IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of: Trial Number: To Be Assigned

U.S. Patent No. 6,407,213

Filed: November 17, 1993

Issued: June 18, 2002

Inventor(s): Paul J. Carter, Leonard G. Presta

Assignee: Genentech, Inc.

Title: Method for making humanized antibodies Panel: To Be Assigned

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Mail Stop *Inter Partes* Review
Commissioner for Patents
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PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 6,407,213
UNDER 35 U.S.C. §311 AND 37 C.F.R. §42.100

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1687	Declaration of Amanda Hollis
1688	Declaration of Christopher Lowden

I. INTRODUCTION

Pursuant to 35 U.S.C. §311 and 37 C.F.R. §42.100, Petitioner Pfizer, Inc. petitions for *Inter Partes* Review ("IPR") of claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–67, 69 and 71–81 ("Challenged Claims") of U.S. Patent No. 6,407,213 ("'213 patent," Ex. 1501). With this Petition is a Power of Attorney pursuant to 37 C.F.R. §42.10(b); and pursuant to 37 C.F.R. §42.103, the fee set forth in §42.15(a).

By a preponderance of the evidence, this Petition proves the prior art renders the Challenged Claims unpatentable. Prior art disclosing methods of making humanized antibodies—including the detailed roadmaps taught in Queen 1989[1] and Queen 1990[2]—in view of antibody structures in the Protein Data Bank ("PDB Database") render the Challenged Claims obvious to a person of ordinary skill in the art ("POSITA") as of the priority date of the '213 patent.[3]

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[1] Kurrle et al., EP Publication Number 0403156, *Improved monoclonal antibodies against the human alphabeta T-Cell receptor, their production and use* (published December 19, 1990) ("Kurrle") (Ex. 1571).

[2] Queen, International Publication No. WO 1990/07861 (published July 26, 1990) ("Queen 1990") (Ex. 1550).

[3] All references herein to the knowledge or understanding of a POSITA or a POSITA's interpretation or understanding of a prior art reference are as of the earliest possible priority date unless specifically stated otherwise.

II. MANDATORY NOTICES – 37 C.F.R. §42.8(A)(1) AND (B)

A. 37 C.F.R. §42.8(b)(1): Real Party-In-Interest

Pfizer, Inc. ("Pfizer" or "Petitioner") is the real party-in-interest for Petitioner.

B. 37 C.F.R. §42.8(b)(2): Related Matters

Petitioner concurrently files two IPR petitions for claims of the '213 patent. Petitioner is aware of two earlier IPR proceedings for the '213 patent, IPR2016–01693 and IPR2016–01694, both filed by third-party Mylan Pharmaceuticals Inc. These proceedings were terminated by the Board on March 10, 2017 after the parties filed a Joint Motion to Terminate. Paper No. 24, IPR2016–01693; Paper No. 23, IPR2016–01694 (March 10, 2017). Petitioner is also aware of two current IPR proceedings for the '213 patent, both filed by third-party Celltrion, Inc.: IPR2017-01373 and IPR2017-01374. Petitioner is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in the proceeding.

The '213 patent is related to the following patents: U.S. Patent No. 6,639,055 (expired due to nonpayment of maintenance fees); U.S. Patent No. 6,800,788 (expired due to nonpayment of maintenance fees); U.S. Patent No. 6,719,971 (expired due to nonpayment of maintenance fees); and U.S. Patent No. 8,075,890 (patented).

C. 37 C.F.R. §42.8(b)(3): Lead and Back-Up Counsel

Petitioner designates the following counsel:

Lead Counsel	**Back-up Counsel**
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D. 37 C.F.R. §42.8(b)(4): Service Information

Please address all correspondence to lead counsel at the contact information above. Petitioner consents to service by electronic mail at Pfizer_Genentech_IPRs@kirkland.com. A Power of Attorney is being filed concurrently herewith. 37 C.F.R. §42.10(b).

III. PAYMENT OF FEES – 37 C.F.R. §42.103

The undersigned authorizes the PTO to charge the fee set forth in 37 C.F.R.

§42.15(a) for this Petition and any additional fees that may be due in connection with this Petition to Deposit Account No. 506092.

IV. GROUNDS FOR STANDING – 37 C.F.R. §42.104(A)

Petitioner certifies that the ’213 patent is available for IPR and that the Petitioner is not barred or estopped from requesting IPR on the grounds identified herein. 35 U.S.C. § 315.

V. IDENTIFICATION OF CHALLENGE – 37 C.F.R. §42.104(B)

Petitioner requests IPR and cancellation of the Challenged Claims under pre-AIA 35 U.S.C. §103, as set forth in Petitioner’s detailed “Statement of Reasons for Relief Requested.”

Petitioner provides copies of the exhibits, and this Petition is supported by the Declarations of Dr. Jefferson Foote (Ex. 1503) and Mr. Timothy Buss (Ex. 1504). Dr. Foote is the CSO of Arrowsmith Technologies, a biotechnology startup developing immunologic cancer treatments, with over thirty years of experience in the antibody engineering and humanization field. Mr. Buss is an antibody engineering consultant with over thirty years of experience in the antibody engineering field, particularly with respect to cancer treatments. This Petition is also supported by authenticating Declarations from Mr. Christopher Lowden, Ms. Amanda Hollis, and Ms. Karen Younkins.

The Challenged Claims involve humanized antibodies and humanized antibody variable domains (Ex. 1503 ¶¶44–65) and are unpatentable as follows:

Ground	Proposed Statutory Rejection of the '213 Patent
1	Claims 1, 2, 12, 25, 29, 63, 64, 66, 67 and 71–81 are invalid under 35 U.S.C. §103(a) as obvious in view of: **Queen 1989** and **PDB Database**
2	Claims 1, 2, 4, 12, 25, 29, 62–64, 66, 67, 69 and 71–81 are invalid under 35 U.S.C. §103(a) as obvious in view of: **Queen 1990** and **PDB Database**
3	Claims 75–77, 79 and 65 are invalid under 35 U.S.C. §103(a) as obvious in view of: **Queen 1989**, **PDB Database** and **Tramontano**
4	Claims 75–77, 79 and 65 are invalid under 35 U.S.C. §103(a) as obvious in view of: **Queen 1990**, **PDB Database** and **Tramontano**

Ground	Proposed Statutory Rejection of the '213 Patent
5	Claims 4, 62, 64 and 69 are invalid under 35 U.S.C. §103(a) as obvious in view of: **Queen 1989**, **PDB Database** and **Kabat 1987**
6	Claims 30, 31, 42 and 60 are invalid under 35 U.S.C. §103(a) as obvious in view of: **Queen 1989**, **PDB Database** and **Hudziak**
7	Claims 30, 31, 33, 42 and 60 are invalid under 35 U.S.C. §103(a) as obvious in view of: **Queen 1990**, **PDB Database** and **Hudziak**

VI. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

A petition for IPR must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. §314(a). This Petition meets and exceeds this threshold because there is more than a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

VII. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

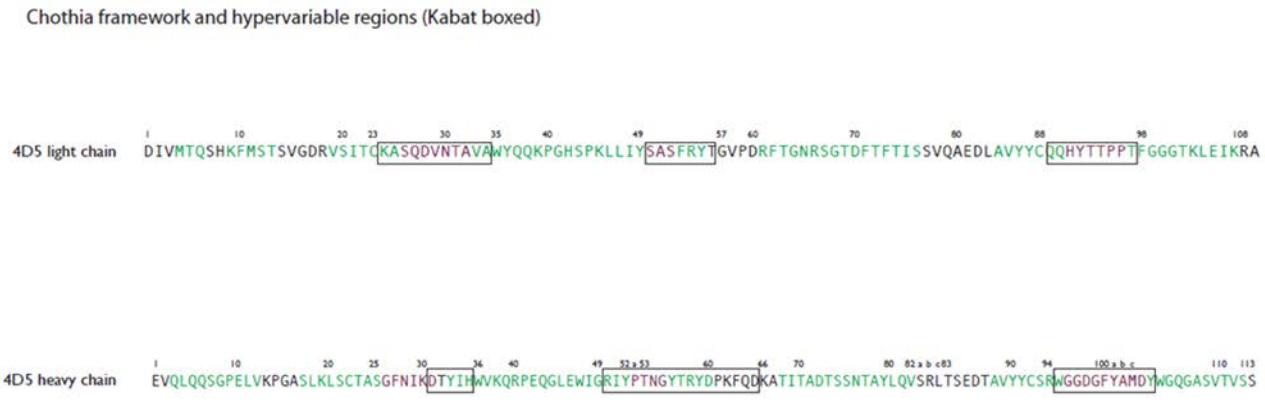
A. Summary of the Argument

In 1975, *Nature* published Köhler and Milstein's ground-breaking study manufacturing monoclonal antibodies, or "predefined specific antibodies by means of permanent tissue culture cell lines." Ex. 1522 at 3. Mouse monoclonal antibodies exhibited therapeutic and diagnostic promise, but researchers discovered patients receiving them experienced a human anti-mouse antibody ("HAMA") immunogenicity response. Exs. 1503 ¶¶97–100; 1504 ¶35.

To neutralize the HAMA response, mouse antibodies were re-engineered to make them "more human" by replacing parts of the mouse antibody with human counterparts. First generation (early 1980s) versions replaced only the mouse antibody's constant region with corresponding human antibody residues. Exs. 1503 ¶¶99–100; 1504 ¶¶38–40. While these "chimeric" antibodies retained the parent mouse's affinity (*i.e.*, the strength of the bond between the antibody and target receptor) and specificity (*i.e.*, the antibody's ability to interact with a specific receptor), patients still experienced HAMA responses from the mouse variable domain. Next, scientists replaced mouse variable domain framework regions ("FR") flanking the complementarity determining regions ("CDR") with human sequences. Ex. 1503 ¶101–106.

However, because adding human FRs to the regions between the mouse CDRs was known to disrupt binding affinity, the next logical step in the evolution of humanized antibody technology was to switch select residues in the human FRs back to the mouse residue. Ex. 1503 ¶¶103–106, 108–109. Scientists were able to do so because they had accumulated an extensive antibody sequence database as well as information about the structure of antibodies by the mid-1980s. Ex. 1503 ¶¶76–81.

For example, Kabat 1987[4] identified which heavy and light chain sequence positions were consistently similar (FRs) or consistently varying from antibody to antibody CDRs. *See* Ex. 1552. Kabat 1987 classified the antibody variable domain structure through comparison of over a hundred antibodies (Ex. 1503 ¶¶91–96, 115–20):



[4] Kabat et al., Sequences of Proteins of Immunological Interest 41–175 (1987).

Id. ¶91. Kabat 1987's antibody map, and later work by Chothia (Ex. 1562), gave scientists clearly defined regions to target for further humanization of chimeric antibodies: FRs (green) within the variable domain. Ex. 1503 ¶¶91–96, 108–109.

