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CELLTRION, INC.
Petitioner,
v.

GENENTECH, INC.
Patent Owner.

IPR2017-01374
U.S. 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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EXHIBIT NO.	DESCRIPTION
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)
1124	US Patent No. 5,795,965 *Reshaped human antibody to human interleukin-6 receptor* (claiming priority to April 25, 1991) (Issued August 18, 1998)
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I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Celltrion, Inc. ("Celltrion") petitions for *Inter Partes* Review ("IPR") of claims 1, 2, 4, 12, 25, 29-31, 33, 42, 60, 62–67, 69 and 71–81 of U.S. Patent No. 6,407,213 to Carter, titled "Method for Making Humanized Antibodies" ("the '213 patent," Ex. 1001). With this Petition is a Power of Attorney pursuant to 37 C.F.R. § 42.10(b); and pursuant to 37 C.F.R. § 42.103, the fee set forth in § 42.15(a). The Commissioner is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

The challenged claims are unpatentable because they would have been anticipated by or obvious from prior art that disclosed methods of making humanized antibodies, including the detailed roadmaps in EP0403156 ("Kurrle") [Ex. 1071] and PCT Application No. WO 90/07861 to Queen ("Queen 1990") [Ex. 1050]. The '213 patent's challenged claims are also obvious in view of Furey [Ex. 1125], Chothia & Lesk [Ex. 1062], Chothia 1985 [Ex. 1063] and/or Hudziak [Ex. 1021].

II. MANDATORY NOTICES

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

The real parties-in-interest for Petitioner are Celltrion Inc., Celltrion Healthcare Co. Ltd, and Teva Pharmaceuticals International GmbH.

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

Petitioner is not aware of any litigation related to the ’213 patent. The ’213 patent is related to the following patents: U.S. Pat. No. 6,639,055 (expired, maintenance fee non-payment); U.S. Pat. No. 6,800,738 (expired, maintenance fee non-payment); U.S. Pat. No. 6,719,971 (expired, maintenance fee non-payment); and U.S. Pat. No. 8,075,890.

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

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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 *inter partes* review and cancellation of claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–67, 69 and 71–81 of the ’213 patent under pre-AIA 35 U.S.C. §§ 102 and 103, as Petitioner’s detailed statement of the reasons for the relief requested sets forth below. Under 37 C.F.R. § 42.6(c), Petitioner provides exhibit copies, and the Declarations of Dr. Lutz Riechmann, Ph.D. (Ex. 1003) and Dr. Robert Charles Fredrick Leonard, M.D. (Ex. 1004).

Dr. Lutz Riechmann received his Ph.D. in Biology at the University of Bremen in Germany in 1986. He was a postdoctoral fellow in Sir Greg Winter’s laboratory at the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) in Cambridge, U.K., from 1986–1988, and later acted as Senior Scientific Officer with Sir Greg Winter at the MRC-LMB. The MRC-LMB is a world-class research laboratory and one of the birthplaces of modern molecular biology. Ex. 1003 at ¶2. Many techniques have been pioneered at the laboratory, including the development of monoclonal antibodies. *Id*. His work resulted in numerous publications and patents in this field. *Id*. at ¶7. Dr. Riechmann has also worked as an antibody humanization consultant to many biotechnology companies. *Id*. at ¶5.

Dr. Robert Charles Fredrick Leonard is currently a physician in private practice, focusing on breast cancer oncology care at British United Provident

Association (BUPA) Cromwell Hospital as part of the Imperial College Hospitals group in London, United Kingdom. Dr. Leonard has over 20 years training and clinical practice working with immunological aspects of human cancers, in particular focusing on research and treatment of breast cancer and myeloma, including the use of antibody therapies. Dr. Leonard has published extensively in this field, including several academic studies investigating the use of trastuzumab in breast cancer care.

The challenged claims generally involve humanized antibodies and humanized antibody variable domains. Ex. 1003 at ¶¶38–61. Claims 1, 2, 4,12, 25, 29–31, 33, 42, 60, 62–67, 69 and 71–81 of the ’213 patent are unpatentable as follows:

Ground	**Claims and Basis**
1	Claims 1–2, 25, 29, 63, 66, 71, 75–76, 78, 80–81, anticipated by Kurrle
2	Claims 1–2, 4, 29, 62–64, 80–81, anticipated by Queen 1990
3	Claims 1–2, 4, 25, 29, 62–64, 66–67, 69, 71–72, 75–76, 78, 80–81 as obvious over Queen 1990 and Kurrle
4	Claim 12 obvious over Queen 1990 and Kurrle, and also in view of Furey
5	Claims 73, 74, 77, 79, and 65 as obvious over Queen 1990 and Kurrle, and also in view of Chothia & Lesk and Chothia 1985
6	Claims 30, 31 and 33 as obvious over Queen 1990, in view of Hudziak
7	Claim 42 as obvious over Queen 1990 and Kurrle, in view of Hudziak and Furey
8	Claim 60 as obvious over Queen 1990, in view of Hudziak and Chothia & Lesk

V. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

An inter *partes* review petition must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). As set forth below, this Petition meets and exceeds this threshold.

A. Summary of the Argument

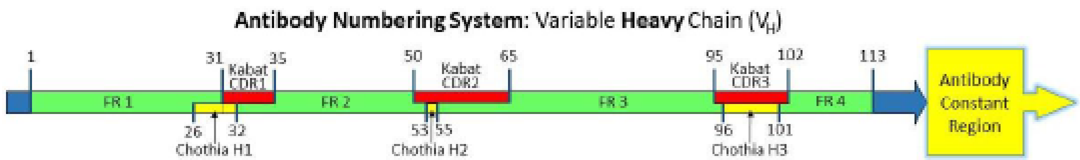
In 1975, the journal *Nature* published Kohler and Milstein's ground-breaking study manufacturing "predefined specific antibodies by means of permanent tissue culture cell lines." Ex. 1022 at 1. Mouse monoclonal antibodies exhibited therapeutic and diagnostic promise, but use in patients resulted in a human anti-mouse antibody (HAMA) immunogenicity response. Ex. 1003 at ¶¶68–70; Ex. 1004 at ¶30.

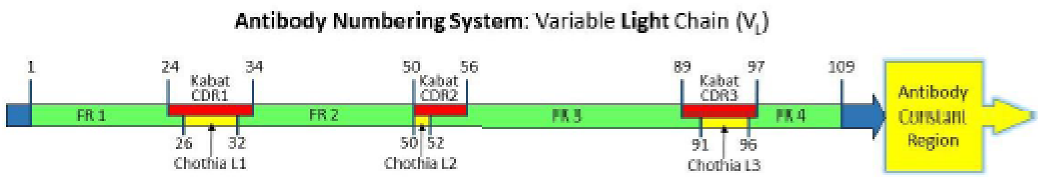
To neutralize the HAMA response, mouse antibodies were first re-engineered to make them "more human" by replacing parts of the mouse antibody with human counterparts. First generation (early 1980s) versions replaced the mouse antibody's constant regions with corresponding human antibody residues. Ex. 1003 at ¶¶87–89; Ex. 1004 at ¶¶33–34. 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 ¶90.

However, because adding human FRs to the regions between the mouse CDRs was known to disrupt binding affinity, the next logical step in the evolution of humanized antibody technology was to switch select residues in the human FRs back to the mouse residues. Ex. 1003 at ¶¶90-109. These techniques were well known and well mapped out prior to the earliest priority date (June 14, 1991) of the '213 patent. *Id.* at 1107. Kurrle [Ex. 1071] is just one example disclosing combining human FRs with mouse CDRs, wherein select residues in the human FRs were switched back to mouse. Kurrle's switched residues include claimed residues **4L**, **69H**, **71H**, **73H** and **76H**. Ex. 1071 at 3:9–10. Kurrle's result was "essentially a human antibody with a much lower immunogenicity in patients." *Id.* at 3, 11–12. Kurrle thus anticipates claims 1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80 and 81. Ex. 1003 at ¶¶144–60.

