therefore, the instantly claimed antibodies are useful, among other things, for treating chronic disorders such as cancer.

As suggested by the Examiner in the interview, Applicants attach a Declaration under 37 CFR §1.132 by Dr. Steven Shak. In his declaration, Dr. Shak discusses human clinical data which demonstrates the lack of significant immunogenicity of humanized antibodies of the present application. Dr. Shak is a very experienced clinician with over 20 years experience as is evident from his curriculum vitae attached as Exhibit A to his declaration.

Dr. Shak explains in paragraph 2 of his declaration that the instant application describes humanized antibodies which were anticipated to lack significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient.

Dr. Shak further states that the humanized anti-HER2 antibody, huMAb4D5-8 (HERCEPTIN®), disclosed in Example 1 of the above-

identified patent application has been repeatedly administered to patients in breast cancer clinical trials (paragraph 3 of the declaration). Using an ELISA to detect antibodies to HERCEPTIN® antibody in the serum of treated patients, Dr. Shak reports in paragraph 4 that only one patient out of the 885 patients evaluated as of December 31, 1997 had detectable human antihuman antibodies (HAHA).

Dr. Shak further reviews in paragraphs 5-7 of his declaration human clinical data relating to a humanized variant of a murine anti-IgE antibody which was humanized according to the teachings of the present application. Dr. Shak explains that human patients suffering from allergic rhinitis and asthma (both chronic diseases) have received repeated administrations of the humanized anti-IgE antibody (rhuMAb-E25), but no patients were found to have HAHA to rhuMAb-E25. This is particularly impressive given that the patients who were treated with rhuMAb-E25 were hyper-reactive to foreign antigens.

Dr. Shak states in the final two paragraphs of his declaration that no significant immunogenic response has been observed in patients treated with two further antibodies which were humanized according to the teachings of the present application; *i.e.*, anti-VEGF and anti-CD11a (paragraphs 8 and 9 of the declaration). The patients received multiple doses of these two antibodies.

Accordingly, Applicants submit that it is apparent that the instant specification describes humanized antibodies which lack significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient.

In accordance with a recommendation of the Examiner in the interview, for clarity reasons, independent claim 106 herein

includes functional language concerning the unexpected lack of significant immunogenicity of the antibody claimed therein.

In addition to the above-discussed unexpected result pertaining to lack of immunogenicity of the humanized antibodies of the present invention, binding affinity is essentially retained and in some instances is surprisingly improved in the humanized antibody compared to the non-human parent antibody. As shown, for example, in the second to last column of Table 3 on page 72, anti-HER2 humanized variants huMAb4D5-6 and huMAb4D5-8 had binding affinities which were superior to the non-human parent antibody. This could not have been predicted from the prior art, especially from the '762 patent, which advocated the best-fit method (see above) to generate a "high affinity" humanized antibody. The above-mentioned anti-HER2 variants on the other hand were not generated using the "best-fit" method said to be essential in the '762 patent.

As suggested by the Examiner in the interview, claim 113 herein refers to this unexpected property of the humanized variant in that claim (*i.e.* a variant which binds an antigen with better affinity than the non-human parent antibody).

The '762 patent fails to teach humanized antibodies which bind antigen with better affinity than the parent antibody. The reported affinity comparisons in the '762 patent are summarized here for the Examiner's convenience:

- The humanized anti-Tac antibody in Example 1 of the '762 patent allegedly had "approximately the same" binding affinity as the murine parent anti-Tac antibody (lines 25-31 in column 41). The corresponding scientific publication, Queen *et al. PNAS (USA)* 86:10029-10033 (1989) (of record) states that the humanized

anti-Tac antibody actually had an affinity about 1/3 that of murine anti-Tac (see the abstract).

- The humanized mik-β1 humanized antibody of Example 5 had a binding affinity 2-fold worse than the mouse mik-β1 antibody (lines 50-52 in column 52 and Figure 28).

- The humanized Fd79 antibody of the '762 patent apparently displayed a 2-fold decrease in affinity and the affinity of the humanized Fd138-80 antibody was apparently "comparable" to that of the murine antibody (lines 42-46 in column 56).

- The humanized M195 antibody is stated to have an "affinity the same as the mouse M195 antibody to within experimental error" (lines 31-32 in column 60).

- In the line bridging columns 63-64, the humanized CMV5 antibody is stated to have "approximately the same binding affinity as mouse CV5".

- Finally, lines 9-11 in column 67 state that "Mouse AF2 and humanized AF2 will compete similarly, showing that their binding affinities for γ-IFN are approximately the same".

Hence, the '762 patent, in addition to its deficiencies with respect to the use of a consensus human variable domain as in the present application, fails to report any humanized antibody with better binding affinity than the non-human parent antibody.

