IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

GENENTECH, INC. and CITY OF HOPE, Plaintiffs and Counterclaim Defendants, v. PFIZER INC., Defendant and Counterclaim Plaintiff.	C.A. No. 19-638-CFC [redacted] PUBLIC VERSION FILED: May 28, 2019
PFIZER INC., Counterclaim Plaintiff, v. HOFFMANN-LA ROCHE, INC., Counterclaim Defendant.	

PLAINTIFFS AND COUNTERCLAIM DEFENDANTS' OPENING BRIEF IN SUPPORT OF THEIR MOTION TO DISMISS DEFENDANT'S COUNTERCLAIMS AND TO STRIKE CERTAIN AFFIRMATIVE DEFENSES

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I. NATURE AND STAGE OF PROCEEDINGS

Plaintiff Genentech, Inc. ("Genentech") invented and developed the best-selling cancer drug Avastin® (bevacizumab). Seeking to profit from this groundbreaking work, Defendant Pfizer Inc. ("Pfizer") is seeking FDA approval to sell a biosimilar version of Avastin®. Because Pfizer's proposed product infringes patents held by or exclusively licensed to Genentech and Plaintiff City of Hope (collectively, "Plaintiffs")—including patents covering Avastin®, methods of using it, and methods of manufacturing it—Plaintiffs sued Pfizer for patent infringement on April 5, 2019. D.I. 1. Initiation of litigation followed months of pre-litigation exchanges under the Biologics Price Competition and Innovation Act, Pub. L. No. 111-148, §§ 7001-7003, 124 Stat. 119 ("BPCIA").

Pfizer filed its Answer, Affirmative Defenses, and Counterclaims on April 29, 2019. D.I. 14. In filing its Answer, Affirmative Defenses, and Counterclaims, Pfizer brought at least eight counterclaims against Hoffmann-La Roche, Inc. ("HLR")[1] as the owner of four of the patents-in-suit. D.I. 14 at Preamble; *see also id.* Counterclaim ¶¶ 7, 46, 50, 52, 58. HLR, however, did not file suit against Pfizer and has not joined this case as a plaintiff. Pfizer asserts forty-five counterclaims seeking declaratory judgments of noninfringement, invalidity, or unenforceability of all of the patents-in-suit. Pfizer also asserted corresponding affirmative defenses of noninfringement, invalidity, and unenforceability.

Plaintiffs and HLR now move under Rule 12(b)(6) to dismiss all of Pfizer's declaratory judgment counterclaims as barred by the BPCIA. Alternatively, Plaintiffs move under Rule 12(b)(6) to dismiss Pfizer's invalidity counterclaims and under Rule 12(f) to strike Pfizer's corresponding Third Affirmative Defense as barred by the BPCIA to the extent that those claims

[1] Pfizer incorrectly spelled Hoffmann-La Roche, Inc. throughout its Answer, Affirmative Defenses, and Counterclaims filed April 29, 2019 (D.I. 14).

are based on invalidity theories beyond those provided during the parties' pre-litigation exchanges. Plaintiffs also move under Rule 12(b)(6) to dismiss Pfizer's counterclaim for inequitable conduct and under Rule 12(f) to partially strike Pfizer's corresponding Fourth Affirmative Defense.

II. LEGAL STANDARD

"To survive a motion to dismiss" under Rule 12(b)(6), "a complaint must contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face.'" *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (quoting *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007)). When evaluating a motion to dismiss, "courts accept all factual allegations as true, construe the complaint in the light most favorable to the plaintiff, and determine whether, under any reasonable reading of the complaint, the plaintiff may be entitled to relief." *Fowler v. UPMC Shadyside*, 578 F.3d 203, 210 (3d Cir. 2009) (quoting *Phillips v. Cty. of Allegheny*, 515 F.3d 224, 233 (3d Cir. 2008)). A complaint cannot survive where a court can only infer that a claim is merely possible rather than plausible. *Iqbal*, 556 U.S. at 679.

Rule 12(f) authorizes the Court to "strike from a pleading an insufficient defense or any redundant, immaterial, impertinent, or scandalous matter." Fed. R. Civ. P. 12(f). Factual allegations underlying a defense must be construed in favor of the nonmoving party, but the Court "is not required to accept affirmative defenses that are mere bare bones conclusory allegations, and may strike such inadequately pleaded defenses." *Sun Microsystems, Inc. v. Versata Enters., Inc.*, 630 F. Supp. 2d 395, 408 (D. Del. 2009) (internal quotations omitted).

III. SUMMARY OF ARGUMENT

1. In forty-five counterclaims, Pfizer seeks declaratory judgments of noninfringement, invalidity, or unenforceability of all of the patents-in-suit. The BPCIA forecloses such claims where the biosimilar applicant did not comply with its pre-litigation production obligations, in particular the timely production of both its Abbreviated Biologics License Application ("aBLA")

and "such other information that describes the process or processes used to manufacture the biological product that is the subject of such application." 42 U.S.C. § 262(*l*)(2)(A); (9)(C). Pfizer failed to comply with the section 262(*l*)(2)(A) exchange, and consequently is barred from bringing any of its declaratory judgment counterclaims. All forty-five counterclaims should accordingly be dismissed.[2]

2. Even if these claims were permissible, Pfizer's validity challenges are facially deficient. In twenty-three of Pfizer's counterclaims, Pfizer purports to challenge validity and unenforceability on grounds broader than what was disclosed during its pre-litigation exchanges during the "patent dance," which the BPCIA does not permit. For these reasons, Pfizer's invalidity and inequitable conduct counterclaims should be stricken or dismissed with prejudice. Pfizer's Third and Fourth Affirmative Defenses suffer from the same defect and likewise must be stricken.

3. Pfizer's Counterclaim 8 is also facially deficient and should be dismissed. That counterclaim asserts that Genentech committed inequitable conduct during prosecution of one of the patents-in-suit by allegedly misrepresenting the content of the prior art. Pfizer's Counterclaim is deficient because Pfizer fails to allege that Genentech made any misstatements to the Patent Office. Further, Pfizer fails to adequately plead either deceptive intent or but-for materiality of the references. For these reasons, Pfizer's Counterclaim 8 should be dismissed with prejudice. Pfizer's Fourth Affirmative Defense suffers from the same defects as the inequitable conduct counterclaim, and accordingly, must be stricken-in-part.[3]

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[2] Plaintiffs filed a motion in this Court to dismiss Amgen's counterclaims on similar grounds in *Genentech, Inc. and City of Hope v. Amgen Inc.*, Case No. 17-1471, D.I. 107 (D. Del.). That motion is currently pending.

[3] Plaintiffs moved this court to dismiss similar counter-claims and affirmative defenses in two cases against Amgen, and those motions are currently pending. *See Genentech, Inc. and City of Hope v. Amgen Inc.*, Case No. 17-1471, D.I. 107 (D. Del.); *Genentech, Inc. and City of Hope v. Amgen Inc.*, Case No. 18-924, D.I. 86 (D. Del.).

IV. BACKGROUND

A. Pfizer Seeks to Market a Biosimilar Version of Avastin®.

This patent dispute arises from Pfizer's plans to market a biosimilar version of Avastin®, a drug Genentech developed for the treatment of various cancers. Avastin® is a genetically engineered antibody covered by a multitude of patents that are either owned by or exclusively licensed to Plaintiffs.

Pfizer submitted an aBLA seeking FDA approval to market PF-06439535, a biosimilar version of Avastin®. *See* D.I. 14 Counterclaim ¶ 30. Through a series of exchanges under the BPCIA, known informally as the "patent dance," the parties are encouraged to narrow disputes over infringement, in part by ensuring the "reference product sponsor" (here, Genentech) has received enough information to be able to narrow the patents to be asserted before filing suit. *See Sandoz, Inc. v. Amgen Inc.*, 137 S. Ct. 1664, 1670–71 (2017).

As part of the patent dance, the biosimilar applicant is required to produce to the reference product sponsor both "a copy of the application submitted . . . *and* such other information that describes the process or processes used to manufacture the biological product that is the subject of such application." 42 U.S.C. § 262(*l*)(2)(A) (emphasis added); D.I. 14 Counterclaim ¶ 19. The patent dance also requires the biosimilar applicant to provide the reference product sponsor "a detailed statement that describes" why the applicant believes any relevant patent held by the sponsor will not be infringed or is invalid or unenforceable. 42 U.S.C. § 262(*l*)(3)(B); D.I. 14 Counterclaim ¶ 22. The reference product sponsor then must respond to the biosimilar applicant's detailed statement. 42 U.S.C. § 262(*l*)(3)(C); D.I. 14 Counterclaim ¶ 23. The reference product sponsor may drop patents from its responsive statement based on what the biosimilar applicant says in its own detailed statement. Failure by either the biosimilar applicant or the reference

product sponsor at any step of the patent dance carries consequences in that party's ability to bring suit or obtain certain remedies. *See* 42 U.S.C. § 262(*l*)(9); 35 U.S.C. § 271(e)(6).

B. Pfizer Failed to Comply with the Required Exchanges Under the BPCIA.

Fully aware of its production obligations under the BPCIA, Pfizer nevertheless failed to produce its entire aBLA or all "other information that describes the process or processes used to manufacture the biological product that is the subject of such application," as required by 42 U.S.C. § 262(*l*)(2)(A). Although Pfizer disputes the relevance of its entire aBLA, it is undisputed that that portions of Pfizer's aBLA were not produced. Despite Pfizer's apparent allegation that it fully complied with section 262(*l*)(2)(A), *see* D.I. 14 Counterclaim ¶ 32, when read in light of Pfizer's entire Answer, Affirmative Defenses, and Counterclaims, it is clear that Pfizer has not produced its entire aBLA.[4] This by itself constitutes a failure to comply with the requirement that the biosimilar applicant "*shall* provide to the reference product sponsor a copy *of the application* submitted . . . under subsection (k)." 42 U.S.C. § 262(*l*)(2)(A) (emphases added).

Despite Pfizer's non-compliance, the parties continued with the rest of the patent dance. Genentech timely provided its list of patents pursuant to section 262(*l*)(3)(A). *See* D.I. 14 Counterclaim ¶ 33.[5] Pfizer then provided non-infringement and invalidity/unenforceability contentions for some, but not all patents pursuant to section 262(*l*)(3)(B), *see id.* ¶ 34. Notably, Pfizer did not provide any such contentions for six of the patents Genentech listed on its list pursuant to section 262(*l*)(3)(A). On January 18, 2019, Pfizer provided notice of its intent to

[4] Pfizer in its Counterclaims "repeats and incorporates by reference each of the foregoing Paragraphs of Pfizer's Answer and Affirmative Defenses to the Complaint." D.I. 14 Counterclaim ¶ 2. As such, even though Pfizer has alleged that "in full compliance with 42 U.S.C. § 262(*l*)(2)(A), Pfizer provided Genentech with Pfizer's BLA," *see id.* ¶ 32, its contrary allegation in the same pleading is properly considered by the Court in dismissing these claims.