Queen 1990 established a humanization roadmap with four specific yet universal criteria for producing humanized antibodies from non-human monoclonal antibodies. This included substituting human residues for the mouse monoclonal antibody residue in the FRs "immediately adjacent to one or more of the 3 CDR's in the primary sequence" according to the Kabat numbering system. Queen 1990 [Ex. 1050]. Kabat [Ex. 1052] and Chothia & Lesk [Ex. 1062] had earlier classified the antibody variable domain structure, including defining the boundaries of the Kabat CDRs, the Chothia hypervariable regions and FRs [Ex. 1003 at ¶¶71–89, 133-34; 139-41]:





These defined FR/CDR border positions would have readily allowed a POSA, given Queen 1990's instruction to substitute CDR-adjacent FR residues, to identify at least claimed residues **36H** and **98L** (*see* claims 1, 2, 4, 29, 62, 65, 64, 80 and 81). Queen 1990 thus anticipates at least claims 1, 2, 4, 29, 62, 65, 64, 80 and 81 of the '213 patent. Ex. 1003 at ¶¶161–92.

Moreover, all challenged claims—whether, *e.g.*, they broadly or more specifically list residues or properties, or particular antibodies to humanize—are obvious given the prior art, including Queen 1990; Kurrle; and others. Ex. 1003 at ¶¶193–245; 331–35. A number of prior art references and preeminent researchers in the field taught the importance of specific claimed residues and their predicted contribution to antigen binding, including **93H**, **78H** and **66L**. Ex. 1003 at ¶¶86, 103, 112–19. The inclusion of these specific modifications in the challenged claims thus was not a patentable advance.

The prior art also disclosed both p185^{HER2} as a promising therapeutic target, and a specific monoclonal antibody (4D5) against this target. Celltrion's experts, Drs. Leonard and Riechmann, agree that the next logical and necessary step in the development of 4D5 was humanizing it. Ex. 1003 at ¶¶317–21; Ex. 1004 at ¶¶49–63. Queen 1989 and 1990 provided motivation and a sufficient roadmap to accomplish this humanization. Ex. 1003 at ¶¶322–37. Thus, given Queen 1990 and Kurrle, alone or in combination with other references as detailed below, the challenged '213 patent claims would have been obvious.

B. '213 Patent—Background

1. The '213 Patent

The '213 patent issued June 18, 2002 from a continuation-in-part of an earlier-abandoned U.S. Patent Appl. No. 07/715,272 (filed June 14, 1991). For purposes of this IPR only, Petitioner will assume that the '213 patent 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, 62–64, 66, 79 and 80 are independent claims, and all claim an antibody comprising a "non-human . . . CDR" and a "Framework Region [FR] amino acid substitution" reverting substituted human framework residues back to, *e.g.,* mouse, at "a site selected from the group consisting of" certain recited residues. **Claim 1** chooses from 14 FR light chain residues (4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L); and 10 heavy chain residues (2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H) under Kabat's numbering system. **Claims 30**, **62 and 63** add 4 FR residues to claim 1's list (46L, 75H, 76H and 78H). Claim 30's antibody "binds $p185^{HER2}$ and comprises a humanized antibody variable domain"; and claim 63's humanized antibody "lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient" when treating chronic disease.

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 amino acid substitution: "(a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another."

Claim 64's "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, 25, 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 patent specification's humanization concepts were neither new nor unknown. The patent acknowledges 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" had "increase[d] the antigen binding affinity of a humanized antibody." *Id.* at 3:44–48. The '213 patent applies the same cloning and analysis tools and techniques that Kurrle [Ex.

1071] and Queen 1990 [Ex. 1050] described, including site-directed mutagenesis, molecular modeling, and antibody functionality analysis. The ’213 patent likewise recognizes the known promise of p185^{HER2} monoclonal antibody (4D5) as a therapeutic anticancer agent that may be “immunogenic in humans.” *Id.* at 3:56–4:23.

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.

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[1] would have held a Ph.D. or equivalent in chemistry, biological chemistry, structural biology or a closely related field, or an M.D. with practical academic or industrial experience in antibody development, including humanization of antibodies for therapeutic development and use in humans and/or antibody structural characterization and engineering. *See, e.g.,* Ex. 1003 at ¶¶24–26. Such experience can 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

[1] 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.

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 in which it appears." 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.[2]

"A Humanized Antibody Variable Domain" (Claims 1, 62 and 80), "An antibody" (Claim 30) or "A Humanized Antibody" (Claim 63), "A Humanized Variant of a Non-Human Parent Antibody" (Claims 64 and 79) or "A Humanized Antibody Heavy Chain Variable Domain" (Claim 64). The independent claims of the '213 patent each contain a variation of the preamble phrase, "A Humanized Antibody" set forth above.[3] A POSA would understand "a humanized antibody" to include an antibody or antibody fragment that has been

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

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

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, 30, 62, 63, 66, 79 and 80 of the '213 patent include a Markush Group list of amino acid residues from which a framework region substitution is chosen. Markush Group members are accorded functional equivalency status for purposes of claim construction. *See Ecolochem, Inc. v. Southern California Edison Co*., 91 F.3d 169 (Fed. Cir. 1996) ("By claiming a Markush group ... members of the group are functionally equivalent") (citing *Application of Skoll*, 523 F.2d 1392 (C.C.P.A. 1975)). As none of the claims are limited to a specific antibody, and all Markush Group members are functional equivalents of each other, the broadest reasonable interpretation to a POSA would be that any of the recited residues can be equally substituted for any given antibody.

"***Numbering System Set Forth in Kabat***".   Independent claims 1, 30, 62, 63, 66, 79 and 80 of the '213 patent include the limitation "utilizing the numbering system set forth in Kabat." The '213 patent specifically ties its numbering system to two references: "Kabat, E.A. *et al*., *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md.) (1987) and (1991)". *See* Ex. 1001 at 10:45–49. As noted above, the Kabat 1987 [Ex. 1052] and Kabat 1991

[Ex. 1055] data derive from a database of publicly available antibody sequences, formatted to display the sequences in alignment with each other and in a numerical sequence order. Kabat 1987 and 1991 also show boundaries of known antibody regions, including the three CDRs and four FRs in each antibody chain variable domain. The broadest reasonable construction, "utilizing the numbering system set forth in Kabat," encompasses the Kabat 1987 and Kabat 1991 designations,[4] including the amino acid residue positions set forth in Kabat, but also including the boundary designations for CDR and FR structures.

"***Up To 3-Fold More***". The '213 patent's claim 65 limits independent claim 63 further to a "humanized variant . . . bind[ing] the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." The broadest reasonable interpretation of this claim includes all binding affinity values "up to" 3-fold more, *i.e.*, any value no matter how small and greater than zero "up to" 3-fold more.

E. Patents and Printed Publications Relied On In This Petition

Petitioner relies on the following patents and printed publications:

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

1. EP 0403156 (“Kurrle”) [Ex. 1071]

Kurrle, published on December 19, 1990, detailed the humanization of a mouse monoclonal antibody (BMA 031) against the human alpha/beta T-cell receptor. Ex. 1071 at Abstract. Kurrle provided guidance to a POSA regarding further refinement of the variable domain FR region, making “essentially a human antibody with a much lower immunogenicity in patients.” *See id.* at 3:8–12 (“A further refinement involves humanization of the variable regions. Only the complementarity determining regions *and selected framework amino acids necessary for antigen binding* are maintained murine. The remaining framework regions are converted to human sequences.”) (Emphasis added).

Kurrle taught that the four amino acids on either side of a CDR contribute to antibody binding:

> “Molecular models of antibodies have shown that the actual CDR loops can contain amino acids up to 4 amino acids away from the ‘Kabat’ CDRs. Therefore, maintaining at least the major amino acid differences (in size or charge) within 4 amino acids of the CDRs as murine may be beneficial.”

Kurrle [Ex. 1071] at 8:27–29. Kurrle taught such “differences within 4 amino acids” should be “maintained murine.” *Id.* at 8:28–31. Kurrle further recommended using a simplified computer model based on sequence homology with solved antibody structures to judge the proximity of framework amino acid residues with the CDRs. *Id.* at 8:32–36. Existing human framework residues could be switched to a consensus human residue at such positions. *Id.* at 8:38–46.

