INTERNATIONAL SEARCH REPORT

International Application No PCT/US89/05857

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5) : C12P 21/00; C12N 5/10,7/01,15/00
U.S. Cl : 530/387; 435/69.1,240.1; 536/27

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	530/387; 424/85; 435/69.1,172.3; 536/27; 435/240.1

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y,P	US,A 4,816,567 (CABILLY ET AL) Issued 28 March 1989, See entire document.	1-22
X Y	EP,A 239,400 (WINTER) Issued 30 September 1987 See entire document.	18-22 1-17
X,P Y	WO,A 89/01783 (BODMER ET AL) Issued 09 March 1989, See entire document.	18-22 1-17
X Y	GB,A 2188941 (DIAMANTSTEIN ET AL) Issued 14 October 1987. See entire document.	1-4,7-8,14-15 5-6,9-13 & 16-22
Y	Science, Volume 238 Issued 20 November 1987 (VITETTA ET AL) "Redesigning nature's poisons to create anti-tumor reagents" , pp 1098-1104. See entire document. (con't)	1-22

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [6]	Date of Mailing of this International Search Report [7]
01 June 1990	02 JUL 1990
International Searching Authority [8]	Signature of Authorized Officer [10]
ISA/US	Michelle Marks

Form PCT/ISA/210 (second sheet) (May 1986)

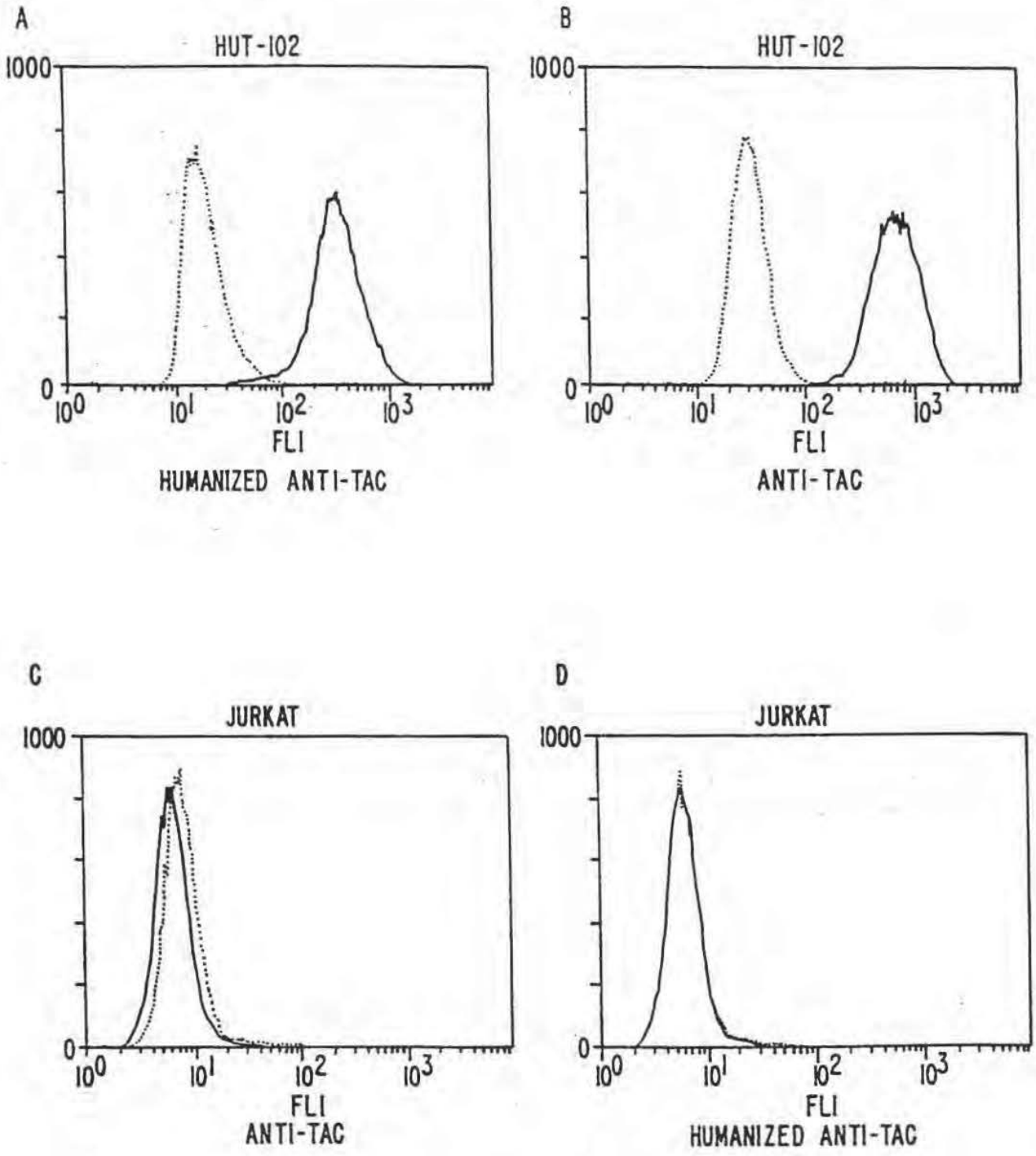
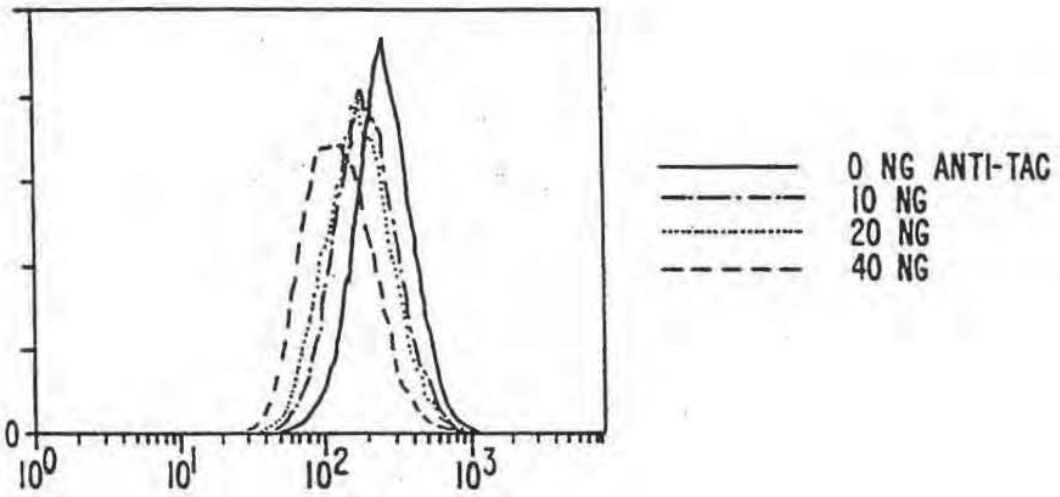


FIG._9.

A



B

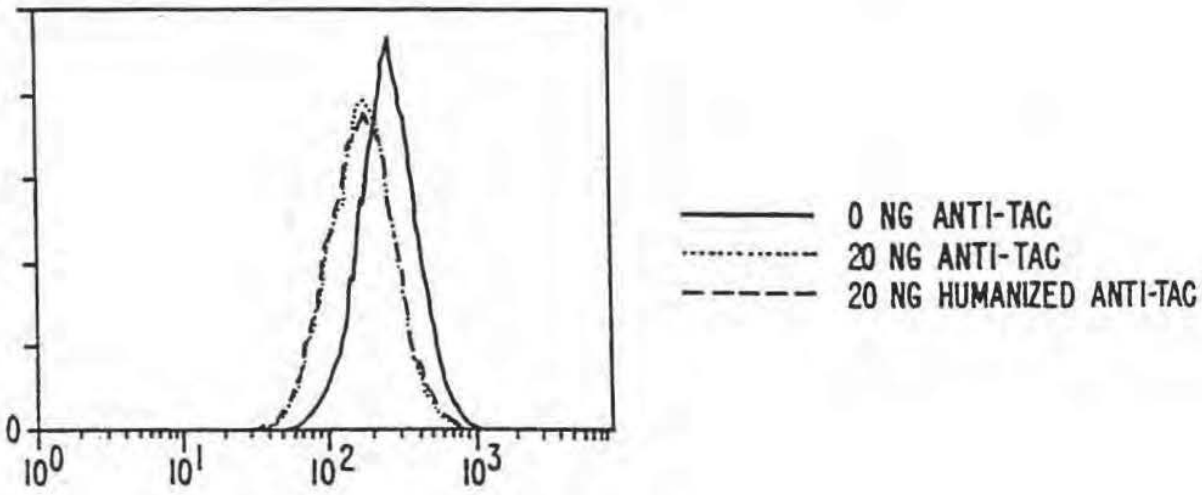


FIG._10.

Form PTO 948 (Rev. 10-93) U.S. DEPARTMENT OF COMMERCE - Patent and Trademark Office Application No. 146,206

NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW

PTO Draftpersons review all originally filed drawings regardless of whether they are designated as formal or informal. Additionally, patent Examiners will review the drawings for compliance with the regulations. Direct telephone inquiries concerning this review to the Drawing Review Branch, 703-305-8404.

The drawings filed (insert date) 11/7/97, are
A. ___ not objected to by the Draftsperson under 37 CFR 1.84 or 1.152.
B. X objected to by the Draftsperson under 37 CFR 1.84 or 1.152 as indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawings must be submitted according to the instructions on the back of this Notice.

1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black ink. Color.
   - ___ Not black solid lines. Fig(s)___
   - ___ Color drawings are not acceptable until petition is granted.

2. PHOTOGRAPHS. 37 CFR 1.84(b)
   - ___ Photographs are not acceptable until petition is granted.

3. GRAPHIC FORMS. 37 CFR 1.84 (d)
   - ___ Chemical or mathematical formula not labeled as separate figure. Fig(s)___
   - ___ Group of waveforms not presented as a single figure, using common vertical axis with time extending along horizontal axis. Fig(s)___
   - ___ Individuals waveform not identified with a separate letter designation adjacent to the vertical axis. Fig(s)___

4. TYPE OF PAPER. 37 CFR 1.84(e)
   - ___ Paper not flexible, strong, white, smooth, nonshiny, and durable. Sheet(s)___
   - ___ Erasures, alterations, overwritings, interlineations, cracks, creases, and folds not allowed. Sheet(s)___

5. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable paper sizes:
   - 21.6 cm. by 35.6 cm. (8 1/2 by 14 inches)
   - 21.6 cm. by 33.1 cm. (8 1/2 by 13 inches)
   - 21.6 cm. by 27.9 cm. (8 1/2 by 11 inches)
   - 21.0 cm. by 29.7 cm. (DIN size A4)
   - ___ All drawing sheets not the same size. Sheet(s)___
   - ___ Drawing sheet not an acceptable size. Sheet(s)___

6. MARGINS. 37 CFR 1.84(g): Acceptable margins:

Paper size	21.6 cm. X 35.6 cm. (8 1/2 X 14 inches)	21.6 cm. X 33.1 cm. (8 1/2 X 13 inches)	21.6 cm. X 27.9 cm. (8 1/2 X 11 inches)	21 cm. X 29.7 cm. (DIN Size A4)
T	5.1 cm. (2")	2.5 cm. (1")	2.5 cm. (1")	2.5cm.
L	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	2.5 cm.
R	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.5 cm.
B	.64 cm. (1/4")	.64 cm. (1/4")	.64 cm. (1/4")	1.0 cm.

   Margins do not conform to chart above.
   Sheet(s)___
   ___Top (T) ___Left (L) ___Right (R) ___Bottom (B)

7. VIEWS. 37 CFR 1.84(h)
   REMINDER: Specification may require revision to correspond to drawing changes.
   - ___ All views not grouped together. Fig(s)___
   - ___ Views connected by projection lines. Fig(s)___
   - ___ Views contain center lines. Fig(s)___

   Partial views. 37 CFR 1.84(h)(2)
   - ___ Separate sheets not linked edge to edge. Fig(s)___
   - ___ View and enlarged view not labeled separately. Fig(s)___
   - ___ Long view relationship between different parts not clear and unambiguous. 37 CFR 1.84(h)(2)(ii) Fig(s)___

   Sectional views. 37 CFR 1.84(h)(3)
   - ___ Hatching not indicated for sectional portions of an object. Fig(s)___
   - ___ Hatching of regularly spaced oblique parallel lines not spaced sufficiently. Fig(s)___
   - ___ Hatching not at substantial angle to surrounding axes or principal lines. Fig(s)___
   - ___ Cross section not drawn same as view with parts in cross section with regularly spaced parallel oblique strokes. Fig(s)___
   - ___ Hatching of juxtaposed different elements not angled in a different way. Fig(s)___

   Alternate position. 37 CFR 1.84(h)(4)
   - ___ A separate view required for a moved position. Fig(s)___

   Modified forms. 37 CFR 1.84(h)(5)
   - ___ Modified forms of construction must be shown in separate views. Fig(s)___

8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i)
   - ___ View placed upon another view or within outline of another. Fig(s)___
   - ___ Words do not appear in a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s)___

9. SCALE. 37 CFR 1.84(k)
   - ___ Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s)___
   - ___ Indication such as "actual size" or "scale 1/2" not permitted. Fig(s)___
   - ___ Elements of same view not in proportion to each other. Fig(s)___

10. CHARACTER OF LINES, NUMBERS, & LETTERS. 37 CFR 1.84(l)
    - ___ Lines, numbers & letters not uniformly thick and well defined, clean, durable, and black (except for color drawings). Fig(s)___

11. SHADING. 37 CFR 1.84(m)
    - ___ Shading used for other than shape of spherical, cylindrical, and conical elements of an object, or for flat parts. Fig(s)___
    - ___ Solid black shading areas not permitted. Fig(s)___

12. NUMBERS, LETTERS, & REFERENCE CHARACTERS. 37 CFR 1.84(p)
    - ___ Numbers and reference characters not plain and legible. 37 CFR 1.84(p)(1) Fig(s)___
    - ___ Numbers and reference characters used in conjuction with brackets, inverted commas, or enclosed within outlines. 37 CFR 1.84(p)(1) Fig(s)___
    - ___ Numbers and reference characters not oriented in same direction as the view. 37 CFR 1.84(p)(1) Fig(s)___
    - ___ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s)___
    - ___ Numbers, letters, and reference characters do not measure at least .32 cm. (1/8 inch) in height. 37 CFR(p)(3) Fig(s)___

13. LEAD LINES. 37 CFR 1.84(q)
    - ___ Lead lines cross each other. Fig(s)___
    - ___ Lead lines missing. Fig(s)___
    - ___ Lead lines not as short as possible. Fig(s)___

14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(t)
    - ___ Number appears in top margin. Fig(s)___
    - ___ Number not larger than reference characters. Fig(s)___
    - ___ Sheets not numbered consecutively, and in Arabic numerals, beginning with number 1. Sheet(s)___

15. NUMBER OF VIEWS. 37 CFR 1.84(u)
    - ___ Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s)___
    - ___ View numbers not preceded by the abbreviation Fig. Fig(s)___
    - ___ Single view contains a view number and the abbreviation Fig.
    - ___ Numbers not larger than reference characters. Fig(s)___

16. CORRECTIONS. 37 CFR 1.84(w)
    - ___ Corrections not durable and permanent. Fig(s)___

17. DESIGN DRAWING. 37 CFR 1.152
    - ___ Surface shading shown not appropriate. Fig(s)___
    - ___ Solid black shading not used for color contrast. Fig(s)___

ATTACHMENT TO PAPER NO. 12 REVIEWER ___ DATE 3/11/98

PATENT DOCKET P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Carter and Presta

Serial No. 08/146,206

Filed: 17 November 1993

For: METHOD OF MAKING HUMANIZED ANTIBODIES

Group Art Unit: 1806

Examiner: ADAMS, D.

CERTIFICATE OF MAILING

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

13 April 1995
(Date of Deposit)

Aida A. Miclat
Name of Depositing Party

Aida A. Miclat
Signature of Depositing Party

13 April 1995
Date of Signature

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of Patents
and Trademarks
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 ($210) 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 $210.00 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.**

[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(b), 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.

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

Respectfully submitted,
GENENTECH, INC.