Wholesale replacement of the mouse FR sequence with human FR sequence increased the risk of losing some sequence features that helped properly position the mouse CDRs so they could achieve their binding affinities. Well prior to the June 14, 1991 priority date of the '213 patent, Queen et al. in 1989 and 1990 published and patented, respectively, humanization methodologies applicable to any antibody to optimize this risk-reward balance of human characteristics (to reduce immunogenicity) and non-human (*e.g.*, mouse) characteristics (to ensure good binding affinity). Exs. 1534 at 3; 1550 at 1; 1503 ¶¶125–37, 252–68.

The fundamental principle was simple: after incorporating human FR sequences, change a limited portion back to the mouse sequence to maintain binding affinity and specificity, particularly those "framework amino acids in the mouse antibody that might interact with the CDRs or directly with antigen." Exs. 1534 at 7; 1503 ¶¶125–37.

Queen 1989 and Queen 1990 specify criteria to target amino acids for substitution in producing humanized antibodies. *See* Exs. 1534 at 15035–15036; 1550 at 12:17–15:2; 1503 ¶¶125–37. Following the teachings of Queen 1989 or Queen 1990, POSITA could readily discern amino acid sequence locations to

target. To do so, Queen 1989 and Queen 1990 taught POSITAs should use the known and available antibody structures in the PDB Database to identify FR residues that are likely to contact the CDRs. After conducting this analysis, the identified amino acids should be "transferred to the human framework along with the CDRs." Exs. 1534 at 7; 1503 ¶¶125–37. A POSITA using the Queen 1989 or Queen 1990 roadmap and the PDB Database would have readily identified many of the same heavy (H) and light (L) chain residues recited in claims 1, 2, 4, 12, 25, 29, 62–67, 69 and 71–81. Ex. 1503 ¶¶252–268. Thus, those claims would have been obvious.

Further, the prior art had already identified specific residue locations that appeared to be consistently involved with CDR conformation and antigen binding. Ex. 1503 ¶¶108–109. For example, Tramontano[5] and colleagues published that residue **71H**[6] was important to retain as mouse to better maintain CDR conformation. Exs. 1551 at 6; 1503 ¶¶108–109, 142–143. Thus, a POSITA would have readily identified residue **71H** for substitution during humanization. *Id.*

The prior art also disclosed $p185^{HER2}$ as a promising therapeutic target, and a specific monoclonal antibody (4D5) against the $p185^{HER2}$ target.

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[5] Tramontano et al., 215 J. Molecular Biology 175–82 (1990).

[6] Petitioner has attempted to use bold font for claimed residues to facilitate the Board's review.

Dr. Foote and Mr. Buss both agree that the next logical and necessary step in the development of 4D5 was to humanize it. Exs. 1503 ¶¶327–36; 1504 ¶¶63–70. Applying the roadmaps in Queen 1989 or Queen 1990 in combination with other references as detailed below, claims 30, 31, 33, 42 and 60 would have also been obvious.

B. ’213 Patent Background

1. The ’213 Patent

The ’213 patent issued June 18, 2002 from a continuation-in-part of an earlier-abandoned U.S. Patent Appl. No. 07/715,272 filed June 14, 1991, the ’213 patent’s earliest possible priority date.

The ’213 patent has 82 claims. Claims 1, 30, 62–64, 66, 79 and 80 are independent, and all claim a “humanized antibody,” “antibody,” “humanized variant of a non-human parent antibody” or “humanized antibody variable domain” comprising a “non-human…CDR,” and a “Framework Region [FR] amino acid substitution” reverting a substituted human framework residue back to, e.g., a mouse at “a site selected from the group consisting of” certain recited residues. **Claim 1** requires the substitution be at any one of 14 FR light chain residues (4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L and 98L); or 10 heavy chain residues (2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H) using Kabat’s numbering system. Ex. 1501 at 85:44–52.

Independent **claims 30**, **62 and 63** add four FR residues to claim l's list (46L, 75H, 76H and 78H). Claim 30's antibody "binds $p185^{HER2}$ and comprises a humanized antibody variable domain." *Id.* at 87:18–28. Claim 63's 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." *Id.* at 88:37–48.

Independent **claim 66** requires substitution at any one of five FR residues: 24H, 73H, 76H, 78H and 93H. *Id.* at 88:66–89:6. Independent **claim 79** recites "substitutions at heavy chain positions 71H, 73H, 78H and 93H, utilizing the numbering system set forth in Kabat." *Id.* at 90:3–10. Independent **claim 80** requires a substitution at any one of the residues recited in claims 1 and 66, and adds that the substituted amino acid: "(a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) 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." *Id.* at 90:11–25.

Independent **claim 64** "humanized variant of a non-human parent antibody" includes "the most frequently occurring amino acid residues at each location in all human immunoglobulins 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." *Id*. at 88:49–62.

The challenged dependent claims require the FR substitution be at specific residues (claims 12, 25, 42, 60 and 71–77); that the substituted residue is "found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained" (claims 2, 31, 67 and 81); that the human antibody variable domain is a "consensus" domain (claims 4, 33 and 69); or an antibody comprising the claimed humanized variable domain of claims 1 or 66 (claims 29 and 78, respectively).

The claimed humanization concepts were obvious. The '213 patent acknowledges the widely held view that the "function of an antibody is dependent on its three dimensional structure, and that amino acid substitutions can change the three-dimensional structure of an antibody" near the CDRs. *Id.* at 3:40–44. It acknowledges past "molecular modeling" had increased "the antigen binding affinity of a humanized antibody." *Id*. at 3:44–48. Indeed, the '213 patent applies the same cloning and analysis tools and techniques Queen 1989 (Ex. 1534) and Queen 1990 (Ex. 1550) already described, including site-directed mutagenesis,

molecular modeling and antibody functionality analysis. The ’213 patent likewise recognizes the known promise of 4D5 as a therapeutic agent against cancer whose murine origin renders it “immunogenic in humans.” Ex. 1501 at 3:56–4:23.

2. Prosecution History and Related Proceedings

’206 Application Prosecution. The ’213 patent issued from Application No. 08/146,206 (“the ’206 application”). The Examiner allowed the claims on December 18, 2001 without giving any reasons for their allowance. *See* Ex. 1502, Vol. 9 at 4462–70 (Notice of Allowability).

During prosecution, the Examiner rejected the claims under 35 U.S.C. §102(b) as being anticipated by Queen 1989. *See, e.g.*, *id.* at 4368–69 (Office Action dated October 25, 2000). According to the Examiner, Queen 1989 taught, among other things, a residue substitution at 93H. The Examiner withdrew this rejection after Genentech argued Queen 1989 disclosed a different residue using the Kabat numbering system. *See id.* at 4383 (Amendment dated April 25, 2001), *id.* at 4462 (Notice of Allowance). However, as discussed below, it would have been obvious to have substituted one or more of the claimed residues according to the Kabat numbering system in view of Queen 1989 and the PDB Database. The Examiner did not consider the PDB database in prosecution. *See* Ex. 1501 at References Cited.

The ’206 application’s claims were also rejected under 35 U.S.C. §103(a) based on combinations of references including Queen 1989 or Kabat 1987. *See, e.g.*, Ex. 1502, Vol. 2 at 694-95 (Office Action dated December 9, 1994), Vol. 7 at 3401-02 (Office Action dated December 23, 1997). The rejections under §103(a) based on combinations with Queen 1989 were withdrawn after Applicant argued “[t]here is no mention of a consensus human variable domain for providing the framework region of the humanized antibody” in Queen 1989. *See id.*, Vol. 5 at 2500 (Amendment dated June 23, 1997). Of the Challenged Claims, only claims 4, 62, and 69 recite “a consensus human variable domain.” Applicant did not highlight that only some of the rejected claims recite a consensus domain or that other references, discussed herein, teach consensus domains.

The rejections under §103(a) based on combinations with Kabat 1987 were withdrawn after Applicant argued “unexpected results attributable to the consensus human variable domain of a human heavy chain immunoglobulin…demonstrat[e] that the presently claimed antibodies are not obvious….” *Id.*, Vol. 9 at 4387 (Amendment dated April 25, 2001) (emphasis in original). As discussed below, Applicant’s unexpected results argument is not commensurate with the scope of the claims. In addition, the Examiner did not consider Applicant’s unexpected results arguments in relation to the PDB database.

C. Level of Ordinary Skill in the Art

The alleged invention relates to humanizing non-human antibodies, *e.g.*, mouse monoclonal antibodies. A POSITA would have held a Ph.D. or equivalent (for example, knowledge gained through 4–5 years of work experience) in molecular biology, immunology, biochemistry or a closely related field, and may work as a member of a team. A team member or advisor or consultant would have an M.D. with clinical experience in the disease or disease area (*e.g.*, oncology) for which the antibody development is intended. *See*, *e.g.*, Exs. 1503 ¶¶29–32; 1504 ¶¶30–33. Such a person would have the educational background above with experience in common laboratory techniques in molecular biology. *Id.* Such experience can include three dimensional computer modeling of protein structures, domain and sequence manipulation and swapping, construction and expression of recombinant proteins, antibody binding assays (for specificity and affinity), immunogenicity testing and the like. *Id.* Such person may have consulted with one or more team members of experienced professionals to develop a humanized monoclonal antibody for therapeutic use, including consulting with others to select non-human monoclonal antibodies (such as a mouse monoclonal antibody) for humanization, as well as subsequent testing of the humanized antibody and its intermediates. *Id.* Such a person would also have been well-versed in the world-wide literature that was available as of the priority date. *Id.*

D. Claim Construction

The Challenged Claims possess their "broadest reasonable construction in light of the specification" of the '213 patent. 37 C.F.R. §42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268 (Fed. Cir. 2015).

1. "a humanized antibody variable domain" (claims 1, 62 and 80), "an antibody" (claim 30) or "a humanized antibody" (claim 63), "a humanized variant of a non-human parent antibody" (claims 64 and 79) or "a humanized antibody heavy chain variable domain" (claim 66).

The independent claims of the '213 patent each contain a variation of the preamble phrase, "a humanized antibody" set forth above. A POSITA would understand "a humanized antibody" to include an antibody or antibody fragment that has been humanized, *i.e.*, made more human-like. A POSITA would also understand that none of the claims relate to a single, specific antibody or antibody fragment. Even in claim 30, where the phrase "[a] humanized antibody" is modified with "which binds $p185^{HER2}$," the claim is not limited to a particular antibody.

2. "and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of…"

Independent claims 1, 30, 62, 63, 66, 79 and 80 include a Markush Group list of amino acid residues from which a framework region substitution is chosen. Markush Group members are accorded functional equivalency status for purposes

of claim construction. *See Ecolochem, Inc.* v. *Southern California Edison Co.*, 91 F.3d 169 (Fed. Cir. 1996).