Applying one or more such criteria, Kurrle made four humanized versions of their antibody (CIV-1, CIV-2, CIV-3 and CIV-4), each time substituting select FR residues in the human antibody for the corresponding residue in the non-human (mouse) antibody. *See id.* at Tables 6A and 6B.[5] Using their roadmap, Kurrle made several FR substitutions in the light and heavy chain, including at positions **4L**, **69H**, **71H**, **73H** and **76H**. *See* Ex. 1003C at 4–7 (Riechmann Exhibit B), ¶¶144–60. The ’213 patent claims these very residue substitutions. *Id*.

2. Queen 1990 [Ex. 1050]

Queen 1990 is a PCT application filed December 28, 1989, and published July 26, 1990. Queen 1990 advanced Queen 1989’s [Ex. 1034] methodology,

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[5]Dr. Riechmann notes that Kurrle did not use the Kabat numbering convention in Tables 6A and 6B for the antibody heavy chain. Ex. 1003 at n.4. To follow ’213 patent’s numerical convention of the “numbering system set forth in Kabat,” Dr. Riechmann included a list of the amino acid sequences in Table 6A (heavy chain) with the Kabat 1987 numbering system [Ex. 1052] in Ex. 1003C at 4-7 as Riechmann Exhibit B.

providing four explicit criteria for humanizing non-human antibodies. Queen 1990 Criterion I relates to the choice of the acceptor 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.

Also like Queen 1989, Queen 1990 teaches 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 15:21–37. The prior art thus knew maintaining highly conserved residues was important to minimize immunogenicity. Ex. 1003 at ¶¶118, 123.

Queen 1990 Criterion III also 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 [mouse] 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 [human] acceptor, to distort the donor CDR's and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen (Amit *et al*., *Science*, 233, 747–53 (1986), which is incorporated herein by reference) and selecting these amino acids from the [mouse] donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.

Id. at 16:1–12. Kabat and Chothia identified the CDR boundaries, both in sequence and structurally. Residues "immediately adjacent" to Kabat's CDRs are limited: 30H, **36H**, 49H, 66H, 94H, 103H in the heavy chain; and 23L, 35L, 49L, 57L, 88L, and **98L** in the light chain; residues "immediately adjacent" to Chothia's hypervariable regions include: 25L, 33L, 49L, 53L, 90L, 97L, 25H, 33H, 52H, 56H, 95H and 102H. '213 patent claims include **36H** and **98L**. Kabat 1987 [Ex. 1052]; Ex. 1003 at ¶¶161-71.

Queen 1990 placed further limitations on the molecular modeling criteria Queen 1989 established, calling for pinpointing framework residues that possess an atom that is within about 3Å of a CDR atom and thus likely to make a CDR contact:

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

Id. at 16:14–31 (citations omitted). Queen 1990 further teaches deriving these "contact" residues from known antibody structures. *Id.* Such framework residues are more likely to be important in influencing how CDRs interact with the antigen.

3. Furey [Ex. 1125]

Well prior to Queen and Kurrle's humanization efforts, Furey *et al.* established the structural importance of framework residues that established tight hydrogen bonding with hypervariable (CDR) residues, including at claimed position **66L** in the light chain variable domain, to maintain CDR2 conformation. Ex. 1125 at Table 4. Furey therefore taught well before the alleged priority date that claimed VL chain residue **66L** contacted CDR2 residues via hydrogen bonds, and thus was a potential candidate for substitution according to the teachings of Kurrle and Queen 1990.

4. Chothia & Lesk [Ex. 1062]

Chothia & Lesk also established certain residues important for maintaining antibody structure, disclosing that "[t]he major determinants of the tertiary structure of the framework are the residues buried within and between the [V_L and V_H] domains," [Ex. 1062 at 4] summarized in Table 4 (reproduced below):

Table 4
Residues commonly buried within V_L and V_H domains

V_L domains			V_H domains		
Position	Residues in known structures	A.S.A.[a] (Å^2)	Position	Residues in known structures	A.S.A.[a] (Å^2)
4	L,M	6	4	L	14
6	Q	12	6	Q,E	16
19	V	11	18	L	21
21	I,M	1	20	L	0
23	C	0	22	C	0
25	G,A,S	13	24	S,V,T,A	8
33	V,L	3	34	M,Y	4
35	W	0	36	W	0
37	Q	30	38	R	13
47	L,I,W	8	48	I,V	1
48	I	24	49	A,G	0
62	F	11	51	I,V,S	4
64	G,A	13	69	I,V,M	13
71	A,F,Y	2	78	L,F	0
73	L,F	0	80	L	0
75	I,V	0	82	M,L	0
82	D	4	86	D	2
84	A,S	11	88	A,G	3
86	Y	0	90	Y	0
88	C	0	92	C	0
90	A,S,Q,N	7	104	G	11
97	V,T,G	18	106	G	19
99	G	3	107	T,S	17
101	G	11	109	V	2
102	T	1			
104	L,V	2			

[a] Mean accessible surface area (A.S.A.) of the residues in the Fab structures NEWM, MCPC603, KOL and J539 and in the V_L structures REI and RHE.

Id. at 7, Table 4. These residues, which maintain tertiary structure (immunoglobulin chain interactions) of the framework, overlap with important CDR contact residues already disclosed in the prior art as well as known highly conserved residues, *see* Ex. 1003 at ¶¶138-40, n.11, narrowing the list of substitutable residues significantly. Such residues—including claimed residues **4L**, **62L**, **73L**, **4H**, **36H**, **69H**, **78H** and **92H**—constitute potential substitution candidates under Kurrle and Queen 1990. *Id*.

5. Chothia 1985 [Ex. 1063]

Chothia 1985 disclosed "buried" residues involved in the "packing of the VL and VH (β-sheets in the conserved 'framework'. . .." Chothia 1985 at Abstract [Ex. 1063 at 2]. "When the VL and VH domains pack together, residues from these edge strands form the central part of the interface and give what we call a three-layer packing; *i.e.* there is a third layer composed of side-chains inserted between the two backbone side-chain layers that are usually in contact. *The 12 residues that form the central part of the three observed VL-VH packings are absolutely or very strongly conserved in all immunoglobulin sequences*." *Id.* (emphasis added). One of the buried residues in the VL-VH interface disclosed by Chothia 1985 includes claimed residue **93H**. *See* Chothia 1985 at Table 4 [Ex. 1063].

6. Hudziak [Ex. 1021]

Hudziak published in March 1989, confirming $p185^{HER2}$'s role in carcinoma development. Ex. 1021 at Abstract. Hudziak had earlier correlated $p185^{HER2}$ gene amplification and carcinoma development, showing high $p185^{HER2}$ levels correlated to negative prognoses and high relapse probability; and amplifying $p185^{HER2}$ *in vitro* created resistance to cytotoxic (TNF-α) treatment. *Id.* Hudziak "prepared monoclonal antibodies against the extracellular domain of $p185^{HER2}$..." and chose "[o]ne monoclonal antibody (4D5)," which "was characterized in more detail and was shown to inhibit in vitro proliferation of human breast tumor cells overexpressing $p185^{HER2}$ and, furthermore, to increase the sensitivity of these cells to the cytotoxic effects of TNF-α." *Id.* In growth inhibition studies, "[*m*]*aximum inhibition* was obtained with monoclonal antibody 4D5, which inhibited cellular proliferation by 56%." *Id.* (emphasis added). Hudziak confirmed that "the combination of TNF-α and monoclonal antibody 4D5 reduced the [listed] tumor cell number to a level below that initially plated," and "indicated the induction of a cytotoxic response." Ex. 1021 at 6.

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

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

Hudziak, Table 1 [Ex. 1021 at 4]. Hudziak concluded that "[m]onoclonal antibodies specific for p185^{HER2} may therefore be useful therapeutic agents for the treatment of human neoplasias, including certain mammary carcinomas, which are characterized by the overexpressing of p185^{HER2}." Ex. 1021 at 7.

