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BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
Petitioner,
v.

GENENTECH, INC.
Patent Owner.

IPR2017-02032
Patent No. 6,407,213

Title: METHOD FOR MAKING HUMANIZED ANTIBODIES

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 6,407,213 B1

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Statutes

Other Authorities

LIST OF EXHIBITS

EXHIBIT NO.	DESCRIPTION
1001	U.S. Patent No. 6,407,213, *Method for making humanized antibodies* (filed Jul. 17, 1993) (issued June 18, 2002)
1002	File History for U.S. Patent No. 6,407,213 (9 volumes)
1003	Declaration of Dr. Geoffrey Hale, Ph.D. in Support of Petition for *Inter Partes* Review of Patent No. 6,407,213
1003A	*Curriculum Vitae* of Dr. Geoffrey Hale, Ph.D.
1003B	Materials Reviewed by Dr. Geoffrey Hale, Ph.D.
1003C	Exhibits A-R of Dr. Geoffrey Hale, Ph.D.
1004	Intentionally left blank
1005	Ball E.D., et al. *Studies on the ability of monoclonal antibodies to selectively mediate complement-dependent cytotoxicity of human myelogenous leukemia blast cells.* J. Immunol. 128(3):1476-81 (March 1982)
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1123	U.S. Patent No. 5,889,157 *HumanizedB3 Antibody Fragments, Fusion Proteins, and Uses Thereof* (humanization of monoclonal antibodies to Lewis -related carbohydrate antigen) (Filed 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, Boehringer Ingelheim Pharmaceuticals, Inc. ("Boehringer") petitions for *Inter Partes* Review ("IPR") of claims 1, 2, 4, 25, 29, 62-64, 66, 67, 69, 71-73, 75-78, and 80-81 of U.S. Patent No. 6,407,213 ("the '213 patent," Ex._1001). The challenged claims are unpatentable because they would have been obvious from prior art that disclosed humanized antibodies, including 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], and from the Protein Data Bank (PDB) database antibody structures. The '213 claims are also obvious over Queen 1989 or Queen 1990, in view of Tramontano [Ex._1051]; or Kabat 1987 [Ex._1052]. The '213 claims are also anticipated by U.S. Patent No. 5,530,101 to Queen [Ex. 1136].

The Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

II. MANDATORY NOTICES

A. Real Parties-In-Interest

The real parties-in-interest for Petitioner are: Boehringer Ingelheim GmbH, Boehringer Ingelheim Corporate Center GmbH; Boehringer Ingelheim Pharma GmbH & Co. KG; Boehringer Ingelheim International GmbH; Boehringer Ingelheim USA Corporation; and Boehringer Ingelheim Pharmaceuticals, Inc.

B. Related Matters

Petitioner concurrently files two IPR petitions for claims of the ’213 patent. Petitioner is aware of two earlier IPR proceedings for the ’213 patent, both filed by third-party Mylan Pharmaceuticals Inc.: IPR2016–01693 and IPR2016–01694. These proceedings were terminated by the Board on March 10, 2017 after the parties filed a Joint Motion to Terminate. Paper No. 24, IPR2016–01693; Paper No. 23, IPR2016–01694 (March 10, 2017). Petitioner is also aware of two current IPR proceedings for the ’213 patent, both filed by third-party Celltrion, Inc.: IPR2017-01373 and IPR2017-01374. Petitioner is also aware of two current IPR proceedings for the ’213 patent, both filed by third-party Pfizer, Inc.: IPR2017-01488 and IPR2017-01489. The present IPR petitions offer different arguments from the previously-filed IPR petitions.

Petitioner is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in this proceeding.

C. Identification of Counsel and Service Information

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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 IPR and that the Petitioner is not barred or estopped from requesting IPR on the grounds identified herein.

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

Petitioner requests IPR and cancellation of claims 1;2;4;25;29;62-64;66;67; 69;71-73;75-78; and 80-81 of the '213 patent under pre-AIA 35 U.S.C. § 103, as set forth below in Petitioner's detailed "Statement of Reasons for Relief Requested." Petitioner provides copies of the exhibits relied upon, and the Declaration of Dr. Geoffrey Hale, Ph.D. (Ex._1003).

Dr. Geoffrey Hale received his Ph.D. in Biochemistry at the University of Cambridge in the U.K. in 1977. In 1986 Dr. Hale collaborated with Professor Waldmann and Sir Gregory Winter to select Campath-1G, an antibody Dr. Hale had developed, as the first therapeutic antibody to be humanized. Ex._1003 at ¶3. His work resulted in numerous publications and patents in his field. Ex._1003A.

The challenged claims generally involve humanized antibodies and humanized antibody variable domains. Ex._1003 at ¶¶36-56. Claims 1;2;4;25;29; 62-64;66;67;69;71-73;75-78; and 80-81 of the ’213 patent are unpatentable as follows:

Ground No	Claims and Basis
1	Claims 1, 2, 25, 29, 63, 66-67, 71-73, 75-78, and 80-81 as obvious over Queen 1989, in view of the Protein Data Bank (PDB) database
2	Claims 1, 2, 4, 25, 29, 62-64, 66-67, 69, 71-73, 75-78, and 80-81 as obvious over Queen 1990, in view of the PDB database
3	Claims 75, 76, and 77 as obvious in view of Queen 1989, the PDB database, and further in view of Tramontano
4	Claims 75, 76, and 77 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 1, 2, 4, 25, 29, 62-64, 66, 67, 69, 71, 73, 75-78, and 80-81 are anticipated by the ’101 patent

V. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

An IPR 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). As set forth below, this Petition meets and exceeds this threshold.

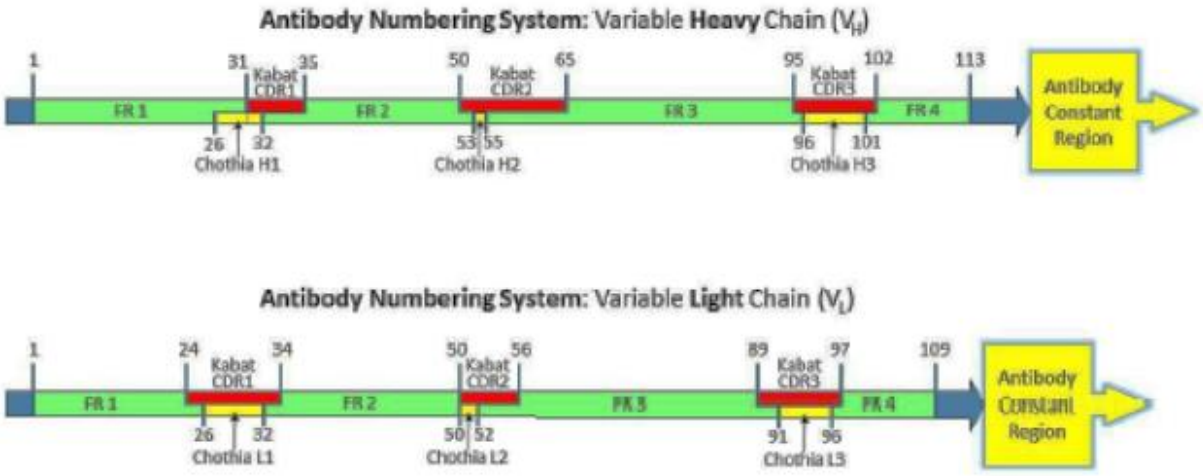
A. Summary of the Argument

In 1975, *Nature* published Kohler and Milstein's ground-breaking study manufacturing "predefined specific antibodies by means of permanent tissue culture cell lines," *i.e.,* monoclonal antibodies. Ex._1022 at 1. Mouse monoclonal antibodies exhibited therapeutic and diagnostic promise, but use in patients resulted in a human anti-mouse-antibody (HAMA) immunogenicity response. Ex._1003 at ¶¶63-65.