As none of the claims are limited to a specific antibody, and all Markush Group members are functional equivalents of each other for the purpose of creating a humanized antibody, the BRI would be that any of the recited residues can be equally substituted for any given antibody. Thus, it is assumed for the purposes of claim construction in this proceeding that each of the recited substitutions is available for humanization of an antibody.

3. "numbering system set forth in Kabat"

Independent claims 1, 30, 62, 63, 66, 79 and 80 recite "utilizing the numbering system set forth in Kabat." The '213 patent specifically ties its numbering system to two references: Kabat 1987 (Ex. 1552) and Kabat 1991 (Ex. 1555). *See* Ex. 1501 at 10:45–49. As noted, the Kabat 1987 and 1991 data derives from a database of publicly available antibody sequences, formatted to display the sequences in alignment with each other and in a numerical sequence order. Kabat 1987 and 1991 also show boundaries of known antibody regions, including the three CDRs and four FRs in each antibody chain variable domain. The BRI of "utilizing the numbering system set forth in Kabat" encompasses the Kabat 1987 and Kabat 1991 designations, including the amino acid residue positions set forth in Kabat and the boundary designations for CDR and FR structures.

4. "up to 3-fold more"

Claim 65, which depends from claim 79,[7] requires a "humanized variant...bind[ing] the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen" (emphasis added). The BRI of this claim includes all binding affinity values "up to" 3-fold more, *i.e.*, any value no matter how small and greater than zero "up to" 3-fold more.

E. Prior Art

Petitioner relies on the following patents and printed publications:

1. Queen 1989 (Ex. 1534)

Queen 1989 (published December 1989) disclosed humanized antibodies which, to reduce immunogenicity, retained only the mouse CDRs. To preserve the structure of the mouse CDRs, Queen 1989 targeted specific residues in the human framework region to switch back to mouse, thus restoring the mouse CDRs' affinity and optimizing the antibody for long-term therapy. Exs. 1534 at 3; 1503 ¶¶126–30. The result was a humanized version of an anti-Tac antibody. *Id.* at ¶126.

[7] The Patent Owner filed a Certificate of Correction dated June 18, 2002, which modified claim 65 to depend from claim 79, stating that it incorrectly depended from claim 63 as a result of a printing error. Ex. 1502, Vol. 9 at 4487–4490.

Queen 1989 provided guidelines for humanizing mouse antibodies, particularly focusing on antibodies' framework regions. Ex. 1534 at 3, Abstract. These guidelines included three concepts:

1) select a human antibody FR sequence homologous to the mouse to minimize distorting the existing shape and positioning of the mouse CDRs; *id.* at 5;

2) use computer modeling to identify mouse amino acid residues in the FR likely interacting with either (a) mouse antibody CDRs or (b) antigen, to better preserve the overall conformation of the mouse CDRs; *id.* at 5–6; and

3) substitute a rare or unusual amino acid in the human FR if the corresponding location in the mouse antibody's FR "actually has a residue much more typical of human sequences," *i.e.*, is common or conserved in humans; *id.* at 6.

This methodology generated a "combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity." *Id.* at 3. Queen 1989 thought their "ideas…may have wider applicability" beyond Queen 1989's anti-Tac antibody. *Id.* at 7.

2. Queen 1990 (Ex. 1550)

Queen 1990 is a PCT application filed December 28, 1989 and published July 26, 1990. Queen 1990 built on Queen 1989 via four explicit criteria for humanizing non-human antibodies. The first step involves choosing the right human framework:

> **Criterion I:** As acceptor, use a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized, or use a consensus framework from many human antibodies....

Exs. 1550 at 12:17–32; 1503 ¶¶132.

Like Queen 1989, Queen 1990 confirms that if a human FR residue is rare or unusual in humans, while the mouse residue is common (or conserved) in humans, the conserved mouse residue at that sequence position should be substituted:

> **Criterion II:** If an amino acid in the framework of the human acceptor immunoglobulin is unusual (*i.e.* "rare", which as used herein indicates an amino acid occurring at that position in no more than about 10% of human heavy (respectively light) chain V region sequences in a representative data bank), and if the donor amino acid at that position is typical for human sequences (*i.e.* "common", which as used herein indicates an amino acid occurring in at least about 25% of sequences in a representative data bank), then the [mouse] donor amino acid rather than the [human] acceptor may be selected....

Exs. 1550 at 13:21–37; 1503 ¶133. Dr. Foote explains that "maintaining conserved residues...is important for avoiding immunogenicity in a humanized antibody." Ex.

1503 ¶129. Dr. Foote explains, however, that applying Criterion II is "not required where a consensus human acceptor antibody is used." *Id.*

Further building on Queen 1989, Queen 1990's Criterion III suggests substituting at CDR-adjacent positions:

> **Criterion III:** In the positions immediately adjacent to the 3 CDR's in the [primary sequence of the] humanized immunoglobulin chain, the [mouse] donor amino acid[s] rather than [human] acceptor amino acid may be selected. These amino acids are particularly likely to interact with the amino acids in the CDR's and, if chosen from the [human] acceptor, distort the [mouse] donor CDR's and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen and selecting these amino acids from the [mouse] donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.

Ex. 1550 at 14:1–12 (citations omitted). As mentioned above, Kabat and Chothia identified the CDR boundaries,[8] both in sequence and structurally. Claimed residues in the '213 patent that are "immediately adjacent" to Kabat and Chothia CDRs include **36H** and **98L**. Exs. 1552; 1503 ¶¶115, 170–80.

Queen 1990 placed further limitations on the molecular modeling criteria Queen 1989 established, pinpointing substitution of framework residues which

[8] As discussed above in Section VII.A, Chothia refers to CDRs as "hypervariable regions".

come within about 3Å of a CDR atom; and thus would be expected to interact with that atom:

> **Criterion IV:** A 3-dimensional model, typically of the original [mouse] donor antibody, shows that certain amino acids outside of the CDR's are close to the CDR's and have a good probability of interacting with amino acids in the CDR's by hydrogen bonding, Van der Waals forces, hydrophobic interactions, etc. At those amino acid positions, the [mouse] donor amino acid rather than the [human] acceptor immunoglobulin amino acid may be selected. Amino acids according to this criterion will generally have a side chain atom within about 3 angstrom units of some site in the CDR's and must contain atoms that could interact with the CDR atoms according to established chemical forces, such as those listed above. Computer programs to create models of proteins such as antibodies are generally available and well known to those skilled in the art.

Ex. 1550 at 14:14–31 (citations omitted). Queen 1990 further teaches deriving these "contact" from "known antibody structures, which are available from the Brookhaven Protein Data Bank." *Id.* at 14:32–36. Such framework residues are more likely to influence CDR/antigen interactions.

3. PBD Database

In 1971, the PDB Database identified by Queen 1990 was established as "a computer archival service…managed by the Brookhaven National Laboratory." *See* Ex. 1503 ¶¶140 (citing to Bernstein (Ex. 1580)). An electronic publication such as an on-line database or Internet publication is considered to be a "printed

publication" within the meaning of 35 U.S.C. 102 so long as the "publication was accessible to persons concerned with the art to which the document relates." MPEP 2128. Further, "[p]rior art disclosures on the Internet or on an on-line database are considered to be publicly available as of the date the item was publicly posted." *Id.* The PDB Database and its contents is a printed publication under 35 U.S.C. §102(b). *See In re Hall*, 781 F.2d 897, 898 (Fed. Cir. 1986) ("printed publication" includes "ongoing advances in the technologies of data storage, retrieval, and dissemination.").

The PDB Database was "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it and recognize and comprehend therefrom the essentials of the claimed invention without need of further research or experimentation." *In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981). In fact, "[t]he purpose of the Bank is to collect, standardize, and distribute atomic co-ordinates and other data from crystallographic studies." Exs. 1580 at 3; 1503 ¶140.

As an early user of the PDB Database well prior to June 1991, Dr. Foote describes the PDB Database as "a repository of protein crystal atomic co-ordinates available to the public....Skilled artisans relied on and contributed to the PDB database, retrieving computer-readable data that could be directly input into

distance calculation and graphic programs for use in visualization and comparison studies, before the earliest priority date of the '213 patent." Ex. 1503 ¶140.

Dr. Foote also details the organization and data uniformity of entries in the PDB Database: "Entries in the PDB included verified co-ordinate information as well as specific information regarding the entry itself." *Id*. ¶141 quoting Ex. 1580 at 537–540, (describing the entry for protein ribonuclease S).

In order to apply Queen 1989 and Queen 1990's instructions to use computer programs "to create models of proteins such as antibodies," including "known antibody structures, which are available from the *Brookhaven Protein Data Bank*," Ex. 1550 at 16:25–36, solved murine monoclonal antibodies and Bence-Jones proteins that were available in the PDB database prior to June 1991 were identified: HYHEL-5, KOL, NEWM, J539, 4–4–20, McPc603, HYHEL-10, 1REI and 2RHE. Ex. 1503 ¶¶261–62.

The atomic coordinates and sequence information from the PDB Database as it would have existed in June 1991 for these molecules were taken, and then the the Queen 1989 and Queen 1990 methodologies (including the computer modeling step) were applied, to identify which amino acid residues a POSITA would have reverted back to murine in a human framework. Ex. 1503 ¶¶261–66. Each solved structure was available pre-June 1991, as their release dates confirm. *See, e.g.*, Exs. 1684¶¶4–21;1503F, 1684A (HYHEL-5; October 16, 1987), 1503G, 1684B (KOL;

July 28, 1983), 1503H, 1684C (NEWM; December 8, 1981), 1503I, 1684D (J539; July 15, 1990), 1503J, 1684E (McPc603; January 2, 1985), 1503K, 1684F (4–4–20; July 15, 1990), 1503L, 1684G (HYHEL-10; July 12, 1989), 1503M, 1684H (1REI; May 19, 1976) and 1503N, 1684I (2RHE; September 15, 1983).

As Dr. Foote explains, evaluating each existing sequence and calculating interatomic distances between each framework residue and CDR region, just as a POSITA would have done, produced a list of amino acid residues in the light and/or heavy chains that correspond to the patent claims. Ex. 1503 ¶¶263, 266.

4. Tramontano (Ex. 1551)

Tramontano, which published in 1990, focused on amino acid residues important in maintaining the conformation of H2, *i.e.*, CDR2 of the heavy chain. *See* Ex. 1551 at 6, Abstract. Tramontano analyzed systematic differences in the position and main chain conformation of known antibody structures, reporting that "the major determinant of the position of H2 is the size of the residue at site 71, a site that is in the conserved framework of the V_H domain." *Id.* Tramontano taught that "[u]nderstanding the relationship between the residue at position 71 and the position and conformation of H2 has applications to the prediction and engineering of antigen-binding sites of immunoglobulins," emphasizing the importance of residue **71H** in maintaining H2 (CDR2) conformation in the heavy chain. *Id*. Thus,

Tramontano taught targeting position **71H** if the human residue differed from the donor (mouse) antibody.

