UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.
Petitioner,
v.

GENENTECH, INC.
Patent Owner.

Patent No. 6,407,213

PETITION FOR *INTER PARTES* REVIEW

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1123	U.S. Patent No. 5,889,157 *Humanized B3 Antibody Fragments, Fusion Proteins, and Uses Thereof* (humanization of monoclonal antibodies to Lewis^{Y}-related carbohydrate antigen) (Filed

Exhibit No.	Description
	October 28, 1994) (Issued March 30, 1999)
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I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Mylan Pharmaceuticals Inc. ("Mylan") petitions for *Inter Partes* Review ("IPR") of claims 1, 2, 4, 12, 25, 29-31, 33, 42, 60, 62-67, 69 and 71-81 of U.S. Patent No. 6,407,213 to Carter, titled "Method for Making Humanized Antibodies" ("the '213 patent," Ex. 1001). 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).

This Petition proves by a preponderance of the evidence that prior art renders unpatentable '213 patent claims 1, 2, 4, 12, 25, 29-31, 33, 42, 60, 62-67, 69 and 71-81. Prior art disclosing methods of making humanized antibodies—the detailed roadmap taught in PCT Application No. WO 90/07861 to Queen ("Queen 1990") [Ex. 1050] and Queen's highly regarded 1989 *Proceedings of the National Academy of Sciences Article* ("Queen 1989") [Ex. 1034]—in view of Protein Data Bank (PDB) database antibody structures, render obvious the challenged claims to a person of ordinary skill in the art ("POSITA") as of the priority date. The '213 patent claims are also obvious over Queen 1989 or Queen 1990, in view of Tramontano [Ex. 1051]; Kabat 1987 [Ex. 1052]; or Hudziak [Ex. 1021].

II. MANDATORY NOTICES

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

The real parties-in-interest for Petitioner are Mylan Pharmaceuticals Inc., Mylan Inc., Mylan GmbH, and Biocon Ltd. Mylan N.V. is identified out of an

abundance of caution, but this in no way constitutes an admission that it is or was a real party-in-interest in any other IPR proceeding.

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

Petitioner is not a party to any litigation related to the '213 patent. The '213 patent is related to the following patents: U.S. Pat. No. 6,639,055; U.S. Pat. No. 6,800,788 (expired, maintenance fee non-payment); U.S. Pat. No. 6,719,971; (expired, maintenance fee non-payment); and U.S. Pat. No. 8,075,890.

C. Identification of Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

Lead Counsel	Back Up Counsel
Jeffrey W. Guise (Reg. No. 34,613) Wilson Sonsini Goodrich & Rosati 650 Page Mill Road Palo Alto, CA 94304 jguise@wsgr.com T: (858) 350-2307; Fax: (858) 350-2399	Deanne M. Mazzochi (Reg. No. 50,158) Rakoczy Molino Mazzochi Siwik LLP 6 West Hubbard Street, Ste. 500 Chicago, IL 60654 dmazzochi@rmmslegal.com T: (312) 222-6305; Fax: (312) 222-6325

Please direct all correspondence to lead counsel and back-up counsel at the contact information above. Petitioner consents to electronic mail service at jguise@wsgr.com and dmazzochi@rmmslegal.com.

III. GROUNDS FOR STANDING AND PROCEDURAL STATEMENT

As required by 37 C.F.R. § 42.104(a), Petitioner certifies that the '213 patent is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting *inter partes* review on the grounds identified herein.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED

Petitioner requests *inter partes* review and cancellation of claims 1, 2, 4, 12, 25, 29-31, 33, 42, 60, 62-67, 69 and 71-81 of the '213 patent 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 the Declarations of Dr. Eduardo Padlan (Ex. 1003) and Prof. Edward T. Ball (Ex. 1004).

Dr. Eduardo Padlan was a tenure track scientist at the National Institutes of Health, specializing in antibody crystal structure characterization and antibody humanization, which involved identifying key antibody amino acid residues responsible for antigen binding specificity and affinity. His work resulted in numerous publications and patents in this field. Dr. Padlan has also worked as an antibody humanization consultant to many biotechnological companies.

Prof. Edward T. Ball is Professor of Medicine and Director and Chief of the Blood and Marrow Transplantation Division and Program at the University of California, San Diego's School of Medicine. Prof. Ball was an early user of monoclonal antibody therapies, administering mouse monoclonal antibodies to patients beginning in the early 1980s. Prof. Ball has 35+ years of experience in oncology, including developing monoclonal antibody therapies for cancer patients.

The '213 patent's challenged claims generally involve humanized antibodies and humanized antibody variable domains. Ex. 1003 at ¶¶40-63. Claims 1, 2, 4, 12,

25, 29-31, 33, 42, 60, 62-67, 69 and 71-81 of the '213 patent are unpatentable:

Ground No.	Claims and Basis
1	Claims 1, 2, 12, 25, 29, 63, 65-67 and 71-81 as obvious over Queen 1989, in view of the Protein Data Bank (PDB) database
2	Claims 1, 2, 4, 12, 25, 29, 62-67, 69 and 71-81 as obvious over Queen 1990, in view of the PDB database
3	Claims 75, 76, 77 and 79 as obvious in view of Queen 1989, the PDB database, and further in view of Tramontano
4	Claims 75, 76, 77 and 79 as obvious in view of Queen 1990, the PDB database, and further in view of Tramontano
5	Claims 4, 62, 64 and 69 as obvious in view of Queen 1989, the PDB database, and further in view of Kabat 1987
6	Claims 30, 31, 42 and 60 as obvious in view of Queen 1989, the PDB database, and further in view of Hudziak
7	Claims 30, 31, 33, 42 and 60 as obvious in view of Queen 1990 and the PDB database, and further in view of Hudziak

V. THRESHOLD REQUIREMENT FOR *INTER PARTES* REVIEW

An *inter partes* review petition 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. As explained below, there is more than a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Summary of the Argument

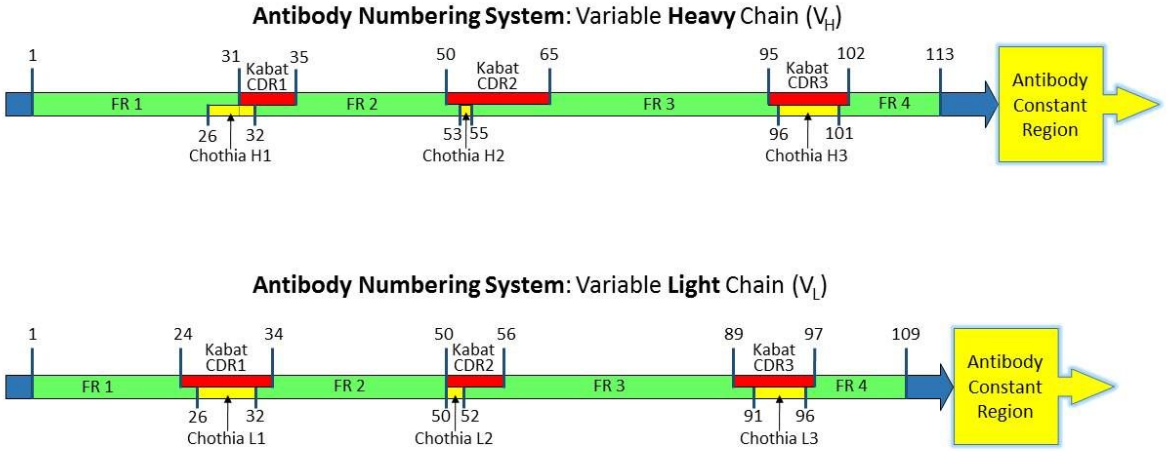
In 1975, *Nature* published Köhler and Milstein's ground-breaking study manufacturing "predefined specific antibodies by means of permanent tissue culture cell lines"–monoclonal antibodies. Ex. 1022 at 1. Mouse monoclonal

antibodies exhibited therapeutic and diagnostic promise, but researchers discovered patients receiving mouse antibodies experienced a human anti-mouse antibody (HAMA) immunogenicity response. Ex. 1003 at ¶¶70-72; Ex. 1004 at ¶45.