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 ¶¶82-84. While "chimeric" antibodies retained the parent mouse's affinity and specificity, patients still experienced HAMA responses. Next, scientists replaced mouse variable domain framework regions (FR) flanking the complementarity determining regions (CDR) with human sequences. Ex._1003 at ¶85; *see also* Ex._1033 (Jones).

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. 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 ¶¶68-86]:



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 ¶¶66-84. Wholesale replacement of mouse FR sequences with human FR sequences increased the risk of losing some sequence features that helped properly position the mouse CDRs to achieve their binding affinities. In 1989 and 1990, Queen *et*

al. published 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 ¶¶110-22, 252-67. The fundamental principle was simple: after incorporating human FR sequences, change a limited number of residues 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 ¶¶110-22.

Queen 1990 provided four specific criteria (I-IV) to target ("AAs") for substitution in producing humanized antibodies. *See* Ex._1050 at 14:17-16:2; Ex._1003 at ¶¶116-22. Following this methodology, the POSA could readily discern AA sequence locations to target. As further instructed by Queen 1989 and 1990, one could 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 AAs to reinstate from the mouse should be "transferred to the human framework along with the CDRs." Ex._1034 at 5; Ex._1003 at ¶¶116-22. 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 ¶¶252-67. 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 ¶¶77-81. 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 ¶¶80, 136. Residue **71H** was thus an automatic candidate for substitution for humanization. Ex._1051 at 1; Ex._1003 at ¶¶80, 136.

Finally, the claims of the ’213 patent are drafted so broadly as to encompass amino acid (“AA”) substitutions that were not intentionally replaced, so long as the humanized variable domains vary from the consensus FRs at the sites recited in the claims. For example, Claim 1 is directed to a humanized antibody variable domain “comprising 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;92H, utilizing the numbering system set forth in Kabat.” Although claim 1 does not specify that the substitutions must be made to a consensus sequence, Claim 4 depends from claim 1 and further requires that “the human antibody variable domain is a consensus human variable domain.” Because claim 1 requires

substitutions in the variable domain, claim 4 must also require substitutions in the variable domain. Claim 4 therefore encompasses humanized antibody variable domains where only *some* of the residues in the sequence are "consensus" residues, and where other, non-consensus residues are "substitutions" in the consensus sequence. A prior art antibody that anticipates claim 4 also anticipates claim 1.

However, for a prior art antibody to anticipate claim 4, the non-consensus residues need not have been intentionally "substituted." The claims of the '213 patent are directed to products, not processes. *See, e.g*., '213 patent claim 1, directed to "[a] humanized antibody variable domain." Whether an AA is present in a sequence because it occurs there naturally or is deliberately inserted through a step of "substitution" does not affect the final AA sequence or structure. Ex._1003 at ¶231. Therefore, the requirement for "substitution" in the AA sequence is not a structural limitation, but a process limitation of a product-by-process claim that should be disregarded in the patentability analysis. *See, e.g., Purdue Pharma L.P. v. Epic Pharma, LLC*, 811 F.3d 1345, 1353-54 (Fed. Cir. 2016) (finding that "derived from 8α[ ]" was a process limitation in a product-by-process claim and thus should be disregarded in the patentability analysis). In other words, a prior art antibody prepared by a different process, but with the same sequence (and thus structure/function) as an antibody prepared according to the claims of the '213 patent, would anticipate those claims. *See id*. at 1354; *see also In re Thorpe*, 777

F.2d 695, 697 (Fed.Cir.1985) ("If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."). Because the '101 patent discloses such a prior art antibody, and as explained in further detail below, the '101 patent anticipates claims 1;2;4;25;29;62-64;66;67; 69;71;73;75-78; and 80-81.

B. Background of the '213 Patent

1. The '213 Patent

The '213 patent issued June 18, 2002 from a continuation-in-part of U.S. Appl. 07/715,272 (filed June 14, 1991). For purposes of this IPR only, Petitioner will assume that the '213 claims are entitled to a priority date of June 14, 1991, the '213 patent's earliest possible priority date.

The '213 patent issued with 82 claims. Ex._1001 at 85:44-90:32. Claims 1, 30;62;63;64;66;79; and 80 are independent, and all claim a "humanized antibody," "antibody," "humanized variant of a non-human parent antibody" or "humanized antibody variable domain" comprising a "non-human . . . CDR," and a "Framework Region [FR] amino acid substitution" 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;92H) when utilizing Kabat's numbering system. **Claims 30, 62 and 63** add 4 FR residues to claim 1's list (46L;75H;76H;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."

Claim 66 offers a different list of 5 FR residues: 24H;73H;76H;78H and 93H. **Claim 79** lists 4 FR "substitutions at heavy chain positions 71H;73H;78H and 93H, utilizing the numbering system set forth in Kabat." **Claim 80** claims the residues of claim 1 plus the 5 residues from claim 66, and adds that the FR AA 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."

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 [CDRs] thereof comprise non-human antibody amino acid residues, and further comprises a [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 and claims were not new. The patent 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 3:40-44. It acknowledges that past "molecular modeling" has been shown to "increase the antigen binding affinity of a humanized antibody." Ex._1001 at 3:44-48. 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.

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

'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.

The examiner also raised Queen Patents 5,530,101 ("the '101 patent") and 5,693,762 ("the '762 patent") as § 102(e) references. Among other things, the examiner pointed out that the '101 patent disclosed antibody species with a number of claimed AA substitutions, including at recited position 73H. *See, e.g.,* Ex._1002 at 739-40. However, Genentech ultimately provided an affidavit signed by the inventors, swearing behind the September 1990 priority date of the '762 and '101 patents. *Id*. at 793, 802-07. They provided pages from a laboratory notebook disclosing proposed sequences for a humanized 4D5 antibody, relying on consensus sequences and at least one substitution at site 73H.[1] *Id*.

[1] Boehringer does not concede that this declaration is sufficient to swear behind the genus of species disclosed by the claims of the '213 patent, even limited to those with 73H substitutions, because there is no evidence that the species of this genus have common properties. *In re Clarke*, 356 F.2d 987, 992-993 (C.C.P.A. 1966). For example, an antibody with a single substitution at 73H could have markedly

The claims were then allowed.