With respect to another unexpected feature of the present invention, Applicants have shown that a consensus human variable domain of a human heavy chain immunoglobulin subgroup can be used to generate many different strong affinity humanized antibodies, including the following:

(a) anti-HER2 (4D5) [see Example 1 of the application];
(b) anti-CD3 [see Example 3 of the application];
(c) anti-CD18 [see Example 4 of the application];
(d) anti-IgE [see Presta *et al. J. Immunol.* 151(5):2623-2632 (1993) (of record)];
(e) anti-CD11a [see Werther *et al. J. Immunol.* 157:4986-4995 (1996) (of record)]; and
(f) anti-VEGF [see Presta *et al. Cancer Research* 57(20): 4593-4599 (1997) (copy attached]

This could not have been predicted based on the teachings of the '762 patent, since this reference taught that an individual human framework region needed to be tailored to each non-human antibody to be humanized (see comments above).

In summary then, Applicants submit that the cited art is deficient in teaching the instantly claimed humanized antibodies and the unexpected results of the present invention.

Turning now to claim 111 herein, this claim recites the selection invention concerning a "V_H subgroup III" consensus sequence. Applicants submit that this claim is independently patentable.

In particular, there is no suggestion in the cited art to use the particular V_H subgroup III consensus sequence.

In fact, the '762 patent taught away from this consensus sequence by advocating the "best-fit" method of humanization using the most homologous human framework for humanization. As noted above, the V_H subgroup III consensus sequence lacks significant homology to the various non-human antibodies humanized according to the teachings of the present invention. Even if (which is strongly

denied), the '762 patent had intended the phrase "consensus framework from many human antibodies" in column 13 thereof to mean a consensus human variable domain as contemplated in the present application, there is nothing in the '762 patent to indicate that a useful consensus sequence is that of a human heavy chain immunoglobulin subgroup in Kabat, let alone V_H subgroup III. For example, even though the V_H subgroup I FR in Kabat was more homologous (67% homology) to the murine anti-HER2 antibody 4D5 in Example 1 than the V_H subgroup III FR (63% homology), the inventors did not use the more homologous consensus sequence. Notwithstanding this, humanized anti-HER2 antibodies produced using this low homology human FR bound target antigen with <u>better</u> affinity than the non-human parent antibody (see comments above).

Moreover, Applicants have subsequently found that V_H subgroup III consensus sequence surprisingly has the same amino acid sequence as the human germline sequence YAC-5 in Fig. 2 of Cook *et al.*, *Nature Genetics* 7:162-168 (1994) (of record). This subsequent finding supports Applicants' observations that antibodies humanized using this FR sequence are non-immunogenic in humans.

In summation then, Applicants submit that there is nothing in the cited references to teach selection of a V_H subgroup III consensus sequence as in claim 111 for forming the V_H FR template of the humanized antibody, much less the advantages associated with such a consensus sequence. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Applicants believe that this case is now in condition for allowance and look forward to receiving early notification of same. If there are outstanding issues however, Applicants invite the Examiner to call the undersigned at the number noted below.

Respectfully submitted,

GENENTECH, INC.

Date: August 24, 1998 By: _____

Wendy M. Lee

Reg. No. 40,378

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
Fax: (650) 952-9881

PATENT
Docket P709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
)
Carter et al.)
) Group Art Unit: 1644
Serial. No. 08/146,206) Examiner: P. Nolan
)
Filed: 17 November 1993)
)
For: Method for Making Humanized Antibodies)

DECLARATION UNDER 37 CFR §1.132

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

I, STEVEN SHAK, do hereby declare and say as follows:

1. I obtained my M.D. degree in 1977 from New York University (NYU) School of Medicine. Following this, I was a Teaching Assistant and then an Assistant Professor of Medicine and Pharmacology at NYU School of Medicine. Since 1986, I have been employed as a Scientist at Genentech, Inc. Presently, I am the Clinical Team Leader for the therapeutic antibody, anti-HER2. A complete listing of my professional experience, project management experience, education, postdoctoral training, certification and licensure, honors and awards, and publications is found in my curriculum vitae attached as Exhibit A.

2. In my capacity as anti-HER2 Clinical Team Leader, I am familiar with human clinical data relating to the humanized anti-HER2 antibody, huMAb4D5-8 (HERCEPTIN®), disclosed in Example 1 of the above-identified patent application. As explained on page 70,

lines 7-9 of the above application, a humanized variant of the murine anti-HER2 antibody was made which was intended to lack significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient.

3. The HERCEPTIN® antibody has been administered to patients in breast cancer clinical trials using a dosing protocol which involves an initial loading dose of 4mg/kg of intravenous (IV) HERCEPTIN® antibody then weekly doses of 2mg/kg (IV) each. Patients have been treated with HERCEPTIN® antibody as a single agent or HERCEPTIN® antibody concomitantly with either (a) cyclophosphamide and doxorubicin or epirubicin (AC) or (b) paclitaxel (TAXOL®).

