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Applicant's election of Group 1, in Paper No. 12, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without
5 traverse. See M.P.E.P. 818.03(a).

Claims 1-10 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 1, 3, 4, 5 and 7 are indefinite
10 in the use of the language "import antibody" in that it is not clear what constitutes an important antibody, ie. what determines what is to be an import antibody. Claim 1 step a) is indefinite in that it is not clear what is meant by a "consensus
human variable domain". Claim 1 step d) is indefinite in that it
15 is not clear what is actually taking place when one aligns the amino acid sequences of the FR, ie. is this a physical or mental step? Claim 1 step e) is unclear in what type of homology is indicated, ie. are conservative amino acids considered as homologs or should their be identical amino acid residues at the indicated
20 portion of the framework. Claim 1 step f), 3 is indefinite in the use of the language "participates" in that the nature of participation is unclear. Claim 1 step f) is indefinite in that it is not clear how one of ordinary skill can determine the effects which are listed in steps 1-3, ie. through antigen binding, through
25 hybridization? Claim 1 step g) is indefinite in that it is not clear what effects are reasonably expected to occur. Claim 2 is indefinite in that the antecedent basis for "the domain" is unclear. Claim 3 is indefinite in that it is not clear when in the process of making the antibody one would search for the
30 glycosylation sites. Claim 4 is indefinite for the same reason that claim 3 is indefinite. Claim 5 is indefinite in that it is believed that the claims up to this point were directed to making a

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"humanized antibody", and it is unclear how "preparing a humanized antibody" in claim 5 differs from the preparation of the antibody up to this point. Furthermore, it is not clear what is intended in the preparation of the antibody of claim 5. Claim 6 is vague in that it is not clear what the numbers are meant to designate. It is suggested that applicant clarify the nature of the numbers or point to a figure. Claim 7 is indefinite in that it is not clear what the method is drawn to. It is suggested that the language "a method of making a humanized antibody" be inserted within the claim.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately describe the invention and failing to adequately teach how to make and or use the invention, ie. failing to provide an enabling disclosure. The following terms lack enablement in the specification:.

Claims 1 and 7 lack enablement in the language "at least a portion of an import variable domain". Applicant has only indicated specific residues which may be transferred, but they are claiming an antibody wherein the a portion of the import antibody are to be transferred. There is no guidance in the specification which would enable one of skill in the art to make antibodies with

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transferred variable domains other than CDRs. Applicant is aware that a portion of the variable domain can be any one of the CDRs as well as the framework regions. However, this language also reads on small amino acid sequences which are incomplete regions of the
5 variable region of the antibody. There is no support in the specification for linking the variable region of the antibody to any or all of the myriad "portions" which are encompassed within this language. One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as
10 is claimed. It is suggested that the specific portion of the human variable region which is described in the specification be recited within the claim or this language be removed completely in order to obviate this rejection.

Claim 1 step c) lacks enablement in that it is not clear how
15 one would determine which amino acids are to be substituted. There is no specific recitation of what characteristics of the amino acids are necessary for deciding whether it is to be replaced or not. Without this description one of skill in the art would not be able to choose the appropriate amino acid residues without
20 hindering the function of the antibody.

Claim 1 step f), lacks enablement in that the protocol for determining whether the amino acid residues in the import amino acid sequence are reasonably expected to interact with the antigen is not described anywhere in the specification. There is no

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explicit step which enables one of ordinary skill in the art to determine the effects which are recited. It would require undue experimentation of one of ordinary skill in the art to make the variations which may be made in order to test the effects of the mutant antibodies.

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Claim 2 lacks enablement in that there is no description in the specification of how to determine which residues are exposed on the surface or which residues are buried within the domain, is this through computer modeling or through x-ray crystallography or other methods?

Heurthen
Claim 3 lacks enablement in that there is no guidance in the specification on how one would determine which glycosylation site affects antigen binding, or what comprises "reasonable expectation".

15 Claims 6, 7 and 9 lack enablement in that it would appear that these amino acids are relevant to IgG and not to other isotypes. There is no indication that one of skill in the art would extrapolate the use of these amino acids to all or other isotypes of immunoglobulins. Furthermore, there is insufficient description
20 and guidance in the specification with regards to the properties of these amino acids which would enable one of ordinary skill in the art to make humanized antibodies with other isotypes using these amino acid sequences.

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Applicant has not shown that antibodies which have been modified as that which is claimed are capable of functioning as that which is being disclosed, ie. maintaining the binding affinity of the parent antibody. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Burgess et. al. Journal of Cell biology, 111: 2129-2138 (1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Lazar et. al. Molecular and Cellular Biology, 8:1247-1252 (1988). Similarly it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies. See Tao et. al. The Journal of Immunology, Vol. 143, No. 8. 2595-2601 (1989) and Gillies et. al. Human Antibodies and Hybridomas, Vol 1, no. 1, 47-54 (1990). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity and characteristic of a protein. Therefore, without sufficient guidance in the

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specification to support the use of the above terms and for the reasons mentioned above one of ordinary skill in the art would be forced into undue experimentation in order to practice the invention as is claimed.

5 Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

35 U.S.C. § 101 reads as follows:

10 Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

15 Claims 1-4, 6-8 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The above claims are drawn to a method of preparing an antibody, however, there is no indication within the claims that actual physical steps are taking place. For example, there is no step
20 which includes isolating an antibody, rather obtaining an amino acid sequence. All of the steps which are listed in the claims can be done on paper as mental steps or on a computer terminal.

 The specification is objected to under 35 U.S.C. § 112, first paragraph, and claims 9-13 are rejected under 35 U.S.C. § 112,
25 first paragraph and 35 U.S.C. § 101 as the specification fails to adequately teach how to use the claimed monoclonal antibodies in the manner in which they are disclosed i.e. for the therapeutic

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purposes. Applicants claims are supported only by in vitro data showing the ability of muMab4D5, which is a humanized anti-p185 antibody which reacts with breast and ovarian cancers, to react with different cell lines (see page 88-90 of the specification).

5 Applicant has made no showing that these data correlate with utility for in vivo therapy in humans of the complex array of diseases encompassed by the claims. In general, effective treatment of human cancers has not been routinely achieved in the art using monoclonal antibodies. Further, in vitro data such as

10 that reported in the specification and animal model studies frequently do not correlate with clinical utility in in vivo trials in patients. Based on the evidence of record, the alleged utility of the claimed composition for the treatment of cancer would not be believable on its face to the person of skill in the art in view of

15 the contemporary knowledge in the art. Applicant has not provided any showing of therapeutic utility of the subject monoclonal antibodies which would lead one of skill in the art to believe that the antibodies are broadly applicable for the treatment of all types of autoimmune diseases. Applicant is required to provide

20 evidence commensurate with the scope of the claims, which would be convincing to those skilled in the art that the claimed compositions have utility for the treatment of malignant and autoimmune diseases in humans. See MPEP 608.01(p).

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Waldmann, in a recent review of the literature pertaining to clinical applications of monoclonal antibodies for diagnosis and therapy of human disease, teaches that effective therapy using monoclonal antibodies has been elusive and indicates that hopes for antibody-based treatment methods engendered by in vitro studies have not correlated well with in vivo clinical trial results in patients with cancer. It does not appear that the exemplary material provided in the specification in support of the assertions that the claimed antibodies have therapeutic utility would be viewed by those skilled in the art as being predictive of their utility for treating humans. Applicant has not exemplified how to use the claimed antibodies in vivo and has not shown that the antibodies would be effective in vivo. It appears that undue experimentation would be required of one skilled in the art to practice the claimed invention for the single utility disclosed in the specification.

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--

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this country or a

foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5 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:

10 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
15 negated by the manner in which the invention was made.

20 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 Claims 1, 2, 5-10 are rejected under 35 U.S.C. § 102(b) as being anticipated by Queen et. al.. The above claims are drawn to a method of producing a humanized antibody wherein the amino acid sequences of an import antibody and a consensus antibody are compared, wherein the CDRs of the import antibody are substituted for the antibody of the consensus antibody, and wherein certain
30 framework residues which are responsible for the binding of antigen, interaction with CDR, or participating in the V1-Vh interaction are also imported to the consensus antibody. In essence, residues of the framework region are also transferred with

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the CDRs in order to retain the antigen binding affinity of the parent antibody.

Queen et. al. describe the production of humanized antibodies wherein the murine antibody is compared to human antibodies and the most homologous human antibody is chosen as the acceptor molecule. The CDRs of the murine antibody are then substituted for the CDRs of the human antibody and certain framework residues are also changed. Queen et. al. describe computer modeling and sequence comparison in order to determine the amino acid residues which are to be substituted (see page 10031-10033). Although the steps of the methods are not in exactly the same order, all of the claimed elements are present with in the reference.

Claims 1,2 and 5-10 are rejected under 35 U.S.C. § 102(a) as being anticipated by Co et. al.. See above discussion.

Co et. al. show the production of humanized anti-HSV using the general concept of Queen et. al. (see Results and Table 1).

Claims 3 and 4 are rejected under 35 U.S.C. § 103 as being unpatentable over Queen et. al. or Co et. al. in view of Wallick et. al.

The above claims are drawn to a method of making a humanized antibody wherein the CDRs of an import antibody are transferred to a consensus human antibody along with certain residues of the framework. Furthermore, the claims require that the glycosylation

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sites, if any, of the import amino acid also be imported with the CDRs and framework regions if these sites have an affect on the binding of antigen.

Queen et. al. and Co et. al. both describe the production of
5 humanized antibodies by transferring the CDRs and certain framework regions of the donor antibody to the human consensus antibody (see Queen et. al. pages 10031-10033 and Co et. al. page 2871). They further state that any residue which might have an affect on the antigen binding of the antibody should be changed substituted in
10 order to maintain the binding affinity of the parent antibody (see page 10033 of Queen et. al. at the last paragraph on the page). They do not however, specifically discuss the glycosylation sites as potential targets for transfer. Wallick et. al. teach the importance of carbohydrate interaction with antigen for maintaining
15 or increasing antigen binding affinity (see pages 1107-1108). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make humanized antibodies using the method of Queen et. al. or Co et. al. and further incorporating the concept taught by Wallick et. al.. One of
20 ordinary skill in the art would have been motivated to combine the teachings of the two references in view of the teaching of Queen that retaining high antigen binding affinity is desirable in the production of humanized antibodies. Knowing the role of carbohydrates in antigen antibody interaction as was pointed out by

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Wallick et. al. one of ordinary skill would have had the means and the motivation to make humanized antibodies using both of the teachings of the primary and secondary references.

Claim 11 is rejected under 35 U.S.C. § 103 as being unpatentable over Queen et. al. or Co et. al. in view of Reichmann et. al.

The above claim is drawn to a humanized antibody wherein only one amino acid (listed in claim 9) in the framework and the CDRs have been substituted in the consensus antibody.

Queen et. al. and Co et. al. both teach the production of humanized antibodies by transferring the CDRs of a murine antibody along with specific residues of the framework region to the acceptor antibody molecule. They do not however teach only substituting one of the framework residues among those listed in claim 9. Queen et. al. introduce the general concept of a scaffold wherein certain amino acid residues of the framework must be present and certain are dispensable. Reichmann et. al. teach that a single amino acid substitution in an antibody is sufficient to retain the antigen binding specificity of the parent antibody (see final paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make only a single substitution in the antibody of Queen et. al. or Co et. al. in positions among those listed in claim 9. It would have been obvious to one of ordinary skill to complete the

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invention in light of the success of Reichmann et. al. in only
mutating one amino acid of the framework. Knowing that each
antibody varies slightly in the non-conserved region, and given the
computer modelling protocol set forth by Queen et. al. one of
5 ordinary skill would have been motivated to make a single mutation
in the variable region with the expectation of obtaining a
functional antibody.

Any inquiry concerning this communication or earlier
communications from the examiner should be directed to Lila Feisee
10 whose telephone number is (703) 308-2731.

Any inquiry of a general nature or relating to the status of
this application should be directed to the Group receptionist whose
telephone number is (703) 308-0196.

Feisee/lf *CP*
15 September 29, 1992

David L. Lacey
DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
9/20/92

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

| FORM PTO-892 (REV. 3-78) | | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | | SERIAL NO. 715272 | GROUP UNIT 1806 | ATTACHMENT TO PAPER NUMBER 13 | | |
|---|---|--|---------|------------------------------------|--------------------|---|----------------------------|--------------|
| NOTICE OF REFERENCES CITED | | | | APPLICANT(S) Paul Carter et al. | | | | |
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| EXAMINER P. B. | | | | DATE 9/29/92 | | | | |

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

FORM PTO-1449

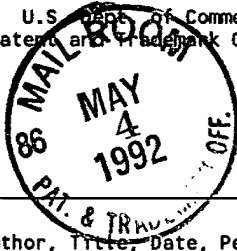
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Atty Docket No.
709

Serial No.
07/715,272

LIST OF PRIOR ART CITED BY APPLICANT

(Use several sheets if necessary)



Applicant
Paul J. Carter et al.

#19 attach
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Filing Date
June 14, 1991

Group

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*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.

FORM PTO-1449

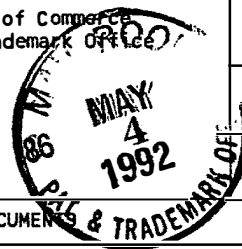
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709

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07/715272

LIST OF PRIOR ART CITED BY APPLICANT

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Applicant
Paul J. Carter et al.

Filing Date
June 14, 1991

Group
1806

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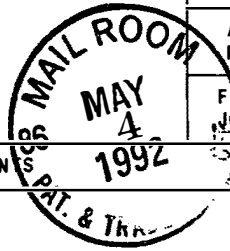
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| FORM PTO-1449 | U.S. Dept. of Commerce Patent and Trademark Office | Atty Docket No. 709 | Serial No. 07/715272 |
| LIST OF PRIOR ART CITED BY APPLICANT (Use several sheets if necessary) | | Applicant Paul J. Carter et al. | |
| | | Filing Date June 14, 1991 | Group 806 |



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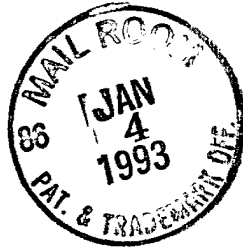
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180C/116 #14 of 1-25-93

PATENT DOCKET 709

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Paul J. Carter et al.
Serial No. 07/715,272
Filed: 14 JUNE 1991
For: IMMUNOGLOBULIN VARIANTS



Art Unit: 1806

Examiner: L. FEISEE

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GROUP 180

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

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

Sir:

The attached materials were received in connection with the prosecution of a foreign patent application corresponding to the captioned case. These materials contain at least two reference citations, the relevance of which is apparent from the communication from the foreign patent office that is also enclosed.

A PTO Form 1449 is submitted herewith to facilitate citation to the record of all references contained in these materials.

Respectfully submitted,
GENENTECH, INC.
Carolyn R. Adler
Carolyn R. Adler
Reg. No. 32,324

December 30, 1992
460 Point San Bruno Boulevard
South San Francisco, CA 94080
415-225-2614

CERTIFICATE OF MAILING (37 CFR 1.8a)

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Louise Strasbaugh
Louise Strasbaugh

Date: December 30, 1992

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Paul J. Carter et al.

Serial No. 07/715,272

Filed: June 14, 1991

For: Immunoglobulin Variants



) Group Art Unit: 1806

) Examiner: L. FEISEE

) 460 Point San Bruno Boulevard
) South San Francisco, CA 94080
) (415) 225-2614
)

CERTIFICATION UNDER 37 C.F.R. § 1.97(e)

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

Sir:

I hereby certify that each item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this statement. Pursuant to §1.97, this information disclosure has been filed in a timely fashion and no fees are required.

Respectfully submitted,

GENENTECH, INC.

Carolyn R. Adler
Reg. No. 32,324

Dated: December 30, 1992

CERTIFICATE OF MAILING (37 CFR 1.8a)

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Louise Strasbaugh

Date: December 30, 1992

AR. 1806



PATENT DOCKET 709

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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|------------------------------|---|-------------------------------|-----|
| In re Application of |) | Group Art Unit: 1806 | #16 |
| Paul J. Carter et al. |) | Examiner: L. Feisee | |
| Serial No. 07/715,272 |) | | |
| Filed: 14 June 1991 |) | | |
| For: Immunoglobulin Variants |) | 460 Point San Bruno Boulevard | |
| |) | South San Francisco, CA 94080 | |
| |) | (415) 225-2614 | |

Amendment and Response

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

Sir:

Responsive to the Office Action mailed 5 October 1992, please amend the claims as follows:

(Amended) A method for making at least a portion of a humanized antibody variable domain comprising amino-acid sequence of a non-human[import] antibody which is desired to be humanized (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-Determining Region (CDR) amino acid sequences in the import and the human amino variable domain sequences;
- c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
- d. aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
- e. identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
- f. determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:
 1. non-covalently binds antigen directly,

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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 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. preparing a humanized antibody variable domain having amino acid sequences determined in steps a-g.
2. (Amended) The method of claim 1, having an additional step of determining if any such non-homologous residues are exposed on the surface of the consensus human antibody variable domain or buried within it, and if the residue is exposed, retaining the consensus residue.
3. (Amended) The method of claim 1, having the additional steps, which may be taken between any two steps in the method of claim 1, of searching the import antibody variable domain amino acid 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 amino acid sequence.
4. (Amended) The method of claim 1, having the additional steps, which may be taken between any two steps in the method of claim 1, of searching the consensus variable domain amino acid sequence for glycosylation sites which are not present at the corresponding amino acid in the import antibody amino acid sequence, and if the glycosylation site is not present in the import sequence, substituting the import amino acid residues for the amino acid residues comprising the consensus glycosylation site.
5. (Amended) The method of claim 1, having an additional step which comprises aligning import antibody and consensus antibody FR amino acid sequences, identifying import antibody FR amino acid residues which are non-homologous with the aligned consensus FR sequence, and for each such non-homologous import antibody FR amino acid residue, determining if the corresponding consensus antibody amino acid 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.

7. (Amended) A method for making a humanized antibody comprising providing [at least a portion of] a non-human antibody variable domain amino acid sequence which is desired to be humanized (import antibody) having a CDR and a FR, obtaining the amino acid sequence of at least a portion of a consensus human antibody variable domain having a CDR and a FR, substituting the non-human CDR for the human CDR in the consensus human antibody variable domain, and then substituting an amino acid residue for the consensus amino acid residue at at least one of the following sites:

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, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.

[Please add the following new claims 17-21:]

- 17. A method of using a consensus human antibody variable domain amino acid sequence in the preparation of a humanized antibody.-- *11/2/2nd no method steps.*
- 18. In a method for making a humanized antibody variable domain, the improvement consisting of using consensus human antibody variable domain amino acid sequence.--
- 19. A method for making an improved antibody, comprising amino acid sequence from a non-human (import) antibody and a human antibody, comprising the steps of:
- obtaining the amino acid sequences of at least a portion of an import antibody variable domain and of a consensus human antibody variable domain;
 - identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human amino variable domain sequences;
 - substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
 - aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
 - identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
 - determining if the non-homologous import amino acid residue is reasonably expected to have at least one of the following effects:
 - non-covalently binds antigen directly,

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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 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. preparing an improved, humanized antibody having amino acid sequences determined in steps a-g; and
 - i. evaluating the antigen binding or immunogenicity of the improved, humanized antibody with respect to the parental antibody.--
- 20. A method comprising, following the identification of an antibody by the method of any one of claims 1, 7, or 17-19, the manufacture of the antibody.--
- 21. A method comprising, following the identification of an antibody by the method of any one of claims 1, 7, or 17-19, the expression of nucleic acid encoding the antibody.--

Remarks

Claims 1-13, and 17-21 are presented herein for examination. Reconsideration of the outstanding rejections is respectfully requested for the reasons that follow. A request for a one-month extension of time to respond is submitted herewith, bringing the due date for this response to 5 February 1993. This response is timely filed.

Amendments

Claims 1, 3, 4, 5 and 7 have been amended to indicate that an import antibody is a non-human antibody which is desired to be humanized. Support for this language is found in the specification at page 6, line 27 to page 7, line 3.

Claim 1, step (f) has been amended to clarify that the word "participates" in the $V_L - V_H$ interface means to affect the proximity or orientation of the V_L and V_H regions with respect to one another. Support for this amendment is found on page 15, lines 30-32. New step (h) has been added to claim 1, directed to the physical step of preparation of a humanized antibody variable domain. Support for this step appear throughout the specification.

Claims 3 and 4 have been amended to provide that the additional steps may be taken between

any two steps in the method of claim 1. Claims 2-7 have been amended to clarify that the residues or sequences referred to relate to amino acids.

New claims 17 - 21 have been added. These claims are alternate approaches to claiming the subject matter claimed in claim 1. Additional support for claims 20-21 is found in Example 1.

It is believed that these amendments introduce no new matter. The inventors respectfully request entry of these amendments.

The rejection under 35 U.S.C. § 112, second paragraph

Claims 1-10 were rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. Claims 1, 3, 4, 5 and 7 were rejected for use of the term "import antibody". These claims have been amended to indicate that the import antibody is a non-human antibody which is desired to be humanized.

Claim 1 step (a) was rejected because of the term "consensus human variable domain". The terms "consensus sequence", "consensus antibody" and "consensus human variable domain" are defined at specification page 16, line 29 to page 17, line 17:

The terms "consensus sequence" and "consensus antibody" as used herein refers to an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass. In preferred embodiments, the consensus human variable domain sequences are derived from the most abundant subclasses in the sequence compilation of Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, National Institutes of Health, Bethesda MD (1987), namely V_L κ subgroup I and V_H group III....

As described in the specification, a "consensus human variable domain" would have an amino acid sequence comprising, amino acid residue by residue, the most frequently occurring amino acid residue gathered from a group of human immunoglobulins. The identity of each amino acid residue making up the consensus sequence is determined separately, requiring merely routine tabulation of the amino acids present in each member of a particular immunoglobulin subclass. To expedite the routine tabulation of the most commonly occurring amino acids, workers in the field are referred to the Kabat *et al.* publication cited in the quoted material above, which presents such tabulations.

Claim 1 step (d) was rejected as indefinite as to whether the alignment of the amino acid sequences is a physical or mental step. This rejection is somewhat confusing. The inventors intend claim 1, step (d) to refer to a maximal homology alignment of representations of amino acid sequences, as described in the specification at page 17, lines 18-27. Preparing such a homology alignment typically combines physical and mental actions. This connotation for the phrase "alignment of sequences" is common in the art to which this invention pertains. Step (d) of claim 1 does not require

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manipulation of the actual, tangible amino acids, merely manipulation of symbolic representations of the actual amino acids.

Claim 1 step (e) was rejected because of the term "homology"; the Examiner questioned whether conservative amino acids are to be considered as homologs. Identity or homology with respect to a specified amino acid sequence of this invention is defined on page 17, lines 18-27. At lines 22-23, the specification indicates that this invention does "not consider[ing] any conservative substitutions as part of the sequence identity". Conservative substitutions are therefore not considered as homologs.

Claim 1 step (f) was rejected for use of the language "participates". Step (f) of claim 1 refers to an amino acid residue which "participates in the in the V_L - V_H interface". This step has been amended to clarify that immunoglobulin residues which so participate are those that affect the proximity or orientation of the V_L and V_H regions with respect to one another.

Claim 1 step (f) was also rejected as indefinite as to how one of ordinary skill can determine the effects listed in steps 1-3. Steps 1-3 presently list the following effects an import amino acid residue might have:

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.

The specification discusses, at pages 13-16, the interactions of amino acid residues within an immunoglobulin and describes at least two methods for evaluating the role of any particular amino acid residue: three dimensional models and assays. As stated at page 14, lines 2-9:

"Three dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen."

The specification provides detailed information how to evaluate the three-dimensional models to determine the various potential effects of amino acid residue changes.

The specification also suggests an alternate method for evaluating the effect of an amino acid residue change. On page 16, lines 14-18, the specification teaches:

"Since it is not entirely possible to predict in advance what the exact impact of a given substitution will be it may be necessary to make the substitution and assay the candidate antibody for the desired characteristic. These steps, however, are *per se*

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routine and well within the ordinary skill of the art."

The inventors submit that methods for determining the effects of amino acid changes are known in the art, and that those skilled in the art would understand what is claimed in step (f).

Claim 1 step (g) was rejected as being indefinite as to what effects are reasonably expected to occur. The word "reasonably" has been deleted from the claim.

Claim 2 was rejected as lacking antecedent basis for "the domain". This claim has been amended to clarify that the intended domain is the consensus human antibody variable domain.

Claims 3 and 4 were rejected as indefinite for not specifying when in the process one would search for the glycosylation sites. These claims have been amended to indicate that one would search for glycosylation sites between any two steps in the method of claim 1.

Claim 5 was rejected as unclear in the use of the phrase "preparing a humanized antibody"; this phrase has now been added by amendment as the last step of claim 1. The phrase is intended to mean the physical making of a humanized antibody, methods for which are described in the specification, including *in vitro* mutagenesis and recombinant engineering. The Examiner also seems to be questioning how claim 5 differs from the previous claims. Claim 5 adds an additional step of determining if a particular amino acid residue in the consensus human variable domain--which differs from the import antibody amino acid residue at that site--also appears at that site in antibodies of other species at that particular site (is conserved). If the particular amino acid residue is conserved across species at that site, than that residue is retained in the humanized antibody, and not substituted by the import antibody amino acid residue at that site, and without requiring evaluation of the impact of such a change on the antibody's characteristics.

Claim 6 was rejected as vague for unclear use of numbers. These numbers refer to particular amino acids in the light (L) and heavy (H) chains of immunoglobulins. By convention, workers in this field generally utilize the immunoglobulin numbering system set forth in Kabat, E. A. *et al.*, *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, MD, 1987)), as described in the specification at page 8, lines 19-21. The Examiner's attention is drawn to Queen *et al.*, already of record in this case, especially at page 10032 column 1 first paragraph (and reference 38 therein) where antibody amino acid residues are referred to with numbers representing certain positions. It is submitted that workers in the field will understand clearly what is claimed in claim 5.

Claim 7 was rejected as indefinite as to what the method is drawn, and has been amended according to the Examiner's suggestion.

According to the CAFC, a decision as to whether a claim is invalid for indefiniteness "requires a determination whether those skilled in the art would understand what is claimed", Amgen v. Chugai,

Handwritten notes: "Withdraw" (vertical, multiple instances), "MacPherson" (vertical), "W/drawn" (vertical), "W/drawn" (vertical), "W/drawn" (vertical).

18 USPQ2d 1116, 1030 (CAFC 1991). The presently pending claims use terminology with clear meanings in the field, especially in light of the definitions provided in the specification. The wordings of the claims comply with the requirements of 35 USC § 112, and this rejection should be reconsidered and withdrawn.

The rejection under 35 U.S.C. § 112, first paragraph

Claims 1-11 were rejected under 35 U.S.C. § 112, first paragraph as lacking enablement.

Claims 1 and 7 were rejected as lacking enablement in the language "at least a portion of an import variable domain". These terms have been deleted from the claims.

Claim 1 step (c) was rejected for being unclear as to how one would determine which amino acids are to be substituted. This step recites "substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence". The identification of the Complementarity Determining Region (CDR) amino acid sequence of the import and the human amino variable domain sequences is made in previous step (b). To accomplish step (c), therefore, one substitutes the amino acids identified in step (b).

Methods for identifying CDRs and distinguishing them from Framework Residues (FRs) are known in the art. As the specification describes on page two, antibody variable domains of natural light and heavy chains have the same general structure, and each domain comprises four framework (FR) regions, whose sequences are somewhat conserved, connected by three hyper-variable or complementarity determining regions (CDRs) (see Kabat, E. A. *et al.*, *Sequences of Proteins of Immunological Interest*, National Institutes of Health, Bethesda, MD, (1987)). The four framework regions largely adopt a β -sheet conformation and the CDRs form loops connecting, and in some cases forming part of, the β -sheet structure. The CDRs in each chain are held in close proximity by the framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. The CDR may be identified following three-dimensional modeling of the antibody. The CDRs may also be identified based on comparison of the an antibody amino acid sequence with a known antibody.

Attached as Exhibit A for the Examiner's convenience are pages from the Introduction to Kabat, E. A. *et al.*, *Sequences of Proteins of Immunological Interest, Fifth Edition*, National Institutes of Health, Bethesda, MD, (1991). This work, along with the earlier Kabat compendiums referred to in the specification and other references, guide the practitioner in the numbering of antibody amino acid sequences, and the assignment of particular amino acids to one of the FR or CDR regions. The Examiner's attention is drawn the sections beginning on page xv, the section entitled "Variable Region Sequence" and especially to Table I, page xvi. Table I presents the amino acid residues associated

with FRs and CDRs of the variable domains of immunoglobulin light and heavy chains. See also Figure 1, page xviii, which shows a schematic view of an immunoglobulin; please note the mention in that figure description to the use of a maximum homology alignment to determine the proper numbering of the amino acids (as referred to in the response to the previous § 112 rejection). The inventors submit that the identification of immunoglobulin amino acid residues as belonging to a CDR or to the framework is routine in the art, requiring no undue experimentation.

The specification teaches, in detail, several ways to substitute amino acid residues, including mutagenesis and the construction of nucleic acid encoding the desired sequence. Alanine scanning mutagenesis is described at page 36, line 20 to page 37, line 3. Oligonucleotide-mediated mutagenesis, PCT mutagenesis and cassette mutagenesis are described in the specification at page 39, line 10 through page 44, line 10. The inventors submit that steps (b) and (c) of claim 1 are fully enabled by the specification.

Claim 1 step (f) was rejected as lacking enablement for determining which amino acid residues may be expected to interact with the antigen. At page 29, lines 4-10, the specification teaches that:

"Differences between the non-human import and the human consensus framework residues are individually investigated to determine their possible influence on CDR conformation and/or binding to antigen. Investigation of such possible influences is desirably performed through modeling, by examination of the characteristics of the amino acids at particular locations, or determined experimentally through evaluating the effects of substitution or mutagenesis of particular amino acids."

Techniques for molecular modeling are described on pages 27-28. Experimental evaluation of the role of particular amino acids will utilize assays tailored to the activities of the antibody to be humanized.

More detailed teaching on identifying residues that influence antigen binding is contained in the specification at page 14, line 10 through page 15, line 6, where it is stated:

"A residue that noncovalently directly binds to antigen is one that, by three dimensional analysis, is reasonably expected to noncovalently directly bind to antigen. Typically, it is necessary to impute the position of antigen from the spatial location of neighboring CDRs and the dimensions and structure of the target antigen. In general, only those humanized antibody residues that are capable of forming salt bridges, hydrogen bonds, or hydrophobic interactions are likely to be involved in non-covalent antigen binding, however residues which are separated spatially by 3.2 Angstroms or less may also non-covalently interact. Such residues typically are the relatively larger amino acids, such as tyrosine, arginine, and lysine. Antigen-binding FR residues also typically will

have side chains that are oriented into an envelope surrounding the solvent oriented face of a CDR which extends about 7 Angstroms into the solvent from the CDR domain and about 7 Angstroms on either side of the CDR domain, again as visualized by three dimensional modeling.

The inventors submit that determining whether a residue may be expected to influence antigen binding is routine in the art, in light of the detailed teachings of the specification.

Claim 2 was rejected as lacking enablement for determining which residues are exposed on the surface or buried within the domain. As indicated in the specification, for example at page 91, lines 18-21, the worker in this field would examine the structural models of the import and human sequences to determine if an amino acid residue is exposed on the surface of the domain or is buried within. Evaluation of structural models, preparation of which are described in the specification, to determine whether a residue is exposed or buried is routine and within the ordinary skill in the art.

Claim 3 was rejected as lacking enablement for how one would determine which glycosylation site affects antigen binding, or what comprises "reasonable expectation". The specification teaches, at page 8, lines 22-32, teaches that determining if the glycosylation is reasonably expected to be important for the desired antigen binding and biological activity of the antibody involves determining if the glycosylation site binds to antigen or changes a side chain of an amino acid residue that binds to antigen, or if the glycosylation enhances or weakens antigen binding, or is important for maintaining antibody affinity. As with other aspects of this invention, evaluation of the impact of glycosylation typically is performed by evaluation of molecular models, or experimental evaluation of a modified polypeptide. Such evaluation is routine within the field.

Claims 6, 7 and 9 were rejected as being enabled only with respect to IgG and not other antibody isotypes. The specification, at page 13 lines 14-22, states:

"The humanized antibody will be selected from any class of immunoglobulins, including IgM, IgG, IgD, IgA and IgE, and any isotype, including IgG₁, IgG₂, IgG₃ and IgG₄. Usually the constant domain is a complement fixing constant domain where it is desired that the humanized antibody exhibit cytotoxic activity, and the class is typically IgG₁. Where such cytotoxic activity is not desirable, the constant domain may be of the IgG₂ class. The humanized antibody may comprise sequences from more than one class or isotype, and selecting particular constant domains to optimize desired effector functions is within the ordinary skill in the art."

The Examples presented in the specification involve the use of a IgG₁ constant domain. As noted in the specification, specific method steps and illustrative reagents for the use of IgG₁ are taught, as well

as their applicability to other antibody isotypes. The inventors respectfully reminds the Examiner that working examples are not a required component of a patent application. As stated in MPEP § 608.01(h), "There is no statutory requirement for the disclosure of a specific example." Thus, the absence of a working example describing particular embodiments of the invention cannot negative the patentability of the invention. The examples included in the specification, which illustrate the preparation of IgG₁ antibodies, are representative of the manner in which the invention may be practiced. From reading these examples and the detailed description of the invention, the ordinarily skilled artisan would immediately deduce the applicability of the methods described in the specification to other immunoglobulin isotypes.

The Examiner has not made a prima facie case for the § 112, first paragraph rejections, supplying no basis for her skepticism about the scope of the claims. The burden is on the Examiner to provide evidence to support rejections of this sort. "Mere broad generalizations and allegations are insufficient for holding of non-enablement," Ex parte Goeddel, 5 U.S.P.Q. 1449, 1450 (TTAB 1987).

If the Examiner is only prepared to allow claims to exemplified embodiments, what incentive exists for an inventor to disclose the invention to the public? Trade secret protection obviously would be superior to the following circumstances foreseen by the CCPA in In re Goffe, 191 USPO 429, 431 (CCPA 1976):

For all practical purposes, the board would limit appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid [literally] infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts. See In re Fuetterer, 50 CCPA 1453, 1462, 319 F.2d 259, 265, 138 USPO 217, 223 (1963).

For a similar case, see In re Strahilevitz, 212 USPO 561 (P.O.B.A. 1982), where the Board was reversed for rejecting as non-enabling an application that was devoid of even a single working example.

The first paragraph of 35 U.S.C. § 112 requires nothing more than objective enablement. Whether this is achieved by the use of illustrative examples or by broad terminology is of no importance, In re Marzocchi et al., 169 USPO 267 (CCPA 1971). Further, an assertion by the Examiner that the enabling disclosure is not commensurate with the protection being sought must be supported by reasons for doubting the truth or accuracy of any statement in the presumptively accurate supporting disclosure. It is also incumbent upon the Examiner to back up such assertions with acceptable evidence or reasoning to substantiate the doubts so expressed, In re Armbruster, 185

USPQ 152 (CCPA 1975), In re Strahilevitz, *op cit*.

See also In re Smith, *supra*, wherein the CCPA reversed an Office ruling that the description in the specification of two categories of prepolymers was not sufficient to support the broad claim for all polymers having a certain desired property. In this case, the court even acknowledged that the specification did not contain language that was precisely identical to the language of the claims. However, the tenor of the specification was that the applicant had made a generic invention rather than one limited to two categories of polymers.

In the present situation, the Examiner has provided no evidence to support the assertion that the invention is not enabled for the preparation of humanized antibodies. Broad claims should be allowed if there is adequate disclosure and where, as in the present situation, there is no pertinent art to prevent such claims. As stated in In re Sus and Schaefer, 134 USPQ 301, 304 (CCPA 1962) (emphasis added):

The public purpose on which the patent law rests required the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. It is neither contemplated by the public purpose of the patent laws nor required by the statute that an inventor shall be forced to accept claims narrower than his invention in order to secure allowance of his patent.

The inventors submit that in view of the detailed information provided in the specification as discussed above, the specification adequately teaches how to practice the claimed invention. The rejections under 35 USC § 112, first paragraph, should be reconsidered and withdrawn, as they are not statutorily based, are inconsistent with court and Patent Office decisions on the subject, and are contrary to public policy.

The rejection under 35 U.S.C. § 101

Claims 1-4, and 6-8 were rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. It is believed that the amendments to the claims made above render moot this ground of rejection.

The rejection under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 101

Claims 9-13 were rejected under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 101 as lacking utility for the treatment of malignant and autoimmune diseases in humans. The inventors request clarification of this rejection, because none of claims 9-13 are directed to methods of treatment. These claims are directed to humanized antibody variable domains and the polypeptides

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of recited sequences. These polypeptides are useful as probes, and in diagnostic assays, as described in the specification at pages 65-66, and need not rely on therapeutic utility.

The rejections under 35 U.S.C. § 102(b) and § 102(a)

Claims 1, 2, and 5-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by Queen *et al.*, and under 35 U.S.C. § 102(a) as being anticipated by Co *et al.*. The inventors respectfully traverse these rejections.

To constitute anticipation, all material elements of a claim must be found in one prior art source. In re Marshall, 198 USPQ 344 (CCPA 1978); In re Kalm, 154 USPQ 10 (CCPA 1967). The inventors will show that neither Queen nor Coe contains all the material elements of these claims, particularly the limitation regarding the use of a consensus sequence.

The rejected claims are directed to the humanization an antibody, namely the combination of amino acid sequence from a non-human antibody desired to be humanized, and from a consensus human variable domain. Methods for preparing such a consensus sequence are fully described in the specification and are discussed above. The inventors believe that the use of a such a consensus sequence achieve a superior result, or a "better" humanized antibody.

The cited prior art utilizes a different approach, which approach had apparently been taken by all other workers in the field prior to the present invention. These workers did not prepare a consensus human antibody to combine with their non-human antibody. Instead, they selected only one human antibody for use, based on the similarity of that human antibody to their non-human antibody. Queen *et al.* state this objective explicitly, at page 10031, column 2. of their paper:

"In selecting a human antibody to provide the variable region framework for the humanized anti-Tac antibody, we 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 framework be to introduce distortions into the CDRs."

Queen continues to describe selecting a human heavy chain V region which was 57% identical to their non-human antibody, after dismissing all other candidate as between 30-52% identical to their non-human. They selected the human light chain V region from the same human antibody for their use.

Co *et al.* are equally explicit describing their similar reasoning. At page 2871, column 1 they state:

"First, a human antibody variable region 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. Based on a sequence homology search against the NBRF protein sequence data base, the antibody Pom was chosen to provide the framework sequences for humanization of Fd79."

The approach of the present invention is quite distinct, in its use of a consensus human variable domain sequence. This consensus sequence might or might not have a high degree of homology with the non-human antibody. Neither Queen *et al.* or Coe *et al.* supply this teaching, and therefore do not anticipate the claimed invention. This rejection should be reconsidered and withdrawn.

The rejection under 35 U.S.C. § 103

Claims 3 and 4 were rejected under 35 U.S.C. § 103 as being obvious over Queen *et al.* or Co *et al.* in view of Wallick *et al.*. Claim 11 was rejected under 35 U.S.C. § 103 as being unpatentable over Queen *et al.* or Co *et al.* in view of Reichmann *et al.*

None of the cited references teaches or suggests the claimed invention, which involves the preparation humanized antibodies using a consensus human antibody variable domain. Such a method is not suggested in any of the prior references, and absent such a teaching there was no motivation to try the methods described in the present specification.

The Obviousness Rejections Do Not Meet the Test of Graham v. Deere

The proper context for determining the issue of obviousness is provided in the seminal decision of Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). In that case, the U.S. Supreme Court set forth the following considerations for deciding this issue:

- (1) The scope and the content of the prior art;
- (2) The difference between the prior art and the claims at issue;
- (3) The level of ordinary skill in the pertinent art; and
- (4) Secondary considerations such as commercial success, long-felt and unresolved needs, failure of others, etc.

a. Scope and Content of the Prior Art.

1. Queen *et al.* teach the humanization of an anti-Tac antibody. They do not teach the use of a human consensus variable domain to provide the framework for their non-human CDRs.

2. Co *et al.* teach the humanization of an anti-HSV antibody. They do not teach the use of a human consensus variable domain to provide the framework for their non-human CDRs.

3. Wallick *et al.* teach the importance of glycosylation for maintaining the affinity of a monoclonal antibody for its antigen. They do not teach methods for humanization of antibodies, nor teach the creation of a human antibody variable domain consensus sequence.

4. Reichmann *et al.* teach the humanization of an anti-CAMPATH-1 antibody. They do not teach the creation of a human antibody variable domain consensus sequence, or suggest that such might be desirable to provide the framework for their non-human antibody CDRs.

b. The Differences Between the Prior Art and the Claims at Issue

The Examiner has chosen various pieces of prior art and concludes that the combination of these references would have rendered the invention obvious.

The prior art shows that it was known as of the filing date to produce antibody fragments comprising sequence from a non-human antibody and from a human antibody. Prior to the present filing date, however, methods were not known which included the use of a consensus human variable domain for mounting the non-human CDRs. There would have been no impetus on the part of the skilled artisan at the filing date to attempt to produce such a consensus sequence or use it in antibody humanization, in view of the teachings of the prior art literature. The cited references do not teach or suggest the claimed invention, alone or in any combination, nor would there have been any reason from these references to practice the claimed methods. The absence of a suggestion of the claimed invention in the art of record precludes the Patent Office from satisfying its initial burden of showing *prima facie* obviousness.

c. Level of Ordinary Skill in the Art.

The Graham inquiries point to a conclusion of non-obviousness of the present claims regardless of the presumed level of skill in the art. However, absent evidence to the contrary, a person of ordinary skill in the art is presumed to be one who essentially follows conventional wisdom and does not undertake to innovate. As stated by the Federal Circuit in Standard Co. v. American Cyanamid Co., 227 U.S.P.Q. 293, 298 (Fed. Cir. 1985):

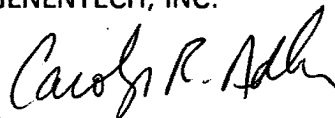
A person of ordinary skill in the art is also presumed to be one who thinks along the line of convention wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which.

The inventors submit that one who followed the conventional wisdom would not have

extrapolated from the teachings of the cited references methods for using a consensus human antibody variable domain for humanizing a non-human antibody. Such an extension of the prior art teachings is based entirely upon hindsight analysis of the inventors' methods. The teachings of this invention should not be considered sufficient to support a conclusion of obviousness in this regard.

The inventors submit that in light of the foregoing amendments and remarks the subject matter defined by the pending claims is useful, enabled, and patentable over the references relied upon by the Examiner, which in no way teach or suggest the invention. The inventors believe the claims are now in condition for allowance and earnestly solicit a Notice to that effect. If the Examiner has any questions, she should feel free to contact the undersigned attorney at the telephone number indicated above.

Respectfully Submitted,
GENENTECH, INC.



Carolyn R. Adler
Reg. No. 32,324

29 January 1993

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 29 January 1993.

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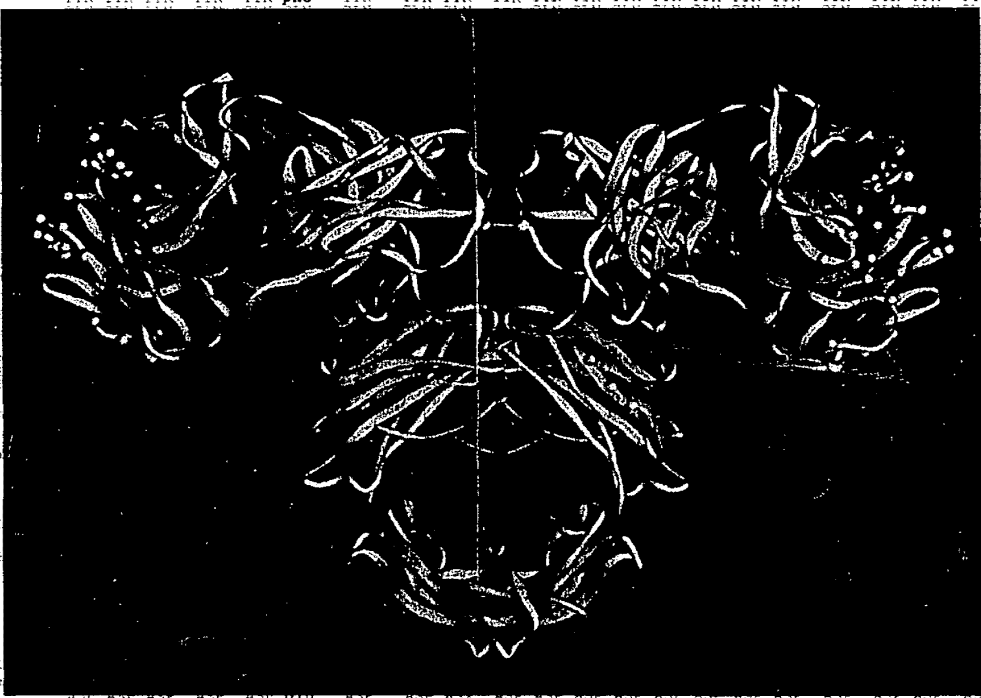

Carolyn R. Adler

Table with columns labeled 0-109 and rows of amino acid sequences. Includes handwritten text 'Carter' and '1991'.

SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST

VOL FIFTH EDITION



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health



SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST

FIFTH EDITION

Tabulation and Analysis of
Amino Acid and Nucleic Acid Sequences of Precursors,
V-Regions, C-Regions, J-Chain, T-Cell Receptors for Antigen,
T-Cell Surface Antigens, β_2 -Microglobulins,
Major Histocompatibility Antigens, Thy-1, Complement,
C-Reactive Protein, Thymopoeitin, Integrins, Post-gamma Globulin,
 α_2 -Macroglobulins, and Other Related Proteins

1991

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INTRODUCTION

Our earlier "Variable Regions of Immunoglobulin Chains" (1), the second edition "Sequences of Immunoglobulin Chains" (2) and the third edition "Sequences of Proteins of Immunological Interest" (3) have been further expanded in the Fourth Edition (4) and now in the Fifth Edition to include amino acid and nucleotide sequences of precursors, variable regions, constant regions, J-chains of immunoglobulins, β 2-microglobulins, antigens of the major histocompatibility complex (HLA, H-2, Ia, DR) as well as of Thy-1, complement, T-lymphocyte receptors for antigens, other T-cell antigens of the immunoglobulin superfamily, interleukins, integrins and various other proteins related to immune functions. The identification and sequencing of clones obtained using recombinant DNA techniques has yielded nucleotide sequences of signal, variable, and constant regions of immunoglobulins (5,6), and these nucleotide sequences have been translated into amino acid sequences. The latter have been included in the tables of amino acid sequences with those determined earlier directly by amino acid sequencing and are indicated by an apostrophe followed by CL after the name of the clone. We have continued to use the PROPHET Software Package of the National Center for Research Resources, National Institutes of Health (7,8) to tabulate the sequences.

In compiling the data for this Fifth Edition we have tried to be as up-to-date as possible and have included only sequences which have been published or which have been accepted for publication. Residues which have not been definitely determined have been excluded. It should be remembered that sequences are often published in review articles without detailed documentary evidence. These have often been revised. We have listed such revisions in the notes in many instances; others can readily be found by comparison with sequences in previous editions. We have compiled sequences determined directly as amino acids and have merged with them those translated from the nucleotide sequences thus making all comparable data available. When antibody activities were known, they have been listed after the amino acid and nucleotide sequence tables and are included in the indexes.

When doubts arise as to the validity of any residue in a sequence, the original reference should be examined to ascertain whether definitive evidence for the sequence has been provided. In earlier editions, we have sent the amino acid and nucleotide sequences as stored in the computer to the original authors for verification. If so verified, this was denoted by "checked by author" at the end of each reference and except for the earliest sequences, the date on which the checked sequence was returned to us is given. Whenever possible, nucleotide sequences from GenBank (9) have been used. Programs for converting a GenBank sequence to the codon format of our tables have been developed. The correctness of the table sequence has been verified by converting back into the linear form and comparing with GenBank. When this has been done the sequence is listed as "from GenBank". Recently we have developed newer programs that automatically process a GenBank entry completely - e.g.: extract the relevant feature, determine the appropriate table, and perform alignment. In such cases, the reference will end with "processed automatically from GenBank:" followed by a list of the GenBank accession numbers from which the data was obtained. Some nucleotide sequences were transmitted to us by electronic mail, and they are indicated by "received from authors through e-mail." If the sequences were entered by us from the literature and then checked with GenBank, this is indicated by "checked with GenBank". We have entered many nucleotide sequences which were not then available from GenBank. In general, we have not included stretches of sequence such as enhancers, switch regions and introns. Much information about such sequences may be found in references (10-13). We have also had access to the Protein Information Resource (14) and to the European Molecular Biology Laboratories Data Base (15).

It is also possible, by examining the numbers of sequences at the

end of each table and the summary tables, to evaluate the probability that a given amino acid at a given position may not be correct. This is most readily done for the framework residues of the V-region and for the C-region; in the complementarity-determining regions this is more difficult because of the high variability.

AMINO ACID SEQUENCES

The first column in each table gives the residue number. Except for complement, T-cell surface antigens, integrins and miscellaneous proteins, the second column is a tabulation of invariant residues. Since exceptions to invariance are found, the frequency, if less than 1.0 and greater than or equal to 0.95, is indicated alongside the residue listed as invariant; when only a single sequence is available, this is not given. These rows are shaded in grey. Each sequence is tabulated in each subsequent column. Three dashes (---) indicate that no amino acid is present at that position and that the sequence continues. In all instances residues considered uncertain by the authors have not been included in the table. In some instances the symbol # is used to indicate that several amino acid residues were found in one position, and these residues are listed in the notes. The four columns at the end of each table give:

1. the number of residues sequenced at that position,
2. the number of different amino acids found at that position,
3. the number of times the most common amino acid occurred and that amino acid in parentheses, and
4. the variability.