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, regarding claims to humanized antibodies with non-human substitutions at specific variable domain framework positions. The Board declared the interference, *Carter v. Adair,* Interference No. 105,744, Declaration of Interference at 4 (Feb. 2, 2010) [Ex._1095], but the Board determined that Adair's claim in interference was barred under 35 U.S.C. § 135(b)(1). Decision on Motions at 9-10 [Ex._1095 at 1588-89], *aff'd 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 invention's field involves humanizing non-human antibodies. A POSA[2] 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

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different properties than an antibody species that additionally has ten other substitutions.

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

industrial experience in the production of recombinant proteins. *See, e.g.*, Ex._1003 at ¶¶24-26. Such experience could include, *e.g.*, 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, and immunogenicity testing. *Id.* Such person may have consulted with one or more other experienced professionals to develop a humanized monoclonal antibody for therapeutic use, including consulting with others to select non-human monoclonal antibodies (such as a mouse monoclonal antibody) for humanization, as well as subsequent testing of the humanized antibody and its intermediates. *Id.*

D. Claim Construction

In an IPR, patent claims possess their "broadest reasonable construction in light of the specification of the patent." 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs. LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016). For purposes of this IPR only, Petitioner adopts the following constructions of each respective term.[3]

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

"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" (Claim 64) 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.[4] A POSA would understand "a humanized antibody" to include an antibody or antibody fragment that has been made more human-like. A POSA would also understand that none of the claims relate to a specific antibody or antibody fragment.

"*And Further Comprising a Framework Region (FR) Amino Acid Substitution at a Site Selected From the Group Consisting Of*". Independent claims 1, 62, 63, 66, and 80 of the '213 patent include a Markush Group list of AA residues from which an FR substitution is chosen. Markush Group members are accorded functional equivalency status for purposes of claim construction. *See Ecolochem, Inc. v. Southern California Edison Co.,* 91 F.3d 169 (Fed. Cir. 1996) ("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

[4] For purposes of the present petition only, Petitioner will assume that the claim preambles are limiting.

members are functional equivalents of each other, the broadest reasonable interpretation to a POSA would be that any of the recited residues can be equally substituted for any given antibody.

The term "Framework Region (FR) substitution" is not expressly defined by the '213 patent. A POSA would understand this term to mean that the AA residue at a given site within the FR has been replaced by a different AA residue.

"Numbering System Set Forth in Kabat". Independent claims 1, 62, 63, 66, 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 10:45-49. 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 [CDRs] and four [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,[5]

[5] Dr. Hale notes there are no significant differences between the Kabat 1987 and Kabat 1991 numbering systems, including CDR and FR boundary designations.

including the AA residue positions set forth in Kabat, but also including the boundary designations for CDR and FR structures.

"Consensus Human Variable Domain" (Claims 4, 62, 69) or "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" (Claim 64). Claims 4, 62, and 69 recite that the HVD comprise a "consensus" human variable domain ("HVD"). The '213 patent defines a "consensus" sequence as "an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." Ex._1001 at 11:33-39. Using similar language, Claim 64 recites that the HVD "compris[es] the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup."

A POSA reading the claims, however, would understand that a "consensus" HVD or the HVD as required in claim 64 must have at least one AA residue that is *not* "the most frequently occurring amino acid residue[] at each location," because the claims require substitutions within the FRs. Claim 4, for example, depends from claim 1, which requires at least one substitution from a site selected from a

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Ex._1003 at n.5. However, the priority document (U.S. Patent Application No. 07/715,272) only relies on Kabat 1987, and not Kabat 1991. *Id.*

Markush group of 24 different sites. Claim 1, however, does not limit the substitutions to the Markush group, and does not limit the substitutions to only one. Therefore, because the claims require that at least one of the residues in a sequence be different from the consensus—and in fact allows for multiple differences from the consensus—a HVD comprises a "consensus" sequence so long as *some* of the residues are consensus residues.

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 human FR 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 ¶¶110-15. Queen 1989 provided guidelines for one to follow when humanizing a mouse antibody. 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 that likely interact with mouse antibody CDRs or 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 14:17-32; Ex._1003 at ¶¶116-22.

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: 21-37. Ex._1003 at ¶¶114, 118. Dr. Hale explains that "maintaining conserved residues ... is important for avoiding immunogenicity in a humanized antibody." Ex._1003 at ¶114. However, Dr. Hale further explains that applying Criterion II is "not required where a consensus human acceptor antibody is used." Ex._1003 at ¶119.

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 16:1-12 (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 ¶¶165-75.

Queen 1990 placed further limitations on the molecular modeling criteria Queen 1989 established, pinpointing framework residues which come within about 3 Å 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 16:14-31. Queen 1990 further explains these "contact" residues could also be derived from other known antibody structures. *Id.* at 14:14-15:2. Such framework residues are more likely to influence CDR/antigen interactions.

3. U.S. Patent No. 5,530,101

The '101 patent issued on June 25, 1996. The '101 patent resulted from U.S. Appl. No. 07/634,278, which was filed on December 19, 1990 as a continuation-in-part of U.S. Appl. No. 590,274, filed on September 28, 1990 (abandoned), which in turn is a continuation-in-part of U.S. Appl. No. 310,252, filed February 13, 1989 (abandoned), which is a continuation-in-part of U.S. Appl. No. 290,975, filed December 28, 1988 (abandoned). The '101 patent is § 102(e) prior art to the '213 patent.

The '101 patent discloses multiple humanized antibodies with substitutions relative to the human consensus framework at positions recited by the claims of the '213 patent. In particular, the '101 patent discloses at least the CMV5 antibody, which discloses substitutions according to Kabat numbering at least at 4L;58L; 85L;69H;71H;73H;75H;78H; 93H. Ex._1003 at 126; Ex._1003C at 780 (Hale Exhibit R). At least residues 4L;58L;69H;71H;73H;75H;78H; 93H are the same as the corresponding murine residue at those locations. *Id.*

4. 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 ¶¶133-34, 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.").

(1) 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 ¶133. Dr. Hale 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 relied on and contributed to the PDB database," and retrieved "computer-readable data that could be directly inputted into distance calculation and graphic programs for use in visualization and comparison studies." Ex._1003 at ¶116.

Dr. Hale 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, as well as specific information regarding the entry itself." Ex._1003 at ¶134, quoting Ex._1080 at 3-6, describing the entry for protein ribonuclease S.

In order to apply the Queen 1989/1990 instructions "to create models of proteins such as antibodies," including "known antibody structures, which are available from the *Brookhaven Protein Data Bank"* (Ex._1050 at 16:25-36 (emphasis added)), Dr. Hale examined 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 ¶¶252-65.

As Dr. Hale explains, evaluation of each existing sequence and calculation of interatomic distances between each framework residue and CDR region, just as a POSA would have done, produced a list of AA residues in the light and/or heavy chains that correspond to the patent claims. Ex._1003 at ¶¶261-65.