[5] HLR owns four of the patents-in-suit, and Genentech is the exclusive licensee of those patents.

commence commercial marketing within 180 days pursuant to section 262(*l*)(8)(A). *Id.* ¶ 35. Genentech responded by serving Pfizer with infringement and validity contentions as required by section 262(*l*)(3)(C)—dropping certain patents in the process and narrowing the dispute as the statute contemplates. *See id.* ¶ 36, Answer ¶¶ 12, 14. After Pfizer informed Genentech that negotiations over the patents had concluded, *see id.* Counterclaim ¶ 37, Plaintiffs brought this suit.

V. ARGUMENT

A. Pfizer's Declaratory Judgment Claims Are Barred Under the BPCIA.

The BPCIA bars Pfizer from seeking declaratory judgments under 28 U.S.C. § 2201 *et seq.*, challenging any of the patents-in-suit. For this reason, all forty-five counterclaims should be dismissed for failure to state a claim under Rule 12(b)(6).

The BPCIA, as explained above, requires innovators and biosimilar makers to engage in a robust pre-litigation exchange of information, starting with the applicant's production of its aBLA within twenty days after the FDA accepts it, along with "such other information that describes the process or processes used to manufacture the biological product"—essential information for the innovator's fair evaluation of the full scope of potential infringement. 42 U.S.C. § 262(*l*)(2)(A). To encourage compliance, the statute provides carrots and sticks. For example, applicants who timely produce their aBLA and required "other information" on the prescribed schedule, and further comply with the statute's remaining requirements, are rewarded with substantial control over the timing and scope of any subsequent patent litigation. *Id.* § 262(*l*)(4), (*l*)(5), (*l*)(8). Conversely, applicants who fail to comply with the BPCIA's information disclosure requirements are prohibited from pursuing claims under the Declaratory Judgment Act:

> If a subsection (k) applicant fails to provide the application *and information* required under paragraph (2)(A), the reference product sponsor, *but not the subsection (k) applicant*, may bring an action under section 2201 of title 28 for a declaration of infringement, validity, or enforceability of any patent that claims the biological product or a use of the biological product.

Id. § 262(*l*)(9)(C) (emphases added).

The BPCIA makes clear, and other courts have held, that "failure to comply with the information exchange requirements of the BPCIA bar[s] the applicant from bringing a declaratory judgment action against the reference product sponsor." *Celltrion Healthcare Co. v. Kennedy Tr. for Rheumatology Research*, No. 14 Civ. 2256, 2014 WL 6765996, at *5 (S.D.N.Y. Dec. 1, 2014) (dismissing declaratory judgment action). The Supreme Court similarly has explained that

> [u]nder § 262(*l*)(9)(C), if an applicant fails to provide its application and manufacturing information to the sponsor under § 262(*l*)(2)(A), then the sponsor, but not the applicant, may immediately bring an action for a declaration of infringement, validity, or enforceability . . . .

Sandoz, 137 S. Ct. at 1666. Every court to consider this question has answered the same way.

It is undisputed that Pfizer failed to provide its entire aBLA to Genentech and for that reason alone it is in violation of section 262(*l*)(9)(C) and precluded from bringing an action for declaratory judgment. Additionally, Pfizer's refusal to provide "information required under paragraph (2)(A)" other than the application (which it failed to provide) constitutes an *additional* basis to find it has not complied with the statute.

This failure precludes Pfizer from asserting counterclaims in this matter. A counterclaim is indisputably an "action," and filing counterclaims constitutes "bring[ing] an action," as used in 42 U.S.C. § 262(*l*)(9)(C). As courts have recognized, seeking to assert counterclaims against a plaintiff "constitutes the initiation of a civil proceeding." *Krisa v. Equitable Life Assur. Soc.*, 109 F. Supp. 2d 316, 322 (M.D. Pa. 2000). Such an interpretation is also consistent with the legislative purpose behind the BPCIA's stick-and-carrot scheme of the patent dance; the BPCIA seeks to prohibit non-compliant subsection (k) applicants, such as Pfizer, from bringing protective

complaints or being able to keep a patent in litigation due to the filing of its own declaratory judgment counterclaim.[6]

Additionally, Pfizer's counterclaims constitute "bring[ing] an action" because Pfizer brought certain counterclaims against HLR. Indeed, Pfizer was required to formally serve HLR with a Summons and its Answer, Affirmative Defenses, and Counterclaims, and did so. *See* D.I. 18. Accordingly, all of Pfizer's counterclaims should be dismissed based on Pfizer's undisputed failure to provide information to Genentech under the BPCIA. As HLR has only been haled into court as a counterclaim defendant, HLR should correspondingly be dismissed as a party.[7]

B. Pfizer's Invalidity and Unenforceability Claims Exceed the Permissible Scope Under the BPCIA.

The Counterclaims challenging the validity of all the patents-in-suit, and the unenforceability of U.S. Patent No. 6,407,213 ("Carter/Presta") (Counterclaim 8) should be dismissed under Rule 12(b)(6), and Pfizer's corresponding Third and Fourth Affirmative Defenses stricken under Rule 12(f), for an additional reason—those allegations exceed the permissible scope under the BPCIA.

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[6] For at least this reason, the court's analysis in *Amgen Inc. v. Sandoz Inc.*, No. 14-cv-04741, 2015 WL 1264756, at *9 (N.D. Cal. Mar. 19, 2015) (portion regarding non-infringement and invalidity counterclaims not appealed), disagreeing in two paragraphs with the argument being put forth in this motion is not persuasive. Similarly, the court's analysis on the meaning of "bring an action" in the context of another statute in *Jonathan H. v. Souderton Area Sch. Dist.*, 562 F.3d 527, 529 (3d Cir. 2009), is not dispositive. As the court in *Jonathan H.* acknowledged, "The meaning of statutory language, plaint or not, depends on context." *Id.* at 529 (citation omitted). Whereas the statutory provision at issue in *Jonathan H.* dealt with the time in which an aggrieved party could effectively appeal an administrative decision, the BPCIA—and section (*l*)(9)(C) in particular—are concerned with creating an efficient pathway for approval of biosimilar products and encouraging compliance with the elaborate statutory scheme.

[7] At a minimum, Counterclaims 18–19, 26–27, 30–31, and 42–43 should be dismissed as against HLR due to Pfizer's non-compliance with the BPCIA, and HLR dismissed as a party.

As part of the patent dance, as discussed above, the parties are required to exchange contentions on the merits of the infringement, validity and enforceability of the asserted claims. Pfizer's Counterclaims and Affirmative Defenses treat the exchanges under the BPCIA as having no force or effect, leaving Pfizer free to assert validity and enforceability positions it did not disclose as part of the statutory exchanges. *See, e.g.*, D.I. 14 Third Defense ("All claims of the asserted patent [sic] are invalid for failure to meet the requirements of patentability under 35 U.S.C. § 101 *et seq.*, including *without limitation* §§ 101, 102, 103, 112 and/or any judicially-created doctrine of invalidity include obviousness-type double patenting.") (emphasis added); *id.* Counterclaim ¶ 62 ("The claims are invalid for failure to satisfy *one or more* provisions of Title 35 of the United States Code, including *but not limited to* 35 U.S.C. §§ 102, 103, and/or 112, and/or under the doctrine of obviousness-type double patenting.") (emphasis added); *see also* D.I. 14 Counterclaim ¶¶ 119–36 and Fourth Defense ("All claims of one or more of the asserted patents are unenforceable at least due to inequitable conduct and/or prosecution laches.") The statute does not permit this. Pfizer already provided its bases for contesting the validity of the patents-in-suit in its detailed statement pursuant to section 262(*l*)(3)(B), and in fact failed to provide any such bases for five of the patents-in-suit. [redacted] It cannot now exceed those positions in its counterclaims and affirmative defenses before this Court.

The "unique and elaborate process for information exchange" enacted in the BPCIA, including the exchange of contentions concerning infringement, validity, and enforceability the parties completed in March, was designed and intended "to resolve patent disputes" prior to the commencement of litigation. *Amgen Inc. v. Sandoz, Inc.*, 794 F.3d 1357, 1352 (Fed. Cir. 2015). Innovator companies, biosimilar applicants, and the courts depend on the exchange of information

that occurs during this process to make these litigations manageable—they determine which patents will be litigated, when they will be litigated, and how the litigation will unfold. By participating in the "patent dance," the applicant obtains valuable information about the innovator's infringement and validity positions, can prevent the innovator from filing a declaratory judgment suit, and gains "substantial control over the scope of the first phase of litigation" by limiting the number of patents in that phase to as few as one. *Sandoz*, 137 S. Ct. at 1671 (citing 42 U.S.C. § 262(*l*)(5)(B)(ii)); *see also* 42 U.S.C. § 262(*l*)(9)(B). If the applicant identifies compelling invalidity or non-infringement positions, the sponsor may drop certain patents from the "patent dance." Indeed, that narrowing occurred here as based on the arguments and representations in Pfizer's section (*l*)(3)(B)(ii)(I) contentions, Genentech declined to serve responsive contentions for certain patents, removing them from the scope of this dispute. The exchange of contentions may also lead the parties to prioritize resolution of certain patent disputes, selecting them for the "immediate patent infringement action" described in section 262(*l*)(6) and leaving other patents to be addressed after the applicant provides notice under section 262(*l*)(8).