4. The presence of antibodies to HERCEPTIN® antibody in the serum of treated patients has been determined by enzyme-linked immunosorbent assay (ELISA). As of December 31, 1997, there is only one case of human antihuman antibodies (HAHA) in 885 patients evaluated. This one patient received nine weekly infusions of HERCEPTIN® antibody and discontinued the study on day 65 due to disease progression. At the termination evaluation, antibody measurements were suggestive of antibody formation against the $F(ab')_2$ portion of the HERCEPTIN® antibody. Antibody formation in this one case was not associated with severe allergic symptoms.

5. I have also reviewed human clinical data in relation to a humanized variant of the murine antibody MaE11 which binds IgE. MaE11 was humanized using a consensus human variable domain of a human heavy chain immunoglobulin subgroup [see Figure 1 of Presta *et al. J. Immunol.* 151(5):2623-2632 (1993), Exhibit B attached].

6. Recombinant humanized MaE11 (rhuMAb-E25) has been administered intravenously (IV) or subcutaneously (SQ) to human

patients suffering from allergic rhinitis and asthma. One hundred eighty one subjects with a documented history of seasonal allergic rhinitis or rhinoconjunctivitis received an initial IV loading dose followed by SQ or IV administrations of rhuMAb-E25 on days 7, 14, 28, 42, 56, 70 and 84 [Abstract of Casale *et al. J. Allergy Clin. Immunol.* 100(1):110-121 (1997); Exhibit C attached]. Nineteen allergic asthmatic subjects received rhuMAB-E25 IV the day after the baseline airway allergen challenge and at weekly intervals for eight weeks [Abstract and Figure 1 of Fahy *et al. Am J. Respir. Crit. Care Med.* 155:1828-1834 (1997); Exhibit D]. Potential HAHA in the serum of treated patients were assayed as described in Casale *et al.* and Fahy *et al.*

7. As reported on page 116 of Casale *et al.* and page 1830 of Fahy *et al.*, no patients were found to have HAHA to rhuMAb-E25.

8. I am also aware that we have not observed a significant immunogenic response in patients receiving multiple doses of a humanized anti-VEGF antibody for inhibiting VEGF-induced angiogenesis. The humanized antibody is question is a variant of murine anti-VEGF antibody A.4.6.1, and was humanized using a consensus human variable domain of a human heavy chain immunoglobulin subgroup [Figure 1 on page 4596 of Presta *et al. Cancer Research* 57(20):4593-4599 (1997); Exhibit E attached].

9. Finally, I have been told that no significant immunogenicity has been associated with repeated administration of a humanized anti-CD11a antibody to psoriasis patients. The humanized anti-CD11a antibody with which the psoriasis patients have been treated was prepared from the murine MHM24 antibody using a consensus human variable domain of a human heavy chain immunoglobulin subgroup [Figure 1 of Werther *et al. J. Immunol.* 157(11):4986-4995(1996), Exhibit F attached].

I declare further that all statements made herein of my own knowledge are true and that all statements made on information 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 such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 9/24/98

STEVEN SHAK

CURRICULUM VITAE

Steven Shak, M.D.

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Tel. No.: (650) 225-2476
Fax No.: (650) 225-5335
E-mail: shak@gene.com

Professional Experience:

1998-	Staff Clinical Scientist, Genentech, Inc.
1996-98	Senior Clinical Scientist, Genentech, Inc.
1989-96	Director, Departments of Immunobiology, Pulmonary Research, and Pathology, Genentech, Inc.
1986-89	Scientist, Genentech, Inc.
1984-86	Assistant Professor of Medicine and Pharmacology New York University School of Medicine
1978-80	Teaching Assistant, Department of Medicine New York University School of Medicine

Project Management:

1996-	Anti-HER2 Clinical Team Leader
1996-97	Anti-VEGF Clinical Team Leader
1996-	Chair, Clinical Assessment Committee
1993-96	Chair, Genentech-GenVec Research Committee
1993-	Board of Directors, Genentech Endowment for Cystic Fibrosis
1991-96	Research Representative on Clinical Research Advisory Committee
1995-96	DNase SLE Biology Team Leader
1992-94	DNase Pulmozyme Chronic Bronchitis Team Leader

EXHIBIT A

1988-91	DNase Pulmozyme Project Team Leader

Education:

1973-77	M.D., New York University School of Medicine
1969-73	B.A., Amherst College

Postdoctoral Training:

Research:

1981-84	University of California, San Francisco Cardiovascular Research Institute Rosalyn Russell Arthritis Research Laboratory Chief: Ira M. Goldstein, M.D.

Fellowship:

1980-84	University of California, San Francisco Cardiovascular Research Institute Subspeciality: Pulmonary Medicine Chairmen: John F. Murray, M.D. and Jay A. Nadel, M.D.

Residency:

1977-80	Bellevue Hospital Specialty: Internal Medicine Chairman: Saul J. Farber, M.D.