Date: April 13, 1995

By: _____
Wendy M. Lee

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So. San Francisco, CA 94080-4990
Phone: (415) 225-1994
Fax: (415) 952-9881

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

LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

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

U.S. PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Name	Class	Subclass	Filing Date
VDS	1	4,816,567	28.03.89	Cabilly et al.	530	387.3	

FOREIGN PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
X	2	0 239 400	30.09.87	EPO				
	3	0 620 276	19.10.94	EPO				
	4	WO 89/01783	09.03.89	PCT				
	5	WO 89/06692	27.07.89	PCT				
	6	WO 90/07861	26.07.90	PCT				
	7	WO 91/09967	11.07.91	PCT				
	8	WO 92/22653	23.12.92	PCT				
	9	WO 93/02191	04.02.93	PCT				

OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

X	10	Amzel and Poljak, "Three-dimensional structure of immunoglobulins" Ann. Rev. Biochem. 48:961-967 (1979)
	11	Bindon et al., "Human monoclonal IgG isotypes differ in complement activating function at the level of C4 as well as C1q" Journal of Experimental Medicine 168(1):127-142 (July 1988)
	12	Boulianne, G. L. et al., "Production of functional chimaeric mouse/human antibody" Nature 312(5995):643-646 (December 1984)
	13	Brown et al., "Anti-Tac-H, a humanized antibody to the interleukin 2 receptor, prolongs primate cardiac allograft survival" Proc. Natl. Acad. Sci. USA 88:2663-2667 (1991)
	14	Bruccoleri, "Structure of antibody hypervariable loops reproduced by a conformational search algorithm" Nature (erratum to article in Nature 335(6190):564-568 and) 336:266 (1988)
	15	Bruggemann, M. et al., "Comparison of the effector functions of human immunoglobulins using a matched set of chimeric antibodies" Journal of Experimental Medicine 166:1351-1361 (1987)
	16	Burgess et al., "Possible Dissociation of the Heparin-binding and Mitogenic Activities of Heparin-binding (Acidic Fibroblast) Growth Factor-1 from Its Receptor-binding Activities by Site-directed Mutagenesis of a Single Lysine Residue" Journal of Cell Biology 111:2129-2138 (1990)
	17	Carter et al., "Humanization of an anti-p185^{HER2} antibody for human cancer therapy" Proc. Natl. Acad. Sci. 89:4285-4289 (1992)
	18	Cheetham, J., "Reshaping the antibody combining site by CDR replacement-tailoting or tinkering to fit?" Protein Engineering 2(3):170-172 (1988)
	19	Chothia and Lesk, "Canonical Structures for the Hypervariable Regions" J. Mol. Biol. 196:901-917 (1987)
	20	Chothia et al., "The predicted structure of immunoglobulin D1.3 and its comparison with the crystal structure" Science 233:755-758 (Aug. 15, 1986)

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.

MINH-TAM DAVIS Deputy CR 10/01

USCOMM-DC 80-398.

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

LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

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

OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

PN	21	Chothia, C. et al., "Conformations of immunoglobulin hypervariable regions" Nature 342(6252):877-883 (1989)
	22	Chothia, Cyrus, "Domain association in immunoglobulin molecules: The packing of variable domains" J. Mol. Biol. 186:651-663 (1985)
	23	Clark et al., "The improved lytic function and in vivo efficacy of monovalent monoclonal CD3 antibodies" European Journal of Immunology 19:381-388 (1989)
	24	Co et al., "Humanized antibodies for antiviral therapy" Proc. Natl. Acad. Sci. USA 88:2869-2873 (1991)
	25	Coussens et al., "Tyrosine Kinase Receptor with Extensive Homology to EGF Receptor Shares Chromosomal Location with neu Oncogene" Science 230:1132-1139 (1985)
	26	Daugherty, BL et al., "Polymerase chain reaction facilitates the cloning, CDR-grafting, and rapid expression of a murine monoclonal antibody directed against the CD18 component of leukocyte integrins" Nucleic Acids Research 19(9):2471-2476 (May 11, 1991)
	27	Davies, D. R. et al., "Antibody-Antigen Complexes" Ann. Rev. Biochem. 59:439-473 (1990)
	28	Epp et al., "The molecular structure of a dimer composed of the variable portions of the Bence-Jones protein REI refined at 2.0-A resolution" Biochemistry 14(22):4943-4952 (1975)
	29	Fendly et al., "Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor or HER2/neu gene product" Cancer Research 50:1550-1558 (1990)
	30	Furey et al., "Structure of a novel Bence-Jones protein (Rhe) fragment at 1.6 A resolution" J. Mol. Biol. 167(3):661-692 (July 5, 1983)
	31	Gorman, SD et al., "Reshaping a therapeutic CD4 antibody" Proc. Natl. Acad. Sci. USA 88(10):4181-4185 (May 15, 1991)
	32	Gregory et al., "The solution conformations of the subclasses of human IgG deduced from sedimentation and small angle X-ray scattering studies" Molecular Immunology 24(8):821-829 (August 1987)
	33	Hale et al., "Remission induction in non-hodgkin lymphoma with reshaped human monoclonal antibody campath-1H" Lancet 1:1394-1399 (1988)
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	35	Huber et al., "Crystallographic structure studies of an IgG molecule and an Fc fragment" Nature 264:415-420 (December 2, 1976)
	36	Hudziak et al., "p185^{HER2} Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor" Molecular & Cellular Biology 9(3):1165-1172 (1989)
	37	Jaffers, G. J. et al., "Monoclonal antibody therapy. Anti-idiotypic and non-anti-idiotypic antibodies to OKT3 arising despite intense immunosuppression" Transplantation 41(5):572-578 (May 1986)
	38	Jones, P. T. et al., "Replacing the complementarity-determining regions in a human antibody with those from a mouse" Nature 321(6069):522-525 (1986)
	39	Junghans et al., "Anti-Tac-H, a humanized antibody to the interleukin 2 receptor with new features for immunotherapy in malignant and immune disorders" Cancer Research 50(5):1495-1502 (Mar 1, 1990)
PN	40	Kabat et al. Sequences of Proteins of Immunological Interest, Bethesda, MD:National Institutes of Health pps. iii-xxvii, 41-176 (1987)

Examiner: Patricia Hazel | 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.

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FORM PTO-1449

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Atty Docket No.	Serial No.
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(Use several sheets if necessary)

OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

41	King et al., "Amplification of a Novel v-erbB-Related Gene in a Human Mammary Carcinoma" Science 229:974-976 (1985)
42	Lazar et al., "Transforming Growth Factor α: Mutation of Aspartic Acid 47 and Leucine 48 Results in Different Biological Activities" Molecular & Cellular Biology 8(3):1247-1252 (1988)
43	Love et al, "Recombinant antibodies possessing novel effector functions" Methods in Enzymology 178:515-527 (1989)
44	Lupu et al., "Direct interaction of a ligand for the erbB2 oncogene product with the EGF receptor and p185^{erbB2}" Science 249:1552-1555 (1990)
45	Margni RA and Binaghi RA, "Nonprecipitating asymmetric antibodies" Ann. Rev. Immunol. 6:535-554 (1988)
46	Margolies et al., "Diversity of light chain variable region sequences among rabbit antibodies elicited by the same antigens." Proc. Natl. Acad. Sci. USA 72:2180-84 (Jun 1975)
47	Marquart et al., "Crystallographic refinement and atomic models of the intact immunoglobulin molecule Kol and its antigen-binding fragment at 3.0 A and 1.0 A resolution" J. Mol. Biol. 141(4):369-391 (Aug 25, 1980)
48	Mian, IS et al., "Structure, function and properties of antibody binding sites" J. Mol. Biol. 217(1):133-151 (Jan 5, 1991)
49	Miller, R. et al., "Monoclonal antibody therapeutic trials in seven patients with T-cell lymphoma" Blood 62:988-995 (1983)
50	Morrison, S. L. et al., "Chimeric human antibody molecules: mouse antigen-binding domains with human constant region domains" Proc. Natl. Acad. Sci. USA 81(21):6851-6855 (Nov. 1984)
51	Neuberger et al., "Recombinant antibodies possessing novel effector functions" Nature 312(5995):604-608 (December 1984)
52	Neuberger, M. S. et al., "A hapten-specific chimaeric IgE antibody with human physiological effector function" Nature 314(6008):268-270 (March 1985)
53	Novotny and Haber, "Structural invariants of antigen binding: comparison of immunoglobulin V_L-V_H and V_L-V_L domain dimers" Proc. Natl. Acad. Sci. USA 82(14):4592-4596 (July 1985)
54	Pluckthun, Andreas, "Antibody engineering: advances from the use of escherichia coli expression systems" Biotechnology 9:545-51 (1991)
55	Queen, M. et al., "A humanized antibody that binds to the interleukin 2 receptor" Proc. Natl. Acad. Sci. USA 86:10029-10033 (1989) Dupl.
56	~~Riechmann, L. et al., "Reshaping human antibodies for therapy" Nature 332:323-327 (1988)~~ Dupl.
57	~~Roitt et al. Immunology (Gower Medical Publishing Ltd., London, England) pps. 5.5 (1985)~~ Dupl.
58	Saul et al., "Preliminary refinement and structural analysis of the Fab fragment from human immonoglobulin new at 2.0 A resolution" Journal of Biological Chemistry 253(2):585-597 (January 25, 1978)
59	Schroff, R. et al., "Human anti-murine immunoglobulin responses in patients receiving monoclonal antibody therapy" Cancer Research 45:879-885 (1985)
60	Segal et al., "The three-dimensional structure of a phosphorylcholine-binding mouse immunoglobulin Fab and the nature of the antigen binding site" Proc. Natl. Acad. Sci. USA 71(11):4298-4302 (Nov 1974)

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	DEC 20 1995
Carter and Presta	
Filing Date	**Group**
17 Nov 1993	~~1806~~ 1816

OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

PN	61	Shalaby et al., "Development of humanized bispecific antibodies reactive with cytotoxic lymphocytes and tumor cells overexpressing the HER2 protooncogene" Journal of Experimental Medicine 175(1):217-225 (Jan 1, 1992)
	62	Shepard and Lewis, "Resistance of tumor cells to tumor necrosis factor" J. Clin. Immunol. 8(5):333-395 (1988)
	63	Sheriff et al., "Three-dimensional structure of an antibody-antigen complex" Proc. Natl. Acad. Sci. USA 84(22):8075-8079 (Nov. 1987)
	64	Sherman et al., "Haloperidol binding to monoclonal antibodies" Journal of Biological Chemistry 263:4064-4074 (1988)
	65	Silverton et al., "Three-dimensional structure of an intact human immunoglobulin" Proc. Natl. Acad. Sci. USA 74:5140-5144 (1977)
	66	Slamon et al., "Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene" Science 235:177-182 (1987)
	67	Slamon et al., "Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer" Science 244:707-712 (1989)
	68	Snow and Amzel, "Calculating three-dimensional changes in protein structure due to amino-acid substitutions: the variable region of immunoglobulins" Protein: Structure, Function, and Genetics, Alan R. Liss, Inc. Vol. 1:267-279 (1986)
	69	Sox et al., "Attachment of carbohydrate to the variable region of myeloma immunoglubulin light chains" Proc. Natl. Acad. Sci. USA 66:975-82 (July 1970)
	70	Spiegelberg et al., "Localization of the carbohydrate within the variable region of light and heavy chains of human γG myeloma proteins" Biochemistry 9:4217-23 (Oct 1970)
	71	Takeda et al., "Construction of chimaeric processed immunoglobulin genes containing mouse variable and human constant region sequences" Nature 314(6010):452-454 (April 1985)
	72	Tao et al., "Role of Carbohydrate in the Structure and Effector Functions Mediated by the H uman IgG Constant Region" J. Immunol. 143(8):2595-2601 (1989)
	73	Tramontano et al., "Framework residue 71 is a major determinant of the position and conformation of the second hypervariable region in the VH domains of immunoglobulins" J-Mol-Biol 215(1):175-182 (Sep 5, 1990)
	74	Verhoeyen, M. et al., "Reshaping human antibodies: grafting an antilysozyme activity" Science 239(4847):1534-1536 (Mar 25, 1988)
	75	Waldmann, T., "Monoclonal antibodies in diagnosis and therapy" Science 252:1657-1662 (1991)
	76	Wallick et al., "Glycosylation of a VH residue of a monoclonal antibody against alpha (1----6) dextran increases its affinity for antigen" Journal of Experimental Medicine 168(3):1099-1109 (Sep 1988)
	77	Winter and Milstein, "Man-made antibodies" Nature 349(6307):293-299 (Jan 24, 1991)
PN	78	Yamamoto et al., "Similarity of protein encoded by the human c-erb-B-2 gene to epidermal growth factor receptor" Nature 319:230-34 (1986)

Examiner: Patricia Fox | 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.

1802 Receipt

PATENT DOCKET 709P1 ~~#~~ 14

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: 1806

Examiner: D. Adams

CERTIFICATE OF MAILING

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

April 10 1995
(Date of Deposit)

Elisa R. Hamby
Name of Depositing Party

Elisa R. Hamby
Signature of Depositing Party

4/10/95
Date of Signature

REQUEST FOR A CORRECTED FILING RECEIPT

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

Sir:

Attached is a copy of the Official Filing Receipt received from the PTO in the above application for which issuance of a corrected filing receipt is respectfully requested. Please make the correction as follows: Under "CONTINUING DATA AS CLAIMED BY APPLICANT-", please delete "07/715,222 06/14/91 PAT D 335,559" and insert --07/715,272 06/14/91 ABD--.

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

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

Respectfully submitted,

GENENTECH, INC.

Date: April 10, 1995

By: _____
Wendy M. Lee

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080-4990
Phone: (415) 225-1994
Fax: (415) 952-9881

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 assigneed 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

PTO-103X
(Rev. 7-93)

FILING RECEIPT

CORRECTED

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

WL

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
08/146,206	11/17/93	1806	$1,592.00	709P1	9	18	9

RECEIVED
MAY 15 1995
GROUP 1800

JANET E. HASAK
GENENTECH, INC.
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SOUTH SAN FRANCISCO, CA 94080-4990

Receipt is acknowledged of this patent application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check of draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Application Processing Division's Customer Correction Branch within 10 days of receipt. Please provide a copy of the Filing Receipt with the changes noted thereon.

Applicant(s) PAUL J. CARTER, SAN FRANCISCO, CA; LEONARD G. PRESTA, SAN FRANCISCO, CA.

CONTINUING DATA AS CLAIMED BY APPLICANT-
THIS APPLN IS A 371 OF PCT/US92/05126 06/15/92
WHICH IS A CIP OF ~~07/715,222 06/14/91 PAT D 335,559~~
07/715,272 06/14/91 ABD

FOREIGN/PCT APPLICATIONS-PCT PCT/US92/05126 06/15/92

TITLE
METHOD FOR MAKING HUMANIZED ANTIBODIES

PRELIMINARY CLASS: 530

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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C07K 13/00, C12N 5/10
G06F 15/00

A1

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(30) Priority data:
715,272 14 June 1991 (14.06.91) US

(60) Parent Application or Grant
(63) Related by Continuation
US 715,272 (CIP)
Filed on 14 June 1991 (14.06.91)

(71) Applicant *(for all designated States except US)*: GENENTECH, INC. [US/US]; 460 Point San Bruno Boulevard, South San Francisco, CA 94080 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : CARTER, Paul, J. [GB/US]; 2074 18th Avenue, San Francisco, CA 94116 (US). PRESTA, Leonard, G. [US/US]; 1900 Gough Street, #206, San Francisco, CA 94109 (US).

(74) Agents: ADLER, Carolyn, R. et al.; Genentech, Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080 (US).

(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
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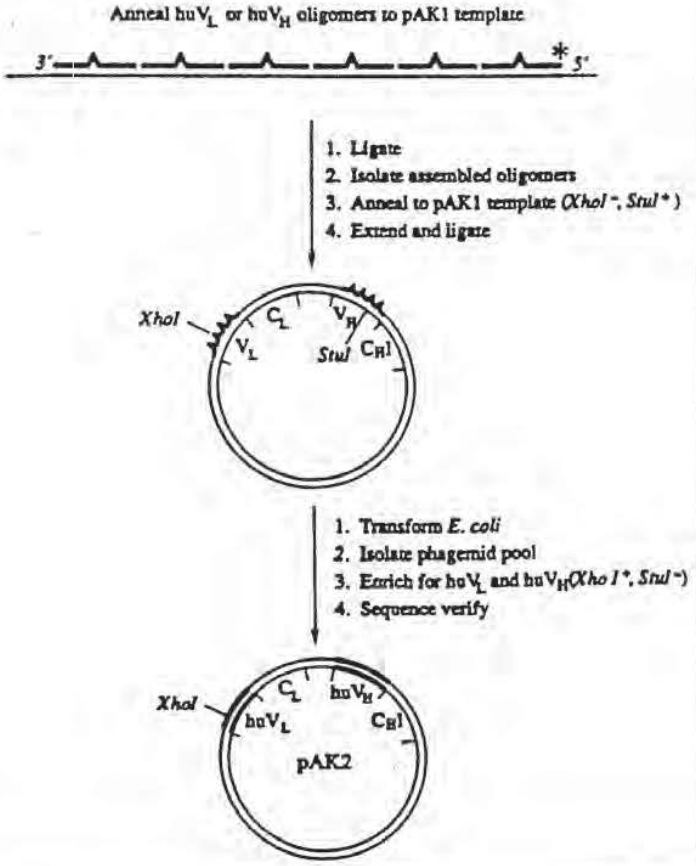
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: METHOD FOR MAKING HUMANIZED ANTIBODIES

(57) Abstract

Variant immunoglobulins, particularly humanized antibody polypeptides are provided, along with methods for their preparation and use. Consensus immunoglobulin sequences and structural models are also provided.



