# Exhibit 15

GP 1644/#

Patent Docket P0150C2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of<br>Shmuel Cabilly et al.<br>Serial No.: 08/422,187<br>Filed: 13 April 1995<br>For: RECOMBINANT IMMUNOGLOBULIN PREPARATIONS | Group Art Unit: 1644<br>Examiner: P. Gambel<br>CERTIFICATE OF MAILING<br>I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on<br>October 1, 1999<br>Wendy Lee |

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## AMENDMENT TRANSMITTAL

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

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

The fee has been calculated as shown below.

| | Claims Remaining After Amendment | | Highest No. Previously Paid For | Present Extra | Rate | Additional Fees |
|---|---|---|---|---|---|---|
| Total | 25 | - | 23 | 2 | $18 | $36.00 |
| Independent | 5 | - | 4 | 1 | $78 | $78.00 |
| 0 Multiple dependent claim(s), if any | | | | | $260 | $0.00 |
| | | | | | **Total Fee Calculation** | $114.00 |

x A Declaration of Dr. Richard Axel (with attached Exhibits A-J) is enclosed.
x The Commissioner is hereby authorized to charge Deposit Account No. 07-0630 in the amount of $114.00. **A duplicate copy of this transmittal is enclosed.**
x Petition for Extension of Time is enclosed.

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

Respectfully submitted,
GENENTECH, INC.

Date: October 1, 1999

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

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

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|---|---|
| Shmuel Cabilly et al. | Group Art Unit: 1644 |
| Serial No.: 08/422,187 | Examiner: P. Gambel |
| Filed: April 13, 1995 | CERTIFICATE OF MAILING<br>I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on<br>October 1, 1999<br>Wendy Lee |
| For: METHODS, VECTORS AND HOST CELLS FOR PRODUCING ANTIBODY POLYPEPTIDES (as amended) | |

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**AMENDMENT UNDER 37 C.F.R. § 1.111**

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action mailed April 20, 1999, please amend the claims and title of the present application as follows:

IN THE TITLE:

Please replace the title with the following title:

--METHODS, VECTORS AND HOST CELLS FOR PRODUCING ANTIBODY POLYPEPTIDES--.

IN THE CLAIMS:

Please cancel pending claims 67, 72, 81-86 and 89 without prejudice or disclaimer and add the following claims:

--90. (NEW) A method for making an antibody heavy chain or fragment thereof and an antibody light chain or fragment thereof each having specificity for a desired antigen, wherein the heavy chain or fragment thereof comprises a human

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constant region sequence and a variable region comprising non human mammalian variable region sequences, the method comprising culturing a recombinant host cell comprising DNA encoding the heavy chain or fragment thereof and the light chain or fragment thereof and recovering the heavy chain or fragment thereof and light chain or fragment thereof from the host cell culture.

91. (NEW) The method of claim 90 wherein the light chain or fragment thereof comprises a human constant region sequence and a variable region comprising non human mammalian variable region sequences.

92. (NEW) The method of claim 90 wherein the host cell comprises a vector comprising DNA encoding the heavy chain or fragment thereof and DNA encoding the light chain or fragment thereof.

93. (NEW) The method of claim 90 wherein the host cell comprises a vector comprising DNA encoding the heavy chain or fragment thereof and a further vector comprising DNA encoding the light chain or fragment thereof.

G1 Cont.

94. (NEW) The method of claim 90 wherein the non human mammalian variable region sequences are murine.

95. (NEW) The method of claim 90 wherein the host cell is a prokaryotic cell.

96. (NEW) The method of claim 95 wherein the prokaryotic cell is an *E. coli* cell.

97. (NEW) The method of claim 90 wherein the host cell is an eukaryotic cell.

98. (NEW) The method of claim 97 wherein the eukaryotic cell is a mammalian cell.