Certification and Licensure:

1982	Diplomate, Pulmonary Disease
1980	Diplomate, American Board of Internal Medicine
1980	Licensed, California (current)
1978	Licensed, New York State

Honors and Awards:

1995	Prix Gallien, Portugal for "Pulmozyme Discovery and Development"
1995	"Parenting Achievement Award," Parenting Magazine
1993	Distinguished Corporate Scientist Award, Cystic Fibrosis

	Foundation
1992	CF Achievement Award, Cystic Fibrosis Research, Inc.
1985	J. Burns Amberson Award, NY Lung Association
1980	Medical School Pulmonary Faculty Training Award
	National Institutes of Health
1977	Alpha Omega Alpha
1974	Valentine Mott Award in Anatomy and Cell Biology
1973	Summa Cum Laude
1973	Phi Beta Kappa
1973	Sigma Xi
1973	Howard Waters Doughty Prize in Chemistry

Personal:

Born: July 21, 1950, Elizabeth, NJ
Married, two children
Social Security No.: 145-42-8006

Publications:

I. Book Chapters.

1. SHAK S, Goldstein IM: The major pathway for leukotriene B_4 catabolism in human polymorphonuclear leukocytes involves ω-oxidation by a cytochrome P-450 enzyme. In PROSTAGLANDINS, LEUKOTRIENES, AND LIPOXINS. (JM Bailey, ed.) Plenum Publishing Corporation, New York, 1985.

2. SHAK S: Leukotriene B_4 catabolism: Quantitation of leukotriene B_4 and its ω-oxidation prducts by reversed phase high-performance liquid chromatography. METHODS IN ENZYMOLOGY. Vol. 141. Cellular Regulators (AR Means and PM Conn, eds.) Academic Press, Florida, pp. 355-371, 1987.

3. SHAK S: Molecular mechanisms for the catabolism of leukotriene B_4. In ADVANCES IN INFLAMMATION RESEARCH. Vol. 12. (A Lewis, ed.) Raven Press, Ltd., New York, pp. 111-124, 1988.

4. Goldstein IM, SHAK S: Humoral and cellular mediators of host defenses. In TEXTBOOK OF RESPIRATORY MEDICINE. (JF Murray and JA Nadel, eds.) W.B. Saunders Company, Philadelphia, pp. 358-373, 1988.

5. Goldstein IM, SHAK S: Host defenses in the lung: Neutrophils, complement, and other humoral mediators. In TEXTBOOK OF RESPIRATORY MEDICINE. (JF Murray and JA Nadel, eds.) W.B. Saunders Company, Philadelphia, pp. 402-418, 1994.

6. S SHAK: Mucins and lung secretions. In THE LUNG--SCIENTIFIC FOUNDATIONS. (RG Crystal, JB West, ER Weibel, and PJ Barnes, eds.) Lippincott-Raven Publishers, Philadelphia, pp. 479-486.

II. Articles

1. SHAK, S, Perez HD, Goldstein IM: A novel dioxygenation product of arachidonic acid posseses potent chemotactic activity for human polymorphonuclear leukocytes. THE JOURNAL OF BIOLOGICAL CHEMISTRY, 258:14948-14953, 1983.

2. Perez HD, Bissell DM, Roll FJ, SHAK S, Goldstein IM: A possible explanation for leukocytic infiltration of the liver in acute alcoholic hepatitis: Ethanol-induced generation by hepatocytes of a lipid chemotactic factor. TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS. 96:56-64, 1983.

3. Charo, IF, SHAK S, Darasek MA, Davison PM, Goldstein IM: Prostaglandin I_2 is not a major metabolite of arachidonic acid in cultured endothelial cells from human foreskin microvessels. THE JOURNAL OF CLINICAL INVESTIGATION. 74:914-919, 1984.

4. Perez HD, Roll JF, Bissell DM, SHAK S, Goldstein IM: Ethanol induces isolated rat hepatocytes to generate chemotactic activity for polymorphonuclear leukocytes. THE JOURNAL OF CLINICAL INVESTIGATION. 74:1350-1357, 1984.

5. SHAK S, Goldstein IM: ω-Oxidation is the major pathway for the catabolism of leukotriene B_4 in human polymorphonuclear leukocytes. THE JOURNAL OF BIOLOGICAL CHEMISTRY. 259:10181-10187, 1984.

6. SHAK S, Goldstein IM: Carbon monoxide inhibits ω-oxidation of leukotriene B_4 by human polymorphonuclear leukocytes: Evidence that catabolism of leukotriene B_4 is mediated by a cytochorme P-450 enzyme. BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. 123:475-481, 1984.

7. SHAK S, Reich N, Goldstein IM, Ortiz de Montellano PM: Leukotriene B_4 ω-hydroxylase in human polymorphonuclear leukocytes: Suicidal inactivation by acetylenic fatty acids. THE JOURNAL OF BIOLOGICAL CHEMISTRY. 260:13023-13028, 1985.

8. SHAK S, Goldstein IM: Leukotriene B_4 ω-hydroxylase in human polymorphonuclear leukocytes: Partial purification and identification as a cytochrome P-450. THE JOURNAL OF CLINICAL INVESTIGATION. 76:1218-1228, 1985.