These columns are included only in tables with more than five sequences. Miscellaneous tables have only columns corresponding to the first two above.

Variability is calculated (16) as:

$$\text{Variability} = \frac{\text{Number of different amino acids occurring at a given position}}{\text{Frequency of the most common amino acid at that position}}$$

An invariant position would have a variability of one; if 20 amino acids occurred with equal frequency, the variability would be 20 divided by 0.05 equals 400. If, for example, four different amino acids Ser, Asp, Pro, and Thr occurred at a given position, and of 100 sequences available at that position, Ser occurred 80 times, the variability would be $4/0.8 = 5$. When any of the amino acid residues, sequenced directly as amino acids, were not identified completely and are listed as Glx (or Asx), two values, separated by a comma, are given in the last three columns. The first value in each of these columns is calculated assuming that only one of the two possibilities, e.g., Glu or Gln (or Asp or Asn) occurred, while the second considers that both were present and maximizes variability. In the variability plots, the horizontal bars indicate the two values.

When two or more amino acids are most common and occur with equal frequency, they are tabulated as a note, and the symbol + is used in the next to last column. If no sequence data have been reported for any position, there are no entries in the last four columns. Variability is not calculated for insertions or if only a single sequence is known. When the translated sequence of a clone corresponds to a previously listed sequence of a plasmacytoma from

which it was prepared, variability computed. If a given sequence is indicated by an antibody specificity constant if available, rabbit heavy chain domain of the antibody sequence is given; usually the most numerous are included, especially Notes are of two types: the symbol #, and s

Signal Sequences

The signal (precursor) chains are listed for light chains, for a total of nine precursor sequences from DNA acid residues in Genomic DNA clones the coding sequence -4, and in rare cases leader peptide to for positions -4 to

The signal amino acid residues in proteins, complement proteins are listed

By conformational Leu-Leu-Leu-Trp-Va alpha helical conformations in the four amino terminus (20).

Variable Region Sequences

The variable regions contain hypervariable (27-30) chains, labeled with haplotypes segments of light chain examination of sequences aligned in these and the three were hypothesized regions or segments contact with variable high resolution x-ray been verified by all antibodies hypervariable region antibody combination the framework (1) framework segments complementarity-determining the three CDRs in Figures 3-47 have comments are given bibliography. The Table I.

which it was prepared, only one sequence is listed so that the variability computations are not affected, and a note is included. If a given sequence is associated with any antibody activity, this is indicated by an asterisk alongside the protein heading, and the antibody specificities are given in a separate list with binding constants if available. The notes list the a-allotypes for the rabbit heavy chain V-region and the b-allotypes for the constant domain of the rabbit kappa light chain. A key reference to the sequence is given; generally the most recent reference since it is usually the most nearly complete, but often several references are included, especially when revisions of a sequence have been made. Notes are of two types: general notes about a table indicated by the symbol #, and specific notes indicated by the sequence number.

Signal Sequences

The signal (precursor) amino acid sequences of immunoglobulin chains are listed as human, mouse, and miscellaneous for kappa light chains, for lambda light chains, and for heavy chains for a total of nine precursor tables. They were obtained either by direct sequencing of signal proteins (17-19) or by translating nucleotide sequences from DNA clones. Signal segments range from 17-29 amino acid residues in length and are thus numbered from -29 to -1. Genomic DNA clones contain introns of varying length that interrupt the coding sequence of the precursor within the codon for position -4, and in rare cases for position -6. Thus, the L-gene encodes the leader peptide to position -4 and the 5' end of the V-gene codes for positions -4 to -1.

The signal amino acid sequences of the T-cell receptors for antigens, β 2-microglobulins, major histocompatibility complex proteins, complement components, integrins, and other related proteins are listed in separate tables.

By conformational energy calculations, the core V_L hydrophobic Leu-Leu-Trp-Val-Leu-Leu (MOPC321, MOPC63) exists in an alpha helical conformation, terminated by chain reversal conformations in the four C-terminal residues Trp-Val-Pro-Gly; the four amino terminal residues are compatible with the alpha helix (20).

Variable Region Sequences

The variable regions (21) of immunoglobulins have been shown to contain hypervariable segments in their light (16,22-26) and heavy (27-30) chains, of which certain residues have been affinity labeled with haptenic determinants (31-44). Three hypervariable segments of light chain were delineated from a statistical examination of sequences of human V_L , human V_L , and mouse V_L light chains aligned for maximum sequence similarity (16,23,24,27). These and the three corresponding segments of the heavy chains (27) were hypothesized (16,27) to be the complementarity-determining regions or segments (CDR) containing the residues which make contact with various antigenic determinants, several years before high resolution x-ray structures were determined, and this has now been verified by X-ray diffraction studies at high resolution for all antibodies examined Figures 3-47. The proposed fourth hypervariable region (cf. 30) of heavy chains is not part of the antibody combining site (27). The rest of the V-region constitutes the framework (16,27,45-54). It is convenient to identify the framework segments (FR1, FR2, FR3, and FR4) and the complementarity-determining segments (CDR1, CDR2, and CDR3) with the three CDRs separating the four FRs. The CDRs in the stereo Figures 3-47 have solid circles for each residue. References and comments are given with each figure and are not listed in the bibliography. The residue numbers for these segments are given in Table I.

TABLE I

Amino Acid Residues Associated with Framework (FR) and Complementarity Determining Regions (CDR) of the Variable Domains of Immunoglobulin Light (V_L) and Heavy (V_H) Chains

| Segment | Light Chain | Heavy Chain |
|------------------|--|--|
| FR1 | 1-23 (with an occasional residue at 0, and a deletion at 10 in V_L chains) | 1-30 (with an occasional residue at 0) |
| CDR1 | 24-34 (with possible insertions numbered as 27A,B,C,D,E,F) | 31-35 (with possible insertions numbered as 35A,B) |
| FR2 ^a | 35-49 ^a | 36-49 |
| CDR2 | 50-56 | 50-65 (with possible insertions numbered as 52A,B,C) ^b |
| FR3 | 57-88 | 66-94 (with possible insertions numbered as 82A,B,C) |
| CDR3 | 89-97 (with possible insertions numbered as 95A,B,C,D,E,F) | 95-102 (with possible insertions numbered as 100A,B,C,D,E,F,G,H,I,J,K) |
| FR4 | 98-107 (with a possible insertion numbered as 106A) | 103-113 |

^a Five Basilea rabbits (λ) immunized with type II pneumococci and which produced anti-type II pneumococcal polysaccharide had Met at position 48 and an insertion of four amino acid residues between positions 48 and 49; in four of the five the sequence was Glu, Leu, Lys, Ser and the fifth was Trp, Leu, Arg, Lys (53,54,63,64); the others were not sequenced at these positions (for references see table of rabbit λ amino acid sequences.)

^b In the rabbit, Mage et al. (65) consider position 65 in V_H to be in FR3, since it is allotype related.

The V-genes for the kappa light chains. by recombination and by the J-minigene. occur at different positions residues may result of the inserted residues for better alignment the V-gene region. I times more frequently

The V-genes for the heavy chain and are followed by extensive variation ability to be read boundary between D and acid position. In addition sequences vary by a factor of D-J joining appears between V and D and correlates with the B cells (60). The order has therefore been re-evidence suggesting perhaps a minigene nucleotides. Light chain V_L -J_L junction (62), probably results from in fetal and neonatal and 17/146 RNA sequences lower than in adults regulated both in T diversity but are te

In the tables of V_H horizontal lines for chain, MPC 11, has between position 1 have internal deletions

The V-genes for the light chains code to amino acid position 95, and the J-minigenes from position 97 to 107 for lambda and 108 for kappa light chains. Position 96 is usually the site of V-J joining by recombination and may be coded partly by the V-gene and partly by the J-minigene. Because the site of V-J recombination could occur at different positions within a codon, different amino acid residues may result at this position. We have changed the location of the inserted residues from 97A-F (2) to 95A-F, since it makes for better alignment by confining chains of different lengths to the V-gene region. In mouse V_k chains, J1 and J2 were used 5 to 10 times more frequently than J4 and J5 (55).

The V-genes for the heavy chains code up to amino acid position 94 and are followed by the D- and J-minigenes. Because of the extensive variation in the lengths of D-minigenes, and their ability to be read in different reading frames (56), the exact boundary between D and J is not always located at the same amino acid position. In addition, the lengths of the J encoded amino acid sequences vary by a few amino acid residues. Moreover, the process of D-J joining appears to involve insertions of extra nucleotides between V and D and between D and J, termed the N region (57-61) and correlates with the appearance of terminal deoxytransferase in B cells (60). The original numbering system for the heavy chains has therefore been retained. Wysocki et al. (61) have provided some evidence suggesting a non-random origin for the V_H-D_H junction, perhaps a minigene, rather than random addition of the N nucleotides. Light chains do not appear to have N sequences at the V_L-J_L junction (62), but show an additional residue 95A which probably results from V_L-J_L joining. N sequences are generally rare in fetal and neonatal mouse V_H-D-J_H junctions (62), only 1/87 DNA and 17/146 RNA sequences contained N regions, an incidence much lower than in adults indicating that N insertion is developmentally regulated both in T and B cells. P elements also contribute to diversity but are templated (62a).

In the tables of V-regions, the FR and CDR are separated by horizontal lines for convenience in reading. One mouse kappa light chain, MPC 11, has an extra segment of 12 amino acid residues between position 1 and the signal sequence (66). Several chains have internal deletions.

Figure 1 (50) shows the domain structure for IgG1 protein EU. Numbering on the left half indicates the CDR for the light and heavy chains (50), while that on the right half gives the EU numbering (67).

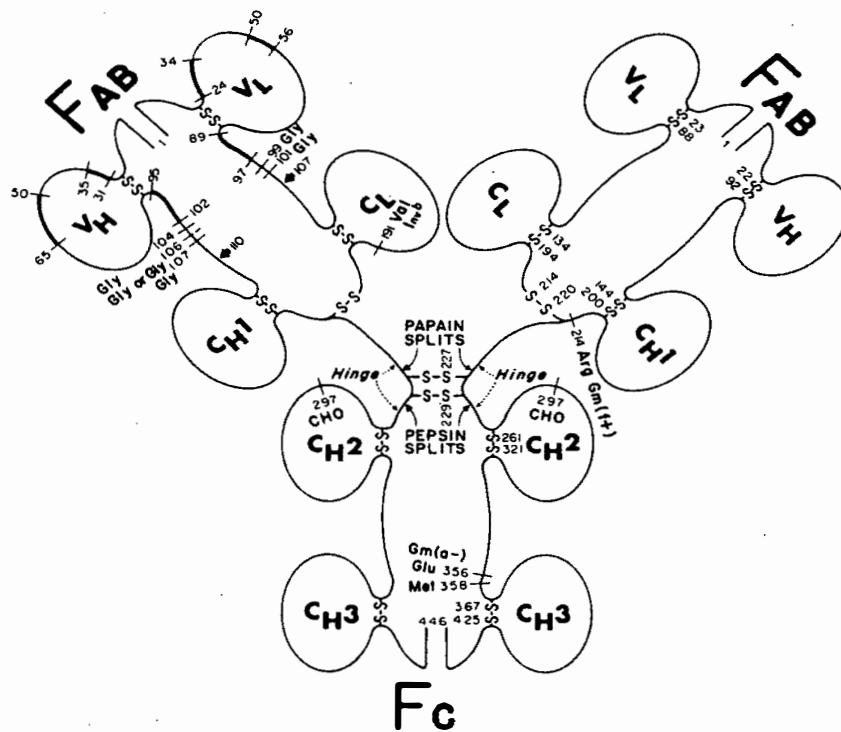


FIG. 1. Schematic view of four-chain structure of human IgG1 molecule. Numbers on right side: actual residue numbers in protein EU [Edelman *et al.* (67)]; Numbers of Fab fragment on left side aligned for maximum homology; light chains numbered as in Wu and Kabat (16) and heavy chains as in Kabat and Wu (27). Heavy chains of EU have residue 52A, three residues 82A,B,C, and lack residues termed 100A,B,C,D,E,F,G,H,I,J,K, and 35A,B. Thus residue 110 (end of variable region) is 114 in actual sequence. Hypervariable regions, complementarity-determining segments or regions (CDR): heavier lines. V_L and V_H : light and heavy chain variable region; C_{H1} , C_{H2} , C_{H3} : domains of constant region of heavy chain; C_L : constant region of light chain. Hinge region in which two heavy chains are linked by disulfide bonds is indicated approximately. Attachment of carbohydrate is at residue 297. Arrows at residues 107 and 110 denote transition from variable to constant regions. Sites of action of papain and pepsin and locations of a number of genetic factors are given. Modified from 50.

Critical understanding sites and the genetic antibody complementarity evaluation of a large and especially of the C and heavy chains of immunoglobulin to locate residues in determinants (68,69) and combining sites will depend on scope V_H and V_L chains must be resolved. In addition to other immunological data in resolution X-ray crystallography.

Through the generous cooperation of Drs. Eduardo Padlan and Dr. Eduardo Padlan a model.

Critical understanding of the architecture of antibody combining sites and the genetics of the generation of diversity and of antibody complementarity depends to a great extent on the evaluation of a large number of sequences of the variable regions and especially of the complementarity-determining segments of light and heavy chains of immunoglobulins of different species. Ability to locate residues in the site making contact with antigenic determinants (68,69) and to predict (70) the structures of antibody combining sites will depend heavily upon such sequences. The role and scope V_H and V_L chains in contributing to binding of the epitope must be resolved. This can be often accomplished by use of immunochemical data in defining antibody combining sites (68,70-73) in addition to other methodologies such as 2D-NMR (71,51) or high resolution X-ray crystallography.

Through the generous cooperation of X-ray crystallographers we have been provided with the α -carbon coordinates of almost all available Fab molecules, V_H dimers and antigen-antibody complexes from which Drs. Eduardo Padlan and Chantal Abergel made the stereo models shown. Legends and key references for each are listed with the model.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Paul J. Carter et al.
Serial No. 07/715,272
Filed: 14 June 1991
For: Immunoglobulin Variants

Group Art Unit: 1806
Examiner: L. Feisee

460 Point San Bruno Boulevard
South San Francisco, CA 94080
(415) 225-2614

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

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 05 October 1992 for one month(s) from 5 January 1993 to 5 February 1993. The extended time for response does not exceed the statutory period.

Please charge Deposit Account Number 07-0630 in the amount of \$110. 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.

Carolyn R. Adler
Carolyn R. Adler
Reg. No. 32,324

Date: 29 January 1993

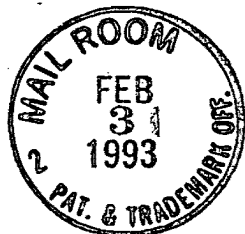
CERTIFICATE OF MAILING (37 CFR 1.8a)

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

Carolyn R. Adler

Carolyn R. Adler

Date: 29 January 1993



GENENTECH, INC.
460 Point San Bruno Boulevard
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#15
J. Seese
02/19/93

Attorney Docket No. 709
Examiner: L. Feisee
Group Art Unit 1806

In re Application of: Paul J. Carter et al.

Serial No.: 07/715,272

Filed: 14 June 1991

For: Immunoglobulin Variants

Handwritten initials

RECEIVED

FEB 19 1993

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

GROUP 180

Sir:

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

The fee has been calculated as shown below.

| | (Col. 1) | | (Col. 2) | | (Col. 3) | | |
|---|----------------------------------|-------|---------------------------------|--|---------------|-------------|------------|
| | Claims Remaining After Amendment | | Highest No. Previously Paid For | | Present Extra | Rate | Addit. Fee |
| Total | * 21 | Minus | ** 21 | | = 0 | x 20= | \$ 0 |
| Indep. | * 10 | Minus | *** 8 | | = 2 | x 72= | \$ 144 |
| _____ First Presentation of Multiple Dep. Claim | | | | | | + 220= | \$ 0 |
| | | | | | | TOTAL . . . | \$ 144. |

*If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.
**If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.
The "Highest Number Previously Paid For" (Total or Independent is the highest number found from the equivalent box in col. 1 of a prior amendment or the number of claims originally filed.)

- No additional fee is required.
- Please charge any additional fees, including any fees necessary for extensions of time, or credit overpayment to Deposit Account No. 07-0630. A duplicate copy of this sheet is enclosed.
 - Any additional filing fees required under 37 CFR 1.16.
 - Any patent application processing fees under 37 CFR 1.17.

Dated: 29 January 1993

Carolyn R. Adler
(Attorney of Record)

Carolyn R. Adler
Registration No. 32,324

SC13193 02/17/93 07715272

07-0630 130 115 110.00CH
CERTIFICATE OF MAILING

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

Dated: 29 January 1993

Carolyn R. Adler
Carolyn R. Adler



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. |
|---------------|-------------|----------------------|---------------------|
|---------------|-------------|----------------------|---------------------|

07/715,272 06/14/91 CARTER

P 709

EXAMINER
PETERSEELE

18M2

GENENTECH, INC.
ATTN: CAROLYN R. ADLER
460 POINT SAN BRUNO BLVD.
SOUTH SAN FRANCISCO, CA 94080

ART UNIT PAPER NUMBER

1806

17

DATE MAILED: 05/19/93

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 2/3/93 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 re Patent Drawing, PTO-948.
- 3. Notice of Art Cited by Applicant, PTO-1449.
- 4. Notice of Informal Patent Application, Form PTO-152.
- 5. Information on How to Effect Drawing Changes, PTO-1474.
- 6. _____

Part II SUMMARY OF ACTION

1. Claims 1-23 are pending in the application.

Of the above, claims 14-16 are withdrawn from consideration.

2. Claims _____ have been cancelled.

3. Claims 12 and 13 are allowed.

4. Claims 1-13, 17-21 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 re Patent Drawing, 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 on _____, has been approved, disapproved (see explanation).

12. Acknowledgment is made of the claim for priority under 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 appears 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, 1835 C.D. 11; 453 O.G. 213.

14. Other

Art Unit 1806

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Some of the rejections under 35 USC 112 second paragraph have been obviated in view of the amendments to the claims. However, the following rejection still remain. The language "consensus human variable domain" is still unclear despite the description in the specification. It is unclear whether the consensus human variable domain is a culmination of different variable domains or a single universal variable domain which is homologous to other human variable domains.

With regards to the language "import amino acid", it is suggested the import amino acid be described in the following manner: "an import antibody comprising the amino acid sequence of a non-human antibody which binds to ...". The language "reasonably expected" is unclear since it is not known what criteria determines what is "reasonable".

Claim 1 remains rejected and new claims 19-21 are rejected under 35 USC 112 first paragraph as lacking enablement for the language "at least a portion" for the same reasons as set forth in pages 3 and 4 of paper #13.

Applicant states that this language has been deleted from claim 1, but, this is not the case. This language has been moved to the beginning of the claim and the claim contains the same objectionable language, therefore, the rejection set forth

Withdraw

Withdraw

previously still applies.

The rejection of claims 1-4, 6-8 under 35 USC 101 is withdrawn in view of the amendment to the claims.

The rejection of claims 9-13 as lacking utility is withdrawn in view of the argument set forth in the letter of 2/3/93.

The objection to the specification and the rejection of claims 1-11 under 35 USC 112 first paragraph is maintained and newly added claims 17-21 are rejected for the reasons of record.

The language "at least a portion" still remains in claim 1 and newly added claims 19-21. Therefore, the rejection set forth previously on pages 3-4 of paper #13 still applies. With regards to substituting an import CDR in place of the human CDR, the rejection still applies, since there is no clear guidance in the specification to enable one of ordinary skill in the art to make the human "consensus variable region" which is to contain the claimed substitution. It is true that once the amino acid sequences are known, it is routine to determine the CDRs according to Kabat, and substitute the rodent CDRs in place of the human CDRs. However, the only guidance presented in the specification with regards to the substitutions is the amino acid sequences of SEQ ID NO: 3 and 4, which are specific variable regions. The specification vaguely alludes to variable domain sequences which are derived from the most abundant subclasses but shows no way of making such variable domains. The fact remains

that applicant has not clearly taught how to determine which amino acids are the ones to be substituted since there is only a single example of the appropriate variable region which is to support the substitutions.

The rejection of claim 2 with regards to determining which residues are surface or buried residues is withdrawn in view of the argument presented explaining that computer modeling is well known in the art to determine the position of various amino acid residues.

The rejection of claims 1 and 3 with regards to the language "reasonably" and newly~~ra~~added claim 19 is maintained, since there is no set standard for determining what is reasonable interaction, or interfacing or what amount of glycosylation reasonably affects binding. *withdraw*

The rejection of claims 6,7 and 9 based on the specific amino acids sequences which are only relevant to IgG is maintained. Applicant argues that he is not required to exemplify every embodiment, however, if the claim requires the presence of a certain sequence which does not exist in a particular isotype, than clearly there is a lack of enablement for making that particular embodiment of the claim.

The rejections of claims 1,2,5-10 under 35 USC 102(a) and 102(b) is maintained and newly added claims 17-21 are rejected under 35 USC 102(a) and 35 USC 102(b) as being anticipated by

Serial No.

-5-

Art Unit

Queen et. al. or Co et. al. for the same reasons as set forth in the previous Office action.

Applicant argues that the distinction between the prior art and the instant invention is that the framework amino acids are chosen from a consensus human variable region. However, as previously mentioned there is no clear indication of what is meant by consensus variable regions and as it is stated by applicant on page 14 of the response the chosen amino acids in the references may indeed be the same as what applicant calls consensus variable domain sequences.

The rejection of claims 3 and 4 under 35 USC 103 is maintained for the same reasons as set forth in the previous Office action. Applicant again argues that the use of "consensus region variable domains" is different from the prior art methods, however, as previously mentioned, the consensus amino acids may be the same as the most homologous murine antibodies of the references. The lack of clarity of the language "consensus amino acid region" is what allows this particular interpretation of the claims.

Claims 17,18, 20 and 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. New claims 17,18,20 and 21 are indefinite in that there are no discrete method steps.

Serial No.

-6-

Art Unit

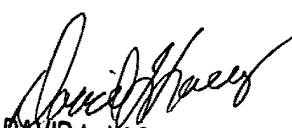
THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

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.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lila Feisee whose telephone number is (703) 308-2731.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Feisee/em
May 18, 1993


DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
5/17/93

FORM PTO-1449

U.S. Dept. of Commerce
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Atty Docket No.
709

Serial No.
07/715,272

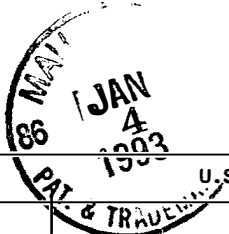
LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

Applicant
Paul J. Carter et al. #14

Filing Date
June 14, 1991

Group
1806



U.S. PATENT DOCUMENTS

| *Examiner Initials | Document Number | Date | Name | Class | Subclass | Filing Date |
|--------------------|-----------------|------|------|-------|----------|-------------|
| AA | | | | | | |
| AB | | | | | | |
| AC | | | | | | |
| AD | | | | | | |
| AE | | | | | | |
| AF | | | | | | |
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| AH | | | | | | |
| AI | | | | | | |
| AJ | | | | | | |
| AK | | | | | | |

FOREIGN PATENT DOCUMENTS

| | Document Number | Date | Country | Class | Subclass | Translation Yes | Translation No |
|-----------|-----------------|---------|---------|-------|----------|-----------------|----------------|
| <i>CP</i> | AL WO 90/07861 | 7/26/90 | PCT | | | | |
| | AM | | | | | | |
| | AN | | | | | | |
| | AO | | | | | | |
| | AP | | | | | | |

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

| | | |
|-----------|----|---|
| <i>CP</i> | AR | Carter et al., Proc. Natl. Acad. Sci., 89: 4285-4289 (1992) |
| | AS | |
| | AT | |
| | AU | |
| | AV | |
| | AW | |
| | AX | |

Examiner

CP

Date Considered

4/29/93

*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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GENENTECH, INC.
 460 Point San Bruno Boulevard
 South San Francisco, CA 94080
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 25 SEP 23 1993
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Attorney Docket No. 709
 Examiner: L. FEISEE
 Group Art Unit 1806

In re Application of: Paul J. Carter et al.

Serial No.: 07/715272

Filed: June 14, 1991

For: Immunoglobulin Variants

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

RECEIVED
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 GROUP 1806

Sir:

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

The fee has been calculated as shown below.

| | (Col. 1) | | (Col. 2) | | (Col. 3) | Rate | Addit. Fee |
|---|----------------------------------|-------|---------------------------------|---|---------------|-------------|------------|
| | Claims Remaining After Amendment | | Highest No. Previously Paid For | | Present Extra | | |
| Total | * 17 | Minus | ** 21 | = | 0 | x 22= | \$ 0 |
| Indep. | * 6 | Minus | *** 10 | = | 0 | x 74= | \$ 0 |
| _____ First Presentation of Multiple Dep. Claim | | | | | | + 230= | \$ |
| | | | | | | TOTAL . . . | \$ 0 |

*If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.
 **If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
 ***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.
 The "Highest Number Previously Paid For" (Total or Independent is the highest number found from the equivalent box in col. 1 of a prior amendment or the number of claims originally filed.)

1. No additional fee is required.
2. Please charge any additional fees, including any fees necessary for extensions of time, or credit overpayment to Deposit Account No. 07-0630. **A duplicate copy of this sheet is enclosed.**
 - Any additional filing fees required under 37 CFR 1.16.
 - Any patent application processing fees under 37 CFR 1.17.

Dated: September 20, 1993

Janet E. Hasak
 (Attorney of Record)

Janet E. Hasak
 Registration No. 28,616

CERTIFICATE OF MAILING

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

Dated: 20 Sept 1993

Louise Strasbaugh
 Louise Strasbaugh

BOX AF

PATENT DOCKET 709

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In 1993 application of
[Name] et al.

Serial No. 07/715272

Filed: June 14, 1991

For: Immunoglobulin Variants

) Group Art Unit: 1806

) Examiner: L. FEISEE

) 460 Point San Bruno Boulevard
) South San Francisco, CA 94080
) (415) 225-1896

#1806
SUGG
9-20-93

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

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 19 May 1993 for one month(s) from 19 August 1993 to 19 September 1993. The extended time for response does not exceed the statutory period.

Please charge Deposit Account Number 07-0630 in the amount of \$110 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.

Janet E. Hasak

Janet E. Hasak
Reg. No. 28,616

Date: September 20, 1993

CS14005 09/24/93 07715272

07-0630 140 115 110.00CH

CERTIFICATE OF MAILING (37 CFR 1.8a)

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

Louise Strasbaugh
Louise Strasbaugh

Date: September 20, 1993

Amendment under 37 CFR 1.116
Expedited Procedure
Examining Group 1806

PATENT DOCKET 709



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|------------------------------|---|-------------------------------|
| Application of |) | Group Art Unit: 1806 |
| Paul J. Carter et al. |) | Examiner: L. FEISEE |
| Serial No. 07/715272 |) | |
| Filed: June 14, 1991 |) | |
| For: Immunoglobulin Variants |) | 460 Point San Bruno Boulevard |
| |) | South San Francisco, CA 94080 |
| |) | (415) 225-1896 |

19/23 (ne)
SUGG
9-20-93

AMENDMENT AFTER FINAL REJECTION PURSUANT TO 37 CFR § 1.116

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

Sir:

This is responsive to the Office Action mailed May 19, 1993, which is a final rejection of claims 1 to 11 and 17 to 21. Claims 12 & 13 have been allowed. A request for a one-month extension of time to respond is submitted herewith, bringing the due date for this response to September 20, 1993 as September 19 is a Sunday. This response is timely filed.

IN THE SPECIFICATION:

On page 19, line 3, please delete "effect or" and insert --effector--.

On page 87, please amend Table 1 as follows:

line 6, please amend the heading of the second to last column to read

--K_d⁺--;

lines 6 & 7, please amend the heading of the last column to read --Relative

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Do not enter

cell proliferation[±]--;

line 8, please delete "proliferation[±]";

line 10, please amend the second to last column to read --25-- and the last column to read --102--.

IN THE CLAIMS:

Please cancel claims 14-16 and 18 from the application, without prejudice. Please amend claims 1, 3, 7, 17, 19, 20 and 21 as follows:

- 1: (Twice amended) A method for making [at least a portion of] a humanized antibody variable domain comprising amino acid sequences of an import antibody comprising a non-human antibody which is desired to be humanized [(import antibody)] and a human antibody, comprising the steps of:
- a. obtaining the amino acid sequences of an import variable domain and of a consensus human variable domain of a human immunoglobulin subgroup; *New*
 - b. identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human amino variable domain sequences;
 - c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
 - d. aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
 - e. identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
 - f. determining if the non-homologous import amino acid residue is [reasonably] expected to have at least one of the following effects:
 1. non-covalently binds antigen directly,
 2. interacts with a CDR; or
 3. participates in the V_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 residue which is 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. preparing a humanized antibody variable domain having amino acid sequences determined in steps a-g.

In claim 3, line 4, please delete "reasonably".

- 7. (Twice amended) A method for making a humanized antibody comprising providing an import antibody comprising a non-human antibody variable domain amino acid sequence which is desired to be humanized [(import antibody)] having a CDR and a 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 an 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, 68H, 69H, 70H, 73H, 74H, 75H, 76H, 78H, 91H, 92H, 93H, and 103H.
- 17. (Amended) A method of making a humanized antibody variable domain comprising the step of substituting Complementary Determining Region (CDR) amino acid residues of a variable domain of a non-human antibody for the corresponding CDR amino acid residues of [using] a consensus human antibody variable domain amino acid sequence of a human immunoglobulin subgroup [in the preparation of a humanized antibody].

19. (Amended) A method for making an improved antibody, comprising amino acid sequences from an import antibody comprising 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 antibody variable domain and of a consensus human antibody variable domain of a human immunoglobulin subgroup;
 - b. identifying Complementarity Determining Region (CDR) amino acid sequences in the import and the human [amino] variable domain sequences;
 - c. substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence;
 - d. aligning the amino acid sequences of a Framework Region (FR) of the import antibody and the corresponding FR of the consensus antibody;
 - e. identifying import antibody FR residues in the aligned FR sequences that are non-homologous to the corresponding consensus antibody residues;
 - f. determining if the non-homologous import amino acid residue is [reasonably] expected to have at least one of the following effects:
 1. non-covalently binds antigen directly,
 2. interacts with a CDR; or
 3. participates in the $V_L - V_H$ 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 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] ; and
 - h. preparing an improved, humanized antibody having amino acid sequences determined in steps a-g; and
 - i. evaluating the antigen binding or immunogenicity of the improved,

humanized antibody with respect to the parental antibody.

20. A method of making a humanized antibody comprising the step of making the antibody identified [, following the identification of an antibody] by the method of any one of claims [1,] 7[,] or 17 [-19, the manufacture of the antibody].
21. A method of making a humanized antibody comprising the step of expressing nucleic acid encoding the antibody identified [, following the identification of an antibody] by the method of any one of claims 1, 7, [or] 17, [-] or 19 [, the expression of nucleic acid encoding the antibody].

REMARKS

The claims pending in this application are claims 1 to 13, 17 and 19 to 21. Applicants have canceled claims 14 to 16 and 18, without prejudice to file divisional applications directed thereto.

The proposed amendments to the claims are purely in response to the rejections of the Final Action. No new matter has been introduced by the claim amendments. These amendments should be considered under Rule 116 because they do not introduce issues not already fully joined in this case and because they are believed to place the claims in better condition for appeal. Further, they are offered in a good faith effort to place this case in condition for allowance.

I. Amendments

The specification has been amended to correct obvious typographical errors. With respect to the amendment to Table 1 on page 87, a copy of Carter *et al.*, *Proc. Natl. Acad. Sci.*, **89**, (1992) is attached, which is a publication of the experimental data disclosed in the above application, and was published after the filing date thereof. It is clear that the

last two column headings of Table 1 were inadvertently superimposed and the amendment to the specification serves merely to correct these errors. It would have been obvious from the information provided on page 87 of the specification, that the last two headings were intended to be "Kd nM", and "Relative cell proliferation", respectively, as the key under Table 1 discloses what the headings indicated by † and ‡ are. Also, it is clear that the figures in the last two columns of the first line of data in Table 1 were intended to be 25 and 102 respectively, and were inadvertently superimposed. Applicants respectfully request that the specification be amended to correct the obvious typographical errors discussed above.

Claims 1, 7, 17 and 19 have been amended to refer to the consensus human variable domain "of a human immunoglobulin subgroup", with support for the amendment found on at least page 16, lines 29-32 and page 17, line 4. Claim 17, 19, and 20 have been amended to recite a preamble and a positive step, which steps are clear from at least the original set of claims filed.

II. Rejections under 35 U.S.C. § 112, second paragraph

Most of the rejections under 35 U.S.C. § 112, second paragraph, which were raised in the earlier Office Action dated October 5, 1992 have been withdrawn. Applicants thank the Examiner for withdrawing these rejections.

The Examiner has, however, maintained some of the rejections under 35 U.S.C. § 112, second paragraph, which relate to claims 1, 3-5 and 7. The separate sets of rejections are addressed separately below.

A. The Examiner has maintained the rejection of claim 1 with respect to the phrase "consensus human variable domain" because it is allegedly not clear whether the consensus domain is a culmination of different variable domains or a single universal variable domain which is homologous to other human variable domains.

In the interests of expediting examination, claims 1, 7, 17 and 19 have been amended to recite that the consensus human variable domain is "of a human

immunoglobulin subgroup". Information concerning the amino acid sequences of the *variable* domains of antibodies belonging to various human immunoglobulin subgroups was compiled by Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, Fourth Edition, U.S. Dept. of Health & Human Services, pubs., (1987), a copy of which is attached to the enclosed Kelley Declaration as Exhibit "B". 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 160-167 of Kabat *et al.*). The "occurrences of most common amino acids" at each position of the variable domain are provided in the second to last column for each immunoglobulin subgroup in Kabat *et al.* The consensus human variable domain claimed in the above application is an amino acid sequence comprising the most commonly occurring amino acid residues at each position of the variable domain for a particular human immunoglobulin subgroup as defined by Kabat *et al.* It would have been readily apparent, to the ordinarily skilled biochemist, what constitutes a consensus human variable domain of a human immunoglobulin subgroup upon reading the above application.

Applicants respectfully request the withdrawal of the rejection of claim 1 as indefinite in light of the above submissions.

B. The Examiner has suggested that the "import amino acid" be described as "an import antibody comprising the amino acid sequence of a non-human antibody which binds to ...". Applicants understand that the Examiner considers that inclusion of the wording "import antibody" in parentheses is unclear and that the rejection relates to claims 1, 3, 4, 5 and 7. In order to overcome the rejection, claims 1, 7 and 19 have been amended to recite "an import antibody comprising a non-human antibody...". The non-human, import antibody may be the muMAb4D5 disclosed in Example 1 of the application, for example. Claims 3-5 depend on claim 1 and because there is clear antecedence basis for the phrases "import antibody variable domain amino acid

sequence", "import sequence" and "import antibody" in claim 1, the rejection of these claims is also rendered moot.

C. The Examiner has maintained the rejection of claim 1 under 35 U.S.C. §112, second paragraph, with respect to the wording "reasonably expected" on the grounds that it is not known what criteria determines what is "reasonable". In order to obviate the rejection, Applicants have deleted the word "reasonably" from claims 1, 3 and 19. Applicants respectfully submit that the amendment to the claims renders the rejection moot.

Applicants respectfully request that the maintained rejections of claims 1, 3-5 and 7 under 35 U.S.C. § 112, second paragraph, be withdrawn in light of the amendments to the claims and the submissions under paragraphs A to C above.

III. Objection and Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has maintained the objection to the specification and the rejection of claims 1 to 11 under 35 U.S.C. § 112, first paragraph as lacking enablement. New claims 17 to 21 have also been rejected under 35 U.S.C. § 112, first paragraph as lacking enablement. The various sets of rejections are addressed separately below.

A. The Examiner has maintained the rejection of claim 1 and has rejected claims 19 to 21 for including the language "at least a portion". In the interests of expediting examination, claims 1, 7 and 19 have been amended by deleting the wording "at least a portion of" therefrom. Applicants submit that the amendment of the claims renders the rejection of claims 1 and 19-20 under 35 U.S.C. § 112, first paragraph, moot and respectfully request the withdrawal thereof.

B. The Examiner has maintained the rejection that step c) of claim 1 (i.e. the step of substituting an import CDR amino acid sequence for the corresponding human CDR amino acid sequence) is not enabled by the specification. The Examiner asserts that there is no clear guidance in the specification to enable one of ordinary skill in the art to make the human "consensus variable domain". The Examiner further asserts that the

only guidance presented in the specification with regards to the substitutions is the amino acid sequences of SEQ ID NO: 3 and 4. Applicants understand that the basis for the Examiner's rejection is that the information provided in the specification would not have enabled the ordinarily skilled biochemist to carry out the methods claimed in order to produce a humanized antibody.

Applicants respectfully traverse this rejection on the grounds that the specification is enabling for the method claimed. In support of the above position, a Declaration pursuant to 37 C.F.R. § 1.132 by Robert Kelley is attached. See specifically his opinion in paragraph 3 and the bases for this opinion set forth in paragraphs 4 to 7.

This Declaration was not earlier submitted because it was believed, in good faith, that the rejection would be overcome without the need for a Declaration. Applicants respectfully request the entry of this Declaration in the above application pursuant to Rule 116, because it does not introduce issues not already fully joined in this case. The Declaration is offered in a good faith effort to place this case in condition for allowance.

As discussed under section II (A) above and in paragraph 4 of the Kelley Declaration, the consensus human variable domain constitutes an amino acid sequence comprising the most commonly occurring amino acids at each position in the variable domain of a particular human immunoglobulin subgroup as defined by Kabat *et al.* The immunoglobulin subgroups referred to in Kabat *et al.* were grouped according to the amino acid sequence homology between human immunoglobulin *variable* domains, and the most commonly occurring amino acids at each position in the variable domain for each subgroup were identified (i.e. the "consensus human variable domain"). The skilled biochemist could have used the consensus human variable domains of the light chain and heavy chain subgroups having the greatest number of sequences therein (i.e. light chains kappa subgroup I and heavy chains subgroup III) as disclosed in Kabat *et al.* (see page 17, first paragraph of the specification) to humanize the non-human antibody of interest. Alternatively, the skilled biochemist could have chosen the consensus human variable domain of another human immunoglobulin subgroup as defined in Kabat *et al.*

i.e. the consensus human variable domain for human kappa light chains subgroups II to IV, human lambda light chains subgroups I to VI, or human heavy chains subgroups I or II (see pages 41-76 and 160-167 of Kabat *et al.*). Therefore, the skilled biochemist could have elected to use a consensus human variable domain other than those defined as SEQ ID NO: 3 & 4 on page 17 of the above application, as the consensus human variable domains for other subgroups were compiled in Kabat *et al.* Page ix of Kabat *et al.* identifies the residues forming the CDR regions of heavy and light chain variable domains tabulated from human and mouse variable domains. Kabat *et al.* have adopted standardized numbering for each of the residue locations. Accordingly, the skilled biochemist could have identified the CDR regions of the consensus human variable domain and the import variable domain using the teachings of Kabat *et al.* Alternatively, the structural definition of Chothia *et al.*, *J. Mol. Biol.*, **196**: 901-917 (1987) (see page 16, third paragraph of the specification) could have been adopted to identify the CDR regions of the consensus and import variable domains. See paragraph 4 of the Kelley Declaration. The above submissions show that steps a & b of claim 1 were enabled by the specification as filed.

Also, step c of claim 1 could have been carried out by the ordinarily skilled biochemist using the information provided in the specification and techniques such as manual tabulation of amino acid sequences or a computer program which was known in the art prior to June 14, 1991. See paragraph 5 of the Kelley Declaration.

Steps d to g of claim 1 would similarly have been straightforward to perform. These steps of claim 1 relate to the identification of Framework Region (FR) residues in the consensus human variable domain which are non-homologous to the corresponding import FR residues and replacement of such non-homologous human residues with corresponding import residues, if the residues are expected to have any one of the effects specified in step f. The locations of FR residues in human and mouse variable domains are indicated in Kabat *et al.* (see page ix) and the structural definition of the FR's was available (see Chothia *et al.*) Hence, it would have been straightforward for the skilled

immunologist to identify the FR residues in the consensus human variable domain and the import sequence. Using computer programs available before June 14, 1991, the skilled biochemist would have been able to study the 3-dimensional structure of the antibody in order to establish whether a particular non-homologous import amino acid residue is likely to have one of the effects discussed in section f of claim 1. Information is provided on pages 14 to 16 of the specification which would have enabled the skilled biochemist to determine whether any non-homologous residue(s) would be expected to have the effects claimed. The techniques claimed in steps d to g of claim 1 could have been carried out routinely by a person versed in the relevant art, prior to June 14, 1991. See paragraph 6 of the Declaration.

As discussed in paragraph 7 of the Declaration, once the primary amino acid sequence of the antibody had been characterized, it would have been routine to make the protein using recombinant techniques or a peptide synthesizer, which techniques were well known in the art prior to the filing date of the above application.

Applicants conclude that, contrary to the Examiner's assertions, the ordinarily skilled biochemist would have been able to carry out the method claimed in the above application, using the information provided in the specification and techniques which were well known in the relevant art, prior to June 14, 1991.

Accordingly, Applicants request that the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn in light of the above submissions and the Declaration.

C. The Examiner has maintained the rejection of claims 1 and 3, and has rejected claim 19 under 35 U.S.C. § 112, first paragraph, with respect to the wording "reasonably" therein. In order to obviate the rejection, the wording "reasonably" has been deleted from claims 1, 3 and 19.

Accordingly, Applicants request that the rejection of claims 1, 3 and 19 under 35 U.S.C. § 112, first paragraph, be withdrawn.

D. The Examiner has maintained the rejection of claims 6, 7 and 9 as lacking

enablement under 35 U.S.C. § 112, first paragraph, the Examiner's position being that the amino acids are relevant to IgG only and not to other isotypes. Applicants respectfully traverse this rejection on the basis that the immunoglobulin *sites* claimed would have been relevant with respect to antibodies, other than IgG antibodies. Applicants refer the Examiner to paragraphs 8 & 9 of the Kelley Declaration which support this position. The Examiner appears to suggest that the rejected claims cover *sequences* which would not be found in immunoglobulin isotypes, other than IgG isotypes. However, as pointed out in paragraph 9 of the Kelley Declaration, the claims refer to *positions* or *sites* of the variable domain, not specific amino acid residues. These sites relate to the position of a residue in the 3-D structure of the variable domain. Kabat *et al.* have used universal numbering for the amino acid residue locations of the variable domains for each of the immunoglobulin subgroups mentioned therein. The FR residue sites indicated may be occupied by an amino acid residue which is non-homologous to the corresponding consensus human variable domain residue, and which residue is likely to have at least one of the effects discussed in step f of claim 1. The residue at the particular site can be any amino acid residue, depending on the antibody in which it is located. These residue locations or sites are applicable *across species* (see page 16, line 8). Accordingly, it is likely that an amino acid residue located at one of the sites indicated in claims 6, 7 and 9 will have one of the effects of claim 1 (step f) regardless of the antibody in which it is located. It is apparent that the particular sites claimed are applicable to immunoglobulins other than IgG.

Accordingly, Applicants submit that the rejection of claims 6, 7 & 9 under 35 U.S.C. § 112, first paragraph, should be reconsidered and withdrawn in light of the above submissions and Declaration.

In light of the submissions presented in paragraphs A to D above, Applicants respectfully request that the objection to the specification and the rejection of claims 1-11 and 17-21 under 35 U.S.C. §112, first paragraph, be withdrawn.

Applicants thank the Examiner for withdrawing the rejections which were raised

under 35 U.S.C. § 101 in the earlier Office Action dated October 5, 1992 .

IV. Rejection of claims 1, 2 and 5-10 under 35 U.S.C. 102 (a) and 102(b)

The rejection of claims 1, 2 and 5-10 under 35 U.S.C. § 102(a) and 102(b) has been maintained and newly added claims 17-21 have been rejected under 35 U.S.C. § 102(a) and 102(b) as being anticipated by Queen *et al.*, *Proc. Natl. Acad. Sci.*, 86:10029-10033 (1989) and Co *et al.*, *Proc. Natl. Acad. Sci.*, 88:2869-2873 (1991). The basis for the rejection is that there is allegedly no clear indication as to what is meant by the consensus human variable domain claimed in the above application.

To constitute anticipation, all material elements of a claim must be found in one prior art source. *In re Marshall*, 198 USPQ 344 (CCPA 1978), *In re Kalm*, 154 USPQ 10 (CCPA 1967). Applicants will show that Queen *et al.* and Co *et al.* do not contain all material elements of claims 1, 2, 5-10 and 17-21.

The nature of the "consensus human variable domain of a human immunoglobulin subgroup" as defined in the claims as amended has been discussed above under Section II(A) of this response and in paragraph 4 of the Kelley Declaration, those discussions being incorporated herein. Applicants submit that the meaning of the phrase consensus human variable domain of a human immunoglobulin subgroup would have been clearly understood by those skilled in the art upon reading the specification. The prior art relied upon in the Office Action fails to disclose a method of making a humanized antibody using a consensus human variable domain to "humanize" a non-human antibody. The Declaration by Kelley supports this position. In particular, Applicants direct the Office's attention to paragraphs 11-13 of the attached Declaration. It is apparent from the information given in Table 1 of Exhibit C and in the Figures of Exhibits D and E of the Kelley Declaration (see paragraphs 12 & 13 thereof), that the variable domains of the human immunoglobulin sequences used by Queen *et al.* and Co *et al.* are not a consensus human variable domain of any human immunoglobulin subgroup as set forth in the claims of the above application.

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Since, as shown above, Queen *et al.* and Co *et al.* do not teach all the material elements of the instant claims as required under *Marshall* and *Kalm, supra*, Applicants respectfully submit that the rejection of claims 1, 2, 5-10 and 17-21 under 35 U.S.C. § 102(a) and (b) can not be upheld and therefore request that the rejections be withdrawn.

V. Rejection of claims 3 and 4 under 35 U.S.C. § 103

The rejection of claims 3 and 4 as unpatentable under 35 U.S.C. § 103 over Queen *et al.* or Co *et al., supra*, in view of Wallick *et al., J. Exp. Med.*, 168 (1988) has been maintained. The basis for the rejection relates to the alleged lack of clarity of the language "consensus human variable domain" in the claims of the above application. The consensus human variable domain as defined in the above application would have been readily understood by the ordinarily skilled biochemist (see paragraph 4 of the Kelley Declaration). Claim 1 of the above application relates to a method of using a consensus human variable domain to "humanize" a non-human antibody (e.g. muMAb4D5). As established in section IV above, use of a consensus human variable domain from a human immunoglobulin subgroup is not disclosed in Queen *et al.* or Co *et al.*

The publication by Wallick *et al.* does not compensate for the deficiencies in the primary references. Wallick *et al.* refer to the importance of glycosylation for maintaining antigen binding affinity of monoclonal antibodies. Wallick *et al.* fail to disclose or suggest a method of humanizing a non-human antibody, much less a method of humanizing a non-human antibody using a consensus human variable domain of a immunoglobulin subgroup. The skilled biochemist would have had no motivation to use a consensus human variable domain based on the prior art referred to in the Office Action, because the prior art techniques had all relied upon using a human variable domain sequence which has the closest sequence homology to the non-human variable sequence (to be humanized) in order to reduce the likelihood of introducing distortions into the CDR's (see column 2 on page 10031 of Queen *et al.*) and "to retain high binding affinity in the humanized antibody" (see column 1 on page 2871 of Co *et al.*). The method claimed in

the above application does not rely on a high degree of homology between the variable domain of the non-human sequence and the consensus variable domain which is used to humanize the non-human sequence.

Also, as supported by paragraph 15 of the Kelley Declaration, the invention claimed in the above application resulted in an unexpected result which could not have been reasonably predicted from the prior art. It was surprising that a consensus variable domain of a selected immunoglobulin subgroup could be used to humanize a non-human antibody, regardless of the degree of homology between the human and non-human amino acid sequences. It was also surprising that the humanized antibody so formed retained, and in some instances, had increased antigen binding affinity compared to the non-human antibody from which it was derived. The above application shows that the huMAb4D5-8 variant actually binds the p185^{HER2} ECD 3-fold more tightly than muMAb4D5 (see page 82 lines 31 & 32 to page 83, line 1 of the specification) which could not have been predicted by the ordinarily skilled biochemist. See paragraph 15 of the Kelley Declaration. The evidence of unexpected results in Applicants' application is sufficient to support a conclusion of nonobviousness. *Ralston Purina Co. Far-Mar-Co., Inc.*, 222 USPQ 863 (DC KS, 1984).

It is apparent that the invention claimed in claim 1 was novel and nonobvious over the citations because the combination of the prior art failed to disclose, or suggest, the invention claimed in claim 1 and, moreover, the method resulted in a new and unexpected result which could not have been reasonably predicted from the art.

Claims 3 & 4 depend on claim 1 which, as established above, is novel and nonobvious over the citations. Claim 3 refers to the step of finding any glycosylation site which is likely to affect the antigen binding or affinity in the import antibody and substituting the glycosylation site *into* the *consensus* amino acid sequence. Claim 4 refers to the step of *replacing* glycosylation sites of the consensus domain with the corresponding import amino acid residues if such glycosylation sites are not present in the import sequence. These claims would not have been obvious over the prior art of

record because the prior art failed to disclose the use of a human consensus variable domain to humanize the non-human antibody. Accordingly, the skilled biochemist would have had no motivation to replace or insert glycosylation sites into a consensus amino acid sequence, as claimed in claims 3 and 4 of the application. See paragraph 15 of the Kelley Declaration.

The law is clear that obviousness cannot be established by combining the teachings of the references to produce the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 USPQ 929, 933 (Fed. Cir. 1984). The above discussion shows that the cited references, alone or in combination, lack the requisite teaching of the use of a consensus human variable domain to humanize a non-human antibody. In this case, the combined art would not have reasonably enabled or motivated the skilled practitioner to use a human consensus variable domain in this manner, which provides a method of making improved humanized antibodies. Accordingly, it is clear that the invention claimed in claims 3 & 4 is novel and nonobvious over the prior art of record.