F. The Prior Art Renders the Challenged Claims Obvious

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

Multiple research institutions—including Genzyme Corp. [Ex. 1071], Protein Design Labs [Ex. 1050], the Medical Research Council [Ex. 1069], and the National Institutes of Health, among others—published before the '213 patent's filing date efforts to humanize antibodies to avoid the immunogenic reactions observed with non-human monoclonal antibody therapeutics. *See* Ex. 1071 at 3:8–12; Ex. 1050 at Abstract; Ex. 1003 at ¶93; Ex. 1004 at ¶37. The field recognized that earlier efforts (*e.g.*, chimeric antibodies, CDR grafting) often resulted in non- or poor binding, with immunogenicity remaining a concern. *See* Ex. 1050 at 5:30–33; Ex. 1073 at 9:12–19; Ex. 1003 at ¶¶87–90; Ex. 1004 at ¶33–34.

Queen 1990 detailed the importance of preserving certain mouse framework positions in the resulting humanized antibody to maintain CDR conformation and antigen binding. Ex. 1050 at 16:2, 14–15. The prior art, thus, already provided detailed pathways to humanize 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 ¶¶92–109.

Kurrle used similar logic, replacing several human FR sites with mouse residues within the variable region of the light and heavy chains. Ex. 1071 at Tables 6A and 6B; Ex. 1003 at ¶¶110–13.

Simply put, many scientific research groups were making "humanized antibodies" more than a year prior to the '213 patent's earliest filing date and publishing detailed instructions for doing the same. The prior art demonstrates that modification and humanization as claimed in each challenged claim was not only anticipated, but obvious.

G. <u>Ground 1</u>: Claims 1, 2, 25, 29, 63, 66, 71, 75, 76, 78, 80 and 81 Are Unpatentable as Anticipated by Kurrle

1. Independent Claim 1 is Anticipated by Kurrle

Independent claim 1 of the '213 patent recites "[a] humanized antibody variable domain comprising," the elements (1) "non-human [CDR] amino acid residues which bind an antigen incorporated into a human antibody variable domain," and (2) FR substitutions 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."

The "humanized antibody variable domain" element is disclosed in Kurrle, which taught "humanised and civilised versions of [mouse monoclonal] antibodies." Ex. 1071 at Abstract; Ex. 1003 at ¶¶110–13,145. Kurrle also disclosed "non-human [CDR] amino acid residues which bind an antigen" and "a [FR] amino acid substitution" incorporated into a human antibody variable domain, referring to the "civilised" antibodies as those where "[o]nly *the complementarity determining regions and selected framework amino acids* necessary for antigen binding are maintained *murine*." Ex. 1071 at 3:9–12 (emphasis added); Ex. 1003 at ¶145.

Kurrle substituted several corresponding murine amino acids for human framework residues under Kabat's numbering system, including **4L** and **69H**, as found in claim 1. *See* Ex. 1071 at 25, 26, Tables 6A and 6B; Ex. 1003C at 4–7 (Riechmann Exhibit B), ¶¶144–47. 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. Therefore, claim 1 is anticipated.

2. Kurrle Anticipates Dependent Claims 2, 25 and 29

Claim 2: Claim 2 depends on claim 1, 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 precisely what Kurrle did. *See* Ex. 1071 at 8:45–47 ("In one position (#93) the human consensus sequence is the same as [in the mouse sequence]. One could rationalize changing [the human acceptor antibody residue] back to [mouse], so this change was incorporated..."). This is a basic step in the humanization process as taught by Kurrle. *See* Ex. 1003 at ¶148. Claim 2 is thus also anticipated by Kurrle.

Claim 25: Claim 25 depends on claim 1, and further recites "wherein the residue at site 69H has been substituted." Because framework residue **69H** was substituted with the murine residue in Kurrle's humanized anti-T-cell receptor antibody, *see* claim 1 (§V.G.1), Kurrle anticipates claim 25. Ex. 1003 at ¶149.

Claim 29: Claim 29 also depends on claim 1, and further recites "[a]n antibody comprising the humanized variable domain of claim 1." Kurrle's explicit goal was to create an antibody comprising the humanized variable domain: "The resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients." Ex. 1071 at 3:9–12; *see also* 2:2–4; Ex. 1003 at ¶150. Kurrle anticipates Claim 29.

3. Independent Claim 63 is Anticipated by Kurrle

Claim 63 of the ’213 patent is drawn to an antibody with structural components substantially identical to those of claim 29, *i.e.*, the same “humanized antibody” incorporating the same claimed non-human CDRs and completely overlapping substituted framework residues as in claim 1. *See* §V.G.2, *supra*. Accordingly, because the structural components are the same, the same function (*i.e.*, “which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient to treat a chronic disease in that patient”) is also present. *See Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (“[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art’s functioning, does not render the old composition patentably new to the discoverer.”); Ex. 1003 at ¶¶151–53.

Not only is this an inherent aspect of the claimed humanized antibodies, this is in fact an explicitly stated goal of all antibody humanization projects. *See* Ex. 1071 at 3:8–12 (“A further refinement involves humanization of the variable regions ... [T]he resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients.”); Ex. 1003 at ¶¶152–53. Because this is simply a statement of the intended result of the claimed composition, this should not be a limitation of the claims. *Bristol-Myers Squibb*

Co. v. BenVenue Labs, Inc., 246 F.3d 1368, 1375-76 (Fed. Cir. 2001). Nonetheless, one of ordinary skill in the art would thus know that Kurrle's humanized antibodies would also "lack immunogenicity compared to a non-human parent antibody upon repeated administration ….". Claim 63 is anticipated.

4. Independent Claim 66 and Dependent Claims 71, 72, 75 and 76 are Anticipated by Kurrle

Independent claim 66 shares elements with claims 1 and 63, which are met as demonstrated above. *See* §§V.G.1 & 3, *supra*; Ex. 1003 at ¶¶154–55. Claim 66's substitutable amino acid residues are "selected from the group consisting of: 24H, 73H, 76H, 78H, and 93H," under Kabat's numbering system. As Kurrle substituted residues **73H** and **76H**, Ex. 1003C at 4–7 (Riechmann Exhibit B) and Ex. 1003 at ¶¶154–55, it anticipates claim 66.

Dependent claims 71, 72, 75 and 76 recite "wherein the residue at site 73H has been substituted" (claim 71), "wherein the residue at site 76H has been substituted" (claim 72), "which further comprises an amino acid substitution at site 71H" (claim 75), and "which further comprises amino acid substitutions at sites 71H and 73H" (claim 76). Kurrle disclosed the substitution of amino acid residues **71H**, **73H** and **76H** in their humanized anti-T-cell receptor monoclonal antibody. *See* Ex. 1071 at Table 6B; Ex. 1003C at 4–7 (Riechmann Exhibit B) and Ex. 1003 at ¶156. Accordingly, and in view of the discussion for claims 1 and 63, *see*

§§V.G.1 & 3, *supra*; Ex. 1003 at ¶¶144–47, 154–56, Kurrle anticipates dependent claims 71, 72, 75 and 76.

5. Independent Claim 80 and Dependent Claim 81 Are Anticipated by Kurrle

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." Claim 80 further recites 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 V_L and V_H regions with respect to one another . . . ." Claim 80 then recites a list of substitutable amino acid residues that differ from claim 1 by adding amino acid residues 73H, 76H, 78H and 93H to the list. As with claims 1 and 63, residues **4L** and **69H**, and additional residues **73H** and **76H** are substituted in Kurrle. §§V.G.1 & 3, *supra*.

The additional recited elements, which are noted functions of the substituted residues, do not add anything new to the claim. *See* claim 63, §V.G.3; Ex. 1003 at ¶¶157–58; *see also Atlas Powder*, 190 F.3d at 1347. Even if the inherency of these functions were discounted (they should not be), Kurrle explicitly teaches interaction of the framework residues with the CDR as a reason for substitutability. *See* Ex. 1071 at 8:28–29 and 32–40 (use of a "simplified computer model" to determine whether or not FR residues were close enough to CDRs to influence binding); Ex. 1003 at ¶¶110–13, 158. Accordingly, Kurrle at least teaches substitution of a framework residue that "interacts with a CDR," *i.e.*, limitation "(b)" from claim 80, and therefore 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." This is taught by Kurrle. *See* §V.G.2, *supra*; Ex. 1071 at Tables 6A and 6B; Ex. 1003 at ¶¶157–60. Claim 81 is thus also anticipated by Kurrle.