It would defeat these objectives and throw the statutory scheme into chaos if the parties' contentions became non-binding once the BPCIA litigation started, as Pfizer's Counterclaims and Affirmative Defenses contemplate. Were applicants like Pfizer allowed to provide new invalidity or unenforceability contentions after completion of the "patent dance," they easily could avoid the obligation to provide meaningful section 262(*l*)(3)(B)(ii)(I) contentions, even for those potentially infringed patents the applicant fully intends to challenge. The applicant could, for example, provide limited contentions for the patents about which the applicant is most confident and then, for other patents, simply make the sort of boilerplate assertion found in Pfizer's counterclaims—"The claims are invalid for failure to satisfy one or more provisions of Title 35 of the United States

Code, including but not limited to 35 U.S.C. §§ 102, 103, and/or 112, and/or under the doctrine of obviousness-type double patenting." *E.g.*, D.I. 14 Counterclaim ¶ 62; *see also id.* ¶¶ 119–36. The applicant could leave the reference product sponsor in the dark about its true invalidity positions, or whether it would allege unenforceability, while still forcing the sponsor to serve responsive contentions, expose its own litigation strategy, and select patents to litigate in the immediate infringement action and later preliminary injunction proceedings based on incomplete information. *See* 42 U.S.C. § 262(*l*)(6), (*l*)(8). Indeed, Pfizer took precisely this approach here. [redacted]

Furthermore, an applicant could even refrain from providing contentions during the patent dance at all. That is precisely what Pfizer did as to the five patents for which Pfizer represented under 42 U.S.C. § 262(*l*)(3)(B)(ii)(II) that "it did not begin commercial marketing of the drug product described in Pfizer's BLA prior to the expiration" of the patents, and now admits that "it manufactured some aBLA product before the expiry" of the patents.[8] *See, e.g.*, D.I. 14 Answer ¶ 39. Yet after having failed to challenge the validity of these five patents during the "patent dance," Pfizer now claims the right to sandbag Plaintiffs with previously undisclosed grounds for invalidity. *See, e.g.*, D.I. 14 Counterclaim ¶ 62. Absent a requirement to disclose their invalidity and unenforceability positions fully during the exchanges, applicants could game the system and severely disadvantage innovator companies who narrowed their infringement cases and selected patents in reliance on the basis of incomplete assertions. Congress did not intend this.

[redacted]

In short, the contentions serve to focus the parties' negotiations; provide the basis for the parties to select which patents to litigate; ensure the orderly resolution of the narrowed disputes; and provide the parties and the court with an approximate timetable in which to conduct the litigation and obtain rulings before the biosimilar applicant changes the market irreversibly by commercializing its product. By stark contrast, under Pfizer's apparent interpretation in broadly pleading its Counterclaims and Affirmative Defenses, the contentions serve no limiting purpose. They cannot meaningfully "resolve patent disputes," *Amgen*, 794 F.3d at 1352, because the true scope of those disputes will not be clear until well after litigation has begun. This is an "absurd result" that the Court should reject. *See, e.g.*, *Lawson v. Suwannee Fruit & S.S. Co.*, 336 U.S. 198, 201 (1949) (rejecting interpretation that would "destroy one of the major purposes" of statute).

This Court should hold Pfizer to its previously served contentions and dismiss Pfizer's invalidity and unenforceability allegations under Rule 12(b)(6), and strike its corresponding Third and Fourth Affirmative Defenses under Rule 12(f).

C. Pfizer Fails to Adequately Plead Inequitable Conduct.

Counterclaim 8 seeks a declaration that one of the asserted patents, Carter/Presta, is unenforceable for inequitable conduct. *See* D.I. 14 Counterclaim ¶¶ 119–36; *see also id.* at Fourth Affirmative Defense (alleging-in-part that all of the asserted patents are unenforceable for inequitable conduct). Carter/Presta is a "composition of matter" patent that claims antibodies including bevacizumab, the active ingredient in Avastin® and the molecule Pfizer has copied. Any manufacture or use of bevacizumab in the United States prior to Carter/Presta's expiry would be infringing. Pfizer alleges in its counterclaims (but not in its section (*l*)(3)(B) contentions) that during prosecution, Genentech misrepresented the teachings of a prior art reference it had disclosed to the Examiner, U.S. Patent No. 5,530,101 (the "'101 Patent"). D.I. 14 Counterclaim ¶¶ 131–33. Although Pfizer claims these statements were "material to patentability" and that

Genentech made the alleged misrepresentations "with the specific intent to mislead or deceive the Patent Office," *id.* ¶ 120, it does not provide any substantive allegations in support.

Pfizer's allegations fail in multiple ways. *First*, Pfizer pleads a claim based on attorney argument, which cannot form the basis of an inequitable conduct claim. *Second*, even if attorney argument could be the basis for a claim, Pfizer does not plead that Genentech actually made a misstatement to the Examiner in response to her rejection. *Third*, even if the attorney argument were actionable misrepresentation, Pfizer has failed to adequately plead deceptive intent and but-for materiality—two required elements of a claim for inequitable conduct. Any of these provides a basis for the Court to dismiss Counterclaim 8 and partially strike Pfizer's Fourth Affirmative Defense.[9]

1. Attorney Argument Is Not Actionable Misconduct.

Pfizer does not allege that Genentech deliberately concealed any reference in its possession from the Patent Office. On the contrary, Pfizer acknowledges that the Patent Office possessed and explicitly considered the identified reference—the '101 Patent, D.I. 14 Counterclaim ¶ 121—the Examiner having cited the '101 Patent as the basis for rejections during prosecution, *id.* ¶¶ 125, 128. Rather, Pfizer's theory challenges Genentech's *arguments* about what that reference teaches. *Id.* ¶¶ 121, 133.

This is a legally inadequate allegation of inequitable conduct. The Federal Circuit has held repeatedly that a patent applicant's characterizations of the prior art cannot as a matter of law give rise to inequitable conduct where the Examiner could review the reference and was able to consider the argument and accept or reject it. *E.g.*, *Rothman v. Target Corp.*, 556 F.3d 1310, 1329 (Fed.

[9] Pfizer's Fourth Affirmative Defense asserts both "inequitable conduct and/or prosecution laches." D.I. 14 at Fourth Defense. This motion does not address prosecution laches, and as such there is no request to strike that portion of the defense.

Cir. 2009); *Young v. Lumenis, Inc.*, 492 F.3d 1336, 1349 (Fed. Cir. 2007). "While the law prohibits genuine misrepresentations of material fact, a prosecuting attorney is free to present argument in favor of patentability without fear of committing inequitable conduct." *Rothman*, 556 F.3d at 1328–29. This makes sense because the Examiner has the underlying references and the "discretion to reject or accept an applicant's arguments based on the examiner's own conclusions regarding the prosecution record." *Id.* at 1329; *see also Akzo N.V. v. U.S. Int'l Trade Comm'n.*, 808 F.2d 1471, 1482 (Fed. Cir. 1986) ("The examiner was free to reach his own conclusion regarding the Blades process based on the art in front of him."). In *Innogenetics, N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008), noting that "our precedent has made clear that an applicant is free to advocate its interpretation of its claims and the teachings of prior art," the Federal Circuit affirmed a summary judgment of no inequitable conduct and an award of attorneys' fees incurred in defending the charge. *Id.* at 1379.

Trial courts including in this District routinely dismiss or reject as a matter of law allegations that an applicant committed inequitable conduct by misrepresenting a reference before the Examiner:

> The court appreciates Precision's position that Shier and Paques expressly contradicted the teachings of Arnould. Precision does not cite authority demonstrating that this fact may substitute for independent evidence of intent to deceive, however, where the prior art at issue was a focus of the examination. Here, both examiners were free to credit or discount Shier and Paques' characterizations of Arnould in view of their own readings.

Cellectis S.A. v. Precision Biosciences, 883 F. Supp. 2d 526, 535 (D. Del. 2012) (citing, *inter alia*, MPEP § 716.01(c) ("The arguments of counsel cannot take the place of evidence in the record.")); *see also Bayer Schering Pharma AG v. Barr Labs., Inc.*, Civ. No. 05-2308, 2008 WL 628592, at *49 n.44 (D.N.J. Mar. 3, 2008) ("An applicant's arguments supporting its patent application do not constitute inequitable conduct when the examiner has the prior art before him throughout the

prosecution and, despite the applicant's attempt to distinguish that prior art, the examiner was free to reach his own conclusion regarding the prior art.") (internal quotation marks omitted); *Sepracor Inc. v. Teva Pharm. USA, Inc.*, Civ. No. 09-1302, 2010 WL 2326262, at *6 (D.N.J. June 7, 2010) (dismissing an inequitable conduct claim where study results were in front of the examiner, such that "any mischaracterization of the data would not rise to the level of inequitable conduct").

Pfizer's allegation of inequitable conduct should be dismissed for the same reason. Pfizer accuses Genentech of mischaracterizing the antibody numbering methodology for a particular antibody in the '101 Patent and submitting an allegedly misleading comparison of the '101 Patent to the claimed sequences. D.I. 14 Counterclaim ¶¶ 121, 133. In all of these instances, the art was disclosed to and considered at length by the Examiner, who was free to reach her own contrary conclusion.

This case is thus unlike cases that involve misrepresentations or omissions uniquely within the knowledge of the prosecuting attorney, and that the examiner is not able to evaluate on her own. *See, e.g.*, *Wyeth Holdings Corp. v. Sandoz, Inc.*, C.A. No. 09-955-LPS-CJB, 2012 WL 600715, at *12 (D. Del. Feb. 3, 2012). Here, the alleged misrepresentations or omissions concerned disclosures on the face of the references that the Examiner was capable of evaluating on her own. Nor are the allegations in this case analogous to cases like *Ring Plus, Inc. v. Cingular Wireless Corp.*, 614 F.3d 1354, 1359–61 (Fed. Cir. 2010), where the patent specification itself contained false statements concerning the disclosure of the prior art and the patent examiner made no independent evaluation of those references during prosecution. *See WesternGeco L.L.C. v. ION Geophysical Corp.*, No. 09-cv-1827, 2012 WL 567430, at *19 & n.10 (S.D. Tex. Feb. 21, 2012) (distinguishing *Ring Plus* from "situations such as this, where the prior art being interpreted by the prosecuting attorney has been provided to the Examiner in full, the attorney's characterizations of

the prior art can be considered only attorney argument, and therefore cannot give rise to a cause of action of inequitable conduct"). Accordingly, Pfizer's allegations in this case are insufficient as a matter of law to support a claim of inequitable conduct, and the Court therefore should dismiss Counterclaim 8 and strike Pfizer's inequitable conduct affirmative defense. *See Senju Pharm. Co. v. Apotex, Inc.*, 921 F. Supp. 2d 297, 307–08 (D. Del. 2013) (granting motion to dismiss unenforceability counterclaim and corresponding affirmative defense, where the only allegation of misrepresentation could not, on its face, constitute a basis for inequitable conduct).

2. Pfizer Fails to Plead Any Misrepresentation.

Even if the attorney argument could be considered the basis for an inequitable conduct claim, Pfizer fails to adequately plead that Genentech made any misrepresentation to the Examiner. "The court is not obligated to accept as true 'bald assertions,' 'unsupported conclusions and unwarranted inferences,' or allegations that are 'self-evidently false' at the motion to dismiss stage. *Senju*, 921 F. Supp. 2d at 304 (quoting *Rader v. ShareBuilder Corp.*, 772 F. Supp. 2d 599, 603 (D. Del. 2011)).[10]

The Examiner rejected certain of the proposed claims of Carter/Presta in view of the '101 Patent because she believed that a humanized antibody disclosed in the '101 Patent, called "anti-Tac," contained amino acid substitutions at a certain position that Genentech had claimed. *See* D.I. 14 Counterclaim ¶ 128; Ex. A (Oct. 25, 2000 Non-Final Rejection) at 7 ("PN=5,530,101, teach [sic] humanized anti-Tac antibody, wherein amino acid 93 is substituted in heavy chain . . .