Applicants submit that the rejection of claims 3 and 4 under 35 U.S.C. § 103 should be reconsidered and withdrawn in light of the above submissions and the Declaration.

VI. Rejection of claims 17,18, 20 and 21 under 35 U.S.C. §112, second paragraph.

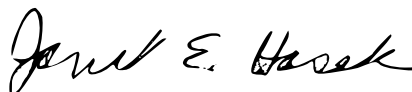
Claims 17, 18, 20 and 21 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in that there are allegedly no discrete method steps. In order to obviate the rejection, claims 17, 20 and 21 have been amended to each recite a definite method step and claim 18 has been deleted.

Applicants respectfully request the withdrawal of the rejection of claims 17, 20, and 21 under 35 U.S.C. § 112, second paragraph, in light of the amendments to the claims.

As all objections and rejections have been addressed and overcome, Applicants

believe that the claims are now in condition for allowance. Notice to that effect is respectfully requested. If the Examiner has any questions concerning the response, she should feel free to call the undersigned attorney at the number indicated above.

Respectfully submitted,
GENENTECH, INC.

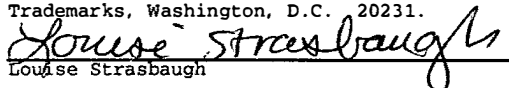


Janet E. Hasak
Reg. No. 28,616

Date: September 20, 1993

CERTIFICATE OF MAILING (37 CFR 1.8a)

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


Louise Strasbaugh

Date: September 20, 1993



THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | |
|------------------------------|---|-------------------------------|
| In re Application of |) | Group Art Unit: 1806 |
| Paul J. Carter et al. |) | Examiner: L. FEISEE |
| Serial No. 07/715272 |) | |
| Filed: June 14, 1991 |) | |
| For: Immunoglobulin Variants |) | 460 Point San Bruno Boulevard |
| |) | South San Francisco, CA 94080 |
| |) | |

#20098
SEP 23
9-20-93

DECLARATION OF ROBERT F. KELLEY PURSUANT TO 37 CFR §1.132

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

Sir:

I, ROBERT F. KELLEY, do hereby declare as follows:

1. I received my Ph.D. in Biochemistry in 1984 from the University of Iowa. Following my Ph.D, I was a NIH postdoctoral fellow in the Department of Molecular Biophysics & Biochemistry at Yale University from July 1984 to December 1985. In 1986, I joined the Biocatalysis Department at Genentech, Inc. as an Associate Scientist. In September 1988, I was promoted to Scientist and I am employed in that capacity at present. (The Biocatalysis Department has been renamed "Protein Engineering"). I am the author or co-author of 22 publications relating to the 3-D structures and folding of various proteins. A copy of my curriculum vitae is attached as Exhibit "A".

2. I understand that the Patent Office has rejected the above application on the basis that the application as filed does not provide sufficient disclosure to enable a skilled biochemist to carry out the method of claim 1 because the Examiner believes no clear guidance exists in the specification to allow a skilled biochemist to make the "consensus human variable domain" and substitute an import (i.e. non-human) Complementary Determining Region (CDR) amino acid sequence for the corresponding human CDR amino acid sequence, as set forth in claim 1. I further understand that the Office considers that

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the only guidance in the specification with regards to the substitutions is the amino acid sequences of SEQ ID NO: 3 and 4.

3. I have read the above application, the Office Action date May 19, 1992 (Paper # 17) rejecting the claims of the application, and the proposed amendment of the claims in response to the rejection. In my opinion, the skilled biochemist could have readily carried out the method of claim 1 in order to make a humanized antibody, using the general knowledge available in the field on and before June 14, 1991, and the information given in the above application. The bases for my opinion are given in paragraphs 4 to 7 below.

4. Claim 1 relates to a method of making a humanized antibody. Steps a and b of claim 1, as amended, discuss identification of the CDR amino acid sequences of a non-human import antibody (to be humanized) and a consensus human variable domain of a human immunoglobulin subgroup. The consensus human variable domain constitutes an amino acid sequence comprising the most commonly occurring amino acids at each position in the variable domain of a particular human immunoglobulin subgroup as defined by Kabat *et al.*, *Sequences of Proteins of Immunological Interest*, Fourth Edition, U.S. Dept. of Health & Human Services, pubs., (1987), a copy of which is attached as Exhibit "B". The immunoglobulin subgroups referred to in Kabat *et al.* were grouped according to the amino acid sequence homology between human immunoglobulin *variable* domains, and the most commonly occurring amino acids at each position in the variable domain for each subgroup were identified (i.e. the "consensus human variable domain"). The skilled biochemist could have used the consensus human variable domains of the light chain and heavy chain subgroups having the greatest number of sequences (i.e. light chains kappa subgroup I and heavy chains subgroup III) as disclosed in Kabat *et al.* (see page 17, first paragraph of the specification) to humanize the non-human antibody of interest. Alternatively, the skilled biochemist could have chosen the consensus human variable domain of another human immunoglobulin subgroup as defined in Kabat *et al.* (i.e. the consensus human variable domain for human kappa light chains subgroups II to IV, human lambda light chains subgroups I to VI, or human

heavy chains subgroups I or II [see pages 41-76 and 160-167 of Kabat *et al.*]). Therefore, the skilled biochemist could have elected to use a consensus human variable domain other than those defined as SEQ ID NO: 3 & 4 on page 17 of the above application, as the consensus human variable domains for other subgroups were compiled in Kabat *et al.* Page ix of Kabat *et al.* identifies the residues forming the CDR regions of heavy and light chain variable domains tabulated from human and mouse variable domains. Kabat *et al.* have adopted standardized numbering for each of the residue locations. Accordingly, the skilled biochemist could have identified the CDR regions of the consensus human variable domain and the import variable domain using the teachings of Kabat *et al.* Alternatively, the structural definition of Chothia *et al.*, *J. Mol. Biol.*, 196: 901-917 (1987) (see page 16, third paragraph of the specification) could have been adopted to identify the CDR regions of the consensus and import variable domains. Hence, it would have been straightforward for the skilled biochemist to carry out steps a and b of claim 1 using the information provided in the specification.

5. Step c of claim 1 discloses the step of replacing the corresponding human CDR sequence with the import CDR amino acid sequence. This step could have been carried out routinely by the skilled biochemist by manual tabulation or using a computer program such as the ALIGN program, (Dayhoff *et al.*, *Meth. Enzymol.*, 91:524-545 [1983]) which was available prior to June 14, 1991. Steps a to c of claim 1 would have resulted in the characterization of a primary amino acid sequence encoding a humanized variable domain with import (non-human) CDR regions.

6. Steps d to g of claim 1 relate to the identification of Framework Region (FR) residues in the consensus human variable domain which are non-homologous to the corresponding import FR residues and replacement of such non-homologous human residues with corresponding import residues, if the residues are expected to have any one of the effects specified in step f. The locations of FR residues in human and mouse variable domains are indicated in Kabat *et al.* (see page ix) and the structural definition of the FR's was available (see Chothia *et al.*) Hence, it would have been straightforward for the skilled immunologist to identify the FR residues in the consensus human variable domain and the

import sequence. Using computer programs (such as the INSIGHT program [Biosym Technologies], available before June 14, 1991), the skilled biochemist would have been able to study the 3-dimensional structure of an antibody in order to establish whether a particular non-homologous import amino acid residue is likely to have one of the effects discussed in section f of claim 1. Information is provided on pages 14 to 16 of the specification which would have enabled the skilled biochemist to determine whether any non-homologous residue(s) would be expected to have the effects claimed. The techniques claimed in steps d to g of claim 1 could have been carried out routinely by a person versed in the relevant art, prior to June 14, 1991.

7. Steps a to g of claim 1 would have lead to the characterization of an amino acid sequence of a humanized antibody having non-human CDR amino acid residues and, optionally, having one or more non-human FR residues. In order to prepare the humanized antibody as claimed in claim 1, step h, the skilled biochemist could have synthesized the antibody using a peptide synthesizer which was commercially available before June 14, 1991. Alternatively, the antibody could have been made in recombinant cell culture (see page 26, last paragraph of the specification). Preparation of the antibody would have been straightforward to perform by the person skilled in the art, once the amino acid sequence of the humanized antibody had been characterized.

8. I understand that the Patent Office has rejected the above application on the basis that the sites in the variable domain referred to in claims 6, 7, and 9 are relevant to IgG antibodies only. It is my opinion that the sites referred to in claims 6, 7, and 9 would be relevant to other immunoglobulins. The basis for my opinion is given in paragraph 9 below.

9. The sites referred to in claims 6, 7, and 9 are the residue locations, or sites, of the FR residues in the heavy or light chain forming the variable domain of immunoglobulins. The residue sites referred to in claims 6, 7 & 9 relate to the position of a residue in the 3-D structure of the variable domain. Kabat *et al.* have used universal numbering for the amino acid residue locations of the variable domains for each of the immunoglobulin subgroups mentioned in the reference. The FR residue sites

indicated may be occupied by an amino acid residue which is non-homologous to the corresponding consensus human variable domain residue, and which is likely to have at least one of the effects discussed in step f of claim 1. These residue locations or sites are applicable *across species* (see page 16, line 8 of the specification). Accordingly, it is likely that an amino acid residue located at one of the sites indicated in claims 6, 7 and 9 will have one of the effects of claim 1 (step f), regardless of the antibody in which it is located, because it will be in the same position in the 3-D structure of the antibody variable domain as the residue sites referred to in the rejected claims. Accordingly, the examples of residue locations to be substituted in the variable domains would be applicable to antibodies, other than IgG antibodies.

10. I understand that the Patent Office has rejected the above application on the grounds that the invention as claimed is disclosed in Queen *et al.*, *Proc. Natl. Acad. Sci.*, 86:10029-10033 (1989) or Co *et al.*, *Proc. Natl. Acad. Sci.*, 88:2869-2873 (1991) and that the Office has suggested that the human variable domains disclosed in these references may have the same amino acid sequences as one of the consensus human variable domains disclosed in Kabat *et al.*

11. The above statements regarding the state of knowledge as of June 14, 1991, do not establish that the invention claimed in this application was known, or would have been obvious, to the skilled biochemist at the time the invention was made. To the contrary, after having read the citations relied upon by the Patent Office, it is my judgement that these documents would not have disclosed, nor suggested, the methods claimed. The basis for my opinion is given below.

12. The invention of the above application can be distinguished on the basis that a *consensus human variable domain* is used to "humanize" a non-human antibody of interest. The Queen *et al.* and Co *et al.* publications fail to disclose a consensus human variable domain. Instead, these publications refer to the use of a human variable domain having the closest sequence homology to the variable domain of the non-human antibody to be humanized. Queen *et al.* used the Eu human variable domain sequence (see Fig 2 thereof) and Co *et al.* used the variable domains of the Pom or Eu human

antibodies (see Fig 1 thereof). The sequences used in Queen *et al.* and Co *et al.* do not constitute a consensus human variable domain of a human immunoglobulin subgroup. The sequence identity between the amino acid sequences of the FR residues of the variable domains of the Pom or Eu heavy or light chains compared to the FR residues of the consensus human variable domains of each of the human immunoglobulin subgroups as defined by Kabat *et al.* is illustrated in Table 1 (see Exhibit "C", attached hereto). The CDR residues were not used in the comparison because of the large number of differences between these residues for variable domains of different antibodies. The Pom and Eu variable domain sequences were taken from Kabat *et al.* The consensus human variable domains of the V_L lambda subgroups IV and V were not compared, as these subgroups have too few members. While the variable domain of Eu is classified in subgroups V_L kappa I and V_H I, and the variable domain of Pom is classified in subgroups V_L kappa III and V_H III, it is apparent that the Eu and Pom variable domain amino acid sequences are not consensus human variable domains of any immunoglobulin subgroup. This is further demonstrated in the following paragraph.

13. Exhibits "D" and "C" attached hereto, show the differences in the amino acid sequences of the Pom and Eu heavy and light chain variable domains compared to the consensus human variable domain of the subgroup in which they are classified. Exhibit D illustrates an alignment of the amino acid sequences of the light chain variable domains of Eu, Pom and the consensus variable domain of the V_L kappa subgroup I (in which the light chain variable domain of Eu is classified). Exhibit E illustrates an alignment of the amino acid sequences of the heavy chain variable domains of Eu, Pom and the consensus variable domain of the V_H subgroup III (in which the heavy chain variable domain of Pom is classified). Even though Eu is classified in V_L kappa I, it has seven framework residues which are different from the framework residues of the kappa I consensus sequence. Furthermore, while Pom is classified in the V_H III subgroup, eight of its framework residues differ from the corresponding framework residues of the V_H III consensus sequence. There are, of course, many differences between the CDR residues of the consensus sequences and the corresponding CDR residues of Pom and Eu.

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It is clear from the information in Exhibits C, D, & E that the Queen *et al.* and Co *et al.* publications fail to disclose a method wherein a non-human import antibody is humanized using a consensus human variable domain of an immunoglobulin subgroup.

14. I understand the Patent Office has rejected the above application on the basis that the invention claimed in claims 3 & 4 would have been obvious in light of Queen *et al.*, or Co *et al.*, when read in conjunction with Wallick *et al.*, *J. Exp. Med.*, 168 (1988). After reading these references, it is my opinion that the invention claimed in claims 3 and 4 is novel and would not have been obvious in light of the citations. The basis for my opinion is given in the following paragraph.

15. Claim 1 of the above application relates to a method of using a consensus human variable domain to "humanize" a non-human antibody (e.g. muMAb4D5). Use of a consensus human variable domain from a human immunoglobulin subgroup to humanize a non-human antibody is not disclosed in Queen *et al.*, Co *et al.* or Wallick *et al.* Wallick *et al.* does not relate to a method of humanizing a non-human antibody, much less a method of humanizing a non-human antibody using a consensus human variable domain of a human immunoglobulin subgroup. The skilled biochemist would have had no motivation at the filing date of this application to use a consensus human variable domain to humanize a non-human antibody, because the techniques in the prior literature had all relied upon using a human variable domain sequence which has the closest sequence homology to the non-human variable sequence (to be humanized) in order to reduce the likelihood of introducing distortions into the CDR's (see column 2 on page 10031 of Queen *et al.*) or to "retain high binding affinity in the humanized antibodies" (see column 1 on page 2871 of Co *et al.*). The method claimed in the above application does not rely on a high degree of homology between the variable domain of the non-human sequence and the consensus variable domain which is used to humanize the non-human sequence. It was surprising that a consensus variable domain of a selected immunoglobulin subgroup could be used to humanize a non-human antibody, regardless of the degree of homology between the human and non-human amino acid sequences. It was also surprising that the humanized antibody so formed retained,

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and in some instances, had increased antigen binding affinity compared to the non-human antibody from which it was derived. The above application shows that the huMAb4D5-8 variant actually binds the p185^{HER2} ECD 3-fold more tightly than muMAb4D5 (see page 82 lines 31 & 32 to page 83, line 1 of the specification), which could not have been predicted by the ordinarily skilled biochemist at the time the specification was filed. Claim 3 refers to the step of finding any glycosylation site which is likely to affect the antigen binding or affinity in the import antibody and substituting the glycosylation site *into* the *consensus* amino acid sequence. Claim 4 refers to the step of *replacing* glycosylation sites of the consensus domain with the corresponding import amino acid residues if such glycosylation sites are not present in the import sequence. In my opinion, these claims would not have been obvious over the prior literature because the reference failed to disclose the use of a human consensus variable domain to humanize the non-human antibody. Accordingly, the skilled biochemist would have had no motivation to replace or insert glycosylation sites into a consensus amino acid sequence, as claimed in claims 3 and 4 of the application.

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

Dated: 9/20/93

Signed: Robert F. Kelley
ROBERT F. KELLEY

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 September 20, 1993.

Dated: September 20, 1993

Louise Strasbaugh
Louise Strasbaugh

Robert F. Kelley**CURRICULUM VITAE****September, 1993****Work address:**

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Personal information:

**Birthdate: November 7, 1957
Married, Wife's name: Wendy L. Kelley
One child: Brian F. Kelley**

Education:

**B.S., Biochemistry, Michigan State University, 1979
Ph. D., Biochemistry, University of Iowa, 1984**

Employment positions:

**Teaching assistant, Chemistry Dept., Michigan State Univ., 1978-1979
Teaching assistant, Biochemistry Dept., University of Iowa, 1979-1981
Graduate research assistant, Biochemistry Dept., University of Iowa, 1982-
April 1984
Postdoctoral associate, Biochemistry Dept., University of Iowa, May 1984-
June 1984
NIH postdoctoral fellow, Dept. of Molecular Biophysics & Biochemistry,
Yale University, July 1984-Dec. 1985
Associate Scientist, Biocatalysis Dept., Genentech, Inc., January 1986-
September 1988
Scientist, Biomolecular Chemistry Dept., Genentech, Inc., September
1988-present**

Awards and membership in professional organizations:

**Biophysical Society, 1983-present
American Chemical Society, 1991-present**

Scientific publications

- Kelley, R.F., & Stellwagen, E. (1984) "Conformational transitions of thioredoxin in guanidine hydrochloride", *Biochemistry* 23, 5095-5102.
- Kelley, R.F., Wilson, J., Bryant, C., & Stellwagen, E. (1986) "Effects of guanidine hydrochloride on the refolding kinetics of denatured thioredoxin", *Biochemistry* 25, 728-732.
- Wilson, J., Kelley, R.F., Shalongo, W., Lowery, D., & Stellwagen, E. (1986) "Equilibrium and kinetic measurements of the conformational transition of thioredoxin in urea", *Biochemistry* 25, 7560-7566.
- Kelley, R., Wilson, J., Bryant, C., Shalongo, W., Ledger, R., Lowery, D., & Stellwagen, E. (1986) "Folding of *E. coli* thioredoxin into its native conformation" in *Thioredoxin and Glutaredoxin Systems: Structure & Function* (Holmgren, A., Branden, C.-L., Jornvall, H., & Sjoberg, B.-M., Eds.) pp 77-85, Raven Press, New York.
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- Cleary, S., Mulkerrin, M.G., & Kelley, R.F. (1989) "Purification and characterization of tissue plasminogen activator kringle-2 domain expressed in *E. coli*", *Biochemistry*, 28, 1884-1891.
- Kelley, R.F., & Cleary, S. (1989) "Effect of residue 65 substitutions on thermal stability of t-PA kringle-2 domain", *Biochemistry* 28, 4047-4054.

TABLE 1
SEQUENCE IDENTITY - (%)

| CONSENSUS VARIABLE DOMAIN SUBGROUP | EU | POM |
|---------------------------------------|----|-----|
| V _L kappa I | 92 | 76 |
| V _L kappa II | 61 | 71 |
| V _L kappa III | 72 | 85 |
| V _L kappa IV | 73 | 78 |
| V _L lambda I | 61 | 59 |
| V _L lambda II | 57 | 54 |
| V _L lambda III | 59 | 56 |
| V _L lambda VI | 52 | 49 |
| V _H I | 83 | 64 |
| V _H II | 53 | 62 |
| V _H III | 61 | 91 |

Variable Light Domain

| | | | | |
|---------|-----------------|--------------|----------|-----------------|
| | 10 | 20 | 30 | 40 |
| EU | DIQMTQSPSTLSASV | GDRVTITCRASQ | SINTWLA | WYQOKPGKAPKLLMY |
| | * | | @ @ @ | * |
| Kappa-I | DIQMTQSPSSLSASV | GDRVTITCRASQ | --ISNYLA | WYQOKPGKAPKLLIY |
| | * * | * * * * * | @ @ @ @ | * * * * |
| POM | EIVMTQSPVTL | SVSPGERATL | SCRASQ | SISNSYLA |
| | | | | WYQOKPSGSPRLLIY |

CDR-L1

| | | | | | | |
|---------|---------------|--------------|-----------|-------------|----------|-------|
| | 50 | 60 | 70 | 80 | 90 | 100 |
| EU | KASSLESGVPSRF | FIGSGSGTEFTL | TISSLOPDD | FATYYCQOYNS | SDSKMFGQ | |
| | @ | * | * | * | @ @ @ @ | |
| Kappa-I | AASSLESGVPSRF | FIGSGSGTEFTL | TISSLOPED | FATYYCQOYNS | LPWTFGQ | |
| | @ @ @ @ | * * | * | * | * | @ @ @ |
| POM | GASTRATGIPAR | FIGSGSGTEFTL | TISSLOSED | FAVYYCQOYNN | WPPTFGQ | |
| | | | | | | |

CDR-L2

CDR-L3

| | |
|---------|-----------|
| EU | GIRVEVKGT |
| | * * |
| Kappa-I | GTKVEIKRT |
| | * |
| POM | GTRVEIKR |

KEY: * = differences in FR residues
@ = differences in CDR residues

EXHIBIT E

Variable Heavy Domain

| | | | | |
|-----------|----------------------|------------------|------------------|----------|
| | 10 | 20 | 30 | 40 |
| EU | QVQLVQSGAEVKKPGSSVKV | SCKASGGTFSRS | AIWVRQAPGQGLEWMG | |
| | * | * * * * * | * * * * * | @ @ * ** |
| human-III | EVQLVESGGGLVQPGGSLRL | SACAASGFTFSSYAMS | WVRQAPGKGLEWVS | |
| | * | | @ | * |
| POM | EVQLLESGGGLVQPGGSLRL | SACAASGFTFSSSAMS | WVRQAPGKGLEWVA | |

CDR-H1

| | | | | | | | |
|-----------|----------------------|----------------------|----------------|-----------|-----------|-----------|---------|
| | 50 | a | 60 | 70 | 80 | abc | 90 |
| EU | GIVPMFGPPNYAOKFQGRVT | ITADESTNTAYMELSSLRSE | DTAFYFCAG | | | | |
| | @ @ @ @ @ | @ @ @ @ | @ @ @ @ | * * * * * | * * * * * | * * * * * | * * * * |
| human-III | VISGDGGSTYYADSVKGRFT | ISRDN SKNTLYLQMN | SLRAEDTAVYYCAR | | | | |
| | @ @ @ @ @ | @ @ @ @ | @ | ** | * | * | * |
| POM | WKYENGNDKHYADSVNGRFT | ISRDN SKNTLYLLMNSL | QAEDTALYYCAR | | | | |

CDR-H2

| | | |
|-----------|---------------------|---------|
| | | 110 |
| EU | GYGIYSPE-----EYNGGL | VTVSS |
| | @ @ @ @ @ | * * * * |
| human-III | GRGGGSDY-----WGQGT | LVTVSS |
| | @ @ @ @ @ | * |
| POM | DAGPYVSPITFFAHYGQGT | LVTVSS |

CDR-H3

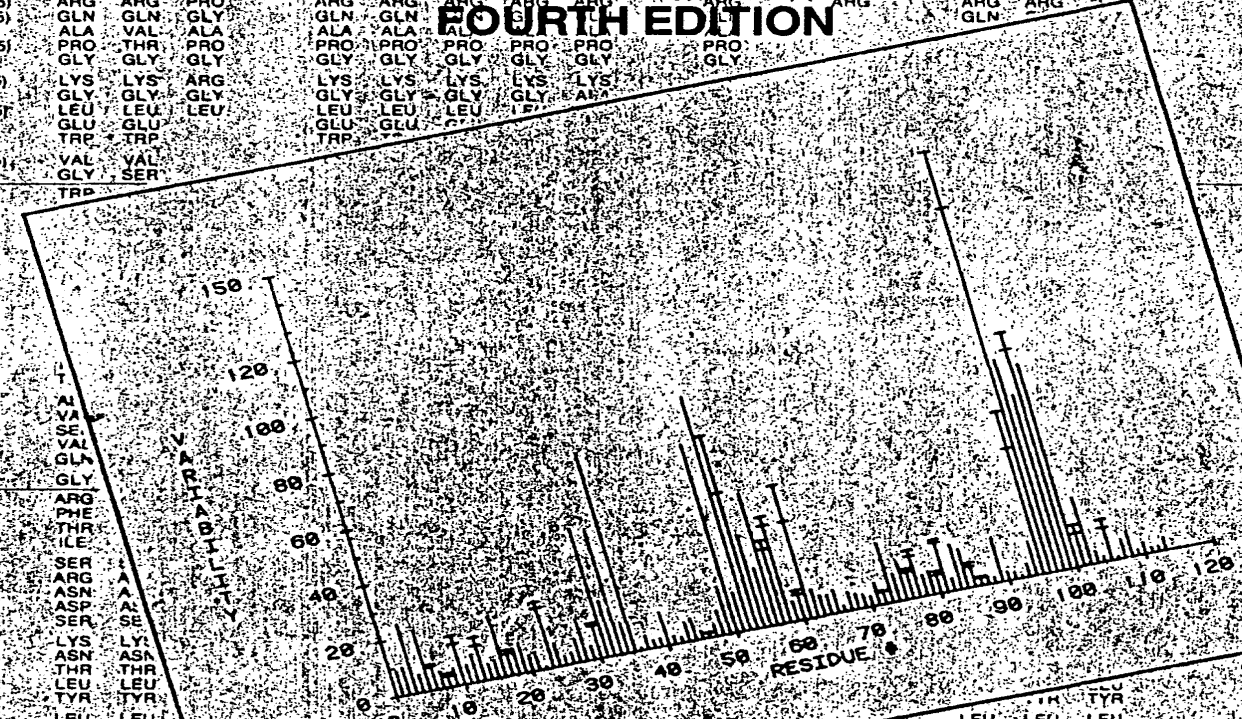
KEY: * = differences in FR residues
 @ = differences in CDR residues

- Byeon, I.-J.L., Kelley, R.F., & Llinas, M. (1989) "¹H-NMR structural characterization of a recombinant kringle-2 domain from human tissue-type plasminogen activator", *Biochemistry* 28, 9350-9360.
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SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST

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SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST

FOURTH EDITION

Tabulation and Analysis of
Amino Acid and Nucleic Acid Sequences of
Precursors, V-Regions, C-Regions, J-Chain,
T-Cell Receptor for Antigen, T-Cell Surface Antigens,
 β_2 -Microglobulins, Major Histocompatibility Antigens,
Thy-1, Complement, C-Reactive Protein, Thymopietin,
Post-gamma Globulin, and α_2 -Macroglobulin

1987

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considered uncertain by the authors have not been included in the table. In some instances the symbol # is used to indicate that several amino acid residues were found in one position, and these residues are listed in the notes. The four columns at the end of each table give:

1. the number of residues sequenced at that position,
2. the number of different amino acids found at that position,
3. the number of times the most common amino acid occurred and that amino acid in parentheses, and
4. the variability.

Variability is calculated (11) as:

$$\text{Variability} = \frac{\text{Number of different amino acids occurring at a given position}}{\text{Frequency of the most common amino acid at that position}}$$

An invariant position would have a variability of one; if 20 amino acids occurred with equal frequency, the variability would be 20 divided by 0.05 equals 400. If, for example, four different amino acids Ser, Asp, Pro, and Thr occurred at a given position, and of 100 sequences available at that position, Ser occurred 80 times, the variability would be $4/0.8 = 5$. When any of the amino acid residues sequenced were not identified completely and are listed as Glx (or Asx), two values, separated by a colon, are given in the last three columns. The first value in each of these columns is calculated assuming that only one of the two possibilities, e.g., Glu or Gln (or Asp or Asn) occurred, while the second considers that both were present and maximizes variability. In the variability plots, the horizontal bars indicate the two values.

When two or more amino acids are most common and occur with equal frequency, they are tabulated as a note, and the symbol + is used in the next to last column. If no sequence data have been reported for any position, there are no entries in the last four columns. Variability is not calculated for insertions or if only a single sequence is known. When the translated sequence of a clone corresponds to a previously listed sequence of a plasmacytoma from which it was prepared, only one sequence is listed so that the variability computations are not affected, and a note is included.

If a given sequence is associated with any antibody activity, this is indicated by an asterisk alongside the protein heading, and the antibody specificities are given in a separate list with binding constants if available. The notes list the a-allotypes for the rabbit heavy chain V-region and the b-allotypes for the constant domain of the rabbit kappa light chain. A key reference to the sequence is given; generally the most recent reference since it is usually the most nearly complete, but often several references are included, especially when revisions of a sequence have been made. Notes are now of two types; general notes about a table indicated by the symbol #, and specific notes indicated by the sequence number.

Signal Sequences

The signal (precursor) amino acid sequences of immunoglobulin chains are listed in three tables: one for kappa light chains, one for lambda light chains, and one for heavy chains. They were obtained either by direct sequencing of signal proteins (12-14) or by translating nucleotide sequences from DNA clones. Signal segments range from 17-29 amino acid residues in length and are thus numbered from -29 to -1. Genomic DNA clones contain introns of varying length that interrupt the coding sequence of the precursor within the codon for position -4, and in rare cases for position -6. Thus, the L-gene encodes the leader peptide to position -4 and the 5' end of the V-gene codes for positions -4 to -1.

The signal amino acid sequences of the T-cell receptors for antigens, β_2 -microglobulins, major histocompatibility complex proteins, and complement components are listed in separate tables.

By conformational energy calculations, the core V_{χ} hydrophobic Leu-Leu-Leu-Trp-Val-Leu-Leu-Leu (MOPC321, MOPC63) exists in an alpha helical conformation, terminated by chain reversal conformations in the four C-terminal residues Trp-Val-Pro-Gly; the four amino terminal residues are compatible with the alpha helix (15).

Variable Region Sequences

The variable regions (16) of immunoglobulins have been shown to contain hypervariable segments in their light (11,17-23) and heavy (22,24-27) chains, of which certain residues have been affinity labeled (28-41). Three hypervariable segments of light chain were delineated from a statistical examination

of sequences of human V_{κ} , human V_{λ} , and mouse V_{κ} light chains aligned for maximum homology (11,22). These and the three corresponding segments of the heavy chains (22,26,27) were hypothesized (11,22) to be the complementarity-determining regions or segments (CDR) containing the residues which make contact with various antigenic determinants, and this has been verified by X-ray diffraction studies at high resolution (42-67). The rest of the V-region constitutes the framework (11,22,66-68). It is convenient to identify the framework segments (FR1, FR2, FR3, and FR4) and the complementarity-determining segments (CDR1, CDR2, and CDR3) with the three CDRs separating the four FRs. The residue numbers for these segments are as follows:

| Segment | Light Chain | Heavy Chain |
|---------|--|--|
| FR1 | 1-23 (with an occasional residue at 0, and a deletion at 10 in V_{λ} chains) | 1-30 (with an occasional residue at 0) |
| CDR1 | 24-34 (with possible insertions numbered as 27A,B,C,D,E,F) | 31-35 (with possible insertions numbered as 35A,B) |
| FR2 | 35-49 | 36-49 |
| CDR2 | 50-56 | 50-65 (with possible insertions numbered as 52A,B,C) ^a |
| FR3 | 57-88 | 66-94 (with possible insertions numbered as 82A,B,C) |
| CDR3 | 89-97 (with possible insertions numbered as 95A,B,C,D,E,F) | 95-102 (with possible insertions numbered as 100A,B,C,D,E,F,G,H,I,J,K) |
| FR4 | 98-107 (with a possible insertion numbered as 106A) | 103-113 |

^a In the rabbit, Mage *et al.* (69) consider position 65 in V_H to be in FR3, since it is allotype related.

In the tables of V-regions, the FR and CDR are separated by horizontal lines for convenience in reading. One mouse kappa light chain, MPC11, has an extra segment of 12 amino acid residues between position 1 and the signal sequence (70). Several chains have internal deletions.

In the tables, the V-genes for the light chains code to amino acid position 95, and the J-minigenes from position 97 to 107 for lambda and 108 for kappa light chains. Position 96 is usually the site of V-J joining by recombination and may be coded partly by the V-gene and partly by the J-minigene. Because the site of V-J recombination could occur at different positions within a codon, different amino acid residues may result at this position. We have changed the location of the inserted residues from 97A-F (2) to 95A-F, since it makes for better alignment by confining chains of different lengths to the V-gene region. In V_{κ} chains, J1 and J2 were used 5 to 10 times more frequently than J4 and J5 (71).

The V-genes for the heavy chains code up to amino acid position 94 and are followed by the D- and J-minigenes. Because of the extensive variation in the lengths of D-minigenes, the exact boundary between D and J is not always located at the same amino acid position. In addition, the lengths of the J encoded amino acid sequences vary by a few amino acid residues. Moreover, the process of D-J joining appears to involve insertions of extra nucleotides between V and D and between D and J, termed the N region (72-76) and correlates with the appearance of terminal deoxytransferase in B cells (75). The original numbering system for the heavy chains has therefore been retained. Wysocki *et al.* (76) have provided some evidence suggesting a non-random origin for the V_H - D_H junction, perhaps a minigene, rather than random addition of the N nucleotides.

It has become evident that a critical understanding of the architecture of antibody combining sites and the genetics of the generation of diversity and of antibody complementarity will depend to a great extent on the evaluation of a large number of sequences of the variable regions and especially of the complementarity-determining segments of light and heavy chains of immunoglobulins of different species. Ability to locate residues in the site making contact with antigenic determinants (77) and to predict (67,78-82) the structures of antibody combining sites will depend heavily upon such sequences.

Figures 1 and 2 are stereoviews of the α -carbon skeletons of the four Fv regions for which high resolution X-ray structures have been determined, NEWM (44), KOL (62), MCPC603 (47, 48, 63), and J539 (64). The residues in the CDRs are shown as solid circles. In Fig. 1 the combining site is at the

| HUMAN KAPPA LIGHT CHAINS SUBGROUP I | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8* | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | |
|-------------------------------------|----------|-----------------------|-----|-----|-----|-------------|-----|-----|-----|-----------------|-----------------|-------------|--------------|--------------|---------------|--------------|--------------|---------------|-----|-----|-----|------------|------------|------------|------------|
| | | ROY | AU | REI | HAU | HK101 CL | SCW | AG | WEA | HK 137 CL | HK 134 CL | DAUDI CL | WALKER CL | HF3- 16/6 | HF2- 1/13B | HF2- 18/2 | HF2- 1/17 | BJ 26 # | RFZ | PSM | HOM | ESM IGG | ESM IGM | ESM IGM | ESM IGM |
| | | INVARIANT RESIDUES | | | | | | | | | | | | | | | | | | | | | | | |
| | | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP |
| | | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE |
| | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| | | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET | MET |
| 5 | THR(.98) | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| 6 | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| 7 | SER(.95) | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 8 | PRO(.98) | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO |
| 9 | | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 10 | | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU |
| 11 | | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 12 | SER(.96) | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA |
| 13 | | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 14 | | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL |
| 15 | VAL(.96) | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY |
| 16 | GLY(.99) | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP |
| 17 | | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG |
| 18 | VAL(.97) | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL |
| 19 | THR(.96) | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| 20 | ILE(.95) | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE |
| 21 | | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| 22 | | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS |
| 23 | | GLN | GLN | GLN | ARG | ARG | GLN | GLN | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | GLN | GLN | GLN | GLN | GLN | ARG | ARG | GLX | |
| 24 | | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA |
| 25 | ALA(.95) | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 26 | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| 27 | | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 27A | | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 27B | | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 27C | | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 27D | | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 27E | | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 27F | | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 27G | | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 27H | | ASP | ASP | ASP | SER | GLY | ASP | ASP | GLY | GLY | GLY | ASN | SER | GLY | GLY | GLY | SER | VAL | ASP | ASP | SER | SER | SER | ASP | |
| 29 | | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE |
| 30 | | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 31 | | PHI | TYR | LYS | TYR | TRP | LYS | HIS | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN |
| 32 | | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU |
| 33 | | ASN | ASN | ASN | SER | ALA | ASN | ASN | THR | ALA | ALA | SER | ASN | GLY | LEU | GLY | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN |
| 34 | | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP |
| 35 | TRP | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| 36 | | LYS | LYS | THR | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS |
| 37 | | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO |
| 38 | | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY |
| 39 | PRO(.95) | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA |
| 40 | | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO |
| 41 | | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU |
| 42 | | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE |
| 43 | LEU(.98) | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR |
| 44 | | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP |
| 45 | | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA |
| 46 | | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 47 | LEU(.98) | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU |
| 48 | ILE(.98) | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| 49 | | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR |
| 50 | | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP |
| 51 | | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA |
| 52 | | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 53 | | LYS | ASN | ASN | ASN | ASN | ASN | ASN | THR | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN |
| 54 | LEU(.98) | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU |
| 55 | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| 56 | | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER |
| 57 | GLY | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL |
| 58 | VAL(.98) | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO |
| 59 | | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 60 | | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG |
| 61 | ARG(.95) | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE |
| 62 | PHE(.95) | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 63 | | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY |
| 64 | | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| 65 | | GLY | GLY | GLY | GLY | | | | | | | | | | | | | | | | | | | | |

HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)

| | 48 HBJ 4 | 49 FRA | 50 GR | 51 PAUL | 52 MON | 53 HEI | 54 POT | 55 S- GUI | 56 AMYLOID BAN | 57 BJ 19 | 58 SEL | 59 JBL | 60 PAP | 61 CAR | 62 MEV | 63 BI | 64 AMYLOID ES305 | 65 CRA | 66 DAV | 67 FIN | 68 KA | 69 VD CL | 70 LUX | 71 NE | 72 Va CL |
|--|----------------|-----------|----------|------------|-----------|-----------|-----------|-----------------|----------------------|----------------|-----------|-----------|-----------|-----------|-----------|----------|------------------------|-----------|-----------|-----------|----------|----------------|-----------|----------|----------------|
| | 0 | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP |
| | 1 | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE |
| | 2 | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| | 3 | MET | MET | MET | MET | MET | MET | leu | leu | leu | leu | MET | MET | MET | MET | leu | MET | MET | MET | MET | MET | leu | leu | leu | leu |
| | 4 | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| | 5 | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| | 6 | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO |
| | 7 | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| | 8 | thr | thr | thr | thr | thr | thr | SER | SER | SER | SER | SER | SER | SER | pro | SER | SER | SER | SER | SER | SER | phe | phe | SER | SER |
| | 9 | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU |
| | 10 | SER | SER | SER | SER | SER | SER | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA |
| | 11 | ALA | ALA | ALA | ALA | ALA | ALA | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| | 12 | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| | 13 | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | tyr | val | ALA | ALA | ALA | SER | SER | SER | SER | thr | val | ALA | ALA | ALA |
| | 14 | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | Gly | arg | arg | arg | arg | arg | arg | arg | arg |
| | 15 | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP | ASP |
| | 16 | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG |
| | 17 | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL |
| | 18 | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| | 19 | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE |
| | 20 | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| | 21 | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| | 22 | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS |
| | 23 | ARG | ARG | ARG | ARG | ARG | ARG | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA |
| | 24 | ALA | ALA | ALA | ALA | ALA | ALA | GLN | GLN | GLX | GLX | ARG | ARG | ARG | ARG | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLX | GLX | GLX |
| | 25 | SER | SER | SER | SER | SER | SER | GLN | GLN | GLX | GLX | SER | SER | SER | SER | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLX | GLX | GLX |
| | 26 | GLN | GLX | ARG | GLN | | | GLN | GLN | GLX | GLX | SER | SER | SER | SER | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLX | GLX | GLX |
| | 27 | | | | | | | | | | | | | | | | | | | | | | | | |
| | 27A | | | | | | | | | | | | | | | | | | | | | | | | |
| | 27B | | | | | | | | | | | | | | | | | | | | | | | | |
| | 27C | | | | | | | | | | | | | | | | | | | | | | | | |
| | 27D | | | | | | | | | | | | | | | | | | | | | | | | |
| | 27E | | | | | | | | | | | | | | | | | | | | | | | | |
| | 27F | | | | | | | | | | | | | | | | | | | | | | | | |
| | 28 | SER | ASE | SER | SER | | | SER | ASP | ASX | SER | | ASN | SER | ASP | | ALA | | ASX | ASX | THR | GLY | | ASX | GLY |
| | 29 | VAL | ILE | ILE | ILE | ILE | ILE | VAL | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | # | ILE | ILE | VAL | ILE | ILE | ILE | ILE | ILE |
| | 30 | ASN | ASX | SER | SER | SER | SER | TYR | ASN | THR | LYS | | SER | VAL | ARG | ASN | ASN | ASN | ASX | SER | SER | TYR | TYR | ASN | TYR |
| | 31 | ASN | ASX | SER | SER | SER | SER | ASN | ASN | THR | LYS | | SER | VAL | ARG | ASN | ASN | ASN | ASX | SER | SER | TYR | TYR | ASN | TYR |
| | 32 | TRP | TYR | TRP | TRP | SER | | TYR | TYR | PHE | LEU | | TRP | TYR | SER | SER | LEU | TRP | TRP | TYR | TYR | TYR | TYR | TYR | TYR |
| | 33 | LEU | LEU | LEU | | | | VAL | VAL | LEU | LEU | | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU |
| | 34 | ALA | ALA | ALA | | | | ALA | ASN | # | | | ALA | ASN | ILE | | | ILE | ILE | ASN | ALA | | ASX | ALA | ALA |
| | 35 | TRP | TRP | TRP | | | | TRP | TRP | TRP | TRP | | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP |
| | 36 | TYR | TYR | TYR | | | | PHE | TYR | TYR | TYR | | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR |
| | 37 | GLN | GLX | GLN | | | | GLN | GLU | GLN | GLN | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLX | GLN | GLN |
| | 38 | GLU | GLX | GLY | | | | GLN | GLN | GLN | GLN | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLX | GLN | GLN |
| | 39 | LYS | | | | | | LYS | # | LYS | LYS | | LYS | LYS | LYS | LYS | LYS | TYR | TYR | LYS | LYS | LYS | LYS | LYS | LYS |
| | 40 | PRO | PRO | ARG | | | | PRO | PRO | PRO | PRO | | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO |
| | 41 | GLY | PRO | | | | | GLY | LYS | GLY | GLY | | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY |
| | 42 | GLX | | | | | | LYS | LYS | LYS | LYS | | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS |
| | 43 | ALA | | | | | | ALA | ALA | ALA | ALA | | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA |
| | 44 | PRO | | | | | | PRO | PRO | PRO | PRO | | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO |
| | 45 | LYS | | | | | | LYS | LYS | LYS | LYS | | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS | LYS |
| | 46 | LEU | | | | | | SER | LYS | LEU | LEU | | VAL | LEU | PHE | LEU | LEU | LEU | LEU | LEU | LEU | LEU | VAL | LEU | LEU |
| | 47 | LEU | | | | | | LEU | LEU | LEU | LEU | | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | VAL | LEU | LEU |
| | 48 | ILE | | | | | | ILE | ILE | ILE | ILE | | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE |
| | 49 | SER | | | | | | TYR | TYR | TYR | TYR | | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR |
| | 50 | LYS | | | | | | ASP | ASP | ASP | | | LYS | ASP | ASP | | | | | ALA | ALA | ALA | | ASP | ALA |
| | 51 | THR | | | | | | ALA | ALA | ALA | | | SER | THR | ALA | | | | | ALA | ALA | ALA | | ALA | ALA |
| | 52 | SER | | | | | | SER | SER | SER | | | SER | SER | GLU | | | | | SER | SER | SER | | SER | SER |
| | 53 | SER | | | | | | THR | THR | THR | | | SER | ASN | ASN | | | | | SER | SER | SER | | SER | SER |
| | 54 | LEU | | | | | | LEU | LEU | LEU | | | LEU | LEU | LEU | | | | | LEU | LEU | LEU | | LEU | LEU |
| | 55 | GLU | | | | | | SER | SER | SER | | | SER | SER | ILE | | | | | THR | THR | THR | | GLU | SER |
| | 56 | ARG | | | | | | THR | THR | THR | | | SER | SER | ILE | | | | | THR | THR | THR | | THR | THR |
| | 57 | GLY | | | | | | GLY | GLY | GLY | | | GLY | GLY | GLY | | | | | GLY | GLY | GLY | | GLY | GLY |
| | 58 | VAL | | | | | | VAL | VAL | VAL | | | VAL | VAL | VAL | | | | | VAL | VAL | VAL | | VAL | VAL |
| | 59 | PRO | | | | | | PRO | GLX | PRO | | | PRO | PRO | | | | | | PRO | PRO | PRO | | PRO | PRO |
| | 60 | SER | | | | | | SER | SER | SER | | | SER | SER | SER | | | | | SER | SER | SER | | SER | SER |
| | 61 | ARG | | | | | | ASN | ARG | ARG | | | ARG | ARG | ARG | | | | | ARG | ARG | ARG | | ARG | ARG |
| | 62 | PHE | | | | | | PHE | PHE | PHE | | | PHE | PHE | PHE | | | | | PHE | PHE | PHE | | PHE | PHE |
| | 63 | ALA | | | | | | THR | THR | SER | | | THR | THR | THR | | | | | SER | SER | SER | | SER | SER |
| | 64 | GLY | | | | | | SER | GLY | GLY | | | GLY | GLY | GLY | | | | | GLY | GLY | GLY | | GLY | GLY |
| | 65 | SER | | | | | | SER | ASX | SER | | | SER | ARG | GLY | | | | | GLY | GLY | GLY | | GLY | GLY |
| | 66 | THR | | | | | | THR | THR | THR | | | THR | THR | THR | | | | | THR | THR | THR | | THR | THR |
| | 67 | ASP | | | | | | ASP | ASP | ASP | | | ASP | ASP | ASP | | | | | ASP | ASP | ASP | | ASP | ASP |
| | 68 | PHE | | | | | | PHE | PHE | PHE | | | PHE | PHE | PHE | | | | | PHE | PHE | PHE | | PHE | PHE |
| | 69 | THR | | | | | | THR | THR | THR | | | THR | THR | THR | | | | | THR | THR | THR | | THR | THR |
| | 70 | ASP | | | | | | ASP | ASP | ASP | | | ASP | ASP | ASP | | | | | ASP | ASP | ASP | | ASP | ASP |
| | 71 | PHE | | | | | | PHE | PHE | PHE | | | PHE | PHE | PHE | | | | | PHE | PHE | PHE | | PHE | PHE |
| | 72 | ILE | | | | | | ILE | THR | THR | | | ILE | LEU | ALA | | | | </ | | | | | | |

HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)

Table with columns for amino acid positions 73 through 96 and rows for chain positions 1 through 109. Each cell contains a three-letter amino acid code (e.g., ASP, ILE, MET, THR, GLN, etc.).

HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)

VARIABILITY

| | | |
|------|---|-----------|
| | 0 | |
| | 1 | 3.2 : 4.4 |
| | 2 | 4.2 |
| | 3 | 8.9 : 9.3 |
| | 4 | 4.6 |
| | 5 | 3.1 |
| | 6 | 1. : 2.1 |
| | 7 | 3.2 |
| | 8 | 3.1 |
| | 9 | 4.2 |
| 10 | | 6.4 |
| 11 | | 5.7 |
| 12 | | 4.2 |
| 13 | | 4.4 |
| 14 | | 7.9 |
| 15 | | 3.1 |
| 16 | | 2. |
| 17 | | 3.2 : 4.7 |
| 18 | | 6.6 |
| 19 | | 3.1 |
| 20 | | 4.2 |
| 21 | | 4.2 |
| 22 | | 6.2 |
| 23 | | 1. |
| 24 | | 8.7 |
| 25 | | 4.2 |
| 26 | | 4.3 |
| 27 | | 4.4 : 5.4 |
| 27A | | |
| 27B | | |
| 27C | | |
| 27D | | |
| 27E | | |
| 27F | | |
| 28 | | 23. : 26. |
| 29 | | 5.8 |
| 30 | | 19. : 21. |
| 31 | | 28. |
| 32 | | 14. |
| 33 | | 4.3 |
| 34 | | 18. : 22. |
| 35 | | 1. |
| 36 | | 2.1 |
| 37 | | 4.3 : 4.9 |
| 38 | | 4.2 : 4.6 |
| 39 | | 4.4 |
| 40 | | 4.2 |
| 41 | | 3.3 |
| 42 | | 6.8 |
| 43 | | 2.2 |
| 44 | | 1. |
| 45 | | 6.9 |
| 46 | | 9.8 |
| 47 | | 2. |
| 48 | | 2. |
| 49 | | 4.3 |
| 50 | | 21. : 24. |
| 51 | | 5.8 |
| 52 | | 4.3 |
| 53 | | 12. : 14. |
| 54 | | 2 |
| 55 | | 15. |
| 56 | | 11. |
| 57 | | 1. |
| 58 | | 2. |
| 59 | | 4.3 |
| 60 | | 1. |
| 61 | | 3.1 |
| 62 | | 3.1 |
| 63 | | 8.4 |
| 64 | | 1. |
| 65 | | 4.4 |
| 66 | | 3.1 |
| 67 | | 3.2 |
| 68 | | 3.2 |
| 69 | | 3.2 |
| 70 | | 8.2 : 11. |
| 71 | | 4.4 |
| 72 | | 4.3 |
| 73 | | 3.9 |
| 74 | | 4.3 |
| 75 | | 3.2 |
| 76 | | 2.1 |
| 77 | | 7.4 |
| 78 | | 2.3 |
| 79 | | 2.1 : 3.4 |
| 80 | | 3.6 |
| 81 | | 4.1 : 7.7 |
| 82 | | 1. : 2.2 |
| 83 | | 5.7 |
| 84 | | 2.1 |
| 85 | | 4.3 |
| 86 | | 2. |
| 87 | | 2.1 |
| 88 | | 1. |
| 89 | | 3.2 : 4.6 |
| 90 | | 3.3 : 5.1 |
| 91 | | 19. : 21. |
| 92 | | 25. : 28. |
| 93 | | 21. |
| 94 | | 38. |
| 95 | | 6.4 |
| 95A | | |
| 95B | | |
| 95C | | |
| 95D | | |
| 95E | | |
| 95F | | |
| 96 | | 4.3 |
| 97 | | 4.6 |
| 98 | | 3.2 |
| 99 | | 1. |
| 100 | | 6.9 : 9.1 |
| 101 | | 1. |
| 102 | | 2.1 |
| 103 | | 5.4 |
| 104 | | 2.6 |
| 105 | | 4.5 : 6.3 |
| 106 | | 14. |
| 106A | | |
| 107 | | 2.1 |
| 108 | | 2.2 |
| 109 | | 1. |

ANTIBODY SPECIFICITIES: HUMAN KAPPA LIGHT CHAINS SUBGROUP I

- 2) WEA: ANTI-3,4-PYRUVYLATED GALACTOSE MONOCLONAL
 25) LOW: COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
 39) LAY: ANTI-HUMAN GAMMA G1 AND G3 GLOBULINS: PO IDIOTYPE
 53) HEI: COLD AGGLUTININ WITH ANTI-GD (MEMBRANE-GLYCOLIPID-DEPENDENT) ACTIVITY
 66) DAV: ANTI-HUMAN GAMMA G GLOBULIN
 67) FIN: ANTI-HUMAN GAMMA G GLOBULIN
 92) WAG: ANTI-DINITROPHENYL
 104) MAR: ANTI-LIPOPROTEIN LIPASE

ALLOTYPES: HUMAN KAPPA LIGHT CHAINS SUBGROUP I

- 79) KUE: INV(2)

CLASS: HUMAN KAPPA LIGHT CHAINS SUBGROUP I

- 8) WEA: IGM-KAPPA
 33) F-GUI: IGG3-KAPPA
 55) S-GUI: IGG3-KAPPA
 74) PW: IGG1-KAPPA
 82) RI: IGG1-KAPPA

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 6) SCW: EULITZ,M.,GOTZE,D. & HILSCHMANN,N. (1972) Z.PHYSIOL.CHEM.353.487-491; EULITZ,M. & HILSCHMANN,N. (1974) Z.PHYSIOL.CHEM.355.842-866. (CHECKED BY AUTHOR)
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 17) BJ26: ALESCIO-ZONTA,L. & BAGLIONI,C. (1970) EUR.J.BIOCHEM.15.450-463. (CHECKED BY AUTHOR)
 18) RFZ: SMITHES,O.,GIBSON,D.,FANNING,E.M.,GOODFLIESH,R.M.,GILMAN,J.G. & BALLANTYNE,D.L. (1971) BIOCHEMISTRY.10.4912-4921. (CHECKED BY AUTHOR)
 19) PSM: SEON,B.K. (1982) MOL.IMMUNOL.19.83-86. (CHECKED BY AUTHOR 05/23/83)
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 59) JBL: SEON,B.K. (1982) MOL.IMMUNOL.19.83-86. (CHECKED BY AUTHOR 05/23/83)
 60) PAP: NIALL,H.D. & EDMAN,P. (1967) NATURE.216.262-263. (CHECKED BY AUTHOR 07/25/79)
 61) CAR: MILSTEIN,C.P. & DEVERSON,E.V. (1974) EUR.J.BIOCHEM.49.377-391. (CHECKED BY AUTHOR)
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- 64) **AMYLOID ES305**: WESTERMARK,P.,SLETTEN,K. & NATVIG,J.B. (1981) ACTA PATH.MICROBIOL.SCAND.,C89,199-203. (CHECKED BY AUTHOR 11/09/81)
- 65) **CRA**: NIALL,H.D. & EDMAN,P. (1967) NATURE.216,262-263. (CHECKED BY AUTHOR 07/25/79)
- 66) **DAV**: CAPRA,J.D. & KUNKEL,H.G. (1970) PROC.NAT.ACAD.SCI.USA.67,87-92. (CHECKED BY AUTHOR)
- 67) **FIN**: CAPRA,J.D. & KUNKEL,H.G. (1970) PROC.NAT.ACAD.SCI.USA.67,87-92. (CHECKED BY AUTHOR)
- 68) **KA**: SHINODA,T. (1975) J.BIOCHEM..77,1277-1296. (CHECKED BY AUTHOR)
- 69) **Vd'CL**: PECH,M.,JAENICHEN,H.-R.,POHLENZ,H.-D.,NEUMAIER,P.S.,KLOBECK,H.-G. & ZACHAU,H.G. (1984) J.MOL.BIOL..176,189-204. (CHECKED BY AUTHOR 12/14/84)
- 70) **LUX**: NIALL,H.D. & EDMAN,P. (1967) NATURE.216,262-263. (CHECKED BY AUTHOR 07/25/79)
- 71) **NE**: MATTHEWS,J.B. & JEFFERIS,R. (1977) IMMUNOCHEM..14,793-797. (CHECKED BY AUTHOR 06/10/79)
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- 73) **NI**: SHINODA,T. (1973) J.BIOCHEM..73,433-446. (CHECKED BY AUTHOR)
- 74) **FiV**: PICK,A.I.,WANG,A.C.,FROHLICHMAN,R. & FUDENBERG,H.H. (1982) ACTA HAEMAT..68,207-214. (CHECKED BY AUTHOR 05/26/83)
- 75) **AMYLOID X**: GLENNEK,G.G.,TERRY,W.,HERADA,M.,ISERSKY,C. & PAGE,D. (1971) SCIENCE.172,1150-1151. (CHECKED BY AUTHOR 09/22/78)
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- 79) **KUE**: EULITZ,M.,KLEY,H.P. & ZEITLER,H.J. (1979) Z.PHYSIOL.CHEM..360,725-734. (CHECKED BY AUTHOR 07/17/79)
- 80) **GO**: WANG,A.C.,FUDENBERG,H.H. & CREYSSEL,R. (1974) EUR.J.IMMUNOL..4,446-448. (CHECKED BY AUTHOR)
- 81) **BOL**: WANG,A.C.,WELLS,J.V.,FUDENBERG,H.H. & GERGELY,J. (1974) IMMUNOCHEM..11,341-345. (CHECKED BY AUTHOR)
- 82) **Ri**: PICK,A.I.,WANG,A.C.,FROHLICHMAN,R. & FUDENBERG,H.H. (1982) ACTA HAEMAT..68,207-214. (CHECKED BY AUTHOR 05/26/83)
- 83) **Ve'CL**: PECH,M.,JAENICHEN,H.-R.,POHLENZ,H.-D.,NEUMAIER,P.S.,KLOBECK,H.-G. & ZACHAU,H.G. (1984) J.MOL.BIOL..176,189-204. (CHECKED BY AUTHOR 12/14/84)
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- 85) **V13'CL**: JAENICHEN,H.-R.,PECH,M.,LINDENMAIER,W.,WILDGRUBER,N. & ZACHAU,H.G. (1984) NUC.ACIDS RES..12,5249-5263. (CHECKED BY AUTHOR 12/14/84)
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- 87) **V19A'CL**: HEIDMANN,O. & ROUGEON,F. (1984) NATURE.311,74-76.
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- 89) **V18B'CL**: HEIDMANN,O. & ROUGEON,F. (1984) NATURE.311,74-76.
- 90) **HF6-21/28**: ATKINSON,P.M.,LAMPMAN,G.W.,FURIE,B.C.,NAPARSTEK,Y.,SCHWARTZ,R.S.,STOLLAR,B.D. & FURIE,B. (1985) J.CLIN.INVEST..75,1138-1143. (CHECKED BY AUTHOR 08/21/85)
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- 93) **HBj1**: HOOD,L.,GRAY,W.R.,SANDERS,B.G. & DREYER,W.J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL..32,133-145.
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- 95) **WEB**: JOHNSTON,S.L.,ABRAHAM,G.N. & WELCH,E.H. (1975) BIOCHEM.BIOPHYS.RES.COMMUN..66,842-847. (CHECKED BY AUTHOR 10/17/77)
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- 97) **LOD**: JOHNSTON,S.L.,ABRAHAM,G.N. & WELCH,E.H. (1975) BIOCHEM.BIOPHYS.RES.COMMUN..66,842-847. (CHECKED BY AUTHOR 10/17/77)
- 98) **HBj10**: HOOD,L.,GRAY,W.R.,SANDERS,B.G. & DREYER,W.J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL..32,133-145.
- 99) **BEN**: CAPRA,J.D.,KEHOE,J.M.,WILLIAMS,R.C.,JR.,FEIZI,T. & KUNKEL,H.G. (1972) PROC.NAT.ACAD.SCI.USA.69,40-43. (CHECKED BY AUTHOR)
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- 104) **MAR**: KAPLAN,A.P. & METZGER,H. (1969) BIOCHEMISTRY.8,3944-3951. (CHECKED BY AUTHOR)
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- 106) **BJ**: MILSTEIN,C. (1966) BIOCHEM.J..101,352-368. (CHECKED BY AUTHOR)
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- 111) **GM131'CL**: MORIN,J.W.,BLACK,A.,WU,M. & BEYCHOK,S. (1985) PROC.NAT.ACAD.SCI.USA.82,7025-7029.

NOTES: HUMAN KAPPA LIGHT CHAINS SUBGROUP I

IDENTICAL SETS OF FRAMEWORK SEGMENTS:

- FR1: SET 1: ROY[1],AU[2],REI[3],HAU[4],HK101'CL[5],SCW[6],AGI[7],WEA[8],HK137'CL[9],HK134'CL[10],DAUDI'CL[11],WALKER'CL[12], HF3-16[13],HF2-1/13B[14],HF2-18/21[15],HF2-1/17[16],BJ26[17],RFZ[18],PSM[19],HOI[20],ESM[21],ESM[22],WAT[23], AMYLOID VIII-B[24],LOW[25],DIE[26],CAR A[27],TEI[28],BJ48[29],CON[30],TRA[31],F-GUI[33],OU[34],DEE[35]. (34 IDENTICAL)
- SET 2: WES[41],Vb'CL[42],Vb'CL[43]. (3 IDENTICAL)
- SET 3: HK102'CL[44],EU[45],DEN[46],FRA[47],HB[48],FRA[49],GR[50],PAUL[51],MON[52]. (9 IDENTICAL)
- SET 4: AMYLOID BAN[56],BJ19[57],BEL[58]. (3 IDENTICAL)
- SET 5: DAV[66],FIN[67]. (2 IDENTICAL)
- SET 6: Vd'CL[69],LUX[70]. (2 IDENTICAL)
- FR2: SET 1: ROY[1],AU[2],WALKER'CL[12],Vb'CL[42],Vb'CL[43],HK102'CL[44],KA[68],Vd'CL[69],Va'CL[72],Ve'CL[83]. (10 IDENTICAL)
- SET 2: HK101'CL[5],HK134'CL[10]. (2 IDENTICAL)
- SET 3: HK137'CL[9],AMYLOID BAN[56]. (2 IDENTICAL)
- SET 4: V18A'CL[86] IDENTICAL TO 7 MOUSE V-KAPPA-III: PC1229(NZB)[1],PC2880(NZB)[2],PC7132(NZB)[3],MOPC70[5],PC2413(NZB)[11], 50S10[127],V-21B18KB'CL[48]; AND 5 RABBIT V-KAPPA: K9-335[1],K9-338[2],K29-21[3],V20'CL[36],K16-16[64].
- SET 5: V19B'CL[88],V18B'CL[89]. (2 IDENTICAL HUMAN V-KAPPA-I; ALSO 4 HUMAN V-KAPPA-IV: VJ'CL[1],VKAPPA IV GERMLINE'CL[2], PB17IV'CL[3],LEN[4]; 1 MOUSE V-KAPPA-I: MCP63[47]; 30 MOUSE V-KAPPA-II: MPC11'CL[6],TEPC111[7],PC3741(NZB)[8], TPC124[9],MOPC211[12],PC7043(NZB)[13],PC7183(NZB)[14],PC6308(NZB)[15],PC6684(NZB)[17],PC7940(NZB)[18],PC7175(NZB)[19], PC2485(NZB)[20],PC4039(NZB)[21],PC7210(NZB)[23],H36-15[26],2242[29],V-21E15 KB'CL[30],V-21C9 5KB'CL[31], PC7461(NZB)[33],PC2960(NZB)[34],97.C(A,B,Y)[35],10.A.(A,TH)[39],H36-5148[40],C.(A,TH)[52],MOPC63[54],ABPC22[55], PC9245(NZB)[58],PC4050(NZB)[57],V-21B18KB'CL[58],11949[62]; 1 MOUSE V-KAPPA-VI: BFPC61A'CL[64]; AND 15 RABBIT V-KAPPA: K9-335-1[19],3368[20],BS-5[38],BS-1[39],K49-50[145],3547[47],K4820[57],K30-267[61],311[65],4422[66],17D9'CL[68], 41927[1],4363[85],1201[93],K-251[12].
- FR3: SET 1: HAU[4],HK101'CL[5],HK137'CL[9],HK134'CL[10],Vb'CL[42],Vb'CL[43],Va'CL[72]. (7 IDENTICAL)
- SET 2: Vd'CL[69],V13'CL[85]. (2 IDENTICAL)
- SET 3: V19B'CL[88],V18B'CL[89]. (2 IDENTICAL)
- FR4: SET 1: AU[2],GAL[5],J36'CL[110]. (3 IDENTICAL HUMAN V-KAPPA-I; ALSO 2 HUMAN V-KAPPA-II: GM 607'CL[5],RPM1-6410'CL[16]; 7 HUMAN V-KAPPA-III: WOL[2],PAY[7],PIE[11],GLO[15],CUR[20],REE[57],VKAPPA3'CL[82]; AND 1 HUMAN V-KAPPA-IV: PB17IV'CL[3])
- SET 2: HAU[4]. (IDENTICAL TO 1 HUMAN V-KAPPA-III: POM[48].)
- SET 3: AGI[7],DEN[46],BI[63]. (3 IDENTICAL HUMAN V-KAPPA-I; ALSO 2 HUMAN V-KAPPA-II: NIM[3],FR[14]; 6 HUMAN V-KAPPA-III: NEUI[5], GOT[6],GAR[10],FLO[12],FR4[21],IARC/BL41'CL[28]; AND 1 HUMAN V-KAPPA-IV: LEN[4].)
- SET 4: WEA[8],BJ48[29],IL[39],E[45]. (IDENTICAL)
- SET 5: WALKER'CL[12],OU[34]. (2 IDENTICAL HUMAN V-KAPPA-I; ALSO 1 HUMAN V-KAPPA-II: TEW[1].)
- SET 6: WES[41],MEV[62]. (2 IDENTICAL)

IDENTICAL SETS OF COMPLEMENTARITY DETERMINING REGIONS:

- CDR1: SET 1: AU[2],NEI[7],SHE[77]. (3 IDENTICAL)
- SET 2: WEA[8],GAL[5]. (2 IDENTICAL)
- SET 3: HK134'CL[10],Vb'CL[42],Vb'CL[43]. (3 IDENTICAL)
- SET 4: HF3-16[13],HF2-1/13B[14],HF2-18/21[15],HF2-1/17[16]. (4 IDENTICAL)
- SET 5: Vd'CL[69],Ve'CL[83]. (2 IDENTICAL)
- CDR2: SET 1: HK101'CL[5],HK137'CL[9],HK134'CL[10],WALKER'CL[12],Vb'CL[42],Vb'CL[43]. (6 IDENTICAL)
- SET 2: AGI[7],NI[73]. (2 IDENTICAL)
- SET 3: HK102'CL[44],Vb'CL[42]. (2 IDENTICAL)
- SET 4: Vd'CL[69],Ve'CL[83],V13'CL[85]. (3 IDENTICAL)
- SET 5: V18A'CL[86]. (IDENTICAL TO 1 RABBIT V-KAPPA: 4153-I[24].)
- SET 6: V19A'CL[87]. (IDENTICAL TO 1 RABBIT V-KAPPA: AH80-5[4].)
- CDR3: SET 1: HK101'CL[5],HK134'CL[10]. (2 IDENTICAL)
- SET 2: LAY[39]. (IDENTICAL TO 1 HUMAN V-KAPPA-III: POM[48].)
- SET 3: Vb'CL[42],Vb'CL[43]. (2 IDENTICAL)

IDENTICAL SETS OF J-MINIGENES:

- SET 1: AU[2]. (IDENTICAL TO 1 HUMAN V-KAPPA-II: RPM1-6410'CL[16]; 2 HUMAN V-KAPPA-III: PIE[11],VKAPPA3'CL[82]; AND 1 HUMAN V-KAPPA-IV: PB17IV'CL[3].)
- SET 2: AGI[7]. (IDENTICAL TO 1 HUMAN V-KAPPA-III: GOT[6].)
- SET 3: WALKER'CL[12]. (IDENTICAL TO 1 HUMAN V-KAPPA-III: TEW[1].)
- SET 4: DEN[46],BI[63]. (2 IDENTICAL HUMAN V-KAPPA-I; ALSO 1 HUMAN V-KAPPA-II: FR[14]; AND 3 HUMAN V-KAPPA-III: GAR[10],FLO[12], IARC/BL41'CL[28].)

NOTES: HUMAN KAPPA LIGHT CHAINS SUBGROUP I (cont'd)**GENERAL NOTES:**

SEE SIGNAL PEPTIDE TABLE IF # OCCURS AT POSITION 0.

SPECIFIC NOTES:

- 5) **HK101'CL**: THE SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF HUMAN FOETAL LIVER DNA.
 7) **AG**: THE AMINO ACID RESIDUES AT POSITIONS 39 AND 41 WERE REPORTED BY THE AUTHORS AS GLY AND LYS RESPECTIVELY; HOWEVER, THE PROOF WAS NOT ABSOLUTE. THUS, THEY ARE OMITTED.
 9) **HK137'CL**: THE AMINO ACID SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF HUMAN FETAL DNA.
 10) **HK134'CL**: THE AMINO ACID SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF HUMAN FETAL DNA.
 17) **BJ26**: ACID RESIDUES AT POSITIONS 39 AND 41 OF BJ26 WERE REPORTED BY THE AUTHORS AS GLY AND LYS RESPECTIVELY. SINCE THIS PROTEIN WAS SEQUENCED BEFORE THE SEQUENCES OF MANY OTHER PROTEINS WERE KNOWN AT THESE TWO POSITIONS, WE HAVE OMITTED THEM.
 33) **F-GUI**: THE SEQUENCES OF F-GUI AND S-GUI WERE FROM THE SAME PATIENT.
 44) **HK102'CL**: THE SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF HUMAN FOETAL LIVER DNA.
 55) **S-GUI**: THE SEQUENCES OF F-GUI AND S-GUI WERE FROM THE SAME PATIENT.
 56) **AMYLOID BAN**: AMINO ACID RESIDUES FOUND AT POSITIONS 104 AND 105 ARE VAL,LEU AND GLN,GLU RESPECTIVELY.
 57) **BJ19**: THE AMINO ACID RESIDUES AT POSITIONS 39 AND 41 WERE REPORTED BY THE AUTHORS AS GLY AND LYS RESPECTIVELY. SINCE THIS PROTEIN WAS SEQUENCED BEFORE THE SEQUENCES OF MANY OTHER PROTEINS WERE KNOWN AT THESE TWO POSITIONS, WE HAVE OMITTED THEM.
 59) **JBL**: THE AMINO ACID RESIDUE FOUND AT POSITION 34 WAS ALA OR SER.
 64) **AMYLOID ES305**: THE AMINO ACID RESIDUES AT POSITIONS 21 AND 29 WERE ILE OR LEU.
 74) **PW**: THE SEQUENCE WAS FROM A PATIENT WITH TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER.
 82) **RI**: THE SEQUENCE WAS FROM A PATIENT WITH TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER.
 109) **AMYLOID MS**: THE AMINO ACID RESIDUE AT POSITION 2 MS WAS ILE OR LEU.
 111) **GM131'CL**: FROM AN EPSTEIN-BARR VIRUS-TRANSFORMED HUMAN LYMPHOID CELL LINE

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|---------------|
| 27C | (LEU,VAL) |
| 27D | (TRP,GLU) |
| 50 | (ALA,ASP) |
| 92 | (TYR,ASP,ASN) |
| 95A | (SER,GLY) |
| 95B | (TRP,GLY) |

HUMAN KAPPA LIGHT CHAINS SUBGROUP II (cont'd)

| | 24* | 25 | 26 | 27* | 28 | 29 | 30 | 31 | # OF | # OF | OCCURRENCES | VARIABILITY |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----------|-------------|---------------------------|-------------|
| | GIL | MEH | SC | TH | SVV | LUT | ROB | RAI | SEQUENCES | AMINO ACIDS | OF MOST COMMON AMINO ACID | |
| | 0 | --- | --- | --- | --- | --- | --- | --- | 31 | 1 | 31(ASP) | 1. |
| | 1 | ASP | ASP | ASP | ASP | ASP | ASP | ASP | 30 | 2 | 29(ILE) | 2.1 |
| | 2 | ILE | ILE | ILE | ILE | ILE | ILE | ILE | 30 | 2 | 29(VAL) | 2.1 |
| | 3 | VAL | VAL | VAL | VAL | VAL | VAL | met | 30 | 3 | 28(MET) | 3.2 |
| | 4 | MET | MET | MET | MET | MET | leu | thr | 27 | 1 | | |
| | 5 | THR | THR | THR | THR | THR | THR | | 28 | 1 | 28(THR) | 1. |
| | 6 | GLN | GLN | GLN | GLN | GLN | GLN | | 27 | 1 | 27(GLN) | 1. |
| | 7 | SER | SER | SER | SER | SER | SER | | 25 | 1 | 25(SER) | 1. |
| | 8 | PRO | PRO | PRO | PRO | PRO | PRO | | 24 | 1 | 24(PRO) | 1. |
| | 9 | LEU | LEU | LEU | LEU | LEU | LEU | | 25 | 1 | 25(LEU) | 1. |
| 1 | 10 | SER | | | | | | | 24 | 1 | 24(SER) | 1. |
| | 11 | LEU | | | | | | | 24 | 1 | 24(LEU) | 1. |
| | 12 | ser | | | | | | | 24 | 2 | 23(PRO) | 2.1 |
| | 13 | | | | | | | | 23 | 2 | 22(VAL) | 2.1 |
| | 14 | | | | | | | | 17 | 1 | 17(THR) | 1. |
| | 15 | | | | | | | | 17 | 2 | 16(PRO) | 2.1 |
| | 16 | | | | | | | | 17 | 1 | 17(GLY) | 1. |
| | 17 | | | | | | | | 17 | 2 | 16(GLU) | 2.1 |
| | 18 | | | | | | | | 17 | 1 | 17(PRO) | 1. |
| | 19 | | | | | | | | 17 | 1 | 17(ALA) | 1. |
| | 20 | | | | | | | | 17 | 1 | 17(SER) | 1. |
| | 21 | | | | | | | | 17 | 1 | 17(ILE) | 1. |
| | 22 | | | | | | | | 17 | 2 | 16(SER) | 2.1 |
| | 23 | | | | | | | | 17 | 1 | 17(CYS) | 1. |
| | 24 | | | | | | | | 16 | 1 | 16(ARG) | 1. |
| | 25 | | | | | | | | 14 | 2 | 13(SER) | 2.2 |
| | 26 | | | | | | | | 14 | 1 | 14(SER) | 1. |
| | 27A | | | | | | | | 14 | 1 : 2 | 14(GLN) : 12(GLN) | 1. : 2.3 |
| | 27B | | | | | | | | 12 | 3 | 10(SER) | |
| | 27C | | | | | | | | 12 | 3 | 12(LEU) | |
| | 27D | | | | | | | | 12 | 5 | 9(LEU) | |
| | 27E | | | | | | | | 7 | 2 | 5(HIS) | |
| | 27F | | | | | | | | 2 | 2 | 6(SER) | |
| | 28 | | | | | | | | 10 | 4 | 7(ASP) : 4(+) | 5.7 : 10. |
| | 29 | | | | | | | | 10 | 3 | 8(GLY) | 3.8 |
| | 30 | | | | | | | | 9 | 4 : 5 | 5(ASN) : 3(ASP) | 7.2 : 15. |
| | 31 | | | | | | | | 9 | 1 | 4(ASN) : 3(+) | 9. : 12. |
| | 32 | | | | | | | | 9 | 1 | 9(TYR) | 1. |
| | 33 | | | | | | | | 8 | 1 | 8(LEU) | 1. |
| | 34 | | | | | | | | 8 | 2 | 6(ASN) : 4(+) | 2.7 : 4. |
| | 35 | | | | | | | | 8 | 1 | 8(TRP) | 1. |
| | 36 | | | | | | | | 8 | 2 | 7(TYR) | 2.3 |
| | 37 | | | | | | | | 8 | 2 | 7(LEU) | 2.3 |
| | 38 | | | | | | | | 8 | 1 : 2 | 8(GLN) : 6(GLN) | 1. : 2.7 |
| | 39 | | | | | | | | 8 | 2 | 7(LYS) | 2.3 |
| | 40 | | | | | | | | 8 | 2 | 7(PRO) | 2.3 |
| | 41 | | | | | | | | 8 | 1 | 8(GLY) | 1. |
| | 42 | | | | | | | | 8 | 1 : 2 | 8(GLN) : 6(GLN) | 1. : 2.7 |
| | 43 | | | | | | | | 6 | 1 | 6(SER) | 1. |
| | 44 | | | | | | | | 7 | 1 | 7(PRO) | 1. |
| | 45 | | | | | | | | 7 | 3 | 5(GLN) : 3(+) | 4.2 : 7. |
| | 46 | | | | | | | | 7 | 2 | 6(LEU) | 2.3 |
| | 47 | | | | | | | | 7 | 1 | 7(LEU) | 1. |
| | 48 | | | | | | | | 7 | 1 | 7(ILE) | 1. |
| | 49 | | | | | | | | 6 | 1 | 6(TYR) | 1. |
| | 50 | | | | | | | | 6 | 3 | 4(LEU) | 4.5 |
| | 51 | | | | | | | | 6 | 4 | 3(GLY) | 8. |
| | 52 | | | | | | | | 7 | 1 | 7(SER) | 1. |
| | 53 | | | | | | | | 7 | 2 | 5(ASN) | 2.8 |
| | 54 | | | | | | | | 7 | 1 | 7(ARG) | 1. |
| | 55 | | | | | | | | 7 | 2 | 5(ALA) | 2.8 |
| | 56 | | | | | | | | 7 | 1 | 7(SER) | 1. |
| | 57 | | | | | | | | 7 | 1 | 7(GLY) | 1. |
| | 58 | | | | | | | | 7 | 1 | 7(VAL) | 1. |
| | 59 | | | | | | | | 7 | 1 | 7(PRO) | 1. |
| | 60 | | | | | | | | 7 | 2 | 6(ASP) | 2.3 |
| | 61 | | | | | | | | 7 | 1 | 7(ARG) | 1. |
| | 62 | | | | | | | | 8 | 1 | 8(PHE) | 1. |
| | 63 | | | | | | | | 8 | 1 | 8(SER) | 1. |
| | 64 | | | | | | | | 8 | 2 | 7(GLY) | 2.3 |
| | 65 | | | | | | | | 8 | 1 | 8(SER) | 1. |
| | 66 | | | | | | | | 8 | 1 | 8(GLY) | 1. |
| | 67 | | | | | | | | 8 | 1 | 8(SER) | 1. |
| | 68 | | | | | | | | 8 | 2 | 7(GLY) | 2.3 |
| | 69 | | | | | | | | 7 | 1 | 7(THR) | 1. |
| | 70 | | | | | | | | 7 | 1 : 2 | 7(ASP) : 6(ASP) | 1. : 2.3 |
| | 71 | | | | | | | | 8 | 1 | 8(PHE) | 1. |
| | 72 | | | | | | | | 8 | 1 | 8(THR) | 1. |
| | 73 | | | | | | | | 8 | 1 | 8(LEU) | 1. |
| | 74 | | | | | | | | 8 | 3 | 6(LYS) | 4. |
| | 75 | | | | | | | | 8 | 1 | 8(ILE) | 1. |
| | 76 | | | | | | | | 8 | 2 | 7(SER) | 2.3 |
| | 77 | | | | | | | | 8 | 1 | 8(ARG) | 1. |
| | 78 | | | | | | | | 8 | 1 | 8(VAL) | 1. |
| | 79 | | | | | | | | 8 | 2 | 6(GLU) : 4(+) | 2.7 : 4. |
| | 80 | | | | | | | | 8 | 2 | 7(ALA) | 2.3 |
| | 81 | | | | | | | | 8 | 1 : 2 | 8(GLU) : 6(GLU) | 1. : 2.7 |
| | 82 | | | | | | | | 8 | 1 : 2 | 8(ASP) : 6(ASP) | 1. : 2.7 |
| | 83 | | | | | | | | 8 | 1 | 8(VAL) | 1. |
| | 84 | | | | | | | | 8 | 1 | 8(GLY) | 1. |
| | 85 | | | | | | | | 8 | 1 | 8(VAL) | 1. |
| | 86 | | | | | | | | 8 | 1 | 8(TYR) | 1. |
| | 87 | | | | | | | | 8 | 1 | 8(TYR) | 1. |
| | 88 | | | | | | | | 8 | 1 | 8(CYS) | 1. |
| | 89 | | | | | | | | 7 | 1 | 7(MET) | 1. |
| | 90 | | | | | | | | 7 | 1 : 2 | 7(GLN) : 6(GLN) | 1. : 2.3 |
| | 91 | | | | | | | | 7 | 3 | 5(ALA) | 4.2 |
| | 92 | | | | | | | | 7 | 2 | 5(LEU) | 2.8 |
| | 93 | | | | | | | | 7 | 3 | 5(GLN) : 4(GLN) | 4.2 : 5.3 |
| | 94 | | | | | | | | 7 | 5 | 2(+) | 18. |
| | 95 | | | | | | | | 7 | 2 | 6(PRO) | 2.3 |
| 95A | | | | | | | | | | | | |
| 95B | | | | | | | | | | | | |
| 95C | | | | | | | | | | | | |
| 95D | | | | | | | | | | | | |
| 95E | | | | | | | | | | | | |
| 95F | | | | | | | | | | | | |
| 96 | | | | | | | | | 7 | 6 | 2(TYR) | 21. |
| 97 | | | | | | | | | 7 | 1 | 7(THR) | 1. |
| | 98 | | | | | | | | 7 | 1 | 7(PHE) | 1. |
| | 99 | | | | | | | | 7 | 1 | 7(GLY) | 1. |
| | 100 | | | | | | | | 7 | 2 | 6(GLN) | 2.3 |
| | 101 | | | | | | | | 7 | 1 | 7(GLY) | 1. |
| | 102 | | | | | | | | 7 | 1 | 7(THR) | 1. |
| | 103 | | | | | | | | 7 | 3 | 5(LYS) | 4.2 |
| | 104 | | | | | | | | 8 | 2 | 4(+) | 4. |
| | 105 | | | | | | | | 8 | 1 : 2 | 8(GLU) : 7(GLU) | 1. : 2.3 |
| | 106 | | | | | | | | 8 | 1 | 8(ILE) | 1. |
| 106A | | | | | | | | | | | | |
| | 107 | | | | | | | | 8 | 2 | 7(LYS) | 2.3 |
| | 108 | | | | | | | | 7 | 1 | 7(ARG) | 1. |
| | 109 | | | | | | | | 4 | 1 | 4(THR) | 1. |

ANTIBODY SPECIFICITIES: HUMAN KAPPA LIGHT CHAINS SUBGROUP II

- 3) **ROB**: COLD AGGLUTININ WITH ANTI-PR1D ACTIVITY
 10) **WILS**: COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
 14) **FR**: ANTI-PHOSPHOCHOLINE(BINDING CONSTANT=6.4X10EXP4)
 24) **GL**: ANTI-IGG
 27) **TH**: COLD AGGLUTININ WITH ANTI-PR2 ACTIVITY (RBC MEMBRANE ANTIGEN ON HUMAN, RAT AND GUINEA PIG ERYTHROCYTES INACTIVATED BY PROTEOLYTIC ENZYMES AND NEURAMINIDASE)

REFERENCE: HUMAN KAPPA LIGHT CHAINS SUBGROUP II

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NOTES: HUMAN KAPPA LIGHT CHAINS SUBGROUP II

IDENTICAL SETS OF FRAMEWORK SEGMENTS:

- FR1**: SET 1: TEW[1],MIL[2],NIM[3],CUM[4],GM 607 'CL[5],BAT[6],BATES[7],ROB[8],SLO[9],WILS[10],GLI[11],AMYLOID TEW[12],RAI[13]. (13 IDENTICAL)
FR2: SET 1: MIL[2],NIM[3],GM 607 'CL[5]. (3 IDENTICAL HUMAN V-KAPPA-II; ALSO 2 MOUSE V-KAPPA-II: VKAPPA 24B'CL[63],2S13[67].)
 SET 2: MIL[2],FR[14]. (2 IDENTICAL)
FR3: SET 1: TEW[1],GM 607 'CL[5],RPM1-6410'CL[16]. (3 IDENTICAL)
FR4: SET 1: GM 607 'CL[5],RPM1-6410'CL[16]. (2 IDENTICAL HUMAN V-KAPPA-II; ALSO 3 HUMAN V-KAPPA-I: AU[2],GAL(II)[36],CL'110: 7 HUMAN V-KAPPA-III: WOL[2],PAY[7],PIE[11],GLO[15],CUR[20],REE[57],VKAPPA3'CL[82]; AND 1 HUMAN V-KAPPA-IV: PB17IV'CL[3].)
 SET 2: NIM[3],FR[14]. (2 IDENTICAL HUMAN V-KAPPA-II; ALSO 3 HUMAN V-KAPPA-I: AGI[7],DEN[46],BI[63]; 6 HUMAN V-KAPPA-III: NEU[5],GOT[8],GAR[10],FLO[12],FR4[21],IARC/BL41'CL[28]; AND 1 HUMAN V-KAPPA-IV: LEN[4].)
 SET 3: TEW[1]. (IDENTICAL TO 2 HUMAN V-KAPPA-I: WALKER'CL[12],OU(OC)[34].)

IDENTICAL SETS OF COMPLEMENTARITY DETERMINING REGIONS:

- CDR1**:
CDR2: SET 1: MIL[2],NIM[3],GM 607 'CL[5]. (3 IDENTICAL)
CDR3:

IDENTICAL SETS OF J-MINIGENES:

- SET 1: RPM1-6410'CL[16]. (IDENTICAL TO 1 HUMAN V-KAPPA-I: AU[2]; 2 HUMAN V-KAPPA-III: PIE[11],VKAPPA3'CL[82]; AND 1 HUMAN V-KAPPA-IV: PB17IV'CL[3].)
 SET 2: TEW[1]. (IDENTICAL TO 1 HUMAN V-KAPPA-I: WALKER'CL[12].)
 SET 3: FR[14]. (IDENTICAL TO 2 HUMAN V-KAPPA-I: DEN[46],BI[63]; AND 3 HUMAN V-KAPPA-III: GAR[10],FLO[12],IARC/BL41'CL[28].)

SPECIFIC NOTES:

- 12) **AMYLOID TEW**: IT HAS THE SAME SEQUENCE AS THAT OF TEW SO FAR AS THE SEQUENCED POSITIONS ARE CONCERNED.
 14) **FR**: AN IDIOTYPIC ANTIBODY TO FR NOT INHIBITABLE BY PHOSPHORYLCHOLINE REACTED BETTER WITH THE FR HEAVY CHAIN THAN WITH THE LIGHT CHAIN. THE CROSS-REACTION WITH MOPC167 WAS 10,000 TIMES WEAKER. (RIESEN,W.F. (1979) EUR.J.IMMUNOL.,9,421-425.)
 16) **RPM1-6410**: THE AMINO ACID SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF HUMAN ADULT DNA.

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|-----------------------|
| 27F | (GLY,ASN) : (GLY,ASP) |
| 28 | (ASP,ASN) |
| 31 | (THR,ASP) |
| 34 | (ASP,ASN) |
| 45 | (GLU,GLN) |
| 79 | (GLU,GLN) |
| 94 | (THR,SER) |
| 104 | (LEU,VAL) |

HUMAN KAPPA LIGHT CHAINS SUBGROUP III (cont'd)

| | 50 AMYLOID SO124 | 51 DOV | 52 SHM | 53 GRA | 54* GOE II | 55 LOW | 56 VER | 57 REE | 58 WE # | 59 HOW | 60 HS4 | 61 HBJ 5 | 62* TEH | 63* CRA (III) | 64* PLA | 65* PIN | 66 MCE | 67 HAC | 68 K- E15 CL | 69 BER | 70* BOR | 71* DRI | 72* WAL | 73* GOL | 74* GAG |
|-----|------------------------|-----------|-----------|-----------|------------------|-----------|-----------|-----------|---------------|-----------|-----------|----------------|------------|---------------------|------------|------------|-----------|-----------|-----------------------|-----------|------------|------------|------------|------------|------------|
| 0 | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 | GLU | GLU | GLU | GLU | asp | GLU | GLU | GLU | asp | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU |
| 2 | ILE | ILE | ILE | met | ILE | ILE | thr | thr | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE |
| 3 | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | gln | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL |
| 4 | met | met | met | met | LEU | met | LEU | LEU | met | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | |
| 5 | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| 6 | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN |
| 7 | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER |
| 8 | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO |
| 9 | ala | ala | ala | ala | ala | ala | ala | ala | ala | GLY | ala | asx | GLY | PRO | GLY | PRO | GLY | PRO | GLY | ala | THR | THR | THR | THR | THR |
| 10 | THR | THR | THR | THR | ser | gln | THR | THR | ser | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| 11 | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | THR | THR | THR | THR | THR | THR |
| 12 | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | THR | THR | THR | THR | THR | THR |
| 13 | val | val | val | met | val | val | val | ser | ala | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | THR | THR | THR | THR | THR | THR |
| 14 | SER | SER | SER | SER | thr | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | THR | THR | THR | THR | THR | THR |
| 15 | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | val | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | THR | THR | THR | THR | THR | THR |
| 16 | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | THR | THR | THR | THR | THR | THR |
| 17 | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | THR | THR | THR | THR | THR | THR |
| 18 | ARG | ser | gln | ARG | ARG | thr | val | val | val | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | THR | THR | THR | THR | THR | THR |
| 19 | val | ALA | ALA | ALA | ALA | ALA | ALA | ALA | val | val | val | val | val | val | val | val | val | val | val | THR | THR | THR | THR | THR | THR |
| 20 | THR | THR | THR | THR | ser | THR | THR | THR | # | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR |
| 21 | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | thr | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | THR | THR | THR | THR | THR | THR |
| 22 | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | THR | THR | THR | THR | THR | THR |
| 23 | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | thr | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | THR | THR | THR | THR | THR | THR |
| 24 | ARG | ARG | ARG | | | SER | LYS | ARG | | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER | ALA | SER |
| 25 | ALA | ALA | ALA | | | ALA | SER | SER | ALA | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | ALA | SER | ALA | SER | ALA | SER |
| 26 | | | | | | GLN | GLN | GLN | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | | | | | |
| 27 | | | | | | | | | | | | | | | | | | | | | | | | | |
| 27A | | | | | | | | | | | | | | | | | | | | | | | | | |
| 27B | | | | | | | | | | | | | | | | | | | | | | | | | |
| 27C | | | | | | | | | | | | | | | | | | | | | | | | | |
| 27D | | | | | | | | | | | | | | | | | | | | | | | | | |
| 27E | | | | | | | | | | | | | | | | | | | | | | | | | |
| 27F | | | | | | | | | | | | | | | | | | | | | | | | | |
| 27G | | | | | | | | | | | | | | | | | | | | | | | | | |
| 28 | | SER | THR | | | SER | LEU | SER | THR | | | | | | | | | | | | | | | | |
| 29 | | VAL | VAL | | | VAL | SER | LEU | SER | | | | | | | | | | | | | | | | |
| 30 | | SER | ALA | | | ASP | SER | LEU | SER | | | | | | | | | | | | | | | | |
| 31 | | THR | LYS | | | GLX | ASP | ASN | THR | | | | | | | | | | | | | | | | |
| 32 | | ASX | SER | | | THR | THR | THR | THR | | | | | | | | | | | | | | | | |
| 33 | | LEU | LEU | | | VAL | LEU | VAL | # | | | | | | | | | | | | | | | | |
| 34 | | ALA | ALA | | | ALA | ALA | ALA | | | | | | | | | | | | | | | | | |
| 35 | | TRP | TRP | | | TRP | TRP | TRP | TRP | | | | | | | | | | | | | | | | |
| 36 | | TYR | TYR | | | TYR | TYR | TYR | TYR | | | | | | | | | | | | | | | | |
| 37 | | GLX | GLX | | | GLX | GLN | GLN | GLN | | | | | | | | | | | | | | | | |
| 38 | | GLX | GLX | | | GLX | GLN | HIS | | | | | | | | | | | | | | | | | |
| 39 | | LYS | | | | LYS | | | | | | | | | | | | | | | | | | | |
| 40 | | PRO | | | | PRO | | | | | | | | | | | | | | | | | | | |
| 41 | | | | | | GLY | PRO | GLY | PRO | | | | | | | | | | | | | | | | |
| 42 | | | | | | VAL | THR | THR | THR | | | | | | | | | | | | | | | | |
| 43 | | | | | | ALA | ALA | ALA | ALA | | | | | | | | | | | | | | | | |
| 44 | | | | | | | LEU | PRO | | | | | | | | | | | | | | | | | |
| 45 | | | | | | ARG | ARG | ARG | | | | | | | | | | | | | | | | | |
| 46 | | | | | | LEU | LEU | LEU | | | | | | | | | | | | | | | | | |
| 47 | | | | | | LEU | LEU | LEU | | | | | | | | | | | | | | | | | |
| 48 | | | | | | ILE | ILE | ILE | | | | | | | | | | | | | | | | | |
| 49 | | | | | | TYR | TYR | TYR | | | | | | | | | | | | | | | | | |
| 50 | | | | | | GLY | ALA | ALA | | | | | | | | | | | | | | | | | |
| 51 | | | | | | VAL | THR | THR | | | | | | | | | | | | | | | | | |
| 52 | | | | | | SER | SER | SER | | | | | | | | | | | | | | | | | |
| 53 | | | | | | THR | THR | THR | | | | | | | | | | | | | | | | | |
| 54 | | | | | | ARG | ARG | ARG | | | | | | | | | | | | | | | | | |
| 55 | | | | | | ALA | PRO | PRO | | | | | | | | | | | | | | | | | |
| 56 | | | | | | ALA | THR | THR | | | | | | | | | | | | | | | | | |
| 57 | | | | | | GLY | ASP | ASP | | | | | | | | | | | | | | | | | |
| 58 | | | | | | ILE | ILE | ILE | | | | | | | | | | | | | | | | | |
| 59 | | | | | | PRO | PRO | PRO | | | | | | | | | | | | | | | | | |
| 60 | | | | | | ASP | ALA | ALA | | | | | | | | | | | | | | | | | |
| 61 | | | | | | ARG | ARG | ARG | | | | | | | | | | | | | | | | | |
| 62 | | | | | | PHE | PHE | PHE | | | | | | | | | | | | | | | | | |
| 63 | | | | | | THR | SER | SER | | | | | | | | | | | | | | | | | |
| 64 | | | | | | GLY | GLY | GLY | | | | | | | | | | | | | | | | | |
| 65 | | | | | | ARG | SER | SER | | | | | | | | | | | | | | | | | |
| 66 | | | | | | ALA | MET | MET | | | | | | | | | | | | | | | | | |
| 67 | | | | | | SER | SER | SER | | | | | | | | | | | | | | | | | |
| 68 | | | | | | GLY | GLY | GLY | | | | | | | | | | | | | | | | | |
| 69 | | | | | | THR | THR | THR | | | | | | | | | | | | | | | | | |
| 70 | | | | | | ASP | GLU | GLU | | | | | | | | | | | | | | | | | |
| 71 | | | | | | PHE | PHE | PHE | | | | | | | | | | | | | | | | | |
| 72 | | | | | | THR | THR | THR | | | | | | | | | | | | | | | | | |
| 73 | | | | | | LEU | LEU | LEU | | | | | | | | | | | | | | | | | |
| 74 | | | | | | THR | THR | THR | | | | | | | | | | | | | | | | | |
| 75 | | | | | | ILE | ILE | ILE | | | | | | | | | | | | | | | | | |
| 76 | | | | | | SER | PHE | PHE | | | | | | | | | | | | | | | | | |
| 77 | | | | | | ASP | ARG | ARG | | | | | | | | | | | | | | | | | |
| 78 | | | | | | LEU | VAL | VAL | | | | | | | | | | | | | | | | | |
| 79 | | | | | | GLU | GLU | GLU | | | | | | | | | | | | | | | | | |
| 80 | | | | | | PRO | SER | SER | | | | | | | | | | | | | | | | | |
| 81 | | | | | | GLU | GLU | GLU | | | | | | | | | | | | | | | | | |
| 82 | | | | | | ASP | ASP | | | | | | | | | | | | | | | | | | |