To neutralize the HAMA response, mouse antibodies were first re-engineered to make them "more human" by replacing parts of the mouse antibody with human counterparts. First generation (early 1980s) versions replaced the mouse antibody's constant region with corresponding human antibody residues. Ex. 1003 at ¶¶89-91; Ex. 1004 at ¶¶46-47. While "chimeric" antibodies retained the parent mouse's affinity and specificity, 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. 1003 at ¶92.

Scientists were able to design mouse-to-human substitutions in the variable domain because they had accumulated an extensive antibody sequence database by the mid-1980s. Indeed, by 1987 Kabat had identified which heavy and light chain sequence positions were consistently similar, or consistently varying from antibody to antibody. *See* Kabat (1987) [Ex. 1052]. Kabat called consistently-similar regions "framework regions" (FRs); and highly variable regions "complementarity determining regions" (CDRs), with CDRs most likely to engage in antigen-specific binding. Starting with position 1, Kabat classified the antibody variable domain

structure through comparison of over a hundred antibodies [Ex. 1003 at ¶¶73-91]:



Kabat's map, and later work by Chothia and colleagues [Ex. 1062] gave scientists clearly defined regions to target for further humanization of chimeric antibodies: FRs (green) within the variable domain. Ex. 1003 at ¶¶73-91. 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, Queen et al. in 1989 and 1990 published and patented, respectively, a humanization methodology 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). Ex. 1034 at 1; Ex. 1050 at 1; Ex. 1003 at ¶¶112-24, 243-61. 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." Ex. 1034 at 5; Ex. 1003 at ¶¶112-24.

Queen 1990 provided four specific criteria (I-IV) to target amino acids for substitution in producing humanized antibodies. *See* Ex. 1050 at 14, l. 17-16, l. 2; Ex. 1003 at ¶¶118-24. Following this methodology, the POSITA could readily discern amino acid sequence locations to target. As further instructed by Queen 1989 and 1990, one should use the known and available antibody structures in the Protein Data Bank (PDB) database to identify FR residues that are likely to contact the CDRs. After conducting this analysis, Queen 1990 explained that the identified amino acids to reinstate from the mouse should be "transferred to the human framework along with the CDRs." Ex. 1034 at 5; Ex. 1003 at ¶¶118-24. Using the Queen roadmap readily identifies many of the same heavy (H) and light (L) chain target residues found in claims 1, 2, 4, 12, 25, 29, 62-67, 69 and 71-81. Ex. 1003 at ¶¶243-61. 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. 1003 at ¶¶84-88. For example, Tramontano and colleagues published in 1990 that residue **71H** was important to retain as mouse to better maintain CDR conformation. Ex. 1051 at 1; Ex. 1003 at ¶¶87, 130. Residue **71H** was thus an automatic candidate for substitution for humanization. *Id*.

The prior art also disclosed both $p185^{HER2}$ as a promising therapeutic target, and a specific monoclonal antibody (4D5) against the $p185^{HER2}$ target. Mylan's experts, Professor Ball and Dr. Padlan, both agree that the next logical and necessary step in the development of 4D5 was to humanize it. Ex. 1003 at ¶¶318-23; Ex. 1004 at ¶¶63-79. Applying the Queen 1990 and/or Queen 1989 roadmap alone, in combination with other references as detailed, claims 30, 31, 33, 42 and 60 of the '213 patent would have also been obvious.

B. Background of the '213 Patent

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 issued with 82 claims. Claims 1, 30, 62, 63, 64, 66, 79 and 80 are independent claims, 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" that returns the substituted human framework residue back to, *e.g.*, mouse, at "a site selected from the group consisting of" certain recited residues. **Claim 1** chooses from 14 FR light chain residues (4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L); and 10 heavy

chain residues (2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H) when utilizing Kabat's numbering system. Ex. 1001 at col. 86, ll. 44-52. **Claims 30, 62 and 63** add 4 FR residues to claim 1's list (46L, 75H, 76H and 78H). Claim 30 targets an antibody that "binds $p185^{HER2}$ and comprises a humanized antibody variable domain"; and claim 63 calls for 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." *Id.*, col. 88, ll. 27-48.

Claim 66 offers a different list of 5 FR residues: 24H, 73H, 76H, 78H and 93H. *Id.* at col. 88, l. 66 to col. 9, l. 6. **Claim 79** lists 4 FR "substitutions at heavy chain positions 71H, 73H, 78H and 93H, utilizing the numbering system set forth in Kabat." *Id.* at col. 90, ll. 3-10. **Claim 80** claims the residues of claim 1 plus the 5 residues from claim 66 and adds that the FR amino acid substitution: "(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 col. 90, ll. 11-25.

Claim 64 adds that the "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."

The dependent claims recite specific residues (claims 12, 42, 60 and 71-77; claims 75-77 further add a substitution at residue 71H); that the substituted humanized antibody 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 of claims 1 or 66 (claim 29 and claim 78, respectively).

The concepts in the patent's specification were not unknown or new. It acknowledges the widely held view that the "function of the 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 col. 3, ll. 40-44. It acknowledges past "molecular modeling" has been shown to "increase the antigen binding affinity of a humanized antibody." Ex. 1001 at col. 3, ll. 44-48. The '213 patent applies the same cloning and analysis tools and techniques Queen

1989 [Ex. 1034] and Queen 1990 [Ex. 1050] described, including site-directed mutagenesis, molecular modeling and antibody functionality analysis. The '213 patent likewise recognizes the existing promise of $p185^{HER2}$ monoclonal antibody (4D5) as a therapeutic agent against cancer, and notes its murine origin renders it "immunogenic in humans." *Id.* at col. 3, l. 56 to col. 4, l. 23.

2. Brief Overview of the '213 Patent's Prosecution History and Related Proceedings in the PTO

'206 Application Prosecution. The '213 patent issued from Application No. 08/146,206 ("the '206 application"). During prosecution, the PTO rejected the'206 application's claims for anticipation, obviousness, lack of written description, lack of enablement, indefiniteness and non-statutory obviousness-type double patenting. The PTO's unpatentability bases included Queen 1989 [Ex. 1034] and Kabat 1987 [Ex. 1052], asserted here.

Interference with Application No. 11/284,261. Applicants for Application No. 11/284,261 ("the '261 application" or "Adair") requested an interference with the '213 patent. The interference count was drawn to humanized antibodies with non-human substitutions at specific variable domain framework positions. The Board declared the interference, identifying the claims corresponding to the count as claims 30, 31, 60, 62, 63, 66, 67, 70, 73, 77-81 of the '213 patent and claim 24 of Adair. *Carter v. Adair*, Interference No. 105,744, Declaration of Interference at 4 (Feb. 2, 2010) [Ex. 1095].

The Board determined, however, that claims in an earlier application, to which Adair claimed priority, did not provide pre-critical date support for claim 24, thereby concluding that Adair's claim 24 was barred under 35 U.S.C. § 135(b)(1). Decision on Motions at 9-10 [Ex. 1095 at 1588-89]. Adair appealed, arguing the Board erred by (1) failing to assess material differences in view of the patent claim being copied, (2) establishing an absolute requirement that pre-critical date claims be patentable, (3) not applying applicable law, and (4) abusing its discretion in failing to consider other claims as pre-critical support for claim 24. The Federal Circuit affirmed the Board. *Adair v. Carter*, 101 U.S.P.Q.2d 1625, 1630 (Fed. Cir. 2012). Ex. 1095.