5. Kabat 1987 (Ex. 1552)

Kabat 1987 compiled known antibody sequences, derived through protein and gene sequencing, and identified the most common amino acids occurring at each position in antibody variable and constant domains grouped by class, *i.e.*, consensus sequence. Ex. 1552. Kabat 1987 provided the occurrences of the most common amino acids at each position in human kappa variable light chain subgroup I and human variable heavy chain subgroup III. *See, e.g.*, *id.* at 13, 22. As discussed above, Kabat 1987 also disclosed boundaries of antibody domains within the heavy and light chain variable domains, including FR and CDR boundaries. *See, e.g.*, *id.* at 9 (horizontal lines demarcating FR1, FR2, FR3 and FR4, and CDR1, CDR2 and CDR3 boundaries).

6. Hudziak (Ex. 1521)

Hudziak, published in March 1989, confirmed $p185^{HER2}$'s role in carcinoma development. Ex. 1521 at 8, Abstract. Hudziak had correlated $p185^{HER2}$ gene amplification and carcinoma development, showing high $p185^{HER2}$ levels correlated with negative prognoses and high relapse possibility in carcinoma development, and amplifying $p185^{HER2}$ *in vitro* created resistance to cytotoxic (TNF-α) treatment. *Id.* at 8. Hudziak "prepared [murine] monoclonal antibodies against the

extracellular domain of $p185^{HER2}$...[t]o further investigate the consequences of alteration in *HER2/c-erbB-2* gene expression in mammary gland neoplasia." *Id*. Hudziak chose "[o]ne monoclonal antibody (4D5)," which "was characterized in more detail and was shown to inhibit in vitro proliferation of human breast tumor cells overexpressing $p185^{HER2}$ and, furthermore, to increase the sensitivity of these cells to the cytotoxic effects of TNF-α." *Id.* In SK-BR-3 breast adenocarcinoma cells growth inhibition studies, "*[m]aximum inhibition* was obtained with monoclonal antibody 4D5, which inhibited cellular proliferation by 56%." *Id.* at 12.[9] Hudziak confirmed "the combination of TNF-α and monoclonal antibody 4D5 reduced the [listed] tumor cell number to a level below that initially plated," and "indicat[ed] the induction of a cytotoxic response." *Id.* at 13.

TABLE 1. Inhibition of SK-BR-3 proliferation by anti-$p185^{HER2}$ monoclonal antibodies[a]

Monoclonal antibody	Relative cell proliferation[b]
7C2	79.3 ± 2.2
2C4	79.5 ± 4.4
7D3	83.8 ± 5.9
4D5	44.2 ± 4.4
3E8	66.2 ± 2.4
6E9	98.9 ± 3.6
7F3	62.1 ± 1.4
3H4	66.5 ± 3.9
2H11	92.9 ± 4.8
40.1.H1	105.8 ± 3.8
4F4	94.7 ± 2.8

Ex. 1521 at 11, Table 1.

[9] All emphasis is added unless otherwise indicated.

Hudziak concluded that "[m]onoclonal antibodies specific for $p185^{HER2}$ may therefore be useful therapeutic agents for the treatment of human neoplasias, including certain mammary carcinomas, which are characterized by the overexpressing of $p185^{HER2}$." *Id.* at 14.

VIII. THE PRIOR ART RENDERS THE CHALLENGED CLAIMS OBVIOUS

Detailed instructions for humanizing murine monoclonal antibodies were widely available before the earliest possible priority date. For example, Queen 1989 (Ex. 1534) and Queen 1990 (Ex. 1550) taught humanization methods which relied on reverting select human framework residues back to mouse in order to preserve the original mouse CDRs' binding affinity. *See* Exs. 1534 at 3, Abstract; 1550 at 1, Abstract; 1503 ¶¶125–37. While other techniques (chimeric antibodies and CDR grafting) were available, the field recognized that those antibodies often exhibited poor binding or resulted in immunogenicity. *See* Exs. 1550 at 3:30–33; 1573 at 8:12–19; 1503 ¶¶97–100; 1504 ¶¶38–39.

Queen 1989 and 1990 addressed these issues by providing POSITAs with the best of both worlds: (1) human FR regions to reduce immunogenicity; with (2) restoration of binding affinity through preservation of mouse CDRs and key mouse residues in the FR that support or maintain CDR conformation.

Queen 1989 provided the following roadmap:

1) Use a human framework structurally closest to the non-human (mouse) monoclonal antibody or a consensus sequence; and

2) Target FR residues within the human sequence that (a) are close enough to influence CDR conformation; (b) interact directly with the antigen; and/or (c) are more 'human' in the mouse or donor immunoglobulin at the same-positioned residue in the human antibody variable domain; and convert them back to the donor residue.

Exs. 1534 at 5–6; 1503 ¶¶127, 130.

Queen 1990 went further, instructing targeting residues which, in the original mouse antibody, possessed side chain atoms within about 3Å of the CDR residues and "could interact with the CDR atoms according to established chemical forces." Ex. 1550 at 14:21–25.

Based on the teachings of Queen 1989 or Queen 1990, a POSITA could have reasonably expected to identify the most important framework positions in any donor antibody to target for substitution. *Id*. at 14:2, 14–15. Thus, by 1991, the prior art provided a detailed roadmap to optimize the humanization of non-human monoclonal antibodies for therapeutic use which would "be substantially non-immunogenic and retain substantially the same affinity as the donor immunoglobulin to the antigen." *See id.* at 1, Abstract; Ex. 1503 ¶¶125–37.

B. Grounds 1 and 2: Claims 1, 2, 4, 12, 25, 29, 62–67, 69 and 71–81 Are Obvious over Queen 1989 or Queen 1990, In View of the PDB Database

1. Ground 1: Claim 1 is Obvious over Queen 1989 in view of the PDB Database

Independent claim 1 is drawn to "[a] humanized antibody variable domain" comprising "non-human" (*e.g.*, mouse) CDRs.

As discussed above, Queen 1989 disclosed making "a humanized antibody variable domain" comprising "non-human CDR amino acid residues which bind an antigen incorporated into a human antibody variable domain." *See* Ex. 1534 at 3, Abstract ("We have therefore constructed a 'humanized' antibody by combining the complementarity determining regions (CDRs) of the anti-Tac antibody with human framework and constant regions."); Ex. 1503 ¶¶126, 253.

Claim 1's humanized antibody "further compris[es] a Framework Region (FR) amino acid 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, utilizing the numbering system set forth in Kabat."

Queen 1989 taught that framework residues that (1) are close enough to influence CDR conformation; (2) interact directly with the antigen; and/or (3) are more 'human' in the mouse or donor immunoglobulin than the residue at the same position in human antibody variable domain (*i.e.*, conserved) are suitable for

substitution. Exs. 1534 at 5–6; 1503 ¶254. A POSITA would have used those simple rules to determine which residues in a human FR region could be switched back to mouse. Ex. 1503 ¶¶255–59.

Queen 1989 did exactly this for the anti-Tac antibody, using programs to compare known antibody structures to show that "a number of amino acid residues…are in fact close enough to [CDRs] to either influence their conformation or interact directly with antigen." Exs. 1534 at 5; 1503 ¶¶255–56. Queen 1989 then substituted these framework positions with the mouse residue. Exs. 1534 at 5; 1503 ¶¶255–56. Queen 1989 taught that such steps "may have wider applicability" to humanize other antibodies. Exs. 1534 at 7; 1503 ¶128.

A POSITA would have applied the same methodology prior to 1991. Many private and public research institutions, including Genzyme Corporation (*see, e.g.*, Ex. 1571[10]), Protein Design Labs (*see, e.g.*, Ex. 1550), the Winter Lab and the Medical Research Council (*see, e.g.*, Ex. 1573[11]), and his laboratory at the National Institutes of Health, were very active in the field of humanization as of June 1991. Ex. 1503 ¶110.

Using publicly available tools such as the PDB Database (§VII.E.3, *supra*) and computer programs, POSITAs measured interatomic distances and created

[10] Kurrle *et al.*, EP Pub. 0403156 (published December 19, 1990).

[11] Winter *et al.*, EP Pub. 0239400 (published September 30, 1987).

three-dimensional graphical models "[i]n order to ensure the preservation of antigen-binding properties, when an antibody is 'humanized' by CDR-grafting, *all the framework residues, that could influence the structure of its combining site, must be retained*." *Id*. Thus, a POSITA engaged in antibody humanization would have followed Queen 1989's guidance to identify the FR residues close enough to influence CDR conformation or interact directly with the antigen. Moreover, where the acceptor and donor sequences are known, a residue by residue comparison of the human FR region sequences against the mouse donor sequence would have revealed whether there are unusual residues in the human FR that should be substituted to a common or conserved residue if present in the mouse donor. Exs. 1534 at 5–6 (residues that "are more 'human' in the mouse or donor immunoglobulin at the same-positioned residue in the human antibody variable domain" should be converted back to the donor residue); 1503 ¶265.

Queen 1989's methodology was performed on antibody structures known and publicly available prior to 1991 through the PDB Database. *See* Ex. 1503 ¶¶261–63. The atomic coordinates of each of the known and available solved antibody structures (*i.e.*, HYHEL-5, KOL, NEWM, J539, MCPC603, 4–4–20, HYHEL-10, 1REI and 2RHE) were extracted, which contained distance calculations between framework and CDR amino acid residues. *Id.* ¶¶262–63. Then, the interatomic (Euclidean) distances between the atom pairs of the

framework residue and the CDR residues were determined, a practice that was considered routine as of 1991. *Id.* ¶¶262–66; Ex. 1503O (interatomic distance calculations). Using this information, framework residue side chains were in contact with the CDRs were identified. *See* Exs. 1503 ¶¶262–66; 1503O and 1503Q.

Following the teachings of Queen 1989, the primary amino acid sequence of each of the antibody structures were aligned according to the Kabat numbering system (*see* Ex. 1503P), and identified contact residues that were targets for substitution. *See* Exs. 1534 at 3–4 and Figure 3; 1503 ¶¶263–66; 1503O and 1503P. It was found that 9 light (L) chain (4L, 58L, 62L, 66L, 67L, 69L, 73L, 85L and 105L) and 11 heavy (H) chain residues (2H, 24H, 39H, 45H, 69H, 71H, 73H, 76H, 78H, 93H and 103H) were readily identified as in contact with CDRs, according to the numbering system of Kabat 1987 (Ex. 1552), *See* Exs. 1503 ¶263; 1503O (interatomic distance calculations), P (antibody alignment), and Q (contact summary). Of these, claim 1 recites residues **4L**, **58L**, **66L**, **67L**, **69L**, **73L**, **2H**, **45H** and **69H**. *See* Ex. 1503 ¶266. As Dr. Foote explains, a POSITA could easily and quickly identify at least 9 claimed residues that one would have had on a list of substitutable residues following Queen 1989's roadmap.