HUMAN KAPPA LIGHT CHAINS SUBGROUP III (cont'd)

| | 75 DOB | 76 HS6 | 77 HBJ 12 | 78 BUR (K) | 79 LEG | 80 B6 | 81 AMYLOID WR # | 82 VKAPPA3 CL # | # OF SEQUENCES | # OF AMINO ACIDS | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|--|-----------|-----------|-----------------|------------------|-----------|----------|--------------------------|--------------------------|-------------------|------------------------|---|-------------|
| | 0 | --- | --- | --- | --- | --- | --- | --- | 79 | 3 : 4 | 74(GLU) : 73(GLU) | 3.2 : 4.3 |
| | 1 | GLU | GLU | GLU | GLU | GLU | --- | --- | 79 | 4 | 74(ILE) | 5.3 |
| | 2 | ILE | ILE | ILE | ILE | ILE | --- | --- | 79 | 3 | 76(VAL) | 4.2 |
| | 3 | met | VAL | VAL | VAL | VAL | --- | --- | 79 | 3 | 65(LEU) | 3.6 |
| | 4 | --- | LEU | val | LEU | --- | --- | --- | 77 | 1 | 77(THR) | 1. |
| | 5 | THR | THR | THR | --- | --- | --- | --- | 77 | 2 | 75(GLN) : 69(GLN) | 2.1 : 2.2 |
| | 6 | GLN | GLN | GLN | --- | --- | --- | --- | 75 | 1 | 75(SER) | 1. |
| | 7 | SER | --- | --- | --- | --- | --- | --- | 74 | 1 | 74(PRO) | 1. |
| | 8 | PRO | --- | --- | --- | --- | --- | --- | 69 | 6 : 7 | 46(GLY) | 9. : 11. |
| | 9 | ala | --- | --- | --- | --- | --- | --- | 70 | 4 | 66(THR) | 4.2 |
| | 10 | --- | --- | --- | --- | --- | --- | --- | 69 | 2 | 67(LEU) | 2. |
| | 11 | --- | --- | --- | --- | --- | --- | --- | 67 | 1 | 67(SER) | 1. |
| | 12 | --- | --- | --- | --- | --- | --- | --- | 67 | 5 | 52(LEU) | 6.4 |
| | 13 | --- | --- | --- | --- | --- | --- | --- | 66 | 2 | 64(SER) | 2.1 |
| | 14 | --- | --- | --- | --- | --- | --- | --- | 66 | 2 | 65(PRO) | 2. |
| | 15 | --- | --- | --- | --- | --- | --- | --- | 62 | 3 : 4 | 56(GLU) : 50(GLU) | 3.3 : 5. |
| | 16 | --- | --- | --- | --- | --- | --- | --- | 62 | 2 | 51(ARG) | 6. |
| | 17 | --- | --- | --- | --- | --- | --- | --- | 60 | 2 | 52(ALA) | 2.3 |
| | 18 | --- | --- | --- | --- | --- | --- | --- | 59 | 5 | 53(THR) | 5.6 |
| | 19 | --- | --- | --- | --- | --- | --- | --- | 60 | 2 | 57(LEU) | 2.1 |
| | 20 | --- | --- | --- | --- | --- | --- | --- | 60 | 3 | 58(SER) | 3.1 |
| | 21 | --- | --- | --- | --- | --- | --- | --- | 50 | 1 | 50(CYS) | 1. |
| | 22 | --- | --- | --- | --- | --- | --- | --- | 51 | 4 | 47(ARG) | 4.3 |
| | 23 | --- | --- | --- | --- | --- | --- | --- | 52 | 2 | 51(ALA) | 2. |
| | 24 | --- | --- | --- | --- | --- | --- | --- | 49 | 2 | 46(SER) | 2.1 |
| | 25 | --- | --- | --- | --- | --- | --- | --- | 47 | 3 | 43(GLN) : 37(GLN) | 3.3 : 3.8 |
| | 26 | --- | --- | --- | --- | --- | --- | --- | 32 | 4 | 29(SER) | --- |
| | 27A | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 27B | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 27C | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 27D | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 27E | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 27F | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 28 | --- | --- | --- | --- | --- | --- | --- | 47 | 7 : 8 | 25(VAL) | 13. : 15. |
| | 29 | --- | --- | --- | --- | --- | --- | --- | 44 | 6 | 27(SER) | 9.8 |
| | 30 | --- | --- | --- | --- | --- | --- | --- | 40 | 7 | 24(SER) | 12. |
| | 31 | --- | --- | --- | --- | --- | --- | --- | 39 | 10 | 24(SER) | 16. |
| | 32 | --- | --- | --- | --- | --- | --- | --- | 40 | 8 | 28(TYR) | 11. |
| | 33 | --- | --- | --- | --- | --- | --- | --- | 41 | 4 | 36(LEU) | 4.6 |
| | 34 | --- | --- | --- | --- | --- | --- | --- | 41 | 5 | 37(ALA) | 5.5 |
| | 35 | --- | --- | --- | --- | --- | --- | --- | 38 | 1 | 38(TRP) | 1. |
| | 36 | --- | --- | --- | --- | --- | --- | --- | 39 | 1 | 39(TYR) | 1. |
| | 37 | --- | --- | --- | --- | --- | --- | --- | 39 | 1 : 2 | 39(GLN) : 33(GLN) | 1. : 2.4 |
| | 38 | --- | --- | --- | --- | --- | --- | --- | 37 | 2 : 3 | 36(GLN) : 30(GLN) | 2.1 : 3.7 |
| | 39 | --- | --- | --- | --- | --- | --- | --- | 33 | 3 | 29(LYS) | 3.4 |
| | 40 | --- | --- | --- | --- | --- | --- | --- | 34 | 3 | 32(PRO) | 3.2 |
| | 41 | --- | --- | --- | --- | --- | --- | --- | 27 | 2 | 26(GLY) | 2.1 |
| | 42 | --- | --- | --- | --- | --- | --- | --- | 27 | 4 | 24(GLN) : 23(GLN) | 4.5 : 4.7 |
| | 43 | --- | --- | --- | --- | --- | --- | --- | 26 | 3 | 23(ALA) | 3.4 |
| | 44 | --- | --- | --- | --- | --- | --- | --- | 27 | 3 | 25(PRO) | 3.2 |
| | 45 | --- | --- | --- | --- | --- | --- | --- | 26 | 3 | 24(ARG) | 3.3 |
| | 46 | --- | --- | --- | --- | --- | --- | --- | 24 | 3 | 23(LEU) | 2.1 |
| | 47 | --- | --- | --- | --- | --- | --- | --- | 23 | 3 | 22(LEU) | 2.1 |
| | 48 | --- | --- | --- | --- | --- | --- | --- | 22 | 3 | 20(ILE) | 3.3 |
| | 49 | --- | --- | --- | --- | --- | --- | --- | 22 | 4 | 19(TYR) | 4.6 |
| | 50 | --- | --- | --- | --- | --- | --- | --- | 21 | 5 | 16(GLY) | 6.6 |
| | 51 | --- | --- | --- | --- | --- | --- | --- | 20 | 3 | 16(ALA) | 3.8 |
| | 52 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 18(SER) | 2.2 |
| | 53 | --- | --- | --- | --- | --- | --- | --- | 21 | 2 | 16(SER) | 2.6 |
| | 54 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 19(ARG) | 2.1 |
| | 55 | --- | --- | --- | --- | --- | --- | --- | 23 | 3 | 21(ALA) | 3.3 |
| | 56 | --- | --- | --- | --- | --- | --- | --- | 22 | 4 | 19(THR) | 4.6 |
| | 57 | --- | --- | --- | --- | --- | --- | --- | 23 | 2 | 22(GLY) | 2.1 |
| | 58 | --- | --- | --- | --- | --- | --- | --- | 23 | 3 | 21(ILE) | 3.3 |
| | 59 | --- | --- | --- | --- | --- | --- | --- | 23 | 1 | 23(PRO) | 1. |
| | 60 | --- | --- | --- | --- | --- | --- | --- | 23 | 5 | 17(ASP) | 6.8 |
| | 61 | --- | --- | --- | --- | --- | --- | --- | 23 | 1 | 23(ARG) | 1. |
| | 62 | --- | --- | --- | --- | --- | --- | --- | 23 | 1 | 23(PHE) | 1. |
| | 63 | --- | --- | --- | --- | --- | --- | --- | 23 | 2 | 21(SER) | 2.2 |
| | 64 | --- | --- | --- | --- | --- | --- | --- | 23 | 1 | 23(GLY) | 1. |
| | 65 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 21(SER) | 2.1 |
| | 66 | --- | --- | --- | --- | --- | --- | --- | 22 | 4 | 17(GLY) | 5.2 |
| | 67 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 21(SER) | 2.1 |
| | 68 | --- | --- | --- | --- | --- | --- | --- | 22 | 1 | 22(GLY) | 1. |
| | 69 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 21(THR) | 2.1 |
| | 70 | --- | --- | --- | --- | --- | --- | --- | 21 | 2 | 19(ASP) | 2.2 |
| | 71 | --- | --- | --- | --- | --- | --- | --- | 21 | 1 | 21(PHE) | 1. |
| | 72 | --- | --- | --- | --- | --- | --- | --- | 21 | 1 | 21(THR) | 1. |
| | 73 | --- | --- | --- | --- | --- | --- | --- | 21 | 1 | 21(LEU) | 1. |
| | 74 | --- | --- | --- | --- | --- | --- | --- | 21 | 2 | 20(THR) | 2.1 |
| | 75 | --- | --- | --- | --- | --- | --- | --- | 21 | 2 | 20(ILE) | 2.1 |
| | 76 | --- | --- | --- | --- | --- | --- | --- | 21 | 3 | 19(SER) | 3.3 |
| | 77 | --- | --- | --- | --- | --- | --- | --- | 22 | 5 | 16(ARG) | 6.9 |
| | 78 | --- | --- | --- | --- | --- | --- | --- | 22 | 3 | 20(LEU) | 3.3 |
| | 79 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 21(GLU) : 20(GLU) | 2.1 : 2.2 |
| | 80 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 19(PRO) | 2.3 |
| | 81 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 21(GLU) | 2.1 |
| | 82 | --- | --- | --- | --- | --- | --- | --- | 22 | 1 | 22(ASP) | 1. |
| | 83 | --- | --- | --- | --- | --- | --- | --- | 22 | 3 | 20(PHE) | 3.3 |
| | 84 | --- | --- | --- | --- | --- | --- | --- | 22 | 1 | 22(ALA) | 1. |
| | 85 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 21(VAL) | 2.1 |
| | 86 | --- | --- | --- | --- | --- | --- | --- | 22 | 1 | 22(TYR) | 1. |
| | 87 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 20(TYR) | 2.2 |
| | 88 | --- | --- | --- | --- | --- | --- | --- | 22 | 1 | 22(CYS) | 1. |
| | 89 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 21(GLN) | 2.1 |
| | 90 | --- | --- | --- | --- | --- | --- | --- | 22 | 1 | 22(GLN) | 1. |
| | 91 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 20(TYR) | 2.2 |
| | 92 | --- | --- | --- | --- | --- | --- | --- | 22 | 2 | 16(GLY) | 6.9 |
| | 93 | --- | --- | --- | --- | --- | --- | --- | 21 | 5 | 12(SER) | 8.8 |
| | 94 | --- | --- | --- | --- | --- | --- | --- | 21 | 4 | 18(SER) | 4.7 |
| | 95 | --- | --- | --- | --- | --- | --- | --- | 21 | 3 | 18(PRO) | 3.5 |
| | 95A | --- | --- | --- | --- | --- | --- | --- | 1 | 1 | 1(PRO) | --- |
| | 95B | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 95C | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 95D | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 95E | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 95F | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 96 | --- | --- | --- | --- | --- | --- | --- | 19 | 10 | 4(TYR) | 48. |
| | 97 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 19(THR) | 2.1 |
| | 98 | --- | --- | --- | --- | --- | --- | --- | 20 | 1 | 20(PHE) | 1. |
| | 99 | --- | --- | --- | --- | --- | --- | --- | 20 | 1 | 20(GLY) | 1. |
| | 100 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 18(GLN) | 2.2 |
| | 101 | --- | --- | --- | --- | --- | --- | --- | 20 | 1 | 22(GLY) | 1. |
| | 102 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 18(THR) | 2.2 |
| | 103 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 18(LYS) | 2.2 |
| | 104 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 11(VAL) | 3.6 |
| | 105 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 18(GLU) | 2.2 |
| | 106 | --- | --- | --- | --- | --- | --- | --- | 20 | 3 | 18(ILE) | 3.3 |
| | 106A | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | 107 | --- | --- | --- | --- | --- | --- | --- | 20 | 2 | 19(LYS) | 2.1 |
| | 108 | --- | --- | --- | --- | --- | --- | --- | 16 | 1 | 16(ARG) | 1. |
| | 109 | --- | --- | --- | --- | --- | --- | --- | 10 | 1 | 10(THR) | 1. |

ANTIBODY SPECIFICITIES: HUMAN KAPPA LIGHT CHAINS SUBGROUP III

- 2) **WOL:** ANTI-HUMAN GAMMA G GLOBULIN; WA IDIOTYPE
- 3) **SIE:** ANTI-HUMAN GAMMA G GLOBULIN; WA IDIOTYPE
- 5) **NEU:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE (KUNKEL.H.G..WINCHESTER.R.J..JOSLIN.F.G. & CAPRA.J.D. (1974) J.EXP.MED..139.128)
- 6) **GOT:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 7) **PAY:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 8) **SON:** CRYOGLOBULIN WITH ANTI-LOW-DENSITY LIPOPROTEIN ACTIVITY; B IDIOTYPE
- 9) **WEI:** CRYOGLOBULIN WITH ANTI-LOW-DENSITY LIPOPROTEIN ACTIVITY; B IDIOTYPE
- 10) **GAR:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 11) **PIE:** AUTOANTIBODY WHICH BINDS SPECIFICALLY TO INTERMEDIATE FILAMENTS
- 12) **FLO:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 13) **LOP:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 14) **SCA:** CRYOGLOBULIN WITH ANTI-LOW-DENSITY LIPOPROTEIN ACTIVITY; B IDIOTYPE
- 15) **GLO:** ANTI-HUMAN GAMMA G GLOBULIN; WA IDIOTYPE; CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 18) **MA:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY (GROUP 1)
- 19) **NIC:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP SMALL I ACTIVITY
- 20) **CUR:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 22) **DRE:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
- 23) **PER:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
- 25) **STE:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
- 26) **GJ:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY (ATYPICAL)
- 27) **TAK:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
- 35) **AJ:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
- 42) **CLA:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 43) **SHE:** CRYOGLOBULIN WITH ANTI-IGG ACTIVITY; B IDIOTYPE
- 48) **POM:** ANTI-HUMAN GAMMA G1 GLOBULIN; PO IDIOTYPE
- 54) **GOEII:** ANTI-MEASLES VIRUS (WOODFOLK STRAIN); ANTI-SUBACUTE SCLEROSING PANENCEPHALITIS VIRUS (LEC STRAIN)
- 62) **TEH:** ANTI-HUMAN GAMMA G GLOBULIN
- 63) **CRA(III):** ANTI-HUMAN GAMMA G GLOBULIN
- 64) **PLA:** ANTI-HUMAN GAMMA G GLOBULIN
- 65) **PIN:** ANTI-HUMAN GAMMA G GLOBULIN
- 70) **BOR:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
- 71) **DRI:** ANTI-HUMAN GAMMA G GLOBULIN
- 72) **WAL:** ANTI-HUMAN GAMMA G GLOBULIN
- 73) **GOL:** ANTI-HUMAN GAMMA G GLOBULIN
- 74) **GAG:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY

CLASS: HUMAN KAPPA LIGHT CHAINS SUBGROUP III

- 5) **NEU:** IGM-KAPPA
- 6) **GOT:** IGM-KAPPA
- 7) **PAY:** IGM-KAPPA
- 8) **SON:** IGM-KAPPA
- 9) **WEI:** IGM-KAPPA
- 10) **GAR:** IGM-KAPPA
- 11) **PIE:** IGM-KAPPA
- 12) **FLO:** IGM-KAPPA
- 13) **LOP:** IGM-KAPPA
- 14) **SCA:** IGM-KAPPA
- 15) **GLO:** IGM-KAPPA
- 20) **CUR:** IGM-KAPPA
- 42) **CLA:** IGM-KAPPA
- 43) **SHE:** IGM-KAPPA

REFERENCE: HUMAN KAPPA LIGHT CHAINS SUBGROUP III

- 1) **TI:** SUTER.L..BARNIKOL.H.U..WATANABE.S. & HILSCHMANN.N. (1969) Z.PHYSIOL.CHEM..350.275-278; (1972) Z.PHYSIOL.CHEM..353.189-208. (CHECKED BY AUTHOR)
- 2) **WOL:** ANDREWS.D.W. & CAPRA.J.D. (1981) PROC.NAT.ACAD.SCI.USA.78.3799-3803. (CHECKED BY AUTHOR 08/25/81); ANDREWS.D.W. & CAPRA.J.D. (1981) BIOCHEMISTRY.20.5816-5822.
- 3) **SIE:** CAPRA.J.D. (1975) ADV.IMMUNOLOGY.20.1-40. (CHECKED BY AUTHOR); ANDREWS.D.W. & CAPRA.J.D. (1981) PROC.NAT.ACAD.SCI.USA.78.3799-3803. (CHECKED BY AUTHOR 08/25/81 WHO SUGGESTED THAT THE SEQUENCE DETERMINED IN 1975 WAS INCORRECT AND SHOULD BE DELETED); ANDREWS.D.W. & CAPRA.J.D. (1981) BIOCHEMISTRY.20.5816-5822.
- 4) **NG9'CL:** BENTLEY.D.L. (1984) NATURE.307.77-80.
- 5) **NEU:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84); GONI.F.,CHEN.P.P.,PONS-ESTEL.B.,CARSON.D.A. & FRANGIONE.B. (1985) J.IMMUNOL..135.4073-4079.
- 6) **GOT:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84); PONS-ESTEL.B.,GONI.F.,SOLOMON.A. & FRANGIONE.B. (1984) J.EXP.MED..160.893-904; GONI.F.,CHEN.P.P.,PONS-ESTEL.B.,CARSON.D.A. & FRANGIONE.B. (1985) J.IMMUNOL..135.4073-4079.
- 7) **PAY:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84); GONI.F.,CHEN.P.P.,PONS-ESTEL.B.,CARSON.D.A. & FRANGIONE.B. (1985) J.IMMUNOL..135.4073-4079.
- 8) **SON:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84); PONS-ESTEL.B.,GONI.F.,SOLOMON.A. & FRANGIONE.B. (1984) J.EXP.MED..160.893-904.
- 9) **WEI:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84)
- 10) **GAR:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84); PONS-ESTEL.B.,GONI.F.,SOLOMON.A. & FRANGIONE.B. (1984) J.EXP.MED..160.893-904; GONI.F.,CHEN.P.P.,PONS-ESTEL.B.,CARSON.D.A. & FRANGIONE.B. (1985) J.IMMUNOL..135.4073-4079.
- 11) **PIE:** PONS-ESTEL.B.,GONI.F.,SOLOMON.A. & FRANGIONE.B. (1984) J.EXP.MED..160.893-904. (CHECKED BY AUTHOR 05/16/86)
- 12) **FLO:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84); GONI.F.,CHEN.P.P.,PONS-ESTEL.B.,CARSON.D.A. & FRANGIONE.B. (1985) J.IMMUNOL..135.4073-4079.
- 13) **LOP:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84)
- 14) **SCA:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84)
- 15) **GLO:** CAPRA.J.D. (1975) ADV.IMMUNOLOGY.20.1-40. (CHECKED BY AUTHOR); LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84); GONI.F.,CHEN.P.P.,PONS-ESTEL.B.,CARSON.D.A. & FRANGIONE.B. (1985) J.IMMUNOL..135.4073-4079.
- 16) **SAL:** CAPRA.J.D.,KEHOE.J.M.,WINCHESTER.R.J. & KUNKEL.H.G. (1971) ANN.N.Y.ACAD.SCI..190.371-381. (CHECKED BY AUTHOR)
- 17) **WIL:** CAPRA.J.D.,KEHOE.J.M.,WINCHESTER.R.J. & KUNKEL.H.G. (1971) ANN.N.Y.ACAD.SCI..190.371-381. (CHECKED BY AUTHOR)
- 18) **MA:** CAPRA.J.D.,KEHOE.J.M.,WILLIAMS.R.C.,JR.,FEIZI.T. & KUNKEL.H.G. (1972) PROC.NAT.ACAD.SCI.USA.69.40-43. (CHECKED BY AUTHOR)
- 19) **NIC:** CAPRA.J.D.,KEHOE.J.M.,WILLIAMS.R.C.,JR.,FEIZI.T. & KUNKEL.H.G. (1972) PROC.NAT.ACAD.SCI.USA.69.40-43. (CHECKED BY AUTHOR)
- 20) **CUR:** LEDFORD.D.K.,GONI.F.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84); GONI.F.,CHEN.P.P.,PONS-ESTEL.B.,CARSON.D.A. & FRANGIONE.B. (1985) J.IMMUNOL..135.4073-4079.
- 21) **FR4:** MILSTEIN.C. (1969) FEBS LETTERS.2.301-304. (CHECKED BY AUTHOR WHO PROVIDED ADDITIONAL RESIDUES TO THOSE PUBLISHED)
- 22) **DRE:** GERGELY.J.,WANG.A.C. & FUDENBERG.H.H. (1973) VOX SANG..24.432-440. (CHECKED BY AUTHOR)
- 23) **PER:** GERGELY.J.,WANG.A.C. & FUDENBERG.H.H. (1973) VOX SANG..24.432-440. (CHECKED BY AUTHOR)
- 24) **CAM:** HOPPER.J.E.,NOYES.C.,HSU.R.,HEINRIKSON.R. & GALLAGHER.W. (1979) J.IMMUNOL..122.2007-2010. (CHECKED BY AUTHOR 01/26/83)
- 25) **STE:** EDMAN.P. & COOPER.A.G. (1968) FEBS LETTERS.2.33-35. (CHECKED BY AUTHOR)
- 26) **GJ:** CAPRA.J.D.,KEHOE.J.M.,WILLIAMS.R.C.,JR.,FEIZI.T. & KUNKEL.H.G. (1972) PROC.NAT.ACAD.SCI.USA.69.40-43. (CHECKED BY AUTHOR)
- 27) **TAK:** GERGELY.J.,WANG.A.C. & FUDENBERG.H.H. (1973) VOX SANG..24.432-440. (CHECKED BY AUTHOR)
- 28) **IARC/BL41'CL:** KLOBECK.H.G.,MEINDL.A.,COMBRIATO.G.,SOLOMON.A. & ZACHAU.H.G. (1985) NUC.ACIDS RES..13.6499-6513.
- 29) **RAD:** MILSTEIN.C. (1969) FEBS LETTERS.2.301-304. (CHECKED BY AUTHOR)
- 30) **DIL:** DAYHOFF.M.O. (1972) ATLAS OF PROTEIN SEQUENCE & STRUCTURE.5.D-250. SUBMITTED BY SMITHIES.O.,GIBSON.D.M. AND FANNING.E.M. (CHECKED BY AUTHOR 07/24/79)

REFERENCE: HUMAN KAPPA LIGHT CHAINS SUBGROUP III (cont'd)

- 31) **CAS**: NIALL.H.D. & EDMAN.P. (1967) NATURE.216.262-263. (CHECKED BY AUTHOR 07/25/79)
- 32) **MCE**: MIDDAGH.C.R.,KEHOE.J.M.,PRYSTOWSKY.M.B.,GERBER-JENSON.B.,JENSON.J.C. & LITMAN.G.W. (1978) IMMUNOCHEM..15.171-187. (CHECKED BY AUTHOR 10/22/80)
- 33) **KEA**: WANG.A.C. & FUDENBERG.H.H. (1975) IMMUNOL.COMMUN.4.483-497. (CHECKED BY AUTHOR 09/23/77); WANG.A.C.,TUNG.E.,WANG.I.,FUDENBERG.H.H.,PICK.A.I. & FROELICHMAN.R. (1980) CANCER IMMUNOL.IMMUNOTHER.9.81-86. (CHECKED BY AUTHOR 03/18/81)
- 34) **SMI**: NIALL.H.D. & EDMAN.P. (1967) NATURE.216.262-263. (CHECKED BY AUTHOR 07/25/79)
- 35) **AJ**: CAPRA.J.D.,KEHOE.J.M.,WILLIAMS.R.C.,JR.,FEIZI.T. & KUNKEL.H.G. (1972) PROC.NAT.ACAD.SCI.USA.69.40-43. (CHECKED BY AUTHOR)
- 36) **BRO'IGG**: HOPPER.J.E.,NOYES.C.,HEINRIKSON.R. & KESSEL.J.W. (1976) J.IMMUNOL..116.743-746. (CHECKED BY AUTHOR 01/26/83)
- 37) **NIG**: NIALL.H.D. & EDMAN.P. (1967) NATURE.216.262-263. (CHECKED BY AUTHOR 07/25/79)
- 38) **IKE**: CAPRA.J.D. (1975) ADV.IMMUNOLOGY.20.1-40. (CHECKED BY AUTHOR)
- 39) **TIL**: PINK.J.R.L.,WANG.A.C. & FUDENBERG.H.H. (1971) ANN.REV.MED..22.145-170. (CHECKED BY AUTHOR)
- 40) **AMYLOID KSA**: SLETTEN.K.,WESTERMARK.P.,PITKANEN.P.,THYRESSON.N. & OLSTAD.O.K. (1983) SCAND.J.IMMUNOL..18.557-560. (CHECKED BY AUTHOR 04/26/84)
- 41) **POL**: WANG.A.C.,WELLS.J.V.,FUDENBERG.H.H. & GERGELY.J. (1974) IMMUNOCHEM..11.341-345. (CHECKED BY AUTHOR)
- 42) **CLA**: LEDFORD.D.K.,GONIF.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84)
- 43) **SHE**: LEDFORD.D.K.,GONIF.,PIZZOLATO.M.,FRANKLIN.E.C.,SOLOMON.A. & FRANGIONE.B. (1983) J.IMMUNOL..131.1322-1325. (CHECKED BY AUTHOR 03/23/84)
- 44) **JH**: JEMMERSON.R.,KAPLAN.B.,DENTON.M.D.,ANDERAS.P.,ANDERSON.B. & MARGOLIASH.E. (1979) BIOCHEMISTRY.18.4676-4683.
- 45) **WIN**: NIALL.H.D. & EDMAN.P. (1967) NATURE.216.262-263. (CHECKED BY AUTHOR 07/25/79)
- 46) **LEA**: WANG.A.C.,WELLS.J.V.,FUDENBERG.H.H. & GERGELY.J. (1974) IMMUNOCHEM..11.341-345. (CHECKED BY AUTHOR)
- 47) **ARP**: WANG.A.C.,TUNG.E.,WANG.I.,FUDENBERG.H.H.,PICK.A.I. & FROELICHMAN.R. (1980) CANCER IMMUNOL.IMMUNOTHER.9.81-86. (CHECKED BY AUTHOR 03/18/81)
- 48) **POM**: KLAPPER.D.G. & CAPRA.J.D. (1976) ANN.IMMUNOL.(INST.PASTEUR).127C.261-271. (CHECKED BY AUTHOR 08/01/79)
- 49) **VAND**: SEON.B.K.,GAILANI.S.,HENDERSON.E.S. & PRESSMAN.D. (1977) IMMUNOCHEM..14.567-572. (CHECKED BY AUTHOR 08/28/78)
- 50) **AMYLOID S0124**: SLETTEN.K.,WESTERMARK.P.,PITKANEN.P.,THYRESSON.N. & OLSTAD.O.K. (1983) SCAND.J.IMMUNOL..18.557-560. (CHECKED BY AUTHOR 04/26/84)
- 51) **DOV**: WANG.A.C.,TUNG.E.,WANG.I.,FUDENBERG.H.H.,PICK.A.I. & FROELICHMAN.R. (1980) CANCER IMMUNOL.IMMUNOTHER.9.81-86. (CHECKED BY AUTHOR 03/18/81)
- 52) **SHM**: WANG.A.C.,TUNG.E.,WANG.I.,FUDENBERG.H.H.,PICK.A.I. & FROELICHMAN.R. (1980) CANCER IMMUNOL.IMMUNOTHER.9.81-86. (CHECKED BY AUTHOR 03/18/81)
- 53) **GRA**: NIALL.H.D. & EDMAN.P. (1967) NATURE.216.262-263. (CHECKED BY AUTHOR 07/25/79)
- 54) **GOEII**: STROSBERG.A.D.,KARCHER.D. & LOWENTHAL.A. (1975) J.IMMUNOL..115.157-160. (CHECKED BY AUTHOR)
- 55) **LOW**: WANG.A.C.,TUNG.E.,WANG.I.,FUDENBERG.H.H.,PICK.A.I. & FROELICHMAN.R. (1980) CANCER IMMUNOL.IMMUNOTHER.9.81-86. (CHECKED BY AUTHOR 03/18/81)
- 56) **VER**: CHERSIA. & NATALI.P.G. (1978) IMMUNOCHEMISTRY.15.585-589. (CHECKED BY AUTHOR 09/13/79)
- 57) **REE**: PRELLI.F.,TUMMOLO.D.,SOLOMON.A. & FRANGIONE.B. (1986) J.IMMUNOL.. IN PRESS.
- 58) **WE**: DWORSKY.E.,SLETTEN.K.,HARBOE.M. & WETTELAND.P. (1980) SCAND.J.IMMUNOL..12.281-287. (CHECKED BY AUTHOR 02/28/1984)
- 59) **HOW**: KAPLAN.A.P. & METZGER.H. (1969) BIOCHEMISTRY.8.3944-3951. (CHECKED BY AUTHOR)
- 60) **HS4**: HOOD.L.,GRAY.W.R.,SANDERS.B.G. & DREYER.W.J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL..32.133-145.
- 61) **HBJS**: HOOD.L.,GRAY.W.R.,SANDERS.B.G. & DREYER.W.J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL..32.133-145.
- 62) **TEH**: JOHNSTON.S.L.,ABRAHAM.G.N. & WELCH.E.H. (1975) BIOCHEM.BIOPHYS.RES.COMMUN..66.842-847. (CHECKED BY AUTHOR 10/17/77)
- 63) **CR(III)**: JOHNSTON.S.L.,ABRAHAM.G.N. & WELCH.E.H. (1975) BIOCHEM.BIOPHYS.RES.COMMUN..66.842-847. (CHECKED BY AUTHOR 10/17/77)
- 64) **PLA**: JOHNSTON.S.L.,ABRAHAM.G.N. & WELCH.E.H. (1975) BIOCHEM.BIOPHYS.RES.COMMUN..66.842-847. (CHECKED BY AUTHOR 10/17/77)
- 65) **PIN**: JOHNSTON.S.L.,ABRAHAM.G.N. & WELCH.E.H. (1975) BIOCHEM.BIOPHYS.RES.COMMUN..66.842-847. (CHECKED BY AUTHOR 10/17/77)
- 66) **MCE**: CAPRA.J.D.,KEHOE.J.M.,WILLIAMS.R.C.,JR.,FEIZI.T. & KUNKEL.H.G. (1972) PROC.NAT.ACAD.SCI.USA.69.40-43. (CHECKED BY AUTHOR)
- 67) **HAC**: HOOD.L. & TALMAGE.D.W. (1970) SCIENCE.168.325-334.
- 68) **K- EV15'CL**: STAVNEZER.J.,KEKISH.O.,BATTER.D.,GRENIER.J.,BALAZS.I.,HENDERSON.E. & ZEGERS.B.J.M. (1985) NUC.ACIDS RES..13.3495-3514.
- 69) **BER**: WANG.A.C.,WELLS.J.V.,FUDENBERG.H.H. & GERGELY.J. (1974) IMMUNOCHEM..11.341-345. (CHECKED BY AUTHOR)
- 70) **BOR**: GERGELY.J.,WANG.A.C. & FUDENBERG.H.H. (1973) VOX SANG..24.432-440. (CHECKED BY AUTHOR)
- 71) **DRI**: CAPRA.J.D. (1975) ADV.IMMUNOLOGY.20.1-40. (CHECKED BY AUTHOR)
- 72) **WAL**: CAPRA.J.D. (1975) ADV.IMMUNOLOGY.20.1-40. (CHECKED BY AUTHOR)
- 73) **GOL**: CAPRA.J.D. (1975) ADV.IMMUNOLOGY.20.1-40. (CHECKED BY AUTHOR)
- 74) **GAG**: CAPRA.J.D.,KEHOE.J.M.,WILLIAMS.R.C.,JR.,FEIZI.T. & KUNKEL.H.G. (1972) PROC.NAT.ACAD.SCI.USA.69.40-43. (CHECKED BY AUTHOR)
- 75) **DOB**: HOOD.L. & TALMAGE.D.W. (1970) SCIENCE.168.325-334.
- 76) **HSB**: HOOD.L.,GRAY.W.R.,SANDERS.B.G. & DREYER.W.J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL..32.133-145.
- 77) **HBJ12**: HOOD.L.,GRAY.W.R.,SANDERS.B.G. & DREYER.W.J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL..32.133-145.
- 78) **BUR(K)**: MOULINA. & FOUGEREAU.M. (1973) NATURE NEW BIOLOGY.246.176-178. (CHECKED BY AUTHOR)
- 79) **LEG**: MOULINA. & FOUGEREAU.M. (1973) NATURE NEW BIOLOGY.246.176-178. (CHECKED BY AUTHOR)
- 80) **BS**: MILSTEIN.C. (1969) FEBS LETTERS.2.301-304. (CHECKED BY AUTHOR)
- 81) **AMYLOID WR**: WESTERMARK.P.,SLETTEN.K.,PITKANEN.P.,NATVIG.J.B. & LINDHOLM.C.E. (1982) MOL.IMMUNOL..19.447-450. (CHECKED BY AUTHOR 06/01/83)
- 82) **VKAPPA3'CL**: BENTLEY.D.L. & RABBITTS.T.H. (1981) CELL.24.613-623. (CHECKED BY AUTHOR 12/07/81)

NOTES: HUMAN KAPPA LIGHT CHAINS SUBGROUP III

IDENTICAL SETS OF FRAMEWORK SEGMENTS:

- FR1: SET 1: TI[1],WOL[2],SIE[3],NG9'CL[4],NEU[5],GOT[6],PAY[7],SON[8],WEI[9],GAR[10],PIE[11],FLO[12],LOP[13],SCA[14],GLO[15],SAL[16],WIL[17],MAI[18],NIC[19],CUR[20],FR4[21],DRE[22],PER[23],CAM[24]. (24 IDENTICAL)
- SET 2: GJ[28],TAK[27]. (2 IDENTICAL)
- SET 3: RAD[29],DIL[30],CASI[31]. (3 IDENTICAL)
- SET 4: KEA[33],SMI[34]. (2 IDENTICAL HUMAN V-KAPPA-III; ALSO 1 MOUSE V-KAPPA-V: Vg'CL[122].)
- SET 5: DRE[22],PER[23],BRO'IGG[36]. (3 IDENTICAL)
- SET 6: CLA[42],SHE[43]. (2 IDENTICAL)
- FR2: SET 1: TI[1],WOL[2],SIE[3],NG9'CL[4],NEU[5],GOT[6],SON[8],GAR[10],PIE[11],FLO[12],GLO[15],CUR[20]. (12 IDENTICAL HUMAN V-KAPPA-III; ALSO 1 MOUSE V-KAPPA-IV: Vh'CL[12].) AND 1 MOUSE V-KAPPA-V: Vg'CL[122].)
- FR3: SET 1: TI[1],WOL[2]. (2 IDENTICAL)
- SET 2: GOT[6],PAY[7],GAR[10],PIE[11],FLO[12],GLO[15],CUR[20]. (7 IDENTICAL)
- FR4: SET 1: WOL[2],PAY[7],PIE[11],GLO[15],CUR[20],REE[57],VKAPPA3'CL[82]. (7 IDENTICAL HUMAN V-KAPPA-III; ALSO 3 HUMAN V-KAPPA-I: AU[2],GAL[138],CL[110]; 2 HUMAN V-KAPPA-II: GM 607'CL[5],RPM1-6410'CL[16]; AND 1 HUMAN V-KAPPA-IV: PB17IV'CL[3].)
- SET 2: POM[48]. (IDENTICAL TO 1 HUMAN V-KAPPA-I: HAU[4].)
- SET 3: NEU[5],GOT[6],GAR[10],FLO[12],FR4[21],IARC/BL41'CL[28]. (6 IDENTICAL HUMAN V-KAPPA-III; ALSO 3 HUMAN V-KAPPA-I: AGI[7],DEN[46],BI[63]; 2 HUMAN V-KAPPA-II: NIM[3],FRI[14]; AND 1 HUMAN V-KAPPA-IV: LEN[4].)
- SET 4: SON[8]. (IDENTICAL TO 1 HUMAN V-KAPPA-IV: VJICL[1].)

IDENTICAL SETS OF COMPLEMENTARITY DETERMINING REGIONS:

- CDR1: SET 1: SIE[3],IKE[38]. (2 IDENTICAL)
- SET 2: NG9'CL[4],PAY[7],SON[8],WEI[9],GAR[10],PIE[11],FLO[12],GLO[15],CUR[20],DRE[22],CAM[24]. (11 IDENTICAL)
- SET 3: TIL[39]. (IDENTICAL TO 1 MOUSE V-KAPPA-V: Vg'CL[122].)
- CDR2: SET 1: WOL[2],SIE[3],NEU[5],GOT[6],PAY[7],SON[8],GAR[10],PIE[11],FLO[12],GLO[15],CUR[20]. (11 IDENTICAL)
- SET 2: POM[48]. (IDENTICAL TO 1 MOUSE V-KAPPA-IV: Vh'CL[12].)
- CDR3: SET 1: POM[48]. (IDENTICAL TO 1 HUMAN V-KAPPA-I: LAY[39].)
- SET 2: GOT[6],CUR[20]. (2 IDENTICAL)
- SET 3: PAY[7],GLO[15]. (2 IDENTICAL)
- SET 4: GAR[10],FLO[12]. (2 IDENTICAL)

IDENTICAL SETS OF J-MINIGENES:

- SET 1: PIE[11],VKAPPA3'CL[82]. (2 IDENTICAL HUMAN V-KAPPA-III; ALSO 1 HUMAN V-KAPPA-I: AU[2]; 1 HUMAN V-KAPPA-II: RPM1-6410'CL[16]; AND 1 HUMAN V-KAPPA-IV: PB17IV'CL[3].)
- SET 2: GOT[6]. (IDENTICAL TO 1 HUMAN V-KAPPA-I: AGI[7].)
- SET 3: GAR[10],FLO[12],IARC/BL41'CL[28]. (3 IDENTICAL HUMAN V-KAPPA-III; ALSO 2 HUMAN V-KAPPA-I: DEN[46],BI[63]; AND 1 HUMAN V-KAPPA-II: FRI[14].)
- SET 4: WOL[2],CUR[20]. (2 IDENTICAL)
- SET 5: PAY[7],GLO[15]. (2 IDENTICAL)

SPECIFIC NOTES:

- 4) **NG9'CL**: THE AMINO ACID SEQUENCE IS TRANSLATED FROM THE NUCLEOTIDE SEQUENCE OF A CLONE OF HUMAN CDNA.
- 2) **MCE**: IT IS A CRYOIMMUNOGLOBULIN. THE AUTHORS ORIGINALLY DESIGNATED IT AS MCE. BUT IN ORDER TO DIFFERENTIATE IT FROM ANOTHER MCE SEQUENCED BY CAPRA ET AL., IT IS DENOTED AS MCE'.
- 42) **CLA**: THE AMINO ACID RESIDUES FOUND AT POSITION 9 WERE GLY AND ALA.
- 43) **SHE**: THE AMINO ACID RESIDUES FOUND AT POSITION 9 WERE GLY AND ALA.

NOTES: HUMAN KAPPA LIGHT CHAINS SUBGROUP III (cont'd)

- 44) JH: THE NAME WAS GIVEN TO US BY THE AUTHORS. IT IS NOT INCLUDED IN THE PAPER.
- 58) WE: AT POSITIONS 20,29 AND 33 OF AMINO ACID SEQUENCE WERE FOUND BOTH LEU AND ILE. IN THE SAME SEQUENCE TWO RESIDUES WERE FOUND IN POSITIONS 1,3,4,9,10,15,17,19,20,21,22 AND 29. THE SECOND RESIDUES WERE GLU,VAL,LEU,GLY,THR,PRO,GLU,ALA,THR,LEU,SER AND VAL, RESPECTIVELY. A DETERMINATION WAS NOT MADE IN THE ARTICLE AS TO WHETHER THE SEQUENCE BELONGED TO SUBGROUP I OR TO SUBGROUP III.
- 81) AMYLOID WR: AMINO ACID RESIDUES FOUND AT POSITION 54 ARE LEU AND ALA.
- 82) VKAPPA3'CL: THE AMINO ACID SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF CDNA FROM A MOUSE-HUMAN HYBRID CELL LINE.

HUMAN KAPPA LIGHT CHAINS SUBGROUP IV (cont'd)

| | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|------|---|-------------|
| | 0 | |
| - 1 | 15(ASP) | 1. |
| 2 | 14(ILE) | 2.1 |
| 3 | 15(VAL) | 1. |
| 4 | 13(MET) | 2.3 |
| 5 | 14(THR) | 2.1 |
| 6 | 15(GLN) | 1. |
| 7 | 14(SER) | 1. |
| 8 | 15(PRO) | 1. |
| 9 | 10(ASP) : 7(ASP) | 7.5 : 11. |
| FR 1 | 11(SER) | 2.4 |
| 11 | 14(LEU) | 1. |
| 12 | 14(ALA) | 1. |
| 13 | 14(VAL) | 1. |
| 14 | 11(SER) | 1. |
| 15 | 8(LEU) | 2.8 |
| 16 | 11(GLY) | 1. |
| 17 | 7(GLU) : 5(GLU) | 3.1 : 6.6 |
| 18 | 5(ARG) | 4.1 |
| 19 | 12(ALA) | 1. |
| 20 | 12(THR) | 1. |
| 21 | 9(ILE) | 4. |
| 22 | 7(ASN) : 4(+) | 5.1 : 9. |
| 23 | 10(CYS) | 1. |
| 24 | 5(LYS) | 6. |
| 25 | 5(SER) | 5.4 |
| 26 | 6(SER) | 2.3 |
| 27 | 7(GLN) : 6(GLN) | 1. : 2.3 |
| 27A | 5(SER) | |
| 27B | 6(VAL) | |
| 27C | 6(LEU) | |
| 27D | 5(TYR) | |
| 27E | 4(SER) | |
| 27F | 4(SER) | |
| 28 | 3(ASN) | 3.3 |
| 29 | 3(ASN) | 2.7 |
| 30 | 5(LYS) | 1. |
| 31 | 4(ASN) | 1. |
| 32 | 4(TYR) | 1. |
| 33 | 4(LEU) | 1. |
| 34 | 4(ALA) | 1. |
| 35 | 4(TRP) | 1. |
| 36 | 4(TYR) | 1. |
| 37 | 4(GLN) | 1. |
| 38 | 4(GLN) | 1. |
| 39 | 4(LYS) | 1. |
| 40 | 5(PRO) | 1. |
| 41 | 5(GLY) | 1. |
| 42 | 5(GLN) | 1. |
| 43 | 4(PRO) | 2.5 |
| 44 | 5(PRO) | 1. |
| 45 | 5(LYS) | 1. |
| 46 | 5(LEU) | 1. |
| 47 | 5(LEU) | 1. |
| 48 | 5(ILE) | 1. |
| 49 | 5(TYR) | 1. |
| 50 | 5(TRP) | 1. |
| 51 | 4(ALA) | 2.5 |
| 52 | 4(SER) | 2.5 |
| 53 | 4(THR) | 1. |
| 54 | 4(ARG) | 1. |
| 55 | 4(GLU) | 1. |
| 56 | 4(SER) | 1. |
| 57 | 4(GLY) | 1. |
| 58 | 4(VAL) | 1. |
| 59 | 4(PRO) | 1. |
| 60 | 4(ASP) | 1. |
| 61 | 4(ARG) | 1. |
| 62 | 4(PHE) | 1. |
| 63 | 5(SER) | 1. |
| 64 | 5(GLY) | 1. |
| 65 | 5(SER) | 1. |
| 66 | 5(GLY) | 1. |
| 67 | 5(SER) | 1. |
| 68 | 4(GLY) | 2.5 |
| 69 | 4(THR) | 1. |
| 70 | 4(ASP) | 1. |
| 71 | 4(PHE) | 1. |
| 72 | 4(THR) | 1. |
| 73 | 4(LEU) | 1. |
| 74 | 4(THR) | 1. |
| 75 | 4(ILE) | 1. |
| 76 | 4(SER) | 1. |
| 77 | 4(SER) | 1. |
| 78 | 4(LEU) | 1. |
| 79 | 4(GLN) | 1. |
| 80 | 4(ALA) | 1. |
| 81 | 4(GLU) | 1. |
| 82 | 4(ASP) | 1. |
| 83 | 4(VAL) | 1. |
| 84 | 4(ALA) | 1. |
| 85 | 4(VAL) | 1. |
| 86 | 4(TYR) | 1. |
| 87 | 4(TYR) | 1. |
| 88 | 4(CYS) | 1. |
| 89 | 4(GLN) | 1. |
| 90 | 4(GLN) | 1. |
| 91 | 4(TYR) | 1. |
| 92 | 3(TYR) | 2.7 |
| 93 | 2(SER) | 6. |
| 94 | 2(THR) | 6. |
| 95 | 4(PRO) | 1. |
| 95A | | |
| 95B | | |
| 95C | | |
| 95D | | |
| 95E | | |
| 95F | | |
| 96 | 1(+) | 4. |
| 97 | 2(THR) | 3. |
| 98 | 3(PHE) | 1. |
| 99 | 3(GLY) | 1. |
| 100 | 2(GLN) | 3. |
| 101 | 3(GLY) | 1. |
| 102 | 3(THR) | 1. |
| 103 | 3(LYS) | 1. |
| 104 | 2(+) | 4. |
| 105 | 4(GLU) | 1. |
| 106 | 4(ILE) | 1. |
| 106A | | |
| 107 | 3(LYS) | 2.7 |
| 108 | 3(ARG) | 1. |
| 109 | 1(THR) | |
| FR 2 | | |
| FR 3 | | |
| FR 4 | | |

ANTIBODY SPECIFICITIES: HUMAN KAPPA LIGHT CHAINS SUBGROUP IV

- 3) **PB17IV'CL:** ANTI-STREPTOCOCCUS GROUP A CARBOHYDRATE WITH SPECIFICITY FOR N-ACETYL GLUCOSAMINE
 5) **R.K.:** COLD AGGLUTININ WITH ANTI-PR1H ACTIVITY (RBC MEMBRANE ANTIGEN ON HUMAN ERYTHROCYTES INACTIVATED BY PROTEOLYTIC ENZYMES AND NEURAMINIDASE)
 6) **L.TH.:** COLD AGGLUTININ WITH ANTI-PR2 ACTIVITY (RBC MEMBRANE ANTIGEN ON HUMAN, RAT AND GUINEA PIG ERYTHROCYTES INACTIVATED BY PROTEOLYTIC ENZYMES AND NEURAMINIDASE)
 7) **TUR:** COLD AGGLUTININ WITH ANTI-PR ACTIVITY

REFERENCE: HUMAN KAPPA LIGHT CHAINS SUBGROUP IV

- 1) **VJ'CL:** KLOBECK,H.G.,BORNKAMMM,G.W.,COMBRIATO,G.,MOCIKAT,R.,POHLENZ,H.D. & ZACHAU,H.G. (1985) NUC.ACIDS RES.,13,6515-6529. (CHECKED BY AUTHOR 02/25/86)
 2) **VKAPPA IV GERMLINE'CL:** KLOBECK,H.G.,BORNKAMMM,G.W.,COMBRIATO,G.,MOCIKAT,R.,POHLENZ,H.D. & ZACHAU,H.G. (1985) NUC.ACIDS RES.,13, 6515-6529.
 3) **PB17IV'CL:** MARSH,P.,MILLS,F. & GOULD,H. (1985) NUC.ACIDS RES.,13,6531-6544. (CHECKED BY AUTHOR 03/19/86 WHO CORRECTED A MISPRINT IN THE ORIGINAL PAPER FOR RESIDUE 50)
 4) **LEN:** SCHNEIDER,M. & HILSCHMANN,N. (1974) Z.PHYSIOL.CHEM.,355,1164-1168. (CHECKED BY AUTHOR)
 5) **R.K.:** WANG,A.C.,FUDENBERG,H.H.,WELLS,J.V. & ROELCKE,D. (1973) NATURE NEW BIOLOGY,243,126-128. (CHECKED BY AUTHOR)
 6) **L.TH.:** WANG,A.C.,FUDENBERG,H.H.,WELLS,J.V. & ROELCKE,D. (1973) NATURE NEW BIOLOGY,243,126-128. (CHECKED BY AUTHOR)
 7) **TUR:** CAPRA,J.D.,KEHOE,J.M.,WILLIAMS,R.C.,JR.,FEI,ZI,T. & KUNKEL,H.G. (1972) PROC.NAT.ACAD.SCI.USA,69,40-43. (CHECKED BY AUTHOR)
 8) **AH:** PICK,A.I.,WANG,A.C.,FROHLICHMAN,R. & FUDENBERG,H.H. (1982) ACTA HAEMAT.,68,207-214. (CHECKED BY AUTHOR 05/26/83)
 9) **DA:** WANG,A.C.,ZHANG,H.S.,BONEWALD,L.,TUNG,E.,BOUVET,J.P. & LIACOPOULOS,P. (1985) MIAMI WINTER SYMP.,17,335-336. (CHECKED BY AUTHOR 02/25/86 WHO CORRECTED RESIDUES AS SHOWN)
 10) **DA-H:** BOUVET,J.P.,LIACOPOULOS,P.,PILLOT,J.,BANDA,R.,TUNG,E. & WANG,A.C. (1980) J.IMMUNOL.,125,213-220. (CHECKED BY AUTHOR 08/04/80); BOUVET,J.P.,LIACOPOULOS,P.,PILLOT,J.,BANDA,R.,TUNG,E. & WANG,A.C. (1982) J.IMMUNOL.,129,1519-1524.
 11) **DA-N:** BOUVET,J.P.,LIACOPOULOS,P.,PILLOT,J.,BANDA,R.,TUNG,E. & WANG,A.C. (1980) J.IMMUNOL.,125,213-220. (CHECKED BY AUTHOR 08/04/80); BOUVET,J.P.,LIACOPOULOS,P.,PILLOT,J.,BANDA,R.,TUNG,E. & WANG,A.C. (1982) J.IMMUNOL.,129,1519-1524.
 12) **JAH:** SLETTEN,K.,HANNESTAD,K. & HARBOE,M. (1974) SCAND.J.IMMUNOL.,3,219-222. (CHECKED BY AUTHOR 12/05/77)
 13) **SCH:** SLETTEN,K.,HANNESTAD,K. & HARBOE,M. (1974) SCAND.J.IMMUNOL.,3,219-222. (CHECKED BY AUTHOR 12/05/77)
 14) **JUV:** SLETTEN,K.,HANNESTAD,K. & HARBOE,M. (1974) SCAND.J.IMMUNOL.,3,219-222. (CHECKED BY AUTHOR 12/05/77)
 15) **AMYLOID GAB:** PRAS,M.,FRANGIONE,B. & FRANKLINE,C. (1980) IN AMYLOID AND AMYLOIDOSIS,G.G.GLENNER,P.P.E COSTA & F.DE FREITAS EDS., EXCEPTA MEDICA AMSTERDAM OXFORD-PRINCETON,249-252. (CHECKED BY AUTHOR 11/18/81)

NOTES: HUMAN KAPPA LIGHT CHAINS SUBGROUP IV**IDENTICAL SETS OF FRAMEWORK SEGMENTS:**

- FR1:** SET 1: VJ'CL[1],VKAPPA IV GERMLINE'CL[2],PB17IV'CL[3],R.K.[5]. (4 IDENTICAL)
 SET 2: LEN[4],R.K.[5]. (2 IDENTICAL)
 SET 3: DA[9],DA-H[10]. (2 IDENTICAL)
FR2: SET 1: VJ'CL[1],VKAPPA IV GERMLINE'CL[2],PB17IV'CL[3],LEN[4]. (4 IDENTICAL HUMAN V-KAPPA-IV; ALSO 2 HUMAN V-KAPPA-I; V19B'CL[88], V18B'CL[89]; 1 MOUSE V-KAPPA-I; MCPC603[47]; 30 MOUSE V-KAPPA-III; MPC11'CL[6],TEPC111[7],PC3741(NZB)[8],TEPC124[9], MOPC32[12],PC7043(NZB)[13],PC7183(NZB)[14],PC6308(NZB)[15],PC6684(NZB)[17],PC7940(NZB)[18],PC7175(NZB)[19], PC2485(NZB)[20],PC4039(NZB)[21],PC7210(NZB)[23],H36-15[26],2242[29],V-21E1.5KB'CL[30],V-21C9.5KB'CL[31], PC7481(NZB)[33],PC2980(NZB)[34],97.C(A,S,Y)[35],10.A(A,TH)[39],H36-5[48],40.C(A,TH)[52],MOPC63[54],ABPC2[55], PC9245(NZB)[56],PC4050(NZB)[57],V-21B16KB'CL[58],11949[62]; 1 MOUSE V-KAPPA-VI; BFPC61A'CL[64]; AND 15 RABBIT V-KAPPA: K9-335-[19],3368[20],BS-538[21],BS-1[39],K49-501[45],3547[47],K4820[57],K30-267[61],311[65],4422[66],17D9'CL[68], 4192[71],4363[85],120[103],K-25[112].)
FR3: SET 1: VJ'CL[1],VKAPPA IV GERMLINE'CL[2],PB17IV'CL[3],LEN[4]. (4 IDENTICAL)
FR4: SET 1: PB17IV'CL[3]. (IDENTICAL TO 3 HUMAN V-KAPPA-I; AU[2],GAL[1][36],CL*[110]; 2 HUMAN V-KAPPA-II; GM 607'CL[5], RPM1-6410'CL[16]; AND 7 HUMAN V-KAPPA-III; WOU[2],PAY[7],PIE[11],GLO[15],CUR[20],REE[57],VKAPPA3'CL[82].)
 SET 2: LEN[4]. (IDENTICAL TO 3 HUMAN V-KAPPA-I; AG[7],DEN[46],BI[63]; 2 HUMAN V-KAPPA-II; NIM[3],FR[14]; AND 6 HUMAN V-KAPPA-III; NEU[5],GOT[6],GAR[10],FLO[12],FR4[21],IARC[BL41]'CL[28].)
 SET 3: VJ'CL[1]. (IDENTICAL TO 1 HUMAN V-KAPPA-III; SON[8].)

IDENTICAL SETS OF COMPLEMENTARITY DETERMINING REGIONS:

- CDR1:** SET 1: VJ'CL[1],VKAPPA IV GERMLINE'CL[2]. (2 IDENTICAL)
CDR2: SET 1: VJ'CL[1],VKAPPA IV GERMLINE'CL[2],PB17IV'CL[3],LEN[4]. (4 IDENTICAL HUMAN V-KAPPA-IV; ALSO 1 MOUSE V-KAPPA-VI; KPN16'CL[70].)
CDR3:

IDENTICAL SETS OF J-MINIGENES:

- SET 1: PB17IV'CL[3]. (IDENTICAL TO 1 HUMAN V-KAPPA-I; AU[2]; 1 HUMAN V-KAPPA-II; RPM1-6410'CL[16]; AND 2 HUMAN V-KAPPA-III; PIE[11],VKAPPA3'CL[82].)