99. (NEW) The method of claim 98 wherein the mammalian cell is selected from the group consisting of a VERO, HeLa, Chinese Hamster Ovary (CHO), W138, BHK, COS-7 and MDCK cell.

100. (NEW) The method of claim 99 wherein the mammalian cell is a CHO cell.

101. (NEW) The method of claim 99 wherein the mammalian cell is a COS-7 cell.

102. (NEW) The method of claim 97 wherein the eukaryotic cell is a yeast cell.

G1 Cont.

103. (NEW) The method of claim 102 wherein the yeast cell is a *Saccharomyces cerevisiae* cell.

104. (NEW) A method for making an antibody or antibody fragment capable of specifically binding a desired antigen, wherein the antibody or antibody fragment comprises (a) an antibody heavy chain or fragment thereof comprising a human constant region sequence and a variable region comprising non human mammalian variable region sequences and (b) an antibody light chain or fragment thereof comprising a human constant region sequence and a variable region comprising non human

mammalian variable region sequences, the method comprising coexpressing the heavy chain or fragment thereof and the light chain or fragment thereof in a recombinant cell.

105. (NEW) The method of claim 104 further comprising recovering the antibody or antibody fragment from a cell culture comprising the recombinant cell.

106. (NEW) The method of claim 104 which results in the production of an antibody fragment.

107. (NEW) The method of claim 106 wherein the antibody fragment is an $F(ab)_2$ fragment.

108. (NEW) The method of claim 106 wherein the antibody fragment is a Fab fragment.

109. (NEW) The method of claim 104 which results in the production of an antibody.

G1 Cont.

110. (NEW) An antibody or antibody fragment capable of specifically binding a desired antigen and comprising (a) an antibody heavy chain or fragment thereof comprising a human constant region sequence and a variable region comprising non human mammalian variable region sequences and (b) an antibody light chain or fragment thereof comprising a human constant region sequence and a variable region comprising non human mammalian variable region sequences, wherein the antibody or antibody fragment has been made by the method of claim 104.

111. (NEW) A method for making an antibody capable of

specifically binding a desired antigen, the antibody comprising heavy and light immunoglobulin polypeptide chains each comprising a human constant region sequence and a variable region comprising non human mammalian variable region sequences, the method comprising the steps of (a) transforming a recombinant host cell with a replicable expression vector comprising DNA encoding the heavy immunoglobulin polypeptide chain and a replicable expression vector comprising DNA encoding the light immunoglobulin polypeptide chain, wherein each of the DNAs is operably linked to a promoter; and (b) culturing the host cell to produce a host cell culture.

112. (NEW) A replicable expression vector comprising DNA encoding an antibody heavy chain or fragment thereof and an antibody light chain or fragment thereof each having specificity for a desired antigen, the heavy chain or fragment thereof and the light chain or fragment thereof each comprising a human constant region sequence and a variable region comprising non human mammalian variable region sequences.

G1 Cont

113. (NEW) A recombinant host cell comprising the vector of claim 112.

114. (NEW) A recombinant host cell comprising (a) a vector comprising DNA encoding an antibody heavy chain or fragment thereof comprising a human constant region sequence and a variable region comprising non human mammalian variable region sequences and (b) a vector comprising DNA encoding an antibody light chain or fragment thereof comprising a human

constant region sequence and a variable region comprising non human mammalian variable region sequences.--

**REMARKS**

1. Interview

The undersigned confirms having met with Examiners Gambel and Schwartz in the interview August 23, 1999 and takes this opportunity to thank the Examiners for the courtesies extended in that interview. The Examiners indicated in the interview that the above claims would be free of new matter/written description rejections (see item 4 below) and that submission of the Axel declaration (see item 5 below) would overcome the outstanding enablement rejection.

2. Amendments

The title has been amended to conform with the claims.

All pending claims have been canceled and replaced with claims 90-114 herein. Former claim/specification basis for these claims can be found at least as follows:

Claim 90 - claims 67 and 89; page 23, lines 14-15
Claim 91 - page 12, lines 15-16
Claim 92 - page 23, lines 5-7
Claim 93 - page 23, lines 4-5
Claim 94 - claim 81
Claim 95 - claim 82
Claim 96 - claim 83
Claim 97 - claim 84
Claim 98 - claim 85
Claims 99 to 101 - claim 86

Claim 102 - page 16, line 34
Claim 103 - page 16, line 35
Claims 104 and 110 - claims 67 and 89; page 23, line 28
Claim 105 - page 23, lines 14-15
Claims 106 and 109 - claim 67
Claim 107 - page 13, line 32
Claim 108 - page 14, line 7
Claim 111 - claim 89
Claim 112 - claim 67
Claim 113 - claim 72
Claim 114 - claim 67; page 23, lines 4-5

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

3. Title

Amendment of the title herein obviates the objection to the title noted in item 5 of the above Office Action.

4. New matter

In item 7 of the above Office Action, claims 67, 72, 81-86 and 89 are rejected with respect to the language "having a human constant region sequence and non-human mammalian variable region sequences"; "transforming at least one recombinant host"; "first and second replicable expression vectors"; "first and second DNAs" and "operably linked to a promoter compatible with said host cell."

Applicants point out that basis for "non human mammalian variable region sequences" in the claims is found on at least page 12, lines 1 and 5-6; and the language "operably linked to a promoter"

in claim 111 finds basis in at least claim 30 of the originally filed application. The Examiner indicated in the above interview that these sections of the specification provided support for the language: "non human mammalian variable region sequences" and "operably linked to a promoter".

With respect to the Examiner's further new matter rejections concerning former claim 89 (now claim 111), in the interests of expediting prosecution and without acquiescing in the rejection, the offending language "at least one", "first and second replicable expression vectors", "first and second DNAs" and "compatible with said host cell" no longer appears in claim 111.

Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested in view of the above.

5. Enablement

In item 8 of the above Office Action, claims 53, 67-74 and 81-86 are rejected under 35 USC Section 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is noted that claims 53, 68-71 and 73-74 are no longer pending. The Examiner is of the view that the specification as of its priority date provided insufficient enablement for suitable vectors (including control regions), host cells, coding sequences and expression of recombinant immunoglobulin molecules, commensurate in scope with the claimed invention.

Applicants respectfully submit that the invention presently claimed was enabled by the application at its filing date. In support of this position, Applicants direct the Examiner's attention to the attached declaration of Dr. Richard Axel. Dr. Axel's declaration demonstrates that, based on the disclosure of the above application, the ordinarily skilled molecular biologist at the filing date could have made the presently claimed antibody polypeptides in a variety of different host cells using various recombinant expression vectors and methodologies, without exercising undue experimentation. As is evident from his curriculum vitae attached to the declaration as Exhibit A, Dr. Axel is a very experienced molecular biologist and was active in the field of recombinant DNA technology at the time of filing the present application.

Dr. Axel notes in paragraph 2 of his declaration that, while the Examples on pages 30-53 of the above application describe production of the recombinant antibody in *E. coli* host cells with recovery of individual immunoglobulin chains and reconstitution of an antibody capable of specifically binding antigen, the present application would have enabled other host cells, recombinant vectors, and methods for making the presently claimed functional antibody polypeptides at the relevant time.

Dr. Axel explains that, aside from prokaryotic host cells such as *E. coli* which are specifically exemplified, the ordinarily skilled molecular biologist at the priority date could have made an antibody or antibody fragment in yeast (*e.g. Saccharomyces cerevisiae;* see the specification at page 16, line 35) based on the teachings of the present application. As noted in paragraph 3 of his declaration, an antibody or antibody fragment expressed

in yeast could have been used, among other things, to detect a desired antigen.

Dr. Axel further states that the specification enabled reconstitution of an antibody or antibody fragment *in vivo* in a microorganism which secreted the IgG chains from the reducing environment of the cytoplasm (page 23, lines 32-33), *e.g.* into the periplasmic space of a gram negative bacteria such as *E. coli* (page 23, lines 21-25). See paragraph 4 of the Axel declaration. Therefore, the specification enabled production of antibodies or antibody fragments by methods which did not involve an *in vivo* reconstitution step.

In paragraph 5 of his declaration, Dr. Axel notes that, aside from the production of antibodies or antibody fragments in prokaryotes and eukaryotic microbes, production of antibodies or antibody fragments in a variety of alternative eukaryotic host cells is enabled by the application. For example, the ordinarily skilled molecular biologist at the relevant date could have expressed an antibody or antibody fragment in COS-7 cells (paragraph 6 of the Axel declaration) or Chinese Hamster Ovary (CHO) cells (paragraph 7 of the declaration), based on the teachings of the present application.

Hence, Applicants respectfully submit that the specification as of its priority date would have provided enabling disclosure for suitable vectors (including control regions), host cells, coding sequences and expression of recombinant immunoglobulin molecules commensurate in scope with the claimed invention.

Reconsideration and withdrawal of the rejection under 35 USC Section 112, first paragraph, is respectfully requested in view of the above.

6. Further Remarks

Applicants note that in earlier prosecution of this application, previously presented claims 53, 54 and 60-66 were rejected as anticipated by Boss *et al.* (US Patent 4,816,397). It is noted that the reference is not a proper reference against the above-captioned application, as its effective U.S. filing date (35 U.S.C. §102(e)) is after the filing date Applicants are entitled to. Boss *et al.* reflects, on its face, a date pursuant to 35 USC §102(e) of November 14, 1984, and a PCT publication date of September 27, 1984. The above-captioned patent application is entitled to an effective filing date of April 18, 1983, the filing date of the grandparent priority document (now US Patent 4,816,567).

The only relevant date for the Boss patent in advance of Applicants' effective filing date is the Boss UK priority date. This does not provide a basis for rejection. A United States patent is not available, as prior art, as of its foreign priority date. *In re Hilmer*, 149 USPQ 480 (CCPA 1966). Accordingly, apart from the distinctions between subject matter claimed herein and disclosed in the reference, it is clear that this reference was not applicable against previously presented claims 53, 54 and 60-66, and is not applicable against claims 90-114, as a matter of law.

Further, Applicants note that in the Amendment responsive to the Office Action (Paper No. 11) in which the rejection over Boss *et*

*al.* was made, a response was filed which relied on certain papers filed in Interference 102,572 and indicated that there was no patentable distinction between the subject matter claimed by Applicants in that interference, and in the above-captioned application. Specifically, on page 9 of the Amendment, Applicants stated:

> Although the evidence concerns the making of unaltered antibodies, it is submitted that the production of altered antibodies, as claimed in the present application, should not be viewed as a separate invention.

Applicants expressly withdraw that statement, and any reliance thereon, to the extent it would have any bearing on the claims presented herein. Applicants were not required to make any such affirmative representation, since the Boss *et al.* reference is not available as prior art.

Moreover, Applicants note that the claims pursued herein are directed to human/non human antibody polypeptides, not altered antibodies, generally. Claims directed to the production of human/non human antibodies or antibody fragments were not previously rejected under 35 USC §102(e) over Boss *et al.*

With respect to Interference 102,572, an appeal of the decision in that interference was filed on October 9, 1998 with the District Court for the Northern District of California, with the title Genentech, Inc. v. Celltech Limited, and has been assigned the case No. C98-3926 MMC ENE.

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Applicants believe that this case is now in condition for allowance and look forward to early receipt of same.

Respectfully submitted,
GENENTECH, INC.

Date: October 1, 1999 By: _____
Wendy M. Lee
Reg. No. 40,378

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



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EXHIBIT 15
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