The '213 patentees followed Queen's roadmap. The specification states the purported invention involved obtaining a donor antibody and a consensus sequence

(Ex. 1501 at 4:47–49); importing CDRs from the donor into the consensus (4:50–54); identifying any residues in the framework that differ (*id.* at 4:59–61); determining whether the residue where the difference lies is involved in CDR interaction and/or antigen binding (*id.* at 4:62–67); and if so, substituting in the donor residue (mouse) for the human residue (*id*. at 5:1–5). In other words, they predictably identified residues already ripe for substitution by following the roadmap of Queen 1989.

The specification reveals further evidence that all the '213 patentees did was follow the teachings of Queen 1989 and 1990:

- "Step 1...crystal structures from the Brookhaven Protein Data Bank were used..." (Ex. 1501 at 16:30–32);
- "Step 2...the structures were superimposed on one another using the INSIGHT computer program..." (*id*. at 17:15–19);
- "[m]odels of a humanized, import or human antibody sequence are used...[to] show residues which may be important in antigen binding, or for maintaining the conformation of the antibody..." (*id*. at 19:58–64).

Given the teachings in Queen 1989 and the readily available structures on the PDB Database, it would have been obvious to humanize an antibody with a framework residue substitution at **4L**, **58L**, **66L**, **67L**, **69L**, **73L**, **2H**, **45H** or **69H**. A POSITA would have been motivated to "reduce immunogenicity while retaining

high binding affinity" in the original non-human (*e.g.*, murine) monoclonal antibody, Exs. 1534 at 3; 1503 ¶¶36, 254, and would have had a reasonable expectation of success in humanizing the antibodies on the PDB Database based on the broad teachings of Queen 1989. *Id.* ¶266. A POSITA considering Queen 1989 would have been directed to antibody structures in the PDB Database by Queen 1989's own disclosure. For these reasons, claim 1 is obvious.

2. Ground 2: Claim 1 is Obvious over Queen 1990 in view of the PDB Database

Queen 1990 also disclosed making "a humanized antibody variable domain" comprising "non-human CDR amino acid residues which bind an antigen incorporated into a human antibody variable domain." Queen 1990 encompassed a human antibody variable domain comprising CDRs from a mouse (donor) monoclonal antibody. Exs. 1550 at 1, Abstract ("[n]ovel methods for designing humanized immunoglobulins having one or more complementary [sic] determining regions (CDR's) from a donor immunoglobulin and a framework region from a human immunoglobulin comprising...."); 1503 ¶¶132, 267.

Further, Queen 1990 provided detailed criteria to identify substitutable framework region positions that are adjacent to or can contact the CDRs (Criterion III (*i.e.*, CDR-adjacent) and Criterion IV (*i.e.*, within 3Å of a CDR)). Exs. 1550 at 14:1–36; 1503 ¶¶135–36, 267–68. Queen 1990 also disclosed detailed information for decreasing immunogenicity by maintaining conserved residues in the human

acceptor framework (Criterion II (*i.e.*, conserved or rare)). Exs. 1550 at 13:22–37; 1503 ¶133 (adopting definition of >90% conservation of residue according to Kabat 1987 as a target for substitution).

Queen 1990 thus provided a detailed rationale for substituting particular amino acids; and *how* to do choose these amino acids in an objective way. Queen 1990 explicitly instructed a POSITA to look to the "Brookhaven Protein Data Bank" (*i.e.*, the PDB Database) (Ex. 1503 ¶137) to identify the framework residues that: "could interact with the CDR atoms" (Criterion IV; Ex. 1550 at 14:14–15:2); were conserved (Criterion II; *id.* at 13:22–37); or were adjacent to CDRs (Criterion III; *id.* at 14:1–12). Ex. 1503 ¶¶133–36, 267.

A POSITA following Queen 1990's roadmap would have quickly determined that 19 light (L) chain and 23 heavy (H) chain residues were readily identified for substitution:

- 4L, 58L, 62L, 66L, 67L, 73L, 85L and 105L (CDR contact residues);
- 23L, 25L, 33L, 35L, 49L, 53L, 57L, 88L, 90L, 97L, 98L (Kabat and Chothia adjacent residues);
- 2H, 24H, 39H, 45H, 69H, 71H, 73H, 76H, 78H, 93H and 103H (CDR contact residues); and
- 25H, 30H, 33H, 36H, 49H, 52H, 56H, 66H, 94H, 95H, 102H and 103H (Kabat and Chothia adjacent residues).

This includes positions **4L**, **58L**, **66L**, **67L**, **69L**, **73L**, **98L**, **2H**, **36H**, **45H** and **69H** recited in claim 1. *See* §VIII.B.1, *supra*; Exs. 1503 ¶268; 1503E (adjacent residues), O (interatomic distance calculations), P (alignment) and Q (contact summary). It therefore would have been obvious to have substituted an amino acid at least at one of these positions.

3. Grounds 1 and 2: Claims 2, 12, 25 and 29 Are Obvious Over Queen 1989 and the PDB Database or Queen 1990 and the PDB Database

Claims 2, 12, 25 and 29 are also obvious in view of either Queen 1989 or Queen 1990 and the PDB Database. Ex. 1503 ¶¶269–70. Claims 2, 12, 25, and 29 depend from claim 1. As discussed above, claim 1 is obvious in view of Queen 1989 or Queen 1990, in view of the PDB Database. *See* §§VIII.B.1 & 2, *supra*.

Queen 1989 and Queen 1990, in view of the PDB Database additionally disclosed "wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained," as recited in **claim 2** (*see* Exs. 1534 at 3; 1550 at 5:36–6:1), "wherein the residue at site 66L has been substituted," as recited in **claim 12** (*see* Ex. 1503 ¶269; §§VIII.B.1 & 2, *supra* (framework residue 66L within 3 Å of CDR)), "wherein the residue at site 69H has been substituted" as recited in **claim 25** (*see* Ex. 1503 ¶269, §§VIII.B.1 & 2, *supra* (69L is a contact residue)), and "[a]n

antibody comprising the humanized variable domain of claim 1," as recited in **claim 29** (*see* Exs. 1534 at 5; 1550 at 4:21–25; 1503 ¶269).

Both Queen 1989 and Queen 1990 provide express motivation to evaluate proteins in the PDB. *Id*. ¶¶137, 258, 268. In view of the discussion above, claims 2, 12, 25 and 29 are obvious over Queen 1989 or Queen 1990, in view of known antibody structures available on the PDB Database.

CLAIM	***GROUND 1:* Queen 1989 + PDB Database**	***GROUND 2:* Queen 1990 + PDB Database**
Claim 2: "wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained.	*See* claim 1; Exs. 1534 at 3 ("When these residues differ between the anti-Tac and Eu antibodies, the residue in the humanized antibody was chosen to be [mouse] rather than [human].)"; 1503 ¶¶269–70.	*See* claim 1; Exs. 1550 at 5:36–6:2 ("substitutions of a human framework amino acid of the [human] acceptor immunoglobulin with a corresponding amino acid from a [mouse] donor immunoglobulin will be made at positions.)"; 1503 ¶¶269–70.
Claim 12: "wherein the residue at site 66L has been substituted."	*See* claim 1; Exs. 1503O and Q (66L substitutable as a conserved residue and in contact with CDR); 1503 ¶¶269–70.	*See* claim 1; Exs. 1503O and Q (66L substitutable as a conserved residue and in contact with CDR—Queen 1990 Criteria IV); 1503 ¶¶269–70.
Claim 25: "wherein the residue at site 69H has been substituted."	*See* claim 1; Exs. 1503O and Q (69H substitutable as a conserved residue and in contact with CDR); 1503 ¶¶269–70.	*See* claim 1; Exs. 1503O and Q (69H substitutable as a conserved residue and in contact with CDR—Queen 1990 Criteria IV); 1503 ¶¶269–70.
Claim 29: "An antibody comprising the	*See* claim 1; Exs. 1534 at 5 ("The CDRs in the humanized antibody	*See* claim 1; Exs. 1550 at 6:21–26 ("When combined into an intact antibody, the

CLAIM	***GROUND 1:* Queen 1989 + PDB Database**	***GROUND 2:* Queen 1990 + PDB Database**
humanized variable domain of claim 1."	were of course chosen to be identical to the anti-Tac CDRs."); 1503 ¶¶269–70.	humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immune-globulin..."); 1503 ¶¶269–70.

4. Ground 2: Claim 4 Is Obvious in View of Queen 1990 and PDB Database

Claim 4 depends from claim 1 and recites "wherein the human antibody variable domain is a consensus human variable domain." As discussed above, claim 1 is obvious over Queen 1990 and the PDB Database. *See* §VIII.B.2. Further, Queen 1990 disclosed using a "consensus human variable domain". *See* Exs. 1550 at 12:19–20; 1503 ¶271. Accordingly, claim 4 is also obvious over Queen 1990, in view of known antibody structures available on the PDB Database.

5. Ground 2: Claim 62 Is Obvious in View of Queen 1990 and PDB Database

As discussed *supra* (§VIII.B.2), independent claim 62 is nearly identical to claim 1, but adds that the human variable domain is a "consensus human variable domain." For the same reasons as for claims 1 and 4, claim 62 is also obvious.

Queen 1990 teaches substituting amino acid residues that contact or interact with a CDR, or are conserved. A POSITA following Queen 1990's criteria would readily identify at least claimed residues **4L**, **58L**, **66L**, **67L**, **73L**, **2H**, **36H**, **45H**

and **69H**. *See* §§VIII.B.2 and 2 *supra,* Ex. 1503 ¶272. Queen 1990 also taught using a "consensus human variable domain" in the humanization process. Exs. 1550 at 12:17–20; 1503 ¶272. Claim 62 is thus obvious over Queen 1990 and the PDB Database.

6. Grounds 1, 2: Claims 63–64 and 66 Are Obvious Over Queen 1989 or Queen 1990 and PDB Database

Independent ***claim 63*** differs from claim 1 by further reciting that the claimed 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...." This is the goal of all monoclonal antibody humanization projects, including that of Queen 1989 and Queen 1990, in which the disclosed humanized immunoglobulins "will be substantially non-immunogenic in humans...." Exs. 1534 at 3; 1550 at 1, Abstract; 1503 ¶¶273–74. Accordingly, as for claim 1 above (§§VIII.B.1 and 2), claim 63 is obvious over Queen 1989 or Queen 1990 in view of the PDB Database. *Id*.