[10] Because Pfizer has quoted directly from the prosecution history and its claim of inequitable conduct is based on statements in the prosecution history, consideration of the prosecution history does not convert this motion into one for summary judgment. *See Schmidt v. Skolas*, 770 F.3d 241, 249 (3d Cir. 2014); *ING Bank, fsb v. PNC Fin. Servs. Grp., Inc.*, 629 F. Supp. 2d 351, 354 (D. Del. 2009); *see also* Fed. R. Civ. P. 10(c).

(column 45).") The '101 Patent discloses a number of different antibodies, and uses two different numbering schemes in referring to the amino acids contain in the antibodies—some are identified using sequential numbering, and some are identified using what is known as Kabat numbering.[11] *See* D.I. 14 Counterclaim ¶ 132 (identifying Kabat and sequential numbering in the '101 Patent).

The anti-Tac antibody in the '101 Patent on which the Examiner based her rejection was numbered using sequential numbering, whereas Genentech had used Kabat numbering to identify the substitutions in its proposed claimed antibody. Genentech in its response pointed out this difference in numbering schemes to the Examiner. D.I. 14 Counterclaim ¶ 129 (quoting Ex. B (Apr. 25, 2001 Amend.) at 7). Genentech further explained that, as a result of those different numbering conventions, the specific amino acid substitution at the 93H position that the Examiner believed that the anti-Tac antibody possessed did not actually correspond with what was covered by Genentech's proposed claims. *Id.* Genentech also provided to the Examiner charts and sequence alignments which identified the sequential numbering and Kabat numbering for many of the amino acid substitutions in the antibodies disclosed in the '101 Patent. *Id.* ¶ 126; Ex. C (Oct. 6, 1997 Suppl. Amend.) at 6–10. The Examiner subsequently allowed Genentech's proposed claims to issue over the '101 Patent. D.I. 14 Counterclaim ¶ 130.

Even accepting Pfizer's facts as true for the purposes of this motion, Pfizer has not pleaded facts showing any ***actual*** misrepresentation or omission by Genentech. Pfizer never alleges that

[11] There are different ways to identify the amino acid positions in an antibody sequence. "Sequential numbering" involves consecutively numbering the amino acids in the sequence; due to sequence variations across antibodies, the amino acid positions identified by sequential numbering may be different from one antibody to another. As Carter/Presta explains, "Kabat numbering" (named for the scientist who devised this numbering convention) is a standardized approach to antibody sequence numbering that assigns fixed numbers to certain positions in the antibody amino acid sequence as determined by amino acid sequence alignments. D.I. 1-1, Ex. D, '213 Patent, 10:46–11:16. A sequence alignment compares the amino acid sequences of multiple antibodies by matching the overlapping portions of the sequences. *See, e.g.*, *id.* at 10:58–11:16.

Genentech misrepresented that the '101 Patent used a sequential numbering convention when referring to a substitution at position 93H in the humanized anti-Tac antibody (it does). And in any event, even if one were to apply Kabat numbering to the humanized anti-Tac antibody in the '101 Patent addressed by Genentech, Pfizer never alleges that it actually has a substitution at 93H under Kabat numbering (it does not). Instead, Pfizer points to ***different*** portions of the '101 Patent that utilized Kabat numbering when describing ***different*** humanized antibodies (not the humanized anti-Tac antibody that Genentech was addressing in its comments to the Examiner) to assert that Genentech misrepresented the contents of the '101 Patent. *See id.* ¶ 131–33 (referring to Table 5 and Figures 2B, 6B, 30A, and 40B in the '101 Patent that describe various humanized and murine antibodies, none of which is humanized anti-Tac). Those factual allegations do not add up to a misrepresentation by Genentech; the statements that are the basis for Pfizer's inequitable conduct defense were addressing a different issue for different antibodies.

Because Pfizer's non-conclusory allegations, taken as true, fail to allege that Genentech made a misrepresentation or omission to the Patent Office, Counterclaim 8 must be dismissed and the Fourth Affirmative Defense partially stricken.

3. Pfizer Fails to Plead All the Necessary Elements of Inequitable Conduct.

Pfizer's allegations of inequitable conduct also fail because Pfizer fails to plead deceptive intent or but-for materiality of the statements.

a) Pfizer has not pleaded facts sufficient to show a specific intent to deceive.

To prove inequitable conduct, Pfizer must demonstrate a "specific intent to deceive the PTO," and intent may not be inferred "solely from materiality." *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1290 (Fed. Cir. 2011) (en banc). As the court held in *Cellectis*, however, even where the allegation is that the applicants "expressly contradicted the teachings" of

a prior art reference, that does not "substitute for independent evidence of intent to deceive . . . where the prior art at issue was a focus of the examination." 883 F. Supp. 2d at 535. Pfizer alleges just that—that the Court should infer deceptive intent based on the existence of purported "misrepresentations". *See* D.I. 14 Counterclaim ¶ 133. Pfizer has alleged no other evidence of a specific intent to deceive; indeed, it cannot, as Genentech's statements were not erroneous as explained above. For this reason alone, Pfizer's inequitable conduct allegation should fail, Counterclaim 8 should be dismissed, and Pfizer's Fourth Affirmative Defense correspondingly partially struck.

b) Pfizer has not pleaded facts sufficient to show the alleged mischaracterization was "but-for" material.

In addition to deceptive intent, Pfizer is required to adequately plead "but-for materiality" in order to establish inequitable conduct. *Therasense*, 649 F.3d at 1291. Pfizer's counterclaim fails to do so. Allegations that an applicant mischaracterized a reference that is before the examiner fail to demonstrate but-for materiality. *See SunPower Corp. v. PaneClaw, Inc.*, C.A. No. 12-1633-MPT, 2016 WL 5107029, at *10 (D. Del. Sept. 19, 2016). And as explained above, Pfizer relies solely on allegations of mischaracterization (which are inaccurate) to allege inequitable conduct.

Even if allegations of mischaracterization could feasibly provide the necessary but-for materiality, the only allegation Pfizer offers in support of materiality—that the Examiner would not have withdrawn her rejection absent Genentech's alleged mischaracterization, *see* D.I. 14 Counterclaim ¶ 134—is inadequate. As Pfizer concedes, the alleged misrepresentation on April 25, 2001 cites back to similar earlier arguments Genentech provided to the Examiner on October 7, 1997. *See id.* ¶ 129. By Pfizer's own concession, Genentech's arguments were specifically rejected at least once, as there was a Non-Final Rejection in October 25, 2000, *after* these arguments were submitted to the Examiner. *Id.* ¶ 128. And a full examination of the file history

available on Public PAIR (https://portal.uspto.gov/pair/PublicPair) reveals that there was an additional rejection on December 23, 1997 after Genentech first made its argument to the Examiner about the numbering of amino acids in the anti-Tac antibody in question in the '101 Patent.[12] Where the PTO has considered and rejected an argument, the argument cannot be but-for material, and thus cannot support a claim for inequitable conduct. *See Courtesy Prods. LLC v. Hamilton Beach Brands Inc.*, C.A. No. 13-2012-SLR-SRF, 2015 WL 6159113, at *6 (D. Del. Oct. 20, 2015) (citing *Unverferth Mfg. Co., Inc. v. Par-Kan Co.*, No. 3:13-cv-97-TLS, 2014 WL 2206922, at *4–5 (N.D. Ind. May 27, 2014)). In light of the PTO's initial rejection of the claims after Genentech first submitted the alleged mischaracterization, the argument cannot provide the but-for materiality Pfizer needed to plead. Accordingly, Counterclaim 8 should be dismissed, and Pfizer's Fourth Affirmative Defense correspondingly partially struck.

VI. CONCLUSION

Plaintiffs and Counterclaim Defendants respectfully request that the Court dismiss each of Pfizer's Counterclaims, fully strike Pfizer's Third Affirmative Defense, partially strike Pfizer's Fourth Affirmative Defense, and dismiss HLR as a party to this case.

[12] Moreover, in its section (*l*)(3)(B) contentions, Pfizer did not assert that the '101 Patent either anticipates Carter/Presta or, in combination with other art, renders obvious the claims of Carter/Presta.

Dated: May 20, 2019

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CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on May 20, 2019 on the following counsel in the manner indicated:

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EXHIBIT A

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/146,206	11/17/93	CARTER	P 709P1

HM22/1025

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EXAMINER	
DAVIS,M	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/25/00

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

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/146,206	Applicant(s)
	Examiner	Group Art Unit 1642

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 8/30/99.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 43-105, 113-128 is/are pending in the application.

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

☐ Claim(s)____ is/are allowed.

☒ Claim(s) 43-105, 113-128 is/are rejected.

☐ Claim(s)____ is/are objected to.

☐ Claim(s)____ are subject to restriction or election requirement.

Application Papers

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

☐ The proposed drawing correction, filed on____ is ☐ approved ☐ disapproved.

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

☐ 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 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(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 1 7.2(a)).

*Certified copies not received:____.

Attachment(s)

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

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

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

☐ Other____

Office Action Summary

Effective February 7, 1998, the Group Art Unit location has been changed, and the examiner of the application has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Minh-Tam Davis, Group Art Unit 1642.

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 amendment filed on 08/26/98 has been entered.

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

Applicant cancels claims 106-112, and adds new claims 115-128, which are related to claims 43-105, and are not new matter.

Accordingly, claims 43-105, 113-128 are being examined.

The following are the remaining rejections.

REJECTION UNDER 35 USC 112 FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claims 43-105, 113-128 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized antibody muMAb4D5, and an anti-CD3 antibody, or variable domains thereof, comprising CDR amino acids which bind specifically to p185, or CD3, does not reasonably provide enablement for any humanized antibody , or variable

domain thereof, comprising CDR amino acids which binds non-specifically to any antigen, wherein the framework region amino acids are substituted at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, or of 24H, 73H, 76H, 78H and 93H, for treating any chronic diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 43-105, 113-128 are drawn to a humanized antibody , or variable domain thereof, comprising CDR amino acids which bind an antigen, or which bind $p185^{HER2}$. The framework region amino acids of said antibody or variable domain are substituted at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, or of 24H, 73H, 76H, 78H and 93H. Claim 105 is further drawn to a humanized antibody which lacks immunogenicity upon repeated administration for treating a chronic disease, and wherein its non-human CDR amino acids bind an antigen.