9. SHAK S, Goldstein IM: The leukotriene B_4 ω-hydroxylase in human polymorphonuclear leukocytes is a membrane-associated, NADPH-dependent cytochrome P-450 enzyme. TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS. 48:352-360, 1985.

10. Kruskal BA, SHAK S, Maxfield FR: Spreading of human neutrophils is immediately preceded by a large increase in cytoplasmic free calcium concentration. PROCEEDINGS OF THE NATIONAL ACADEMY OF THE SCIENCES USA. 83:2919-2923, 1986.

11. Davitz MA, Hereld D, SHAK S, Krakow JL, Englund PT, Nussenzweig V: A glycan-phosphatidylinositol-specific phospholipase D in human serum. SCIENCE. 238:81-4, 1987.

12. SHAK S, Davitz MA, Wolinsky ML, Nussenzweig V, Turner MJ, Gurnett A: Partial characterization of the cross reacting determinant, a carbohydrate epitope shared by decay accelerating factor (DAF) and the variant surface glycoprotein (VSG) of the african Trypanosoma brucei. THE JOURNAL OF IMMUNOLOGY. 140:2046-2050, 1988.

13. SHAK S, Capon DJ, Hellmiss R, Marsters SA, Baker CL: Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. PROCEEDINGS OF THE NATIONAL ACADAMY OF SCIENCES, USA. 87:9188-9192, 1990.

14. Aitken ML, Burke W, McDonald G, SHAK S, Montgomery AB, Smith A: Recombinant human DNase inhalation in normal and patients with cystic fibrosis: A phase I study. THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION. 267:1947-1951, 1992.

15. Hubbard RC, McElvaney NG, Birrer P, SHAK S, Robinson WW, Jolley C, Wu M, Chernick MS, Crystal RG: A preliminary study of aerosolized recombinant human deoxyribonuclease I in the treatment of cystic fibrosis. THE NEW ENGLAND JOURNAL OF MEDICINE. 326:812-815, 1992.

16. Ramsey BW, Astley SJ, Aitken ML, Burke W, Colin AA, Dorkin HL, Eisenberg JD, Gibson RL, Harwood IR, Schidlow DV, WilmottRW, Wohl ME, Myerson LJ, SHAK S, Fuchs H, Smith AL: Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. AMERICAN REVIEW OF RESPIRATORY DISEASE. 148:145-151, 1993.

17. Ranasinha C, Assoufi B, SHAK S, Christiansen D, Fuchs H, Empey D, Geddes D, Hodson M: Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis. THE LANCET. 342:199-202, 1993.

18. Chamow SM, Kogan TP, Venuti M, Gadek T, Harris RJ, Peers DH, Mordenti J, SHAK S, Ashkenazi A: Modification of CD4 immunoadhesin with monomethoxypoly(ethylene glycol) aldehyde via reductive alkylation. BIOCONJUGATE CHEMISTRY. 5:133-140, 1994.

19. Sinicropi D, Baker DL, Prince WS, Shiffer K, SHAK S: Colorimetric determination of DNase I activity with a DNA-methyl green substrate. ANALYTICAL BIOCHEMISTRY. 222:351-358, 1994.

20. SHAK S: Aerosolized recombinant human DNase I for the treatment of cystic fibrosis. CHEST 107:65S-70S, 1995.

21. Zahm JM, Girod de Bentzmann S, Deneuville E, Perrot-Minnot C, Dabadie A, Pennaforte F, Roussey M, SHAK S, Puchelle E: Dose-dependent in vitro effect of recombinant human DNase on rheological and transport properties of cystic fibrosis respiratory mucus. EUROPEAN RESPIRATORY JOURNAL. 8:381-6, 1995.

22. Puchelle E, Zahm JM, de Bentzmann S, Grosskopf C, SHAK S, Mougel D, Polu JM: Effects of rhDNase on purulent airway secretions in chronic bronchitis. EUROPEAN RESPIRATORY JOURNAL. 9:765-9, 1996.

23. Macanovic M, Sinicropi D, SHAK S, Baughman S, Thiru S, Lachmann PJ: The treatment of systemic lupus erythematosus (SLE) in NZB/W F1 hybrid mice; studies with recombinant murine DNase and with dexamethasone. CLINICAL AND EXPERIMENTAL IMMUNOLOGY. 106:243-252, 1996.

24. Ulmer JS, Herzka A, Toy KJ, Baker DL, Dodge AH, Sinicropi D, SHAK S, Lazarus RA: Engineering Actin Resistant Human DNase I for Treatment of Cystic Fibrosis. PROCEEDINGS NATIONAL ACADEMY OF SCIENCE, USA. 93:8225-8229, 1996.

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: P. Nolan CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on August 24, 1998 Wendy M. Lee

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicants submit herewith patents, publications or other information (attached hereto and listed on the attached Form PTO-1449) of which they are aware, which they believe may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR §1.56.

This Information Disclosure Statement:

(a) [] accompanies the new patent application submitted herewith. 37 CFR §1.97(a).