C. Level of Ordinary Skill in the Art

The field of the invention relates to humanizing non-human antibodies, *e.g.*, mouse monoclonal antibodies. A POSITA[1] would have held a Ph.D. or equivalent in chemistry, biological chemistry, structural biology or a closely related field, or an M.D. with practical academic or industrial experience in antibody development, including humanization of antibodies for therapeutic development and use in humans.

[1] 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.

See, e.g., Ex. 1003 at ¶¶26-28; Ex. 1004 at ¶¶38-39. Such a person would have the educational background above with experience related to antibody structural characterization and engineering. *Id*. Such experience can include three dimensional computer modeling of immunoglobulin structures, antibody domain and sequence manipulation and swapping, CDR grafting and framework substitution in humanizing antibodies, construction and expression of recombinant antibodies, antibody binding (specificity and affinity) testing, immunogenicity testing and the like. *Id*. Such person may have consulted with one or more members of a team 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 ’213 patent claims presumably possess their “broadest reasonable construction in light of the specification of the patent in which it appears.” 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268 (Fed. Cir. 2015) (affirming broadest reasonable construction standard in *inter partes* review). Under the broadest reasonable construction, a POSITA would understand the claim

terms below at least include the following meanings.[2]

"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 64). 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.

"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 of the '213 patent include a Markush Group list of amino acid residues from which a framework region substitution is chosen.

[2] Mylan does not concede that the claims can be construed to achieve reasonable certainty. Mylan explicitly does not waive any argument or invalidity position under 35 U.S.C. § 112, or any other invalidity position not presented herein.

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) ("By claiming a Markush group ... members of the group are functionally equivalent" citing *Application of Skoll*, 523 F.2d 1392 (C.C.P.A. 1975)). 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 broadest reasonable interpretation to a POSITA would be that any of the recited residues can be equally substituted for any given antibody. Thus, it is assumed for purposes of claim construction in this proceeding that each of the recited substitutions is available for humanization of an antibody.

"Numbering System Set Forth in Kabat". Independent claims 1, 30, 62, 63, 66, 79 and 80 of the '213 patent include the limitation "utilizing the numbering system set forth in Kabat." The '213 patent specifically ties its numbering system to two references: "Kabat, E.A. et al., *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md.) (1987) and (1991)". *See* Ex. 1001 at col. 10, lns. 45-49. As noted, the Kabat 1987 [Ex. 1052] and Kabat 1991 [Ex. 1055] data derives from a database of publicly available antibody sequences, formatted to display 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 Complementarity Determining Regions (CDRs) and

four Framework Regions (FRs) in each antibody chain variable domain. The broadest reasonable construction, "utilizing the numbering system set forth in Kabat," encompasses the Kabat 1987 and Kabat 1991 designations,[3] including the amino acid residue positions set forth in Kabat, but also including the boundary designations for CDR and FR structures.

"Up To 3-Fold More". The '213 patent's claim 65 limits independent claim 79 further to a "humanized variant ... bind[ing] the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." The broadest reasonable interpretation 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. Patents and Printed Publications Relied On In This Petition

Petitioner relies on the following patents and printed publications:

1. Queen 1989 [Ex. 1034]

Queen 1989 (published December 1989) disclosed humanized antibodies which, to reduce immunogenicity, retained only the mouse CDRs. To preserve the precise structure of the mouse CDRs, Queen targeted specific residues in the

[3] Dr. Padlan notes there are no significant differences between the Kabat 1987 and Kabat 1991 numbering systems, including CDR and FR boundary designations. Ex. 1003 at fn. 6. However, the priority document (U.S. Patent Application No. 07/715,272) only relies on Kabat 1987, and not Kabat 1991. *Id.*

human framework region to switch back to mouse, thus restoring the mouse CDRs' affinity and optimizing the mAb for long-term therapy. Ex. 1034 at 1; Ex. 1003 at ¶¶112-17. Queen 1989 provided guidelines for one to follow when humanizing a mouse antibody, particularly focusing on antibodies' framework regions. Ex. 1034 at 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 3;

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 3-4; 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 4.

This methodology generated a "combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity." *Id.* at 1. Queen confirmed their "ideas ... may have wider applicability" beyond Queen's engineered mouse anti-Tac antibody. *Id*. at 5.

2. Queen 1990 [Ex. 1050]

Queen 1990 is a patent application filed December 28, 1989, and published on July 26, 1990. Queen 1990 advanced Queen 1989's methodology 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....

Ex. 1050 at 14, ll. 17-32; Ex. 1003 at ¶¶118-24.

Also 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, substitute for the conserved mouse residue at that sequence position:

> **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 donor amino acid rather than the acceptor may be selected....

Id. at 13, ll. 21-37; Ex. 1003 at ¶¶116, 121. Dr. Padlan explains that "maintaining conserved residues . . . is important for avoiding immunogenicity in a humanized antibody." Ex. 1003 at ¶121. However, Dr. Padlan further explains 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 one or more of the 3 CDR's in the primary sequence of the humanized immunoglobulin chain, the donor amino acid(s) rather than 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 acceptor, to distort the donor CDR's and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen and selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.

Id. at 16, ll. 1-12 (citations omitted). Kabat and Chothia identified the CDR boundaries, both in sequence and structurally. Claimed residues in the '213 patent that are "immediately adjacent" to Kabat and Chothia CDRs include **36H** and **98L**. Kabat 1987 [Ex. 1052]; Ex. 1003 at ¶¶159-69.

Queen 1990 placed further limitations on the molecular modeling criteria Queen 1989 established, pinpointing framework residues which 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 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 donor amino acid rather than the 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.

Id. at 16, ll. 14-31. Queen 1990 further explains these "contact" residues could also be derived from other known antibody structures. As the above describes, such framework residues are more likely to influence CDR/antigen interactions.

3. Protein Data Bank (PDB) Database

In 1971, the Protein Data Bank (PDB) database Queen 1990 identifies was established as "a computer archival service managed by the Brookhaven National Laboratory." *See* Ex. 1003 at ¶¶127-28, citing to Bernstein [Ex. 1080]. 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." Ex. 1080 at 1; Ex. 1003 at ¶127. As an early user of the PDB database well prior to June 1991, Dr. Padlan describes the PDB database as "a repository of protein crystal atomic co-ordinates available to the public. Those of ordinary skill in the art in 1991, including myself, relied on and contributed to the PDB database, retrieving computer-readable data that could be directly inputted into distance calculation and graphics programs for use in visualization and comparison studies." Ex. 1003 at ¶127.

Dr. Padlan also details the organization and data uniformity of PDB entries: "The PDB entries contained in the database included verified co-ordinate information from protein crystallographers like myself, as well as specific information regarding the entry itself." Ex. 1003 at ¶128, quoting Ex. 1080 at 3-6, describing the entry for protein ribonuclease S. Dr. Padlan and his colleagues at the NIH had free access to the PDB database in June 1991. *Id.*

In order to duplicate and apply the Queen 1989/1990 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. 1050 at 16 ll. 25-36 (emphasis added)), Dr. Padlan identified

solved monoclonal antibodies and Bence-Jones proteins that were available in the PDB database prior to June 1991: HYHEL-5, KOL, NEWM, J539, 4-4-20, McPc603, HYHEL-10, 1REI and 2RHE. Ex. 1003 at ¶¶243-59.