5. Tramontano [Ex._1051]

Tramontano, which published in 1990, focused on AA 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 VH 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.

6. Kabat 1987 [Ex._1052]

Kabat 1987 compiled known antibody sequences, derived through protein and gene sequencing, and identified the most common AAs 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 AAs 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).

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 to preserve the original mouse CDRs' binding affinity. *See* Ex._1034 at Abstract; Ex._1050 at Abstract; Ex._1003 at ¶¶110-22. 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: 30-33; Ex._1073 at 9:12-19; Ex._1003 at ¶¶82-87.

Queen 1989 and Queen 1990 addressed these issues by combining 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. Ex._1003 at ¶¶110-22.

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 ¶¶116-22.

Queen 1990 expanded on Queen 1989 and explicitly 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: 21-25.

In this way, a POSA could reasonably expect to identify the most important framework positions in any donor antibody to target for substitution. Ex._1050 at 16:2, 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 ¶¶94-107.

G. Grounds 1 and 2: Claims 1;2;4;25;29;62-64;66-67;71-73;75-78; and 80-81 Are Unpatentable as Obvious Over Queen 1989 or Queen 1990, in View of the PDB Database

1. <u>Ground 1</u>: Claim 1 is Obvious Over Queen 1989, in View of the PDB Database

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

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 [CDRs] of the anti-Tac antibody with human framework and constant regions."); Ex._1003 at ¶¶252-65.

Claim 1 "further compris[es] a [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 ¶254. A POSA would have used those simple rules to determine which residues in a human FR region could be switched back to

mouse. Ex._1003 at ¶¶254-57. 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 ¶256. Queen 1989 substituted these framework positions with the mouse residue. Ex._1034 at 3; Ex._1003 at ¶256. Queen 1989 taught that such steps "may have wider applicability" to humanize other antibodies. Ex._1034 at 5; Ex._1003 at ¶113.

Many private and public research institutions, including Genzyme Corporation *(see, e.g.,* Ex._1071), Protein Design Labs *(see, e.g.,* Ex._1050), the National Institutes of Health *(see, e.g.,* Ex._1073), and the Winter Lab *(see, e.g.,* Ex._1069), were very active in the field of humanization as of June 1991. Ex._1003 at ¶89. 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.

These early conferences show that POSAs in the field were applying the precise methodology described in Queen 1989. Using publicly available tools, POSAs like Dr. Eduardo Padlan from the NIH performed the methods taught in Queen 1989 "[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 (§V.E.3, *supra),* as well as computer programs (either commercially purchased or created) to measure interatomic distances and create three-dimensional graphical models. Using these tools, a POSA 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 ¶¶110-22.

Dr. Hale confirmed that the same exercise Queen 1989 taught on antibody structures known and publicly available prior to 1991 through the PDB database would have resulted in the substitutions recited in claim 1 of the '213 patent. *See* Ex._1003 at ¶¶252-65. Dr. Hale reviewed 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 AA residues. *Id.* at ¶¶226-27. Dr. Hale also reviewed the interatomic (Euclidean) distances

between the atom pairs of the framework residue and the CDR residues, the determination of which was considered routine as of 1991. *Id.* at ¶¶254, Ex._1003C at 649-770 (Hale Exhibit M (interatomic distance calculations)). As would have been understood by a POSA in view of Queen 1989 *(see* Ex._1003 at ¶261), Dr. Hale confirmed the identification of which framework residue side chains were in contact with the CDRs. *See* Ex._1003 at ¶¶252-65, Ex._1003C at 649-770, 776-77 (Hale Exhibits M and O).

Dr. Hale confirmed the alignment of the primary AA sequence of each pre-1991 antibody structure above according to the Kabat numbering system following the teaching of Queen 1989 *(see* Ex._1003C at 771-75 (Hale Exhibit N)), and confirmed the contact residues that were targets for substitution. *See* Ex._1034 at 3-4 and Figure 3; Ex._1003 at ¶¶252-65, Ex._1003C at 649-775 (Hale Exhibits M and N). When compared to the list of residues recited in claim 1, Dr. Hale found that 8 light (L) chain (4L;58L;62L;66L;67L;73L;85L; and 105L and 11 heavy (H) chain residues (2H;24H;39H;45H;69H;71H;73H;76H;78H;93H; 103H) were readily identified as in contact with CDRs, according to the numbering system of Kabat 1987 [Ex._1052]. *See* Ex._1003 at ¶263; Ex._1003C at 649-777 (Hale 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; 69H.** *See* Ex._1003 at ¶265. Dr. Hale thus identified at least 9

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

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

- “Step 1 ... crystal structures from the Brookhaven Protein Data Bank were used...” (Ex._1001 at 16:30-32);
- “Step 2 ... the structures were superimposed on one another using the INSIGHT computer program...” (id. at 17:15-19);
- “[m]odels of a humanized, import or human antibody sequence are used ... to show residues which may be important in antigen binding,

or for maintaining the conformation of the antibody..." (id. at 19:58-64).

Given the teachings in Queen 1989 and the readily-available structures on the PDB database, a POSA 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.** The '213 patent does not provide any evidence that the particular residues recited in the claim are more important or critical to the claimed invention than others recited in the prior art. 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 ¶265. For these reasons, claim 1 is obvious over Queen 1989 and the PDB database.

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

Queen 1990[6] 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

[6] Genentech may argue that Queen 1990 is not prior art to the '213 patent. Boehringer has not seen any evidence that supports this argument, and reserves the right to contest the sufficiency of any evidence that Genentech may introduce.

"[n]ovel methods for designing humanized immunoglobulins having one or more [CDRs] from a donor immunoglobulin and a framework region from a human immunoglobulin." Ex._1050 at Abstract; Ex._1003 at ¶¶116-22, 266. 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 FR 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 16:1-36; Ex._1003 at ¶¶266-67. 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 15:22-37; Ex._1003 at ¶119 (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 AAs, and *how* to do it in a detailed and objective way. Queen 1990 explicitly instructed a POSA to look to the "Brookhaven Protein Data Bank" *(i.e.,* the PDB database; Ex._1003 at ¶¶116-22) to identify the framework residues that: "could interact with the CDR atoms" (Criterion IV; Ex._1050 at 14:21-25); were conserved (Criterion II; *id.* at 15:22-37); or were adjacent to CDRs (Criterion III;

id. at 16:1-12). Ex._1003 at ¶¶116-22, 266-67. A POSA following this roadmap would have quickly determined 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* §V.G.1, *supra;* Ex._1003 at ¶¶168-69, 259-60, Ex._1003C at 8-9, 649-777 (Hale Exhibits C (adjacent residues), M (interatomic distance calculations), N (alignment) and O (contact summary)). The '213 patent does not provide any evidence that the particular residues recited in the claim are more important or critical to the claimed invention than others recited in the prior art.