The specification discloses examples of humanized antibody muMAb4D5, anti-CD3, and anti-CD18 antibody, or variable domain thereof, comprising CDR amino acids which bind specifically to p185, CD3, and CD18, respectively. The substituted framework residues for the heavy chain of antibody muMAb4D5 are amino acids number 71, 73, 78, 93, and for the light chains are amino acid number 66 (table 3, and p.68). Only one humanized antibody, huMab4D5-8,

with all of the above five substitutions in the framework region binds to p185 3-fold more tightly than the murine counterpart. The humanized antibodies, huMab4D5-2 and huMab4D5-3, with one and four substitutions in the framework region, respectively, are, however, at least 10-fold less potent than the murine counterpart, having a K_d of 4.7nM and 4.4nM, respectively, as compared to a K_d value of 0.30nM of the murine counterpart. The substituted framework residues for the heavy chain of antibody anti-CD3 are amino acids number 75 and 76. Although the specification discloses that humanized anti-CD3 antibody enhances the cytotoxic effects of cytotoxic T cells 4-fold against tumor cells expressing $p185^{HER2}$, there is no disclosure in the specification concerning the binding affinity of the humanized anti-CD3 or anti-CD18 as compared to the murine counterpart. The claims however encompass any humanized antibody, without any specificity, binding to $p185^{HER2}$ or any antigen, with just any one of substitution at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, of 24H, 73H, 76H, 78H and 93H. The claims further encompass any humanized antibody for treating any chronic disease.

One cannot extrapolate from humanizing one antibody, which binds to $p185^{HER2}$ 3-fold more tightly than the murine counterpart, to humanizing any antibody, wherein its affinity would be up to 3-fold or at least 3-fold more tightly than the murine counterpart, or wherein its affinity would be still intact for therapeutic purposes. In addition, one cannot extrapolate from humanizing an anti-p185 antibody by substitution at all five framework amino acids number H71, H73, H78, H93 and L66 in an anti-p185 antibody, or from humanizing an anti-CD3 antibody by

substitution at both framework amino acids number H75 and H76 in an anti-CD3 antibody, with humanizing any antibody by substitution at only any one amino acid selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, or of 24H, 73H, 76H, 78H and 93H. Patent '101 teach that different antibodies require different combinations of different substitutions in the light chain and heavy chain (table 1). Even the specification discloses that only one variant, huMab4D5-8, wherein all five framework amino acids number H71, H73, H78, H93 and L66 are substituted, binds to p185 3-fold more tightly than the murine counterpart. Other variants, with only one or even four substitutions have much less binding affinity than the murine counterpart(table 3). Thus it is unpredictable that substitution at only one framework amino acid in any antibody, or any kind of combination of framework amino acid substitutions would result in a humanized antibody that binds to its antigen 3-fold more tightly than its murine counterpart, or retains adequate affinity for therapeutic purposes. The specification does not disclose whether subtitution at only one of the claimed amino acid positions would produce a humanized antibody that has 3-fold more in affinity as the murine counterpart, or retains adequate affinity for therapeutic purposes. The specification does not disclose which combination of what substituted framework amino acids, other than H71, H73, H78, H93 and L66 for anti-p185 antibody, and H75 and H76 in anti-CD3 antibody would produce a humanized antibody that has 3-fold more in affinity as the murine counterpart, or retains adequate affinity for therapeutic purposes. It is well known in the art that not any substitution at any amino acids would produce a humanized

antibody having an affinity similar to the murine counterpart, unless it is tested by binding assays. The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to make the claimed humanized antibodies with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Moreover, a humanized antibody that does not have a specificity for a particular antigen is of little practical use for treating a chronic disease, because said antibody would not target to the target tissues. In addition, although the specification discloses that murine anti-$p185^{HER2}$ antibody has been suceessfully used in treating tumor cell growth in culture (p.5), $p185^{HER2}$ and CD-3 are not specific for any tissues responsible for chronic disease, e.g. chronic headache, chronic lung inflammation, or chronic kidney disease. The specification does not disclose how to treat any chronic disease using the claimed humanized antibody. In the absence of a teaching of a method of treating any chronic disease, using the claimed humanized antibody, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

REJECTION UNDER 35 USC 102, NEW REJECTION

1. New claims 115-117, 123, 127 are rejected under 35 USC 102(e) or 102(b) pertaining to anticipation by PN=5,530,101 or Queen et al, 1989, PNAS, USA, 86: 10029-10033.

Claims 115-117, 123, 127 are drawn to a humanized antibody or its heavy chain variable domain comprising non-human CDR amino acids, and a framework region amino acid wherein amino acid position 93H is substituted, utilizing the numbering system of Kabat, and wherein the substituted residue is the residue found in the corresponding location of the non-human antibody.

PN=5,530,101, teach humanized anti-Tac antibody, wherein amino acid 93 is substituted in heavy chain, using the aligned Kabat Eu sequence to provide the framework for the humanized antibody (column 45).

Queen et al, PNAS, teach humanized anti-Tac antibody, wherein amino acid 93 is substituted in heavy chain, using the aligned Kabat Eu sequence to provide the framework for the humanized antibody (figure 2).

Since anti-Tac antibody is a mouse antibody, its inherent heavy chain variable domain would comprise non-human CDR amino acids. Thus the humanized antibody and its heavy chain variable domain taught by patent '101 or Queen et al is the same as the claimed invention.

2. Claims 43, 44, 48, 55, 67, 71, 105, 115-117, 120, 127 are rejected under 35 USC 102(e) pertaining to anticipation by PN=5,530,101.

It is noted that PN=5,530,101 is filed on Sept, 1990, which is within a year before the claimed filing date of 06/14/91.

Claims 43, 44, 48, 55, 67, 71, 105, 115-117, 120, 127 are drawn to a humanized antibody or its heavy chain variable domain comprising non-human CDR amino acids, and a framework region amino acid wherein amino acid position 38L, 67L, 69H, 73H or 93H is substituted,

utilizing the numbering system of Kabat, and wherein the substituted residue is the residue found in the corresponding location of the non-human antibody. Claim 105 is further drawn to said humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient.

PN=5,530,101 teaches humanized antibodies, wherein amino acid 38 or 67 are substituted in light chain (table 1, antibody Fd79 and M195, respectively), and amino acid 69, 73 or 93 is substituted in heavy chain (table 1, antibody CMV5, mik-beta-1, and Fd138-80, respectively), using the aligned Kabat Eu sequence to provide the framework for the humanized antibody. The humanized antibodies in table 1 would comprise non-human CDR amino acids (Summary). Patent '101 further teaches that the humanized antibodies will be substantially non-immunogenic in humans (Abstract). Thus the humanized antibody taught by patent '101 and its variable domain is the same as the claimed invention.

REJECTION UNDER 35 USC 102

1. Claim 128 is rejected under 35 USC 102(e) as being anticipated by PN=5,530,101, for the same reasons set forth in paper No.27 for the rejection of previous claims 23-24.

Applicant amends the claim 128 to read that the humanized antibody binds the antigen up to about 3-fold more tightly than the parent antibody. The language "up to" 3-fold reads on anything below 3-fold. Thus the structure and binding affinity of the claimed humanized antibody is the same as that of the humanized antibody taught by '101.

2. Claim 113 is rejected under 35 USC 102(e) as being anticipated by PN=5,693,762, for the same reasons set forth in paper No.27 for the rejection of previous claims 22-25, 38 and 39.

Applicant argues that the "consensus sequence" in '762 is the most homologous sequence from a single human immunoglobulin, and is thus different from the consensus sequence of the claimed invention.

Applicant's arguments set forth in paper No. 39 have been considered but are not deemed to be persuasive for the following reasons:

Although '762 uses the most homologous sequence from a single human immunoglobulin as an example, '762 also teach that as a principle, a framework is used from either a human immunoglobulin which is unusually homologous to the donor immunoglobulin, **or** a consensus framework from many human antibodies is used (column 13, first paragraph, lines 4-7). Thus the consensus sequence taught by '762 is the same as the claimed consensus sequence, as defined by the specification, i.e. the most frequently occurring amino acids, based on immunoglobulin of a particular species (p.14).

REJECTION UNDER 35 USC 103

Claims 113, 115-118, 123, 127-128 are rejected under 35 USC 103 as being unpatentable over US PN=5,693,762 in view of Kabat et al, for the same reasons set forth in paper No:27, for the rejection of previous claims 26-36 and 40-41.

Applicant argues as follows:

The rejection is made using hindsight reconstruction of the present invention. Patent '762 actually teaches away from the invention. The term "consensus framework" from '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acids in the present invention. Furthermore, Kabat et al do not use the term "consensus", but rather "occurrences of most common amino acid". Thus there is no motivation to combine "consensus framework" from '762 patent with "occurrences of most common amino acid", especially the term "consensus framework" from '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acids. Moreover, the present invention produces humanized antibodies with unexpected results, such as 1) lack of significant immunogenecity, as disclosed in the Declaration by Dr. Shak, 2) higher increase in binding affinity as compared to that of humanized antibodies known in the art, and 3) the same consensus sequence could be used to generate many different strong affinity humanized antibodies.

Applicant's arguments set forth in paper No. 39 have been considered but are not deemed to be persuasive for the following reasons:

Although '762 uses the most homologous sequence from a single human immunoglobulin as an example, '762 also teach that **as a principle**, a framework is used from either a human immunoglobulin which is unusually homologous to the donor immunoglobulin, **or** use a consensus framework **from many human antibodies** is used (column 13, first paragraph, lines 4-7). Thus the consensus sequence taught by '762 is the same as the claimed consensus sequence, as defined by the specification, i.e. the most frequently occurring amino acids, based on immunoglobulin of a

particular species (p.14). It is only Applicant's interpretation that the term "consensus framework" from '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acids in the present invention. Furthermore, although Kabat et al do not use the term "consensus", but rather "occurrences of most common amino acid", one of ordinary skill in the art would readily understand that " a consensus sequence" from many antibodies is a sequence that occurs most frequently.

In addition, .In re Kerkhoven (205 USPQ 1069, CCPA 1980) summarizes:

"It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose: idea of combining them flows logically from their having been individually taught in prior art."