H. Ground 2: Claims 1, 2, 4, 29, 62, 63, 64, 80 and 81 are Anticipated by Queen 1990

1. Independent Claim 1 is Anticipated by Queen 1990

The first part of claim 1, "[a] humanized antibody variable domain," is disclosed in Queen 1990. Queen's stated goal was creating "a humanized antibody variable domain" by not only swapping CDRs, but also manipulating the framework region of the variable domain, as claim 1 of the '213 patent recites. Queen explicitly provides for "novel methods for designing humanized immunoglobulins having one or more complementarity determining regions (CDR's) from a donor immunoglobulin and a framework region from a human immunoglobulin...." Ex. 1050 at Abstract; Ex. 1003 at ¶162. Queen 1990 provides a detailed roadmap with specific criteria used in designing humanized immunoglobulins. Ex 1050 at 14:9-15 Ex. 1003 at ¶¶162–71, 145–53. Queen 1990 emphasized the importance of framework positions adjacent to the CDR: "Each humanized immunoglobulin chain may comprise about 3 or more amino acids from the donor immunoglobulin in addition to the CDR's, ***usually at least one of which is immediately adjacent to a CDR in the donor immunoglobulin***." Ex. 1050 at Abstract. The POSA can readily envision such locations. *See* Ex. 1003 at ¶¶166–68.

Queen 1990 encapsulated this rule in Criterion III, which states:

> 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 [mouse] amino acid(s) rather than acceptor [human] amino acid may be selected. These amino acids are particularly likely to interact with the amino acids in the CDR's and ... [m]oreover, 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.

Ex. 1050 at 16:1–12 (emphasis added, citations omitted); Ex. 1003 at ¶166.

Celltrion's expert, Dr. Riechmann, explained that "one of ordinary skill in the art at the time of the '213 patent… would have readily understood that Queen 1990 (specifically Criterion III) explicitly taught the substitution of framework sites **immediately adjacent** to CDRs." Ex. 1003 at ¶167. Using the numbering system set forth by Kabat 1987,[6] the "immediately adjacent" framework residues to CDRs as taught by Queen 1990 and recited in claim 1 include **98L** and **36H**. *See* Ex. 1003C at 8–9 (Riechmann Exhibit C) and Ex. 1003 at ¶¶161–71; § V.E.2, *supra*.

Thus, Queen 1990's explicit teaching to substitute CDR-adjacent framework region amino acid positions would inevitably include substitutions at the claimed amino acid residues of **98L** and **36H**. 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 1990 thus anticipates claim 1.

2. Queen 1990 Anticipates Dependent Claims 2, 4 and 29

Claim 2: Claim 2's additional limitation "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" is also disclosed by Queen 1990. *See* Ex. 1050 at 7:36–8:1 ("substitutions of a human framework amino acid of the acceptor (*i.e.*, human) immunoglobulin with a corresponding

[6] While Dr. Riechmann uses the Kabat 1987 reference for designating the amino acid positions according to the Kabat numbering system, there were "no meaningful differences in the Kabat numbering system, including the CDR boundaries, between Kabat 1987 and Kabat 1991." Ex. 1003 at n.5.

amino acid from a donor (*i.e.*, non-human) immunoglobulin"); Ex. 1003 at ¶172. Queen 1990 anticipates claim 2.

Claim 4: Claim 4 depends on claim 1, and further recites "wherein the human antibody variable domain is a consensus human variable domain." Queen 1990 expressly teaches this by disclosing in Criterion I that "[a]s acceptor,... use ***a consensus framework*** from many human antibodies." *See* Ex. 1050 at 14:17–20 (Criterion I); Ex. 1003 at ¶¶121, 173. Queen 1990 anticipates claim 4.

Claim 29: Claim 29 depends on claim 1, and further recites "[a]n antibody comprising the humanized variable domain of claim 1." As Dr. Riechmann explains, the goal of antibody humanization programs was to create a humanized variable domain. *See*, *e.g.*, Ex. 1050 at 6:21–25 ("mouse complementarity determining regions, with or without additional naturally-associated mouse amino acid residues, can be used to produce human-like antibodies . . . ."); Ex. 1003 at ¶174. A POSA would thus recognize that Queen's aim was to create therapeutic-quality antibodies with a humanized variable domain to maintain a high level of binding and affinity. Ex. 1003 at ¶174. Queen 1990 anticipates claim 29.

3. Independent Claim 62 is Anticipated by Queen 1990

Claim 62 shares claim 1's FR substitutable residues list, including residues 98L and 36H, but adds residues 46L, 75H, 76H and 78H. As discussed above for claim 1, *see* §V.H.1, *supra*, Queen 1990 discloses residues **98L** and **36H** as also inevitably requiring substitution.

Claim 62 also differs from claim 1 by adding the phrase, "incorporated into a consensus human variable domain." Ex. 1003 at ¶175. Queen 1990 also disclosed in Criterion I that "[a]s acceptor,... use ***a consensus framework*** from many human antibodies." *See* Ex. 1050 at 14:17–20; Ex. 1003 at ¶176; §V.H.2, *supra*. Queen 1990 thus anticipates claim 62 of the '213 patent.

4. Independent Claim 63 is Anticipated by Queen 1990

Claim 63 differs from claim 62 (incorporating into the claimed "antibody" the "humanized variable domain" comprising the recited CDRs and substituted FR residues from claim 1) by further describing the claimed humanized antibody as lacking "immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient."

As above, this is a non-patentable distinction. *See* §V.G.3, citing to *Atlas Powder*, 190 F.3d 1342; Ex. 1003 at ¶178. As simply a statement of the intended result of the claimed composition, this should not be a limitation of the claims. *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Nonetheless, Queen 1990 explicitly taught this goal: "When combined into an intact antibody, the humanized immunoglobulins of the present invention *will be substantially non-immunogenic* in humans..." Ex. 1050 at Abstract; Ex. 1003 at ¶178–79. Claim 63 is also anticipated by Queen 1990.

5. Independent Claim 64 is Anticipated by Queen 1990

Claim 64 recites "a humanized variant of a non-human parent antibody which binds an antigen; comprising 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 Framework Region 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 VH regions with respect to one another." (Emphasis added).

Queen 1990 anticipates claim 64. As with claims 1, 4 and 29, Queen 1990 disclosed 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.H.2 & 3, *supra*; Ex. 1003 at ¶¶185–87; Ex. 1050 at 14:17–20 ("As acceptor, ... use ***a consensus framework*** from many human antibodies.").

While the remaining limitations are merely stated functions of the humanized antibody, *see* §V.G.3, *supra*, Queen 1990 also disclosed at least functions (a) and (b) above in Criterion III:

> Immediately adjacent... amino acids 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 ... and selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.

Ex. 1050 at 16:1–12 (emphasis added); Ex. 1003 at ¶187. Because Queen 1990 teaches one to substitute "immediately adjacent" residues **98L** and **36H**, *see* §V.H.1 *supra*, and because Queen 1990 teaches that those residues "are particularly likely to interact with the amino acids in the CDR's and ... may interact directly with the antigen," Queen 1990 anticipates claim 64. Ex. 1003 at ¶¶185–87.

6. Claims 80 and 81 are Anticipated by Queen 1990

Claim 80: Claim 80 is also anticipated by Queen 1990. As discussed with claims 1 and 64, Criterion III of Queen 1990 explicitly teaches the selection of framework residues immediately adjacent to CDRs for substitution—this would include claimed residues **36H** and **98L**. *See* §§V.H.1 & 5, *supra*; Ex. 1003C at 8–9 (Riechmann Exhibit C) and Ex. 1003 at ¶¶188–91 (citing Ex. 1050 at 16:4–8).

Queen 1990 explains that "selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody." Ex. 1050 at 16:10–12; Ex. 1003 at ¶189.

Moreover, Criterion IV in Queen 1990 teaches "interact[ion] with a CDR" by disclosing 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." Ex. 1050 at 16:15–19; Ex. 1003 at ¶190. Given that, Queen 1990 anticipates Claim 80.

<u>Claim 81</u>: Claim 81 (which depends on claim 80) is also taught by Queen 1990, which disclosed "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." *See* Ex. 1050 at 7:36–8:1; Ex. 1003 at ¶192. Claim 81 is also anticipated by Queen 1990.