#16

PATENT DOCKET 709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In 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: 1806

Examiner: D. Adams 1802

CERTIFICATE OF MAILING

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

June 9, 1995
(Date of Deposit)

Wendy Lee
Name of Depositing Party

Wendy Lee
Signature of Depositing Party

June 9, 1995
Date of Signature

AMENDMENT TRANSMITTAL

Honorable Commissioner of Patents
and Trademarks
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 Fee(s)
Total	24	Minus	23	= 1	x 22 =	$ 22.00
Indep.	6	Minus	10	= 0	x 76 =	$ 0
___ First Presentation of Multiple Dependent Claim					+ 240 =	$ 0
					TOTAL	**$ 22.00**

____ No additional fee is required.

__X__ The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $22.00. **A duplicate copy of this transmittal is enclosed.**

__X__ 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.**

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

Respectfully submitted,
GENENTECH, INC.

Date: June 9, 1995

By: _____
Wendy M. Lee

460 Pt. San Bruno Blvd.
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PATENT DOCKET 709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Paul J. Carter et al.

Serial No. 08/146,206

Filed: 17 November 1993

For: METHOD FOR MAKING HUMANIZED ANTIBODIES

Group Art Unit: 1806

Examiner: D. Adams

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

AUG 7 1995

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

Sir:

Applicant petitions the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated 12/9/94 for three month(s) from 3/9/95 to 6/9/95. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $870.00 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.

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

Respectfully submitted,
GENENTECH, INC.

Date: June 9, 1995

By: W M Lee
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250 TL 07-0630 07/12/95 08146206
25181 117 870.00CH 709P1

PATENT DOCKET 709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Paul J. Carter et al.

Serial No. 08/146,206

Filed: 17 November 1993

For: METHOD FOR MAKING HUMANIZED ANTIBODIES

Group Art Unit: 1806

Examiner: D. Adams

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June 9, 1995
(Date of Deposit)
Wendy Lee
Name of Depositing Party
Wendy Lee
Signature of Depositing Party
June 9, 1995
Date of Signature

AMENDMENT UNDER 37 C.F.R. §1.111

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

Sir:

This amendment is responsive to the Office Action dated 12/9/94. Attached is a petition and petition fee for a three-month extension of time making this response timely filed on or before 6/9/95. Please amend the application as follows:

IN THE SPECIFICATION:

On page 1, beneath the title and before the subheading "Field of the Invention", please insert the following:

--Cross References

This application is a continuation-in-part of U.S. Application Serial No. 07/715,272 filed 14 June 1991 (abandoned) which application is incorporated herein by reference and to which application priority is claimed under 35 USC §120.--;

On page 65, line 5, change "Relative" to read --Relative cell proliferation--;
line 6, delete "cell";
line 8, delete "proliferation†";
line 11, delete "407" and insert --4.7 101--;

line 12, delete "466" and insert --4.4 66--;
line 13, delete "0.86" and insert --0.82 56--;
line 14, delete "148" and insert --1.1 48--;
line 15, delete "0.22" and insert --0.22 51--;
line 16, delete "0.63" and insert --0.62 53--;
line 17, delete "0.50" and insert --0.10 54--; and
line 18, delete "0.30" and insert --0.30 37--.

IN THE CLAIMS:

Please cancel claims 13 and 14 without prejudice.

1. (Amended) A method for making a humanized antibody comprising amino acid sequences of a non-human, import antibody and a human antibody, comprising the steps of:

[a][.] obtaining the amino acid sequences of at least a portion of an import variable domain and of a consensus human variable domain;

[b][.] identifying [Complementarity] Complementary Determining Region (CDR) amino acid sequences in the import variable domain and the consensus human [amino] variable domain [sequences];

[c][.] substituting an import CDR amino acid sequence for the corresponding consensus human CDR amino acid sequence;

[d][.] aligning the amino acid sequences of a Framework Region (FR) of the import [antibody] variable domain and [the] a corresponding FR of the consensus [antibody] human variable domain;

[e][.] identifying import [antibody] FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus [antibody] FR residues;

[f][.] determining if the non-homologous import [amino acid] FR residue is [reasonably] expected to have at least one of the following effects:

[1][.] non-covalently binds antigen directly,

[2][.] interacts with a CDR; or

[3][.] participates in the V_L - V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another; and

[g][.] for any non-homologous import [antibody amino acid] FR residue which is [reasonably] expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus [antibody] FR [sequence].

2. (Amended) The method of claim 1, having an additional step of determining [if] whether any such non-homologous import residue[s are] is exposed on the surface of the consensus human variable domain or buried within it, and if the non-homologous import residue is exposed, retaining the corresponding consensus residue.

3. (Amended) The method of claim 1 or 19, having the additional steps of searching the import variable domain sequence for glycosylation sites, determining if any such glycosylation site is [reasonably] expected to affect the antigen binding or affinity of the antibody, and if so, substituting the glycosylation site into the consensus [sequence] human variable domain.

4. (Amended) The method of claim 1 or 19, having the additional steps of searching the consensus human variable domain sequence for glycosylation sites which are not present at the corresponding amino acid in the import variable domain sequence, and if [the] any such glycosylation site is not present in the import variable domain sequence, substituting the import amino acid residue[s] for the amino acid residue[s] comprising the consensus glycosylation site.

5. (Amended) The method of claim 1 or 19, having [an] the additional steps if [which comprises] aligning the import [antibody] FR sequence and consensus [antibody] FR sequence[s], identifying import [antibody] FR residues which are non-homologous [with] to the aligned consensus FR [sequence] residues, and for each such non-homologous import [antibody] FR residue, determining if the corresponding consensus [antibody] residue represents a residue which is highly conserved across all species at that site, and if it is so conserved, preparing a humanized antibody which comprises the consensus [antibody amino acid] residue at that site.

6. (Amended) The method of claim 1, wherein the corresponding consensus FR [antibody] residues substituted in step (g) are selected from the group consisting of 4L, 35L, [36L,] 38L, 43L, 44L, 46L, 58L, [62L, 63L,] 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, [87L,] 98L, 2H, 4H, 24H, 36H, [37H,] 39H, 43H, 45H, 49H, [58H, 60H, 67H, 68H,] 69H, 70H, 73H, 74H, 75H, 76H, and 78H[, 91H, 92H, 93H, and 103H].

7. (Amended) A method comprising providing at least a portion of an import, non-human [antibody] variable domain amino acid sequence having a Complementary Determining Region (CDR) and a Framework Region (FR), obtaining the amino acid sequence of at least a portion of a consensus human [antibody] variable domain of a human immunoglobulin subgroup having a CDR and a FR, substituting the non-human CDR for the human CDR in the consensus human

[antibody] variable domain, and [then] substituting a[n] non-human amino acid residue for the consensus amino acid residue at at least one of the following sites:
4L, 35L, [36L,] 38L, 43L, 44L, 46L, 58L, [62L, 63L,] 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, [87L,] 98L, 2H, 4H, 24H, 36H, [37H,] 39H, 43H, 45H, 49H, [58H, 60H, 67H, 68H,] 69H, 70H, 73H, 74H, 75H, 76H, and 78H[, 91H, 92H, 93H, and 103H].

In claim 8, line 2, please replace "antibody" with --variable domain--.
In claim 9, line 1, please delete "~~or 7~~".

10. (Amended) A humanized antibody variable domain having a non-human Complementary Determining Region (CDR) incorporated into a consensus human variable domain [a human antibody variable domain], wherein [the improvement comprises substituting an] a human amino acid residue [for the human residue] has been substituted by a non-human amino acid residue at a site selected from the group consisting of:
4L, 35L, [36L,] 38L, 43L, 44L, 46L, 58L, [62L, 63L,] 64L, 65L, 66L, 67L, 68L, 69L, 70L, 71L, 73L, 85L, [87L,] 98L, 2H, 4H, 24H, 36H, [37H,] 39H, 43H, 45H, 49H, [58H, 60H, 67H, 68H,] 69H, 70H, 73H, 74H, 75H, 76H, and 78H[, 91H, 92H, 93H, and 103H].

In claim 12, line 1, please replace "FR" with --Framework Region (FR)--.

15. (Amended) A method for engineering a humanized antibody comprising introducing amino acid residues from a[n] non-human, import [antibody] variable domain into [an amino acid sequence representing a] consensus [of mammalian antibody] human variable domain [sequences] of a human immunoglobulin subgroup.

19. (Amended) A method for making a humanized antibody comprising amino acid sequences of a non-human, import antibody and a human antibody, comprising the steps of:
[a][.] obtaining the amino acid sequences of at least a portion of an import variable domain and of a consensus human variable domain;
[b][.] identifying [Complementarity] Complementary Determining Region (CDR) amino acid sequences in the import variable domain and the consensus human [amino] variable domain [sequences];
[c][.] substituting an import CDR amino acid sequence for the corresponding consensus human CDR amino acid sequence;

{d}[.] aligning the amino acid sequences of a Framework Region (FR) of the import [antibody] variable domain and [the] a corresponding FR of the consensus [antibody] human variable domain;

{e}[.] identifying import [antibody] FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus [antibody] FR residues;

{f}[.] determining if the non-homologous import [amino acid] FR residue is [reasonably] expected to have at least one of the following effects:

{1}[.] non-covalently binds antigen directly,

{2}[.] interacts with a CDR; or

{3}[.] participates in the V_L - V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another;

{g}[.] for any non-homologous import [antibody amino acid] FR residue which is [reasonably] expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus [antibody] FR [sequence]; and

{h}[.] for any non-homologous import antibody amino acid residue, determining [if] whether any such non-homologous import residue is exposed on the surface of the consensus human variable domain or buried within it, and if the non-homologous import residue is exposed, retaining the corresponding consensus residue.

Please add the following claims:

--20. The method of claim 1 wherein step (g) is followed by a step wherein the humanized antibody is prepared which has a variable domain having amino acid sequences determined in steps (a)-(g)--

--21. The method of claim 1 wherein the consensus human variable domain is of a human immunoglobulin subgroup.--

--22. The method of claim 19 wherein the consensus human variable domain is of a human immunoglobulin subgroup.--

--23. A humanized antibody comprising a consensus human variable domain of a human immunoglobulin subgroup wherein the amino acid residues forming the Complementary Determining Regions (CDRs) thereof comprise non-human import antibody amino acid residues.--

--24. The humanized antibody of claim 23 further comprising a Framework Region (FR) residue of the non-human import antibody, wherein the FR residue either:

(a) non-covalently 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.--

--25. The humanized antibody of claim 24 comprising more than one FR residue of the non-human import antibody.--

--26. The humanized antibody of claim 25 comprising from about 1 to about 7 FR residues of the non-human import antibody.--

REMARKS

The specification has been amended to correct obvious typographical errors in Table 3 on page 65. It is clear that the last two columns of Table 3 were inadvertently superimposed and the amendment to the specification serves merely to correct these errors. Please refer to Table 1 of Carter *et al., Proc. Natl. Acad. Sci.,* **89,** (1992), of record, which shows the correct Kd and Relative Cell Proliferation values of the variants described in Table 3 of the instant application. Applicants respectfully request that the specification be amended to correct the typographical errors discussed above.

The claims have been revised and additional claims added with specification support for the claim revisions being found at least as follows:

Claim	Wording	Specification Support
1, step (f)(3) 19, step (f)(3)	"by affecting....one another"	Page 11, lines 37-38
7, 15, 23	"of a human immunoglobulin subgroup"	Page 8, lines 27-29 Page 14, lines 3-4
21, 22	Entire Claim	
10, 23	"consensus human variable domain"	Claim 1 originally filed
20	Entire Claim	Page 1, line 6

23	"wherein the....import antibody amino acid residues"	Page 9, lines 32-38
24, 25	Entire Claim	Claims 1 and 3 originally filed
26	Entire Claim	See below

Claim 26 refers to the number of non-human import FR residues substituted into the humanized antibodies described in the examples (*i.e.* from about 1 to about 7 residues). In Example 1, 1-7 residues in the FR region were replaced with non-human import residues (see Table 3 on page 65). Murine residues are shown in three letter amino acid code (see lines 20-21 on page 65). Example 3 refers to replacement of 4 of the consensus FR residues with murine import residues (see Fig 5). Replacement residues are indicated with a "#" and residues in the CDRs are indicated by a line and/or carets.

The other claim revisions are clerical in nature. Following entry of this amendment, claims 1-12, 15 and 19-26 will be pending in this case.

Applicants note that the restriction requirement has been made final. Accordingly, claims 13 and 14 have been cancelled without prejudice to file a continuing application directed thereto.

Applicants note that claims 1-12 and 15 are currently under consideration. It should be noted that independent claim 19 (and claims 3, 4 and 5 which depend thereon) are also in this case, having been introduced in the amendment (dated June 12, 1993) to the PCT application on which this application is based. See the International Preliminary Examination Report dated September 20, 1993. Applicants ask that this claim also be considered in the prosecution of the instant application.

Formality Matters

The Examiner asserts that the declaration is defective because it does not state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 USC §120 which discloses and claims subject matter in addition to that disclosed in the prior copending application acknowledged the duty to disclose material information as defined in 37 CFR §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

Applicants refer to the Combined Declaration and Power of Attorney submitted November 17, 1993. Since the declaration meets all the requirements of 37 CFR §1.63, applicants submit that a new declaration pursuant to 37 CFR §1.67(a) [see also MPEP 602.01 and 602.02] is not required. In particular, the last paragraph on page 1 of the declaration meets the requirements of 37 CFR §1.63(d). Accordingly, applicants request that the objection to the declaration be reconsidered and withdrawn.

The Examiner has objected to the drawings. Applicants ask that this matter be held in abeyance until the application is allowed.

The specification has been updated to refer to continuing data as proposed under item #29 in the Office Action.

The Rejection Under 35 USC §112, First Paragraph

The specification has been objected to and claims 1-12 and 15 rejected under 35 USC §112, first paragraph as allegedly failing to adequately teach how to use the claimed antibody or antibody produced by the claimed methods. The Examiner acknowledges that the exemplary antibody 4D5 does have a diagnostic utility for the detection of $p185^{HER2}$. However, the Examiner is of the opinion that it is unclear whether any other antibody will have a diagnostic or therapeutic utility. The Examiner believes that determining which other antibodies are useful would be an unpredictable event and would require undue experimentation for an ordinarily skilled person.