As will be discussed in detail below, challenged dependent claims 2, 4, and 29 are also obvious. These arguments are summarized in the claim chart 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	"When these residues differ between the anti-Tac and Eu antibodies, the residue in the humanized antibody was	". . . substitutions of a human framework amino acid of the acceptor (human) immunoglobulin with a corresponding amino acid from

'213 Patent Claim	***GROUND 1:* Queen 1989 + PDB Database**	***GROUND 2:* Queen 1990 + PDB Database**
of the non-human antibody from which the non-human CDR amino acid residues are obtained."	chosen to be [mouse]rather than [human]." Ex._1034 at 3; Ex._1003 at ¶¶268-69.	a donor (non-human) immunoglobulin will be made at positions." Ex._1050 at 7:36-8:2; Ex._1003 at ¶¶268-69.
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 14:17-20; Ex._1003 at ¶270.
Claim 25 recites: "wherein the residue at site 69H has been substituted."	*See* claim 1 and Ex._1003C at 649-770, 776-77 (Hale Exhibits M and O (69H substitutable as a conserved residue and in contact with CDR)) and ¶¶268-69.	*See* claim 1 and Ex._1003 at 649-770, 776-77 (Hale Exhibits M and O (69H substitutable as a conserved residue and in contact with CDR - Queen 1990 Criteria IV)) and ¶¶268-69
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 ¶268-69.	"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 8:21-26; Ex._1003 at ¶268-69.

3. <u>Grounds 1 and 2</u>: Dependent Claims 2, 25 and 29 Are Obvious Over Queen 1989 and the PDB Database or Queen 1990 and the PDB Database

Claims 2, 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 ¶268. 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 7:36-8, **claim 25** (69H substitutable as a conserved residue and in contact with CDR; *see* Ex._1003 at ¶¶252-69, *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 6:21-25 ("mouse complementarity determining regions...can be used to produce human-like antibodies..."). Ex._1003 at ¶269. Both provide express motivation to evaluate proteins in the PDB. Ex._1003 at ¶¶252-69. Claims 2, 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. <u>Ground 2</u>: Dependent Claim 4 Is Obvious in View of Queen 1990 and PDB Database

Claim 4 depends from claim 1 and further requires the use of a "consensus" HVD. As discussed above, claim 1 is obvious. *See* §V.G.1 and 2 *supra*. Queen 1990 disclosed "us[ing] a consensus framework from many human antibodies".

See Ex._1050 at 14:19-20; Ex._1003 at ¶270. 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* (§V.B.1), independent claim 62 is nearly identical to claim 1, but adds that the HVD is a "consensus" HVD. For the same reasons as for claims 1 and 4, claim 62 is also obvious. Queen 1990, discussed above, teaches substituting AA residues that contact or interact with a CDR, or are conserved. A POSA following Queen 1990's criteria would have readily identified at least claimed residues **4L;58L;66L;67L;73L;2H;36H; 45H;** and **69H.** *See* §§V.G.1 and 2 *supra;* Ex._1003 at ¶¶266-67. Queen 1990 also explicitly teaches using a "consensus" HVD in the humanization process. Ex._1050 at 14:17-20; Ex._1003 at ¶¶117, 271. Thus, like claim 1, claim 62 is 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." Since it merely states the intended result of the claimed composition, this is not a limitation of the claims. *Bristol-Myers Squibb*

Co. v. BenVenue Labs, Inc., 246 F.3d 1368, 1375-76 (Fed. Cir. 2001). Nonetheless, this is the goal of all monoclonal antibody humanization projects, including that of Queen 1989 and Queen 1990, which disclosed humanized immunoglobulins that "will be substantially non-immunogenic in humans... " Ex._1034 at 1; Ex._1050 at Abstract; Ex._1003 at ¶¶272-73. Accordingly, as for claim 1 above (§§V.G.1 and 2), claim 63 is obvious over Queen 1989 or Queen 1990 in view of the PDB database. Ex._1003 at ¶¶272-73.

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 specific framework residue substitutions *(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 the properties of obvious compositions 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 that AAs "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 16:1-12 (emphasis added); Ex._1003 at ¶¶275-76. This teaches at least limitations (a) and (b). Queen 1990 disclosed humanized antibodies which bind an antigen and comprise an HVD with a "consensus framework from many human antibodies." *See* §V.G.4 *supra;* Ex._1003 at ¶¶274-77. 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 AA positions that: 1) contact a CDR; or 2) are adjacent to a CDR. *See* §§V.G.1 and 2; Ex._1003 at ¶¶279-80. As discussed above, given the Queen 1989 and Queen 1990 disclosures teaching computer modeling and comparison with known antibody structures from the PDB database, a POSA would have readily recognized that framework positions at **24H, 73H, 76H, 78H,** and **93H** satisfy Queen's criteria. *See* Ex._1003 at ¶¶278-82, Ex._1003C at 649-770, 776-77 (Hale Exhibits M (interatomic distance calculations), and O (Contacts Summary)). The '213 patent provides no evidence that the recited residues are more important or critical to the claimed invention than others recited in the prior art. Claim 66 is thus also obvious over Queen 1989 or Queen 1990 and the PDB database.

The obviousness of claims 62-64 and 66 is summarized in the chart below.

'213 Patent Claim	***GROUND 2:* Queen 1990 + PDB Database**
Claim 62 recites: "A humanized antibody variable domain comprising non-human [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." **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 [CDR] amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of: 4L;38L;43L, 44L; 46L;58L;62L;65L;66L; 67L;68L;69L; 73L;85L;98L;2H;4H;36H;39H;43H; 45H;69H;70H;74H;75H;76H;78H and 92H, utilizing the numbering system set forth in Kabat"	*See* discussion of 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; §§V.G.1 and 2, *supra*. *See also* Ex._1050 at 14:17-20 ("As acceptor use a consensus framework from many human antibodies."); Ex._1003 at ¶271. *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. §§V.G.2 and 3, *supra*. *See* Ex._1050 at Abstract ("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._1003 at ¶¶272-73.
Claim 64 recites: "A humanized variant of a non-human parent antibody which	See discussion of claim 1 for "humanized antibody variable domain

'213 Patent Claim	***GROUND 2:* Queen 1990 + PDB Database**
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 [CDRs] thereof comprise non-human antibody amino acid residues, and further comprises a [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 VL-VH interface by affecting the proximity or orientation of the VL and VH regions with respect to one another." **Claim 66 recites:** "A humanized antibody heavy chain variable domain comprising non-human [CDR] amino acid residues which bind antigen incorporated into a human antibody variable domain, and further comprising a [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"	comprising non-human ... CDR; §§V.G.1 and 2, *supra*, Ex._1003 at ¶¶274-77. *See also* for "comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins" Ex._1050 at 14:17-20 ("As acceptor ... use a consensus framework from many human antibodies."). For functional limitations (a), (b) and (c), *see* Ex._1050 at 16:4-12 ("These amino acids are particularly likely to interact with the amino acids in the CDR's ... [and] interact directly with the antigen."). *See* discussion of claim 1 for "humanized antibody variable domain comprising non-human ... CDR; and claimed substituted amino acids. §§V.G.1 and 2, *supra. See also* Ex._1003 at ¶¶278-82 and Ex._1003C at 649-770, 776-77 (Hale Exhibits M and O) for substitution of residues **24H; 73H;76H;78H** and **93H.**

6. <u>Grounds 1, 2</u>: Dependent Claims 67, 71-73 and 78 Are Obvious Given Queen 1989 or Queen 1990 and PDB Database

Dependent claims 67, 71-73 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), and "[a]n antibody comprising the humanized variable domain of claim 66" (claim 78). Each of residues **73H, 76H,** and **78H** are CDR contact residues as disclosed by Queen 1989 [Ex._1034] and Queen 1990 [Ex._1050] in view of the PDB Database,[7] and thus would have been prime candidates for reverting to the mouse residue in any humanization project. *See* §§V.G.1 and 2, *supra;* Ex._1003 at ¶¶278-83, Ex._1003C at 776-77 (Hale Exhibit O). Furthermore, the '213 patent does not provide any evidence that the particular residues recited in the claims are more important or critical to the claimed invention than others recited in the prior art. Moreover, like claims 2 and 29, which include claims 67 and 78's comparable limitations, respectively, these claims are also obvious. *See* §V.G.3; Ex._1003 at

[7] Dr. Hale points to antibody 4-4-20 (available in 1989) with a cluster of close (<3.0Å) contacts at 73H and 78H, emphasizing the relative importance of these residues for maintaining antibody conformation. Ex._1003 at ¶273.

¶¶268-69. Claims 67, 71-73 and 78 are thus 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 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* §§V.G.1 and 2; Ex._1003 at ¶287. 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 ¶¶116-22, a POSA would have readily identified FR position **71H** as such a CDR-contact AA residue. *See* Ex._1003 at ¶287, 248, Ex._1003C at 649-770, 776-77 (Hale 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 ¶287.

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).

As noted above, each of residues **71H, 73H,** and **78H** 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* §§V.G.1 and 2, *supra;* Ex._1003 at ¶¶252-67, Ex._1003C at 649-770, 776-77 (Hale Exhibits M (interatomic distance calculations) and O (contact summary)). This limited list of substitutable residues alone teaches a POSA towards the claimed "amino acid substitutions at sites 71H and 73H" of claim 76, and "amino acid substitutions at sites 71H, 73H and 78H" of claim 77, given the limited set of residues already targeted for substitution. Ex._1003 at ¶¶290-301. This renders obvious residue 71H (claim 75), 71H and 73H (claim 76), and 71H, 73H and 78H (claim 77).

The substitutability of residues 71H, 73H, and 78H 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 ¶¶287-88. Dr. Hale also cites to antibody 4-4-20 (4Fab), having a cluster of close contacts (less than 3Å) at 73H and 78H, which "emphasizes the relative importance of these contacts made . . . in maintaining antibody conformation." Ex._1003 at ¶280.

Moreover, the typical scenario to a POSA was that more than one framework substitution was often needed to restore function and antigen binding of the resultant humanized antibody. Ex._1003 at ¶295. 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 ¶295. 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 12:13-15; Ex._1003 at ¶295.

Further, a substitution's value can be further limited given the antibody sequence itself. For example, as Dr. Hale explains, and as the patentee did when it compared mouse monoclonal antibody 4D5 sequence[8] and a human consensus AA sequence from Figures 1A and 1B in the '213 patent, *see* Ex._1001 at 7-8, and using the knowledge readily derived from the PDB database and the Queen references, a POSA would have quickly arrived at a short list of light and heavy

[8]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 POSA to obtain the AA sequence of the variable domain through routine protein sequencing. *See, e.g.*, Wilson & Goulding [Ex._1090]; Ex._1003 at n.20. In fact, many sequences present in the Kabat database (Kabat 1987 [Ex._1052]) were obtained through routine protein sequencing. Ex._1003 at n.20, citing to Edelman [Ex._1091]; Capra and Kehoe [Ex._1092].

chain AA 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 ¶¶299-300, Ex._1003C at 649-77 (Hale Exhibits M-O).

Applying Queen Criterion IV, a POSA would have thus targeted claimed residues **71H;73H; 78H** given their differences in size and/or characteristics. *See, e.g.*, Ex._1003 at ¶299 (71H); ¶294 (73H (polar to charged: aspartic acid in human acceptor vs. threonine in mouse 4D5)); ¶293 (78H (small to large: leucine in human acceptor vs. alanine in mouse 4D5)). Thus, a POSA in view of Queen 1989 or Queen 1990 and known available antibody structures on the PDB database, would have been motivated to substitute framework residues at least at **71H;73H;78H** *(i.e.*, claims 75, 76, and 77) for the humanization of mouse 4D5 using a human consensus sequence as the acceptor antibody. *See* Ex._1050 at 14:19-20; Ex._1003 at ¶¶290-301. A POSA 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 ¶¶272-73. Claims 75-77 thus would have been obvious in view of Queen 1989 or Queen 1990, and the PDB database.

8. 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 [CDR] amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a [FR] amino acid substitution," and further requires that the "substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the VL -VH interface by affecting the proximity or orientation of the VL and VH regions with respect to one another...," while reciting a set of FR residues which differ from claim 1 only by *adding* AA 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 substitutable residues that interact with a CDR. *See* §V.G.5, *supra;* Ex._1003 at ¶¶303-07, Ex._1003C at 649-770, 776-77 (Hale Exhibits M and O). Therefore, like claim 1, claim 80 would have been 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 7:36-8, Ex._1003 at ¶308. Thus, claim 81 is obvious over Queen 1989 or Queen 1990, in view of the PDB database.

H. Grounds 3 and 4: Claims 75-77 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 importance of residue **71H** in maintaining CDR conformation. As Dr. Hale explains, a POSA would have been motivated to look in the literature to identify potential framework residues. Ex._1003 at ¶¶28-31. Specifically, Tramontano 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 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 demonstrated the importance of framework residue **71H.** *See* Ex._1051 at Abstract; Ex._1003 at ¶¶135-36, 288-89. This would have motivated a POSA to switch the human residue at position **71H** to the mouse residue in order to preserve the conformation of the H2 CDR loop. *See* Tramontano [Ex._1051]; Ex._1003 at ¶¶288-301. 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, §§V.G.7 *supra*, these claims are further rendered obvious in combination with Tramontano [Ex._1051]. Ex._1003 at ¶¶288-301.

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 ¶¶309-18. As Dr. Hale explains, the '213 patent's claiming a "consensus" sequence is somewhat misleading because the FR sequences "are relatively conserved . . . with respect to both sequence and structure." Ex._1003 at ¶77; *see also* ¶298, citing 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 FR, observing that replacing AA 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 ¶312. From Queen 1989 and Kabat 1987, which provided all consensus AAs at each FR position, a POSA 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 ¶312.

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 FR, a POSA would have incorporated "a consensus" HVD as the FR with a reasonable expectation of success. Ex._1003 at ¶312. Thus, claims 4, 62, 64 and 69 are obvious given Queen 1989, the PDB database and Kabat 1987.

J. <u>Ground 6:</u> Claims 1;2;4;25;29;62-64;66;67;69;71;73;75-78, and 80-81 are anticipated by the '101 patent

1. Independent Claim 1 is Anticipated by the '101 patent

The '101 patent teaches compositions of "humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional AAs from a donor immunoglobulin and a FR from an accepting human immunoglobulin." Ex._1136 at Abstract. Thus, the '101 patent discloses 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" as recited in claim 1 of the '213 patent.

The '101 patent also discloses an antibody "comprising 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;92H, utilizing…Kabat." As discussed above at §V.A, this claiming structure yields a product-by-process claim. *See Purdue Pharma*, 811 F.3d at 1353. (Fed. Cir. 2016). The *Purdue* claim, as the court noted, is directed to the "end product," not a method for creating that product. *Id*. However, because the "derived from 8α[ ]" limitation could not be a structural limitation, it had to be a process limitation. *Id*. Once the Federal Circuit determined that this limitation was a process limitation, the court concluded that it could be disregarded in a patentability analysis, because "[i]n determining validity of a product-by-process claim, the focus is on the product and not the process of making it." *Id*. at 1354.

Claim 1 of the '213 patent presents the same situation as in *Purdue*. As Dr. Hale explains, the *source* of the AA at a particular position in an HVD—whether it occurs there naturally or is deliberately substituted—has no effect on the structure or function of the HVD. Ex._1003 at ¶321. Just like the limitation analyzed in *Purdue*, claim 1's requirement for an AA "substitution" is a process limitation that does not affect the structure or function of a humanized variable domain falling

within its scope. As a process limitation, "substitution" can be disregarded for the purposes of a patentability analysis. Therefore, a prior art antibody prepared without intentional substitutions, but with the same sequence (and thus structure and function) as an antibody prepared according to the claims of the '213 patent, would anticipate those claims. *See Purdue,* 811 F.3d at 1354; *see also In re Thorpe,* 777 F.2d 695, 697 (Fed.Cir.1985) ("If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.").

The '101 patent discloses just such a prior art antibody. As explained in § V.E.3, the '101 patent prepared a humanized CMV5 antibody with substitutions at least at 4L;58L;85L; and 69H. Ex._1003 at 126; Ex._1003C at 780 (Hale Exhibit R). At least residues 4L;58L; and 69H are the same as the corresponding murine residue at those locations.

Thus, the '101 patent did not start with an artificially constructed consensus sequence, and it did not intentionally substitute AAs within the FR of the human Wol antibody for different AA residues. However, as Dr. Hale explains, most of the framework residues in the Wol antibody are the most frequently occurring residues at each location because framework residues are known to be highly conserved. Ex._1003 at ¶ 72. To illustrate this point, Dr. Hale compared the sequence of the Wol antibody with the consensus sequence HUV_HIII (as disclosed

in ’213 patent Fig. 1B). Ex._1003C at 780 (Hale Exhibit R). As can be seen in this comparison, there are both consensus and non-consensus residues in the humanized CMV5 variable domain. However, any differences from the consensus sequence can be considered a “substitution” of the consensus residue for a non-consensus residue, whether or not it was deliberately replaced. Thus, the sequence of the humanized CMV5 variable domain disclosed by the ’101 patent is the same as the sequence of a human consensus variable domain comprising substitutions at least at FR sites 4L;58L;85L; and 69H, according to Kabat and as recited in claim 1. Ex._1003 at 126; *see also* Ex._1003C at 780 (Hale Exhibit R). Because the immunoglobulin disclosed by the ’101 patent could have been prepared by substituting a consensus HVD according to the substitutions recited by claim 1, the ’101 patent anticipates claim 1.

2. The ’101 patent Anticipates Dependent Claims 2, 4, 25 and 29

Claim	**Prior Art**
2: “*wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the nonhuman CDR amino acid residues are obtained*.”	As Dr. Hale demonstrates in Ex._1003C at 780 (Hale Exhibit R),at least residues 4L, 58L, and 93H in the variable domain are the same as the corresponding murine residue at those

	locations. Ex._1003 at 126; *see also* Ex._1136 at Fig. 6A and 6B.
4. *"wherein the human antibody variable domain is a consensus human variable domain."*	As discussed above for claim 1, the '101 patent also discloses the "consensus" HVD.
25. *"wherein the residue at site 69H has been substituted."*	Because framework residue **69H** is not the same as the human consensus sequence as it is in the humanized CMV5 antibody, it meets the "substitution" requirement according to the analysis provided above for claim 1. Ex._1003 at ¶149.
29. ***"****An antibody comprising the humanized variable domain of claim 1."*	The humanized CMV5 antibody constitutes a full antibody with the humanized variable domain of claim 1. Ex._1136 at Example 8; *see also* Ex._1003 at 324.

3. Independent Claim 62 is Anticipated by the ’101 patent

Claim 62 shares claim 1’s FR substitutable residues list, including residues 4L and 69H, but adds residues 46L;75H;76H; and 78H. Claim 62 also differs from claim 1 by adding the phrase, “incorporated into a consensus human variable domain.” Ex._1003 at ¶179. For the reasons the ’101 patent anticipates claims 1 and 4, and because the ’101 patent also discloses substitutions at 75H and 78H, the ’101 patent anticipates claim 62 of the ’213 patent.

4. Independent Claim 63 is Anticipated by the ’101 patent

The ’101 patent teaches that, in contrast to the non-human CMV antibody which leads to significant immunogenicity upon “repeated therapeutic regimens,” the humanized CMV immunoglobulins wil be “substantially non-immunogenic in humans.” Ex. 1136 at 32:40-67. Thus, the humanized CMV5 antibody disclosed by the ’101 patent “lacks immunogenicity compared to a non-human parent antibody,” and the ’101 patent anticipates claim 63.

5. Independent Claim 64 is Anticipated by the ’101 patent

As explained for claims 1, 4 and 29, the ’101 patent discloses an antibody incorporating a humanized variable domain with a consensus sequence (*i.e.*, “most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup”). *See* §§V.J.1 & 2, *supra;* Ex._1003 at ¶¶184-86.

The ’213 patent specifically teaches that “[r]esidues involved with the [V_L-V_H] interface include… 93H.” Ex._1001 at 55:61-62. As Dr. Hale explains, the variable domain disclosed by the ’101 patent includes a substituted FR residue at 93H. Ex._1003 at ¶ 221; Ex._1003C at 780 (Hale Exhibit R). Because the ’101 patent discloses an antibody with a substituted residue that “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 ’101 patent anticipates claim 64.

6. Independent Claim 66 and Dependent Claims 67, 69, 71, 73, and 75-78 are Anticipated by the ’101 patent

Independent claim 66 shares elements with claims 1 and 63, which are met as demonstrated above. *See* §§V.J.1 & 4, *supra;* Ex._1003 at ¶¶154-55. Claim 66’s substitutable AA residues are “selected from the group consisting of: 24H;73H;76H;78H; and 93H,” under Kabat. As the humanized CMV5 antibody disclosed by the ’101 patent substituted residues **73H, 78H**, and **93H**, Ex._1003C at 780 (Hale Exhibit R) and Ex._1003 at ¶¶218, the ’101 patent anticipates claim 66.

Dependent claim 67 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.” As explained *supra* for claim 2, the humanized CMV5 antibody disclosed by the ’101 patent meets this limitation. Accordingly, the ’101 patent anticipates claim 67.

Dependent claim 69 further recites that "the human antibody variable domain is a consensus human variable domain." As explained *supra* for claim 4, the '101 patent meets this limitation. Accordingly, the '101 patent anticipates claim 69.

Dependent claim 71 further recites "wherein the residue at site 73H has been substituted." Dependent claim 73 recites "wherein the residue at site 78H has been substituted." Dependent claim 75 recites "which further comprises an amino acid substitution at site 71H." Dependent claim 76 recites "which further comprises amino acid substitutions at sites 71H and 73H." Dependent claim 77 recites "which further comprises amino acid substitutions at sites 71H, 73H and 78H."

The '101 patent disclosed the substitution of AA residues at least at 71H, 73H, 78H, and 93H. *See* Ex._1136 at Figs. 6A and 6B; Ex._1003C at 780 (Hale Exhibit R) and Ex._1003 at ¶126. Accordingly, and in view of the discussion for claims 1 and 63, *see* §§V.J.1 & 4, *supra*, the '101 patent anticipates dependent claims 71, 73, and 75-77. Ex._1003 at 330-31.

Claim 78, which depends on claim 66, recites "[a]n antibody comprising the humanized variable domain of claim 66." The '101 patent discloses a humanized variable domain based on the human Wol antibody framework sequences. Ex. 1136 at 61:62-67. The humanized variable domain was then incorporated into a full antibody. *Id*. at 63:8-26 (noting that "antibody" was purified using protein A

columns, which only bind antibody constant regions); *see also id*. at 11:18-24 (defining an "antibody" was comprising both variable regions and constant regions). The '101 patent therefore discloses a humanized CMV5 antibody that comprises a humanized variable domain. The '101 patent therefore anticipates Claim 78.

7. Independent Claim 80 and Dependent Claim 81 Are Anticipated by the '101 patent

Claim 80: At least residues at 4L, 58L, 85L, 69H, 73H, 78H, and 93H are substituted in the '101 patent. §§V.J.1 & 4, *supra.* As discussed for claim 64, at least residue 93H "participates in the V_L-V_H interface." The '101 patent thus anticipates claim 80.

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." As explained above for claim 2, this is taught by the '101 patent. *See* §V.J.2, *supra;* Ex._1136 at Figures 6A and 6B (comparing murine CMV5 with humanized CMV5 sequences); Ex._1003 at ¶¶161-64; see also Ex. 1003C at 780 (Hale Exhibit R). Claim 81 is thus anticipated by the '101 patent.

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 is

"insufficient" where, as here, there is a "strong [case] of obviousness". *See 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); *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 breadth of the challenged claims. *See, e.g., Ex Parte Takeshi Shimono*, Appeal 2013-003410 (PTAB Apr. 29, 2015). And secondary considerations are irrelevant to the anticipation arguments set out above. Boehringer 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 that residues important for maintaining CDR conformation and binding were well known prior to June 1991. *See* Ex._1001 at 2:63-67; Ex._1003 at ¶¶342-43. Given the extensive prior art, successful antibody humanization was readily achievable, not surprising or unexpected. Ex._1003 at ¶¶78-88. More specifically, successfully humanizing an antibody using a consensus sequence would also have been expected. Ex._1003 at ¶ 344. As Dr. Hale explains, the residues in the consensus sequence are by definition the ones most commonly found in natural human

antibody variable regions. *Id.* Thus, a POSA would have expected the consensus sequence to be effective across a wide variety of antibodies.

During prosecution, Genentech argued:

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

Ex._1002 at 540.

But Genentech's arguments are not reasonably commensurate with the full scope of the Challenged Claims. *See Ex Parte Takeshi Shimono*, 2015 WL 1952506, at *4 ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims," citing *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)). Only challenged claim 63 even mentions immunogenicity and none recites a method. Ex._1001 at 88:36–38 (claim 63: "humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient"). Claim 63 does not require a "lack of *significant* immunogenicity."

Additionally, the data allegedly showing enhanced (allegedly 3-times more) target binding does not show unexpected improvement. Ex._1003 at ¶ 345. As Dr. Hale explains, the data provided in the '213 patent and provided to the PTO during prosecution is scientifically insufficient to establish any difference in binding at all.

Id. These properties were also not unexpected based on the teachings of the prior art. For example, the '213 patent recognizes with respect to affinity that residues important for maintaining CDR conformation and binding were well known prior to June 1991. *See* Exs. 1001 at 2:63–3:8; 1003 ¶¶110–6, 280, 347–348. Indeed, Queen 1990 taught that an increase in affinity would have been expected. Ex._1050 at 6:26–28 ("[A]ffinity levels can vary…and may be within about 4 fold of the donor immunoglobulin's original affinity to the antigen."). Likewise, prior art such as Panka 1988 also disclosed framework changes that increase binding affinity, and stated that "[t]he finding that a framework mutation can alter binding to antigen is not unexpected. Ex._1135 at 3083.

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, Dr. Hale explains that 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 ¶344-45.

Further, 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) (claims obvious where "[prior art patent] solved similar problems

in a similar way"); *see also In re PepperBall Techs., Inc.*, 469 F. App'x 878, 88283 (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 asserts that the invention could provide methods "for the preparation of antibodies that are less antigenic in humans . . . but have desired antigen binding." Ex._1001 at 3:53-55 and 4:24-35. Queen 1989, Queen 1990 and others had already set forth why one would desire to humanize and provided a detailed roadmap on how to do it. Any problems identified in the '213 specification had already been explicitly addressed and solved by the prior art. Ex._1003 at ¶¶252-67; 344.

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

Any commercial success experienced with Herceptin[9] does not provide any indicia of nonobviousness of the challenged claims of the '213 patent. *First,* any alleged commercial success of Herceptin has no nexus to the challenged claims because none of the heavy chain residues cited in claim 1 are modified in Herceptin. *Second,* any alleged success is not commensurate in scope with the challenged claims because they are not limited to any antibody or class of

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

antibodies. Ex._1003 at ¶346. Therefore, even if Patent Owner can identify one embodiment in its evidence of objective indicia, they will be unable to "demonstrate that untested embodiments falling within the claimed range will behave in the same manner." *Id.* at 4.

Respectfully submitted,

Dated: August 31, 2017

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CERTIFICATE OF WORD COUNT

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 6,407,213 contains 13,928 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: August 31, 2017

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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** and the exhibits cited therein by *Federal Express Next Business Day Delivery* on this day, August 31, 2017 on the Patent Owner's correspondence address of record for the subject patent as follows:

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