Dr. Padlan took the atomic coordinates and sequence information as it would have existed in June 1991; applied the Queen 1989/Queen 1990 methodologies (including the computer modeling step), and identified the amino acid residues to revert back to murine in a human framework. Ex. 1003 at ¶128. Each solved structure was available pre-June 1991, as their entry dates (upper right hand corner) confirm. *See, e.g.*, Ex. 1003 at Padlan Exhibit D (HYHEL-5; August 17, 1987), Padlan Exhibit E (KOL; May 9, 1983), Padlan Exhibit F (NEWM; September 29, 1981), Padlan Exhibit G (J539; August 18, 1989), Padlan Exhibit H (McPc603; July 9, 1984), Padlan Exhibit I (4-4-20; April 10, 1989), Padlan Exhibit J (HYHEL-10; August 11, 1988), Padlan Exhibit K (1REI; March 17, 1976) and Padlan Exhibit L (2RHE; June 13, 1983).

As Dr. Padlan explains, evaluating each existing sequence and calculating interatomic distances between each framework residue and CDR region, just as a POSA would have done, produced a list of amino acid residues in the light and/or heavy chains that correspond to the patent claims. Ex. 1003 at ¶¶254-59.

4. Tramontano [Ex. 1051]

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. 1051 at 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. Thus, Tramontano taught targeting position **71H** if the human residue differed from the donor (mouse) antibody.

5. Kabat 1987 [Ex. 1052]

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. 1052. Kabat 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 8, 17. Kabat 1987 importantly disclosed, through sequence comparison and variability analysis, boundaries of antibody domains within the heavy and light chain variable

domains, including FR and CDR boundaries as above-discussed. *See, e.g.*, *id.* at 4 (horizontal lines demarcating FR1, FR2, FR3 and FR4, and CDR1, CDR2 and CDR3 boundaries).

6. Hudziak [Ex. 1021]

Hudziak published in March 1989, confirming $p185^{HER2}$'s role in carcinoma development. Ex. 1021 at Abstract. Hudziak had earlier-correlated $p185^{HER2}$ gene amplification and carcinoma development, showing high $p185^{HER2}$ levels correlated to negative prognoses and high relapse probability; and amplifying $p185^{HER2}$ *in vitro* created resistance to cytotoxic (TNF-α) treatment. *Id.* Hudziak "prepared 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." Ex. 1021 at 1. 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 5 (emphasis added). 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 "indicated the

induction of a cytotoxic response." *Id.* at 6.

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

Hudziak, Table 1 [Ex. 1021 at 4]. 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 7.

F. The Prior Art Renders The Challenged Claims Obvious

1. Detailed Instructions for Humanizing Antibodies Were Widely Available Before the '213 Patent Filing

As discussed, Queen 1989 [Ex. 1034] and Queen 1990 [Ex. 1050] taught an improved humanization methodology prior to June 1991, which relied on reverting select human framework residues back to mouse in order to preserve the original mouse CDRs' binding affinity. *See* Ex. 1034 at Abstract; Ex. 1050 at Abstract; Ex. 1003 at ¶¶112-24. 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* Ex. 1050 at 5, ll. 30-33; Ex. 1073 at 9, ll. 12-19; Ex. 1003 at ¶¶89-92; Ex. 1004 at ¶¶46-53.

Queen 1989 and Queen 1990 addressed these issues by providing the person of ordinary skill in the art 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 a detailed roadmap and methodology for identifying the key FR residues:

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.

Ex. 1034 at 3-4; Ex. 1003 at ¶¶118-24.

Queen 1990 went further: Specifically, it instructed 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. 1050 at 16, ll. 21-25.

In this way, a POSITA could reasonably expect to identify the most

important framework positions in any donor antibody to target for substitution. Ex. 1050 at 16, ll. 2, 14–15. Thus, by 1991, the prior art provided a detailed roadmap to optimize the humanization of non-human 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 Abstract; Ex. 1003 at ¶¶97-109.

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

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

Independent claim 1 of the '213 patent is drawn to "[a] humanized antibody variable domain" comprising "non-human" (*e.g.*, mouse) CDRs.

As 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. 1034 at 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. 1003 at ¶¶243-59.

Claim 1 "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 candidates for substitution with the donor antibody residue in the humanization process. Ex. 1034 at 3-4; Ex. 1003 at ¶245. A POSITA would have used those simple rules to determine which residues in a human FR region could be switched back to mouse. Ex. 1003 at ¶¶245-48. 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." Ex. 1034 at 3; Ex. 1003 at ¶247. Queen 1989 substituted these framework positions with the mouse residue Ex. 1034 at 3; Ex. 1003 at ¶247. Queen 1989 taught that such steps "may have wider applicability" to humanize other antibodies. Ex. 1034 at 5; Ex. 1003 at ¶115.

Mylan's expert Dr. Padlan applied the same methodology prior to 1991, "identifying contact residues between the CDRs and framework residues, critical buried and intra-chain contact residues, as well as exposed residues at the surface of the antibody." Ex. 1003 at ¶94. Dr. Padlan, a protein crystallographer and structural biologist, generated antibody structures that were subsequently uploaded

into the PDB database. *Id.* at ¶128. Dr. Padlan also wrote and distributed software to those of skill in the art prior to June 1991 in order to calculate interatomic distances and identify framework region contact residues and buried and exposed inter- and intra-chain residues. *Id.* at ¶250. As a result, Dr. Padlan was approached by others in the field to assist in humanizing non-human monoclonal antibodies. *Id.* at ¶94. Dr. Padlan concluded that in his experience, "the need to reduce immunogenicity drove the humanization of all non-human antibodies" in the 1991 time frame. *Id.* at ¶95.

Dr. Padlan was not alone. Many private and public research institutions, including Genzyme Corporation (*see, e.g.*, Ex. 1071), Protein Design Labs (*see, e.g.*, Ex. 1050), the Winter Lab and the Medical Research Council (*see, e.g.*, Ex. 1073), and his laboratory at the National Institutes of Health, were very active in the field of humanization as of June 1991. Ex. 1003 at ¶94. In fact, the first International Business Communications (IBC) Conference on Antibody Engineering in San Diego showcasing the latest humanization technology, began in December 1990, and continues to the present. During the Second IBC International Conference on Antibody Engineering in December 1991, Dr. Padlan gave a talk on selecting the best framework for use in humanizing monoclonal antibodies. *See* Ex. 1120. Dr. Padlan noted that "the structures of various Fabs reveals that [framework] residues are different for different antibodies,

emphasizing the need for a well-characterized, three-dimensional structure to serve as a guide during 'humanization.'" *Id.*

Using publicly available tools, Dr. Padlan and POSAs performed the analysis "[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*." Ex. 1120 (emphasis added). This included the publicly available Protein Data Bank (PDB) database (§VI.E.3, *supra*), as well as computer programs (either commercially purchased or created, as with Dr. Padlan) to measure interatomic distances and create three-dimensional graphical models. Using these tools, 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 also reveal 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. Ex. 1034 at 3-4; Ex. 1003 at ¶¶112-24.

Dr. Padlan performed the same exercise Queen 1989 taught on antibody structures known and publicly available prior to 1991 through the PDB database. *See* Ex. 1003 at ¶¶222-26. Dr. Padlan accessed the atomic coordinates of each of

the known and available solved antibody structures in the PDB prior to 1991 (*i.e.*, HYHEL-5, KOL, NEWM, J539, MCPC603, 4-4-20, HYHEL-10, 1REI and 2RHE), which contained distance calculations between framework and CDR amino acid residues. *Id.* at ¶¶226-27. Dr. Padlan determined the interatomic (Euclidean) distances between the atom pairs of the framework residue and the CDR residues, a practice that was considered routine as of 1991. *Id.* at ¶¶222-29, Padlan Exhibit M (interatomic distance calculations). As would have been understood by a POSITA in view of Queen 1989 (*see* Ex. 1003 at ¶229), Dr. Padlan identified which framework residue side chains were in contact with the CDRs. *See* Ex. 1003 at ¶¶243-59, Padlan Exhibits M and O.