(b) [] is filed within three months after the filing date of the application or within three months after the date of entry of the national stage of a PCT application as set forth in 37 CFR§1.491.

(c) [] as far as is known to the undersigned, is filed before the mailing date of a first Office action on the merits.

(d) [] is filed after the first Office Action and more than three months after the application's filing date or PCT national stage date of entry filing but, as far as is known to the undersigned, prior to the mailing date of either a final rejection or a notice of allowance, whichever occurs first, and is accompanied by either the fee ($240) set forth in 37 CFR §1.17(p) **or** a statement as specified in 37 CFR §1.97(e), as checked below. Should any fee be due, the U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $240.00 to cover

the cost of this Information Disclosure Statement. Any deficiency or overpayment should be charged or credited to this deposit account. **A duplicate of this sheet is enclosed.**

(e) [] is filed after the mailing date of either a final rejection or a notice of allowance, whichever occurred first, and is accompanied by the fee ($130) set forth in 37 CFR § 1.17(i) **and** a statement as specified in 37 CFR § 1.97(e), as checked below. **This document is to be considered as a petition requesting consideration of the information disclosure statement.** The U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $130.00 to cover the cost of this Information Disclosure Statement. Any deficiency or overpayment should be charged or credited to this deposit account. **A duplicate of this sheet is enclosed.**

(f) [x] is filed after the mailing date of a final rejection, but a request to withdraw the finality thereof under 37 CFR § 1.129(a) is submitted herewith. The U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 to cover the cost of this Information Disclosure Statement in the event that any fees are due. **A duplicate of this sheet is enclosed.**

[If either of boxes (d) or (e) is checked above, the following statement under 37 CFR § 1.97(e) may need to be completed.] The undersigned states that:

[] Each item of information contained in the information disclosure statement was cited in a communication mailed from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.

[] No item of information contained in this information disclosure statement was cited in a communication mailed from a foreign patent office in a counterpart foreign application and, to the knowledge of the undersigned after making reasonable inquiry, was known to any individual designated in 37 CFR § 1.56(c) more than three months prior to the filing of this information disclosure statement.

A list of the patent(s) or publication(s) is set forth on the attached Form PTO-1449 (Modified).

A copy of the items on PTO-1449 is supplied herewith:

[] each [] none [x] only those listed below:

5,677,171

5,772,997

Brown, Jr. et al.

Mathieson et al.

Presta et al.

Casale et al.

Fahy et al.

A concise explanation of relevance of the items listed on PTO-1449 is:

[x] not given

[] given for each listed item

[] given for only non-English language listed item(s) [Required]

[] in the form of an English language copy of a Search Report from a foreign patent office, issued in a counterpart application, which refers to the relevant portions of the references.

The Examiner is reminded that a "concise explanation of the relevance" of the submitted prior art "may be nothing more than identification of the particular figure or paragraph of the patent or publication which has some relation to the claimed invention," MPEP §609.

While the information and references disclosed in this Information Disclosure Statement may be "material" pursuant to 37 CFR §1.56, it is not intended to constitute an admission that any patent, publication or other information referred to therein is "prior art" for this invention unless specifically designated as such.

In accordance with 37 CFR §1.97(g), the filing of this Information Disclosure Statement shall not be construed to mean that a search has been made or that no other material information as defined in 37 CFR §1.56(a) exists. It is submitted that the Information Disclosure Statement is in compliance with 37 CFR §1.98 and MPEP §609 and the Examiner is respectfully requested to consider the listed references.

Respectfully submitted,
GENENTECH, INC.

Date: August 24, 1998 By: _____
Wendy M. Lee
Reg. No. 40,378

1 DNA Way
So. San Francisco, CA 94080-4990
Phone: (650) 225-1994
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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

#41

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

INTERVIEW SUMMARY

All participants (applicant, applicant's representative, PTO personnel):

(1) MINH-TAM DAVIS (3) Wendy Lee

(2) Lisa Teisse (4)

Date of Interview 10/16/01

Type: ☐ Telephonic ☐ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☐ No If yes, brief description:

Agreement ☐ was reached. ☐ was not reached.

Claim(s) discussed: all pending claims

Identification of prior art discussed:

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: 1/112, 2nd, 1st para issue of cls 43-105 with respect to binding of CDR, 2/112, 2nd para issue of cls 101-112 with respect to "significant" immunogenicity

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary. A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has are ready been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign this form unless it is an attachment to another form.

FORM **PTOL-413** (REV.1-96)

Minh Tam Davis

1116198

#42

Official Document

GENENTECH, INC.