Applicants submit that the specification does enable the instantly claimed invention. This application discloses and claims a unique method for antibody humanization which can be used to humanize any antibody of interest. The instantly claimed humanization technique has been successfully used to humanize several different non-human antibodies including anti-HER2 (see Example 1); anti-CD3 (see Example 3); anti-CD18 (see Example 4); and anti-IgE (see Presta *et al.*, *J. Immunol.* **151**:2623-2632 [1993], copy attached). These antibodies had known diagnostic and/or therapeutic uses at the priority date of the instant application. For example, humanized anti-HER2 could be used for clinical intervention in and imaging of carcinomas in which $p185^{HER2}$ is overexpressed (see page 4, lines 20-28 of the application); humanized anti-CD3 antibodies could be used to detect CD3 in biological samples (*e.g.* to detect $CD3^+$ CTL; see page 69, line 22 of the application) or for making bispecific antibodies such as the anti-HER2/anti-CD3 bispecific antibody for tumor immunotherapy (see page 70, lines 23-38 of the application); anti-CD18 antibodies could be used for detecting the CD18 antigen in biological specimens and for indications such as reducing inflammation associated with meningitis or encephalitis (see U.S. Patent 5,147,637, copy attached), for example; anti-IgE could be used for detecting IgE and for treating allergy as described in Presta *et al.*, *supra*. In addition to these antibodies, the application refers to many other antibodies available at the priority date which were known to have diagnostic and/or therapeutic uses. These antibodies presented potential candidates for humanization using the procedures disclosed and claimed. Examples are provided in the background section of the application. See, for example, Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, National Institutes of Health, Bethesda, MD, (1987); U.S. patent No. 4,816,567; Morrison *et al.*, *Proc. Natl. Acad. Sci. USA* **81**:6851-6855 (1984); Boulianne *et al.*, *Nature* **312**:643-646 (1984); Neuberger *et al.*, *Nature* **314**:268-270 (1985); Brüggemann *et al.*, *J. Exp. Med.* **166**:1351-1361 (1987); Riechmann *et al.*, *Nature* **332**:323-327 (1988); Love *et al.*, *Methods in Enzymology* **178**:515-527 (1989); Bindon *et al.*, *J. Exp. Med.* **168**:127-142 (1988); Jaffers *et al.*, *Transplantation* **41**:572-578 (1986); Jones *et al.*, *Nature* **321**:522-525 (1986); Verhoeyen, M. *et al.*, *Science* **239**:1534-1536

(1988); Hale *et al.*, *Lancet* **i**:1394-1399 (1988); Queen *et al.*, *Proc. Natl. Acad. Sci. USA* **86**:10029-10033 (1989); Co *et al.*, *Proc. Natl. Acad. Sci. USA* **88**:2869-2873 (1991); Gorman *et al.*, *Proc. Natl. Acad. Sci. USA* **88**:4181-4185 (1991); Daugherty *et al.*, *Nucleic Acids Research* **19(9)**:2471-2476 (1991); Brown *et al.*, *Proc. Natl. Acad. Sci. USA* **88**:2663-2667 (1991); and Junghans *et al.*, *Cancer Research* **50**:1495-1502 (1990), all of record. Therefore, any of the antibodies described in these references could have been chosen to be humanized using the techniques described in the instant application. In addition, an antibody to the antigens described in these references or other antigens of interest could have been generated using the techniques for making antibodies described on pages 27-29 of the application, for example. Therapeutic and diagnostic uses for the humanized antibodies were also taught on, *e.g.*, pages 50-55 of the application.

In addition to the numerous examples of antibodies which were specifically disclosed in the application, the skilled practitioner at the priority date would have had many, many other antibodies with established uses (including diagnostic and therapeutic uses) to choose from. To demonstrate this, several review articles are attached which show that antibodies which were used (a) as probes for oncogene products; (b) as tools in genetic studies on carbohydrate blood group antigens; (c) for diagnosis and therapy of lymphoproliferative diseases; (d) in the diagnosis and treatment of bacterial infections; (e) in the diagnosis and prognosis of breast cancer; (f) in the flow cytometric analysis of benign and malignant cells; and (g) as proliferation markers (*e.g.* Ki-67) for immunohistological diagnostic and prognostic evaluation of human malignancies, were available at the priority date which could have been humanized using the instantly claimed method. See Niman, *Immunodiagnosis of Cancer*, Second Edition, pp. 189-204 (1990); Watkins *et al.*, *Journal of Immunogenetics* **17**:259-276 (1990); Campana *et al.*, *The Turkish Journal of Pediatrics* **32**:143-151 (1990); Verhoef and Torensma, *Eur. J. Clin. Microbiol. Infect. Dis.* **9(4)**:247-250 (1990); Ellis *et al.*, *Pathology Annual* **25**:193-235 (1990); Beck *et al.*, *Cancer Biology* **1**:181-188 (1990); and Gerdes, *Cancer Biology* **1**:199-206 (1990), copies attached. Once the method of humanization disclosed in the instant application was discovered, it would have been routine to select any one of these antibodies and humanize them using the disclosed procedures. Therefore, applicants submit that it would have been clear to the skilled artisan that many antibodies other than anti-HER2 were available which had diagnostic and/or therapeutic utilities. Applicants further submit that determining which other antibodies would have been useful at the priority date would not have been an unpredictable event and would not have required undue experimentation for an ordinarily skilled person.

Accordingly, applicants ask that this rejection under 35 USC §112, second paragraph be reconsidered and withdrawn.

The Rejection Under 35 USC §103 - Winter, Queen *et al.* and Riechmann *et al.*

Claims 1, 2, 4-12 and 15 are rejected under 35 USC §103 as being unpatentable over EP239,400 (Winter); Riechmann *et al.* Nature: **332**: 323-327 (1988); and Queen *et al.* PNAS, USA **86**: 10029-10033 (1989). Applicants traverse this rejection as it may apply to the claims as amended herein.

EP239,400 describes a procedure for partial antibody "humanization" wherein the FR residues of the heavy chain of the engineered antibody are provided by the framework region of an individual human antibody V_H. In particular, the heavy chain framework region of the humanized B1-8 antibody (*i.e.* HuV_{NP}) described in Example 1 and the humanized anti-lysozyme antibody D1.3 described in Example 2 was derived from the human myeloma heavy chain NEWM (see page 17, lines 1-2 and lines 9-10 on page 26). The $NEWV_H$ framework region was chosen because the crystallographic structure thereof was known. See page 17, lines 2-3 of EP239,400. The light chains of the B1-8 and D1•3 antibodies were never humanized. Furthermore, only the CDRs were transferred; none of the non-human FR residues were incorporated into the engineered molecule. EP239,400 briefly mentions further work with the antibody CAMPATH-1 (see pages 30-31), but fails to describe in detail how this antibody was humanized. The detailed description of the "CAMPATH-1" work appears to be described in Riechmann *et al.* Using the same strategy as disclosed in EP239,400, Riechmann and his colleagues made a humanized heavy-chain variable domain which had the framework regions of human NEW alternating with the CDRs of rat YTH 34.5HL anti-CAMPATH-1 antibody. Thus, the same heavy chain framework region as disclosed in EP239,400 was used once again. The rationale for this was that the crystallographic structure of NEW was available (see page 325, second to last paragraph of Riechmann *et al.*). For humanization of the light chain of rat YTH 34.5HL, the human REI light chain variable domain was used, as the human NEW light chain region could not be used (because there is a deletion at the beginning of the third framework region of NEW; see page 325, second to last paragraph of Riechmann *et al.*). Also, a crystallographic structure for REI was available. Thus, Riechmann *et al.* used FR residues from a single antibody for humanizing a non-human antibody variable domain. Riechmann *et al.* describe mutating one or two FR residues in order "to restore the packing of the loop" (see page 326, column 1).

Queen *et al.* describe the methods they employed for humanizing their anti-Tac monoclonal antibody which binds to the p55 chain of the human interleukin 2 receptor. As mentioned in the abstract of this paper, the "human framework regions were chosen to maximize homology with the anti-Tac antibody sequence". Queen *et al.* reasoned that the more homologous the human antibody was to the original anti-Tac antibody, the less likely would combining the anti-Tac CDRs with the human FR be to introduce distortions into the CDRs. See page 10031, column 2, paragraph 2 of Queen *et al.* Queen *et al.* further reiterate this in the summary on page 10033 where they state that "the human framework was chosen to be as homologous as possible to the original mouse antibody to reduce any

deformation of the mouse CDRs". Thus, based on a comparison of the anti-Tac heavy chain sequence to all human heavy chain sequences in the National Biomedical Research Foundation Protein Identification Resource database, the heavy chain V region of the human Eu antibody was selected. Because no one human light chain V region was especially homologous to the anti-Tac light chain, the Eu light chain was also selected to provide the framework residues for the light chain of the humanized antibody. Accordingly, the framework regions of the humanized antibody described by Queen *et al.* were derived from a single antibody. Queen *et al.* transferred a number of the murine FR residues into the humanized antibody (two in the V_L and nine in the V_H; see Fig. 2 of this reference). These transferred residues were thought to be close enough to the CDRs to either influence their conformation or interact directly with antigen (see page 10031, column 2, paragraph 3). It was thought that this transfer of FR residues would better preserve the precise structure of the CDRs at the cost of possibly making the humanized antibody slightly less "human". Queen *et al.* also noted that a given human variable domain will contain exceptional FR amino acids which are atypical of other human V regions. The human Eu antibody had seven such residues in the heavy chain and two in the light chain. Because the murine antibody had a residue much more typical of human sequences, the murine residues were retained at these sites rather than the Eu residue.

The instantly claimed invention differs from the teachings of each of the above-mentioned references in that it provides a method for humanization and humanized antibodies wherein the framework regions of the humanized antibodies are essentially formed by a "consensus human variable domain", *i.e.*, an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure (see page 13, lines 20-22 of the application). Preferably, the consensus is from one of the "human immunoglobulin subgroups" described by Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, National Institutes of Health, Bethesda MD (1987) (*e.g.*, V_L κ subgroup I and V_H subgroup III). See page 14, first paragraph of the application. The instant application demonstrates, for the first time, that a number of non-human antibodies can be humanized using such a consensus human variable domain to provide the framework regions of the antibody. Applicants submit that the use of such a consensus sequence for humanizing non-human antibodies was not disclosed or alluded to by the cited references. Accordingly, a *prima facie* case of obviousness has not been established by the Office.

In addition, the prior art taught away from the claimed invention. EP239,400 and Riechmann *et al.* taught that a framework region of an individual antibody should be used for humanization, especially where a crystallographic structure of the chosen antibody was available. On the contrary, crystal structures of consensus human variable domains as claimed in the instant application were not available. Therefore, the method for humanization claimed in the above application diverged from that taught by EP239,400 and Riechmann *et al.*

Queen *et al.* also taught that the FR residues of the humanized antibody should be provided by an individual antibody (*i.e.* the Eu antibody). Furthermore, Queen *et al.* taught that the sequence used for humanization should be as homologous as possible to the non-human sequence to be humanized in order to reduce the likelihood of introducing distortions into the CDRs. Therefore, according to the teachings of Queen *et al.* framework region sequences needed to be tailored to each non-human antibody to be humanized. Because Queen *et al.* used the human Eu antibody sequence, they found that they needed to replace "atypical" residues from the human sequence with the corresponding murine residues (where the murine residues were more typical). See page 10032, column 1, paragraph 1 of Queen *et al.* The approach adopted by Queen *et al.* was also followed by Co *et al.*, PNAS USA, 88:2869-2873 (1991), of record. It is apparent that Co *et al.* felt it was necessary to follow the strategy of Queen *et al.* if one considers the statements made on 2871 (column 1) of their paper. In particular, Co *et al.* say "To retain high binding affinity in the humanized antibodies, the general procedures of Queen *et al.*(15) were followed. First, a human antibody variable domain with maximal homology to the mouse antibody is selected to provide the framework sequence for humanization of the mouse antibody. Normally the heavy chain and light chain from the same human antibody are chosen so as to reduce the possibility of incompatibility in the assembly of the two chains". The humanization technique of Queen *et al.* and Co *et al.* has now been coined the "best-fit" method for humanization insofar as it relies on selecting an individual human antibody which is as homologous in sequence as possible to the non-human sequence which is to be humanized. Furthermore, these references teach that the heavy chain and light chain used for humanization should be derived from the same human antibody.

On the other hand, the instantly claimed invention constitutes a bold new approach to humanization that does not rely on a high degree of sequence homology between the human and non-human sequences and does not require the existence of a crystallographic structure of the human antibody; the framework regions of the antibodies humanized using the instantly claimed techniques are consensus human variable domain sequences. Applicants submit that the skilled practitioner would have had no motivation to use consensus sequences to form the framework regions of humanized antibodies at the priority date, since the prior art taught that the framework regions should be provided by individual human antibody sequences. Furthermore, the skilled artisan would have been motivated not to use a consensus human variable domain, as the Queen *et al.* and Co *et al.* references taught that the framework region sequences should be chosen based on their sequence homology to the non-human antibody. The instantly claimed invention shows that, contrary to what would have been expected, the claimed consensus sequences can be used for humanization of many different non-human antibodies. This is a significant finding for at least the following two reasons.

First, one must consider why antibodies are humanized. Antibody humanization provides a means for reducing immunogenicity, tailoring effector functions and increasing serum half-life. The

instantly claimed invention provides an improvement in relation to the first of these, *i.e.*, reducing immunogenicity. By using a consensus sequence, which is a sequence comprising the most commonly occurring amino acid at each site in the heavy or light chain, the likelihood that an "atypical" amino acid residue may be present in the framework of the humanized antibody is reduced. Such atypical framework region residues are thought to be detrimental because the human immune system may recognize these as foreign. Thus, the instantly claimed invention obviates the need to replace atypical human residues as taught by Queen *et al.* Therefore, the instantly claimed invention also constitutes a "minimalistic" approach wherein as few non-human residues as possible are incorporated into the humanized antibody, thus reducing the potential immunogenicity of the humanized antibody (see 75, lines 9-11 of the instant application).

The other advantage of the instantly claimed invention is that applicants have shown that a selected V_H consensus sequence and selected V_L consensus sequence can be used to humanize many different non-human antibodies including anti-HER2 (see Example 1); anti-CD3 (see Example 3); anti-CD18 (see Example 4); and anti-IgE (see Presta *et al.*, *supra*). In particular, applicants have seen that humanized anti-HER2 and humanized anti-IgE do not lead to detectable immunogenic responses upon administration to humans. Thus, the claimed method is clearly useful for the production of humanized antibodies with reduced immunogenicity. The techniques advocated by the prior art, especially Queen *et al.* and Co *et al.*, would not allow for this flexibility, since for each new non-human antibody to be humanized, a human antibody sequence with high homology thereto must be used.

To further emphasize the differences between the approaches of the cited references (where FRs from individual human antibodies are used) and the consensus approach which is instantly claimed, applicants refer to the following references. In particular, Sims *et al.*, *J. Immunol.* **151(4)**:2296-2308 (1993), copy attached, used the "best-fit" method to humanize their anti-CD18 antibody. See column 2, paragraph 3 on page 2302. Kolbinger *et al.* further contrast the differences between the individual antibody approach and the consensus approach which is claimed in the above application. See Kolbinger *et al.*, *Protein Engineering* **6**:971-980 (1983) (copy attached). As mentioned in the abstract of Kolbinger *et al.* "Two approaches to the selection of human FRs were tested: (i) selection from human consensus sequences and (ii) selection from individual human antibodies". Kolbinger *et al.* used the consensus sequences for human κ V_L subgroup III and human V_H subgroup I (see Figures 2 and 3) for one version of a humanized antibody. The other humanized antibody was made using the "best-fit" method (see page 977, column 1). In the best-fit method, the V_L of the human antibody KAF and the V_H of the human antibody HAY were used for humanization (see Figures 2 and 3 of Kolbinger *et al.*). Thus, those skilled in the art have acknowledged that the techniques of the prior art and the technique of the instant applicant are certainly different. Accordingly, applicants believe that the invention recited in the claims at issue is clearly non-obvious over the references and the rejection should therefore be reconsidered and withdrawn.

Not only do the cited references fail to disclose or suggest the use of the consensus human antibody variable domain for humanization, but they also fail to address other aspects of the instantly claimed invention. In particular, the references fail to describe steps (f) and (g) of claims 1 and 19 of the instant application. These steps instruct the practitioner concerning selection of human FR residues to be replaced with corresponding non-human residues. In particular, non-homologous non-human FR amino acid residue(s) which are expected to non-covalently bind antigen directly, interact with a CDR, or participate 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 are introduced into the consensus FR. The cited references fail to enable these steps. In particular, EP239,400 does not elaborate in sufficient detail how one would go about selecting non-human FR residues to be incorporated into the humanized antibody. Significantly, no non-human FR residues were transferred in the examples of EP239,400. While Riechmann *et al.* made one and two FR residue mutations to "restore the packing of the loop", this reference fails to describe each of the types of non-homologous residue identified in items (1)-(3) of step (f) of claims 1 and 19 of the instant application. Queen *et al.* also fail to describe the transfer of non-homologous residues which participate 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 (see step (f)(3) of claims 1 and 19 of the instant application). Hence, the invention recited in claims 1 and 19 is clearly not obvious over the references.

The instantly claimed invention has other novel and non-obvious features. For example, claim 2 and step (h) of claim 19 of the instant application involve retaining consensus residues, where the corresponding non-homologous import residues are exposed of the surface of the consensus human variable domain. The cited references fail to describe anywhere such a step. Claim 4 involves replacing consensus glycosylation sites which are not present in the import sequence with the corresponding non-human residue. The references are silent as to such a step. Similarly, the references fail to describe the additional step of claim 5 of the instant application. Also, the FR residues which can be substituted and are listed in claims 6, 7 and 10 as revised herein are not disclosed or alluded to in the cited references. Thus, applicants submit that the invention recited in the claims of the instant application is clearly non-obvious over the cited references.

Accordingly, applicants request that the above section 103 rejection be reconsidered and withdrawn.