Applicant asserts that the claimed humanized antibodies are not obvious in view of the cited references because the cited prior art does not suggest such a combination. However, the instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, given the teaching of the prior art that as a principle, a framework is used from either a human immunoglobulin which is unusually

homologous to the donor immunoglobulin, **or** a consensus framework from many human antibodies is used, and the structures of sequences that are most commonly occurred among many antibodies, it would have been obvious to humanize antibodies as taught by patent '762, using the most commonly occurred sequences taught by Kabat et al, because the idea of doing so would have logically followed from their having been individually taught in the prior art, and because patent '762 teaches the use of "consensus sequence", for the same purpose of producing humanized monoclonal antibodies for therapeutic purposes. One of ordinary skill in the art would have motivated to make humanized antibodies using the methods taught by '762 and the sequences taught by Kabat et al with a reasonable expectation of success. In addition, the arguments that the claimed invention is unexpected are not applicable, because the claims are broad, and drawn to any antibodies, and not specifically the claimed antibodies, wherein their specific target antigens, and their binding properties are not disclosed in the claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Tam B. Davis whose telephone number is (703) 305-2008. The examiner can normally be reached on Monday-Friday from 9:30am to 3:30pm, except on Wesnesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4227.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0916.

Minh-Tam B. Davis

October 13, 2000

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Notice of References Cited

Application No.	Applicant(s)		
08/146,206	Carter et al.		
Examiner	Group Art Unit	Page 1 of 1	
M. T. Davis	1642		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
	A					
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
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FOREIGN PATENT DOCUMENTS

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

NON-PATENT DOCUMENTS

*		DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
	U	~~Queen et al. PNAS, USA, 86: 10029 - 10033~~ Dupl.	~~1989~~
	V		
	W		
	X		

* A copy of this reference is not being funished with this Office action.
(See Manual of Patent Examining Procedure, Section 707.05(a).)

U.S. Patent and Trademark Office
PTO-892 (Rev. 9-96)

Part of Paper No. 57

*U.S. GPO: 1996-420-311/40176

EXHIBIT B

1642

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: M. Davis **CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on April 25, 2001 Wendy M. Lee

59/60
5-2-01

AMENDMENT UNDER 37 C.F.R. §1.111

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action dated 10/25/00, reconsideration of the present application is respectfully requested in view of the following amendments and remarks. A request for a 3 month extension of time and the requisite fee accompany this amendment.

IN THE CLAIMS:

Please amend claims 113 and 114 as follows:

Sub O1

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

N'

respect to one another.

114. (Amended) The humanized variant of claim ~~128~~ which binds the antigen ~~about~~ up to 3-fold more ~~tightly~~ in the binding affinity than the parent antibody binds antigen.

REMARKS

Claims 43-105 and 113-128 are in the application. Claims 113 and 114 have been amended. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made".

Claim 113 no longer requires that the humanized variant bind antigen with better affinity than the parent antibody, up to about 3-fold tighter binding than the parent antibody. Hence, claim 114 has been amended herein to depend on claim 128, which claim requires that the humanized variant bind antigen more tightly than the parent antibody.

Prosecution History of the Present Application

Applicants first wish to express their concern about the undue prejudice to them due to the repeated transfer of this case from patent examiner to patent examiner, and to explain that this is a case which has thrice previously been indicated to be in condition for allowance.

The case was originally with Examiner Adams, then was transferred to Examiner Nolan. In the 8/13/98 interview, Examiner Nolan indicated that unexpected results would overcome the 103 rejection based on Queen Patent 5,693,762 (hereinafter "the '762 patent"). An amendment was filed 8/24/98 presenting the unexpected results. Shortly thereafter, the case was transferred to the present Examiner. Pending claims 43-114 were discussed in an interview on 10/16/98 between the undersigned, the present Examiner and Examiner Feisee at which time the only outstanding issue in the case related to the clarity of the terms "binding of CDR" and "significant immunogenicity". An amendment was filed 11/6/98 addressing those issues. The case was then transferred to Examiner Reeves, who issued a restriction requirement 3/29/99 at that late stage in prosecution. In an 8/23/99 interview, Examiners Reeves/Burke and Feisee indicated that the case would be in order for allowance with the filing of a terminal disclaimer for claim 111 and addition of an upper limit to affinity in claims 113 and 128. Claims 113 and 128 were amended as suggested by the Examiners and claim 111 was canceled to avoid the

obviousness-type double patenting rejection (see 8/30/99 amendment). Now the case has been transferred yet again to the present Examiner and prosecution has been re-opened on a case that was indicated to be in condition for allowance three times previously.

To the extent that any issues remain following entry of this amendment, Applicants specifically request an interview with the present Examiner and her supervisor to discuss this case so as to ensure speedy resolution of the issues and allowance of the application. It is noted that this is a pre-GATT case and two 129(a) responses have previously been filed.

Section 112, first paragraph, Scope, New Rejection

Claims 43-105 and 113-128 are rejected under 35 USC Section 112, first paragraph on the basis that the specification, while being enabling for humanized antibody muMAb4D5 and an anti-CD3 antibody, or variable domains thereof, "does not reasonably provide enablement for any humanized antibody, or variable domain thereof, comprising CDR amino acids which binds non-specifically to any antigen, wherein the framework region amino acids are substituted at a site selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H and 92H, or of 24H, 73H, 76H, 78H and 93H, for treating any chronic disease."

The Examiner contends that the specification discloses examples of humanized muMAb4D5, anti-CD3 and anti-CD18 antibodies or variable domains thereof; that the substituted FR residues for muMAb4D5 are 71H, 73H, 78H, 93H and 66L; and that only one humanized antibody (huMAb4D5-8) with all the above five substitutions binds to p185 3-fold more tightly than the murine counterpart. The Examiner further contends that the substituted framework residues for the heavy chain of antibody anti-CD3 are FR residues 75 and 76, and that there is no disclosure concerning the binding affinity of the humanized anti-CD3 or anti-CD18 as compared to the murine counterpart. The Examiner contends that one cannot extrapolate from humanizing one antibody, which binds to $p185^{HER2}$ 3-fold more tightly than the murine counterpart, to humanizing any antibody,

wherein its affinity would be up to 3-fold or at least 3-fold tighter than the murine counterpart, or wherein its affinity would still be intact for therapeutic purposes. The Examiner further argues that one cannot extrapolate from humanizing an anti-p185 antibody by substitution of all five FR residues at positions 71H, 73H, 78H, 93H and 66L in an anti-p185 antibody, or from humanizing an anti-CD3 antibody by substitution at both framework residues 75H and 76H, with humanizing any antibody by substitution at only one amino acid residue selected from the group consisting of 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H and 92H, or of 24H, 73H, 76H, 78H and 93H. The Examiner opines that the specification does not disclose whether substitution at only one of the claimed amino acid positions would produce a humanized antibody that has 3-fold more affinity, or which combination of what substituted FR residues (other than 71H, 73H, 78H, 93H and 66L for an anti-p185 antibody or 75H and 76H in an anti-CD3 antibody) would produce a humanized antibody that has 3-fold more affinity than the murine counterpart, or retains adequate affinity for therapeutic purposes. The Examiner contends that a humanized antibody that does not have specificity for a particular antigen is of little practical use for treating a chronic disease and that the specification does not disclose how to treat any chronic disease using the claimed humanized antibody.

Applicants submit that claims 43-105 and 113-128 are enabled by the present application.

First, Applicants point out that none of the claims (other than claim 114) require that the humanized antibody bind antigen about 3-fold more tightly than the parent antibody binds antigen, as the Office Action seems to imply. The independent claims herein merely recite that the humanized antibody variable domain comprises CDR residues which bind an antigen (claims 43, 104 and 115); the antibody comprising the humanized antibody variable domain binds $p185^{HER2}$ (claim 72); the humanized antibody comprises CDR residues which bind an antigen (claim 105); the humanized variant bind antigen (claim 113 herein); or the humanized variant bind

antigen more tightly than the parent antibody - up to about 3-fold more tightly than the parent antibody (claim 128).

Second, Applicants submit that the claims herein encompass the humanized variable domain or antibody having at least one of the FR substitutions specified, but optionally having further FR substitution(s) in order to improve affinity to a level at which an antibody comprising the variable domain is able to bind antigen.

Finally, Applicants wish to clarify some issues concerning the Office's characterization of the working examples. First, it is noted that Example 1 actually describes several humanized anti-$p185^{HER2}$ variants with FR substitution(s) as set forth in the claims herein: huMAb4D5-2, huMAb4D5-3, huMAb4D5-4, huMAb4D5-5, huMAb4D5-6, huMAb4D5-7, huMAb4D5-8 (Table 3 on page 72). Thus, it is clear that this example teaches humanized variants which do not include substitution of all of FR residues 71H, 73H, 78H, 93H and 66L. Each of these FR substitution variants bound antigen with better affinity than the initial antibody (huMAb4D5-1) comprising non-human CDR amino acid residues, but lacking any FR substitution(s). Two of the humanized anti-$p185^{HER2}$ variants surprisingly bound antigen better than the murine parent antibody muMAb4D5, *i.e.* huMAb4D5-6 and huMAb4D5-8. With regard to Example 3 concerning the humanized anti-CD3 variants, aside from the 75H and 76H FR substitutions noted by the Office, this Example further teaches the following FR substitutions: L71, 71H, 73H and 78H. See, *e.g.*, Fig. 5 which aligns the murine anti-CD3 "muxCD3" sequences, the humanized variant "huxCD3v1" sequences, and the human sequences, "huκI" and "huIII".

The specification clearly teaches how to make humanized antibody variable domains and antibodies comprising such domains, and identifies FR residues that can be substituted to improve the binding affinity of an antibody comprising the humanized variable domain. See, *e.g.* pages 12-13, 20-26 and 28-29; Example 1 on pages 63-74; Example 3 on pages 79-88; and Example 4 on page 89. The specification teaches FR substitution(s)

individually or in combination. Based on the disclosure of the present application, one is able to make an antibody comprising a humanized antibody variable domain which binds antigen. The Office has provided no evidence that the humanized antibody variable domains or humanized antibodies comprising the FR substitution(s) claimed herein would not be functional, beyond speculating that the affinity might not be about 3-fold better than the parent antibody (and, as noted above, the claims other than claim 114 do not require this improvement in affinity). Hence, Applicants submit that the presently claimed variable domains and antibodies are enabled by the specification.

Reconsideration and withdrawal of the enablement rejection is respectfully requested in view of the above.

Section 102 - Claims 115-117, 123 and 127

Claims 115-117, 123 and 127 are rejected under 35 USC Section 102(e) or 102(b) as anticipated by US Patent No. 5,530,101 (hereinafter "the '101 patent") or Queen *et al. PNAS (USA)* 86:10029-10033 (1989) (hereinafter "Queen *et al.*"). The Examiner contends that the '101 patent and Queen *et al.* teach a humanized anti-Tac antibody wherein amino acid 93 is substituted in the heavy chain, using the aligned Kabat Eu sequence to provide the framework for the humanized antibody.