Following the teaching of Queen 1989, Dr. Padlan aligned the primary amino acid sequence of each of the pre-1991antibody structures above according to the Kabat numbering system (*see* Padlan Exhibit N), and identified contact residues that were targets for substitution. *See* Ex. 1034 at 3-4 and Figure 3; Ex. 1003 at ¶¶255-59, Padlan Exhibits M and N. When compared to the list of residues recited in claim 1, Dr. Padlan found that 8 light (L) chain (4L, 58L, 62L, 66L, 67L, 73L), 85L, 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. 1052]. *See* Ex. 1003 at ¶256; Padlan Exhibits M (interatomic distance calculations), N (antibody

alignment), and O (contact summary). Of these, claim 1 includes residues **4L**, **58L**, **66L**, **67L**, **69L**, **73L**, **2H**, **45H** and **69H**. *See* Ex. 1003 at ¶259. Dr. Padlan thus easily and quickly identified at least 9 claimed residues a POSITA would have had on a list of substitutable residues following the detailed Queen 1989 roadmap.

The '213 patentees followed Queen's roadmap practically to a T. The specification states the purported invention involved obtaining a donor antibody and a consensus sequence (Ex. 1001 at col. 4:47-49); importing CDRs from the donor into the consensus (col. 4:50-54); identifying any residues in the framework that differ (*id.* at col. 4:59-61); determining whether the residue where the difference lies is involved in CDR interaction and/or antigen binding (*id.* at col. 4:62-67); and if so, substituting in the donor residue (mouse) for the human residue (*id. at* col. 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. 1001 at col. 16:30-32);
- "Step 2 ... the structures were superimposed on one another using the INSIGHT computer program..." (*id.* at col. 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 col. 19:58-64).

Given the teachings in Queen 1989 and the readily available structures on the PDB database, a POSITA would have been motivated and would have had a reasonable expectation of success in humanizing an antibody with a framework residue substitution at least at **4L**, **58L**, **66L**, **67L**, **69L**, **73L**, **2H**, **45H** and **69H**. Queen 1989 also provided additional motivation to "reduce immunogenicity while retaining high binding affinity" in the original non-human (*e.g.*, murine) monoclonal antibody. Ex. 1034 at 1; Ex. 1003 at ¶259. For these reasons, claim 1 is obvious over Queen 1989 and the PDB database.

2. Ground 2: Independent 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," stating that they have "[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 ...." Ex. 1050 at Abstract; Ex. 1003 at ¶¶118-24, 260. Queen 1990 thus encompassed a human antibody variable domain comprising CDRs from a mouse (donor) monoclonal

antibody.

Queen 1990 provides 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)). Ex. 1050 at 16, ll. 1-36; Ex. 1003 at ¶¶260-261. 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)). Ex. 1050 at 15, ll. 22-37; Ex. 1003 at ¶121 (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 it in a detailed and objective way. Queen 1990 explicitly instructed a POSITA to look to the "Brookhaven Protein Data Bank" (*i.e.*, the PDB database; Ex. 1003 at ¶¶118-24) to identify the framework residues that: "could interact with the CDR atoms" (Criterion IV; Ex. 1050 at 16, l. 14-15, l.2); were conserved (Criterion II; *id.* at 15, ll. 22-37); or were adjacent to CDRs (Criterion III; *id.* at 16, ll.1-12). Ex. 1003 at ¶¶118-24, 260-61. A POSITA following this roadmap would quickly determine that 19 light (L) chain ((4L, 58L, 62L, 66L, 67L, 73L, 85L and 105L (CDR contact residues) and 23L, 25L, 33L, 35L, 49L, 53L, 57L, 88L, 90L, 97L, 98L) (Kabat and Chothia adjacent residues)) and 23 heavy (H) chain 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)), including claim 1 positions **4L**, **58L**, **66L**, **67L**, **69L**, **73L**, **2H**, **36H, 45H** and **69H**, as well as adjacent residues **98L** and **36H**, meet these requirements. *See* §VI.G.1*, supra*; Ex. 1003 at ¶¶164-65, 260-61, Padlan Exhibits C (adjacent residues), M (interatomic distance calculations), N (alignment) and O (contact summary).

Challenged dependent claims 2, 4, 12 and 29 are also obvious in view of the claim chart and arguments below:

'213 Patent Claim	***GROUND 1*: Queen 1989 + PDB Database**	***GROUND 2*: Queen 1990 + PDB Database**
Claim 2 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.	"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]." Ex. 1034 at 3; Ex. 1003 at ¶¶262-63.	". . . substitutions of a human framework amino acid of the acceptor (human) immunoglobulin with a corresponding amino acid from a donor (non-human) immunoglobulin will be made at positions." Ex. 1050 at 7, l. 36-8, l.2; Ex. 1003 at ¶¶262-63.
Claim 4 recites: "wherein the human antibody variable domain is a consensus human variable domain"		"As acceptor ... use a consensus framework from many human antibodies." Ex. 1050 at 14, l. 17-20; Ex. 1003 at ¶264.

'213 Patent Claim	*GROUND 1*: Queen 1989 + PDB Database	*GROUND 2*: Queen 1990 + PDB Database
Claim 12 recites: "wherein the residue at site 66L has been substituted."	*See* claim 1 and Ex. 1003 at Padlan Exhibits M and O (66L substitutable as a conserved residue and in contact with CDR) and ¶¶262-63.	*See* claim 1 and Ex. 1003 at Padlan Exhibits M and O (66L substitutable as a conserved residue and in contact with CDR – Queen 1990 Criteria IV) and ¶¶262-63.
Claim 25 recites: "wherein the residue at site 69H has been substituted."	*See* claim 1 and Ex. 1003 at Padlan Exhibits M and O (69H substitutable as a conserved residue and in contact with CDR) and ¶¶262-63.	*See* claim 1 and Ex. 1003 at Padlan Exhibits M and O (69H substitutable as a conserved residue and in contact with CDR – Queen 1990 Criteria IV) and ¶¶262-63.
Claim 29 recites: "An antibody comprising the humanized variable domain of claim 1."	"The CDRs in the humanized antibody were of course chosen to be identical to the anti-Tac CDRs." Ex. 1034 at 2; Ex.1003 at ¶262-63.	"When combined into an intact antibody, the 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 immuno-globulin..." Ex. 1050 at 8, ll. 21-26; Ex. 1003 at ¶262-63.

3. Grounds 1 and 2: Dependent 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 when applied to pre-1991 structures on the PDB Database. Ex. 1003 at ¶262. Queen 1989 and Queen 1990 disclosed the additional recitations of **claim 2** ("substitutions of a human framework amino acid of the acceptor (*i.e.*, human) immunoglobulin with a corresponding amino acid from a donor (*i.e.*, non-human)

immunoglobulin"; s*ee* Queen 1989 at 3 ("selecting human antibody "to provide the variable domain framework for the humanized anti-Tac antibody"); Queen 1990 at 7, l. 36 - 8, l.1, **claim 12** (*see* Ex. 1003 at ¶¶243-63, *supra* (framework residue 66L within 3 Å of CDR), **claim 25** (*see* Ex. 1003 at ¶¶243-63, *supra*) and **claim 29** Queen 1989 [Ex. 1034 at 3] ("The CDRs in the humanized antibody were of course chosen to be identical to the anti-Tac CDRs."); Queen 1990 [Ex. 1050] at 6, ll. 21-25 ("mouse complementarity determining regions… can be used to produce human-like antibodies…"). Ex. 1003 at ¶262. Both provide express motivation to evaluate proteins in the PDB. Ex. 1003 at ¶¶243-63. Claims 2, 12, 25 and 29 of the '213 patent are thus obvious over Queen 1989 or Queen 1990, in view of known antibody structures available on the PDB database.