The Rejection Under 35 USC §103 - *In re* Durden

Claims 1, 2, 4-12 and 15 are rejected under 35 USC §103 as being unpatentable over EP239,400 (Winter); Riechmann *et al.* Nature: **332**: 323-327 (1988); and Queen *et al.* PNAS, USA **86**: 10029-10033 (1989) in view of In re Durden 226 USPQ 359 (Fed. Cir. 1985).

The Examiner states that the claimed methods for producing humanized antibodies and humanized antibodies do not appear to differ from what was disclosed in the references. For the

reasons given in the previous section, applicants submit that the instantly claimed methods for humanization and the humanized antibodies are clearly different from what was disclosed in the cited reference, especially with respect to the consensus human variable domain forming the FR of the humanized antibody. Therefore, applicants request that this rejection be reconsidered and withdrawn.

The Rejection Under 35 USC §103 - Claim 3

Claim 3 is rejected under 35 USC §103 as being unpatentable over EP 239,400 (Winter); Riechmann *et al.* Nature: **332**: 323-327 (1988); and Queen *et al.* PNAS, USA **86**: 10029-10033 (1989) as applied to claims 1, 2, 4-12 and 15 and further in view Roitt *et al.*, Immunology Gower Medical Publishing Ltd., London, England, pg. 5.5 (1985). It is the Examiner's position that, since Roitt *et al.* allegedly teaches that antibodies contain carbohydrate residues in the variable region, a person skilled in the art would realize that carbohydrate residues can produce stearic modifications in the folding characteristics of polypeptides. The Examiner concludes that it would have been *prima facie* obvious to carry out the step recited in claim 3.

Applicants submit that the claim 3 is clearly not obvious in light of the cited references. The three primary references have been discussed above. Roitt *et al.* merely shows that IgA1 immunoglobulins may possibly have carbohydrate units in their variable domains. No such carbohydrate or oligosaccharide units are depicted in the diagrams of IgD and IgE variable domains in this reference. This reference is not concerned with antibody humanization, much less the use of a consensus human variable domain for humanization or how to deal with glycosylation sites in humanization. Since claim 3 depends on claim 1 which specifies the use of a consensus human variable domain, and since neither the primary references nor Roitt *et al.* disclose or allude to the use of such a consensus sequence, claim 3 must also be nonobvious over the references. Furthermore, the primary references and Roitt *et al.* fail to address how one would deal with glycosylation sites in the context of humanization. In fact, 4D5 referred to in Example 1 is fairly unusual in that it has a glycosylation site in its variable region (*i.e.* residue number 65 of the light chain). Thus, as far as applicants are aware, the instant application teaches, for the first time, how to deal with glycosylation sites in antibody humanization.

Accordingly, applicants conclude that claim 3 is clearly not obvious in light of the references cited and therefore ask that the §103 rejection be withdrawn.

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

Respectfully submitted,
GENENTECH, INC.

Date: June 9, 1995 By: _____
Wendy M. Lee

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Enclosures

U.S. Patent No. 5,147,637
Presta *et al., J. Immunol.* **151**:2623-2632 (1993)
Niman, *Immunodiagnosis of Cancer*, Second Edition, pp. 189-204 (1990)
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Beck *et al., Cancer Biology* **1**:181-188 (1990)
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Kolbinger *et al., Protein Engineering* **6**:971-980 (1983)

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 assigneed 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 709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Paul J. Carter et al.

Serial No. 08/146,206

Filed: 17 November 1993

For: METHOD FOR MAKING HUMANIZED ANTIBODIES

Group Art Unit: 1806

Examiner: D. Adams

CERTIFICATE OF MAILING

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

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SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

BOX DD
Honorable Commissioner of Patents
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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 ($210) 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 $210.00 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.

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

Respectfully submitted,
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Paper #13

Sheet 1 of 1

FORM PTO-1449

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

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

LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

FOREIGN PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
AWD	79	WO 92/04381	19.03.92	PCT				
	80	WO 92/05274	02.04.92	PCT				
	81	WO 92/15683	17.09.92	PCT				

Examiner: Donald E 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.

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

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	18

DATE MAILED: 10/27/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12, 15 & 19-25 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 13, 14 & 16-18 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-12, 15 & 19-25 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be 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.

14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

15. Claims 16-18 have been cancelled.

16. Claims 13-16 have been cancelled.

17. Applicant attempted to amend a previously non-existent claim, Claim 19. This amendment was not entered into the record. Newly added claims 20-25 were renumbered 19-25.

18. The dependency of the renumbered claims has been changed as follows:

(a) renumbered claim 23, depends from renumbered claim 22;
(b) renumbered claim 24, depends from renumbered claim 23;
(c) renumbered claim 25, depends from renumbered claim 24.

19. Claims 19-25 (renumbered) have been added.

20. Claims 1-12, 15 and 19-25 are currently under consideration.

21. The amendments to page 65 were not entered. The comments referring to these corrections at page 6 of the response are unclear with regard to these amendments. The cited phrases at the page and lines do not exist.

22. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. Applicant's request to hold this requirement in abeyance until the application is allowed is acknowledged.

23. Claims 19-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 19-21 are substantial duplicates of claim 1. There appears to be no difference in scope between these claims, see MPEP 706.03(k).

24. 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.

25. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, 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 C.F.R. § 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 potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

26. Claims 1, 2, 4-12, 15, and renumbered claims 19-22 and 24-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Winter [EP 0239400], Riechmann et al. [Nature 332:323-327 (1988)] and Queen et al. [Proc. Natl. Acad. Sci. 86:10029-10033 (1989)]. Briefly the claims are drawn to a method for producing humanized antibodies and humanized antibodies. Winter, teaches the production of altered, chimeric, antibodies by replacing the complementarily determining regions (CDRs), see abstract. Winter, teaches the requirements for CDR fusions, see page 6 to page 8, line 29. Particularly, page 8, lines 11-18, where Winter, teaches that "merely by replacing one or more CDRs with complementary CDRs may not always result in a functional altered antibody..... it will be well within the competence of the man skilled in the art, either by carrying out routine experimentation or by trail and error testing to obtain a functional altered antibody. Note at page 8, last full paragraph that Winter states that framework region replacement and sequence changing may be necessary to obtain a functional humanized antibody. On page 9, lines 13-16, Winter suggests that the antibodies would be of importance for use in human therapy. Winter, teaches a method of producing the antibody, see page 10, paragraph 3 to page 15, paragraph 2. Consistent with Winter, Riechmann et al. teach a method of reshaping human antibodies for therapy by CDR grafting, see whole document and Queen et al. teach the humanization of antibodies by CDR grafting, see entire document. Riechmann et al. teach altering the sequence of the antibody to restore packing or to increase binding affinity, see page 326, first column, first full paragraph. Queen et al. teach the use of computer modeling to assist in the production of humanized antibodies, specifically to predict which amino acids to change thereby effecting molecular interactions, note that of

the amino acids predicted to change include those identified by applicant in claims 7 and 10. A person of ordinary skill in the art would have realized that dependent upon the framework region selected and the sequence of the CDR regions amino acid changes would need to be made and they would depend upon the precise amino acid interactions of the polypeptide. The combination of Winter, Riechmann et al. and Queen et al. teach a comprehensive method for producing humanized antibodies which include the steps outlined in applicant's claims. Therefore, it would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made to take the combined teachings of Winter, Riechmann et al. and Queen et al. to produce a method of making a humanized antibody and to have a humanized antibody for either diagnostic or therapeutic use.

Applicant argues that the claimed invention is distinct from that taught by the above combination of references because a consensus sequence is used and further modifications are not necessary. Applicant further argues that the combination of references do not teach a humanized antibody with reduced immunogenicity.

Regarding the consensus sequence, the combination of references teach the human framework regions having a significantly high degree of sequence homology (conservative regions). Queen et al. in particular point to Kabat as demonstrating that this was known in the art well in advance of applicant's filing date, see reference 38, cited by Queen et al. In essence there is no functional/structural distinction from what applicant has claimed and that taught by the combination of references. Ex parte C, 27 U.S.P.Q.2d 1492 (BPAI 1993). Applicants recitation of Co et al. is unclear, it was not used in the prior art rejection. Applicant then points to several other references concluding that the techniques of the prior art and the technique of the instant application are "certainly different". However, the minor differences between the prior art and the claimed invention are obvious differences. Modifications in the framework regions which affect the proximity or orientation of the V_L-V_H interface regions is the same as substituting that FR residue from the import regions that is involved in the effects set forth in paragraph (f) of claim 1. The combination of references clearly teach reduced immunogenicity associated with the humanized antibody. See e.g. Riechmann et al. page 323, column 2, lines 5-8. Applicant's comments have been fully considered and were as a whole not found persuasive.

27. Claims 1, 2, 4-12 and 15, and renumbered claims 19-22 and 24-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Winter [EP 0239400], Riechmann et al. [Nature 332:323-327 (1988)] and Queen et al. [Proc. Natl. Acad. Sci. 86:10029-10033

(1989)] in view of In re Durden 226 U.S.P.Q. 359 (Fed. Cir. 1985). Briefly the claims are drawn to a method for producing humanized antibodies and humanized antibodies. As discussed above the combination of Winter, Riechmann et al. and Queen et al. teach humanized antibodies and methods for their production. Applicant's claimed invention does not appear to differ from what has previously known in the art.

Applicant cites the above comments in their response to this rejection.

Applicant's comments were fully considered as described above and were not found persuasive, to the extent that they apply to this rejection.

28. Claim 3 and renumbered claim 23 are rejected under 35 U.S.C. § 103 as being unpatentable over Winter [EP 0239400], Riechmann et al. [Nature 332:323-327 (1988)] and Queen et al. [Proc. Natl. Acad. Sci. 86:10029-10033 (1989)] as applied to claims 1, 2, 4-12 and 15 and further in view of Roitt [Immunology, published 1985, by Gower Medical Publishing Ltd. (London, England) page 5.5]. Briefly the claim is drawn to a method for producing humanized antibodies having the additional steps of searching the import variable domain sequence for glycosylation sites, determining if any such glycosylation site is reasonable expected to affect the antigen binding or affinity of the antibody and if so substituting the glycosylation site into the consensus sequence. As discussed above the combination of Winter, Riechmann et al. and Queen et al. teach humanized antibodies and methods of producing humanized antibodies. The combination of Winter, Riechmann et al. and Queen et al. do not teach the importance of carbohydrate residues. However, Roitt teaches that antibodies contain carbohydrate residues in the variable region. A person of ordinary skill in the art would realize that carbohydrate residues can produce steric modifications in the folding characteristics of polypeptides. Therefore it would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made to include a step in the method taught by the combination of Winter, Riechmann et al. and Queen et al. which determines if the presence of carbohydrate residues occur in the variable region that can affect antigen binding and then include in the antibody sequence the appropriate glycosylation signal, by adding the appropriate consensus sequence. A person of ordinary skill in the art would have been motivated to add the additional step of identifying glycosylation that may affect antigen binding to ensure that the antibody produced will have the appropriate binding affinity. A person of ordinary skill in the art would have been motivated to produce such an method to produce antibodies having diagnostic or therapeutic utility.

The bulk of applicant's argument is that the references relied on in the above rejection do not render the invention obvious and Roitt adds nothing to these references to overcome the deficiency.

From the above discussion, the references used render the claimed invention obvious. Roitt fulfills the deficiency of the references discussed above to the extent that Roitt teaches antibodies contain carbohydrate residues in the variable region. A person of ordinary skill in the art would realize that carbohydrate residues can produce steric modifications in the folding characteristics of polypeptides.

29. Applicant's deposit account has been charged for the information disclosure statements. References 2, 6, 55-57 and 73 were lined through since they were previously made of record in this application. All other references cited on applicant's 1449 form were not received by the Office and therefore were not considered.

30. No claim allowed.

31. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 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 C.F.R. § 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.

32. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4227.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donald E. Adams whose telephone number is (703) 308-0570. The examiner can normally be reached Monday through Thursday from 7:30 to 6:00. A

message may be left on the examiners voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. Margaret Moskowitz Parr can be reached at (703) 308-2554. The fax phone number for Group 1806 is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

October 25, 1995

Donald E. Adams, Ph.D.
Primary Examiner
Group 1800

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **Carter et al.** Serial No.: 08/146,206 Filed: November 17, 1993 For: **METHOD FOR MAKING HUMANIZED ANTIBODIES**	Group Art Unit: 1816 1851 1801 Examiner: D. Adams

CERTIFICATE OF HAND DELIVERY
I hereby certify that this correspondence is being delivered to Examiner D. Adams of the United States Patent and Trademark, Washington, D.C. 20231 on
December 8, 1995
Signature
Printed Name:

ASSOCIATE POWER OF ATTORNEY (37 CFR 1.34)

RECEIVED
DEC 08 1995
GROUP 1800

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

Sir:

Please recognize as Associate Attorney in this case:

Wendy M. Lee*

Please direct all communications relative to said pending patent application to the following address:

Genentech, Inc.
460 Point San Bruno Boulevard
South San Francisco, CA 94080
Telephone: (415) 225-1994

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

Respectfully submitted,
GENENTECH, INC.

Date: December 7, 1995

By: Janet E. Hasak
Janet E. Hasak
Reg. No. 28,616

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080-4990
Phone: (415) 225-1896
Fax: (415) 952-9881

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

LIMITED RECOGNITION UNDER 37 CFR § 10.9(b)

Wendy M. Lee is hereby given limited recognition under 37 CFR § 10.9(b) as an employee of Genentech, Inc., to prepare and prosecute patent applications and to represent patent applicants wherein Genentech, Inc., is the assignee of record of the entire interest. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to July 15, 1996: (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) Wendy M. Lee ceases to remain or reside in the United States on a H-1B 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: July 15, 1996

Karen L. Bovard, Director
Office of Enrollment and Discipline

#19
Time Pluntett

Patent Docket P0709P1 12/26/95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **Carter et al.** Serial No.: 08/146,206 Filed: November 17, 1993 For: **METHOD FOR MAKING HUMANIZED ANTIBODIES**	Group Art Unit: 1816 Examiner: D. Adams CERTIFICATE OF HAND DELIVERY I hereby certify that this correspondence is being delivered to Examiner D. Adams, examining group 1816, of the United States Patents and Trademarks, Washington, D.C. 20231 on December ___, 1995 Signature Printed Name:

MAILED
DEC 26 1995
GROUP 1800

TRANSMITTAL LETTER

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

Sir:

Applicants submit herewith, courtesy copies of the previously filed Information Disclosure Statement, PTO-1449 with 78 references and a copy of the date stamped postcard indicating receipt of these documents and references by the United States Patent and Trademark Office on April 17, 1995.

In view of the outstanding FINAL office action, Applicants provide these references by hand delivery to expedite their consideration by the Examiner. While the fee for filing these documents has already been paid, should there be any additional fees associated with the deposit of these documents with the Examiner, the Commissioner is hereby authorized to charge deposit account 07-0630 for said fees.

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

Respectfully submitted,
GENENTECH, INC.

Date: December 7, 1995

By: _____
Wendy M. Lee

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080-4990
Phone: (415) 225-1994
Fax: (415) 952-9881

In re Application of: Carter and Presta
Serial No. 08/1 ,206
Filed on 17 N. ember 1993
Mailed on 13 April 1995

Docket No. P0709P1
By: V ly M. Lee
Reg.

J.T.

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

___	Amendment/Response	___	U.S. Patent Application
___	Extension of Time Request	___	Rule 60 ___ Rule 62
___	Communication/Transmittal Letter	___	Declaration/ Power of Attorney
___	Notice of Appeal		
___	Issue Fee Transmittal Form	___	Assignment
X	Information Disclosure Statement	___	Drawings: ___ Sheets
X	Form 1449 with 78 References	___	Informal ___ Formal
X	Certificate of Mailing	___	Sequence Listing & Diskette
___	Express Mail No. _____	___	PCT Patent Application
X	Other Limited Recognition Under 37 CFR 10.9(b)		

PATENT DOCKET P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#19 T Dais

In re Application of

Carter and Presta

Serial No. 08/146,206

Filed: 17 November 1993

For: METHOD OF MAKING HUMANIZED ANTIBODIES

Group Art Unit: 1806

Examiner: ADAMS, D.

CERTIFICATE OF MAILING

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

13 April 1995
(Date of Deposit)

Aida A. Miclat
Name of Depositing Party

Aida A. Miclat
Signature of Depositing Party

13 April 1995
Date of Signature

MAILED

DEC 26 1995

GROUP 1800

INFORMATION DISCLOSURE STATEMENT

Honorable Commissioner of Patents
and Trademarks
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 ($210) 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 $210.00 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.**

[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(b), 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.

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

Respectfully submitted,
GENENTECH, INC.