Applicants point out that - as explained earlier in prosecution - the substituted 93 FR residue in the cited references is not 93H "utilizing the numbering system set forth in Kabat" (see page 13, line 33 through to line 22 on page 14 of the present application) as required by claims 115-117, 123 and 127 of the present application. In particular, as noted on page 6 of the amendment hand carried to the Office on 10/7/97, residue no. 93 in the heavy chain of the anti-Tac antibody in the cited references, is actually 89H utilizing the numbering system set forth in Kabat. The cited references use a sequential numbering system, rather than the Kabat numbering system claimed herein.

Reconsideration of the 102(e) and 102(b) rejections based on the '101

patent and Queen *et al.* is respectfully requested in view of the above.

Section 102 - Claims 43, 44, 48, 55, 67, 71, 105, 115-117, 120 and 127

Claims 43, 44, 48, 55, 67, 71, 105, 115-117, 120 and 127 are rejected under 35 USC Section 102(e) as being anticipated by the '101 patent. The Examiner urges that FR substitutions 38L, 67L, 69H, 73H and 93H are taught by the '101 patent. Specifically, the Examiner contends that amino acids 38 or 67 are substituted in the light chain of the Fd79 and M195 antibodies, respectively, and amino acids 69, 73 or 93 are substituted in the heavy chains of the CMV5, mik-β1 and Fd138-80 antibodies, respectively. The '101 patent is further alleged to teach (in the abstract thereof) that the humanized antibodies therein will be substantially non-immunogenic in humans.

Applicants submit that the presently claimed FR 38L, 67L, 69H and 93H substitutions are different from those in the '101 patent to which the Examiner refers, since the numbering of the presently claimed FR substitutions utilizes the numbering system set forth in Kabat, whereas the '101 patent uses sequential numbering for the residues. In particular, VL residue 38 of Fd79 is a CDR residue, as opposed to a FR residue (note Table 1 in column 43 of the '101 patent which states that residue 38 is in "Category 1" and therefore is a CDR residue; see lines 66-67 in column 13 of the '101 patent); VL residue 67 of M195 is FR residue 63L utilizing the numbering system set forth in Kabat (see page 8 of Applicants' 10/7/97 amendment); VH residue 69 of CMV5 is 68H utilizing the numbering system set forth in Kabat (see page 9 of the 10/7/97 amendment); and VH residue 93 of Fd138-80 is FR residue 89H utilizing the numbering system set forth in Kabat (see page 7 of the 10/7/97 amendment).

As to the FR 73H substitution (utilizing the numbering system set forth in Kabat) claimed herein, Applicants submit that the disclosure of the humanized mik-β1 antibody is too late to qualify as Section 102 prior art to claim 115 which recites that substitution. See page 11, first full paragraph of Applicants' 1/15/99 amendment.

Finally, as to the recitation in claim 105 herein that the humanized antibody "lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient", Applicants have shown that antibodies humanized according to one preferred embodiment of the present invention possess this property. See the Shak Declaration filed 8/24/99. The '101 patent merely states that the humanized antibodies will be "substantially non-immunogenic" in humans, but fails to disclose that the humanized antibodies lack substantial immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient.

Reconsideration and withdrawal of the Section 102(e) rejection is respectfully requested in view of the above.

Section 102(e) - Claim 128

Claim 128 is rejected under 35 USC Section 102(e) as being anticipated by the '101 patent. The Examiner states that the language "up to" 3-fold reads on anything below 3-fold.

Claim 128 pertains to a humanized antibody which binds antigen more tightly than the parent antibody (up to about 3-fold more tightly). The Queen patents state that the humanized antibodies therein bind the target antigen with the same affinity, or bind less tightly, than the parent antibody. See pages 21-22 of Applicants' amendment filed 8/24/98. While humanized M195 was later discovered to bind antigen up to about 3-fold more tightly than the parent antibody bound antigen (see paragraph 2 on page 2 of the 8/30/99 amendment), this property of the humanized M195 antibody is not described in the '101 patent (see lines 28-29 in column 60 of the '101 patent).

Reconsideration and withdrawal of the Section 102(e) rejection of claim 128 is respectfully requested.

Section 102(e) - Claim 113

Claim 113 is rejected under 35 USC Section 102(e) as being anticipated

by US Patent 5,693,762 ("the '762 patent") for the same reasons set forth in paper No. 27 for the rejection of previous claims 22-25, 38 and 39.

The Examiner contends that the '762 patent teaches "as a principle, a framework is used from either a human immunoglobulin which is unusually homologous to the donor immunoglobulin, or a consensus framework from many human antibodies is used".

Applicants submit that this disclosure in the '762 patent simply fails to anticipate the presently claimed "consensus human variable domain" in claim 113 as defined by the present specification. See the discussion of the '762 patent on pages 13-14 of the 8/24/98 amendment. The Examiner states on page 11 of the above Office Action that it 'is only Applicant's interpretation that the term "consensus framework" from '762 patent was not intended to refer to a sequence representing the most frequently occurring amino acids in the present invention'. Applicants respectfully disagree. Indeed the Office initially suggested the alternative interpretation for the term "consensus framework" as it was used by Queen *et al.* See page 4 of the Office Action dated 12/23/96 in which Examiner Nolan stated:

> "Regarding the consensus sequence, the combination of references teach the human framework regions having a significantly high degree of sequence homology (conservative regions). Queen et al. in particular point to Kabat as demonstrating that this was known in the art well in advance of applicant's filing date, see reference 38, cited by Queen et al." (Emphasis added).

The Queen *PNAS* paper to which Examiner Nolan referred, was concerned with using a human framework region from a human immunoglobulin which was unusually homologous to the donor immunoglobulin, and failed to mention a consensus human variable domain as that expression is used in the present application. Hence, the Office has previously used the expression "consensus sequence" to describe the highly homologous approach taught by Queen *et al.*

Nothwithstanding this, Applicants note that in order to anticipate a claimed invention, the reference alone much teach each and every element of the claim. Even if it were the case that the "consensus framework" in the '762 patent was intended to refer to an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins (see page 14, lines 29-31 of the present application), which is denied, the Office has not shown that the '762 patent unambiguously disclosed the selection invention recited in claim 113 herein pertaining to a "consensus human variable domain of a human heavy chain immunoglobulin subgroup". The Office has combined the '762 patent with Kabat *et al.* (see Section 103 discussion below) in an attempt to show that this particular consensus sequence had been disclosed previously. Hence, Applicants submit that claim 113 is novel over the '762 patent. Applicants will demonstrate in the following section how the invention set forth in claim 113 is also nonobvious over the '762 patent, due to the unexpected results attributable thereto.

Reconsideration and withdrawal of the Section 102 rejection based on the '762 patent is respectfully requested in view of the above.

Section 103

Claims 113, 115-118, 123 and 127-128 are rejected under 35 USC Section 103 as being unpatentable over the '762 patent in view of Kabat *et al.*

First, it is noted that the Examiner relies on the rejection based on the '762 patent in view of Kabat *et al.* for the same reasons as set forth in paper no. 27 (Applicants assume paper no. 34 - Examiner Nolan's Office Action dated 12/23/97 is intended). Examiner Nolan previously indicated that the unexpected results would overcome the 103 rejection based on the '762 patent combined with Kabat *et al.* (see Paper no. 37; 8/13/98 Interview Summary).

Applicants rely on the unexpected results attributable to the consensus human variable domain of a human heavy chain immunoglobulin subgroup as demonstrating that the presently claimed antibodies are not obvious over

the '762 patent combined with Kabat *et al.* See pages 18-23 of the 8/24/98 amendment and the Shak declaration attached thereto.

The Examiner urges that "the arguments that the claimed invention is unexpected are not applicable, because the claims are broad, and drawn to any antibodies, and not specifically the claimed antibodies, wherein their specific target antigens, and their binding properties are not disclosed in the claims."

Applicants submit that the Examiner's basis for ignoring the evidence of unexpected results is legally flawed - at least with respect to (1) the lack of significant immunogenicity of the claimed humanized antibodies upon repeated administration to a human patient, *e.g.* to treat a chronic disease in that patient and (2) the ability to make many strong affinity antibodies, thus avoiding tailoring each human framework to each non-human antibody to be humanized. Those unexpected results provide objective evidence of non-obviousness. *Specialty Composites v. Cabot Corp.*, 845 F. 2d 981, 6 USPQ 2d 1601 (Fed. Cir. 1988).

As to unexpected result (1), Applicants have demonstrated that antibodies humanized using a consensus human variable domain of a human heavy chain immunoglobulin subgroup as set forth in claim 113 herein lack significant immunogenicity upon repeated administration to a human patient in order to treat a chronic disease in that patient. This was shown in the Shak Declaration for humanized anti-HER2, anti-IgE, anti-VEGF and anti-CD11a antibodies. See pages 18-21 of the 8/24/98 amendment and the Shak Declaration attached thereto. Hence, this unexpected property is not linked to certain antibodies or specific target antigens, but is generally applicable and the claims are commensurate in scope with the unexpected result relied upon.

Turning now to unexpected result (2), Applicants have shown that a consensus human variable domain of a human heavy chain immunoglobulin subgroup as set forth in claim 113 can be used to generate many different strong affinity humanized antibodies, including anti-HER2, anti-CD3,

anti-CD18, anti-IgE, anti-CD11a and anti-VEGF humanized antibodies (see pages 22-23 of the 8/24/98 amendment). Again, this further unexpected property is not dependent on the antibody or target antigen, and hence should be considered with respect to the non-obviousness of the presently claimed antibodies.

Hence, Applicants submit that claim 113 directed to a humanized variant comprising a consensus human variable domain of a human heavy chain immunoglobulin subgroup is non-obvious over the cited art, because of unexpected results (1) and (2) noted above.