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|---------------|
| 22 | (SER,ASP,ASN) |
| 96 | (TRP,TYR) |
| 104 | (LEU,VAL) |

HUMAN LAMBDA LIGHT CHAINS SUBGROUP I (cont'd)

| | 24 FUL # | # OF SEQUENCES | # OF AMINO ACIDS | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|------|----------|----------------|------------------|---------------------------------------|-------------|
| 0 | | 20 | 2 | 19(PCA) | 2.1 |
| 1 | | 20 | 1 | 20(SER) | 1. |
| 2 | | 21 | 2 | 20(VAL) | 2.1 |
| 3 | | 21 | 1 | 21(LEU) | 1. |
| 4 | | 22 | 1 | 22(THR) | 1. |
| 5 | | 21 | 1 : 2 | 21(GLN) : 20(GLN) | 1. : 2.1 |
| 6 | | 21 | 1 | 21(PRO) | 1. |
| 7 | | 21 | 1 | 21(PRO) | 1. |
| 8 | | 21 | 1 | 21(SER) | 1. |
| 9 | | 21 | 1 | 21(SER) | 1. |
| 10 | | 21 | 3 | 11(ALA) | 5.7 |
| 11 | | 22 | 1 | 22(SER) | 1. |
| 12 | | 22 | 2 | 16(GLY) | 2.8 |
| 13 | | 22 | 3 | 11(THR) | 6. |
| 14 | | 21 | 2 | 20(PRO) | 2.1 |
| 15 | | 21 | 1 | 21(GLY) | 1. |
| 16 | | 21 | 2 | 20(GLN) : 19(GLN) | 2.1 : 2.2 |
| 17 | | 21 | 6 | 14(ARG) | 9. |
| 18 | | 20 | 2 | 19(VAL) | 2.1 |
| 19 | | 20 | 4 | 16(THR) | 5. |
| 20 | | 19 | 2 | 18(ILE) | 2.1 |
| 21 | | 19 | 2 | 18(SER) | 2.1 |
| 22 | | 19 | 1 | 19(CYS) | 1. |
| 23 | CYS | 18 | 3 | 15(SER) | 3.8 |
| 24 | SER | 18 | 1 | 18(GLY) | 1. |
| 25 | GLY | 17 | 3 | 13(SER) | 3.9 |
| 26 | ASN | 16 | 5 | 12(SER) | 6.7 |
| 27 | SER | 15 | 3 | 12(SER) | 1. |
| 27A | --- | 15 | 3 | 12(ASN) | 1. |
| 27B | --- | 15 | 3 | 2(ILE) | 7.5 |
| 27C | --- | 15 | 5 | 10(ILE) | 7.5 |
| 27D | SER | 14 | 3 | 12(GLY) | 3.5 |
| 27E | SER | 14 | 7 | 4(SER) | 25. |
| 27F | SER | 14 | 4 | 11(ASN) | 5.1 |
| 28 | | 14 | 6 | 5(TYR) | 17. |
| 29 | | 14 | 1 | 14(VAL) | 1. |
| 30 | | 14 | 7 | 4(+) | 25. |
| 31 | | 14 | 1 | 14(TRP) | 1. |
| 32 | | 14 | 2 | 13(TYR) | 2.2 |
| 33 | | 14 | 3 | 2(GLN) | 3.5 |
| 34 | | 14 | 3 | 9(GLN) | 4.7 |
| 35 | | 14 | 4 | 9(LEU) | 6.2 |
| 36 | | 14 | 1 | 14(PRO) | 1. |
| 37 | | 14 | 1 | 14(GLY) | 1. |
| 38 | | 14 | 3 | 12(THR) | 3.5 |
| 39 | | 14 | 2 | 13(ALA) | 2.2 |
| 40 | | 14 | 1 | 14(PRO) | 1. |
| 41 | | 14 | 2 | 13(LYS) | 2.2 |
| 42 | | 14 | 1 | 14(LEU) | 1. |
| 43 | | 14 | 2 | 13(LEU) | 2.2 |
| 44 | | 14 | 2 | 13(ILE) | 2.2 |
| 45 | | 14 | 2 | 12(TYR) | 2.3 |
| 46 | | 14 | 2 | 12(TYR) | 2.3 |
| 47 | | 14 | 6 | 4(SER) | 28. |
| 48 | | 14 | 3 | 8(ASN) | 5.3 |
| 49 | | 14 | 5 | 6(GLN) | 12. |
| 50 | | 14 | 3 | 12(ARG) | 3.5 |
| 51 | | 14 | 3 | 10(PRO) | 3.6 |
| 52 | | 14 | 1 | 12(SER) | 1. |
| 53 | | 12 | 1 | 12(GLY) | 1. |
| 54 | | 12 | 2 | 9(VAL) | 2.7 |
| 55 | | 12 | 2 | 10(PRO) | 2.4 |
| 56 | | 12 | 2 | 11(ASP) | 2.2 |
| 57 | | 13 | 1 | 13(ARG) | 1. |
| 58 | | 14 | 2 | 12(PHE) | 2.3 |
| 59 | | 14 | 1 | 14(SER) | 1. |
| 60 | | 14 | 3 | 9(GLY) | 4.7 |
| 61 | | 14 | 1 | 14(SER) | 1. |
| 62 | | 14 | 1 | 14(LYS) | 1. |
| 63 | | 14 | 1 | 14(SER) | 1. |
| 64 | | 14 | 1 | 14(GLY) | 1. |
| 65 | | 14 | 3 | 12(THR) | 3.5 |
| 66 | | 14 | 1 | 14(SER) | 1. |
| 67 | | 14 | 1 | 14(SER) | 1. |
| 68 | | 14 | 1 | 14(GLY) | 1. |
| 69 | | 14 | 3 | 12(THR) | 3.5 |
| 70 | | 14 | 1 | 14(SER) | 1. |
| 71 | | 14 | 1 | 14(ALA) | 1. |
| 72 | | 14 | 2 | 9(SER) | 3.1 |
| 73 | | 14 | 1 | 14(LEU) | 1. |
| 74 | | 14 | 2 | 11(ALA) | 2.5 |
| 75 | | 14 | 1 | 14(ILE) | 1. |
| 76 | | 14 | 2 | 9(SER) | 3.1 |
| 77 | | 14 | 1 | 14(GLY) | 1. |
| 78 | | 14 | 1 | 14(LEU) | 1. |
| 79 | | 14 | 4 | 9(GLN) | 6.2 |
| 80 | | 14 | 4 | 8(SER) | 7. |
| 81 | | 14 | 2 | 10(GLU) | 2.8 |
| 82 | | 14 | 2 | 13(ASP) | 2.2 |
| 83 | | 14 | 1 | 14(GLU) | 1. |
| 84 | | 14 | 3 | 11(ALA) | 3.8 |
| 85 | | 14 | 3 | 12(ASP) | 3.5 |
| 86 | | 14 | 1 | 14(TYR) | 1. |
| 87 | | 14 | 3 | 11(TYR) | 3.8 |
| 88 | | 14 | 1 | 14(CYS) | 1. |
| 89 | | 14 | 3 | 10(ALA) | 4.2 |
| 90 | | 14 | 3 | 7(THR) | 6. |
| 91 | | 14 | 2 | 12(TRP) | 2.3 |
| 92 | | 14 | 2 | 12(ASP) | 2.3 |
| 93 | | 14 | 5 | 8(ASP) | 8.8 |
| 94 | | 14 | 2 | 12(SER) | 2.3 |
| 95 | | 14 | 2 | 13(LEU) | 2.2 |
| 95A | | 11 | 3 | 6(ASP) | 1. |
| 95B | | 11 | 4 | 6(GLY) | 1. |
| 95C | | 11 | 4 | 6(GLY) | 1. |
| 95D | | 11 | 4 | 6(GLY) | 1. |
| 95E | | 11 | 4 | 6(GLY) | 1. |
| 95F | | 11 | 4 | 6(GLY) | 1. |
| 96 | | 14 | 7 | 6(PRO) | 16. |
| 97 | | 14 | 3 | 12(VAL) | 3.5 |
| 98 | | 14 | 1 | 14(PHE) | 1. |
| 99 | | 14 | 1 | 14(GLY) | 1. |
| 100 | | 14 | 2 | 13(GLY) | 2.2 |
| 101 | | 14 | 1 | 14(GLY) | 1. |
| 102 | | 14 | 1 | 14(THR) | 1. |
| 103 | | 14 | 5 | 10(LYS) | 7. |
| 104 | | 14 | 2 | 7(+) | 4. |
| 105 | | 14 | 1 | 14(THR) | 1. |
| 106 | | 14 | 1 | 14(VAL) | 1. |
| 106A | | 14 | 3 | 12(LEU) | 1. |
| 107 | | 14 | 3 | 11(GLY) | 3.8 |
| 108 | | 12 | 1 | 12(GLN) | 1. |
| 109 | | 12 | 1 | 12(PRO) | 1. |

ANTIBODY SPECIFICITIES: HUMAN LAMBDA LIGHT CHAINS SUBGROUP I

- 1) **NEWM:** ANTI-3-(3'-HYDROXY-3',7',11',15'-TETRAMETHYL HEXADECYL) 2-METHYL 1,4 NAPHTHOQUINONE(VIT.K10H)
 16) **KOH:** ANTI-HUMAN GAMMA G GLOBULIN

REFERENCE: HUMAN LAMBDA LIGHT CHAINS SUBGROUP I

- 1) **NEWM:** CHEN,B.L. & POLJAK,R.J. (1974) BIOCHEMISTRY,13,1295-1302. (CHECKED BY AUTHOR 01/24/78)
 2) **HA:** SHINODA,T.,TITANI,K. & PUTNAM,F.W. (1970) J.BIOL.CHEM.,245,4475-4487. (CHECKED BY AUTHOR 06/15/83)
 3) **LR:** CAULIN-GLASER,T.,PRELLI,F. & FRANKLIN,E.C. (1982) J.LAB.CLIN.MED.,99,845-851. (CHECKED BY AUTHOR 12/10/82)
 4) **NIG-64:** TONOIKE,H.,KAMETANI,F.,HOSHI,A.,SHINODA,T. & ISOBET,T. (1985) BIOCHEM.BIOPHYS.RES.COMMUN.,126,1228-1234.
 5) **NEW:** LANGER,B.,STEINMETZ-KAYNE,M. & HILSCHMANN,N. (1968) Z.PHYSIOL.CHEM.,349,945-951.
 6) **BL2 'CL:** TSUJIMOTO,Y. & CROCE,C.M. (1984) NUC.ACIDS RES.,12,8407-8414.
 7) **WAH:** TAKAHASHI,Y.,TAKAHASHI,N.,TETAERT,D. & PUTNAM,F.W. (1983) PROC.NAT.ACAD.SCI.USA,80,3686-3690. (CHECKED BY AUTHOR 06/15/83)
 8) **NIG-77:** TONOIKE,H.,KAMETANI,F.,HOSHI,A.,SHINODA,T. & ISOBET,T. (1985) BIOCHEM.BIOPHYS.RES.COMMUN.,126,1228-1234.
 9) **VOR:** ENGELHARD,M.,HESS,M. & HILSCHMANN,N. (1974) Z.PHYSIOL.CHEM.,355,85-88; ENGELHARD,M. & HILSCHMANN,N. (1975) Z.PHYSIOL.CHEM.,356,1413-1444.
 10) **RHE:** FUREY,W. JR.,WANG,B.C.,YOO,C.S. & SAX,M. (1983) J.MOL.BIOL.,167,661-692. (CHECKED BY AUTHOR 05/15/84)
 11) **LOC:** ZHU,D.,KIM,H.S. & DEUTSCH,H.F. (1983) MOL.IMMUNOL.,20,1107-1116.
 12) **OKA:** ZHU,D.,KIM,H.S. & DEUTSCH,H.F. (1983) MOL.IMMUNOL.,20,1107-1116.
 13) **AMYLOID EPS:** TOFT,K.G.,SLETTEN,K. & HUSBY,G. (1985) BIOL.CHEM.HOPPE-SEYLER,366,617-625.
 14) **HBJ7:** HOOD,L.,GRAY,W.R.,SANDERS,B.G. & DREYER,W.J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL.,32,133-145.
 15) **COX:** ZHU,D.,KIM,H.S. & DEUTSCH,H.F. (1983) MOL.IMMUNOL.,20,1107-1116.
 16) **KOH:** KAPLAN,A.P. & METZGER,H. (1969) BIOCHEMISTRY,8,3944-3951.
 17) **HS92:** HOOD,L. & EIN,D. (1968) NATURE,220,764-767; (1968) SCIENCE,166,679-681.
 18) **HS78:** HOOD,L. & EIN,D. (1968) NATURE,220,764-767; (1968) SCIENCE,166,679-681.
 19) **NIG-51:** TAKAHASHI,N.,TAKAYASU,T.,SHINODA,T.,ITO,S.,OKUYAMA,T. & SHIMIZU,A. (1980) BIOMED.RES.,1,321-333. (CHECKED BY AUTHOR 01/28/81)
 20) **HS94:** HOOD,L. & EIN,D. (1968) NATURE,220,764-767; (1968) SCIENCE,166,679-681.
 21) **HBJ11:** HOOD,L.,GRAY,W.R.,SANDERS,B.G. & DREYER,W.J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL.,32,133-145.
 22) **BJ98:** BAGLIONI,C. (1967) BIOCHEM.BIOPHYS.RES.COMMUN.,26,82-89.
 23) **MZ:** MILSTEIN,C.,FRANGIONE,B. & PINK,J.R.L. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL.,32,31-36. (CHECKED BY AUTHOR 10/17/77)
 24) **FUL:** SOX,H.C.,JR. & HOOD,L. (1970) PROC.NAT.ACAD.SCI.USA,66,975-982.

NOTES: HUMAN LAMBDA LIGHT CHAINS SUBGROUP I

IDENTICAL SETS OF FRAMEWORK SEGMENTS:

- FR1: SET 1: WAH[7],NIG-77[8],VOR[9],RHE[10],LOC[11],OKA[12]. (6 IDENTICAL)
 FR2: SET 1: NEWM[1],AMYLOID EPS[13]. (2 IDENTICAL)
 SET 2: HA[2],NIG-64[4]. (2 IDENTICAL)
 SET 3: NIG-77[8],LOC[11]. (2 IDENTICAL)
 FR3: SET 1: NIG-64[4],BL2 'CL[6]. (2 IDENTICAL)
 FR4: SET 1: NEWM[1]. (IDENTICAL TO 1 HUMAN V-LAMBDA-II: WHI[3]; AND 1 HUMAN V-LAMBDA-V: BOI[1])
 SET 2: NEW[5],VOR[9],COX[15]. (3 IDENTICAL HUMAN V-LAMBDA-I; ALSO 1 HUMAN V-LAMBDA-VI: AMYLOID-AR[1]; AND 6 MOUSE V-LAMBDA: MOPC315[25],TEPC952[26],MA8-13[27],5-7[29],MOPC315-26'CL[30],MOPC315-37'CL[32].)
 SET 3: BL2 'CL[6],RHE[10],OKA[12],NIG-51[19]. (4 IDENTICAL HUMAN V-LAMBDA-I; ALSO 5 HUMAN V-LAMBDA-II: MES[2],ES492[8],TRO[14], VIL[17],WIN[21]; 4 HUMAN V-LAMBDA-III: HIL[1],CAI[4],BAU[12],DEL[14]; 1 HUMAN V-LAMBDA-IV: SHI[1]; 3 HUMAN V-LAMBDA-VI: SUT[2],THO[4],LBV'CL[5]; AND 24 MOUSE V-LAMBDA: MOPC104E[1],J558[2],XS104[3],HOPC[4],J698[5],H206[16],W3159[7], Y543[18],Y5485[9],Y5830[10],Y5669[11],MOPC511(L)[12],S178[13],Y5444[14],Y5606[15],S176[16],H2020[17],RPC20[18],IG 303LAMBDA'CL[19],S43'CL[21],S2H5'CL[38],S2E9'CL[39],S1F12'CL[40],IG 25LAMBDA'CL[41].)
 SET 4: LOC[11]. (IDENTICAL TO 1 HUMAN V-LAMBDA-V: MCG[3].)

IDENTICAL SETS OF COMPLEMENTARITY DETERMINING REGIONS:

- CDR1:
 CDR2: SET 1: NIG-64[4],BL2 'CL[6]. (2 IDENTICAL)
 CDR3: SET 1: VOR[9],NIG-51[19]. (2 IDENTICAL)

IDENTICAL SETS OF J-MINIGENES:

- SET 1: NEW[5]. (IDENTICAL TO 1 HUMAN V-LAMBDA-VI: AMYLOID-AR[1].)
 SET 2: BL2 'CL[6]. (IDENTICAL TO 2 HUMAN V-LAMBDA-VI: SUT[2],THO[4]; AND 24 MOUSE V-LAMBDA: MOPC104E[1],J558[2],XS104[3],HOPC[4], J698[5],H206[16],W3159[7],Y543[18],Y5485[9],Y5830[10],Y5669[11],MOPC511(L)[12],S178[13],Y5444[14],Y5606[15],S176[16], H2020[17],RPC20[18],IG 303LAMBDA'CL[19],S43'CL[21],S2H5'CL[38],S2E9'CL[39],S1F12'CL[40],IG 25LAMBDA'CL[41].)
 SET 3: VOR[9],COX[15]. (2 IDENTICAL)
 SET 4: OKA[12],NIG-51[19]. (2 IDENTICAL)

SPECIFIC NOTES:

- 24) **FUL:** SOX AND HOOD HAVE REPORTED FOUR HUMAN V KAPPA AND ONE V LAMBDA CHAINS WITH ASN-SER/THR TO CONTAIN CARBOHYDRATE.

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|-----------|
| 34 | (SER,ASN) |
| 104 | (LEU,VAL) |

HUMAN LAMBDA LIGHT CHAINS SUBGROUP II (cont'd)

| | 25 WAL | 26 4A CL | # OF SEQUENCES | # OF AMINO ACIDS | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|------|-----------|----------------|-------------------|------------------------|---|-------------|
| 0 | --- | --- | | | | |
| 1 | PCA | gln | 26 | 3 | 24(PCA) | 3.3 |
| 2 | SER | thr | 26 | 2 | 25(SER) | 2.1 |
| 3 | val | val | 26 | 3 | 23(ALA) | 3.4 |
| 4 | LEU | val | 26 | 2 | 25(LEU) | 2.1 |
| 5 | THR | THR | 26 | 3 | 23(THR) | 3.4 |
| 6 | GLN | GLN | 26 | 1 | 26(GLN) : 25(GLN) | 1. : 2.1 |
| 7 | PRO | gln | 26 | 3 | 24(PRO) | 3.3 |
| 8 | pro | --- | 26 | 3 | 18(ALA) | 4.3 |
| 9 | SER | SER | 26 | 2 | 25(SER) | 2.1 |
| 10 | --- | --- | | | | |
| 11 | ala | leu | 26 | 3 | 23(VAL) | 3.4 |
| 12 | SER | thr | 26 | 2 | 25(SER) | 2.1 |
| 13 | GLY | val | 26 | 4 | 23(GLY) | 4.5 |
| 14 | thr | SER | 26 | 2 | 25(SER) | 2.1 |
| 15 | PRO | PRO | 26 | 2 | 25(PRO) | 2.1 |
| 16 | GLY | GLY | 26 | 1 | 26(GLY) | 1. |
| 17 | GLN | GLN | 26 | 4 | 23(GLN) | 4.5 |
| 18 | arg | thr | 26 | 3 | 23(SER) | 3.4 |
| 19 | --- | val | 25 | 3 | 18(ILE) | 4.2 |
| 20 | --- | THR | 25 | 1 | 25(THR) | 1. |
| 21 | --- | leu | 19 | 3 | 17(ILE) | 3.4 |
| 22 | --- | thr | 18 | 2 | 17(SER) | 2.1 |
| 23 | --- | CYS | 18 | 1 | 18(CYS) | 1. |
| 24 | --- | ALA | 15 | 4 | 9(THR) | 6.7 |
| 25 | --- | SER | 15 | 2 | 14(GLY) | 2.1 |
| 26 | --- | SER | 15 | 5 | 10(THR) | 7.5 |
| 27 | --- | THR | 15 | 5 | 7(SER) | 11. |
| 27A | --- | --- | | | | |
| 27B | --- | --- | | | | |
| 27C | --- | --- | | | | |
| 27D | --- | GLY | 15 | 4 | 12(SER) | |
| 27E | --- | ALA | 15 | 2 | 11(ASP) | |
| 27F | --- | VAL | 15 | 2 | 14(VAL) | |
| 28 | --- | THR | 15 | 5 | 10(GLY) | 7.5 |
| 29 | --- | SER | 14 | 5 | 6(GLY) | 12. |
| 30 | --- | GLY | 14 | 6 | 9(TYR) | 9.3 |
| 31 | --- | TYR | 14 | 7 | 8(ASN) : 7(ASN) | 12. : 14. |
| 32 | --- | TYR | 14 | 5 | 5(TYR) | 14. |
| 33 | --- | PRO | 13 | 3 | 1(VAL) | 3.5 |
| 34 | --- | ASN | 13 | 2 | 12(SER) | 2.2 |
| 35 | --- | TRP | 14 | 1 | 14(TRP) | 1. |
| 36 | --- | PHE | 14 | 1 | 10(TYR) | 2.8 |
| 37 | --- | ASN | 14 | 2 | 14(GLN) : 13(GLN) | 1. : 2.2 |
| 38 | --- | GLN | 14 | 2 | 13(GLN) : 12(GLN) | 2.2 : 3.5 |
| 39 | --- | LYS | 14 | 5 | 10(HIS) | 7. |
| 40 | --- | PRO | 14 | 1 | 14(PRO) | 1. |
| 41 | --- | GLY | 14 | 2 | 13(GLY) | 2.2 |
| 42 | --- | GLN | 14 | 4 | 11(LYS) | 5.1 |
| 43 | --- | ALA | 14 | 2 | 13(ALA) | 2.2 |
| 44 | --- | PRO | 14 | 1 | 14(PRO) | 1. |
| 45 | --- | ARG | 14 | 3 | 13(LYS) | 2.2 |
| 46 | --- | ALA | 14 | 3 | 12(LEU) | 3.5 |
| 47 | --- | LEU | 14 | 3 | 5(-) | 8.4 |
| 48 | --- | ILE | 14 | 1 | 14(ILE) | 1. |
| 49 | --- | TYR | 14 | 3 | 9(TYR) | 4.7 |
| 50 | --- | SER | 14 | 5 | 7(ASP) | 10. |
| 51 | --- | THR | 14 | 4 | 11(VAL) | 5.1 |
| 52 | --- | SER | 14 | 5 | 5(SER) | 14. |
| 53 | --- | ASN | 14 | 6 | 4(-) | 21. |
| 54 | --- | LYS | 14 | 2 | 13(ARG) | 2.2 |
| 55 | --- | HIS | 14 | 2 | 13(PRO) | 2.2 |
| 56 | --- | SER | 14 | 1 | 14(SER) | 1. |
| 57 | --- | TRP | 14 | 2 | 13(GLY) | 2.2 |
| 58 | --- | THR | 14 | 3 | 10(VAL) | 4.2 |
| 59 | --- | PRO | 14 | 2 | 7(+) | 4. |
| 60 | --- | ALA | 14 | 7 | 5(ASP) | 20. |
| 61 | --- | ARG | 14 | 1 | 14(ARG) | 1. |
| 62 | --- | PHE | 15 | 2 | 14(PHE) | 2.1 |
| 63 | --- | SER | 15 | 1 | 15(SER) | 1. |
| 64 | --- | GLY | 15 | 1 | 15(GLY) | 1. |
| 65 | --- | SER | 15 | 1 | 15(SER) | 1. |
| 66 | --- | LEU | 15 | 3 | 13(LYS) | 3.5 |
| 67 | --- | LEU | 14 | 2 | 13(SER) | 2.2 |
| 68 | --- | GLY | 14 | 2 | 12(GLY) | 2.3 |
| 69 | --- | GLY | 14 | 4 | 10(ASN) : 9(ASN) | 5.6 : 6.2 |
| 70 | --- | LYS | 14 | 3 | 12(THR) | 3.5 |
| 71 | --- | ALA | 14 | 1 | 14(ALA) | 1. |
| 72 | --- | ALA | 14 | 2 | 13(SER) | 2.2 |
| 73 | --- | LEU | 14 | 1 | 14(LEU) | 1. |
| 74 | --- | THR | 14 | 1 | 14(THR) | 1. |
| 75 | --- | LEU | 14 | 2 | 13(ILE) | 2.2 |
| 76 | --- | SER | 14 | 1 | 14(SER) | 1. |
| 77 | --- | GLY | 14 | 2 | 14(GLY) | 1. |
| 78 | --- | VAL | 14 | 2 | 13(LEU) | 2.2 |
| 79 | --- | GLN | 14 | 3 | 12(GLN) | 3.5 |
| 80 | --- | PRO | 14 | 3 | 10(ALA) | 4.2 |
| 81 | --- | GLU | 14 | 3 | 11(GLU) | 3.8 |
| 82 | --- | ASP | 14 | 2 | 13(ASP) | 2.2 |
| 83 | --- | GLU | 14 | 1 | 14(GLU) | 1. |
| 84 | --- | ALA | 14 | 1 | 14(ALA) | 1. |
| 85 | --- | GLU | 14 | 3 | 11(ASP) : 10(ASP) | 3.8 : 5.6 |
| 86 | --- | TYR | 14 | 1 | 14(TYR) | 1. |
| 87 | --- | TYR | 14 | 2 | 12(TYR) | 2.3 |
| 88 | --- | CYS | 14 | 1 | 14(CYS) | 1. |
| 89 | --- | LEU | 14 | 4 | 8(SER) | 7. |
| 90 | --- | LEU | 14 | 2 | 13(SER) | 2.2 |
| 91 | --- | TYR | 14 | 2 | 12(TYR) | 2.3 |
| 92 | --- | TYR | 14 | 7 | 5(ALA) | 20. |
| 93 | --- | GLY | 14 | 4 | 7(GLY) | 8. |
| 94 | --- | GLY | 14 | 5 | 5(SER) | 14. : 17. |
| 95 | --- | ALA | 13 | 7 | 3(+) | 30. |
| 95A | --- | --- | 11 | 3 | 5(+) | |
| 95B | --- | --- | 2 | 2 | 1(+) | |
| 95C | --- | --- | | | | |
| 95D | --- | --- | | | | |
| 95E | --- | --- | | | | |
| 95F | --- | --- | | | | |
| 96 | --- | --- | 13 | 8 | 5(VAL) | 21. |
| 97 | VAL | --- | 16 | 3 | 10(VAL) | 4.8 |
| 98 | PHE | --- | 16 | 1 | 16(PHE) | 1. |
| 99 | GLY | --- | 18 | 1 | 18(GLY) | 1. |
| 100 | SER | --- | 18 | 4 | 10(GLY) | 7.2 |
| 101 | GLY | --- | 18 | 1 | 18(GLY) | 1. |
| 102 | THR | --- | 18 | 1 | 18(THR) | 1. |
| 103 | LYS | --- | 18 | 5 | 13(LYS) | 6.9 |
| 104 | VAL | --- | 15 | 2 | 9(LEU) | 3.3 |
| 105 | THR | --- | 15 | 3 | 13(THR) | 3.5 |
| 106 | --- | --- | 13 | 1 | 13(VAL) | 1. |
| 106A | --- | --- | 13 | 1 | 13(LEU) | 1. |
| 107 | --- | --- | 13 | 3 | 8(GLY) | 4.9 |
| 108 | --- | --- | 10 | 1 | 10(GLN) : 9(GLN) | 1. : 2.2 |
| 109 | --- | --- | 10 | 1 | 10(PRO) | 1. |

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NOTES: HUMAN LAMBDA LIGHT CHAINS SUBGROUP II

IDENTICAL SETS OF FRAMEWORK SEGMENTS:

- FR1: SET 1: NIG-84[1],MES[2],WH[3],NEI[4],KAR[5],RIM[6],SLA[7]. (7 IDENTICAL)
 SET 2: TRO[14],BOH[15]. (2 IDENTICAL)
- FR2: SET 1: WH[3],BOH[15],NIG-58[16],BUR[22]. (4 IDENTICAL)
- FR3:
- FR4: SET 1: WH[3]. (IDENTICAL TO 1 HUMAN V-LAMBDA-I: NEWM[1]; AND 1 HUMAN V-LAMBDA-V: BOI[1].)
 SET 2: MES[2],ES492[8],TRO[14],VIL[17],WINI[21]. (5 IDENTICAL HUMAN V-LAMBDA-I; ALSO 4 HUMAN V-LAMBDA-I: BL2 [CL]6],RHE[10], OKAI[12],NIG-51[19]; 4 HUMAN V-LAMBDA-III: HIL[1],CAP[4],BAUI[12],DEL[14]; 1 HUMAN V-LAMBDA-IV: SH[1]; 3 HUMAN V-LAMBDA-VI: SU[2],THO[4],LBV[5]; AND 24 MOUSE V-LAMBDA: MOPC104E[1],J558[2],XS104[3],HOPC114[4],J698[5],H206[6], WS159[7],Y543[8],Y548[9],Y5830[10],Y5869[11],MOPC511[12],S178[13],Y5444[14],Y5606[15],S176[16],H2020[17], RPC20[18],IG_30[LAMBDA-CL][19],S43[CL][21],S2H5[CL][38],S2E9[CL][39],S1F12[CL][40],IG_25[LAMBDA-CL][41].)
 SET 3: NIG-84[1]. (IDENTICAL TO 1 HUMAN V-LAMBDA-III: GARI[7].)

IDENTICAL SETS OF COMPLEMENTARITY DETERMINING REGIONS:

- CDR1: SET 1: MES[2],VIL[17]. (2 IDENTICAL HUMAN V-LAMBDA-II; ALSO 1 HUMAN V-LAMBDA-V: MCG[3].)
 CDR2: SET 1: NIG-84[1],TOG[10]. (2 IDENTICAL)
- CDR3:

IDENTICAL SETS OF J-MINIGENES:

- SET 1: MES[2],TRO[14]. (2 IDENTICAL HUMAN V-LAMBDA-II; ALSO 1 HUMAN V-LAMBDA-III: BAUI[12].)
 SET 2: ES492[8],VIL[17]. (2 IDENTICAL HUMAN V-LAMBDA-II; ALSO 1 HUMAN V-LAMBDA-III: DEL[14].)

SPECIFIC NOTES:

- 1) **SM:** IT HAS O-LINKED CARBOHYDRATE ATTACHED TO SER AT POSITION 22 AND N-LINKED CARBOHYDRATE ATTACHED TO ASX AT POSITION 25.

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|-----------|
| 47 | (ILE,MET) |
| 53 | (LYS,ASN) |
| 59 | (PRO,SER) |
| 95 | (SER,ASN) |
| 95A | (THR,SER) |
| 95B | (LEU,ARG) |

HUMAN LAMBDA LIGHT CHAINS SUBGROUP III (cont'd)

| | 23 SG | 24 GIM | 25 111 | 26 119 | 27 VIN | 28 MIL | # OF SEQUENCES | # OF AMINO ACIDS | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|------|----------|-----------|-----------|-----------|-----------|-----------|-------------------|------------------------|---|-------------|
| | --- | --- | --- | --- | --- | | 12 | 3 | 10(SER) | 3.6 |
| 1 | tyr | --- | --- | --- | tyr | | 27 | 2 | 26(TYR) | 2.1 |
| 2 | tyr | tyr | tyr | tyr | | | 26 | 6 : 7 | 13(GLU) : 11(GLU) | 12. : 17. |
| 3 | val | val | tyr | tyr | | | 26 | 2 | 25(LEU) | 2.1 |
| 4 | leu | leu | leu | leu | | | 26 | 3 | 23(THR) | 3.4 |
| 5 | thr | thr | thr | thr | | | 26 | 1 : 2 | 26(GLN) : 22(GLN) | 1. : 2.4 |
| 6 | gln | gln | gln | gln | | | 26 | 1 | 23(PRO) | 2.2 |
| 7 | pro | pro | pro | pro | | | 25 | 2 | 26(PRO) | 1. |
| 8 | pro | pro | pro | pro | | | 26 | 1 | 24(SER) | 1. |
| 9 | ser | ser | ser | ser | | | 24 | 1 | | |
| 10 | --- | --- | --- | --- | | | 24 | 3 | 20(VAL) | 3.6 |
| 11 | val | val | val | val | | | 24 | 1 | 24(SER) | 1. |
| 12 | ser | ser | ser | ser | | | 24 | 2 | 23(VAL) | 2.1 |
| 13 | val | val | val | val | | | 22 | 3 | 18(SER) | 3.7 |
| 14 | | | | | | | 22 | 2 | 21(PRO) | 2.1 |
| 15 | | | | | | | 21 | 1 | 21(GLY) | 1. |
| 16 | | | | | | | 20 | 1 : 2 | 20(GLN) : 17(GLN) | 1. : 2.4 |
| 17 | | | | | | | 21 | 3 | 19(THR) | 3.3 |
| 18 | | | | | met | | 20 | 2 | 19(ALA) | 2.1 |
| 19 | | | | | | | 18 | 6 | 8(ARG) | 14. |
| 20 | | | | | | | 19 | 1 | 19(ILE) | 1. |
| 21 | | | | | | ile | 19 | 1 | 19(THR) | 1. |
| 22 | | | | | | thr | 19 | 1 | 17(CYS) | 1. |
| 23 | | | | | | cys | 17 | 1 | | |
| 24 | | | | | | gly | 17 | 3 : 4 | 13(SER) | 3.9 : 5.2 |
| 25 | | | | | | gly | 16 | 2 | 15(GLY) | 2.1 |
| 26 | | | | | | asp | 17 | 3 | 14(ASP) : 12(ASP) | 3.6 : 4.3 |
| 27 | | | | | | glu | 15 | 7 | 5(ALA) | 21. |
| 27A | | | | | | | | | | |
| 27B | | | | | | | | | | |
| 27C | | | | | | | | | | |
| 27D | | | | | | | | | | |
| 27E | | | | | | | | | | |
| 27F | | | | | | | | | | |
| 28 | | | | | | | 16 | 2 | 13(LEU) | 2.5 |
| 29 | | | | | | | 13 | 5 : 6 | 5(GLY) | 13. : 16. |
| 30 | | | | | | | 15 | 6 : 7 | 5(GLU) : 3(+) | 18. : 35. |
| 31 | | | | | | | 14 | 6 | 5(LYS) | 17. |
| 32 | | | | | | | 13 | 4 | 8(TYR) | 6.5 |
| 33 | | | | | | | 13 | 2 | 9(VAL) | 2.9 |
| 34 | | | | | | | 11 | 4 | 4(TYR) | 11. |
| 35 | | | | | | | 13 | 1 | 13(TRP) | 1. |
| 36 | | | | | | | 11 | 2 | 10(TYR) | 2.2 |
| 37 | | | | | | | 11 | 1 : 2 | 11(GLN) : 10(GLN) | 1. : 2.2 |
| 38 | | | | | | | 11 | 3 | 9(GLN) | 3.7 |
| 39 | | | | | | | 11 | 2 | 7(LYS) | 3.1 |
| 40 | | | | | | | 10 | 2 | 9(PRO) | 2.2 |
| 41 | | | | | | | 10 | 1 | 10(GLY) | 1. |
| 42 | | | | | | | 10 | 2 : 3 | 8(GLN) : 7(GLN) | 2.3 : 3.9 |
| 43 | | | | | | | 9 | 2 | 5(ALA) | 3.6 |
| 44 | | | | | | | 10 | 1 | 10(PRO) | 1. |
| 45 | | | | | | | 10 | 3 | 7(VAL) | 4.3 |
| 46 | | | | | | | 9 | 3 | 6(LEU) | 4.5 |
| 47 | | | | | | | 10 | 1 | 10(VAL) | 1. |
| 48 | | | | | | | 10 | 2 | 8(ILE) | 2.5 |
| 49 | | | | | | | 10 | 2 | 9(TYR) | 2.2 |
| 50 | | | | | | | 10 | 5 : 6 | 4(GLU) : 3(GLU) | 13. : 20. |
| 51 | | | | | | | 10 | 2 | 7(ASP) | 2.9 |
| 52 | | | | | | | 11 | 4 | 4(SER) | 11. |
| 53 | | | | | | | 11 | 5 | 4(LYS) | 14. |
| 54 | | | | | | | 11 | 1 | 11(ARG) | 1. |
| 55 | | | | | | | 11 | 2 | 10(PRO) | 2.2 |
| 56 | | | | | | | 10 | 2 | 9(SER) | 2.2 |
| 57 | | | | | | | 11 | 3 | 8(GLY) | 4.1 |
| 58 | | | | | | | 10 | 2 | 9(ILE) | 2.2 |
| 59 | | | | | | | 10 | 1 | 10(PRO) | 1. |
| 60 | | | | | | | 11 | 3 | 9(GLU) : 8(GLU) | 3.7 : 4.1 |
| 61 | | | | | | | 11 | 1 | 11(ARG) | 1. |
| 62 | | | | | | | 11 | 1 | 11(PHE) | 1. |
| 63 | | | | | | | 10 | 1 | 10(SER) | 1. |
| 64 | | | | | | | 10 | 2 | 9(GLY) | 2.2 |
| 65 | | | | | | | 10 | 2 | 9(SER) | 2.2 |
| 66 | | | | | | | 10 | 4 | 4(ASN) | 10. |
| 67 | | | | | | | 10 | 1 | 10(SER) | 1. |
| 68 | | | | | | | 10 | 1 | 10(GLY) | 1. |
| 69 | | | | | | | 10 | 3 | 5(THR) | 6. |
| 70 | | | | | | | 10 | 2 | 8(THR) | 9.8 |
| 71 | | | | | | | 10 | 2 | 8(ALA) | 2.5 |
| 72 | | | | | | | 10 | 3 | 8(THR) | 3.8 |
| 73 | | | | | | | 10 | 1 | 10(LEU) | 1. |
| 74 | | | | | | | 10 | 1 | 10(THR) | 1. |
| 75 | | | | | | | 10 | 1 | 10(ILE) | 1. |
| 76 | | | | | | | 10 | 2 | 9(SER) | 2.2 |
| 77 | | | | | | | 10 | 2 | 8(GLY) | 2.5 |
| 78 | | | | | | | 10 | 3 | 5(VAL) | 6. |
| 79 | | | | | | | 10 | 2 | 7(GLN) | 2.9 |
| 80 | | | | | | | 10 | 3 | 7(ALA) | 4.3 |
| 81 | | | | | | | 10 | 5 | 3(+) | 17. |
| 82 | | | | | | | 10 | 1 : 2 | 10(ASP) : 8(ASP) | 1. : 2.5 |
| 83 | | | | | | | 10 | 1 : 2 | 10(GLU) : 9(GLU) | 1. : 2.2 |
| 84 | | | | | | | 10 | 1 | 10(ALA) | 1. |
| 85 | | | | | | | 10 | 1 : 2 | 10(ASP) : 8(ASP) | 1. : 2.5 |
| 86 | | | | | | | 10 | 1 | 10(TYR) | 1. |
| 87 | | | | | | | 10 | 2 | 8(TYR) | 2.5 |
| 88 | | | | | | | 10 | 1 | 10(CYS) | 1. |
| 89 | | | | | | | 10 | 3 | 7(GLN) : 5(GLN) | 4.3 : 6. |
| 90 | | | | | | | 10 | 4 | 4(ALA) | 10. |
| 91 | | | | | | | 10 | 3 | 7(TRP) | 4.3 |
| 92 | | | | | | | 10 | 3 | 8(ASP) : 7(ASP) | 3.8 : 4.3 |
| 93 | | | | | | | 10 | 5 | 4(SER) | 13. |
| 94 | | | | | | | 10 | 6 | 2(+) | 30. |
| 95 | | | | | | | 9 | 6 | 3(THR) | 18. |
| 95A | | | | | | | 4 | 4 | 1(+) | |
| 95B | | | | | | | 2 | 2 | 1(+) | |
| 95C | | | | | | | | | | |
| 95D | | | | | | | | | | |
| 95E | | | | | | | | | | |
| 95F | | | | | | | | | | |
| 96 | | | | | | | 9 | 5 | 5(VAL) | 9. |
| 97 | | | | | | | 10 | 3 | 6(VAL) | 5. |
| 98 | | | | | | | 10 | 1 | 10(PHE) | 1. |
| 99 | | | | | | | 11 | 1 | 11(GLY) | 1. |
| 100 | | | | | | | 11 | 3 | 9(GLY) | 3.7 |
| 101 | | | | | | | 11 | 1 | 11(GLY) | 1. |
| 102 | | | | | | | 11 | 1 | 11(THR) | 1. |
| 103 | | | | | | | 11 | 4 | 8(LYS) | 5.5 |
| 104 | | | | | | | 10 | 2 | 9(LEU) | 2.2 |
| 105 | | | | | | | 10 | 2 | 9(THR) | 2.2 |
| 106 | | | | | | | 10 | 1 | 10(VAL) | 1. |
| 106A | | | | | | | 10 | 1 | 10(LEU) | 1. |
| 107 | | | | | | | 8 | 2 | 6(GLY) | 2.7 |
| 108 | | | | | | | 7 | 1 | 7(GLN) | 1. |
| 109 | | | | | | | 7 | 1 | 7(PRO) | 1. |

ANTIBODY SPECIFICITIES: HUMAN LAMBDA LIGHT CHAINS SUBGROUP III

7) GAR: ANTI-RIBOFLAVIN

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NOTES: HUMAN LAMBDA LIGHT CHAINS SUBGROUP III

IDENTICAL SETS OF FRAMEWORK SEGMENTS:

FR1: SET 1: HIL[1], YO[2], PS[3], CAPI[4]. (4 IDENTICAL)
SET 2: LOY A[5], LOY G[6]. (2 IDENTICAL)

FR2:

FR3:

FR4: SET 1: HIL[1], CAPI[4], BAU[12], DEL[14]. (4 IDENTICAL HUMAN V-LAMBDA-III; ALSO 4 HUMAN V-LAMBDA-I: BL2 [CL[6], RHE[10], OKA[12], NIG-51[19]; 5 HUMAN V-LAMBDA-II: MES[2], ES492[8], TRO[14], VIL[17], WIN[21]; 1 HUMAN V-LAMBDA-IV: SH[1]; 3 HUMAN V-LAMBDA-VI: SUT[2], THO[4], LBV [CL[5]; AND 24 MOUSE V-LAMBDA: MOPC104E[1], J558[2], XS104[3], HOPC[14], J698[5], H206[16], W315[9], Y543[18], Y548[5], Y583[10], Y566[11], MOPC51[1], L[12], S178[13], Y5444[14], Y5606[15], S176[16], H2020[17], RPC20[18], IG 303[LAMBDA CL[19], S43 CL[21], S2H5 CL[38], S2E9 CL[39], S1F12 CL[40], IG 25[LAMBDA CL[41]])
SET 2: GAR[7]. (IDENTICAL TO 1 HUMAN V-LAMBDA-II: NIG-84[1])
SET 3: KERN[10]. (IDENTICAL TO 1 HUMAN V-LAMBDA-VI: NIG-48[10])

IDENTICAL SETS OF J-MINIGENES:

SET 1: BAU[12]. (IDENTICAL TO 2 HUMAN V-LAMBDA-II: MES[2], TRO[14].)
SET 2: DEL[14]. (IDENTICAL TO 2 HUMAN V-LAMBDA-II: ES492[8], VIL[17].)

SPECIFIC NOTES:

18) MOT: THERE ARE TWO RESIDUES IN FRONT OF POSITION 1: THEY ARE VAL AND THR.