1 DNA Way, South San Francisco, CA 94080-4990 Tel: 650-225-1994 Fax: 650-952-9881

FAX TRANSMISSION COVER SHEET

Date: November 6, 1998

To: Lila Feisee ~~Examiner M.T. Davis~~ Group Art Unit: 1642 of US PTO

Fax: (703) 308-~~4426~~ 0294

Re: U.S. Ser. No 08/146,206 filed November 17, 1993 (Attorney Docket No.: P0709P1)

Sender: Wendy M. Lee

CERTIFICATION OF FACSIMILE TRANSMISSION
I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.
Ann Savelli
Type or print name of person signing certification
Ann S
Signature Date

YOU SHOULD RECEIVE 5 PAGES, INCLUDING THIS COVER SHEET. IF YOU DO NOT RECEIVE ALL THE PAGES, PLEASE CALL 650-225-7039

Comments:

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1644 Examiner: Tam Davis

SUPPLEMENTAL AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Further to the amendment dated August 24, 1998, Applicants request that the above-identified application be amended as follows:

IN THE CLAIMS:

Please amend claims 43, 72, 104-106 and 112 as follows:

43. (Amended) A humanized antibody variable domain comprising a non-human Complementarity Determining Region (CDR) which binds an antigen incorporated into a human antibody variable domain, and further comprising an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H and 92H, utilizing the numbering system set forth in Kabat.

72. (Amended) An antibody which binds p185^{HER2} and comprises a humanized antibody variable domain comprising a non-human Complementarity Determining Region (CDR) which binds p185^{HER2} incorporated into a human antibody variable domain, and further

comprises an amino acid substitution at a site selected from the group consisting of:
4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

104. (Amended) A humanized antibody variable domain comprising a non-human Complementarity Determining Region (CDR) which binds an antigen incorporated into a consensus human variable domain, and further comprising an amino acid substitution at a site selected from the group consisting of:
4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

105. (Amended) An antibody which lacks [significant] immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient and comprises a non-human Complementarity Determining Region (CDR) which binds an antigen incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of:
4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

106. (Amended) An antibody which lacks [significant] immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient and comprises a consensus human

variable domain of a human heavy chain immunoglobulin subgroup, wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprising a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) comprises a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another.

112. (Amended) The humanized antibody of claim 111 which lacks [significant] immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient.

REMARKS

The undersigned confirms having met with Examiners Davis and Feisee in the interview October 16, 1998. In that interview, the Examiners suggested that independent claims 43, 72, 104 and 105 be amended for claim precision to refer to a CDR which binds an antigen. Without acquiescing in any objection or rejection and purely to facilitate allowance, claims 43, 104 and 105 have been revised herein as recommended by the Office to refer to a CDR "which binds an antigen" and claim 72 refers to a CDR "which binds p185^{HER2}".

Moreover, the Examiners proposed in the interview that, for clarity reasons, claims 105, 106 and 112 (refering to antibodies with diminished immunogenicity) be revised to refer to an antibody which "lacks immunogenicity compared to a non-human

parent antibody". Without acquiescing in any objection or rejection and purely to facilitate allowance, Applicants have adopted the language proposed by the Office. Hence, the instantly claimed antibodies display significantly reduced immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient (see page 70, lines 6-8 of the instant application), as opposed to the immunogenicity observed with the prior art humanized antibody in Isaacs *et al.*, *The Lancet* 340:748-752 (1992) (see first paragraph on page 19 of the amendment dated August 24, 1998).

Applicants look forward to early receipt of a notice of allowance in the above application.

Respectfully submitted,
GENENTECH, INC.

Date: November 6, 1998

By: _____
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#44

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FAX TRANSMISSION COVER SHEET

Date: January 15, 1999

To: Examiner Julie Reeves Group Art Unit: 1642 of US PTO

Fax: (703) 308-4426

Re: U.S. Ser. No 08/146,206 filed November 17, 1993 (Attorney Docket No.: P0709P1)

Sender: Wendy M. Lee

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Patent and Trademark Office on the date shown below.

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Comments:

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: J. Reeves

AMENDMENT TRANSMITTAL

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated as shown below

	Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Rate	Additional Fees
Total	86	-	72	14	$18	$252.00
Independent	9	-	7	2	$78	$156.00
__ Multiple dependent claim(s), if any					$260	$0.00
					Total Fee Calculation	$408.00

_____
_____ x
_____

No additional fee is required.
The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $408.00. A duplicate copy of this transmittal is enclosed.
Petition for Extension of Time is enclosed.

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 07-0630. A duplicate copy of this sheet is enclosed.

Respectfully submitted,
GENENTECH, INC.

Date: January 15, 1999

By. _____
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paper # 44 - Amdt J

Patent Docket P07099

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

1/15/99 JK

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: Julie Reeves

SUPPLEMENTAL AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend the claims as indicated below. Pending claims which are not amended herein are marked "(Reiterated)" for the Examiner's convenience.

1 ~~43~~. (TWICE AMENDED) A humanized antibody variable domain comprising [a] non-human Complementarity Determining Region (CDR) amino acid residues which bind[s] an antigen incorporated into a human antibody variable domain, and further comprising ~~an~~ amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H and 92H, utilizing the numbering system set forth in Kabat.