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

Queen 1990 disclosed the additional recitation of claim 4 regarding the use of a "consensus human variable domain" in claim 1. *See* Ex. 1050 at 14, ll. 19-20; Ex. 1003 at ¶264. Accordingly, claim 4 is also obvious over Queen 1990, in view of known antibody structures available on the PDB database.

5. Grounds 1, 2: Independent Claims 62-64 and 66 Are Obvious Over Queen 1989 or Queen 1990 and PDB Database

Claim 62: As discussed *supra* (§VI.B.1), 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, discussed above, 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 §§*VI.G.1 and 2 *supra*; Ex. 1003 at ¶¶260-61. Queen 1990 also explicitly teaches using a "consensus human variable domain" in the humanization process. Ex. 1050 at 14, ll. 17-20; Ex. 1003 at ¶¶119, 265. Claim 62 is thus obvious over Queen 1990 and the PDB database.

Claim 63: 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 humanized immunoglobulins disclosed "will be substantially non-immunogenic in humans ...." Ex. 1034 at 1; Ex. 1050 at Abstract; Ex. 1003 at ¶¶266-67. Accordingly, as for claim 1 above (§§VI.G.1 and 2), claim 63 is obvious over Queen 1989 or Queen 1990 in view of the PDB database. Ex. 1003 at ¶¶266-67.

Claim 64: Independent claim 64 recites a "humanized variant of a non-human parent antibody which binds an antigen;" recites non-human CDRs; and rather than require framework substitution residues (*cf.* claims 1, 62, 63), recites

functional elements: "(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). Such elements reflect inherent humanized antibody properties; even so, Queen 1990 explicitly states 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." Ex. 1050 at 16, ll. 1-12 (emphasis added); Ex. 1003 at ¶¶269-70. This satisfies at least limitations (a) and (b). Queen 1990 disclosed humanized antibodies which bind an antigen and comprise a human variable domain with a "consensus framework from many human antibodies." *See* § VI.G.4 *supra*; Ex. 1003 at ¶¶268-71. Queen 1990, given the PDB database, renders claim 64 obvious.

Claim 66: Independent claim 66 is similar to claim 1, but its residue list is "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* §§VI.G.1 and 2; Ex. 1003 at ¶¶273-74. 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 framework positions at **24H, 73H**, **76H, 78H**, and **93H** satisfy Queen's criteria. *See* Ex. 1003 at ¶¶272-76, Padlan Exhibit M (interatomic distance calculations), Padlan Exhibit O (Contacts Summary). Claim 66 is also obvious over Queen 1989 or Queen 1990 and the PDB database.

'213 Patent Claim	***GROUND 2*: Queen 1990 + PDB Database**
Claim 62 recites: "A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a consensus human variable domain, and further comprising 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 claim 1 for "humanized antibody variable domain comprising non-human ... CDR; and claimed substituted amino acids **4L**, **58L**, **66L**, **67L**, **73L**, **2H**, **36H, 45H** and **69H**; §§VI.G.1 and 2, *supra*. *See also* Ex. 1050 at 14, ll. 17-20 ("As acceptor ... use a consensus framework from many human antibodies."); Ex. 1003 at ¶265.
Claim 63 recites: "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	*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**. §§VI.G.2 and 3, *supra*. *See* Ex. 1050 at Abstract (" the humanized immunoglobulins of the present invention will be

’213 Patent Claim	*GROUND 2*: Queen 1990 + PDB Database
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”	substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen.”); Ex. 1003 at ¶¶266-67.
Claim 64 recites: “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; §§VI.G.1 and 2, *supra*, Ex. 1003 at ¶¶268-71. *See also* for “comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins” Ex. 1050 at 14, ll. 17-20 (“As acceptor ... use a consensus framework from many human antibodies.”). For functional limitations (a), (b) and (c), *see* Ex. 1050 at 16, ll. 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 66 recites: “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. §§VI.G.1 and 2, *supra*. *See also* Ex. 1003 at ¶¶272-76 and Padlan Exhibits M and O for substitution of residues **24H**, **73H**, **76H**, **78H** and **93H**.

6. Grounds 1, 2: Dependent Claims 67, 71-74 and 78 Are Obvious Given Queen 1989 or Queen 1990 and PDB Database

Dependent 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 residues **73H**, **76H**, **78H** and **93H** are CDR contact residues as disclosed by Queen 1989 [Ex. 1034] and Queen 1990 [Ex. 1050] in view of the PDB Database,[4] and thus would have been prime candidates for reverting to the mouse residue in any humanization project. *See* §§VI.G.1 and 2, *supra*; Ex. 1003 at ¶¶272-77, Padlan Exhibit O. Moreover, like claims 2 and 29, which include claims 67 and 78's comparable limitations, respectively, these claims are also obvious. *See* §VI.G.3; Ex. 1003 at

[4] Dr. Padlan 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. 1003 at ¶274.

¶¶262-63. Claims 67, 71-74 and 78 are also obvious over Queen 1989 or Queen 1990, in view of known antibody structures available on the PDB database.

7. Grounds 1, 2: Dependent 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." Queen 1989 and Queen 1990 teach substituting framework residues that: 1) contact a CDR; or 2) are adjacent to a CDR. *See* §§VI.G.1 and 2; Ex. 1003 at ¶¶272-76. 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* Ex. 1050 at 16 (Criterion IV)), Ex. 1003 at ¶¶118-24, a POSITA would have readily identified FR position **71H** as such a CDR-contact amino acid residue. *See* Ex. 1003 at ¶281, 246, Padlan Exhibits M (interatomic distance calculations) and O (contact summary). Accordingly, claim 75 is also obvious over Queen 1989 or Queen 1990, given known antibody structures available in the PDB database. Ex. 1003 at ¶¶281.

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, each of residues **71H**, **73H**, **78H** and **93H** are among those disclosed by Queen 1989 [Ex. 1034] and Queen 1990 [Ex. 1050] in view of the PDB database, that would have been targeted for substitution. *See* §§VI.G.1 and 2, *supra*; Ex. 1003 at ¶¶243-61, Padlan Exhibits M (interatomic distance calculations) and O (contact summary). This limited list of substitutable residues alone teaches a POSITA towards the claimed "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," given the limited set of residues already targeted for substitution. Ex. 1003 at ¶¶284-95. This renders obvious residue 71H (claim 75), 71H and 73H (claim 76), 71H, 73H and 78H (claim 77) and 71H, 73H, 78H and 93H (claim 79).

The substitutability of residues 71H, 73H, 78H and 93H would not have been surprising or unexpected. The importance of heavy chain residue 71H was well-known by those in the field, including patentees. *See* Ex. 1001 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 [included as Ex. 1051]); Ex. 1003 at ¶¶281-82. Dr. Padlan also cites to antibody 4-4-20 (4Fab), having 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. 1003 at ¶274.

Moreover, the typical scenario to a POSITA was that more than one framework substitution was often needed to restore function and antigen binding of the resultant humanized antibody. Ex. 1003 at ¶289. 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 at positions 48L, 60L, 63L, 27H, 30H, 48H, 66H, 67H, 89H, 91H, 94H, 103H, 104H, 105H and 107H. *See* Ex. 1034 at 3, Fig. 2; Ex. 1003 at ¶289. 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* Ex. 1050 at 14, ll. 9-15; Ex. 1003 at ¶289.

Further, a substitution's value can be further limited given the antibody sequence itself. For example, comparing mouse monoclonal antibody 4D5 sequence[5] and a human consensus amino acid sequence from Figures 1A and 1B in

[5] Monoclonal antibody 4D5 was made available for use by outside investigators prior to June 1991. *See, e.g.*, Kumar [Ex. 1088]; Soomro [Ex. 1089], allowing a

the ’213 patent, *see* Ex. 1001 at 7-8, and using the knowledge readily derived from the PDB database and the Queen references, a POSITA could quickly arrive at a short list of light and heavy chain amino acid residues that were substitution candidates 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* Ex. 1003 at ¶¶293-94, Padlan Exhibits M-O.