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|----------------------|
| 30 | (ASP, ASN, GLN) |
| 81 | (MET, GLU) |
| 94 | (ILE, ARG, SER, GLY) |
| 95A | (TYR, ALA, GLY, ASP) |
| 95B | (HIS, GLU) |

HUMAN LAMBDA LIGHT CHAINS SUBGROUP IV

| | INVARIANT RESIDUES | 1 SH | 2 NEV | 3 USH | 4 PFA | 5 FRA | # OF SEQUENCES | # OF AMINO ACIDS | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|------|--------------------|------|-------|-------|-------|-------|----------------|------------------|---------------------------------------|-------------|
| 0 | | --- | --- | --- | --- | --- | | | | |
| 1 | | --- | --- | --- | --- | --- | | | | |
| 2 | SER | SER | SER | SER | SER | --- | 4 | 1 | 4(SER) | 1. |
| 3 | | GLU | GLU | GLU | GLU | ala | 5 | 2 | 4(GLU) | 2.5 |
| 4 | LEU | LEU | LEU | LEU | LEU | LEU | 5 | 1 | 5(LEU) | 1. |
| 5 | | THR | THR | THR | THR | val | 5 | 2 | 4(THR) | 2.5 |
| 6 | GLN | GLN | GLN | GLN | GLN | GLN | 5 | 1 | 5(GLN) | 1. |
| 7 | | ASP | ASP | pro | pro | pro | 5 | 2 : 3 | 3(PRO) | 3.3 : 5. |
| 8 | | PRO | PRO | PRO | PRO | ala | 5 | 2 | 4(PRO) | 2.5 |
| 9 | | ALA | ALA | ser | ser | ser | 5 | 2 | 3(SER) | 3.3 |
| 10 | | --- | --- | --- | --- | --- | | | | |
| 11 | VAL | VAL | VAL | VAL | VAL | VAL | 5 | 1 | 5(VAL) | 1. |
| 12 | | SER | SER | SER | SER | gix | 5 | 2 | 4(SER) | 2.5 |
| 13 | | VAL | VAL | VAL | VAL | gly | 5 | 2 | 4(VAL) | 2.5 |
| 14 | | ALA | ALA | ser | ser | ALA | 5 | 2 | 3(ALA) | 3.3 |
| 15 | | LEU | LEU | pro | pro | pro | 5 | 2 | 3(PRO) | 3.3 |
| 16 | GLY | GLY | GLY | GLY | GLY | GLY | 5 | 1 | 5(GLY) | 1. |
| 17 | | THR | GLX | GLN | GLN | GLX | 5 | 1 : 2 | 5(GLN) : 3(GLN) | 1. : 3.3 |
| 18 | | THR | THR | THR | THR | ser | 5 | 2 | 4(THR) | 2.5 |
| 19 | | VAL | VAL | ala | ala | ile | 5 | 3 | 2(+) | 7.5 |
| 20 | | ARG | ARG | ser | val | ala | 5 | 4 | 2(ARG) | 10. |
| 21 | ILE | ILE | ILE | ILE | ILE | ILE | 5 | 1 | 5(ILE) | 1. |
| 22 | | THR | THR | THR | THR | gly | 5 | 2 | 4(THR) | 2.5 |
| 23 | CYS | CYS | THR | THR | THR | CYS | 4 | 1 | 4(CYS) | 1. |
| 24 | | GLN | SER | SER | ILE | --- | 4 | 3 | 2(SER) | 6. |
| 25 | GLY | GLY | GLY | GLY | GLY | GLY | 4 | 1 | 4(GLY) | 1. |
| 26 | ASP | ASP | ASP | ASP | ILE | --- | 4 | 2 | 3(ASP) | 2.7 |
| 27 | SER | LYS | LYS | --- | SER | --- | 4 | 2 | 2(+) | 4. |
| 27A | | --- | --- | --- | --- | --- | | | | |
| 27B | | --- | --- | --- | --- | --- | | | | |
| 27C | | --- | --- | --- | --- | --- | | | | |
| 27D | | --- | --- | --- | --- | --- | | | | |
| 27E | | --- | --- | --- | --- | --- | | | | |
| 27F | | --- | --- | --- | --- | --- | | | | |
| 28 | | LEU | LEU | LEU | ILE | ASX | 1 | 1 | 1(ASN) : 1(ASP) | |
| 29 | | ARG | GLY | GLY | GLY | ILE | 4 | 2 | 3(LEU) | 2.7 |
| 30 | GLY | ASP | GLN | ALA | ALA | --- | 4 | 4 | 1(+) | 16. |
| 31 | TYR | TYR | ASN | ALA | TYR | --- | 4 | 3 | 2(TYR) | 6. |
| 32 | ASP | ALA | TYR | --- | ASX | --- | 3 | 2 : 3 | 2(ASP) : 1(+) | 3. : 9. |
| 33 | ALA | ALA | ALA | GLN | TYR | --- | 3 | 2 | 2(ALA) | 3. |
| 34 | | ALA | SER | --- | ILE | --- | 3 | 3 | 1(+) | 9. |
| 35 | TRP | TRP | TRP | TRP | TRP | --- | 3 | 1 | 3(TRP) | 1. |
| 36 | TYR | TYR | TYR | TYR | --- | --- | 3 | 1 | 3(TYR) | 1. |
| 37 | GLN | GLN | GLN | GLN | --- | --- | 2 | 1 | 2(GLN) | 1. |
| 38 | GLN | GLN | GLN | --- | --- | --- | 2 | 1 | 2(GLN) | 1. |
| 39 | LYS | LYS | LYS | --- | --- | --- | 2 | 1 | 2(LYS) | 1. |
| 40 | PRO | PRO | --- | --- | --- | --- | 1 | 1 | 1(PRO) | |
| 41 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 42 | GLN | GLN | --- | --- | --- | --- | 1 | 1 | 1(GLN) | |
| 43 | ALA | ALA | --- | --- | --- | --- | 1 | 1 | 1(ALA) | |
| 44 | PRO | PRO | --- | --- | --- | --- | 1 | 1 | 1(PRO) | |
| 45 | LEU | LEU | --- | --- | --- | --- | 1 | 1 | 1(LEU) | |
| 46 | LEU | LEU | --- | --- | --- | --- | 1 | 1 | 1(LEU) | |
| 47 | VAL | VAL | --- | --- | --- | --- | 1 | 1 | 1(VAL) | |
| 48 | ILE | ILE | --- | --- | --- | --- | 1 | 1 | 1(ILE) | |
| 49 | TYR | TYR | --- | --- | --- | --- | 1 | 1 | 1(TYR) | |
| 50 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 51 | ARG | ARG | --- | --- | --- | --- | 1 | 1 | 1(ARG) | |
| 52 | ASN | ASN | --- | --- | --- | --- | 1 | 1 | 1(ASN) | |
| 53 | ASN | ASN | --- | --- | --- | --- | 1 | 1 | 1(ASN) | |
| 54 | ARG | ARG | --- | --- | --- | --- | 1 | 1 | 1(ARG) | |
| 55 | PRO | PRO | --- | --- | --- | --- | 1 | 1 | 1(PRO) | |
| 56 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 57 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 58 | ILE | ILE | --- | --- | --- | --- | 1 | 1 | 1(ILE) | |
| 59 | PRO | PRO | --- | --- | --- | --- | 1 | 1 | 1(PRO) | |
| 60 | ASP | ASP | --- | --- | --- | --- | 1 | 1 | 1(ASP) | |
| 61 | ARG | ARG | --- | --- | --- | --- | 1 | 1 | 1(ARG) | |
| 62 | PHE | PHE | --- | --- | --- | --- | 1 | 1 | 1(PHE) | |
| 63 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 64 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 65 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 66 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 67 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 68 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 69 | HIS | HIS | --- | --- | --- | --- | 1 | 1 | 1(HIS) | |
| 70 | THR | THR | --- | --- | --- | --- | 1 | 1 | 1(THR) | |
| 71 | ALA | ALA | --- | --- | --- | --- | 1 | 1 | 1(ALA) | |
| 72 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 73 | LEU | LEU | --- | --- | --- | --- | 1 | 1 | 1(LEU) | |
| 74 | THR | THR | --- | --- | --- | --- | 1 | 1 | 1(THR) | |
| 75 | ILE | ILE | --- | --- | --- | --- | 1 | 1 | 1(ILE) | |
| 76 | THR | THR | --- | --- | --- | --- | 1 | 1 | 1(THR) | |
| 77 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 78 | ALA | ALA | --- | --- | --- | --- | 1 | 1 | 1(ALA) | |
| 79 | GLN | GLN | --- | --- | --- | --- | 1 | 1 | 1(GLN) | |
| 80 | ALA | ALA | --- | --- | --- | --- | 1 | 1 | 1(ALA) | |
| 81 | GLU | GLU | --- | --- | --- | --- | 1 | 1 | 1(GLU) | |
| 82 | ASP | ASP | --- | --- | --- | --- | 1 | 1 | 1(ASP) | |
| 83 | GLU | GLU | --- | --- | --- | --- | 1 | 1 | 1(GLU) | |
| 84 | ALA | ALA | --- | --- | --- | --- | 1 | 1 | 1(ALA) | |
| 85 | ASP | ASP | --- | --- | --- | --- | 1 | 1 | 1(ASP) | |
| 86 | TYR | TYR | --- | --- | --- | --- | 1 | 1 | 1(TYR) | |
| 87 | TYR | TYR | --- | --- | --- | --- | 1 | 1 | 1(TYR) | |
| 88 | CYS | CYS | --- | --- | --- | --- | 1 | 1 | 1(CYS) | |
| 89 | ASN | ASN | --- | --- | --- | --- | 1 | 1 | 1(ASN) | |
| 90 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 91 | ARG | ARG | --- | --- | --- | --- | 1 | 1 | 1(ARG) | |
| 92 | ASP | ASP | --- | --- | --- | --- | 1 | 1 | 1(ASP) | |
| 93 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 94 | SER | SER | --- | --- | --- | --- | 1 | 1 | 1(SER) | |
| 95 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 95A | LYS | LYS | --- | --- | --- | --- | 1 | 1 | 1(LYS) | |
| 95B | HIS | HIS | --- | --- | --- | --- | 1 | 1 | 1(HIS) | |
| 95C | --- | --- | --- | --- | --- | --- | | | | |
| 95D | --- | --- | --- | --- | --- | --- | | | | |
| 95E | --- | --- | --- | --- | --- | --- | | | | |
| 95F | --- | --- | --- | --- | --- | --- | | | | |
| 96 | VAL | VAL | --- | --- | --- | --- | 1 | 1 | 1(VAL) | |
| 97 | LEU | LEU | --- | --- | --- | --- | 1 | 1 | 1(LEU) | |
| 98 | PHE | PHE | --- | --- | --- | --- | 1 | 1 | 1(PHE) | |
| 99 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 100 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 101 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 102 | THR | THR | --- | --- | --- | --- | 1 | 1 | 1(THR) | |
| 103 | LYS | LYS | --- | --- | --- | --- | 1 | 1 | 1(LYS) | |
| 104 | LEU | LEU | --- | --- | --- | --- | 1 | 1 | 1(LEU) | |
| 105 | THR | THR | --- | --- | --- | --- | 1 | 1 | 1(THR) | |
| 106 | VAL | VAL | --- | --- | --- | --- | 1 | 1 | 1(VAL) | |
| 106A | LEU | LEU | --- | --- | --- | --- | 1 | 1 | 1(LEU) | |
| 107 | GLY | GLY | --- | --- | --- | --- | 1 | 1 | 1(GLY) | |
| 108 | GLN | GLN | --- | --- | --- | --- | 1 | 1 | 1(GLN) | |
| 109 | PRO | PRO | --- | --- | --- | --- | 1 | 1 | 1(PRO) | |

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- 4) PFA: TISCHENDORF,F.W.,TISCHENDORF,M.M. & WITTMANN-LIEBOLD,B. (1976) Z.NATURFORSCH.31C.758-760.
- 5) FRA: WANG,A.C. & FUDENBERG,H.H. (1974) J.IMMUNOGENETICS.1,303-313. (CHECKED BY AUTHOR)

NOTES: HUMAN LAMBDA LIGHT CHAINS SUBGROUP IV

IDENTICAL SETS OF FRAMEWORK SEGMENTS:

FR1: SET 1: SH11,NEV2]. (2 IDENTICAL)

FR2:

FR3:

FR4: SET 1: SH11]. (IDENTICAL TO 4 HUMAN V-LAMBDA-I: BL2`CL[6],RHE[10],OKA[12],NIG-51[19]; 5 HUMAN V-LAMBDA-IF: MES[2],ES492[8], TRO[14],VIL[17],WIN[21]; 4 HUMAN V-LAMBDA-III: HIL[1],CPI[4],BAU[12],DEL[14]; 3 HUMAN V-LAMBDA-VI: SUT[2],THO[4], LBV`CL[5]; AND 24 MOUSE V-LAMBDA: MOPC104E[1],J558[2],XS104[3],HOPC[14],J698[5],H2061[6],W3159[7],Y5431[8],Y5485[9], Y5830[10],Y5669[11],MOPC511(L)[12],S178[13],Y5444[14],Y5608[15],S176[16],H2020[17],RPC20[18],IG 303LAMBDA`CL[19], S43`CL[21],S2H5`CL[38],S2E9`CL[39],S1F12`CL[40],IG 25LAMBDA`CL[41].)

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|-------------------|
| 19 | (VAL,ALA) |
| 27 | (LYS,SER) |
| 30 | (ALA,GLY,ASP,GLN) |
| 32 | (TYR,ASP,ASN) |
| 34 | (ILE,ALA,SER) |

HUMAN LAMBDA LIGHT CHAINS SUBGROUP V

| | INVARIANT RESIDUES | 1 BO | 2 HBJ 2 | 3* MCG | # OF SEQUENCES | # OF AMINO ACIDS | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|------|--------------------|------|---------|--------|----------------|------------------|---------------------------------------|-------------|
| 0 | PCA | PCA | PCA | PCA | 3 | 1 | 3(PCA) | 1. |
| 1 | SER | SER | SER | SER | 3 | 1 | 3(SER) | 1. |
| 2 | ALA | ALA | ALA | ALA | 3 | 1 | 3(ALA) | 1. |
| 3 | LEU | LEU | LEU | LEU | 3 | 1 | 3(LEU) | 1. |
| 4 | THR | THR | THR | THR | 3 | 1 | 3(THR) | 1. |
| 5 | GLN | GLN | GLN | GLN | 3 | 1 | 3(GLN) | 1. |
| 6 | PRO | PRO | PRO | PRO | 3 | 1 | 3(PRO) | 1. |
| 7 | PRO | PRO | PRO | PRO | 3 | 1 | 3(PRO) | 1. |
| 8 | SER | SER | SER | SER | 3 | 1 | 3(SER) | 1. |
| 9 | --- | --- | --- | --- | --- | --- | --- | --- |
| 10 | ALA | ALA | ALA | ALA | 3 | 1 | 3(ALA) | 1. |
| 11 | SER | SER | SER | SER | 3 | 1 | 3(SER) | 1. |
| 12 | GLY | GLY | GLY | GLY | 3 | 1 | 3(GLY) | 1. |
| 13 | SER | SER | SER | SER | 3 | 1 | 3(SER) | 1. |
| 14 | --- | --- | --- | --- | --- | --- | --- | --- |
| 15 | GLY | PRO | GLY | ILE | 3 | 2 | 2(PRO) | 3. |
| 16 | GLN | GLN | GLN | GLN | 3 | 1 | 3(GLN) | 1. |
| 17 | SER | SER | SER | SER | 3 | 1 | 3(SER) | 1. |
| 18 | VAL | VAL | VAL | VAL | 3 | 1 | 3(VAL) | 1. |
| 19 | THR | THR | THR | THR | 3 | 1 | 3(THR) | 1. |
| 20 | ILE | ILE | ILE | ILE | 3 | 1 | 3(ILE) | 1. |
| 21 | SER | SER | SER | SER | 3 | 1 | 3(SER) | 1. |
| 22 | CYS | CYS | CYS | CYS | 3 | 1 | 3(CYS) | 1. |
| 23 | --- | --- | --- | --- | --- | --- | --- | --- |
| 24 | THR | THR | THR | THR | 3 | 1 | 3(THR) | 1. |
| 25 | GLY | GLY | GLY | GLY | 3 | 1 | 3(GLY) | 1. |
| 26 | THR | THR | THR | THR | 3 | 1 | 3(THR) | 1. |
| 27 | SER | SER | SER | SER | 2 | 1 | 2(SER) | 1. |
| 27A | --- | --- | --- | --- | --- | --- | --- | --- |
| 27B | --- | --- | --- | --- | --- | --- | --- | --- |
| 27C | --- | SER | --- | --- | 2 | 1 | 2(SER) | 1. |
| 27D | SER | ASP | --- | --- | 2 | 1 | 2(ASP) | 1. |
| 27E | VAL | VAL | --- | --- | 2 | 1 | 2(VAL) | 1. |
| 27F | GLY | GLY | --- | --- | 2 | 1 | 2(GLY) | 1. |
| 26 | --- | --- | --- | --- | --- | --- | --- | --- |
| 29 | --- | ASP | --- | GLY | 2 | 2 | 1(+) | 4. |
| 30 | --- | ASN | --- | TYR | 2 | 2 | 1(+) | 4. |
| 31 | --- | LYS | --- | ASN | 2 | 2 | 1(+) | 4. |
| 32 | TYR | TYR | --- | TYR | 2 | 1 | 2(TYR) | 1. |
| 33 | VAL | VAL | --- | VAL | 2 | 1 | 2(VAL) | 1. |
| 34 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 35 | TRP | TRP | --- | TRP | 2 | 1 | 2(TRP) | 1. |
| 36 | TYR | TYR | --- | TYR | 2 | 1 | 2(TYR) | 1. |
| 37 | GLN | GLN | --- | GLN | 2 | 1 | 2(GLN) | 1. |
| 38 | GLN | GLN | --- | GLN | 2 | 1 | 2(GLN) | 1. |
| 39 | HIS | HIS | --- | HIS | 2 | 1 | 2(HIS) | 1. |
| 40 | PRO | PRO | --- | ALA | 2 | 2 | 1(+) | 4. |
| 41 | GLY | GLY | --- | GLY | 2 | 1 | 2(GLY) | 1. |
| 42 | --- | ARG | --- | LYS | 2 | 2 | 1(+) | 4. |
| 43 | ALA | ALA | --- | ALA | 2 | 1 | 2(ALA) | 1. |
| 44 | PRO | PRO | --- | PRO | 2 | 1 | 2(PRO) | 1. |
| 45 | LYS | LYS | --- | LYS | 2 | 1 | 2(LYS) | 1. |
| 46 | --- | LEU | --- | VAL | 2 | 2 | 1(+) | 4. |
| 47 | --- | VAL | --- | ILE | 2 | 2 | 1(+) | 4. |
| 48 | ILE | ILE | --- | ILE | 2 | 1 | 2(ILE) | 1. |
| 49 | --- | PHE | --- | TYR | 2 | 2 | 1(+) | 4. |
| 50 | GLU | GLU | --- | GLU | 2 | 1 | 2(GLU) | 1. |
| 51 | VAL | VAL | --- | VAL | 2 | 1 | 2(VAL) | 1. |
| 52 | --- | SER | --- | ASN | 2 | 2 | 1(+) | 4. |
| 53 | --- | GLY | --- | LYS | 2 | 2 | 1(+) | 4. |
| 54 | ARG | ARG | --- | ARG | 2 | 1 | 2(ARG) | 1. |
| 55 | PRO | PRO | --- | PRO | 2 | 1 | 2(PRO) | 1. |
| 56 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 57 | GLY | GLY | --- | GLY | 2 | 1 | 2(GLY) | 1. |
| 58 | VAL | VAL | --- | VAL | 2 | 1 | 2(VAL) | 1. |
| 59 | PRO | PRO | --- | PRO | 2 | 1 | 2(PRO) | 1. |
| 60 | ASP | ASP | --- | ASP | 2 | 1 | 2(ASP) | 1. |
| 61 | ARG | ARG | --- | ARG | 2 | 1 | 2(ARG) | 1. |
| 62 | PHE | PHE | --- | PHE | 2 | 1 | 2(PHE) | 1. |
| 63 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 64 | GLY | GLY | --- | GLY | 2 | 1 | 2(GLY) | 1. |
| 65 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 66 | LYS | LYS | --- | LYS | 2 | 1 | 2(LYS) | 1. |
| 67 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 68 | --- | ASP | --- | GLY | 2 | 2 | 1(+) | 4. |
| 69 | ASN | ASN | --- | ASN | 2 | 1 | 2(ASN) | 1. |
| 70 | THR | THR | --- | THR | 2 | 1 | 2(THR) | 1. |
| 71 | ALA | ALA | --- | ALA | 2 | 1 | 2(ALA) | 1. |
| 72 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 73 | LEU | LEU | --- | LEU | 2 | 1 | 2(LEU) | 1. |
| 74 | THR | THR | --- | THR | 2 | 1 | 2(THR) | 1. |
| 75 | VAL | VAL | --- | VAL | 2 | 1 | 2(VAL) | 1. |
| 76 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 77 | GLY | GLY | --- | GLY | 2 | 1 | 2(GLY) | 1. |
| 78 | LEU | LEU | --- | LEU | 2 | 1 | 2(LEU) | 1. |
| 79 | --- | ARG | --- | GLN | 2 | 2 | 1(+) | 4. |
| 80 | ALA | ALA | --- | ALA | 2 | 1 | 2(ALA) | 1. |
| 81 | GLU | GLU | --- | GLU | 2 | 1 | 2(GLU) | 1. |
| 82 | ASP | ASP | --- | ASP | 2 | 1 | 2(ASP) | 1. |
| 83 | GLU | GLU | --- | GLU | 2 | 1 | 2(GLU) | 1. |
| 84 | ALA | ALA | --- | ALA | 2 | 1 | 2(ALA) | 1. |
| 85 | ASP | ASP | --- | ASP | 2 | 1 | 2(ASP) | 1. |
| 86 | TYR | TYR | --- | TYR | 2 | 1 | 2(TYR) | 1. |
| 87 | TYR | TYR | --- | TYR | 2 | 1 | 2(TYR) | 1. |
| 88 | CYS | CYS | --- | CYS | 2 | 1 | 2(CYS) | 1. |
| 89 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 90 | SER | SER | --- | SER | 2 | 1 | 2(SER) | 1. |
| 91 | TYR | TYR | --- | TYR | 2 | 1 | 2(TYR) | 1. |
| 92 | --- | VAL | --- | GLU | 2 | 2 | 1(+) | 4. |
| 93 | --- | ASP | --- | GLY | 2 | 2 | 1(+) | 4. |
| 94 | --- | --- | --- | SER | 2 | 2 | 1(+) | 4. |
| 95 | --- | ASN | --- | ASN | 2 | 2 | 1(+) | 4. |
| 95A | ASN | ASN | --- | ASN | 2 | 1 | 2(ASN) | 1. |
| 95B | --- | --- | --- | --- | --- | --- | --- | --- |
| 95C | --- | --- | --- | --- | --- | --- | --- | --- |
| 95D | --- | --- | --- | --- | --- | --- | --- | --- |
| 95E | --- | --- | --- | --- | --- | --- | --- | --- |
| 95F | --- | --- | --- | --- | --- | --- | --- | --- |
| 96 | PHE | PHE | --- | PHE | 2 | 1 | 2(PHE) | 1. |
| 97 | VAL | VAL | --- | VAL | 2 | 1 | 2(VAL) | 1. |
| 98 | PHE | PHE | --- | PHE | 2 | 1 | 2(PHE) | 1. |
| 99 | GLY | GLY | --- | GLY | 2 | 1 | 2(GLY) | 1. |
| 100 | GLY | GLY | --- | THR | 2 | 2 | 1(+) | 4. |
| 101 | THR | THR | --- | THR | 2 | 1 | 2(THR) | 1. |
| 102 | --- | --- | --- | --- | --- | --- | --- | --- |
| 103 | LYS | LYS | --- | LYS | 2 | 1 | 2(LYS) | 1. |
| 104 | THR | THR | --- | VAL | 2 | 2 | 1(+) | 4. |
| 105 | THR | THR | --- | THR | 2 | 1 | 2(THR) | 1. |
| 106 | VAL | VAL | --- | VAL | 2 | 1 | 2(VAL) | 1. |
| 106A | LEU | LEU | --- | LEU | 2 | 1 | 2(LEU) | 1. |
| 107 | --- | ARG | --- | GLY | 2 | 2 | 1(+) | 4. |
| 108 | GLN | GLN | --- | GLN | 2 | 1 | 2(GLN) | 1. |
| 109 | PRO | PRO | --- | PRO | 2 | 1 | 2(PRO) | 1. |

ANTIBODY SPECIFICITIES: HUMAN LAMBDA LIGHT CHAINS SUBGROUP V

- 3) **MCG**: ANTI-EPSILON-DNP-LYS, EPSILON-DNP-AMINOCAPROATE, DNP-LEU, TRIACETIN, SODIUM MERTHIOLATE, METHADONE, 1,10-PHENANTHROLINE, CAFFEINE, THEOPHYLLINE, DI-DNP-LYS, DNP-TRP, DNP-PHE, DI-DNP-TYR, COLCHICINE, P-NITROANILINE, P-NITROPHENYLPHOSPHORYL CHOLINE, S-ACETYLLURACIL, MENADIONE, MEPERIDINE, TRIBUTYRIN, OMEGA-BROMOHEPTANOATE, O-CHLOROMERCURIPHENOL, P-CHLOROMERCURIPHENOL, PHENYLMERCURIC COMPOUNDS, METHYL-MERCURIC CHLORIDE.

REFERENCE: HUMAN LAMBDA LIGHT CHAINS SUBGROUP V

- 1) **BO**: WIKLER, M. & PUTNAM, F. W. (1970) J. BIOL. CHEM., 245, 4488-4507. (CHECKED BY AUTHOR 06/15/83)
 2) **HBJ2**: HOOD, L., GRAY, W. R., SANDERS, B. G. & DREYER, W. J. (1967) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL., 32, 133-145.
 3) **MCG**: FETT, J. W. & DEUTSCH, H. F. (1974) BIOCHEMISTRY, 13, 4102-4114. (CHECKED BY AUTHOR)

NOTES: HUMAN LAMBDA LIGHT CHAINS SUBGROUP V**IDENTICAL SETS OF FRAMEWORK SEGMENTS:**

- FR1: SET 1: BO11, HBJ212. (2 IDENTICAL)
 FR2:
 FR3:
 FR4: SET 1: BO11. (IDENTICAL TO 1 HUMAN V-LAMBDA-I: NEWM11); AND 1 HUMAN V-LAMBDA-II: WH131.)
 SET 2: MCG13. (IDENTICAL TO 1 HUMAN V-LAMBDA-I: LOC111.)

IDENTICAL SETS OF COMPLEMENTARITY DETERMINING REGIONS:

- CDR1: SET 1: MCG13. (IDENTICAL TO 2 HUMAN V-LAMBDA-II: MESI2, VILI171.)
 CDR2:
 CDR3:

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|------------|
| 29 | (GLY, ASP) |
| 30 | (TYR, ASN) |
| 31 | (LYS, ASN) |
| 40 | (PRO, ALA) |
| 42 | (LYS, ARG) |
| 46 | (LEU, VAL) |
| 47 | (ILE, VAL) |
| 49 | (TYR, PHE) |
| 52 | (SER, ASN) |
| 53 | (LYS, GLY) |
| 68 | (GLY, ASP) |
| 79 | (ARG, GLN) |
| 92 | (VAL, GLU) |
| 93 | (GLY, ASP) |
| 94 | (SER, ASN) |
| 95 | (ASP, ASN) |
| 100 | (THR, GLY) |
| 104 | (LEU, VAL) |
| 107 | (ARG, GLY) |

HUMAN LAMBDA LIGHT CHAINS SUBGROUP VI

| * | INVARIANT RESIDUES | 1 AMYLOID-OR # | 2 SUT # | 3 AMYLOID-RS | 4 THO # | 5 LSV-CL # | 6 GIO | 7 YAM | 8 WAN | 9 WIN | 10 NIG-48 # | 11 JAM | 12 MOR | 13 KIN | # OF SEQUENCES | # OF AMINO ACIDS | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|-----|--------------------|----------------|---------|--------------|---------|------------|-------|-------|-------|-------|-------------|--------|--------|--------|----------------|------------------|---------------------------------------|-------------|
| 0 | | | | | | | | | | | | | | | | | | |
| 1 | | ASP | ASP | ASP | asn | asn | asn | ASP | asn | asn | asn | ASP | asn | asn | 13 | 2 | 8(ASN) | 3.3 |
| 2 | | PHE | PHE | PHE | asn | PHE | PHE | PHE | asn | PHE | PHE | PHE | asn | PHE | 13 | 2 | 11(PHE) | 2.4 |
| 3 | LEU | MET | MET | LEU | MET | MET | LEU | LEU | asn | asn | MET | MET | asn | asn | 13 | 1 | 12(MET) | 2.2 |
| 4 | | | | | | | | | | | | | | | 13 | 1 | 13(LEU) | 1 |
| 5 | | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | 13 | 3 | 11(THR) | 3.5 |
| 6 | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | glu | GLN | 13 | 2 | 12(GLN) | 2.2 |
| 7 | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | 13 | 1 | 13(PRO) | 1 |
| 8 | | HIS | HIS | HIS | HIS | HIS | HIS | HIS | HIS | HIS | pro | HIS | HIS | HIS | 11 | 2 | 10(HIS) | 2.2 |
| 9 | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | 13 | 1 | 13(SER) | 1 |
| 10 | | | | | | | | | | | | | | | 13 | 2 | 12(VAL) | 2.2 |
| 11 | SER | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | asn | VAL | 13 | 1 | 13(SER) | 1 |
| 12 | | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | GLU | asn | 12 | 2 | 11(GLU) | 2.2 |
| 13 | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | 11 | 1 | 11(SER) | 1 |
| 14 | | | | | | | | | | | | | | | 12 | 1 | 12(PRO) | 1 |
| 15 | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | 12 | 1 | 12(VAL) | 1 |
| 16 | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | THR | 12 | 1 | 12(GLY) | 1 |
| 17 | | LYS | LYS | asn | LYS | LYS | LYS | LYS | lys | LYS | LYS | LYS | LYS | THR | 12 | 3 | 10(LYS) | 3.6 |
| 18 | | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | THR | 11 | 1 | 10(THR) | 2.2 |
| 19 | | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | THR | THR | 11 | 2 | 10(VAL) | 2.2 |
| 20 | | THR | ile | THR | THR | THR | THR | THR | ser | THR | THR | THR | THR | THR | 11 | 3 | 8(THR) | 4.1 |
| 21 | | PHE | SER | SER | ile | SER | SER | SER | ile | SER | met | SER | SER | SER | 10 | 3 | 8(ILE) | 3.8 |
| 22 | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | SER | 10 | 1 | 10(SER) | 1 |
| 23 | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | CYS | 10 | 1 | 10(CYS) | 1 |
| 24 | | THR | THR | THR | THR | THR | THR | SER | | | THR | | THR | | 9 | 2 | 8(THR) | 2.3 |
| 25 | | GLY | ARG | GLY | THR | GLY | ARG | GLY | | | ARG | | ALA | | 7 | 3 | 3(+) | 7 |
| 26 | | SER | SER | SER | SER | ASN | THR | SER | | | THR | | ASN | | 7 | 3 | 4(SER) | 5.3 |
| 27 | | GLY | ASP | GLY | SER | SER | SER | GLY | ALA | | SER | | GLY | | 7 | 3 | 3(-) | 7 |
| 27A | | GLY | GLY | ASP | GLY | GLY | | GLY | | | GLY | | GLY | | 7 | 3 | 5(GLY) | 7 |
| 27B | | SER | THR | SER | SER | SER | | SER | | | ASN | | ASN | | 6 | 3 | 4(SER) | |
| 27C | | | | | | | | | | | | | | | | | | |
| 27D | | | | | | | | | | | | | | | | | | |
| 27E | | | | | | | | | | | ASP | | | | 1 | 1 | 1(ASP) | |
| 27F | | | | | | | | | | | SER | | | | 1 | 1 | 1(SER) | |
| 28 | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | | | ILE | | ILE | | 7 | 1 | 7(ILE) | 1 |
| 29 | | ALA | ALA | ALA | ALA | ALA | ALA | ALA | | | ALA | | GLY | | 7 | 2 | 6(ALA) | 2.3 |
| 30 | | ASP | TYR | TYR | TYR | ASN | TYR | ASN | | | SER | | SER | | 7 | 3 | 4(SER) | 4.5 |
| 31 | | SER | TYR | SER | TYR | TYR | TYR | TYR | | | ASN | | PRO | | 7 | 3 | 2(-) | 14 |
| 32 | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | | | VAL | | VAL | | 7 | 1 | 7(VAL) | 4.2 |
| 33 | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | | | GLN | | GLN | | 5 | 1 | 5(GLN) | 1 |
| 34 | GLN | GLN | GLN | GLN | GLN | GLN | GLN | GLN | | | GLN | | GLN | | 5 | 1 | 5(GLN) | 1 |
| 35 | TRP | TRP | TRP | TRP | TRP | TRP | TRP | TRP | | | TRP | | TRP | | 6 | 1 | 6(TRP) | 1 |
| 36 | TYR | TYR | TYR | TYR | TYR | TYR | TYR | TYR | | | TYR | | TYR | | 6 | 1 | 6(TYR) | 1 |
| 37 | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | | | ARG | | LYS | | 6 | 3 | 4(GLN) | 4.5 |
| 38 | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | | | GLN | | GLN | | 5 | 2 | 4(GLN) | 2.5 |
| 39 | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | | | ARG | | PRO | | 5 | 2 | 5(ARG) | 1 |
| 40 | | PRO | PRO | PRO | PRO | ARG | PRO | ARG | | | PRO | | PRO | | 6 | 2 | 5(PRO) | 2.4 |
| 41 | | GLY | GLY | VAL | VAL | GLY | VAL | GLY | | | GLY | | GLY | | 6 | 3 | 4(GLY) | 4.5 |
| 42 | | SER | SER | SER | SER | SER | SER | SER | | | SER | | SER | | 6 | 3 | 4(SER) | 4.5 |
| 43 | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | | | ALA | | ALA | | 5 | 1 | 5(ALA) | 1 |
| 44 | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | | | PRO | | PRO | | 5 | 1 | 5(PRO) | 1 |
| 45 | THR | THR | THR | THR | THR | THR | THR | THR | | | THR | | THR | | 5 | 1 | 5(THR) | 1 |
| 46 | | THR | THR | THR | THR | THR | THR | THR | | | THR | | THR | | 5 | 1 | 4(THR) | 2.5 |
| 47 | | VAL | VAL | VAL | VAL | VAL | VAL | VAL | | | LEU | | LEU | | 5 | 2 | 4(VAL) | 2.5 |
| 48 | ILE | ILE | ILE | ILE | ILE | ILE | ILE | ILE | | | ILE | | ILE | | 5 | 1 | 5(ILE) | 1 |
| 49 | | TYR | PHE | PHE | TYR | TYR | TYR | TYR | | | TYR | | TYR | | 5 | 2 | 4(TYR) | 2.5 |
| 50 | | ASP | GLU | GLU | GLU | GLU | GLU | ASP | | | ASP | | ASP | | 5 | 2 | 3(GLU) | 3.3 |
| 51 | GLN | ASP | ASP | ASP | ASN | ASP | ASN | THR | | | THR | | THR | | 5 | 2 | 4(ASP) | 2.5 |
| 52 | | ASN | THR | THR | ASN | ASN | ASN | ASN | | | ASN | | ASN | | 5 | 2 | 4(ASN) | 2.5 |
| 53 | | GLN | GLN | GLN | GLN | GLN | GLN | GLN | | | GLN | | GLN | | 5 | 1 | 5(GLN) | 1 |
| 54 | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | | | ARG | | ARG | | 5 | 1 | 5(ARG) | 1 |
| 55 | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | | | PRO | | PRO | | 5 | 1 | 5(PRO) | 1 |
| 56 | | SER | SER | SER | SER | LEU | LEU | TYR | | | TYR | | TYR | | 5 | 3 | 3(SER) | 5 |
| 57 | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | | | GLY | | GLY | | 5 | 1 | 5(GLY) | 1 |
| 58 | VAL | VAL | VAL | VAL | VAL | VAL | VAL | VAL | | | VAL | | VAL | | 5 | 1 | 5(VAL) | 1 |
| 59 | PRO | PRO | PRO | PRO | PRO | PRO | PRO | PRO | | | PRO | | PRO | | 5 | 1 | 5(PRO) | 1 |
| 60 | | ASP | ASP | ASN | ASN | ASN | ASN | ASN | | | ASN | | ASN | | 5 | 1 | 4(ASP) | 2.5 |
| 61 | ARG | ARG | ARG | ARG | ARG | ARG | ARG | ARG | | | ARG | | ARG | | 5 | 1 | 5(ARG) | 1 |
| 62 | PHE | PHE | PHE | PHE | PHE | PHE | PHE | PHE | | | PHE | | PHE | | 5 | 1 | 5(PHE) | 1 |
| 63 | SER | SER | SER | SER | SER | SER | SER | SER | | | SER | | SER | | 5 | 1 | 5(SER) | 1 |
| 64 | GLY | GLY | GLY | GLY | GLY | GLY | GLY | GLY | | | GLY | | GLY | | 5 | 1 | 5(GLY) | 1 |
| 65 | SER | SER | SER | SER | SER | SER | SER | SER | | | SER | | SER | | 5 | 1 | 5(SER) | 1 |
| 66 | | # | # | # | # | # | # | # | | | # | | # | | 5 | 1 | 5(SER) | 1 |
| 67 | SER | SER | SER | SER | SER | SER | SER | SER | | | SER | | SER | | 5 | 2 | 4(SER) | 2.5 |
| 68 | | ALA | ALA | ALA | ALA | ALA | ALA | ALA | | | ALA | | ALA | | 5 | 1 | 5(ASN) | 1 |
| 69 | ASN | ASN | ASN | ASN | ASN | ASN | ASN | ASN | | | ASN | | ASN | | 5 | 1 | 5(ASN) | 1 |
| 70 | SER | SER | SER | SER | SER | SER | SER | SER | | | SER | | SER | | 5 | 1 | 5(SER) | 1 |
| 71 | ALA | ALA | ALA | ALA | ALA | ALA | ALA | ALA | | | ALA | | ALA | | 5 | 1 | 5(ALA) | 1 |
| 72 | SER | SER | SER | SER | SER | SER | SER | SER | | | SER | | SER | | 5 | 1 | 5(SER) | 1 |
| 73 | LEU | LEU | LEU | LEU | LEU | LEU | LEU | LEU | | | LEU | | LEU | | 5 | 1 | 5(LEU) | 1 |
| 74 | THR | THR | THR | THR | THR | THR | THR | THR | | | THR | | THR | | 5 | 1 | 5(THR) | 1 |
| 75 | | ILE | ILE | ILE | ILE | ILE | ILE | ILE | | | ILE | | ILE | | 5 | 2 | 4(ILE) | 2.5 |
| 76 | SER | SER | SER | SER | SER | SER | SER | SER | | | SER | | SER | | 5 | 1 | 5(SER) | 1 |
| 77 | LEU | GLY | GLY | GLY | GLY | GLY | GLY | GLY | | | GLY | | GLY | | 5 | 2 | 4(GLY) | 2.5 |
| 78 | | LEU | LEU | LEU | LEU | LEU | LEU | LEU | | | LEU | | LEU | | 5 | 1 | 5(LEU) | 1 |
| 79 | | LYS | GLN | GLN | LYS | LYS | LYS | LYS | | | THR | | THR | | 5 | 3 | 3(LYS) | 5 |
| 80 | | THR | THR | THR | THR | THR | THR | THR | | | ASN | | ASN | | 5 | 2 | 4(THR) | 2.5 |
| 81 | | GLU | GLU | GLU | GLU | GLU | GLU | GLU | | | ASP | | ASP | </ | | | | |

HUMAN HEAVY CHAINS SUBGROUP I (cont'd)

| | 25* KOH | 26 RIC | 27 WIS | 28 VAU | 29 LEB | 30 SAC | 31 DEE | 32 LEA | 33 HAR | 34 HUS | # OF SEQUENCES | # OF AMINO ACIDS | OCCURRENCES OF MOST COMMON AMINO ACID | VARIABILITY |
|------|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-------------------|------------------------|---|-------------|
| 0 | | | | | | | | | | | 30 | 5 | 21(PCA) | 7.1 |
| 1 | gln | PCA | PCA | PCA | PCA | gly | | | | | 30 | 6 | 25(VAL) | 7.2 |
| 2 | VAL | VAL | VAL | VAL | VAL | ala | | | | | 29 | 6 | 22(GLN) | 7.9 |
| 3 | GLN | leu | GLN | | | | | pca | | | 25 | 2 | 24(LEU) | 2.1 |
| 4 | LEU | | | | | | | LEU | pca | | 14 | 4 | 11(VAL) | 5.1 |
| 5 | | | | | | | | | | | 14 | 2 | 10(GLN) | 2.8 |
| 6 | | | | | | | | | | | 14 | 1 | 14(SER) | 1. |
| 7 | | | | | | | | | | | 15 | 2 | 14(GLY) | 2.1 |
| 8 | | | | | | | | | | | 15 | 4 | 12(ALA) | 5. |
| 9 | | | | | | | | | | | 14 | 3 | 12(GLU) | 3.5 |
| 10 | | | | | | | | | | | 14 | 5 | 12(VAL) | 2.3 |
| 11 | | | | | | | | | | | 15 | 5 | 9(LYS) | 6.3 |
| 12 | | | | | | | | | | | 14 | 2 | 13(LYS) | 2.2 |
| 13 | | | | | | | | | | | 14 | 2 | 13(PRO) | 2.2 |
| 14 | | | | | | | | | | | 12 | 3 | 12(GLY) | 3.5 |
| 15 | | | | | | | | | | | 11 | 2 | 4(+) | 12. |
| 16 | | | | | | | | | | | 11 | 2 | 10(SER) | 7.2 |
| 17 | | | | | | | | | | | 12 | 5 | 7(VAL) | 8.6 |
| 18 | | | | | | | | | | | 13 | 3 | 6(+) | 6.5 |
| 19 | | | | | | | | | | | 12 | 4 | 6(VAL) | 8. |
| 20 | | | | | | | | | | | 11 | 3 | 9(SER) | 3.7 |
| 21 | | | | | | | | | | | 9 | 2 | 8(CYS) | 2.3 |
| 22 | | | | | | | | | | | 11 | 5 | 9(LYS) | 3.7 |
| 23 | | | | | | | | | | | 11 | 4 | 4(ALA) | 14. |
| 24 | | | | | | | | | | | 10 | 3 | 8(SER) | 3.8 |
| 25 | | | | | | | | | | | 10 | 2 | 9(GLY) | 6.2 |
| 26 | | | | | | | | | | | 10 | 4 | 5(TYR) | 4. |
| 27 | | | | | | | | | | | 8 | 3 | 6(THR) | 4. |
| 28 | | | | | | | | | | | 8 | 2 | 7(PHE) | 2.3 |
| 29 | | | | | | | | | | | 8 | 5 | 3(SER) | 13. |
| 30 | | | | | | | | | | | 8 | 7 | 2(ASP) | 28. |
| 31 | | | | | | | | | | | 8 | 2 | 5(TYR) | 3.2 |
| 32 | | | | | | | | | | | 8 | 6 | 2(+) | 24. |
| 33 | | | | | | | | | | | 8 | 4 | 4(ILE) | 8. |
| 34 | | | | | | | | | | | 8 | 5 | 3(HIS) | 13. |
| 35A | | | | | | | | | | | | | | |
| 35B | | | | | | | | | | | | | | |
| 36 | | | | | | | | | | | 8 | 2 | 7(TRP) | 2.3 |
| 37 | | | | | | | | | | | 8 | 3 | 5(VAL) | 4.8 |
| 38 | | | | | | | | | | | 8 | 2 | 7(ARG) | 2.3 |
| 39 | | | | | | | | | | | 8 | 2 | 7(GLN) | 2.3 |
| 40 | | | | | | | | | | | 8 | 3 | 6(ALA) | 4. |
| 41 | | | | | | | | | | | 8 | 2 | 7(PRO) | 2.3 |
| 42 | | | | | | | | | | | 8 | 2 | 7(GLY) | 2.3 |
| 43 | | | | | | | | | | | 7 | 4 | 2(+) | 14. |
| 44 | | | | | | | | | | | 7 | 1 | 7(GLY) | 1. |
| 45 | | | | | | | | | | | 7 | 1 | 7(LEU) | 1. |
| 46 | | | | | | | | | | | 7 | 1 | 7(GLU) | 1. |
| 47 | | | | | | | | | | | 7 | 1 | 7(TRP) | 1. |
| 48 | | | | | | | | | | | 7 | 2 | 4(VAL) | 3.5 |
| 49 | | | | | | | | | | | 7 | 2 | 6(GLY) | 2.3 |
| 50 | | | | | | | | | | | 7 | 7 | 1(+) | 49. |
| 51 | | | | | | | | | | | 7 | 3 | 5(ILE) | 4.2 |
| 52 | | | | | | | | | | | 7 | 6 | 2(ASN) | 21. |
| 52A | | | | | | | | | | | 6 | 3 | 4(PRO) | |
| 52B | | | | | | | | | | | | | | |
| 52C | | | | | | | | | | | | | | |
| 53 | | | | | | | | | | | 7 | 6 | 2(SER) | 21. |
| 54 | | | | | | | | | | | 7 | 5 | 2(+) | 18. |
| 55 | | | | | | | | | | | 7 | 3 | 4(GLY) | 5.3 |
| 56 | | | | | | | | | | | 7 | 5 | 2(+) | 18. |
| 57 | | | | | | | | | | | 7 | 4 | 4(THR) | 7. |
| 58 | | | | | | | | | | | 7 | 7 | 2(ASN) | 21. |
| 59 | | | | | | | | | | | 7 | 3 | 5(TYR) | 4.2 |
| 60 | | | | | | | | | | | 6 | 4 | 3(ALA) | 8. |
| 61 | | | | | | | | | | | 6 | 3 | 3(PRO) | 6. |
| 62 | | | | | | | | | | | 6 | 4 | 2(+) | 12. |
| 63 | | | | | | | | | | | 6 | 3 | 3(PHE) | 6. |
| 64 | | | | | | | | | | | 7 | 4 | 4(GLN) | 7. |
| 65 | | | | | | | | | | | 7 | 5 | 3(GLY) | 12. |
| 66 | | | | | | | | | | | 7 | 1 | 7(ARG) | 1. |
| 67 | | | | | | | | | | | 6 | 2 | 5(VAL) | 2.4 |
| 68 | | | | | | | | | | | 6 | 3 | 5(THR) | 2.4 |
| 69 | | | | | | | | | | | 7 | 3 | 3(+) | 7. |
| 70 | | | | | | | | | | | 7 | 2 | 4(THR) | 3.5 |
| 71 | | | | | | | | | | | 7 | 3 | 3(+) | 7. |
| 72 | | | | | | | | | | | 7 | 2 | 5(ASP) | 2.8 |
| 73 | | | | | | | | | | | 7 | 5 | 2(+) | 18. |
| 74 | | | | | | | | | | | 7 | 1 | 7(SER) | 1. |
| 75 | | | | | | | | | | | 7 | 3 | 3(+) | 7. |
| 76 | | | | | | | | | | | 7 | 3 | 4(ASN) | 5.3 |
| 77 | | | | | | | | | | | 7 | 3 | 4(THR) | 5.3 |
| 78 | | | | | | | | | | | 7 | 3 | 4(ALA) | 5.3 |
| 79 | | | | | | | | | | | 7 | 3 | 5(TYR) | 4.2 |
| 80 | | | | | | | | | | | 7 | 2 | 6(MET) | 2.3 |
| 81 | | | | | | | | | | | 8 | 3 | 5(GLU) | 4.2 |
| 82 | | | | | | | | | | | 8 | 2 | 7(LEU) | 2.3 |
| 82A | | | | | | | | | | | 8 | 5 | 3(SER) | |
| 82B | | | | | | | | | | | 8 | 3 | 6(SER) | |
| 82C | | | | | | | | | | | 8 | 2 | 7(LEU) | |
| 83 | | | | | | | | | | | 8 | 4 | 4(ARG) | 8. |
| 84 | | | | | | | | | | | 8 | 4 | 5(SER) | 6.4 |
| 85 | | | | | | | | | | | 8 | 4 | 5(SER) | 6.4 |
| 86 | | | | | | | | | | | 8 | 3 | 5(GLU) : 4(GLU) | 4.8 : 8. |
| 86 | | | | | | | | | | | 8 | 3 | 8(ASP) : 7(ASP) | 1. : 2.3 |
| 87 | | | | | | | | | | | 8 | 3 | 6(THR) | 4. |
| 88 | | | | | | | | | | | 8 | 1 | 8(ALA) | 1. |
| 89 | | | | | | | | | | | 8 | 3 | 6(VAL) | 4. |
| 90 | | | | | | | | | | | 9 | 2 | 8(TYR) | 2.3 |
| 91 | | | | | | | | | | | 9 | 2 | 8(TYR) | 2.3 |
| 92 | | | | | | | | | | | 9 | 1 | 9(CYS) | 1. |
| 93 | | | | | | | | | | | 9 | 2 | 8(ALA) | 2.3 |
| 94 | | | | | | | | | | | 9 | 3 | 6(ARG) | 4.5 |
| 95 | | | | | | | | | | | 7 | 5 | 2(+) | 18. |
| 96 | | | | | | | | | | | 7 | 6 | 2(TYR) | 21. |
| 97 | | | | | | | | | | | 7 | 6 | 2(GLY) | 21. |
| 98 | | | | | | | | | | | 6 | 6 | 2(PHE) | 15. |
| 99 | | | | | | | | | | | 6 | 5 | 2(TYR) | 15. |
| 100 | | | | | | | | | | | 6 | 5 | 2(SER) | 15. |
| 100A | | | | | | | | | | | 5 | 4 | 2(ASN) : 2(ASP) | |
| 100B | | | | | | | | | | | 5 | 4 | 2(ASP) | |
| 100C | | | | | | | | | | | 4 | 3 | 2(TYR) | |
| 100D | | | | | | | | | | | 4 | 4 | 1(+) | |
| 100E | | | | | | | | | | | 2 | 2 | 1(+) | |
| 100F | | | | | | | | | | | 2 | 2 | 1(+) | |
| 100G | | | | | | | | | | | 2 | 2 | 1(+) | |
| 100H | | | | | | | | | | | 2 | 2 | 1(+) | |
| 100I | | | | | | | | | | | 1 | 1 | 1(TYR) | |
| 100J | | | | | | | | | | | 1 | 1 | 1(THR) | |
| 100K | | | | | | | | | | | 3 | 3 | 1(+) | |
| 101 | | | | | | | | | | | 7 | 4 | 3(ASP) : 2(+) | 9.3 : 18. |
| 102 | | | | | | | | | | | 8 | 5 | 3(TYR) | 13. : 16. |
| 103 | | | | | | | | | | | 8 | 3 | 6(THR) | 2.7 : 4. |
| 104 | | | | | | | | | | | 8 | 3 | 6(GLY) | |
| 105 | | | | | | | | | | | 8 | 5 | 5(GLN) : 4(GLN) | 4.8 : 10. |
| 106 | | | | | | | | | | | 8 | 1 | 8(GLY) | 1. |
| 107 | | | | | | | | | | | 9 | 4 | 4(THR) | 9. |
| 108 | | | | | | | | | | | 8 | 3 | 6(LEU) | 4. |
| 109 | | | | | | | | | | | 8 | 3 | 6(VAL) | 4. |
| 110 | | | | | | | | | | | 9 | 3 | 6(THR) | 2.3 |
| 111 | | | | | | | | | | | 9 | 1 | 9(VAL) | 1. |
| 112 | | | | | | | | | | | 10 | 2 | 9(SER) | 2.2 |
| 113 | | | | | | | | | | | 10 | 1 | 10(SER) | 1. |

ANTIBODY SPECIFICITIES: HUMAN HEAVY CHAINS SUBGROUP I

- 2) **SIE:** ANTI-HUMAN GAMMA G GLOBULIN; WA IDIOTYPE
 4) **WOL:** ANTI-HUMAN GAMMA G GLOBULIN; WA IDIOTYPE
 10) **STE:** COLD AGGLUTININ WITH ANTI-BLOOD GROUP I ACTIVITY
 16) **MAR:** ANTI-LIPOPROTEIN LIPASE
 25) **KOH:** ANTI-HUMAN GAMMA G GLOBULIN

CLASS: HUMAN HEAVY CHAINS SUBGROUP I

- 1) **EU:** IGG1-KAPPA
 2) **SIE:** IGM-KAPPA
 4) **WOL:** IGM-KAPPA
 5) **CA:** IGG1-
 6) **ND'CL:** IGE-
 7) **MOT:** IGG-
 8) **BRO'IGG:** IGG-KAPPA
 10) **STE:** IGG1-
 11) **BEN(I):** IGG3-
 12) **ZUC:** IGG3-
 13) **DI:** IGM-
 14) **BOT:** IGM-
 15) **OMM'CL:** IGG3-
 16) **MAR:** IGM-
 19) **WAR:** IGG1-
 20) **VIL:** IGG3-LAMBDA
 21) **DUN:** IGG4-
 22) **ADA:** IGA-
 23) **NOR:** IGA-
 24) **SAW:** IGG2-
 25) **KOH:** IGM-LAMBDA
 26) **RIC:** IGG3-
 27) **WIS:** IGG3-
 28) **VAU:** IGG1-
 29) **LEB:** IGG1-
 30) **SAC:** IGG1-KAPPA
 34) **HUS:** IGG3-

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 22) **ADA:** KAPLAN,A.P.,HOOD,L.,TERRY,W.D. & METZGER,H. (1971) IMMUNOCHEMISTRY,8,801-811. (CHECKED BY AUTHOR)
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 24) **SAW:** KAPLAN,A.P.,HOOD,L.,TERRY,W.D. & METZGER,H. (1971) IMMUNOCHEMISTRY,8,801-811. (CHECKED BY AUTHOR)
 25) **KOH:** KAPLAN,A.P.,HOOD,L.,TERRY,W.D. & METZGER,H. (1971) IMMUNOCHEMISTRY,8,801-811. (CHECKED BY AUTHOR)
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NOTES: HUMAN HEAVY CHAINS SUBGROUP I**IDENTICAL SETS OF FRAMEWORK SEGMENTS:**

- FR1: SET 1: VAU[28],LEB[29]. (2 IDENTICAL)
 FR2: SET 1: EU[1],HG3'CL[3]. (2 IDENTICAL)
 SET 2: WOL[4]. (IDENTICAL TO 2 HUMAN V-H-III: TI[4],TEI[10].)
 FR3: SET 1: ND'CL[6]. (IDENTICAL TO 1 HUMAN V-H-III: U266'CL[106].)
 FR4: SET 1: WOL[4]. (IDENTICAL TO 2 HUMAN V-H-II: MCE[14],NZU[15]; 4 HUMAN V-H-III: TI[4],DOB[31],WEA[33],NIE[34]; AND 1 MOUSE V-H-III: MOPC47A[48].)
 SET 2: ND'CL[6]. (IDENTICAL TO 1 HUMAN V-H-II: HIG1'CL[10]; 1 HUMAN V-H-III: U266'CL[106]; AND 1 MOUSE V-H-III: HDEX12[15].)

IDENTICAL SETS OF COMPLEMENTARITY DETERMINING REGIONS:

- CDR1:
 CDR2:
 CDR3: SET 1: HG3'CL[3]. (IDENTICAL TO 1 HUMAN V-H-III: LAMBDA-VH26'CL[2]; 1 MOUSE V-H-IB: PJ14'CL[22]; AND 5 MOUSE V-H-IIB: 186-2'CL[3]. 186-1'CL[5],102'CL[15],23'CL[18],3'CL[26].)
 SET 2: ND'CL[6]. (IDENTICAL TO 1 HUMAN V-H-III: U266'CL[106].)

IDENTICAL SETS OF J-MINIGENES:

- SET 1: ND'CL[6]. (IDENTICAL TO 1 HUMAN V-H-II: HIG1'CL[10]; AND 1 HUMAN V-H-III: U266'CL[106].)