I. <u>Ground 3</u>: Claims 1, 2, 4, 25, 29, 62–64, 66–67, 69, 80 and 81 Are Unpatentable As Obvious over Queen 1990 and Kurrle

1. Claim 1 is Obvious Over Queen 1990 and Kurrle

Queen 1990 disclosed to a POSA a detailed pathway for humanizing non-human monoclonal antibodies, with the expectation that the antibodies "will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen …," including:

- Criterion I: Choose an acceptor human framework antibody, including one that is "unusually homologous to the donor immunoglobulin to be humanized, or use a consensus framework from many human antibodies." Ex. 1050 at 14:17–15:20; Ex. 1003 at ¶¶121, 196;
- Criterion II: Once the human antibody is selected, evaluate whether amino acid residues in the framework of the human acceptor antibody are "rare" amongst human antibodies. If the residue is "rare" and the donor [mouse] antibody is more "typical for human sequences," choose the donor residue. Criterion II "helps ensure that an atypical amino acid in the human framework does not disrupt the antibody structure." Ex. 1050 at 15:22–37; Ex. 1003 at ¶¶122–23, 196;
- Criterion III: "In the positions immediately adjacent to the 3 CDR's in the humanized immunoglobulin chain, the donor [mouse] amino acid rather than acceptor [human] amino acid may be selected." Ex. 1050 at 15:1–12; Ex. 1003 at ¶¶124, 196; and
- Criterion IV: Generate a 3-dimensional model of the original donor antibody, and select amino acid positions where:

> [C]ertain 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 .... 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.

Ex. 1050 at 16:14–17:2; Ex. 1003 at ¶¶125, 196.

Queen 1990 concludes that when the humanized variable regions are "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 immunoglobulin to the antigen...." Ex. 1050 at 8:21–26; Ex. 1003 at ¶197. Queen 1990 thus provided "the explicit motivation to follow these steps to obtain a monoclonal antibody that can be used in human therapeutics." Ex. 1003 at ¶197.

Kurrle employed a similarly detailed roadmap to obtain a "humanized antibody variable domain" as claimed in claim 1, including the steps of: choosing the most similar human acceptor sequence (Criterion I of Queen 1990; *see* Ex. 1071 at 8:16–18), accounting for the adjacent residue rules of Queen 1990 (Criterion III of Queen 1990; *see* Ex. 1071 at 8:25–31), substituting CDR-contact residues using computer models based on solved structures (Criterion IV of Queen 1990; *see* Ex. 1071 at 8:32–36) and substituting "rare" amino acids in the human acceptor framework for "common" (consensus) amino acid residues (Criterion II of Queen 1990; *see* Ex. 1071 at 8:36–40). Ex. 1003 at ¶¶110–13, 198.

Using these guidelines, Kurrle made a total of 13 substitutions in the light chain framework region and 18 substitutions in the heavy chain framework region according to the Kabat numbering system, including claimed residues **4L** and **69H**. *See* §§V.E.1 & G.1, *supra*; Ex. 1003C at 4–7 (Riechmann Exhibit B), Ex. 1003 at ¶¶144–47, 199.

A POSA would have been motivated to combine the teachings of Queen 1990 and Kurrle because of the similarity in the approaches implemented in these references and to improve on the successes of both. Ex. 1003 at ¶¶199-200. The combination of Queen 1990 and Kurrle thus provided ample motivation and a reasonable expectation of success that a humanized monoclonal antibody could be obtained with "a much lower immunogenicity in patients", Ex. 1071 at 3:11–12, while maintaining the binding affinity and specificity of the donor monoclonal antibody, and targeted the very species residues satisfying the claim 1 genus. Claim 1 is obvious over Queen 1990 in view of Kurrle. Ex. 1003 at ¶¶196–200.

2. Claims 2, 25 and 29 are Obvious Over Queen 1990 and Kurrle

Claim 2: Claim 2 is also taught by Queen 1990 and Kurrle. As discussed, this is a basic step in humanization, followed by many in the field, including Queen (Ex. 1050 at 7:36–8:1) and Kurrle (Ex. 1071 at 8:28–29). *See* §V.G.2 *supra*; Ex. 1003 at ¶201. Claim 2 is obvious over Queen 1990 and Kurrle.

<u>Claim 25</u>: Claim 25 depends on claim 1, and further recites "wherein the residue at site 69H has been substituted." Residue 69H was substituted in Kurrle's humanized anti-T-cell receptor antibody. *See* §§V.G.1 & 2, *supra*; Ex. 1003 at ¶202. Accordingly, claim 25 is also obvious over Queen 1990 and Kurrle.

<u>Claim 29</u>: Claim 29 depends on claim 1, and further recites "[a]n antibody comprising the humanized variable domain of claim 1." The explicit goals of Queen 1990 and Kurrle was to create antibodies comprising a humanized variable domain: "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 immunoglobulin to the antigen." Ex. 1050 (Queen 1990) at 8:21–26; *see also* Ex. 1071 (Kurrle) at 3:26–28 and 2:2–4; Ex. 1003 at ¶203. Claim 29 is also obvious over Queen 1990 in view of Kurrle.

3. Claim 4 is Obvious Over Queen 1990 and Kurrle

Claim 4, which depends from claim 1, recites: "wherein the human antibody variable domain is a consensus human variable domain." Queen 1990 teaches the use of a human consensus variable domain as the human acceptor framework antibody, *see* Ex. 1050 at 14:17–20 ("As acceptor ... use a consensus framework from many human antibodies."), which would have motivated a POSA to use the human "acceptor" framework together with the humanization methods of Kurrle. Ex. 1003 at ¶¶121, 204. Claim 4 is also obvious over Queen 1990 and Kurrle.

4. Claim 62 is Obvious Over Queen 1990 and Kurrle

Claim 62 differs from claim 1 by adding that the human variable domain is a "consensus human variable domain." *See* §§V.B.1 & I.1 *supra*. Queen 1990 discloses the use of a consensus human variable domain in Criterion I of its humanization roadmap. Ex. 1050 at 14:17–20 ("As acceptor,... use ***a consensus framework*** from many human antibodies."); Ex. 1003 at ¶¶208–09. Queen 1990 and Kurrle provided both the motivation and a reasonable expectation of success to make and use the remaining limitations, including substituting at claimed positions **98L** and **36H** (Ex. 1050; §H.1) and **4L**, **69H** and **76H** (Ex. 1071; §G.1). Ex. 1003 at ¶209. Claim 62, as for claims 1 and 4 (*see* §§V.I.1 & 2, *supra*) of the '213 patent is obvious over Queen 1990 and Kurrle.

5. Claim 63 is Obvious Over Queen 1990 and Kurrle

Claim 63 is similar to claim 62 (incorporating the CDRs and substituted FR residues of claim 1), and adds that the claimed humanized antibody "lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient to treat a chronic disease in that patient." As simply a statement of the intended result of the claimed composition, this should not be a limitation of the claims. *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Nonetheless, this is the stated goal of all humanization projects, including that of Queen 1990 and Kurrle. *See* Ex. 1050 at Abstract ("the humanized immunoglobulins of the present invention *will be substantially non-immunogenic* in humans...”); Ex. 1071 at 3:11–12 (“The resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients.”); Ex. 1003 at ¶¶210-13. Claim 63 is also obvious over Queen 1990 and Kurrle.

6. Claim 64 is Obvious Over Queen 1990 and Kurrle

Queen 1990 and Kurrle also disclose the limitations of claim 64. Queen 1990 discloses an antibody incorporating a humanized variable domain comprising a consensus sequence. *See* §§V.H.2 & 5, *supra*; Ex. 1050 at 14:17–20 (“As acceptor, . . . use ***a consensus framework*** from many human antibodies.”); Ex. 1003 at ¶¶214–17. Both Queen 1990 and Kurrle also taught humanized antibodies containing a non-human CDR and substituted FR residues. *See*, *e.g.*, Ex. 1071 (Kurrle) (“Only the complementarity determining [sic] regions and selected framework amino acids necessary for antigen binding are maintained murine. The remaining framework regions are converted to human sequences.”); Ex. 1003 at ¶215.