Independent ***claim 64*** recites a "humanized variant of a non-human parent antibody which binds an antigen;" a "human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup"; non-human CDRs; and, rather than require a FR substitution at one of a variety of locations (*cf.*

claims 1, 62, 63), recites *functional* elements of 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."

Listing such properties does not render "the old composition patentably new to the discoverer." *Atlas Powder Co.* v. *Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999). Instead, such elements reflect inherent humanized antibody properties. Even so, Queen 1990 stated amino acids "immediately adjacent" to the CDRs "are particularly likely to interact with the amino acids in the CDR's and, if chosen from the acceptor, distort the donor CDR's and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen." Exs. 1550 at 14:1–12; 1503 ¶¶276–77. This satisfies at least limitations (a) and (b).

Further, Queen 1990 disclosed humanized antibodies which bind an antigen and comprise a human variable domain with a "consensus framework from many human antibodies." *See* §VIII.B.4 *supra*; Ex. 1503 ¶277. Queen 1990, given the PDB database, renders claim 64 obvious.

Claim 66. Independent claim 66 is similar to claim 1, but requires an amino acid substitution "selected from the group consisting of 24H, 73H, 76H, 78H and 93H" under Kabat's numbering system. Queen 1989 and Queen 1990 teach

residues that are substitutable in a human FR region by identifying amino acid positions that: 1) contact a CDR; or 2) are adjacent to a CDR. *See* §§VIII.B.1 and 2; Ex. 1503 ¶280. Given Queen 1989 and Queen 1990 disclosures teaching computer modeling and comparison with known antibody structures from the PDB Database, a POSITA would have readily recognized that all of the claimed FR options (**24H**, **73H**, **76H**, **78H**, and **93H)** satisfy Queen's criteria. *See id.*; 1503C, Exhibit O (interatomic distance calculations), Exhibit Q (Contacts Summary). Claim 66 is also obvious over Queen 1989 or Queen 1990 and the PDB database.

Claim	***GROUND 1:* Queen 1989 + PDB Database**	***GROUND 2:* Queen 1990 + PDB Database**
Claim 63: "A humanized antibody which 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, wherein the humanized antibody comprises non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat"	*See* discussion of claims 1 and 29 for "humanized antibody" comprising non-human...CDR; and claimed substituted amino acids **4L**, **58L**, **66L**, **67L**, **73L**, **2H**, **36H**, **45H** and **69H**. §§VIII.B.1 and 3, *supra*. *See also* Exs. 1534 at 1; 1503 ¶¶273–74.	*See* discussion of claims 1 and 29 for "humanized antibody" comprising non-human...CDR; and claimed substituted amino acids **4L**, **58L**, **66L**, **67L**, **73L**, **2H**, **36H**, **45H** and **69H**. §§VIII.B.2 and 3 *supra*. *See also* Exs. 1550 at 1, Abstract ("the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans…."); 1503 ¶¶273–74.

Claim	***GROUND 1:* Queen 1989 + PDB Database**	***GROUND 2:* Queen 1990 + PDB Database**
Claim 64: "A humanized variant of a non-human parent antibody which binds an antigen and comprises a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins 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."		*See* discussion of claim 1 for "humanized antibody variable domain comprising non-human...CDR; §§VIII.B.1 and 2, *supra*, Ex. 1503 ¶¶275–78. *See also* for "the most frequently occurring amino acid residues at each location in all human immunoglobulins," Ex. 1550 at 12:17–20 ("As acceptor...use a consensus framework from many human antibodies."). For functional limitations (a), (b) and (c), *see id*. at 14:4–12 ("These amino acids are particularly likely to interact with the amino acids in the CDR's...[and] interact directly with the antigen.").

Claim	***GROUND 1:* Queen 1989 + PDB Database**	***GROUND 2:* Queen 1990 + PDB Database**
Claim 66: "A humanized antibody heavy chain variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution at a site selected from the group consisting of: 24H, 73H, 76H, 78H, and 93H, utilizing the numbering system set forth in Kabat"	*See* discussion of claim 1 for "humanized antibody variable domain comprising non-human...CDR; and claimed substituted amino acids. §§VIII.B.1 and 2, *supra*. *See also* Exs. 1503 ¶¶279–83; 1503O and Q, for substitution of residues **24H**, **73H**, **76H**, **78H** and **93H**	*See* discussion of claim 1 for "humanized antibody variable domain comprising non-human...CDR; and claimed substituted amino acids. §§VIII.B.1 and 2, *supra*. *See also* Exs. 1503 ¶¶279–83; 1503O and Q, for substitution of residues **24H**, **73H**, **76H**, **78H** and **93H**

7. Ground 2: Claim 69 Is Obvious in View of Queen 1990 and PDB Database

Claim 69 depends from claim 66 and recites "wherein the human antibody variable domain is a consensus human variable domain." As discussed above, claim 66 is obvious over Queen 1990 and the PDB Database. *See* §VIII.B.6. Further, Queen 1990 disclosed using a "consensus human variable domain". *See* §VIII.B.4; Exs. 1550 at 12:19–20; 1503 ¶305. For these reasons, claim 69 is also obvious over Queen 1990, in view of known antibody structures available on the PDB Database.

8. Grounds 1, 2: Claims 67, 71–74 and 78 Are Obvious in View of Queen 1989 or Queen 1990 and PDB Database

Claims 67, 71–74 and 78 depend from claim 66, and further recite "wherein the substituted residue is the residue found at the corresponding location of the

non-human antibody from which the non-human CDR amino acid residues are obtained" (***claim 67***), "wherein the residue at site 73H has been substituted" (***claim 71***), "wherein the residue at site 76H has been substituted" (***claim 72***), "wherein the residue at site 78H has been substituted" (***claim 73***), "wherein the residue at site 93H has been substituted" (***claim 74***) and "[a]n antibody comprising the humanized variable domain of claim 66" (***claim 78***).

Each of **73H**, **76H**, **78H** and **93H** are CDR contact residues as disclosed by Queen 1989 (Ex. 1534) and Queen 1990 (Ex. 1550) in view of the PDB Database,[12] and thus would have been readily identified for reverting to the mouse residue in any humanization project. *See* §§VIII.B.1 and 2, *supra*, Exs. 1503 ¶284; 1503Q. Moreover, like claims 2 and 29, claims 67 and 78 are also obvious. *See* §VIII.B.3; Ex. 1503 ¶284. For these reasons, claims 67, 71–74 and 78 are also obvious over Queen 1989 or Queen 1990, in view of known antibody structures in the PDB Database.

[12] Dr. Foote points to antibody 4–4–20 (available 1989) with a cluster of close (<3.0Å) contacts at 73H, 78H and 93H, emphasizing the relative importance of these residues for maintaining antibody conformation. Ex. 1503 ¶281.

9. Grounds 1, 2: Claims 75–77 and 79 Are Obvious in View of Queen 1989 or Queen 1990 and PDB Database

Claim 75 depends from independent claim 66, and recites a humanized variable domain "which further comprises an amino acid substitution at site 71H." As discussed above, Queen 1989 and Queen 1990 teach substituting framework residues that: 1) contact a CDR; or 2) are adjacent to a CDR. *See* §§VIII.B.1 and 2; Ex. 1503 ¶¶127, 135–36. Moreover, based on Queen 1989 and Queen 1990's teachings of computer modeling and comparison with known antibody structures from, *e.g.*, the PDB Database (*see* Exs. 1550 at 14:14–15:2 (Criterion IV); 1503 ¶¶128, 137, 258), a POSITA would have readily identified FR position **71H** for substitution. *See id*. ¶288; Ex. 1503O (interatomic distance calculations) and Q (contact summary). Accordingly, claim 75 is also obvious over Queen 1989 or Queen 1990, given known antibody structures available in the PDB Database. Ex. 1503 ¶288.

Claims 76–77 depend from independent claim 66 and recite the additional limitations of "amino acid substitutions at sites 71H and 73H" (***claim 76***) and "amino acid substitutions at sites 71H, 73H and 78H" (***claim 77***). ***Claim 79*** is an independent claim, and recites "[a] humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-human parent antibody incorporated into a human antibody variable domain, and

further comprises Framework Region (FR) substitutions at heavy chain positions 71H, 73H, 78H and 93H" using Kabat's numbering system.

As noted above, residues **71H**, **73H**, **78H** and **93H** are among those that would have been targeted for substitution in view of Queen 1989 (Ex. 1534) or Queen 1990 (Ex. 1550) and the PDB Database. *See* §§VIII.B.1, 2, *supra*; Exs. 1503 ¶¶263, 268; 1503O (interatomic distance calculations) and Q (contact summary). Therefore, it would have been obvious to have had "amino acid substitutions at sites 71H and 73H" of claim 76, "amino acid substitutions at sites 71H, 73H and 78H" of claim 77 and "substitutions at heavy chain positions 71H, 73H, 78H and 93H" of claim 79, given the limited set of residues already targeted for substitution. Ex. 1503 ¶¶292–303.

Further, the substitutability of residues 71H, 73H, 78H and 93H would not have been surprising or unexpected to a POSITA. The importance of heavy chain residue **71H** was well-known by those in the field, including patentees. *See* Exs. 1501 at 3:1–8 (recognizing framework residues that "critically affect[] the conformation of particular CDRs and thus their contribution to antigen binding," (citing to Tramontano (Ex. 1551)); 1503 ¶294, n.23. Dr. Foote also cites to antibody 4–4–20 (4Fab) which has a cluster of close contacts (less than 3Å) at 73H, 78H and 93H, which "emphasizes the relative importance of these contacts made…in maintaining antibody conformation." Ex. 1503 ¶281.

Moreover, the typical scenario was that more than one framework substitution was often needed to restore function and antigen binding of the resultant humanized antibody. Ex. 1503 ¶297. This is exemplified in Queen 1989 and Queen 1990, which both describe humanizing antibodies with multiple FR substitutions. Specifically, Queen 1989 taught 15 mouse substitutions. *See* Exs. 1534 at 5, Fig. 2; 1503 ¶297. Similarly, Queen 1990 states that the Queen CDR-contact criterion can be "used singly, or when necessary in combination" with other criteria to "achieve the desired affinity or other characteristics." *See* Exs. 1550 at 12:9–15; 1503 ¶297.

Further, a substitution's value can be limited given the antibody sequence itself. For example, comparing the mouse monoclonal antibody 4D5 sequence[13] and a human consensus amino acid sequence from Figures 1A and IB of the '213

[13] 4D5 was made available for use by outside investigators prior to June 1991 (Kumar *et al*., 11(2) MOLECULAR CELLULAR BIOLOGY 979–86 (1991) (Ex. 1588); Soomro *et al*., 44 J. CLINICAL PATHOLOGY 211–14 (1991) (Ex. 1589)), allowing a POSITA to obtain the amino acid sequence of the variable domain through routine protein sequencing. *See, e.g.,* Wilson & Goulding (Ex. 1590); Ex. 1503 ¶301 n.26. Many sequences present in the Kabat database (Kabat 1987 (Ex. 1552)) were obtained through routine protein sequencing. *Id*, citing to Edelman (1969) (Ex. 1591); Capra & Kehoe (1974) (Ex. 1592).

patent, *see* Ex. 1501 at 7–8, and using the knowledge readily derived from the PDB Database and the Queen references, a POSITA would have arrived at a short list of light and heavy chain amino acid residues for substitution for humanization: **66L**, **71H**, **73H**, **76H**, **78H**, **93H**, and VL:VH contacts **43L**, **73L**, **85L and 43H**, all of which are claimed in the '213 patent. *See* Exs. 1503 ¶¶299–302; 1503O–Q.

Applying Queen 1990's Criterion IV, a POSITA would have thus targeted claimed residues **71H**, **73H**, **78H** and **93H** given the differences in size and/or characteristics of these residues in the mouse and human positions. *See, e.g.*, Ex. 1503 ¶301 (71H); ¶302 (73H (polar to charged: aspartic acid in human acceptor vs. threonine in mouse 4D5)); ¶302 (78H (small to large: leucine in human acceptor vs. alanine in mouse 4D5)); ¶302 (93H (polar to hydrophobic: alanine in human acceptor vs. serine in mouse 4D5)). Thus, a POSITA in view of Queen 1989 or Queen 1990 and known available antibody structures in the PDB Database, would have been motivated to substitute framework residues at least at **71H**, **73H**, **78H** and **93H** (*i.e.*, claims 75, 76, 77 and 79) for the humanization of mouse 4D5 using a human consensus sequence as the acceptor antibody. *See* Exs. 1550 at 12:19–20; 1503 ¶¶302–03. A POSITA would have had a reasonable expectation of success given the teachings of Queen 1989 and Queen 1990 that the resultant humanized antibody would be "substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin..." Exs. 1550 at 1,

Abstract; 1503 ¶¶302–03. For these reasons, claims 75–77 and 79 were obvious in view of Queen 1989 or Queen 1990, and the PDB Database.

10. Grounds 1 and 2: Claim 65 Is Obvious in View of Queen 1989 or Queen 1990 and the PDB Database

Claim 65 depends from claim 79, and recites the humanized variant "binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." Queen 1990 stated "affinity levels can vary…and may be *within about 4 fold* of the donor immunoglobulin's original affinity to the antigen." See Ex. 1550 at 6:26–28. Queen 1990 thus taught that a humanized antibody would have been expected to be "within about 4-fold," in affinity as the original mouse antibody, disclosing a greater increase in affinity than the 3-fold increase recited in claim 65. The range of increase in affinity disclosed in Queen 1990 therefore encompasses the range recited in claim 65. A prior art reference that discloses a range encompassing a narrower claimed range is sufficient to establish a prima facie case of obviousness. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *see also* MPEP §2144.04. Ex. 1533 ¶¶306–310.

Moreover, as explained by Dr. Foote, "it was the expectation when humanizing antibodies...that a similar affinity, *i.e.*, slightly better or worse, would be obtained as compared to the parent (mouse) antibody. Thus, it would not have been surprising that at least a moderate improvement in affinity would be achieved" when humanizing some antibodies. Ex. 1503 ¶308. Thus, any increase in

affinity, including small and moderate increases within the scope of claim 65, would have been expected, in view of the humanization techniques disclosed in Queen 1989 and Queen 1990. Exs. 1550 at 6:26–28; 1503 ¶308. For these reasons, claim 65 is obvious over Queen 1989 or Queen 1990 and the PDB Database.

11. Grounds 1, 2: Claims 80 and 81 Are Obvious in View of Queen 1989 or Queen 1990 and PDB Database

Independent ***Claim 80*** recites "[a] humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution," and further recites the "substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) 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...," while reciting a set of FR residues which differ from claim 1 only by *adding* amino acid residues 73H, 76H, 78H and 93H to the list of possible locations. As before, residues **4L**, **58L**, **66L**, **67L**, **73L**, **2H**, **24H**, **36H**, **45H**, **69H**, **73H**, **76H**, **78H** and **93H** were readily identifiable residues for substitution. *See* §§VIII.B.1 and 2; Exs. 1503 ¶¶312–14; 1503O and Q.

The additional recited elements—noted functions of the substituted residues—cannot impart novelty. *See* claim 64, § VIII.B.5, 6; *see also Atlas Powder*, 190 F.3d at 1347. Even if the inherency of these functions were

discounted (they should not be), Queen 1989 and Queen 1990 each explicitly teach interaction of the framework residues with the CDR as a reason for substitutability. *See* Exs. 1534 at 5; 1550 at 14:32–15:2 (using computer model to assess CDR proximity); 1503 ¶¶312–15. Accordingly, Queen 1989 or Queen 1990 and the PDB Database, also teaches substitution of a framework residue that "interacts with a CDR", rendering claim 80 obvious.

Claim 81 depends on claim 80, and further recites "wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained." This is taught by Queen 1989 and Queen 1990. *See* Exs. 1534 at 3 ("selecting a human antibody to provide the variable region framework for the humanized anti-Tac antibody"); 1550 at 5:36–6:1; 1503 ¶316. Thus, claim 81 is obvious over Queen 1989 or Queen 1990, in view of the PDB Database.

C. Grounds 3 and 4: Claims 75–77, 79, and 65 Are Obvious over Queen 1989 or Queen 1990 and PDB Database and Further in View of Tramontano.

While the teachings of Queen 1989 and Queen 1990 in view of the PDB Database would have readily identified residue **71H** for substitution based on its CDR contacts, independent work also emphasized the criticality of residue **71H** in maintaining CDR conformation. Specifically, Tramontano definitively demonstrated the importance of **71H** to maintain the H2 loop and antigen binding.

See Tramontano (Ex. 1551). This publication was the first to specifically report that:

> the major determinant of the position of H2 is the size of the residue at site 71, a site that is in the conserved framework of the V_H domain. ***It is likely that for about two thirds of the known V_H sequences the size of the residue at this site is also a major determinant of the conformation of H2***.

Id. at 6, Abstract. The publication also confirmed Queen's teachings that residues outside of the CDR (*e.g.*, in the FR) help maintain CDR conformation and antigen binding.

The teachings of Queen 1989 (Ex. 1534) or Queen 1990 (Ex. 1550), and Tramontano (definitively demonstrating the importance of framework residue **71H**, *see* Exs. 1551 at 6, Abstract; 1503 ¶¶143, 289), would have motivated a POSITA to switch the human residue at position **71H** to the mouse residue in order to preserve the conformation of the H2 CDR loop. *See* Exs. 1551; Ex. 1503 ¶290. Indeed, this would have been an automatic substitution to a POSITA. *Id*. Thus, together with Queen 1989 or Queen 1990 and the PDB Database, and for the same reasons above with regards to the obviousness of claims 75–77 and 79, §§VIII.B.9 *supra*, claims 75–77, 79, and 65 are obvious in view of Queen 1989 or Queen 1990, the PDB Database and Tramontano (Ex. 1551). Ex. 1503 ¶¶291, 304.

D. Ground 5: Claims 4, 62, 64 and 69 are Obvious in View of Queen 1989 and the PDB Database, and Further in View of Kabat 1987

Claims 4, 62, 64 and 69 are also obvious over Queen 1989 and the PDB Database in view of Kabat 1987. *See* Ex. 1503 ¶¶317–26. As Dr. Foote explains, the '213 patent's claiming a "consensus" sequence is somewhat misleading because the framework region sequences "are relatively conserved…with respect to both sequence and structure." Ex. 1503 ¶174; *see also* ¶300 (citing to Ex. 1534 at 5 ("Different human light or heavy chain V regions exhibit strong amino acid homology outside of the CDRs within the framework regions.")).

Nevertheless, recognizing the importance of maintaining FR conservation to reduce immunogenicity and "make the antibody more human," Queen 1989 taught moving toward a consensus framework region, observing that replacing amino acid residues with ones that are "more typical" and common would make the resulting antibody more human and less immunogenic. *See* Exs. 1534 at 5–6; 1503 ¶320. A POSITA considering Queen 1989 would have looked to Kabat 1987 to identify these "more typical" and common residues. Kabat 1987 provided all consensus amino acids at each framework region position. In view of the teachings of Queen 1989 and Kabat 1987, a POSITA would have "substitute[d] residues in the framework region itself with the most common amino acid in human antibodies to maximize a reduction in immunogenicity." Ex. 1503 ¶¶319–20.

In view of Kabat 1987 and the motivation in Queen 1989 to use a consensus framework region, a POSITA would have incorporated "a consensus human variable domain" as the framework region with a reasonable expectation of success. Ex. 1503 ¶321. As discussed with regards to claim 1 above, a POSITA would have readily identified residues **4L**, **58L**, **66L**, **67L**, **73L**, **2H**, **45H** and **69H** for substitution. *See id.*; §§VIII.B.1 & 2. Thus, claims 4, 62, 64 and 69 are obvious in view of Queen 1989, the PDB Database and Kabat 1987.

E. Grounds 6 and 7: Claims 30, 31, 33, 42 and 60 Are Obvious in View of Queen 1989 or Queen 1990; PDB Database; and Hudziak

Independent claim 30 differs from claim 1 by requiring the CDRs (and antibody) to bind to $p185^{HER2}$ and includes additional options for the location of the FR substitution: 46L, 75H and 76H.

Humanized antibodies were developed for a single purpose: realizing the therapeutic promise of mouse monoclonal antibodies for the treatment of human diseases. Exs. 1503 ¶330; 1504 ¶36. While mouse monoclonal antibodies were capable of targeting antigens in a highly specific manner, immunogenicity issues severely limited the applicability of this technology in humans. *See* Exs. 1503 ¶¶97–100; 1504 ¶¶38–45.

Molecular targets of particular interest included HER2/*c-erbB-2*, whose amplification in breast cancer patients correlated with poor prognosis and high relapse rate. *See* Exs. 1521 at 8, Abstract, 1; 1504 ¶¶46–55; 1503 ¶331. Hudziak

specifically found the HER2/*c-erbB-2* gene product $p185^{HER2}$: (1) amplified in ~30% of breast cancer tumors (Exs. 1521 at 8); (2) "Correlated with a negative prognosis and high probability of relapse" (Exs. 1521 at 8); (3) caused transformation and tumorigenesis when its expression was increased and the transformed cells were implanted in athymic mice (Ex. 1521 at 8; 1504 ¶52); and (4) caused cells to form anchorage-independent colonies in soft agar and at low density in low serum concentration—characteristics of a transformed phenotype (Exs. 1521 at 8; 1504 ¶52). Mr. Buss concluded the above findings "strongly suggested that the HER-2*/neu* receptor was a ripe target for therapeutic development." Ex. 1504 ¶53. Based on the teachings of Hudziak, a POSITA would have been motivated to develop a therapeutic monoclonal antibody against $p185^{HER2}$.

A POSITA would have also been motivated to develop a therapeutic monoclonal antibody against $p185^{HER2}$ because monoclonal antibodies were known to have the potential for achieving a high degree of specificity, which would allow one to target HER-2 without cross-reactivity with other structurally similar growth factor receptors, including epidermal growth factor receptor (EGFR). *See* Ex. 1504 ¶¶54–55. These benefits were demonstrated well prior to June 1991 for 4D5, a well-characterized mouse monoclonal antibody that targeted the $p185^{HER2}$ protein with high affinity, specificity (no binding or recognition of, for example, EGFR)

and efficacy in *in vitro* and *in vivo* studies. *Id.* ¶¶56–58. The 4D5 investigators insisted it provided a "new potential for diagnostic approaches and therapeutic strategies for treatment of human malignancies." Exs. 1547 at 6[14]; 1504 ¶52.

Given published accounts regarding other monoclonal antibody humanization efforts and the strength of 4D5 as a clinical target, the logical and necessary next step would have been to humanize 4D5. Exs. 1504 ¶70; 1503 ¶332. The 4D5 investigators urged artisans to follow precisely this path: "The muMAb *4D5 also serves as a template for antibody engineering efforts to construct humanized versions* more suitable for chronic therapy." Exs. 1548 at 12; 1504 ¶67.

As discussed above, Queen 1989 and Queen 1990 provided the detailed roadmap for humanizing mouse monoclonal antibodies, such as 4D5, and represented the state of the art of antibody humanization by 1991. Ex. 1503 ¶¶332–33. Further, Queen 1989 and Queen 1990 provided the explicit motivation, and provided a POSITA with a reasonable expectation that a humanized antibody, such as 4D5, would be capable of binding to its antigen, in this case $p185^{HER2}$. *See* Exs. 1550 at 1, Abstract ("When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen …"); 1534 at 3 ("For the humanized antibody, sequence homology

[14] Hudziak *et al*., 84 PNAS USA 7159– 163 (1987).

and molecular modeling were used to select a combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity.").

From Queen 1989 or Queen 1990, together with known antibody structures available in the PDB Database, a POSITA would have recognized that claimed framework positions **4L**, **58L**, **66L**, **67L**, **73L**, **98L**, **2H**, **36H**, **45H** and **69H** were readily identifiable as residues that: 1) are adjacent to CDRs; or 2) contact CDRs. *See* Ex. 1503E (adjacent residues), O (distance calculations) and Q (summary); *see also* Ex. 1503 ¶¶333, 335–36, §§VIII.B.1 and 2, *supra*.

Further, Queen 1989 and Queen 1990 disclosed that a POSITA would have had a reasonable expectation that humanizing a mouse monoclonal antibody, such as 4D5, would have worked. *See* Exs. 1550 at 1, Abstract ("When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen..."); 1534 at 3 (expectation that humanized antibodies would "retain[] high binding affinity"); 1503 ¶333. For at least these reasons, claim 30 is obvious over Queen 1989 (Ground 6) or Queen 1990 (Ground 7), in view of known antibody structures available in the PDB Database, and in view of Hudziak.

Claim 31. Claim 31 depends from claim 30 and additionally recites "the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained." Queen 1989 and Queen 1990 both disclosed this limitation. *See* Exs. 1534 at 5; 1550 at 5:36–6:1; 1503 ¶337; *see supra* §§VIII.B.3 and 11 (claims 2 and 81). Therefore, claim 31 is obvious over Queen 1989 or Queen 1990, the PDB Database and Hudziak

Claims 42 and 60. Claims 42 and 60 depend from claim 30 and recite the residue at site 66L or 78H, respectively, is substituted. For the same reasons above for claim 30, which details positions **66L** and **78H** as recognized substitutable positions, claims 42 and 60 are also obvious over Queen 1989 or Queen 1990, the PDB Database and Hudziak. Ex. 1503 ¶¶338–39.

Claim 33. Claim 33 depends from claim 30 and recites "the human antibody variable domain is a consensus human variable domain." Queen 1990 disclosed this limitation. *See* Exs. 1550 at 12:19–20 ("[U]se a consensus framework from many human antibodies."); 1503 ¶¶340–41. Thus, claim 33 is obvious over Queen 1990, the PDB Database, and Hudziak.

F. Secondary Considerations Cannot Overcome Obviousness

Patent Owner may attempt to assert secondary considerations of nonobviousness, despite no showing of such in the patent. Such evidence would be

"insufficient" to "overcome the strong [case] of obviousness" here, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). Patent Owner cannot show the required nexus between any purportedly novel feature and any secondary consideration. *See, e.g.*, *Merck & Co. v. Teva Pharms. USA*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Patent Owner cannot show secondary considerations are commensurate with claim scope given the extraordinary breadth of the challenged claims here. *See, e.g.*, *Ex Parte Takeshi Shimono*, 2015 WL 1952506, Appeal 2013–003410 (PTAB Apr. 29, 2015). Pfizer nonetheless preliminarily addresses potential Patent Owner theories below.

1. The Challenged Claims Produced No Relevant Unexpected Results

During prosecution, Genentech argued that the claimed methods achieved unexpected results. *See, e.g.*, Ex. 1502, Vol. 2 at 3431–37. Specifically, Genentech stated:

> The unexpected properties…include: lack of significant immunogenicity of the claimed humanized antibodies upon repeated administration to a human patient, e.g., to treat a chronic disease in the patient…

Id. at 3431.

But Genentech's arguments are not reasonably commensurate with the full scope of the Challenged Claims. *See Ex Parte Takeshi Shimono*, 2015 WL

1952506, at *4 ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims"). Only Challenged Claim 63 even mentions immunogenicity and none recites a method. Ex. 1501 at 88:36–38 (claim 63: "humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient"). Claim 63 does not require a "lack of ***significant*** immunogenicity."

Genentech also argued that:

> The unexpected properties…include…binding affinities superior to those of the non-human parent antibody; and the ability to use the same consensus human variable domain to make many strong affinity antibodies, thus avoiding tailoring each human FR to each non-human antibody to be humanized.

Id. at 3431.

But only challenged dependent claim 65 even mentions binding affinity. *Id.* at 88:63–65 (claim 65: "The humanized variant of claim 63 which binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen."). Further, ***no Challenged Claim*** requires "use of the same consensus human variable domain" or the making of "many strong affinity antibodies." Moreover, this argument appears to relate to a ***method*** of making numerous antibodies as opposed to the ***products*** recited in the Challenged Claims. *See In re*

Kubin, 561 F.3d 1351, 1356 (Fed. Cir. 2009) ("the obviousness inquiry requires this court to review the Board's decision that the claimed sequence, not appellants' unclaimed cloning technique, is obvious").

These properties were also not unexpected based on the teachings of the prior art. For example, the '213 patent recognizes with respect to affinity that residues important for maintaining CDR conformation and binding were well known prior to June 1991. *See* Exs. 1501 at 2:63–3:8; 1503 ¶¶110–6, 280, 347–348. In addition, Dr. Foote observes that a modest increase in binding affinity (which is all claim 65 requires) was not unexpected given the prior art. Ex. 1503 ¶¶248–250, 307–308. Indeed, Queen 1990 taught that an increase in affinity would have been expected. Exs. 1550 at 6:26–28 ("[A]ffinity levels can vary…and may be within about 4-fold of the donor immunoglobulin's original affinity to the antigen.").

Successful antibody humanization was readily achievable, not surprising or unexpected, as of the earliest priority date of the '213 patent. Exs. 1503 ¶¶350–51; 1504 ¶¶38–45, 68–70.

2. The '213 Patent Satisfied No Long-Felt but Unmet Need

There was no long-felt but unmet need for humanized mouse monoclonal antibody 4D5. First, the full scope of the Challenged Claims exceeds antibody 4D5. Further, if 4D5 satisfied any need, the mouse monoclonal antibody 4D5

disclosures, which claimed and disclosed the original mouse monoclonal antibody, satisfied it. *See*, *e.g.*, Exs. 1596; 1503 at ¶352.

Patent Owner cannot even show the purported invention solved the problem that the specification identified. *See*, *e.g.*, *Norgren Inc. v. ITC*, 699 F.3d 1317, 1324 n.12 (Fed. Cir. 2012) (patent obvious where "[prior art patent] solved similar problems in a similar way."). The '213 patent's purported problem was that "[m]ethods are needed for rationalizing the selection of sites for substitution in preparing [humanized] antibodies" and claimed their invention could provide methods "for the preparation of antibodies that are less antigenic in humans…but have desired antigen binding." Ex. 1501 at 3:53–55, 4:24–35. Queen 1990, Kurrle and others had already described exactly this process—they set forth why one would desire to humanize and provided detailed roadmaps on how to achieve it. Any problems identified in the '213 specification had already been solved and addressed by the prior art. Ex. 1503 ¶¶350–52.

3. No Nexus Between Commercial Success of Genentech Drugs and the Challenged Claims

The Board has explained that "evidence of commercial success is 'only significant if there is a nexus between the claimed invention and the commercial success.'" IPR2014-00652 Final Written Decision at 35, citing *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–12 (Fed. Cir. 2006).

Any commercial success of drugs Genentech sells is not a direct result of the Challenged Claims. Indeed, important features of these drugs are not recited in the Challenged Claims, only three of which include more than a single residue substitution. As an example, Genentech's marketed drug Herceptin® has heavy chain residue substitutions at seven positions: 71H, 73H, 78H, 93H, 55L, 66L, and 102L. None of the Challenged Claims recite substitutions at these seven positions. In fact, positions 55L and 102L do not even appear in the '213 patent. Genentech will be unable to show that the claimed features resulted in the commercial success of Herceptin®.

Moreover, any alleged commercial success of Genentech's drugs is not commensurate with the full scope of the Challenged Claims because they are not limited to any particular antibody or even any particular class of antibodies. Ex. 1503 ¶353. Even claim 30—which recites that the antibody binds $p185^{HER2}$—is exceptionally broad and not limited to any specific anti-$p185^{HER2}$ antibodies.

IX. CONCLUSION

Pfizer respectfully requests IPR of the Challenged Claims.

Date: May 24, 2017

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CERTIFICATE OF COMPLIANCE

This Petition complies with the type-volume limitations as mandated in 37 C.F.R §42.24, totaling 13,612 words. Counsel has relied upon the word count feature provided by Microsoft Word.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,407,213, along will all exhibits and other supporting documents, were served on May 24, 2017, via FedEx Overnight delivery directed to the assignee for the patent and correspondence address of record as follows:

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