Date: April 13, 1995

By: _____
Wendy M. Lee

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080-4990
Phone: (415) 225-1994
Fax: (415) 952-9881

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **Carter et al.** Serial No.: 08/146,206 Filed: November 17, 1993 For: **METHOD FOR MAKING HUMANIZED ANTIBODIES**	Group Art Unit: 1816 Examiner: D. Adams CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on March 27, 1996 Susan Tafoya

NOTICE OF APPEAL

Box AF
Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicant hereby appeals to the Board of Appeals and Interferences from the decision dated October 27, 1995, of the Primary Examiner finally rejecting claims 1-12, 15 and 19-25.

The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $290 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.**

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

Respectfully submitted,
GENENTECH, INC.

Date: March 27, 1996

By: _____
Wendy M. Lee

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080-4990
Phone: (415) 225-1994
Fax: (415) 952-9881

Corres. and Mail
BOX AF

#22

Patent Docket P0709P1 4/24/96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of **Carter et al.** Serial No.: 08/146,206 Filed: November 17, 1993 For: **METHOD FOR MAKING HUMANIZED ANTIBODIES**	Group Art Unit: 1816 Examiner: D. Adams CERTIFICATE OF MAILING I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on March 27, 1996 Susan Tafoya

APR 11 1996 RECEIVED

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

Box AF
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 October 27, 1995 for two (2) months, from January 27, 1996 to March 27, 1996. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $380.00 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.

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

Respectfully submitted,
GENENTECH, INC.

Date: March 27, 1996

By: _____
Wendy M. Lee

460 Pt. San Bruno Blvd.
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Phone: (415) 225-1994
Fax: (415) 952-9881

21[illegible] PD 07-0630 [illegible]
21022 [illegible]

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

LIMITED RECOGNITION UNDER 37 CFR § 10.9(b)

Wendy M. Lee is hereby given limited recognition under 37 CFR § 10.9(b) as an employee of Genentech, Inc., to prepare and prosecute patent applications and to represent patent applicants wherein Genentech, Inc., is the assignee of record of the entire interest. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to July 15, 1996: (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) Wendy M. Lee ceases to remain or reside in the United States on a H-1B 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: July 15, 1996

Karen L. Bovard, Director
Office of Enrollment and Discipline

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

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKETT NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	21

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

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

(1) Ms Wendy M. Lee (3) _____

(2) Donald E Adams (4) _____

Date of Interview 4/8/96

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

Exhibit shown or demonstration conducted: ☐ Yes ☐ No. If yes, brief description: N/A

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

Claims discussed: All generally

Identification of prior art discussed: All cited Art.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Discussed problems w/spec. identified a difference in format between PTO & Orientated copies. Discussed Kabat Consensus Sequence & How the method taught by prior art refs teach away from using A Consensus Sequence. Suggested adding claim 19 originally not entered as a new claim #26 & Correcting all previous dependancy on claim 19 To claim 26

(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.

Donald E Adams
Examiner's Signature

PTOL-413 (REV. 2 -93)

In re Application of: Paul J. Carter et al.
Serial No.: 08/146,206
Filed On: 17 November 1993
Mailed On: 27 August 1996

Docket No.: P0709P1
By: Wendy M. Lee
Reg. No.: P-40,378

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

X	Transmittal Letter (dup)	___	Notice To File Missing Parts (dup)
X	Extension of Time Request (dup)	___	Declaration/Power of Atty
X	Submission under 37 CFR 1.129(a)	___	Assignment
X	Supplemental Information Disclosure Statement	___	Recordation Form
X	Form 1449/PTO 1S__ References	___	Drawings: __ Sheets
___	Notice of Appeal	___	Informal ___ Formal
___	Issue Fee Transmittal	___	Certificate re: Sequence Listing
X	Certificate of Mailing	___	Sequence Listing & Diskette
___	Certificate of Express Mailing	___	Fees: $__
	Express Mail Label No.:	___	Other:

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: D. Adams 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 27, 1996 Duane Alexander Vick Duane Alexander Vick

SUBMISSION UNDER 37 CFR §1.129(a)

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

The accompanying papers are being filed in response to the Office Action mailed October 27, 1995 issuing a final rejection of the claims pending in the application. On March 27, 1996, Applicants filed a Notice of Appeal. Submitted herewith is a three month extension of time for making this submission.

The present submission, in the form of a Supplemental Information Disclosure Statement, is being submitted under Section 1.129(a) along with the fee set forth in Section 1.17(r).

Respectfully submitted,
GENENTECH, INC.

Date: August 27, 1996

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

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080 4990
Phone: (415) 225-1994
Fax: (415) 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: 1816 Examiner: D. Adams 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 27, 1996 Duane Alexander Vick Duane Alexander Vick

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 ($220) 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.**

Revised (10/20/95)

(c) [] 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.**

(d) [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 "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. 07/715,272, filed 14 June 1991 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: August 27, 1996

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

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080-4990
Phone: (415) 225-1994
Fax: (415) 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: 1816 Examiner: D. Adams 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 27, 1996 Duane Alexander Vick Duane Alexander Vick

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 Notice of Appeal dated 3/27/96 for 3 month(s) from 5/27/96 to 8/27/96. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $ 900.00 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.

Respectfully submitted,
GENENTECH, INC.

Date: August 27, 1996

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

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080-4990
Phone: (415) 225-1994
Fax: (415) 952-9881

Revised (10/17/95)

#29
Dane Plunkett
9/14/96

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: D. Adams SEP 10 1996 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 27, 1996 Duane Alexander Vick Duane Alexander Vick

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 ($220) 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.**

Revised (10/20/95)

(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**.

(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 "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. 07/715,272, filed 14 June 1991 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: August 27, 1996 By: _____
Wendy M. Lee
Reg. No. P-40,378

460 Pt. San Bruno Blvd.
So. San Francisco, CA 94080-4990
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Fax: (415) 952-9881

#25

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: D. Adams **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 27, 1996 Duane Alexander Vick Duane Alexander Vick

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 Notice of Appeal dated 3/27/96 for 3 month(s) from 5/27/96 to 8/27/96. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $ 900.00 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.

Respectfully submitted,
GENENTECH, INC.

Date: August 27, 1996

By: _____
Wendy M. Lee
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AG70175 09712/96 08146206 07-0630 070 117 900.00CH

#26

FAX TRANSMISSION

GENENTECH, INC.
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415-225-1994
FAX: 415-952-9881

OFFICIAL

26

To: **Examiner Chris Eisenschenk**
Group 1816
Tel: (703) 308-0452
U.S. Patent and Trademark Office
Washington, D.C. 20231

Date: December 3, 1996

Fax #: 703-308-4242

Pages: 9 , including this cover sheet.

From: Wendy M. Lee

Subject: U.S. Serial No. 08/146,206
Our Docket No. P0709P1

COMMENTS:

PLEASE DELIVER THESE DOCUMENTS DIRECTLY TO EXAMINER EISENSCHENK.

DEC 03 1996

12/03/1996

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.
08/71:46,206	11/17/93	CARTER P	709P1

18M1/1223

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

EXAMINER	
NOLAN, P	
ART UNIT	**PAPER NUMBER**
1816	#27

DATE MAILED: 12/23/96

6407213

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

Commissioner of Patents and Trademarks

PTO-90C (REV. 2/95) 1-File Cop

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

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

☒ Responsive to communication(s) filed on *Dec 3, 1996*.

☐ 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) *1-12, 15, and 19-25* is/are pending in the application.

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

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12, 15, and 19-25* is/are rejected.

☐ Claim(s) _____ 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). *19, 24,26*

☐ 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 ---

1. Claims 1-12, 15 and 19-25 are pending.

2. Claims 19-21 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19-21 are substantial duplicates of claim 1. There appears to be no difference in scope between these claims, see MPEP 706.03(k).

3. 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.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, 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 C.F.R. § 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 potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

5. Claims 1, 2, 4-12, 15, and renumbered claims 19-22 and 24-25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Winter [EP 0239400], Riechmann et al. [Nature 332:323-327 (1988)]

and Queen et al. [Proc. Natl. Acad. Sci. 86:10029-10033 (1989)], all of record for the same reasons set forth in paper No. 18.

Briefly the claims are drawn to a method for producing humanized antibodies and humanized antibodies. Winter, teaches the production of altered, chimeric, antibodies by replacing the complementarily determining regions (CDRs), see abstract. Winter, teaches the requirements for CDR fusions, see page 6 to page 8, line 29. Particularly, page 8, lines 11-18, where Winter, teaches that "merely by replacing one or more CDRs with complementary CDRs may not always result in a functional altered antibody..... it will be well within the competence of the man skilled in the art, either by carrying out routine experimentation or by trail and error testing to obtain a functional altered antibody. Note at page 8, last full paragraph that Winter states that framework region replacement and sequence changing may be necessary to obtain a functional humanized antibody. On page 9, lines 13-16, Winter suggests that the antibodies would be of importance for use in human therapy. Winter, teaches a method of producing the antibody, see page 10, paragraph 3 to page 15, paragraph 2. Consistent with Winter, Riechmann et al. teach a method of reshaping human antibodies for therapy by CDR grafting, see whole document and Queen et al. teach the humanization of antibodies by CDR grafting, see entire document. Riechmann et al. teach altering the sequence of the antibody to restore packing or to increase binding affinity, see page 326, first column, first full paragraph. Queen et al. teach the use of computer modeling to assist in the production of humanized antibodies, specifically to predict which amino acids to change thereby effecting molecular interactions, note that of the amino acids predicted to change include those identified by applicant in claims 7 and 10. A person of ordinary skill in the art would have realized that dependent upon the framework region selected and the sequence of the CDR regions amino acid changes would need to be made and they would depend upon the precise amino acid interactions of the polypeptide. The combination of Winter, Riechmann et al. and Queen et al. teach a comprehensive method for producing humanized antibodies which include the steps outlined in applicant's claims. Therefore, it would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made to take the combined teachings of Winter, Riechmann et al. and Queen et al. to produce a method of making a humanized antibody and to have a humanized antibody for either diagnostic or therapeutic use.

Applicant's arguments filed 6/12/95 have been fully considered but they are not persuasive. Applicant argues that the claimed invention is distinct from that taught by the above combination of

references because a consensus sequence is used and further modifications are not necessary. Applicant further argues that the combination of references do not teach a humanized antibody with reduced immunogenicity.

Regarding the consensus sequence, the combination of references teach the human framework regions having a significantly high degree of sequence homology (conservative regions). Queen et al. in particular point to Kabat as demonstrating that this was known in the art well in advance of applicant's filing date, see reference 38, cited by Queen et al. In essence there is no functional/structural distinction from what applicant has claimed and that taught by the combination of references. Ex parte C, 27 U.S.P.Q.2d 1492 (BPAI 1993). Applicants recitation of Co et al. is unclear, it was not used in the prior art rejection. Applicant then points to several other references concluding that the techniques of the prior art and the technique of the instant application are "certainly different". However, the minor differences between the prior art and the claimed invention are obvious differences. Modifications in the framework regions which affect the proximity or orientation of the V_L-V_H interface regions is the same as substituting that FR residue from the import regions that is involved in the effects set forth in paragraph (f) of claim 1. The combination of references clearly teach reduced immunogenicity associated with the humanized antibody. See e.g. Riechmann et al. page 323, column 2, lines 5-8. Applicant's comments have been fully considered and were as a whole not found persuasive.

6. Claims 1, 2, 4-12 and 15, and renumbered claims 19-22 and 24-25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Winter [EP 0239400], Riechmann et al. [Nature 332:323-327 (1988)] and Queen et al. [Proc. Natl. Acad. Sci. 86:10029-10033 (1989)] in view of In re Durden 226 U.S.P.Q. 359 (Fed. Cir. 1985), all of record, for the same same reasons set forth in paper No. 18.

Briefly the claims are drawn to a method for producing humanized antibodies and humanized antibodies. As discussed above the combination of Winter, Riechmann et al. and Queen et al. teach humanized antibodies and methods for their production. Applicant's claimed invention does not appear to differ from what has previously known in the art.

Applicant cites the above comments in their response to this rejection.

Applicant's comments were fully considered as described above and

were not found persuasive, to the extent that they apply to this rejection.

7. Claim 3 and renumbered claim 23 stand rejected under 35 U.S.C. § 103 as being unpatentable over Winter [EP 0239400], Riechmann et al. [Nature 332:323-327 (1988)] and Queen et al. [Proc. Natl. Acad. Sci. 86:10029-10033 (1989)] as applied to claims 1, 2, 4-12 and 15 and further in view of Roitt [Immunology, published 1985, by Gower Medical Publishing Ltd. (London, England) page 5.5], all of record for the same reasons set forth in paper No. 18.

Briefly the claim is drawn to a method for producing humanized antibodies having the additional steps of searching the import variable domain sequence for glycosylation sites, determining if any such glycosylation site is reasonable expected to affect the antigen binding or affinity of the antibody and if so substituting the glycosylation site into the consensus sequence. As discussed above the combination of Winter, Riechmann et al. and Queen et al. teach humanized antibodies and methods of producing humanized antibodies. The combination of Winter, Riechmann et al. and Queen et al. do not teach the importance of carbohydrate residues. However, Roitt teaches that antibodies contain carbohydrate residues in the variable region. A person of ordinary skill in the art would realize that carbohydrate residues can produce steric modifications in the folding characteristics of polypeptides. Therefore it would have been prima facia obvious to a person of ordinary skill in the art at the time the invention was made to include a step in the method taught by the combination of Winter, Riechmann et al. and Queen et al. which determines if the presence of carbohydrate residues occur in the variable region that can affect antigen binding and then include in the antibody sequence the appropriate glycosylation signal, by adding the appropriate consensus sequence. A person of ordinary skill in the art would have been motivated to add the additional step of identifying glycosylation that may affect antigen binding to ensure that the antibody produced will have the appropriate binding affinity. A person of ordinary skill in the art would have been motivated to produce such an method to produce antibodies having diagnostic or therapeutic utility.

> *The bulk of applicant's argument is that the references relied on in the above rejection do not render the invention obvious and Roitt adds nothing to these references to overcome the deficiency.*

From the above discussion, the references used render the claimed invention obvious. Roitt fulfills the deficiency of the references

discussed above to the extent that Roitt teaches antibodies contain carbohydrate residues in the variable region. A person of ordinary skill in the art would realize that carbohydrate residues can produce steric modifications in the folding characteristics of polypeptides.

THE FOLLOWING REJECTIONS ARE NEW GROUNDS OF REJECTIONS

Double Patenting

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).

8. 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. Although the conflicting claims are not identical, they are not patentably distinct from each other because the invention claimed in claims 1-12, 15 and 19 of copending application Serial No. 08/439,004 encompasses the invention claimed in claims 1-12, 15 and 19, of the instant application.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

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.

9. Claims 1-12, 15 and 19-25 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent 5,530,101 (82).

Claims 1-2 and 19-25:

The '101 patent teaches methods for the production of humanized antibodies wherein the CDR amino acid sequences from the import (i.e. donor) are exchanged for the human (i.e. acceptor) CDR amino acid sequences (abstract, in particular). The '101 patent teaches alignment of import and human framework regions and selection of substituted human framework antibody residues based on the following effects; the import framework residue non-covalently binds antigen directly (i.e. Category three, column 14, in particular), interacts with a CDR (i.e. Category three or four, column 14-15, in particular), or participates in the V_L-V_H interface (i.e. Category 3,4 or 5, column 14-15, in particular).

The '101 patent teaches that if a residues is exposed on the surface of the domain (i.e. interacts with CDR) and doesn't have one of the effects of step f in claim 1, then to leave the human residue intact (column 13-14, in particular). The term "consensus" has been interpreted to include the aligning of murine import framework residues to human acceptor framework residues, in addition to the aligning of all human framework resiudues and compiling a single "consensus" human framework to be used as a template in every humanized antibody. Since "consensus" has limitless interpretations as vaguely defined in the specification, the prior art reads on the claimed invention.

Claims 3 and 4:

The additional step of determining whether or not a substituted residue is glycosylated is determined by the residue makeup of the import peptide, a fact well known in the art prior to

the invention and therefore lends no patentable import to the invention.

Claim 5:

The '101 patent teaches retaining those residues that are highly conserved (i.e. not rare) in the human framework region (Category 2 and 5, Column 14-16, in particular).

Claims 6-8:

The '101 patent teaches which human and import residues are likely to be selected for substitution. In addition the '101 patent teaches corresponding import for human substitution at specific sites (Column 15, in particular).

Claim 9:

The '101 patent teaches a method employing a consensus human variable domain based on human variable domains and additionally variable domains from species other than human (Column 13, in particular).

Claims 10-12:

The '101 patent teaches a humanized antibody variable domain having a non-human CDR incorporated into a human antibody variable domain, wherein the improvement comprises the substitution of only specific corresponding human and import amino acid residues (column 15, in particular).

Claim 15:

The '101 patent teaches a method for engineering a humanized antibody comprising introducing residues from an import antibody variable domain into an amino acid sequence representing a consensus of mammalian antibody variable domain sequences (column 12-13, in particular).

The prior art teachings anticipate the claimed invention.

10. The references crossed out in the form PTO-1449 filed on 12/3/96 are the duplicates of the references stated in the formn PTO-1449 filed 8/30/96.

11. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants cooperation is requested in correcting any errors of which applicant may become aware of in the specification.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick

Nolan whose telephone number is (703) 305-1987. The examiner can normally be reached on Monday through Friday from 8:30 am to 4:30 pm.

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, 1996

Christina Chan

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP 1800

DDS received on 08/30/96

Sheet 1 of 1

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

Atty Docket No.	Serial No.
P0709P1	08/146,206
Applicant	
Carter et al.	
Filing Date	**Group**
17 Nov 1993	~~1800~~ 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	81	~~5,225,539~~ 6-93	~~06.09.93~~	Winter, G.	~~C07K~~	~~15/28~~	~~25.10.91~~ 10-25-91
PN	82	~~5,530,101~~ 6-25-96	~~25.06.96~~	Queen et al.	~~A61K~~	~~39/395~~	~~19.12.90~~ 12-19-90

FOREIGN PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
PN	83	~~85058/91~~ 2-20	~~30.03.92~~	AUSTRALIA	~~C07K~~	~~15/12~~		
	84	~~328,404 A1~~ 8-16	~~16.08.89~~	EPO	~~A61K~~	~~39/395~~		
	85	~~451,216 B1~~ 1-24	~~24.01.96~~	EPO	~~C12P~~	~~21/08~~		
	86	~~WO 91/09966~~ 7-11-	~~11.09.91~~	PCT	~~C12P~~	~~21/08~~		
	87	~~WO 91/09968~~ 7-11-91	~~11.07.91~~	PCT	~~C12P~~	~~21/08~~		
PN	88	~~WO 92/11018~~ 9-7-92	~~09.09.92~~	PCT	~~A61K~~	~~35/14~~		

OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

PN	89	~~Carter et al., "High level escherichia coli expression and production of a bivalent humanized antibody fragment."~~ Bio/Technology 10:163-167 (1992)
	90	~~Foote et al., "Antibody Framework Residues Affecting the Conformation of the Hypervariable Loops" J. Mol. Biol. 224:487-499 (1992)~~
	91	~~Foote, J., "Humanized Antibodies" Nova acta leopoldina 61(269):103-110 (1989)~~
	92	~~Kabat et al., "Sequences of Proteins of Immunological Interest", Bethesda, MD:National Institute of Health pps. 14-32 (1983)~~
	93	~~Kettleborough et al., "Humanization of a Mouse Monoclonal Antibody by CDR-grafting: The Importance of Framework Residues on Loop Conformation" Protein Engineering 4(7):773-783 (1991)~~
	94	~~Maeda et al., "Construction of Reshaped Human Antibodies with HIV-Neutralizing Activity" Hum. Antibod. Hybridomas 2:124-134 (July 1991)~~
	95	~~Riechmann et al, "Expression of an Antibody Fv Fragment in Myeloma Cells" J. Mol. Biol. 203:825-828 (1988)~~
	96	~~Routledge et al., "A Humanized Monovalent CD3 Antibody which Can Activate Homologous Complement" European Journal of Immunology 21:2717-2725 (1991)~~
	97	~~Shearman et al., "Construction, Expression and Characterization of Humanized Antibodies Directed Against the Human α/β T Cell Receptor" J. Immunol. 147(12):4366-4373 (December 15, 1991)~~
PN	98	~~Tempest et al., "Reshaping a Human Monoclonal Antibody to Inhibit Human Respiratory Syncytial Virus Infection In Vivo" Bio/Technology 9:266-271 (March 1991)~~

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

Patent Docket P0709P1

#29

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 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, 1997

Sandra K. T. Sullivan

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	31	-	24	7	x 22 =	$154.00
Independent	7	-	10	0	x 80 =	$0.00
__ First Presentation of Multiple Dependent Claims					+ 260 =	
					Total Fee Calculation	$154.00

_____ No additional fee is required.
X The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $154.00. **A duplicate copy of this transmittal is enclosed.**
X 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: June 23, 1997

By: Janet E. Hasak
Janet Hasak
Reg. No. 28,616
(for Wendy M. Lee
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Revised (10/13/96)

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 RECEIVED JUL 2 0 1997 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 June 23, 1997 Sandra K. T. Sullivan

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 OFFICIAL ACTION dated 23 December 1996 for three month(s) from 23 March 1997 to 23 June 1997. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $930.00 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.

Respectfully submitted,
GENENTECH, INC.

Date: June 23, 1997

By: Janet E. Hasak
Janet Hasak
Reg. No. 28,616
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07/25/1997 KCOOPER 00000101 08146206
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Revised (10/17/95)

D

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: 17 November 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1816 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, 1997 Sandra K. T. Sullivan

AMENDMENT UNDER 37 C.F.R. §1.111

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

In response to the Office Action dated December 23, 1996, the period for response having been extended as a result of the enclosed Petition for a three-month Extension of Time and requisite fee, Applicants respectfully request reconsideration of the above-identified application in view of the following amendments and remarks.

IN THE CLAIMS:

1. (Twice Amended) A method for making a humanized antibody comprising amino acid sequences of a non-human, import antibody and a human antibody, comprising the steps of:

(a) obtaining the amino acid sequences of at least a portion of an import heavy chain variable domain and of a consensus human variable domain of a human heavy chain immunoglobulin subgroup;

(b) identifying Complementarity Determining Region (CDR) amino acid sequences in the import variable domain and the consensus human variable domain;

(c) substituting an import CDR amino acid sequence for the corresponding consensus human CDR amino acid sequence;

(d) aligning the amino acid sequences of a Framework Region (FR) of the import variable domain and a corresponding FR of the consensus human variable domain;

(e) identifying import FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus FR residues;

(f) determining if the non-homologous import FR residue is expected to have at least one of the following effects:

(1) non-covalently binds antigen directly;[,]

(2) interacts with a CDR; or

(3) participates in the V_L - V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another; and

(g) for any non-homologous import FR residue which is expected to have at least one of these effects, substituting that residue for the corresponding amino acid residue in the consensus FR .

6. (Twice Amended) The method of claim 1, wherein the corresponding consensus FR residues substituted in step (g) are selected from the group consisting of 4L, [35L,] 36L, 38L, 43L, 44L, 46L, 58L, 62L, [64L,] 65L, 66L, 67L, 68L, 69L, 70L, [71L,] 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, [and] 78H and 92H.

7. (Twice Amended) A method comprising providing at least a portion of an import, non-human heavy chain variable domain amino acid sequence having a Complementarity Determining Region (CDR) and a Framework Region (FR), obtaining the amino acid sequence of at least a portion of a consensus human variable domain of a human heavy chain immunoglobulin subgroup having a CDR and a FR, substituting the non-human CDR for the human CDR in the consensus human variable domain, and substituting a non-human amino acid residue for the consensus amino acid residue at at least one of the following sites:
4L, [35L,] 36L, 38L, 43L, 44L, 46L, 58L, 62L, [64L,] 65L, 66L, 67L, 68L, 69L, 70L, [71L,] 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 69H, 68H, 70H, 73H, 74H, 75H, 76H, [and] 78H or 92H.

Please cancel claim 9, without prejudice.

10. (Twice Amended) A humanized antibody variable domain having a non-human Complementarity Determining Region (CDR) incorporated into a [consensus] human antibody variable domain, wherein an [human] amino acid residue has been substituted [by a non-] for the human amino acid residue at a site selected from the group consisting of: 4L, [35L,] 36L, 38L, 43L, 44L, 46L, 58L, 62L, [64L,] 65L, 66L, 67L, 68L, 69L, 70L, [71L,] 73L, 85L, 87L, 98L, 2H, 4H, 24H, 36H, 37H, 39H, 43H, 45H, 49H, 68H, 69H, 70H, 73H, 74H, 75H, 76H, [and] 78H and 92H.

15. (Twice Amended) A method for engineering a humanized antibody comprising introducing amino acid residues from a non-human, import heavy chain variable domain into a consensus human variable domain of a human heavy chain immunoglobulin subgroup.

Please cancel claims 19-21, without prejudice.

22. (Amended) A humanized antibody comprising a consensus human variable domain of a human heavy chain immunoglobulin subgroup wherein the amino acid residues forming the Complementarity Determining Regions (CDRs) thereof comprise non-human import antibody amino acid residues.

In claim 25, line 1, please replace "about 7" with --about 5--.

Please add the following claims:

--26. The humanized antibody of claim 22 wherein the human heavy chain immunoglobulin subgroup is V_H subgroup III.

27. The humanized antibody of claim 26 wherein the consensus human variable domain comprises the amino acid sequence of SEQ ID NO:4.

28. The humanized antibody of claim 22 further comprising a consensus human light chain variable domain comprising the amino acid sequence of SEQ ID NO:3 wherein the amino acid residues forming the CDRs of the light chain variable domain comprise non-human import antibody amino acid residues.

29. The humanized antibody of claim 23 wherein the FR residue noncovalently binds antigen directly.

30. The humanized antibody of claim 23 wherein the FR residue interacts with a CDR.

31. The humanized antibody of claim 23 wherein the FR residue comprises a glycosylation site which affects the antigen binding or affinity of the antibody.

32. The humanized antibody of claim 23 wherein the FR residue 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.

33. The humanized antibody of claim 22 which comprises one or more CDR residues from the consensus human variable domain.

34. The humanized antibody of claim 22 which binds antigen more tightly than the non-human antibody.

35. The humanized antibody of claim 22 which mediates antigen dependent cellular cytotoxicity (ADCC) to a greater extent than the non-human antibody.

36. The humanized antibody of claim 35 which is an IgG.

37. The humanized antibody of claim 36 which has an IgGγ1 constant region, wherein residue 359 of the constant region is D and residue 361 of the constant region is L.

38. A method for making a humanized antibody comprising amino acid sequences of a non-human antibody and of a human antibody, comprising the steps of aligning the amino acid sequence of a Framework Region (FR) of the non-human antibody and the corresponding amino acid sequence of a FR of the human antibody, identifying non-human antibody residue(s) in the aligned FR sequences that are non-homologous to the corresponding human antibody residue(s); and if any such non-homologous residue(s) is/are exposed on the surface of the variable domain, providing the corresponding human antibody residue(s) in the humanized antibody.--

REMARKS

Amendments

Claims 1, 7, 15 and **22** have been revised herein to refer to a consensus human variable domain of a "human heavy chain immunoglobulin subgroup," as supported, for example, on page 15, lines 18-25 and page 64, line 33 through to page 65, line 2 of the specification. Basis for heavy chain variable domain in **claims 1, 7** and **15** is found on at least page 11, line 9 of the specification. **Claims 6, 7** and **10** have been amended to include FR substitutions as in the claims as originally filed. **Claim 10** has been amended to have wording as in the claim as originally filed, and basis for the revision to **claim 25** is found, for example, in Table 3 in Example 1.

Claims 26-38 have been added herein and find basis at least as follows: claims **26 and 27** (page 15, lines 18-25 and page 64, line 33 through to page 65, line 2); **claim 28** (page 15, lines 18-21); **claims 29-32** (part f of claim 1 and originally filed, now canceled claim 3); **claim 33** (page 27, lines 1-8; page 27 lines 8-9 and page 65, lines 5-9); **claim 34** (page 68, lines 25-27 and Table 3 on page 65 with respect to Kd values for the murine antibody and two humanized variants huMAb4D5-6 and huMAb4D5-8); **claim 35** (page 69, lines 32-34 and Table 4 on page 74); **claim 36** (page 11, lines 11-14); **claim 37** (page 65, line 29 through to page 66, line 1); and **claim 38** (claims 1 and 10, and originally filed, now canceled claim 2).

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

Section 112, second paragraph

Claims 19-21 are rejected under 35 USC §112, second paragraph, as substantial duplicates of claim 1. In the interest of expediting examination, and without acquiescing in the rejection, claims 19-21 have been canceled, thus rendering this rejection moot.

§103

Claims 1, 2, 4-12, 15 and renumbered claims 19-22 and 24-25 stand rejected under 35 USC §103 as unpatentable over EP239,400A2 (Winter patent application); Riechmann *et al. Nature* **332**:323-327 (1988); and Queen *et al. PNAS, USA* **86**:10029-10033 (1989). The Examiner states that Applicants' arguments filed 6/12/95 are not considered to be persuasive. Concerning the consensus sequence, the Examiner alleges that "the combination of references teach [the] human framework regions having a significantly high degree of sequence homology (conservative regions)" and states that Queen *et al.* point to Kabat as demonstrating that this was known in the art. The Examiner urges that "In essence there is no functional/structural distinction from what applicant has claimed and that taught by the combination of references." The Examiner contends that modifications in the framework regions which affect the proximity or orientation of the V_L-V_H interface regions are the same as substituting that FR residue from the import regions that is involved in the effects set forth in paragraph (f) of claim 1. According to the Examiner, the references, *e.g.*, Riechmann *et al.*, teach reduced immunogenicity associated with the humanized antibody.

Applicants respectfully traverse this rejection as it may apply to the claims as amended herein.

With respect to the cited references, Applicants point out that the Winter patent application fails to disclose or suggest the use of a consensus human variable domain in antibody humanization. On the contrary, the heavy chain framework region of the humanized B1-8 antibody of Example 1 and of the humanized anti-lysozyme antibody D1.3 of Example 2 was derived from the human myeloma heavy chain NEWM (see page 17, lines 1-2 and lines 9-10 on page 26), which was chosen because the crystallographic structure thereof was known (see page 17, lines 2-3). The light chains of the B1-8 and D1.3 antibodies were never humanized in EP 239,400 A2.

Furthermore, only the CDRs were transferred in the Examples of this patent application; none of the non-human FR residues were incorporated into the engineered molecule.

Using the same strategy as disclosed in the Winter patent application, Riechmann and his colleagues made a humanized heavy chain variable domain which had the framework regions of human NEWM alternating with the CDRs of the rat CAMPATH-1 antibody. Thus, the same heavy chain framework region as disclosed in the Winter patent application was used once again, in view of the availability of a crystallographic structure for it (see page 325, second to last paragraph of Riechmann *et al.*). In this respect, Riechmann *et al.* fails to disclose or suggest the use of a "consensus human variable domain of a human heavy chain immunoglobulin subgroup" (*e.g.,* human heavy chain immunoglobulin V_H subgroup III (claim 26) having the amino acid sequence of SEQ ID NO:4 (claim 27), for example) for providing the framework region of the heavy chain variable domain of the humanized antibody. For humanization of the light chain of the rat CAMPATH-1 antibody, Riechmann *et al.* states that a framework sequence based on the human REI light chain variable domain (for which a crystallographic structure was available) was used (see, Figure 1 legend and page 325, second column). Applicants have now learnt that the humanized light chain gene of the CAMPATH-1 antibody in Riechmann *et al.* was converted from an anti-lysozyme construct (see page 108 of Foote, J., *Nova acta Leopoldina* NF **61(269)**:103-110 (1989), of record). Foote's anti-lysozyme construct was prepared by combining CDR sequences from the kappa light chain of the anti-lysozyme antibody with consensus human kappa frameworks (see page 106, third paragraph of Foote, *supra*).

Queen *et al.* teaches that human framework regions used in humanization must be chosen to maximize homology with the murine antibody in order to avoid introducing "distortions into the CDRs" (see page 10031, column 2, paragraph 2). Using their "best-fit" approach, Queen *et al.* used the heavy and light chain variable regions of the human Eu antibody to form the framework of their humanized anti-Tac antibody. There is no mention of a consensus human variable domain for providing the framework region of the humanized antibody. In fact, Queen *et al.* taught away from the instantly claimed invention, in that they proposed that the framework region sequence of the humanized antibody be derived from a single human antibody amino acid sequence which was as homologous as possible to the non-human sequence to be humanized.

Therefore, according to the teachings of Queen *et al.*, human framework region sequences needed to be tailored to each non-human antibody to be humanized. Furthermore, this reference taught that the heavy chain and light chain used for humanization should be derived from the same human antibody.

Applicants submit that the invention recited in independent **claims 1, 7, 15 and 22** herein differs from the teachings of each of the cited references in that it provides humanized antibodies wherein the heavy chain framework region of the humanized antibody is provided by a consensus human variable domain of a human heavy chain immunoglobulin subgroup, such as the V_H subgroup III consensus human variable domain, *e.g.*, of SEQ ID NO:4. The references cited by the Office fail to disclose or suggest the use of such a heavy chain consensus human variable domain.

First, Applicants will comment on the statement by the Examiner that "there is no functional/structural distinction from what applicant has claimed and that taught by the combination of references." As noted above, independent claims 1, 7, 15 and 22 herein recite a "consensus human variable domain of a human heavy chain immunoglobulin subgroup." As noted on page 15, lines 15-25 of the application, consensus sequences (*i.e.*, most commonly occurring residue or pair of residues) of human heavy chain immunoglobulin subgroups are compiled in Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, Fourth Edition, U.S. Dept. of Health & Human Services, pubs., (1987). Kabat *et al.* grouped various heavy and light chain variable domains according to their amino acid sequence identity to form several human immunoglobulin *subgroups, i.e.*, human kappa light chains subgroups I to IV, human lambda light chains subgroups I to VI and human heavy chains subgroups I to III (see pages 41-76 and 160-175 of Kabat *et al.*, copies attached). The "occurrences of most common amino acid" (*i.e.*, "consensus human variable domain" of the instant claims) at each position of the variable domain are provided in the second to last column for each immunoglobulin subgroup in Kabat *et al.* The cited references fail to disclose or suggest the use of a consensus human variable domain of a human heavy chain immunoglobulin subgroup having such an amino acid sequence in antibody humanization. Thus, Applicants submit that the heavy chain framework region of the claims herein, in fact, is <u>structurally</u> distinct from the framework regions of the cited references.

Second, with respect to the Examiner's comment that a modification in the framework regions which affects the proximity or orientation of the V_L-V_H interface regions is the same as substituting that FR residue from the import regions that is involved in the effects set forth in paragraph (f) of claim 1, Applicants respectfully invite the Office to point out where exactly the references teach the invention set forth in part (f)(3) of claim 1.

Finally, concerning the allegation that Riechmann *et al.* teaches reduced immunogenicity associated with the humanized antibody, Applicants enclose a copy of Isaacs *et al. The Lancet* **340**:748-752 (1992). Isaacs *et al.* demonstrate that three out of four patients treated with Riechmann's humanized CAMPATH-1H antibody 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, repeated administration (*i.e.*, loading dose and 10 weekly doses) of the humanized anti-HER2 antibody (huMAb4D5-8) of Example 1 of the instant application has not lead to an immunogenic response in patients treated therewith (*i.e.* no antibodies against rhuMAb HER2 were detected in any patients). See abstract of Baselga *et al.*, *J. Clin. Oncol.* **14(3)**:737-744 (1996), copy attached. Likewise, multidose administrations of an anti-IgE antibody humanized according to the teachings of the instant application and having a consensus human variable domain as claimed herein, did not induce a human antihuman antibody response in any of the patients treated therewith (see column 1, last paragraph on page 311 of Shields *et al.*, *Int. Arch. Allergy Immunol.* **107**:308-312 (1995), copy attached). These data point to the functional distinctness of the claimed consensus human variable domain.

In addition to the desirable lack of immunogenicity of the claimed humanized antibodies, as is apparent from the examples, the binding affinity of an antibody humanized using the claimed method is essentially retained and in some instances is *improved* in the humanized antibody compared to the non-human antibody from which it was derived. As shown, for example, in Table 3 of Example 1, anti-HER2 humanized variants huMAb4D5-6 and huMAb4D5-8 had binding affinities which were superior to the murine antibody from which they were derived. This could not have been predicted from the prior art, especially from Queen *et al.*, which advocated

the best-fit method (see above) and incorporated many (*i.e.*, 15; see Figure 2) murine residues back into the humanized sequence to generate a "high affinity" humanized antibody. The above-mentioned anti-HER2 variants, on the other hand, had only five FR substitutions and were not generated using the "best-fit" method said to be essential by Queen *et al.*

The instantly claimed invention has other novel and non-obvious features. For example, claim 2 involves retaining the human residue, where the corresponding non-homologous import residue is exposed on the surface of the domain. The cited references fail to describe anywhere such a step. Claim 3 is independently patentable, as will be elaborated below. Claim 4 involves replacing consensus glycosylation sites which are not present in the import sequence with the corresponding import residue. The references are silent as to such a step. Similarly, the references fail to describe the additional step of claim 5 of the instant application. Also, the FR residues which can be substituted as now listed in claims 6, 7 and 10 are not disclosed in the cited references. Thus, Applicants submit that the invention recited in the claims of the instant application is clearly non obvious over the cited references.

Accordingly, Applicants request that the above section 103 rejection be withdrawn.

§103 - *In re Durden*

Claims 1, 2, 4-12 and 15 and renumbered claims 19-22 and 24-25 stand rejected under 35 USC §103 as being unpatentable over the Winter patent application, Riechmann *et al.* and Queen *et al.* in view of *In re Durden* 226 USPQ 359 (Fed. Cir. 1985).

The Examiner states that the claimed methods for producing humanized antibodies and for humanization do not appear to differ from what was disclosed in the references. For the reasons given in the previous section, Applicants submit that the instantly claimed methods for humanization and the humanized antibodies are clearly different from what was disclosed in the cited references, especially with respect to the consensus human variable domain forming the FR of the humanized antibody.

Further, the Examiner is respectfully referred to the recent CAFC decisions of In re Brouwer, 37 USPQ2d 1663 (Fed. Cir. 1996) and In re Ochiai, 37 USPQ2d 1127 (Fed. Cir. 1995). These cases stand for the proposition that a *prima facie* case of obviousness cannot be based on Durden, but rather needs to rest on particularized findings. It was held in Brouwer that there are no Durden obviousness rejections *per se*, only sec. 103 obviousness rejections. In the case of the instant claims, where the particular end product is unobvious, these cases hold that the method of making them is also unobvious. In this regard, the Examiner is referred to the Official Gazette notice of 3/26/96, copy enclosed, which establishes guidelines for PTO personnel and the public on the proper consideration of method claims in light of these cases. In this Notice, it is stated that:

> [I]nterpreting a claimed invention as a whole requires consideration of all claim limitations. Thus, language in a process claim which recites making or using a nonobvious product must be treated as a material limitation, and a motivation to make or use the nonobvious product must be present in the prior art for a § 103 rejection to be sustained.
>
> In light of Ochiai and Brouwer, Office personnel will consider all claim limitations when analyzing process claims which make or use nonobvious products under § 103. Office personnel will focus on treating claims as a whole and follow the analysis set forth in Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966). (emphasis in original)

Therefore, since there is no motivation in the cited art, as a whole, to make or use the nonobvious product, the claimed methods herein are non-obvious, and Applicants respectfully request that this rejection be reconsidered and withdrawn.

§103 - Claims 3 and 23

Claim 3 and renumbered claim 23 stand rejected under 35 USC §103 as being unpatentable over the Winter patent application, Riechmann *et al.* and Queen *et al.* as applied to claims 1, 2, 4-12, and 15 and further in view of Roitt *et al., Immunology* Gower Medical Publishing Ltd., London, England, pg. 5.5 (1985) for the same reasons set forth in Paper #18.

Applicants submit that claim 3 and FR substitution (c) of claim 23 clearly would not have been obvious in light of the cited references. The three primary references have been discussed

above. Roitt *et al.* merely shows that IgA1 immunoglobulins may possibly have carbohydrate units in their variable domains. No such carbohydrate or oligosaccharide units are depicted in the diagrams of IgD and IgE variable domains in this reference. This reference is not concerned with antibody humanization, much less how to deal with glycosylation sites in humanization. In fact, the 4D5 antibody referred to in Example 1 is fairly unusual in that it has a glycosylation site in its variable region (*i.e.*, residue number 65 of the light chain). As far as Applicants are aware, the instant application teaches, for the first time, how to deal with glycosylation sites in antibody humanization.

Accordingly, Applicants submit that claim 3 and FR substitution (c) of claim 23 are clearly not obvious in light of the references cited and therefore respectfully request that the §103 rejection be withdrawn.

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. Given the provisional nature of this rejection, Applicants respectfully request that it be held in abeyance pending resolution as to allowable subject matter in this application or in the application on which this provisional rejection is based.

§102

Claims 1-12, 15 and 19-25 are rejected under 35 USC §102(e) as being anticipated by US Patent 5,530,101 (the "101 patent"). With respect to claims 1-2 and 19-25, the Examiner is of the view that the 101 patent teaches methods for the production of humanized antibodies wherein the CDR amino acid sequences from the import/donor are exchanged for the human/acceptor CDR amino acid sequences, as well as the alignment of import and human framework regions and selection of substituted human framework antibody residues based on the following effects; the import framework residue noncovalently binds antigen directly, interacts with a CDR, or participates in the V_L-V_H interface. The Examiner asserts that the 101 patent teaches that, if a residue is exposed on the surface of the domain and does not have one of the effects of step (f) of claim 1, one should leave the human residue intact. The Examiner states

that the term "consensus" has been interpreted to include the aligning of murine import framework residues to human acceptor framework residues, in addition to the aligning of all human framework residues and compiling a single "consensus" human framework. The Examiner comments separately on claims 3 and 4, 5, 6-8, 9, 10-12 and 15 and contends that these claims are also anticipated by the 101 patent.

Applicants submit that the instantly claimed invention is not anticipated by the 101 patent for the reasons that follow.

The 101 patent fails to teach the use, in antibody humanization, of a consensus human variable domain, such as that of a human heavy chain immunoglobulin subgroup, as set forth in independent **claims 1, 7, 15 and 22** herein. As to claim 1 (and FR substitution (d) of claim 23), the 101 patent further fails to teach the step of identifying and altering FR residues that participate in the interface between the light chain variable domain and the heavy chain variable domain of an antibody (*i.e.*, the "V_L-V_H interface"). The Examiner takes the view that categories 3, 4 and 5 in columns 14 and 15 of the 101 patent teach selection and substitution of such FR residues, but Applicants respectfully disagree. The FR residues to be identified in categories 3, 4 and 5 of the 101 patent are those which "interact with amino acids in the CDR's", "interact directly with the antigen" or are "rare" for human sequences. There is no explicit teaching in the 101 patent as to category (f)(3) of claim 1 or FR substitution (d) of claim 23 herein.

Hence, Applicants submit that independent claims 1, 7, 15 and 22 as well as FR substitution (d) of claim 23 are clearly novel over the 101 patent.

As to the other rejected claims, Applicants submit that they are further novel over the 101 patent for the reasons which follow.

Claim 2 is concerned with determining whether non-homologous residues are exposed on the surface of the domain or buried within it. Where the non-homologous residue is exposed, the human residue is retained. Applicants submit that determining whether a residue is exposed on the surface of a domain or buried within it as recited in claim 2 is not the same as determining

whether a residue "interacts with a CDR". Applicants contend that the 101 patent in columns 13-14 does not teach the additional step of claim 2 of the instant application.

With respect to **claims 3 and 4** (as well as FR substitution (c) of claim 23), Applicants submit that since the Examiner has failed to show where the 101 patent mentions glycosylation, let alone the invention recited in claims 3 and 4 and part (c) of claim 23, these claims must be novel over the 101 patent. If this rejection is to be maintained, Applicants request that the Examiner point out specifically where the 101 patent teaches the method steps of claims 3 and 4 and part (c) of claim 23 herein.

As to **claim 5**, this refers to a step wherein non-homologous residues are identified and the human residue is used, where it represents a residue which is highly conserved across all species at that site. Category 2 in column 14 of the 101 patent refers, on the other hand, to using the "donor amino acid rather than the acceptor". Category 5 in the paragraph bridging columns 15-16 of the 101 patent suggests that neither the donor nor the acceptor residue be used where the donor and acceptor residues are "rare". Clearly, the 101 patent fails to anticipate the method of claim 5 herein.

Turning now to **claims 6-8**, the residues specifically mentioned as candidates for substitution in column 15 of the 101 patent (to which the Examiner refers) have been removed from claim 6 and claim 7 (on which claim 8 depends).

Concerning **claim 9**, Applicants submit that the 101 patent fails to enable the consensus human variable domain of this claim, but nevertheless the rejection is moot, due to the cancellation of claim 9.

With respect to **claims 10-12**, the residue positions mentioned in column 15 of the 101 patent have been removed from claim 10 (on which claims 11 and 12 depend).

As to **claims 19-21**, Applicants submit that these claims are novel over the 101 patent, but they were canceled, and thus the §102 rejection is moot insofar as it applies to these claims.

Finally, with respect to **claims 24-25**, Applicants submit that the Examples of the 101 patent require many more FR substitutions than "about 1 to about 5" as recited in these claims.

Applicants submit that, for the reasons given above, **claims 1-12, 15** and **19-25** are clearly novel over the 101 patent, and therefore respectfully request that this rejection be reconsidered and withdrawn.

Applicants believe that the amendments and comments here put this case in condition for allowance. Nevertheless, should the Examiner have any further comments or questions, he is invited to call Wendy Lee at (415) 225-1994 concerning these.

Respectfully submitted,
GENENTECH, INC.

Date: June 23, 1997

By: Janet E. Hasak
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Reg. No. 28,616
(for Wendy M. Lee
Reg. No. 40,378)

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Enclosures:
Isaacs *et al.*
Baselga *et al.*
Shields *et al.*
Kabat *et al.*
OG Notice of 3/26/96

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	
	28
ART UNIT	PAPER NUMBER

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

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

(1) PATRICIA NOLAN (3) CHRIS EISENSCHENK

(2) WENDY LEE (4)

Date of Interview 7/23/97

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 with respect to some or all of the claims in question. ☑ was not reached.

Claims discussed: All

Identification of prior art discussed:

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: It was discussed that Applicant define "consensus" by Framework region residues.

(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.

Patricia J. Nolan
Examiner's Signature

PTOL-413 (REV. 2-93)

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: 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 September 2, 1997 Martin P. Hoffman Printed Name: MARTIN P. HOFFMAN

SUPPLEMENTAL AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231
Sir:

Please amend the application in the following respects:

IN THE SPECIFICATION:

On page 9, line 1, please replace "muMAb4d5" with --muMAb4D5--.

On page 9, lines 24, 29, 30 and 31, please replace "huxCD3v9" with --huxCD3v1--.

On page 9, line 30, please replace "20" with --26--.

On page 9, line 33, please replace "(○)" with --(●)--.

On page 84, line 29, please replace "(Fig. 5)" with --(SEQ ID NO:20)--.

On page 90, please substitute the "SEQUENCE LISTING" with the enclosed paper copy of the "SEQUENCE LISTING".

REMARKS

This amendment is prepared for the purposes of introducing a substitute sequence listing into the application. Applicants have found that SEQ ID NO:20 from the previously submitted sequence listing corresponds to the heavy chain variable domain sequence of huxCD3v9 (see page 84, line 29), whereas Figure 5 shows the sequence of huxCD3v1. The description of Figure 5 on page 9 has been corrected in this respect and the sequence of huxCD3v1 in Figure 5 is included in the substitute sequence listing as SEQ ID NO:26. Further typographical errors in lines 1 and 33 on page 9 are corrected herein. Furthermore, page 84, line 29 now refers to SEQ ID NO:20, the huxCD3v9 heavy chain variable domain sequence. 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.

Respectfully submitted,

GENENTECH, INC.

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

Date: August 29, 1997

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South San Francisco, CA 94080-4990
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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:

F1 (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

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 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: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

f1

(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
```

4

(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

F1

(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:

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

F1

(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:

(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
```

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
```

F1

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
```

#33

10/7/97

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 Sept. 2 ~~August~~ ___, 1997 MARTIN P. HOFFMAN Printed Name Martin P. Hoffman

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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: August 29, 1997 By: _____

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

LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

Atty Docket No.	Serial No.
P0709P1	08/146,206
Applicant	
Carter et al.	
Filing Date	**Group**
17 Nov 1993	1806

U.S. PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Name	Class	Subclass	Filing Date
TDS	100	4,845,198	04.07.89	Urdal et al.	530	388.22	
	101	5,132,405	21.07.92	Huston et al.	530	387.3	
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	103	5,585,089	17.12.96	Queen et al.	424	133.1	

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	112	WO 91/07500	30.05.91	PCT				
	113	WO 92/01047	23.01.92	PCT				
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Examiner M. T. DAVIS Date Considered 12/05/01

*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

LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

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

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Examiner	Date Considered
M. T. DAVIS	12/07/01

*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.

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Applicant: Carter et al.	
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Examiner: M. T. DAVIS Date Considered: 12/01/01

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

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