Applying Queen Criterion IV, a POSITA would have thus targeted claimed residues **71H**, **73H**, **78H** and **93H** given their differences in size and/or characteristics. *See, e.g.,* Ex. 1003 at ¶293 (71H); ¶294 (73H (polar to charged: aspartic acid in human acceptor vs. threonine in mouse 4D5)); ¶294 (78H (small to large: leucine in human acceptor vs. alanine in mouse 4D5)); ¶294 (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 on the PDB database, would have been motivated to substitute

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POSITA to obtain the amino acid sequence of the variable domain through routine protein sequencing. *See, e.g.*, Wilson & Goulding [Ex. 1090]; Ex. 1003 at fn. 21. In fact, many sequences present in the Kabat database (Kabat 1987 [Ex. 1052]) were obtained through routine protein sequencing. Ex. 1003 at fn. 21, citing to Edelman [Ex. 1091]; Capra and Kehoe [Ex. 1092].

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* Ex. 1050 at 14, ll. 19-20; Ex. 1003 at ¶¶284-95. 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..." Ex. 1050 at Abstract; Ex. 1003 at ¶¶266-67. Claims 75-77 and 79 thus were obvious in view of Queen 1989 or Queen 1990, and the PDB database.

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

Claim 65 depends from 79 and further recites that the humanized variant "binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." The broadest reasonable interpretation of this limitation includes any increase in binding affinity "up to" the upper limit of "3-fold more," *i.e.*, any amount greater than 1-fold (*i.e.*, the parent binding affinity) and "up to 3-fold more." §VI.D, *supra*; Ex. 1003 at ¶¶297-301.

Claim 65 is taught by Queen 1990, which states "affinity levels can vary . . . and may be *within about 4 fold* of the donor immunoglobulin's original affinity to the antigen." *See* Ex. 1050 at 8, ll. 21-26 (emphasis added). Queen 1990 thus explicitly disclosed the "up to 3-fold" limitation. Ex. 1003 at ¶297.

Moreover, as explained by Dr. Padlan, "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 unexpected that at least a moderate improvement in affinity would be achieved when humanizing some antibodies." Ex. 1003 at ¶299. Thus any increase in affinity, including small and moderate increases incorporated within the scope of the claim, would have been expected, in view of Queen 1989 and Queen 1990. Ex. 1050 at 8, ll.26-28; Ex. 1003 at ¶¶297-301. For these reasons, claim 65 is also obvious over Queen 1989 or Queen 1990 and the PDB database.

9. Grounds 1, 2: Independent Claim 80 and Dependent Claim 81 Are Obvious in View of Queen 1989 or Queen 1990 and PDB Database

Claim 80: 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. As

with claims 63 and 66, residues **4L**, **58L**, **66L**, **67L**, **73L**, **2H**, **24H**, **36H, 45H**, **69H**, **73H**, **76H**, **78H** and **93H** were readily identifiable as candidate substitutable residues. *See* §VI.G.5, *supra*; Ex. 1003 at ¶¶303-05, Padlan Exhibits M and O.

The additional recited elements—noted functions of the substituted residues—cannot impart novelty. *See* claim 64, §VI.G.5; Ex. 1003 at ¶268; *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* Ex. 1034 at 3; Ex. 1050 at 14, l. 32 to 15, l. 2 (using computer model to assess CDR proximity); Ex. 1003 at ¶¶302-06. 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: 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* Ex. 1034 at 3 ("selecting human antibody to provide the variable region framework for the humanized anti-Tac antibody"); Ex. 1050 at 7, l.36 - 8, l.1; Ex. 1003 at ¶307. Claim 81 is obvious over Queen 1989 or Queen 1990, in view of the PDB database.

H. Grounds 3 and 4: Claims 75-77 and 79 Are Unpatentable As 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 highlighted residue **71H** as a prime substitution candidate based on its CDR contacts, independent work also emphasized the criticality of residue **71H** in maintaining CDR conformation. Specifically, Tramontano's 1990 publication definitively demonstrated the importance of framework residue **71H** to maintain the H2 loop and antigen binding. *See* Tramontano [Ex. 1051]. 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 Abstract. The publication also confirmed Queen's teachings that residues outside of the CDR and in the FR help maintain CDR conformation, and antigen binding.

The humanization process established by Queen 1989 [Ex. 1034] and Queen 1990 [Ex. 1050], and other references, including Tramontano's work definitively demonstrating the importance of framework residue **71H**, *see* Ex. 1051 at Abstract; Ex. 1003 at ¶¶129-30, 281-82, would have motivated a POSITA to switch the human residue at position **71H** to the mouse residue in order to preservethe

conformation of the H2 CDR loop. *See* Tramontano [Ex. 1051]; Ex. 1003 at ¶¶282-95. This would have been an automatic substitution to a POSITA. Ex. 1003 at ¶282. 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, §§VI.G.7 *supra,* these claims are further rendered obvious in combination with Tramontano [Ex. 1051]. Ex. 1003 at ¶¶282-95.

I. 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. 1003 at ¶¶308-17. As Dr. Padlan 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. 1003 at ¶84; *see also* ¶292, citing to Queen 1989 at 3 ("Different human light or heavy chain V regions exhibit strong amino acid homology outside of the CDRs within the framework regions." (Emphasis added)). Nevertheless, recognizing the importance of maintaining FR conservation to reduce immunogenicity and "make the antibody more human," Queen 1989 explicitly taught moving towards 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* Ex. 1034 at 3-4; Ex. 1003 at ¶311. From Queen 1989 and Kabat 1987, which provided

all consensus amino acids at each framework region position, 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. 1003 at ¶311.

As discussed with regards to claim 1 above regarding the substitutability of residues **4L**, **58L**, **66L**, **67L**, **73L**, **2H**, **45H** and **69H**, and in combination with 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. 1003 at ¶311. Thus, claims 4, 62, 64 and 69 are obvious given Queen 1989, the PDB database and Kabat 1987.

J. 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 FR substitution sites: 46L, 75H and 76H. Such elements remain obvious, individually and as a whole.

Humanized antibodies were developed for a single purpose: realizing the therapeutic promise of mouse monoclonal antibodies for the treatment of human diseases. Ex. 1003 at ¶321; Ex. 1004 at ¶¶41-45. While mouse monoclonals were capable of targeting antigens in a highly specific manner, immunogenicity issues severely limited the applicability of this technology to human therapeutics. *See* Ex.

1003 at ¶¶70-72; Ex. 1004 at ¶42.

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* Ex. 1021 at Abstract, 1165; Ex. 1004 at ¶¶54-71; Ex. 1003 at ¶322. Hudziak specifically found the HER2/*c-erbB-2* gene product $p185^{HER2}$: (1) amplified in ~30% of breast cancer tumors; Ex. 1021 at 1; Ex. 1004 at ¶58; (2)"Correlated with a negative prognosis and high probability of relapse"; Ex. 1021 at 1; Ex. 1004 at ¶58; (3) caused transformation and tumorigenesis when its expression was increased and the transformed cells were implanted in athymic mice, Ex. 1021 at 1; Ex. 1004 at ¶60; 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, Ex. 1021 at 1; Ex. 1004 at ¶60. Reviewing Hudziak [Ex. 1021] and other literature, Mylan's expert Dr. Edward T. Ball, a practicing oncologist with clinical experience in developing therapeutic antibodies, concluded the above findings "strongly suggested that the HER-2/*neu* receptor was a ripe target for therapeutic development." Ex. 1004 at ¶61.

A POSITA would have been motivated to develop a monoclonal antibody therapeutic against $p185^{HER2}$, based on Hudziak and because monoclonal antibodies were known to have the potential for achieving a high degree of specificity, which would allow one to target HER2 without cross-reactivity with

other structurally similar growth factor receptors, including epidermal growth factor receptor (EGFR). *See* Ex. 1004 at ¶63. This was demonstrated well prior to June 1991 for 4D5, a well-characterized mouse monoclonal antibody targeting $p185^{HER2}$ protein with high affinity, specificity (no binding or recognition of, for example, EGFR) and efficacy in *in vitro* and *in vivo* studies. *Id.* at ¶65. The 4D5 investigators insisted such antibody provided a "new potential for diagnostic approaches and therapeutic strategies for treatment of human malignancies." Ex. 1047 at 4; Ex. 1004 at ¶70.

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. Ex. 1004 at ¶79; Ex. 1003 at ¶324. 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.

Ex. 1048 at 10; Ex. 1004 at ¶75 (emphasis added).

Queen 1989 and Queen 1990 provided the detailed roadmap for humanizing mouse monoclonals, such as 4D5, and represented the state of the art of antibody humanization by 1991. Ex. 1003 at ¶324. 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* Ex. 1050 at 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 ..."); Ex. 1034 at 1 ("For the humanized antibody, sequence homology and molecular modeling were used to select a combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity.").

Hudziak provided explicit motivation to develop 4D5 for therapeutic use, disclosing "monoclonal antibodies specific for $p185^{HER2}$ (*e.g.*, 4D5) [as] useful therapeutic agents for the treatment of human neoplasias." *See* Ex. 1021 at 7; Ex. 1003 at ¶325; Ex. 1004 at ¶70. As a POSITA would have recognized in June 1991, 4D5 required humanization before clinical use. *See* Ex. 1048 at 10 ("4D5 also serves as a template for antibody engineering efforts to construct humanized versions more suitable for chronic therapy ..."); Ex. 1003 at ¶¶324-26, 294-95; Ex. 1004 at ¶75. 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* Padlan Exhibits C (adjacent residues), M (distance calculations) and O (summary). *See* §§VI.G.1 and 2, *supra*; Ex. 1003 at ¶¶318-32. Further, Queen 1989

and Queen 1990 explicitly disclosed that a POSITA would have had a reasonable expectation that humanizing a mouse monoclonal antibody, such as 4D5, would have worked. *See* Ex. 1050 at 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 ..."); Ex. 1034 at 1 (expectation that humanized antibodies would "retain[] high binding affinity"); Ex. 1003 at ¶¶325-26; Ex. 1004 at ¶70. 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 on the PDB database, and in view of Hudziak.

Claim 31. Claim 31 additionally recites that "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 explicitly disclosed this limitation. *See* Ex. 1034 at 3; Ex. 1050 at 7, l.36 - 8, l.1; Ex. 1003 at ¶¶329-30 *see supra* §§VI.G.3 and 9 (claims 2 and 81). Claim 31 is obvious over Queen 1989 or Queen 1990 and the PDB database, and further in view of Hudziak.

Claims 42 and 60. Claims 42 and 60 recite that 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, in view of the PDB database, and further in view of Hudziak. Ex. 1003 at ¶¶329-30.

Claim 33. Claim 33 additionally requires that "the human antibody variable domain is a consensus human variable domain." Queen 1990 explicitly disclosed this limitation. *See* Ex. 1050 at 14, ll. 19-20 ("[U]se a consensus framework from many human antibodies."); Ex. 1003 at ¶¶329-30. For these and claim 30's reasons, claim 33 is also obvious over Queen 1990 and the PDB database, and further in view of Hudziak.

K. 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); *see also Torrent Pharms. Ltd. v. Novartis AG*, IPR2014-00784 at 12 (PTAB Sep. 24, 2015), or that secondary considerations are commensurate with claim scope given the extraordinary breadth of the challenged claims here. *See, e.g., Ex Parte Takeshi Shimono*, Appeal 2013-003410 (PTAB Apr. 29, 2015). Mylan nonetheless addresses potential Patent Owner theories below.

1. The Methods Recited in the '213 Patent Produced No Relevant Unexpected Results.

The '213 patent makes no claim that the claimed methods achieve any unexpected result. To the contrary, the '213 patent recognizes the work of others, including Mylan's expert Dr. Eduardo Padlan, that residues important for maintaining CDR conformation and binding were well known prior to June 1991. *See* Ex. 1001 at col. 2, l. 63 – 67; Ex. 1003 at ¶¶340-41. Given the extensive prior art, successful antibody humanization was readily achievable, not surprising or unexpected. Ex. 1003 at ¶¶85-92, 301-302; Ex. 1004 at ¶¶46-53.

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. The challenged claims' scopes exceed antibody 4D5 specifically; 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.*, U.S. Patent No. 5,677,171 (Ex. 1096); Ex. 1003 at ¶342.

Patent Owner cannot show the purported invention solved the problem the specification identified. *See, e.g., Norgren Inc. v. ITC*, 699 F.3d 1317 (Fed. Cir. 2012) (patent obvious where "[prior art patent] solved similar problems in a similar way."); *see also In re PepperBall Techs., Inc*., 469 F. App'x 878, 882-83 (Fed. Cir. 2012). 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. 1001 at col. 3, ll. 53-55 and col. 4, ll. 24-35. Queen 1989, Queen 1990 and others had already set forth why one would desire to humanize and provided a detailed roadmap on exactly how to do it. Any problems identified in the '213 specification had already been solved and explicitly addressed by the prior art. Ex. 1003 at ¶¶243-61; 342.

3. No nexus/commercial success with respect to Herceptin.

First, none of the heavy chain residues cited in claim 1 are modified in Herceptin,[6] and only 1 of the 13 heavy chain residues (78H) cited in claims 30, 62 and 63 is modified in Herceptin. *Second*, the challenged claims are not limited to any antibody or class of antibodies. Ex. 1003 at ¶343. Even claim 30, which recites that the antibody binds $p185^{HER2}$, is exceptionally broad, not being limited to any specific anti-$p185^{HER2}$ antibody. Therefore, even if Patent Owner can identify one embodiment in its evidence of objective indicia, they will be unable to

[6] While Mylan presumes that Patent Owner will attempt to rely on Herceptin, Mylan does not concede that Herceptin provides support for any asserted secondary considerations.

"demonstrate that untested embodiments falling within the claimed range will behave in the same manner." *Id.* at 4.

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Jeffrey W. Guise, Ph.D.
Lead Counsel
Reg. No. 34,613
Wilson Sonsini Goodrich & Rosati PC
650 Page Mill Road
Palo Alto, CA 94304
Telephone: (858) 350-2225
Facsimile: (650) 493-6811
E-mail: jguise@wsgr.com

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that I caused to be served a true and correct copy of the foregoing: **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,407,213** by *Federal Express Next Business Day Delivery* on this day, August 30, 2016 on the Patent Owner's correspondence address of record for the subject patent as follows:

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

GENENTECH, INC.
460 POINT SAN BRUNO BLVD.
SO. SAN FRANCISCO, CA 94080

SIDLEY AUSTIN LLP
2001 ROSS AVENUE
Suite 3600
DALLAS, TEXAS 75201

Respectfully submitted,

Dated: August 30, 2016

Jeffrey W. Guise, Ph.D.
Lead Counsel
Reg. No. 34,613

Wilson Sonsini Goodrich & Rosati PC
650 Page Mill Road
Palo Alto, CA 94304
Telephone: (858) 350-2225
Facsimile: (650) 493-6811
E-mail: jguise@wsgr.com