NOTES: HUMAN HEAVY CHAINS SUBGROUP I (cont'd)

SPECIFIC NOTES:

- 3) **HG3'CL**: THE AMINO ACID SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF HUMAN FETAL LIVER GENOMIC DNA.
- 6) **ND'CL**: THE AMINO ACID SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF MOUSE CDNA. IT CORRESPONDS TO THE AMINO ACID SEQUENCE DETERMINED EARLIER EXCEPT THAT THE AMINO ACID SEQUENCE DETERMINATION GAVE PCA AT POSITION 1, VAL AT 2, VAL AT 34, GLY AT 35, ILE AT 48 AND HIS AT 49.
- 7) **MOT**: PAPAINE CLEAVES BETWEEN ARG 56 AND THR 57, AND BETWEEN ARG 62 AND SER 63.
- 12) **ZUC**: IT WAS FROM A CASE OF HEAVY CHAIN DISEASE.
- 14) **BOT**: IT WAS FROM A CASE OF IGM HEAVY CHAIN DISEASE.
- 15) **OMM'CL**: THE AMINO ACID SEQUENCE IS OBTAINED BY TRANSLATING THE NUCLEOTIDE SEQUENCE OF A CLONE OF HUMAN CELL LINE CDNA. IT WAS FROM A CASE OF HEAVY CHAIN DISEASE.
- 27) **WIS**: IT WAS FROM A CASE OF HEAVY CHAIN DISEASE. ITS RESIDUES AT POSITIONS 108 AND 109 ARE ASN AND CYS RESPECTIVELY, WHICH DO NOT CORRESPOND TO THE USUAL RESIDUES FOUND AT THESE POSITIONS IN HUMAN HEAVY CHAIN SUBGROUP I.
- 28) **VAU**: IT WAS FROM A CASE OF HEAVY CHAIN DISEASE.
- 29) **LEB**: IT WAS FROM A CASE OF HEAVY CHAIN DISEASE.
- 30) **SAC**: IT WAS FROM A CASE OF HEAVY CHAIN DISEASE.

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|-------------------------------|
| 16 | (ALA,SER) |
| 19 | (LYS,ARG) |
| 33 | (TYR,ALA) |
| 43 | (LYS,ARG,GLN) |
| 50 | (TRP,ILE,VAL,SER,GLY,GLU,GLN) |
| 54 | (PHE,SER) |
| 56 | (PRO,GLY) |
| 62 | (LYS,ARG) |
| 69 | (VAL,MET) |
| 71 | (LEU,ARG) |
| 73 | (PRO,THR) |
| 75 | (PHE,THR) |
| 95 | (GLY,GLU) |
| 100D | (TYR,PRO,SER,ASN) |
| 100E | (PHE,GLY) |
| 100F | (THR,ASP) |
| 100G | (TYR,SER) |
| 100H | (LEU,SER) |
| 100K | (TYR,PHE,LEU) |
| 101 | (PRO,ASP) |

HUMAN HEAVY CHAINS SUBGROUP II (cont'd)

VARIABILITY

| | | |
|---|------|-----------|
| | 0 | |
| | 1 | 4.5 |
| | 2 | 5.3 |
| | 3 | 8 |
| | 4 | 2.2 |
| | 5 | 11. : 14. |
| | 6 | 2.2 : 2.4 |
| | 7 | 3.7 |
| | 8 | 1. |
| | 9 | 2.2 |
| | 10 | 7.5 |
| | 11 | 1. |
| | 12 | 1. |
| | 13 | 2.5 |
| | 14 | 2.2 |
| 1 | 15 | 6. |
| | 16 | 6. |
| | 17 | 2.2 |
| | 18 | 1. |
| | 19 | 3.3 |
| | 20 | 1. |
| | 21 | 1. |
| | 22 | 1. |
| | 23 | 3.6 |
| | 24 | 6. |
| | 25 | 2.2 |
| | 26 | 1. |
| | 27 | 14. |
| | 28 | 3.7 |
| | 29 | 8 |
| | 30 | 5.7 |
| 1 | 31 | 13. |
| | 32 | 35. |
| | 33 | 8. |
| | 34 | 10. |
| | 35 | 40. |
| | 35A | |
| | 35B | |
| | 36 | 1. |
| | 37 | 2.2 |
| | 38 | 1. |
| | 39 | 2.2 |
| | 40 | 3.8 |
| | 41 | 1. |
| | 42 | 1. |
| | 43 | 5. |
| | 44 | 4. |
| | 45 | 1. |
| | 46 | 1. |
| | 47 | 1. |
| | 48 | 3.3 |
| | 49 | 3.3 |
| | 50 | 23. |
| | 51 | 6.7 |
| | 52 | 20. |
| | 52A | |
| | 52B | |
| | 52C | |
| | 53 | 11. |
| | 54 | 10. : 13. |
| | 55 | 3.3 |
| | 56 | 8. |
| | 57 | 15. |
| | 58 | 6.7 |
| | 59 | 5.7 |
| | 60 | 17. : 20. |
| | 61 | 6. |
| | 62 | 2.2 |
| | 63 | 1. |
| | 64 | 7.5 |
| | 65 | 6. |
| | 66 | 1. |
| | 67 | 3.3 |
| | 68 | 3.8 |
| | 69 | 6.7 |
| | 70 | 4.3 |
| | 71 | 8. |
| | 72 | 2.2 |
| | 73 | 2.2 |
| | 74 | 1. |
| | 75 | 2.9 |
| | 76 | 1. |
| | 77 | 2.2 |
| | 78 | 3.3 |
| | 79 | 3.3 |
| 3 | 80 | 1. |
| | 81 | 20. |
| | 82 | 10. |
| | 82A | |
| | 82B | |
| | 82C | |
| | 83 | 11. |
| | 84 | 3.1 |
| | 85 | 6.6 |
| | 86 | 1. |
| | 87 | 2.4 |
| | 88 | 2.4 |
| | 89 | 4.7 |
| | 90 | 1. |
| | 91 | 2.4 |
| | 92 | 1. |
| | 93 | 2.2 |
| | 94 | 2.8 |
| | 95 | 26 |
| | 96 | 50. |
| | 97 | 19. |
| | 98 | 26. |
| | 99 | 35. |
| | 100 | 40. |
| | 100A | |
| | 100B | |
| | 100C | |
| | 100D | |
| | 100E | |
| | 100F | |
| | 100G | |
| | 100H | |
| | 100I | |
| | 100J | |
| | 100K | |
| | 101 | 3.6 |
| | 102 | 6.3 |
| | 103 | 2.2 |
| | 104 | 2.2 |
| | 105 | 6. |
| | 106 | 2.2 |
| | 107 | 5.3 |
| | 108 | 12. |
| | 109 | 2.2 |
| | 110 | 5.3 |
| | 111 | 2.2 |
| | 112 | 2.2 |
| | 113 | 4. |

ANTIBODY SPECIFICITIES: HUMAN HEAVY CHAINS SUBGROUP II

8) **NEWM**: ANTI-3-(3'-HYDROXY-3',7',11',15',TETRAMETHYL HEXADECYL) 2-METHYL 1,4 NAPHTHOQUINONE(VIT.K10H)

CLASS: HUMAN HEAVY CHAINS SUBGROUP II

- 1) **COR**: IGG1-
- 2) **DAW**: IGG1-LAMBDA
- 3) **OU**: IGM-KAPPA
- 4) **MCE**: IGM-KAPPA
- 6) **HE**: IGG1-
- 8) **NEWM**: IGG1-LAMBDA
- 9) **WAH**: IGD-LAMBDA
- 12) **SA**: IGG2-LAMBDA
- 15) **NZU**: IGM-
- 16) **ERI**: IGD-

REFERENCE: HUMAN HEAVY CHAINS SUBGROUP II

- 1) **COR**: PRESS,E.M. & HOGG,N.M. (1970) BIOCHEM.J.,117,641-660. (CHECKED BY AUTHOR)
- 2) **DAW**: PRESS,E.M. & HOGG,N.M. (1970) BIOCHEM.J.,117,641-660. (CHECKED BY AUTHOR)
- 3) **OU**: PUTNAM,F.W.,SHIMIZU,A.,PAUL,C.,SHINODA,T. & KOHLER,H. (1971) ANN.N.Y.ACAD.SCI.,190,83-103. (CHECKED BY AUTHOR 06/15/83)
- 4) **MCE**: GERBER-JENSON,B.,KAZIN,A.,KEHOE,J.M.,SCHEFFEL,C.,ERICKSON,B.W. & LITMAN,G.W. (1981) J.IMMUNOL.,126,1212-1216. (CHECKED BY AUTHOR 12/15/80)
- 5) **CE-1 'CL**: TAKAHASHI,N.,NOMATA,T. & HONJO,T. (1984) PROC.NAT.ACAD.SCI.USA,81,5194-5198.
- 6) **HE**: CUNNINGHAM,B.A.,GOTTLIEB,P.D.,PFLUMM,M.N. & EDELMAN,G.M. (1971) PROGRESS IN IMMUNOLOGY (B.AMOS,ED.),ACADEMIC PRESS,N.Y.,PP.3-24. (CHECKED BY AUTHOR)
- 7) **SUP-T1 VH-JA'CL**: DENNY,C.T.,YOSHIKAI,Y.,MAK,T.W.,SMITH,S.D.,HOLLIS,G.F. & KIRSCH,I.R. (1986) NATURE,320,549-551.
- 8) **NEWM**: POLJAK,R.J.,AMZEL,L.M.,CHEN,B.L.,PHIZACKERLEY,R.P. & SAULF. (1974) PROC.NAT.ACAD.SCI.USA,71,3440-3444. (CHECKED BY AUTHOR WHO CORRECTED RESIDUES 6,9,15,16,24,26,27,29 THROUGH 35B,59,60 AS GIVEN IN TABLE OF THE FIRST EDITION OF THIS BOOK, AND HAS MORE RECENTLY REVISED RESIDUES 5,24,28,29,30,31,33,34,35,35A,35B,59,60 AND 101); POLJAK,R.J.,AMZEL,L.M.,CHEN,B.L.,CHIU,Y.Y.,PHIZACKERLEY,R.P.,SAULF, & YSERN,X. (1976) COLD SPRING HARBOR SYMP. QUANTITATIVE BIOL.,41,639-645; POLJAK,R.J.,NAKASHIMA,Y.,CHEN,B.L. & KONIGSBERG,W. (1977) BIOCHEMISTRY,16,3412-3420. THE SEQUENCE LISTED IN THE LAST REFERENCE IS GIVEN IN THE TABLE. (CHECKED BY AUTHOR, W.K., 09/30/78)
- 9) **WAH**: PUTNAM,F.W.,TAKAHASHI,N.,TETAERT,D.,DEBUJRE,B. & LIN,L.C. (1981) PROC.NAT.ACAD.SCI.USA,78,6168-6172. (CHECKED BY AUTHOR 11/30/81); TAKAHASHI,N.,TETAERT,D.,DEBUJRE,B.,LIN,L. & PUTNAM,F.W. (1982) PROC.NAT.ACAD.SCI.USA,79,2850-2854.
- 10) **HIG1'CL**: KUDO,A.,ISHIHARA,T.,NISHIMURA,Y. & WATANABE,T. (1985) GENE,33,181-189. (CHECKED BY AUTHOR 10/01/85)
- 11) **CAR**: FRANGIONE,B. (1968) PH.D. THESIS, UNIVERSITY OF CAMBRIDGE. (CHECKED BY AUTHOR)
- 12) **SA**: MILSTEIN,C. & FRANGIONE,B. (1971) BIOCHEM.J.,121,217-225. (CHECKED BY AUTHOR)
- 13) **IO**: MONTGOMERY,P.C.,BELLO,A.C. & ROCKEY,J.H. (1970) BIOCHIM.BIOPHYS.ACTA,200,258-266. (CHECKED BY AUTHOR)
- 14) **SPA**: FRANGIONE,B. & FRANKLIN,E.C. (1979) J.IMMUNOL.,122,1177-1179. (CHECKED BY AUTHOR 07/18/79)
- 15) **NZU**: ERICKSON,B.W.,GERBER-JENSON,B.,WANG,A.C. & LITMAN,G.W. (1981) MOL.IMMUNOL.,19,357-365. (CHECKED BY AUTHOR 11/30/81)
- 16) **ERI**: MILSTEIN,C.P. & DEVERSON,E.V. (1980) IMMUNOLOGY,40,657-664. (CHECKED BY AUTHOR 11/30/82)

NOTES: HUMAN HEAVY CHAINS SUBGROUP II

IDENTICAL SETS OF FRAMEWORK SEGMENTS:

- FR1:
FR2: SET 1: SUP-T1 VH-JA'CL[7],WAH[9]. (2 IDENTICAL)
FR3:
FR4: SET 1: MCE[14],NZU[15]. (2 IDENTICAL HUMAN V-H-II; ALSO 1 HUMAN V-H-I: WOL[4]; 4 HUMAN V-H-III: TIL[4],DOB[31],WEA[33],NIE[34]; AND 1 MOUSE V-H-III: MOPC47A[48].)
SET 2: HIG1'CL[10]. (IDENTICAL TO 1 HUMAN V-H-I: ND'CL[6]; 1 HUMAN V-H-III: U266'CL[106]; AND 1 MOUSE V-H-III: HDEX12[15].)

IDENTICAL SETS OF J-MINIGENES:

- SET 1: HIG1'CL[10]. (IDENTICAL TO 1 HUMAN V-H-I: ND'CL[6]; AND 1 HUMAN V-H-III: U266'CL[106].)

SPECIFIC NOTES:

- 4) **MCE**: IT IS A CRYOIMMUNOGLOBULIN AND IS DESIGNATED BY THE AUTHORS AS MCE. IN ORDER TO DIFFERENTIATE IT FROM ANOTHER MCE SEQUENCED BY CAPRA ET AL., IT IS DENOTED AS MCE.
- 5) **CE-1 'CL**: CELL LINE CESS
- 7) **SUP-T1 VH-JA'CL**: IT IS FROM A PATIENT SUFFERING FROM CHILDHOOD T-CELL LYMPHOMA WITH inv(14)(q11.2;q32.2). THE INVERSION ON CHROMOSOME 14 BRINGS THE VH GENE AND JA MINIGENE TOGETHER, GIVING RISE TO A HYBRID MOLECULE CONTAINING PART OF THE IMMUNOGLOBULIN GENE AND PART OF THE T-LYMPHOCYTE RECEPTOR FOR ANTIGEN GENE.
- 14) **SPA**: IT WAS FROM A CASE OF HEAVY CHAIN DISEASE.
- 15) **NZU**: IT IS A CRYOIMMUNOGLOBULIN.

+ THE FOLLOWING WERE EQUALLY AND MOST FREQUENTLY OCCURRING:

| AT POSITION | RESIDUES |
|-------------|----------------------|
| 5 | (ARG, GLN) |
| 10 | (ALA, GLY) |
| 32 | (THR, SER, ASP) |
| 35 | (CYS, SER) |
| 44 | (ALA, GLY) |
| 52A | (TYR, HIS) |
| 60 | (SER, ASN) |
| 81 | (LYS, THR) |
| 82 | (LEU, MET) |
| 82A | (THR, SER) |
| 82B | (SER, ASN) |
| 82C | (VAL, MET) |
| 85 | (VAL, ALA) |
| 96 | (PRO, LEU) |
| 99 | (PRO, ARG, GLY) |
| 100 | (TYR, PHE) |
| 100A | (ALA, THR) |
| 100D | (TYR, LEU) |
| 100F | (TYR, GLY) |
| 100H | (TYR, SER, ASP, ASN) |
| 100I | (SER, GLY, ASP) |

HUMAN HEAVY CHAINS SUBGROUP III

Table with columns for amino acid residues (1-23) and rows for protein sequences (0-113). Includes sub-headers for N-Terminal, N-Domain, C-Domain, and C-Terminal regions.



PATENT DOCKET NO. 709

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#23
8/20/93
11-12-93

In re Application of)
Paul J. Carter et al.)
Serial No. 07/715,272)
Filed: 14 June 1991)
For: Immunoglobulin Variants)

Group Art Unit: 1806
Examiner: L. Feisee

RECEIVED
NOV 05 1993
GROUP 1800

460 Point San Bruno Boulevard
South San Francisco, CA 94080
(415) 225-1896

NOTICE OF APPEAL

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

Sir:

Applicant hereby appeals to the Board of Appeals and Interferences from the decision dated May 19, 1993, of the Primary Examiner finally rejecting claims 1-11 and 17-21.

The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of \$270 to cover the fees for this appeal and to charge the deposit account for any further fees in regard to this patent application. A duplicate copy of this Notice is enclosed for this purpose.

Respectfully submitted,
GENENTECH, INC.

Janet E. Hasak

Janet E. Hasak
Reg. No. 28,616

Dated: October 15, 1993

CERTIFICATE OF MAILING (37 CFR 1.8a)

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

Louise Strasbaugh
Louise Strasbaugh

Date: October 15, 1993

RP14167 11/04/93 07715272 07-0630 140 119 270.00CH
w020.u



GP1806

PATENT DOCKET 709

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

18D1/10/25/93

In re Application of)
 Paul J. Carter et al.)
 Serial No. 07/715,272)
 Filed: 14 June 1991)
 For: Immunoglobulin Variants)

Group Art Unit: 1806

Examiner: L. Feisee

#22098
 RECEIVED
 NOV 05 1993
 GROUP 1800

460 Point San Bruno Boulevard
 South San Francisco, CA 94080
 (415) 225-1896

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

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 May 19, 1993 for an additional month, from September 19, 1993 to October 19, 1993. The extended time for response does not exceed the statutory period.

Please charge Deposit Account Number 07-0630 in the amount of \$250 to cover the cost of the second month extension fee less the first month extension fee paid in relation to the request for a one month extension of time filed on September 20, 1993. Any deficiency or overpayment should be charged or credited to this deposit account. A duplicate of this sheet is enclosed.

Respectfully submitted,
 GENENTECH, INC.

Janet E. Hasak
 Reg. No. 28,616

Date: October 15, 1993

RP14166 11/04/93 07715272 07-0630 140 116 250.00CH

CERTIFICATE OF MAILING (37 CFR 1.8a)

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

Louise Strasbaugh

Date: October 15, 1993



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 DOCKET NO. |
|---------------|-------------|-----------------------|---------------------|
| 07715,272 | 06/14/91 | CARIER | 209 |

GENENTECH, INC.
 ATTN: CAROLYN R. ADLER
 460 POINT SAN BRUNO BLVD.
 SOUTH SAN FRANCISCO, CA 94080

18M2/1021

| EXAMINER | |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
| | 21 |

DATE MAILED:

10/21/93

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

THE PERIOD FOR RESPONSE:

- is extended to run 4 months or continues to run _____ from the date of the final rejection
- expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

- Appellant's Brief is due in accordance with 37 CFR 1.192(a).
- Appellant's response to the final rejection, filed 9/20/93 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

- 1. The proposed amendments to the claim and/or specification will not be entered and the final rejection stands because:
 - There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.
 - They raise new issues that would require further consideration and/or search. (See Note).
 - They raise the issue of new matter. (See Note).
 - They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
 - They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: The language "of a human immunoglobulin subgroup" has not been defined with respect to the variable domain of a consensus antibody.

- 2. Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

- 3. Upon the filing an appeal, the proposed amendment will be entered will not be entered and the status of the claims will be as follows:

Claims allowed: None 12 and 13
 Claims objected to: None
 Claims rejected: 1-11, 17-21

DAVID L. LACEY
 SUPERVISORY PATENT EXAMINER
 GROUP 180 10/17/93

- 4. Applicant's response has overcome the following rejection(s): The rejection under 35 USC 112 first paragraph regarding "at least a portion" and "reasonably".
- 5. The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because the introduction of the language "human subgroup" is defined in the application but not in the affidavit. Also, it is not clear that the "consensus antibody" of the application would be identical to 846 or 859 of Queen et al. The definition of "consensus antibody" is not added in the affidavit.
- 6. The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

- The proposed drawing correction has has not been approved by the examiner.

Other

that the "consensus antibody" of the application would be identical to 846 or 859 of Queen et al. The definition of "consensus antibody" is not added in the affidavit.



AF

PATENT DOCKET 709

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Group Art Unit: 1806

Paul J. Carter et.al.

Examiner: L. FEISEE

Serial No. 07/715272

RECEIVED

Filed: June 14, 1991

DEC 29 1993

For: Immunoglobulin Variants GROUP 1806

460 Point San Bruno Boulevard
South San Francisco, CA 94080
(415) 225-1896

Handwritten notes:
JH/D
5/19/94
1-5-94

Handwritten: 1806

AMENDMENT PURSUANT TO 37 CFR § 1.116(a)

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

Sir:

Pursuant to 37 CFR § 1.116(a), please cancel claims 1-11, 17, and 19-21 of the above application. Claim 18 was canceled in the Amendment filed September 20, 1993. Applicants trust that the above-mentioned application with allowed claims 12 and 13 will be in condition for allowance following the entry of this amendment and look forward to receiving the Notice to this effect.

Handwritten: OK to enter 11/11/94

Respectfully submitted,
GENENTECH, INC.

Handwritten signature: Janet E. Hasak

Dated: December 13, 1993

Janet E. Hasak
Reg. No. 28,616

CERTIFICATE OF MAILING

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

Dated: 13 DEC 1993

Handwritten signature: Louise Strasbaugh
Louise Strasbaugh



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 DOCKET NO. |
|---------------|-------------|-----------------------|---------------------|

EXAMINER

| | |
|----------|--------------|
| ART UNIT | PAPER NUMBER |
|----------|--------------|

25

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

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

(1) Ward Lee (3) _____

(2) Nita Feiser (4) _____

Date of interview 1/11/94

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: _____

Identification of prior art discussed: _____

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Finality would be withdrawn.
Action both coming.

(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.)

Unless the paragraphs below have 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.

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

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.



UNITED STATES DEPARTMENT OF COMMERCE
 Patent and Trademark Office
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| SERIAL NUMBER | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---------------|-------------|----------------------|---------------------|

07/715,272 06/14/91 CARTER

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| F 709 |
| EXAMINER |

18M2/0203

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|-------------------------|
| FEISEE, L. |
| ART UNIT PAPER NUMBER |

GENENTECH, INC.
 ATTN: CAROLYN R. ADLER
 460 POINT SAN BRUNO BLVD.
 SOUTH SAN FRANCISCO, CA 94080

1806

DATE MAILED: 02/03/94

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 12/17/93 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. <input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-948. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> |

Part II SUMMARY OF ACTION

1. Claims 12 and 13 are pending in the application.
 Of the above, claims _____ are withdrawn from consideration.
2. Claims 1-11, 14-21 have been cancelled.
3. Claims _____ are allowed.
4. Claims 12-13 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. Acknowledgment 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 appears 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

Serial No. 715272

Art Unit 1806

The finality of the previous Office action is withdrawn in view of the following new grounds of rejection.

Claims 12 and 13 are pending in this application, and these claims are humanized light and heavy chain variable regions of a
5 previously referenced antibody 4D5.

Claims 12 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Hudziak et. al. or Fendly et. al. in view of Queen et. al.

Hudziak et. al. and Fendly et. al. both teach the production
10 and characterization of the 4D5 antibody (see Hudziak et. al. 1166-1167 and Fendly et. al. pages 1553-1554). Hudziak et. al. suggests the possible therapeutic role of the 4D5 antibody in human neoplasias which overexpress p185-HER2 (pages 1171, last paragraph) while Fendly et. al. disclose the possible use of anti-p185 HER2
15 antibodies for in vivo radioimaging for detection of relevant primary tumors. They do not describe the production of these antibodies in the humanized form.

Queen et. al. teach the production of antibodies against 1L-2 receptor in the humanized form, using computer modeling in order to
20 determine the modification of certain framework regions in conjunction with CDR grafting. The antibodies produced are than to be used for in vivo administration to human patients, either for diagnosis or therapy. It is known in the art that murine and even chimeric antibodies have characteristics which may severely limit
25 their use in human therapy. As foreign proteins, murine and chimeric antibodies may elicit immune reactions that reduce or destroy their therapeutic efficacy and/or evoke allergic or hypersensitivity reactions in patients. The probable need for readministration of such therapeutic modalities in neoplastic

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disorders increases these risks. The result would be tissue injury by virtue of antigen-antibody deposition.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make
5 humanized antibodies having the sequences of the 4D5 antibody. The methods of Queen et. al. were clear and self explanatory, and resulted in a high affinity antibody. One of ordinary skill in the art would have been motivated to humanize the 4D5 antibody in light of its potential therapeutic and diagnostic applicability.

10 Although the claims are drawn to specific amino acid sequences, it is maintained that the differences in amino acid sequence which would have been obtained using the method of Queen et. al. would not have been patentably distinct from the claimed amino acid sequences. Absent sufficient factual evidence to the
15 contrary the claims are obvious over the cited prior art.

35 U.S.C. § 101 reads as follows:

20 **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.**

Claims 12 and 13 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. These claims are
25 drawn to a light chain variable region polypeptide and a heavy chain variable region polypeptide which in and of themselves have no patentable utility. The specification does not disclose any

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practical utility for the individual polypeptides and does not present evidence that these polypeptides are capable of binding in any particular manner when not in association with each other.

Claims 12 and 13 are directed to an invention not patentably
5 distinct from claims 1, 3-9, and 40 of commonly assigned
07/977,453.

Specifically, the claims of the instant invention are drawn to the humanized version of the 4D5 antibody which is disclosed in copending application.

10 Commonly assigned 07/977,453, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In
15 order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. 1.78(c) and 35 U.S.C. § 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with
20 this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

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Claims 12 and 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1,3-9, and 40 of copending application Serial No. 07/977,453 in view of Queen et. al.. The
5 instant claims are drawn to the heavy chain and light chain variable regions of the 4D5 antibody. Copending application 07/977,453 claims an antibody with the same characteristics as 4D5, and also states within the claims that 4D5 antibody was useful for diagnosis and therapy of tumors expressing the p185 HER2 antigen on
10 their surface. The induction of HAMA responses upon repeated administration of rodent antibodies has led to the desirability of producing antibodies which are even more "near human" than chimeric antibodies. Queen et. al. describes the production of antibodies which contain essentially the CDR of rodents and are grafted into
15 human framework regions. These antibodies are also mutated in certain framework residues in order to produce functional and high affinity molecules. The procedure in Queen et. al. clearly teaches the particular framework residues that need to be changed in order to yield high affinity antibodies, and they teach how to determine
20 the appropriate residues using computer modeling programs. This protocol is adaptable to any number of antibodies. Therefore, not only was the production of non-immunogenic 4D5 antibodies desirable, but the procedure for producing the antibodies was also well known and practiced. It would have been prima facie obvious

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to one of ordinary skill in the art at the time the invention was made to use the claims of the copending application in combination with the reference of Queen et. al. in order to obtain high affinity functional humanized antibodies.

5 The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 U.S.P.Q. 619 (CCPA
10 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.78(d).

15 Claims 12 and 13 are provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 07/977,453 in view of Queen et. al.

20 The instant claims are drawn to the heavy chain and light chain variable regions of the 4D5 antibody. Copending application 07/977,453 discloses an antibody with the same characteristics as 4D5, and also discloses that 4D5 antibody is useful for diagnosis and therapy of tumors expressing the p185 HER2 antigen on their surface. The induction of HAMA responses upon repeated administration of rodent antibodies has led to the desirability of

Serial No. 715272

Art Unit 1806

producing antibodies which are even more "near human" than chimeric antibodies. Queen et. al. describes the production of antibodies which contain essentially the CDR of rodents and are grafted into human framework regions. These antibodies are also mutated in
5 certain framework residues in order to produce functional and high affinity molecules. The procedure in Queen et. al. clearly teaches the particular framework residues that need to be changed in order to yield high affinity antibodies, and they teach how to determine the appropriate residues using computer modeling programs. This
10 protocol is adaptable to any number of antibodies. Therefore, not only was the production of non-immunogenic 4D5 antibodies desirable, but the procedure for producing the antibodies was also well known and practiced. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was
15 made to use the claims of the copending application in combination with the reference of Queen et. al. in order to obtain high affinity functional humanized antibodies.

Copending application Serial No. 07/977,453 has a common assignee with the instant application. Based upon the earlier
20 effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

Serial No. 715272

Art Unit 1806

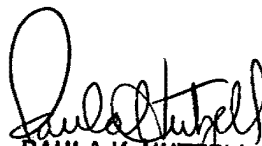
This provisional rejection might be overcome either by a showing under 37 C.F.R. 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by
5 another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lila Feisee whose telephone number is (703) 308-2731.

10 Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Feisee/lf
January 11, 1994

15


PAULA K. HUTZELL
PRIMARY EXAMINER
GROUP 1800

TO SEPARATE. D TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

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|-----------------------------|--|------------------------------|--------------------|---|
| FORM PTO-692 (REV. 2-92) | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | SERIAL NO. 07/715272 | GROUP UNIT 1806 | ATTACHMENT TO PAPER NUMBER 26 |
| NOTICE OF REFERENCES CITED | | APPLICANT(S) Carter et al | | |

U.S. PATENT DOCUMENTS

| * | DOCUMENT NO. | DATE | NAME | CLASS | SUB-CLASS | FILING DATE IF APPROPRIATE |
|---|--------------|------|------|-------|-----------|----------------------------|
| A | | | | | | |
| B | | | | | | |
| C | | | | | | |
| D | | | | | | |
| E | | | | | | |
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| H | | | | | | |
| I | | | | | | |
| J | | | | | | |
| K | | | | | | |

FOREIGN PATENT DOCUMENTS

| * | DOCUMENT NO. | DATE | COUNTRY | NAME | CLASS | SUB-CLASS | PERTINENT SHTS. PP. | |
|---|--------------|------|---------|------|-------|-----------|------------------------|-------|
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| P | | | | | | | | |
| Q | | | | | | | | |

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

| | |
|---|--|
| R | Queen et al. PNAS 86: 10029-10033 (1989) |
| S | Fendley et al. Cancer Research 5: 1550-1558 (1985) |
| T | Hudzi et al. Molecular and Cellular Biochemistry 1989 p. 1165-1172 |
| U | |

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|--------------------------------|------------------|
| EXAMINER <i>[Signature]</i> | DATE 11/11/94 |
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with this office action.
on 707.05 (a).)



UNITED STATES DEPARTMENT OF COMMERCE
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| SERIAL NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
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07/715,272 06/14/91 CARTER EXAMINER P 709

18M2/0506 ART UNIT PAPER NUMBER FEISEE, L.

GENENTECH, INC.
 ATTN: CAROLYN R. ADLER
 460 POINT SAN BRUNO BLVD.
 SOUTH SAN FRANCISCO, CA 94080

DATE MAILED:

27

1806

NOTIFICATION OF DEFECTIVE NOTICE OF APPEAL OR DEFECTIVE BRIEF

09/06/94

1. The Notice of Appeal filed _____ is:

A. Not acceptable for reason(s) that:

- (1) The Appeal fee required by 35 U.S.C. 41 (a)(6) and 37 CFR 1.17(e) was not submitted with the Notice of Appeal.
- (2) The submitted fee of \$ _____ is insufficient. The appeal fee required by 37 CFR 1.17(e) is \$ _____.
- (3) The Notice of Appeal was not timely filed.
- (4) The Appeal fee received on _____ was not timely filed.
- (5) The Appeal is not in compliance with 37 CFR 1.191 in that the claims have not been finally or twice rejected.
- (6) A Notice of Allowability was mailed by the Office on _____.

B. Defective and should be corrected as indicated. Applicant is given a TIME LIMIT of ONE MONTH from the date of this letter OR the TIME REMAINING IN THE RESPONSE PERIOD OF THE LAST OFFICE ACTION, whichever is longer, to complete the appeal. NO EXTENSION OF THIS ONE MONTH PERIOD MAY BE GRANTED UNDER 37 CFR 1.136(a) or (b) BUT THE PERIOD FOR RESPONSE SET IN THE LAST ACTION MAY POSSIBLY BE EXTENDED. If the appeal is not timely completed, the application will be abandoned.

- (1) The Notice of Appeal is not signed.
- (2) Identification of the appealed claim or claims is required under 37 CFR 1.191 (b).

2. The Brief filed _____ is NOT acceptable for the reason(s) indicated below.

The Appeal in this application will be dismissed unless the applicant makes the Brief acceptable. Extensions of time may be obtained under 37 CFR 1.136(a).

- A. The Brief and/or Brief fee is untimely. See 37 CFR 1.192.
- B. The requisite fee which must accompany the Brief has been omitted. See 37 CFR 1.17(f).
- C. The submitted Brief fee of _____ is not the proper amount. The Brief fee required by 37 CFR 1.17(f) is _____.

3. The Appeal in this application is DISMISSED because

- A. The fee for filing the Brief as required under 37 CFR 1.17(f) was not submitted or timely submitted and the period for obtaining an extension of time to file the brief under 37 CFR 1.136 has expired.
- B. The Brief was not filed, or was not timely filed and the period for obtaining an extension of time to file the brief under 37 CFR 1.136 has expired.

4. As the result of the dismissal in "3" above, this application:

- A. is abandoned since there are no allowed claims.
- B. is being returned to the examiner for disposition since it contains allowed claims. Prosecution on the merits is CLOSED.

David L. Lacey
 DAVID L. LACEY
 SUPERVISORY PATENT EXAMINER
 GROUP 180

9/1/94

REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

FRUITS 'H-BI
OCT 19 1999
FBI

In re Application of

Application Number

Filed

07/715,272

6-14-91

Group Art Unit

Examiner

Paper No. #28

Assistant Commissioner for Patents
Washington, DC 20311

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

- (A) referred to in United States Patent Number 5821337, column 1
- (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____ filed _____ on page _____ of paper number _____
- (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____ filed _____ or
- (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

2001 Jefferson Davis Hwy Apt. 0a-22202
Suite # 806

Brian Willingham

Signature

10 / 19 / 99

Date

Brian Willingham

Typed or printed name

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Approved by: [Signature]

(Initials)

Unit: [Signature]

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| In re Application of | |
| Application Number | Filed |
| 07/715272 | 6-14-91 |
| Group Art Unit | Examiner |

Paper No. #29

Assistant Commissioner for Patents
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

- (A) referred to in United States Patent Number 5821337 column _____
- (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____
- (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____, or
- (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

[Signature]
Signature

11-30-99
Date

Typed or printed name

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| Unit: | <u><i>[Initials]</i></u> |

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

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| In re Application of | |
| Application Number | Filed |
| 07/215272 | 6/14/91 |
| Group Art Unit | Examiner |
| | |

Paper No. 30

Assistant Commissioner for Patents
 Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE):

- (A) referred to in United States Patent Number 6054297 column _____
- (B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____, on page _____ of paper number _____.
- (C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____ or
- (D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:

Wayne Croteau
 Signature
WAYNE CROTEAU
 Typed or printed name

9-10-01
 Date

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REQUEST FOR ACCESS OF ABANDONED APPLICATION UNDER 37 CFR 1.14(a)

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In re Application of

Application Number

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Group Art Unit

Examiner

07/715272

6-14-91

Paper No. #31

Assistant Commissioner for Patents
Washington, DC 20231

I hereby request access under 37 CFR 1.14(a)(3)(iv) to the application file record of the above-identified ABANDONED application, which is: (CHECK ONE)

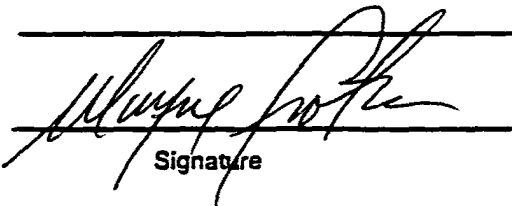
(A) referred to in United States Patent Number 6054997 column _____

(B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11, i.e., Application No. _____, filed _____ on page _____ of paper number _____

(C) an application that claims the benefit of the filing date of an application that is open to public inspection, i.e., Application No. _____, filed _____ or

(D) an application in which the applicant has filed an authorization to lay open the complete application to the public.

Please direct any correspondence concerning this request to the following address:


Signature

9-28-01
Date

Typed or printed name

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(Initials)

Unit: F.I.U.

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

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| In re Application of <i>Carter</i> | |
| Application Number <i>07/715272</i> | Filed <i>6/14/91</i> |
| Art Unit | Examiner |

Paper No. *#32*

Assistant Commissioner for Patents
Washington, DC 20231

1. I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

(A) referred to in:

United States Patent Application Publication No. *5821837*, page _____, line _____,
United States Patent Number _____, column _____, line _____, or
an International Application which was filed on or after November 29, 2000 and which
designates the United States, WIPO Pub. No. _____, page _____, line _____.

(B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or 1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Devita Miles

Signature

3/11/02

Date

Devita Miles

Typed or printed name

| | |
|------------------|--------------------|
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| Approved by: | <i>[Signature]</i> |
| | (Initials) |
| Unit: | <i>[Signature]</i> |

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

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| In re Application of | |
| Application Number 07/715,272 | Filed Jun. 14, 1999 |
| Art Unit | Examiner |

Paper No. **#33**

Assistant Commissioner for Patents
Washington, DC 20231

1. I hereby request access under 37 CFR 1.14(e)(2) to the application file record of the above-identified ABANDONED Application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and is: (CHECK ONE)

(A) referred to in:

United States Patent Application Publication No. _____, page _____, line _____,
United States Patent Number **6,407,213**, column **63**, line _____, or
an International Application which was filed on or after November 29, 2000 and which
designates the United States, WIPO Pub. No. _____, page _____, line _____.

(B) referred to in an application that is open to public inspection as set forth in 37 CFR 1.11(b) or 1.14(e)(2)(i), i.e., Application No. _____, paper No. _____, page _____, line _____.

2. I hereby request access under 37 CFR 1.14(e)(1) to an application in which the applicant has filed an authorization to lay open the complete application to the public.

Chris Riley
Signature

6/24/02
Date

Chris Riley
Typed or printed name

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| Approved by: <u>J. Bryant</u> (initials) |
| Unit: _____ |

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REQUEST FOR ACCESS TO AN APPLICATION UNDER 37 CFR 1.14(e)

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| In re Application of | |
| Application Number 07/715,272 | Filed 6-14-91 |
| Art Unit | Examiner |

Paper No. **#34**

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| Application Number <u>07/715,272</u> | Filed <u>6-14-91</u> |
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Paper No. 35

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| Application Number <u>07/715,272</u> | Filed <u>6-14-91</u> |
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Paper No. #36

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US006407213B1

(12) **United States Patent**
Carter et al.

(10) **Patent No.: US 6,407,213 B1**
(45) **Date of Patent: Jun. 18, 2002**

- (54) **METHOD FOR MAKING HUMANIZED ANTIBODIES**
- (75) **Inventors: Paul J. Carter; Leonard G. Presta, both of San Francisco, CA (US)**
- (73) **Assignee: Genentech, Inc., South San Francisco, CA (US)**
- (*) **Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.**
- (21) **Appl. No.: 08/146,206**
- (22) **PCT Filed: Jun. 15, 1992**
- (86) **PCT No.: PCT/US92/05126**
§ 371 (c)(1),
(2), (4) **Date: Nov. 17, 1993**

Related U.S. Application Data

- (63) **Continuation-in-part of application No. 07/715,272, filed on Jun. 14, 1991, now abandoned.**
- (51) **Int. Cl.⁷ C07K 16/00**
- (52) **U.S. Cl. 530/387.3; 435/69.6; 435/69.7; 435/70.21; 435/91; 536/23.53; 424/133.1**
- (58) **Field of Search 435/69.6, 69.7, 435/70.21, 91, 172.2, 240.1, 240.27, 252.3, 320.1, 328; 536/23.53; 424/133.1; 530/387.3**

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(List continued on next page.)

Primary Examiner—Anthony C. Caputa
Assistant Examiner—Minh-Tam Davis
(74) *Attorney, Agent, or Firm*—Wendy M. Lee

(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.

82 Claims, 9 Drawing Sheets

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| Application Number <i>07/715 272</i> | Filed <i>June 14, 91</i> |
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Paper No. 38

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| Application Number: <i>07/715,272</i> | Filed: <i>6/14/91</i> |
| Paper No. <i>#43</i> | |

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file records of the above-identified ABANDONED application, which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page _____, line _____

United States Patent Number *6639055*, column _____, line _____, or

WIPO Pub. No. _____, page _____, line _____

Related Information about Access to Pending Applications (37 CFR 1.14):

Direct access to pending applications is not available to the public but copies may be available and may be purchased from the Office of Public Records upon payment of the appropriate fee (37 CFR 1.19(b)), as follows. For published applications that are still pending, a member of the public may obtain a copy of:

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- any document in the file of the pending application.

For unpublished applications that are still pending:

- If the benefit of the pending application is claimed under 35 U.S.C. 119(a), 120, 121, or 365 in another application that has: (a) issued as a U.S. patent, or (b) published as a statutory invention registration, a U.S. patent application publication, or an International patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
 - the file contents;
 - the pending application as originally filed; or
 - any document in the file of the pending application.
- If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an International patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
 - the pending application as originally filed.

[Signature]

Signature

Rick Jordan

Typed or printed name

Registration Number, if applicable

703-418-2848

Telephone Number

4/2/04

Date

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In re Application of
CARTER
 Application Number: **07/175272** Filed: **6/14/91**
 PEPER No. **#44**

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I hereby request access under 37 CFR 1.14(a) to the application file records of the above-identified ABANDONED application, which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page _____, line _____
 United States Patent Number 6407213, column _____, line _____ or
 WIPO Pub. No. _____, page _____, line _____

Related Information about Access to Pending Applications (37 CFR 1.14):
 Direct access to pending applications is not available to the public but copies may be available and may be purchased from the Office of Public Records upon payment of the appropriate fee (37 CFR 1.19(b)), as follows:
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For unpublished applications that are still pending:
 (1) If the benefit of the pending application is claimed under 35 U.S.C. 119(a), 120, 121, or 365 in another application that has: (a) issued as a U.S. patent, or (b) published as a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
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 any document in the file of the pending application.
 (2) If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
 the pending application as originally filed.

[Signature]
 Signature
Rick Jordan
 Typed or printed name

 Registration Number, if applicable
703-418-2848
 Telephone Number

5/4/04
 Date

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In re Application of Carter
Application Number 07/715272 Filed 6/14/95

Paper No. #45

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,
United States Patent Number 6407213, column _____, line, _____ or
WIPO Pub. No. _____, page _____, line _____.

Related Information about Access to Pending Applications (37 CFR 1.14):

Direct access to pending applications is not available to the public but copies may be available and may be purchased from the Office of Public Records upon payment of the appropriate fee (37 CFR 1.19(b)), as follows:
For published applications that are still pending, a member of the public may obtain a copy of:

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 - the pending application as originally filed.

Andra Nyles
Signature

6/7/04
Date

Andra Nyles
Typed or printed name

Registration Number, if applicable
(703) 4154630
Telephone Number

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(initials)
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In re Application of _____

Application Number

Filed

07/15,272

06-14-91

Paper No. #46

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United States Patent Application Publication No. _____, page, _____ line _____.

United States Patent Number US 6,407,213 B1, column _____, line, _____ or

WIPO Pub. No. _____, page _____, line _____.

Related Information about Access to Pending Applications (37 CFR 1.14):

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For unpublished applications that are still pending:

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 - the file contents;
 - the pending application as originally filed; or
 - any document in the file of the pending application.
- (2) If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
 - the pending application as originally filed.

Rachel Hail

Signature

06-09-04

Date

Rachel Hail

Typed or printed name

Registration Number, if applicable

703-486-1150

Telephone Number

| | | |
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| Approved | <u>9/2003</u> | <u>Rick</u> |
| Unit | <u>RECEIVED</u> | <u>File Information Unit</u> |

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In re Application of

Carter

Application Number:

07/71522

Filed

6/14/91

Paper No. *# 47*

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____.

United States Patent Number *640723*, column _____, line, _____ or

WIPO Pub. No. _____, page _____, line _____.

Related Information about Access to Pending Applications (37 CFR 1.14):

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Dickson Pindexter
Signature

8/16/04
Date

Dickson Pindexter
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In re Application of _____

Application Number

07715272

Filed

Jun. 15, 91

Paper No. 48

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United States Patent Application Publication No. 6800730, page, _____ line _____

United States Patent Number _____, column _____, line, _____ or

WIPO Pub. No. _____, page _____, line _____

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- any document in the file of the pending application.

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Kevin Rodriguez

Signature

KEVIN RODRIGUEZ

Typed or printed name

Registration Number, if applicable

(703) 418-2772

Telephone Number

11-1504

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In re Application of

Chatter

Application Number

Filed

07/15/92

7/14/91

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Paper No. #49

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United States Patent Application Publication No. _____, page, _____ line

United States Patent Number 640723, column _____, line _____

WIPO Pub. No. _____, page _____, line _____

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Related Information about Access to Pending Applications (37 CFR 1.14) Information Unit

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- the file contents;
- the pending application as originally filed; or
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For unpublished applications that are still pending:

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 - any document in the file of the pending application.
- If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
 - the pending application as originally filed.

[Handwritten Signature]

Signature

11/29/04

Date

[Handwritten Name]
Typed or printed name

Registration Number, if applicable

7486113

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Arlington, VA 22202-3514

Telephone: (703) 308-2733

In re Application of

Application Number

07/713272

Filed

June 14, 1991

Paper No. 450

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is not within the file jacket of a pending Continued Prosecution Application (CPA) (37 CFR 1.53(d)) and which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,

United States Patent Number 6054297, column _____, line, _____ or

WIPO Pub. No. _____, page _____, line _____.

Related Information About Access to Applications Maintained in the Image File Wrapper System (IFW) and Access to Pending Applications in General

A member of the public, acting without a power to inspect, cannot order applications maintained in the IFW system through the FIU. If the member of the public is entitled to a copy of the application file, then the file is made available through the Public Patent Application Information Retrieval system (Public PAIR) on the USPTO internet web site (www.uspto.gov). Terminals that allow access to Public PAIR are available in the Public Search Room. The member of the public may also be entitled to obtain a copy of all or part of the application file upon payment of the appropriate fee. Such copies must be purchased through the Office of Public Records upon payment of the appropriate fee (37 CFR 1.19(b)).

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- (2) If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of the pending application as originally filed.

Darlene Jones

Signature

Darlene Jones

Typed or printed name

Registration Number, if applicable

7/418.0330

Telephone Number

Jan. 18, 05

Date

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| JAN 18 2005 |
| Approved by: _____ |
| (initials) |
| Unit: _____ |

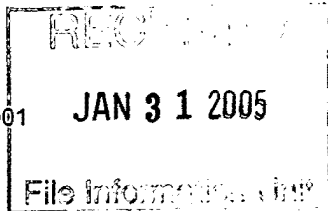
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| | |
|---|-------------------------|
| In re Application of <i>Carter et al</i> | |
| Application Number <i>07/715,272</i> | Filed <i>6/14/91</i> |

Paper No. *#51*

I hereby request access under 37 CFR 1.14(a)(1)(iv) to the application file record of the above-identified ABANDONED application, which is identified in, or to which a benefit is claimed, in the following document (as shown in the attachment):

United States Patent Application Publication No. _____, page, _____ line _____,
 United States Patent Number *6,800,738*, column *1*, line, _____ or
 WIPO Pub. No. _____, page _____, line _____.

Related Information about Access to Pending Applications (37 CFR 1.14):

Direct access to pending applications is not available to the public but copies may be available and may be purchased from the Office of Public Records upon payment of the appropriate fee (37 CFR 1.19(b)), as follows:
For published applications that are still pending, a member of the public may obtain a copy of:

- the file contents;
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- any document in the file of the pending application.

For unpublished applications that are still pending:

- (1) If the benefit of the pending application is claimed under 35 U.S.C. 119(e), 120, 121, or 365 in another application that has: (a) issued as a U.S. patent, or (b) published as a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
 - the file contents;
 - the pending application as originally filed; or
 - any document in the file of the pending application.
- (2) If the application is incorporated by reference or otherwise identified in a U.S. patent, a statutory invention registration, a U.S. patent application publication, or an international patent application publication in accordance with PCT Article 21(2), a member of the public may obtain a copy of:
 - the pending application as originally filed.

Rayline K. Petitt

Signature

Rayline K. Petitt

Typed or printed name

n/a

Registration Number, if applicable

703-415-3060

Telephone Number

Jan. 31, 2005

Date

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| In re Application of | |
| Application Number 07/715972 | Filed 6-14-91 |
| Paper No. #52 | |

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 Signature
WAYNE CROTEAU
 Typed or printed name

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Application Number
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Filed
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Application Number

07/715272

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459

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Eric White
Signature

3/27/06
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Paper No. #53

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US006407213B1

(12) **United States Patent**
Carter et al.(10) **Patent No.:** **US 6,407,213 B1**
(45) **Date of Patent:** **Jun. 18, 2002**(54) **METHOD FOR MAKING HUMANIZED ANTIBODIES**(75) **Inventors:** **Paul J. Carter; Leonard G. Presta,**
both of San Francisco, CA (US)(73) **Assignee:** **Genentech, Inc.,** South San Francisco,
CA (US)(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.(21) **Appl. No.:** **08/146,206**(22) **PCT Filed:** **Jun. 15, 1992**(86) **PCT No.:** **PCT/US92/05126**

§ 371 (c)(1),

(2), (4) **Date:** **Nov. 17, 1993****Related U.S. Application Data**(63) **Continuation-in-part of application No. 07/715,272,** filed on
Jun. 14, 1991, now abandoned.(51) **Int. Cl.⁷** **C07K 16/00**(52) **U.S. Cl.** **530/387.3; 435/69.6; 435/69.7;**
435/70.21; 435/91; 536/23.53; 424/133.1(58) **Field of Search** **435/69.6, 69.7,**
435/70.21, 91, 172.2, 240.1, 240.27, 252.3,
320.1, 328; 536/23.53; 424/133.1; 530/387.3(56) **References Cited****U.S. PATENT DOCUMENTS**

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(List continued on next page.)

Primary Examiner—Anthony C. Caputa
Assistant Examiner—Minh-Tam Davis
(74) **Attorney, Agent, or Firm**—Wendy M. Lee

(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.

82 Claims, 9 Drawing Sheets