K J1

2 ~~44~~. (AMENDED) The humanized variable domain of claim ~~43~~ 1 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are [was] obtained.

J2

45. (Reiterated) The humanized variable domain of claim 43 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.

Duplicate

/cc

J

46. (Reiterated) The humanized variable domain of claim 43 wherein the human antibody variable domain is a consensus human variable domain.

47. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 4L has been substituted.

48. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 38L has been substituted.

49. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 43L has been substituted.

50. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 44L has been substituted.

51. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 58L has been substituted.

52. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 62L has been substituted.

53. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 65L has been substituted.

54. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 66L has been substituted.

55. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 67L has been substituted.

56. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 68L has been substituted.

57. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 69L has been substituted.

58. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 73L has been substituted.

59. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 85L has been substituted.

60. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 98L has been substituted.

61. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 2H has been substituted.

62. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 4H has been substituted.

63. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 36H has been substituted.

64. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 39H has been substituted.

65. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 43H has been substituted.

66. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 45H has been substituted.

67. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 69H has been substituted.

68. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 70H has been substituted.

69. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 74H has been substituted.

70. (Reiterated) The humanized variable domain of claim 43 wherein the residue at site 92H has been substituted.

71. (Reiterated) An antibody comprising the humanized variable domain of claim 43.

J3

72. (TWICE AMENDED) An antibody which binds $p185^{HER2}$ and comprises a humanized antibody variable domain, wherein the humanized antibody variable domain comprises [comprising a] non-human Complementarity Determining Region (CDR) amino acid residues which bind[s] $p185^{HER2}$ incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of:
4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

J4

73. (AMENDED) The antibody of claim 72 wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are [was] obtained.

74. (Reiterated) The antibody of claim 72 wherein no human Framework Region (FR) residue other than those set forth in the group has been substituted.

75. (Reiterated) The antibody of claim 72 wherein the human antibody variable domain is a consensus human variable domain.

76. (Reiterated) The antibody of claim 72 wherein the residue at site 4L has been substituted.

77. (Reiterated) The antibody of claim 72 wherein the residue at site 38L has been substituted.

78. (Reiterated) The antibody of claim 72 wherein the residue at site 43L has been substituted.

79. (Reiterated) The antibody of claim 72 wherein the residue at site 44L has been substituted.

80. (Reiterated) The antibody of claim 72 wherein the residue at site 46L has been substituted.

81. (Reiterated) The antibody of claim 72 wherein the residue at site 58L has been substituted.

82. (Reiterated) The antibody of claim 72 wherein the residue at site 62L has been substituted.

83. (Reiterated) The antibody of claim 72 wherein the residue at site 65L has been substituted.

84. (Reiterated) The antibody of claim 72 wherein the residue at site 66L has been substituted.

85. (Reiterated) The antibody of claim 72 wherein the residue at site 67L has been substituted.

86. (Reiterated) The antibody of claim 72 wherein the residue at site 68L has been substituted.

87. (Reiterated) The antibody of claim 72 wherein the residue at site 69L has been substituted.

88. (Reiterated) The antibody of claim 72 wherein the residue at site 73L has been substituted.

89. (Reiterated) The antibody of claim 72 wherein the residue at site 85L has been substituted.

90. (Reiterated) The antibody of claim 72 wherein the residue at site 98L has been substituted.

91. (Reiterated) The antibody of claim 72 wherein the residue at site 2H has been substituted.

92. (Reiterated) The antibody of claim 72 wherein the residue at site 4H has been substituted.

93. (Reiterated) The antibody of claim 72 wherein the residue at site 36H has been substituted.

94. (Reiterated) The antibody of claim 72 wherein the residue at site 39H has been substituted.

95. (Reiterated) The antibody of claim 72 wherein the residue at site 43H has been substituted.

96. (Reiterated) The antibody of claim 72 wherein the residue at site 45H has been substituted.

97. (Reiterated) The antibody of claim 72 wherein the residue at site 69H has been substituted.

98. (Reiterated) The antibody of claim 72 wherein the residue at site 70H has been substituted.

99. (Reiterated) The antibody of claim 72 wherein the residue at site 74H has been substituted.

100. (Reiterated) The antibody of claim 72 wherein the residue at site 75H has been substituted.

101. (Reiterated) The antibody of claim 72 wherein the residue at site 76H has been substituted.

102. (Reiterated) The antibody of claim 72 wherein the residue at site 78H has been substituted.

103. (Reiterated) The antibody of claim 72 wherein the residue at site 92H has been substituted.

J5

104. (TWICE AMENDED) A humanized antibody variable domain comprising [a] non-human Complementarity Determining Region (CDR) amino acid residues which bind[s] an antigen incorporated into a consensus human variable domain, and further comprising an amino acid substitution at a site selected from the group consisting of:
4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.

J6

105. (TWICE AMENDED) [An] A humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient [and], wherein the humanized antibody comprises [a] non-human Complementarity Determining Region (CDR) amino acid residues which bind[s] an antigen incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of:
4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat.