EXHIBIT U

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

08/422,187

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/422,187	04/13/95	CABILLY	S 100/150C2

HM11/0706

GENENTECH INC
1 DNA WAY
SOUTH SAN FRANCISCO CA 94080-4990

EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1644	22

DATE MAILED: 07/06/98

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

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 4/22/98.

☐ This action is **FINAL**.

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

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

Disposition of Claims

☑ Claim(s) 53, 67-88 is/are pending in the application.

Of the above, claim(s) 75-80, 87, 88 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 53, 67-74, 81-86 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

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

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

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

☐ The specification is objected to by the Examiner.

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

Priority under 35 U.S.C. § 119

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

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

☐ received.

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

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

*Certified copies not received: _____.

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

Attachment(s)

☑ Notice of Reference Cited, PTO-892

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

☐ Interview Summary, PTO-413

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

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

PTOL-326 (Rev. 10/95)

* U.S. GPO: 1996-410-238/40050

Exhibit U
3

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1644, Technology Center 1600.

2. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 1/12/98 (Paper No. 19) has been entered.

3. Applicant's amendments, filed 1/12/98 and 4/22/98 (Paper Nos. 19/21), are acknowledged.
Claims 54-66 have been canceled. Claims 1-52 have been canceled previously.
Claim 53 has been amended.
Claims 81-88 have been added.

Claims 53 and 67-88 are pending
Claims 67-80 have been previously removed from consideration as drawn to the non-elected invention.

Upon reconsideration and in the interest of compact prosecution, the instant claims 67-74, drawn to replicable expression vectors and recombinant host cells are recombined with the instant process of producing an immunoglobulin.

Newly submitted claims 87-88 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons. Newly submitted claims 87-88 are drawn to immunoglobulins, previously withdrawn to a non-elected invention. The instant process and immunoglobulins are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case, the immunoglobulins can be made via a variety of recombinant and biochemical means.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 75-80 and 87-88 are withdrawn from consideration as being directed to a non-elected invention. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

Claims 53, 67-74 and 81-86 are under consideration in the instant application.

Non-elected claims 75-80 and 87-88 are held to be withdrawn from further consideration under 37 CFR 1.142(b).

4. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 1/12/98 (Paper No. 19).

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

6. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

7. Claims 53 and 81-86 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "specifically binding a particular known antigen" (recited in claim 53), "wherein said DNA sequences is in appropriate reading frame for production of said chain" (recited in claim 53), "wherein, if the immunoglobulin is deposited within the cells as insoluble particles, the mature heavy or light chains are recovered from the particles by cell lysis followed by solubilization in denaturant and reconstitution of the immunoglobulin" (recited in claim 53) and "murine" (recited in claim 81)

Applicant's amendment, filed 1/12/98 (Paper No. 19), directs support to various sections of the instant specification, but the exact wording or connotation of the instant claims are not readily apparent from said sections.

For example, page 3, lines 5-8 of the instant specification discloses antibodies to a desired antigen. However, it is not clear whether applicant intends "known" to be the same as "desired". Also, it is not clear whether "particular known antigen" would be limited to only those antigens known at the time the application was filed or disclosed in the specification. The metes and bounds of "particular known antigen" in the context of the application as filed is ambiguous and does not have written support in the application as filed.

For example, the instant specification discloses the recombinant expression of chimeric immunoglobulins. However, it is not clear where is the written support for "wherein said DNA sequences is in appropriate reading frame for production of said chain"

For example, the recitation of "wherein, if the immunoglobulin is deposited within the cells as insoluble particles, the mature heavy or light chains are recovered from the particles by cell lysis followed by solubilization in denaturant and reconstitution of the immunoglobulin" is not readily apparent from the cited sections, including the contemplation of "if" as well as the metes and bounds of "denaturant" and "reconstitution of the immunoglobulin".

For example, the specification discloses "mouse" and "non-human", but does not appear to support the term "murine" which encompasses both mouse and rat.

Therefore, the specification as filed does not provide sufficient written description or set forth sufficient metes and bounds of the above-mentioned phrases and limitations. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action Alternatively, applicant is invited to provide clear written support for the above-mentioned limitations.

8. The specification is objected to and claims 53, 67-74 and 81-86 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention essentially for the reasons set forth of record (Paper Nos. 11/15). In evaluating the facts of the instant case, the following is noted:

Applicant's arguments and citations, filed 1/12/98 (Paper No. 19) in conjunction with the Ravetch declaration under 37 C.F.R. § 1.132, filed 7/17/95 (Paper No. 4), have been fully considered but are not found convincing for the reasons of record set forth in Paper Nos. 11/15 and for the reasons set forth herein.

With respect to claims 67-74 with particular attention to issues concerning "altered antibody", "fragments" and those issues encompassed by the varying or one or more predetermined amino acid residues; applicant should address those issues raised in the 112, first paragraph, rejections of record (see Paper No. 15, Section 2). Applicant's amendment, filed 1/12/98 (Paper No. 19), which addresses similar issues concerning "altered antibodies" with respect to previous claims, does not address such issues with instant claims 67-74 now under consideration in the instant application.

Applicant acknowledges the rejection of record, which provides a number of references addressing the lack of predictability in producing chimeric immunoglobulins at the time the invention was made.

Applicant argues that the present application has a detailed disclosure of the recombinant production of chimeric antibodies, including the recombinant production of a CEA-specific chimeric antibody in E. coli host cells. Applicant argues that in view of the instant disclosure, particularly Examples E.1-E.3 as well as Examples E1.1-E1.10; a person skilled in the art would not have had difficulty at the priority date of the present application (4/8/83) to perform these steps. Also, applicant argues that while the amount of the anti-CEA antibody disclosed is low and this particular embodiment does not produce commercial quantities of antibody; this has no bearing on patentability. Applicant argues in conjunction with the Ravetch Declaration and certain references that various prokaryote would have been good candidates for the secretion expression of antibodies and would have been devoid of the difficulties with the formation of inclusion bodies in E. coli. Further, applicant in conjunction with various references argues that a number of host organisms would have suitable for the recovery of antibodies at the time the invention was made. Here, applicant also argues that the production of heterologous polypeptides in yeast was known in the art at the priority date of the present application.

In contrast to applicant's assertions, the various references of record and disclosed herein do indicate that the instant application was not enabled at the time the invention was made to support the recombinant production of the claimed chimeric immunoglobulins and fragments thereof in a wide variety of hosts that had activity which could be used by the skilled artisan. Therefore applicant did not provide sufficient guidance on how to make and how to use chimeric immunoglobulins, commensurate in scope with the claimed invention at the time the instant invention was made. There is insufficient guidance and directions as to the nature of the appropriate coding and regulatory sequences and protocol associated with the ability to producing a wide variety of specific chimeric antibodies in a wide hosts and expression systems.

In addition to the rejection of record under 35 USC 112, first paragraph; the following is noted. Also, it is noted that the following relies upon references including the Morrison review article cited in applicant's arguments.

The following references provide objective evidence that the generation of recombinant chimeric antigen-binding immunoglobulin molecules was not enabled at the time the invention was made. A specification must be enabling as of the filing date. It is noted that post-filing date references can be used as evidence of the state of the art existing on the filing date of the application. See MPEP 2164.05(a), including In re Hogan , 194 USPQ 527 (CCPA 1977) and In re Wright , 27 USPQ2d 1510 (Fed. Cir. 1993).

In contrast to applicant's assertions, the skilled artisan recognized the difficulties and limitations of producing proteins in various host cells, including bacterial and yeast cells at the time the invention was made and that the ability to generate recombinant active antibodies in a variety of host cells did not occur until after the priority date of the instant application. The difficulties and conditions associated with producing the instant disclosed CEA-specific chimeric antibodies supports the lack of predictability of providing for producing chimeric immunoglobulins by recombinant DNA technology at the time the invention was made..

The specification does not provide sufficient guidance and direction to specific host cells and expression vectors suitable for immunoglobulin gene expression in a variety of host cells, including yeast and bacterial cells, commensurate in scope with the claimed invention.

Morrison et al. (Adv. Immunol., 1989) reviews genetically engineered antibody molecules (see entire document, particularly section II. Antibody Production in Bacteria and Yeast on pages 66-69). Herein it is stated that:

Page 66-67, overlapping paragraph: Attempts to generate intact functional antibodies by expression in bacteria until recently met with limited success. Here it is stated to see note added in proof, which relies upon two 1988 references (see page 92). Efforts were made to produce antibody binding the hapten NP (Boss et al. 1984). The hapten specific λ chain lacking the hydrophobic leader sequence was expressed in E. coli; however it ended up as insoluble material which accumulated in inclusion bodies. In addition to the full-length light chain, a number of smaller, distinct proteins reactive with anti-λ antibodies were detected. These fragments could have resulted from proteolytic degradation, from premature termination of transcription, or from internal initiation of translation. Similarly the NP-specific μ heavy chain expressed

in bacteria was insoluble. When both heavy and light chains were expressed in the same bacterium, no antigen-binding activity was detected. Mild denaturation and treatment with reagents to promote disulfide interchange resulted in antigen-binding activity; however this in vitro reassembly was very inefficient with low specific activity. Again, low levels of antigen-binding activity could be reconstituted from the insoluble products by treatment with denaturing agents and reagents which promote disulfide interchange (Cabilly, 1984). Therefore, in contrast to applicant's reliance on the instant Example(s) of a CEA-specific chimeric antibody to support the enablement of the claimed invention; the art recognized that the instant Example(s) was/were not enabling for how to use the instant process for producing chimeric immunoglobulin to bind a particular antigen at the time the invention was made.

Page 69, paragraph one: Generally bacterial expression of antibody molecules has met with limited success. The bacterial expression of IgE Fc-like dimers remains an exception. It is clear that the E. coli biosynthetic environment does not support protein folding that required specific disulfide bond formation , glycosylation and polymeric polypeptide chain assembly. In each situation where all of these are required for protein function. The proteins synthesized did not exhibit any biologic activity.

Page 69, paragraph two: Efficient expression of the λ and μ chains from an NP-binding myeloma was achieved in yeast (Wood et al., 1985). .... However, antibodies isolated from the yeast cell extract had a specific activity only of 0.5% and no antigen binding could be observed in secreted antibodies.

With respect to generating antibodies in yeast cells; Horowitz et al. (PNAS, 1988) states that: while a number of single-chain heterologous proteins have been secreted from yeast, the secretion of foreign multimeric or heterodimeric proteins has not been reported (Introduction).

With respect to generating antibodies in bacteria or E. coli; Skerra et al. (Protein Engineering, 1991) states that: The development of methods for the expression of functional antigen-binding fragments of antibodies in E. Coli, (Better et al., 1988); Skerra and Pluckthun, 1988; Plucthun and Skerra, 1989) paved the way for the facile and rapid access to engineered antibodies (Introduction).

With respect to chimeric antibody molecules; Morrison et al. (Adv. Immunol., 1989; particularly sections VII-IX on pages 79-85) discloses that the first mouse/human chimeric antibodies were generated by others using systems not disclosed in the instant specification and after applicant's priority date (see Section VII). Here, it is acknowledged that manipulation of systems to produce chimeric antibodies encompassed by the claimed invention in a variety of hosts and to a variety of antigens relied upon manipulations and information subsequent to applicant's priority date. A number of studies subsequent to applicant's priority date were necessary to establish the requirements for assembly and secretion of chimeric antibody molecules.

Therefore the skilled artisan recognized the difficulties and limitations of producing proteins in bacterial and yeast cells at the time the invention was made and that the ability to generate antibodies in these host cells did not occur until after the priority date of the instant application. The specification does not provide sufficient guidance and direction to specific host cells and expression vectors suitable for immunoglobulin gene expression in eukaryotic cells, yeast, bacterial cells, commensurate in scope with the claimed methods. The ability to express and obtain functionally assembled immunoglobulins in bacterial and yeast host cells was unpredictable to one of skill in the art at the time the invention was made and guidance for

the skilled artisan to express and obtain functionally assembled immunoglobulin did not occur until after applicant's priority date. Furthermore, the enablement of such expression in bacterial and yeast host cells required various elements including expression vectors, host cells and conditions not disclosed in the specification as filed, as evidenced by Morrison et al. (Adv. Immuno., 1989), Skerra et al. (Protein Engineering, 1991) and Horowitz et al. (PNAS, 1988). Again, it is noted that applicant has relied upon references which support producing antibody and antibody fragments in various expression systems including bacteria and has relied upon conventional techniques at the time the invention was made. However, the success of producing functional recombinant immunoglobulins in a variety of host cells, including bacterial and yeast expression systems, as well as manipulating recombinant systems to produce functional chimeric immunoglobulins and fragments thereof did not occur until after applicant's priority date.

Although the instant application has provided methods for producing the particular CEA-specific chimeric immunoglobulins employing the particular plasmids and host cells and processing disclosed in the instant Examples of the instant specification; the instant application has not provided for the enablement of producing chimeric immunoglobulins encompassed by the claimed invention and asserted by applicant. In contrast to applicant's reliance on the specification as filed, the state of the art at the time the invention was made and evidence subsequent to applicant's priority date; applicant has not provided sufficient guidance and direction encompassing the requisite conditions, vectors and host cells to generate functional immunoglobulin molecules commensurate in scope with the claimed inventions for the reasons or record and set forth. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. The specification does not describe nor enable how to make and how to use functional recombinant chimeric in a manner reasonably correlated with the scope of the claims broadly including any number of immunoglobulin specificities, host cells, vectors, and processes to produce said immunoglobulin molecules. Without such guidance, expressing functional immunoglobulin molecules would be unpredictable and the experimentation left to those skilled in the art at the time the invention was made is unnecessarily, and improperly, extensive and undue.

In view of the lack of predictability of the art to which the invention pertains the lack of established protocols for effective expression of chimeric immunoglobulins at the time the invention was made; undue experimentation would be required to practice the claimed invention with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention and absent working examples providing evidence which is reasonably predictive that the claimed product-by-process immunoglobulins can be expressed in a manner wherein said immunoglobulins have the requisite stability and activity encompassed by the claimed chimeric immunoglobulins.

Applicant's arguments are not found persuasive for the reasons of record and set forth above.

10. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA

1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 67-74 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 53-60 of copending application USSN 08/931,121. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

11. Upon reconsideration of applicant's amended claims and arguments, filed 1/12/98 (Paper No. 19); the previous art rejections have been withdrawn.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Phillip Gambel, Ph.D.
Patent Examiner
Technology Center 1600
June 29, 1998

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP 1600 / 1640