While the remaining limitations are merely stated functions of the humanized antibody, *see* §§V.G.3, & H.5 *supra*, both Queen 1990 and Kurrle disclosed that certain framework residues were important because of their proximity to neighboring CDRs: “These amino acids ***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." *See* Ex. 1050 at 16:1–12 (emphasis added); *see also* Ex. 1071 at 8:27–29; Ex. 1003 at ¶215. Queen 1990 and Kurrle provided the motivation and reasonable expectation of success to make the claimed "humanized variant of a non-human parent antibody." Claim 64 is obvious over Queen 1990 and Kurrle.

7. Claim 66 is Obvious Over Queen 1990 and Kurrle

Both Queen 1990 and Kurrle disclose the claimed "humanized antibody heavy chain variable domain comprising non-human [CDR] amino acid residues which bind antigen incorporated into a human antibody variable domain," which is also essentially recited in claims 1 and 62. *See* §§V.I.1 & 4, *supra*. Claim 66 further requires the framework substitution of one or more residues, *e.g.*, 24H, 73H, 76H, 78H and 93H. Kurrle, using Queen 1990's roadmap, substituted FR amino acids at claimed positions **73H** and **76H**, rendering the humanized antibody "essentially a human antibody with a much lower immunogenicity in patients." Ex. 1071 at 3:11–12; Ex. 1003 at ¶¶223–24.

Both Queen 1990 and Kurrle provide the motivation and a reasonable expectation of success to make "a humanized antibody variable domain" as claimed in claim 66. Ex. 1003 at ¶224. Claim 66 is also obvious over Queen 1990 in view of Kurrle.

8. Claims 67, 71, 72, 75, 76 and 78 are Obvious Over Queen 1990 and Kurrle

Claim 67: Claim 67, which depends from claim 66, 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." Both Queen 1990 and Kurrle disclosed this additional limitation. *See*, *e.g*., Ex. 1050 at 7:36–8:1 (disclosing "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"); Ex. 1003 at ¶225. Claim 67 is also obvious over Queen 1990 and Kurrle.

Claims 71, 72, 75 and 76: Claims 71, 72, 75 and 76, which all depend from claim 66, recite "wherein the residue at site 73H has been substituted" (claim 71), "wherein the residue at site 76H has been substituted" (claim 72), "which further comprises an amino acid substitution at site 71H" (claim 75), and "which further comprises amino acid substitutions at sites 71H and 73H" (claim 76). Kurrle substituted the murine amino acid residues at claimed positions **71H**, **73H** and **76H**. Ex. 1003 at ¶226. 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. Together with claim 66, §V.I.8 *supra*, dependent claims 71, 72, 75 and 76 are also obvious over Queen 1990 in view of Kurrle.

Claim 78: Claim 78, which depends on claim 66, recites an antibody "comprising the humanized variable domain of claim 66." The goal of humanization methods, including Queen 1990 and Kurrle, was to create a therapeutic antibody comprising a humanized variable domain: "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 immunoglobulin to the antigen." *See* Ex. 1050 at 8:21–26; Ex. 1071 at 3:26–28; Ex. 1003 at ¶229. Claim 78 is obvious over Queen 1990 and Kurrle.

9. Claim 69 is Obvious Over Queen 1990 and Kurrle

Claim 69 depends from claim 66, and further recites that, "the human antibody variable domain is a consensus human variable domain." Queen 1990 explicitly teaches using "[a]s acceptor . . . a consensus framework from many human antibodies." Ex. 1050 at 14:17–20; Ex. 1003 at ¶230. In view of claim 66, *see* §V.I.8, *supra*, claim 69 is also obvious over Queen 1990 and Kurrle.

10. Claims 80 and 81 are Obvious Over Queen 1990 and Kurrle

Claim 80: Claim 80 claims the same "humanized antibody variable domain" as claim 1 (*i.e.*, "comprising non-human CDR amino acid residues which bind an antigen ... and further comprising a [FR] amino acid substitution" at residues which completely overlap with claim 1). Like claim 64, claim 80 further recites functional aspects of the humanized antibody, including: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the VL-VH interface ...” Ex. 1003 at ¶¶157–60,188–92, 241–44.

The additional recited elements, which are noted functions of the substituted residues, do not add anything new to the claim. *See* claim 64, §V.I.6; Ex. 1003 at ¶242; *see also Atlas Powder*, 190 F.3d at 1347. Assuming one could discount the inherency of these functions (which Celltrion disagrees with and is unsupported in the law), both Queen 1990 and Kurrle explicitly teach interaction of the framework residues with the CDR as a reason for substitutability. *See* Ex. 1050 at 16:4–8; Ex. 1071 at 8:28–29 and 32–40; Ex. 1003 at ¶¶242–43. For the same reasons as claims 1 and 64 above, *see* §§V.I.1 & 6 *supra*, including the disclosure of framework region substitutions at positions **98L** and **36H** as provided by Queen 1990 (§§V.H.1 & I.1 *supra*), and **4L**, **69H**, **73H** and **76H** (§§V.G.1, G.4 & I.1 *supra*), as provided by Kurrle, as well as the explicit motivation and reasonable expectation of success provided by both Queen 1990 and Kurrle (*see* §§ V.G.1 & H.1), claim 80 of the ’213 patent is obvious over Queen 1990 and Kurrle.

<u>Claim 81</u>: Claim 81 depends on claim 80, adding “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.”

Both Queen 1990 and Kurrle teach this. *See* Ex. 1050 at 7:36–8:1; Ex. 1071 at 8:28–31; Ex. 1003 at ¶244. Claim 81 is also obvious over Queen 1990 and Kurrle.

J. <u>Ground 4</u>: Claim 12 Is Obvious Over Queen 1990 and Kurrle, in View of Furey

The POSA further would have been motivated to identify residues important for antibody binding, *e.g.*, CDR contact residues and V_L:V_H interaction. Ex. 1003 at ¶¶82–86, 205–06.

Claim 12, which depends on claim 1, recites "wherein the residue at site 66L has been substituted." As discussed above, claim 1 is obvious in light of Queen 1990 and Kurrle. *See* §V.I.1. Based on the teachings of Queen 1990 and Kurrle a POSA would have been motivated to look at known antibody structures to determine which residues play a role in maintaining antibody confirmation. Ex. 1003 at ¶205. Furey, one example of a known antibody fragment structure, disclosed the importance of residue 66L as maintaining antigen binding and specificity. *See* Ex. 1125 at Abstract; Ex. 1003 at ¶¶205–06. Specifically, Furey identified position 66L as interacting with CDR2 of the light chain. Ex. 1125 at Table 4; Ex. 1003 at ¶206.

This directly ties to Queen 1990's and Kurrle's teachings, which provided a POSA the motivation and reasonable expectation of success to substitute framework region positions that are close enough to interact directly with antigen, as Furey identified with residue **66L**, which a POSA would have understood as being on a list of substitutable residues to maintain antigen binding and specificity. *See* Ex. 1053 at Table 4; Ex. 1003 at ¶206. Claim 12 is thus obvious over Queen 1990 and Kurrle, and further in view of Furey.

K. Ground 5: Claims 73, 74, 77, 79, and 65 are Obvious Over Queen 1990 and Kurrle, In View of Chothia & Lesk and Chothia 1985

Claims 73 and 77: Claims 73 and 77, which both depend on claim 66, recite "wherein the residue at site 78H has been substituted" (claim 73), and "which further comprises amino acid substitutions at sites 71H, 73H and 78H" (claim 77). As discussed above, claim 66 is obvious in light of Queen 1990 and Kurrle. *See* §V.8. A POSA would have been motivated to identify which residues had been identified as being essential for interchain reactions. Ex. 1003 at ¶227. Residue 78H was already known as being important for maintaining antibody conformation, and thus antigen binding and specificity, as identified by Chothia & Lesk and Queen 1990. *See* Ex. 1062 at Abstract; Ex. 1003 at ¶231. Chothia & Lesk found that "[t]he major determinants of the tertiary structure of the framework are the residues buried within and between the [V_L and V_H] domains," including residue **78H** specifically. Ex. 1062 at 903; Table 4; Ex. 1003 at ¶¶232–33. The Background of the '213 patent also recognized the importance of Chothia & Lesk's findings. *See* Ex. 1001 at 3:1–8 (citing to Chothia, Lesk and colleagues, Ex. 1062, for residues "critically affecting the conformation of particular CDRs and thus their contribution to antigen binding.").