As to the other rejected claims, Applicants point out that claim 115 recites FR substitutions at one or more of positions 24H, 73H, 76H, 78H and 93H, utilizing the numbering system set forth in Kabat. The Office has not shown how the cited art disclosed or suggested substitution of FR residues 24H, 76H, 78H and 93H, utilizing the numbering system set forth in Kabat; and, as noted above, the disclosure concerning substitution of 73H in the mik-β1 antibody is too late to qualify as Section 102 prior art to the invention set forth in claim 115 herein. With regard to claim 117, the Office fails to teach a humanized antibody with FR substitution(s) limited to positions 24H, 73H, 76H, 78H and 93H, utilizing the numbering system set forth in Kabat. As to claim 118, the Office has not demonstrated how the art would have taught combining the listed FR substitution(s) in claim 115 with a consensus human variable domain. With regard to claim 123, as noted previously, substituted 93 FR residue in Queen's anti-Tac or Fd138-80 antibodies is not the same as FR substitution 93H "utilizing the numbering system set forth in Kabat." Finally, with respect to claim 128, as noted above, the Queen patents state that the humanized antibodies therein bind the target antigen with the same affinity, or bind <u>less tightly</u>, than the parent antibody. See pages 21-22 of Applicants' amendment filed 8/24/98. While humanized M195 was later discovered to bind antigen up to about 3-fold more tightly than the parent antibody bound antigen (see paragraph 2 on page 2 of the 8/30/99 amendment), this property of the humanized M195 antibody is not described in the '101 patent (see lines 28-29 in column 60 of the '101

patent). The ability to bind antigen more tightly than the parent antibody was a further unexpected result observed with respect to certain humanized antibodies of the present application.

Reconsideration and withdrawal of the Section 103 rejection of claims 113, 115-118, 123 and 127-128 is respectfully requested in view of the above.

Respectfully submitted,

GENENTECH, INC.

Date: April 25, 2001

By:
Wendy M. Lee
Reg. No. 40,378
Telephone: (650) 225-1994

Serial No.: 08/146,206

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 113 and 114 have been amended as follows:

113. (Three Times Amended) A humanized variant of a non-human parent antibody which binds an antigen [with better affinity than the parent antibody] and comprises a consensus human variable domain of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another [, wherein the humanized variant binds antigen up to about 3-fold more tightly than the parent antibody binds antigen].

114. (Amended) The humanized variant of claim [113] 128 which binds the antigen about 3-fold more tightly than the parent antibody binds antigen.

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of Paul J. Carter et al. Serial No.: 08/146,206 Filed: November 17, 1993 For: METHOD FOR MAKING HUMANIZED ANTIBODIES	Group Art Unit: 1642 Examiner: M. Davis **CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on April 25, 2001 Wendy M. Lee

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

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Applicants petition the Commissioner of Patents and Trademarks to extend the time for response to the Office Action dated October 25, 2000 for three months from January 25, 2001 to April 25, 2001. The extended time for response does not exceed the statutory period.

Please charge Deposit Account No. 07-0630 in the amount of $890.00 to cover the cost of the extension. Any deficiency or overpayment should be charged or credited to this deposit account. A duplicate of this sheet is enclosed.

Respectfully submitted,
GENENTECH, INC.

Date: April 25, 2001

By: _____
Wendy M. Lee
Reg. No. 40,378
Telephone No. (650) 225-1994

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PATENT TRADEMARK OFFICE

EXHIBIT C

Patent Docket P0709P1 #32

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

AMENDMENT TRANSMITTAL

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Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

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

The fee has been calculated as shown below.

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

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

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

Respectfully submitted,
GENENTECH, INC.

Date: October 6, 1997

By: _____
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#32/8
CAPP
10/7/97

Patent Docket P0709P1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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

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

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

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

IN THE SPECIFICATION:

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

EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVRQAPGKGLEWVAVISENGSDTYYADS
VKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARDRGGAVSYFDVWGQGTLVTVSS--

On page 9, line 30, please replace "huĸl" with --hulll--.

IN THE CLAIMS:

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

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

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

Please add the following claims:

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

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

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

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

REMARKS

A. Amendments

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

B. Substitute Sequence Listing

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

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

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

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

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

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

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

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

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

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

last paragraph of this reference).

D. FR substitutions by Queen *et al.*

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

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

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

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

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

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

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

Respectfully submitted,

GENENTECH, INC.

Date: October 6, 1997

By: _____

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EXHIBIT A

Alignment of heavy chains from '101 patent

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

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

EXHIBIT A
(cont.)

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

EXHIBIT B

Alignment of light chains from '101 patent

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

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

EXHIBIT B
(cont.)

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

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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

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

(iii) NUMBER OF SEQUENCES: 30

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

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

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: 08/146206
(B) FILING DATE: 17-Nov-1993
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/715272
(B) FILING DATE: 14-JUN-1991

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

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

(2) INFORMATION FOR SEQ ID NO:1:

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

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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

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

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

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

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

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

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

Ile Lys Arg Thr
            109
```

(2) INFORMATION FOR SEQ ID NO:2:

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

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

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

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

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

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

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

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

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

Ala Met Asp Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
               110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:3:

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

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

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

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

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

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

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

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

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

Ile Lys Arg Thr
             109
```

(2) INFORMATION FOR SEQ ID NO:4:

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

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

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

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

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

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

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

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

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

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

(2) INFORMATION FOR SEQ ID NO:5:

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

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Asp Ile Val Met Thr Gln Ser His Lys Phe Met Ser Thr Ser Val
 1               5                  10                  15

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

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

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

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

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

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

Ile Lys Arg Ala
    109
```

(2) INFORMATION FOR SEQ ID NO:6:

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

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

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

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

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

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

Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser
65                  70                  75

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

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

Ala Met Asp Tyr Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
    110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:7:

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

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

TCCGATATCC AGCTGACCCA GTCTCCA 27

(2) INFORMATION FOR SEQ ID NO:8:

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

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

GTTTGATCTC CAGCTTGGTA CCHSCDCCGA A 31

(2) INFORMATION FOR SEQ ID NO:9:

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

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

AGGTSMARCT GCAGSAGTCW GG 22

(2) INFORMATION FOR SEQ ID NO:10:

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

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

TGAGGAGACG GTGACCGTGG TCCCTTGGCC CCAG 34

(2) INFORMATION FOR SEQ ID NO:11:

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

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

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

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

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

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

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

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

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

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

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

Ile Lys
    107
```

(2) INFORMATION FOR SEQ ID NO:17:

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

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

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

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

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

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

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

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

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

GTAGATAAAT CCTCTAACAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:12:

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

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

GTAGATAAAT CCAAATCTAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:13:

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

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

GTAGATAAAT CCTCTTCTAC AGCCTATCTG CAAATG 36

(2) INFORMATION FOR SEQ ID NO:14:

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

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

CTTATAAAGG TGTTTCCACC TATAACCAGA AATTCAAGGA TCGTTTCACG 50

ATATCCGTAG ATAAATCC 68

(2) INFORMATION FOR SEQ ID NO:15:

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

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

CTATACCTCC CGTCTGCATT CTGGAGTCCC 30

(2) INFORMATION FOR SEQ ID NO:16:

Ile Lys
107

(2) INFORMATION FOR SEQ ID NO:18:

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

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

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

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

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

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

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

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

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

Ile Lys
107

(2) INFORMATION FOR SEQ ID NO:19:

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

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

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

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

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

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

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

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

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

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

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:20:

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

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

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

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

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

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

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

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

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

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

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:21:

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

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

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

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

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

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

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

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

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

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

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 454 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

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

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

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

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

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

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

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

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

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

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

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

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

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val
                185                 190                 195

Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
                200                 205                 210

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Pro Gly Lys
            454
```

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 469 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr
  1               5                  10                  15

Gly Val His Ser Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu
                20                  25                  30

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

Tyr Thr Phe Thr Glu Tyr Thr Met His Trp Met Arg Gln Ala Pro
                50                  55                  60

Gly Lys Gly Leu Glu Trp Val Ala Gly Ile Asn Pro Lys Asn Gly
                65                  70                  75

Gly Thr Ser His Asn Gln Arg Phe Met Asp Arg Phe Thr Ile Ser
                80                  85                  90

Val Asp Lys Ser Thr Ser Thr Ala Tyr Met Gln Met Asn Ser Leu
                95                 100                 105

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ser Pro Gly Lys
            469
```

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 214 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Arg Gly Glu Cys
        214
```

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 233 amino acids
(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```
Met Gly Trp Ser Cys Ile Ile Leu Phe Leu Val Ala Thr Ala Thr
  1               5                  10                  15

Gly Val His Ser Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu
             20                  25                  30
```

```
Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
                35                  40                  45

Gln Asp Ile Asn Asn Tyr Leu Asn Trp Tyr Gln Gln Lys Pro Gly
                50                  55                  60

Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser Thr Leu His Ser
                65                  70                  75

Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr
                80                  85                  90

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr
                95                 100                 105

Tyr Cys Gln Gln Gly Asn Thr Leu Pro Pro Thr Phe Gly Gln Gly
               110                 115                 120

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

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

Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val
               155                 160                 165

Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
               170                 175                 180

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
               185                 190                 195

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

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr
               215                 220                 225

Lys Ser Phe Asn Arg Gly Glu Cys
               230         233
```

(2) INFORMATION FOR SEQ ID NO:26:

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

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

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

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

Gly Tyr Thr Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
                35                  40                  45
```

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

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

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

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

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

Ser Ser
    122
```

(2) INFORMATION FOR SEQ ID NO:27:

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

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

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

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

(2) INFORMATION FOR SEQ ID NO:28:

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

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

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

(2) INFORMATION FOR SEQ ID NO:29:

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

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

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

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

Ala Arg
32

(2) INFORMATION FOR SEQ ID NO:30:

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

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

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

#34

RAW SEQUENCE LISTING
PATENT APPLICATION *US/08/146,206B*

DATE: 10/08/97
TIME: 13:19:47

INPUT SET: S20851.raw

11/12/97

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

ENTERED

SEQUENCE LISTING

(1) General Information:

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

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

(iii) NUMBER OF SEQUENCES: 26

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

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

(vi) CURRENT APPLICATION DATA:
--> OK **(A) APPLICATION NUMBER: 08/146206**
(B) FILING DATE: 17-Nov-1993
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:
(A) APPLICATION NUMBER: 07/715272
(B) FILING DATE: 14-JUN-1991

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

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

(2) INFORMATION FOR SEQ ID NO:1:

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

(B) TYPE: Amino Acid
(D) TOPOLOGY: Linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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

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

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

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

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

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

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

Ile Lys Arg Thr
        109
```

(2) INFORMATION FOR SEQ ID NO:2:

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

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

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

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

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

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

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

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

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

109

(2) INFORMATION FOR SEQ ID NO:6:

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

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

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

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

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

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

Asp Pro Lys Phe Gln Asp Lys Ala Thr Ile Thr Ala Asp Thr Ser
65                  70                  75

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

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

Ala Met Asp Tyr Trp Gly Gln Gly Ala Ser Val Thr Val Ser Ser
   110                 115                 120
```

(2) INFORMATION FOR SEQ ID NO:7:

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

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

```
TCCGATATCC AGCTGACCCA GTCTCCA 27
```

(2) INFORMATION FOR SEQ ID NO:8:

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

PAGE: 1

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

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

INPUT SET: S20851.raw

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