Thus, the field, including the ’213 patent inventors, already recognized the importance of framework residues, such as **78H**, that are important to maintain antigen binding. Ex. 1003 at ¶232. In view of the importance of **78H**, it would have been obvious for a POSA to include **78H** as a substitutable residue. Ex. 1003 at ¶233; *see also* ¶200. Claim 73 is obvious over Queen 1990, Kurrle and Chothia & Lesk.

Adding residue **78H** to the combination of residues **71H** and **73H** does not extend patentability. Ex. 1003 at ¶234. These residues were substituted (**71H** and **73H**) in Kurrle, or would have been substituted (**78H**) if necessary. Ex. 1003 at ¶234. Claim 77 is also obvious over Queen 1990, Kurrle and Chothia & Lesk.

Claim 74: Claim 74, which also depends on claim 66, recites “wherein the residue at site 93H has been substituted.” Chothia 1985 identified residue **93H** as important for maintaining V_L:V_H interactions. *See* Ex. 1063 at Table 4; Ex. 1003 at ¶¶227–28. The inventors of the ’213 patent also recognized the importance of residues that maintain VL:VH interface contact, as disclosed in Chothia. *See* Ex. 1001 at 3:1–8, *supra*; *see also* Ex. 1050 at 17 (recognizing the importance of “residues essential for inter-chain interactions”). Thus, Kurrle and Queen 1990 provided the explicit motivation as well as reasonable expectation of success to substitute residue **93H** for the non-human (*e.g.*, murine) residue, and thus made obvious that residue **93H** would have been substituted. Ex. 1003 at ¶¶227–28. Claim 74 is also obvious over Queen 1990, Kurrle and Chothia & Lesk.

Claim 79: Claim 79 recites "a humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises [CDR] amino acid residues of the non-human parent antibody incorporated into a human antibody variable domain, and further comprises [FR] substitutions at heavy chain positions 71H, 73H, 78H and 93H, utilizing the numbering system set forth in Kabat."

As above, Kurrle already substituted positions **71H** and **73H**. *See* Ex. 1071 at Table 6B; Ex. 1003 at ¶236, Ex. 1003C at 4–7 (Riechmann Exhibit B). Chothia 1985 disclosed residue **93H** as important for maintaining V_L:V_H interactions. Ex. 1063 at Table 4; Ex. 1003 at ¶¶227–28, 237. Finally, Chothia & Lesk disclosed residue **78H** as one specifically and independently important for maintaining antigen binding. Ex. 1062 at Table 4; Ex. 1003 at ¶¶232–33. It would have been obvious to a POSA to combine substitutions at **71H**, **73H**, **78H** and **93H**, as taught by Queen 1990, Kurrle, Chothia & Lesk and Chothia 1985. *See* §§V.G.4, I.1 & I.9, *supra*; Ex. 1003 at ¶¶231–40. Claim 79 is also obvious over Queen 1990 and Kurrle, and further in view of Chothia & Lesk and Chothia 1985.

Claim 65: Claim 65 depends from claim 79 and further recites that the humanized variant "binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." As simply a statement of the intended result of the claimed composition, this should not be a limitation of the claims. *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Nonetheless, the broadest reasonable interpretation of this limitation includes any increase in binding affinity "up to" the upper limit of "3-fold more," *i.e.*, any amount greater than 1-fold (*i.e.*, the parent binding affinity) and "up to 3-fold more." §V.D, *supra*; Ex. 1003 at ¶¶219–22.

Dr. Riechmann explained that to a POSA, "there was the expectation when humanizing antibodies that a similar affinity, *e.g.*, the same, slightly better, or slightly worse, would be obtained as compared to the parent (mouse) antibody. Thus, it would not have been surprising that a small improvement in affinity would be achieved." Ex. 1003 at ¶220. Dr. Riechmann further explains that "it was not unexpected that in this process, one could go beyond the parent antibody's original affinity, *i.e.*, an increase in affinity as claimed in claim 65." Ex. 1003 at ¶221. This is within the stated purpose of humanization, and thus any increase, including small and moderate increases incorporated within the scope of the claim, would have been expected, as stated by Queen 1990. Ex. 1050 at 8:26–28 ("[Affinity levels can vary … and may be within about 4 fold of the donor immunoglobulin's original affinity to the antigen."); Ex. 1003 at ¶¶218–22. For these reasons, claim 65 is also obvious over the combination of Queen 1990 and Kurrle, and further in view of Chothia & Lesk and Chothia 1985.

L. Ground 6: Claims 30, 31 and 33 Are Obvious Over Queen 1990 in View of Hudziak

Claim 30: Claim 30 of the ’213 patent recites “[a]n antibody which binds p185^{HER2} and comprises a humanized antibody variable domain, wherein the humanized antibody variable domain comprises non-human [CDR] amino acid residues which bind p185^{HER2} incorporated into a human antibody variable domain and further comprises a [FR] 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 30 is similar to claim 1, differing in the recitation that the CDRs (and antibody) also bind to p185^{HER2}. As discussed above, claim 1 is obvious and/or anticipated in light of Queen 1990. *See* §V.H.1. Claim 30 also includes additional framework sites for substitution at positions 46L, 75H and 76H.

Antibody humanization was developed for a single purpose: realizing the therapeutic promise of monoclonal antibodies for the treatment of human diseases. Ex. 1003 at ¶320; Ex. 1004 at ¶¶27–30. While monoclonals were capable of targeting antigens (*e.g.*, proteins) in a highly specific manner, immunogenicity issues severely limited the applicability of this technology to human therapeutics. *See* Ex. 1003 at ¶320; Ex. 1004 at ¶28.

A prime molecular target was HER2/*c-erbB-2*, whose amplification in breast cancer patients was correlated with poor prognosis and high relapse rate. *See* Ex. 1021 at Abstract, 1; Ex. 1004 at ¶¶41–60; Ex. 1003 at ¶¶321–22. With respect to the HER2/*c-erbB-2* gene product p185^{HER2}, Hudziak reported that:

- p185^{HER2} was amplified in about 30% of breast cancer tumors; Ex. 1021 at 1; Ex. 1004 at ¶45; Ex. 1003 at ¶321;
- p185^{HER2} "correlated with a negative prognosis and high probability of relapse"; Ex. 1021 at 1; Ex. 1004 at ¶45; Ex. 1003 at ¶321;
- Increased expression of HER-2/*neu* resulted in cellular transformation of the cells and tumorigenesis when the transformed cells were implanted in athymic mice, Ex. 1021 at 1; Ex. 1004 at ¶47; Ex. 1003 at ¶321; and
- High levels of HER-2 gene expression resulted in the cells forming anchorage-independent colonies in soft agar and at low density in low serum concentration, which are characteristics of a transformed phenotype, Ex. 1021 at 1; Ex. 1004 at ¶51; Ex. 1003 at ¶322.

In reviewing Hudziak [Ex. 1021] and other literature, Celltrion's expert Dr. Leonard, a practicing oncologist with clinical experience in developing therapeutic antibodies, concluded that the above findings "strongly suggested that the HER-

2/*neu* receptor was a ripe target for therapeutic development." Ex. 1004 at ¶48; Ex. 1003 at ¶¶321–22.

Moreover, a POSA would have been motivated to develop a monoclonal antibody therapeutic against p185^{HER2}, particularly because of its structural similarity to other growth factor receptors, including epidermal growth factor receptor (EGFR). *See* Ex. 1004 at ¶48; Ex. 1003 at ¶323. This was demonstrated well prior to June 1991 for 4D5, a well-characterized mouse monoclonal antibody targeting p185^{HER2} protein with high affinity, specificity (no cross-reactivity with, for example, EGFR) and efficacy in *in vitro* and *in vivo* studies. *Id.* at ¶65; Ex. 1003 at ¶324. The investigators concluded that 4D5 provided "new potential for diagnostic approaches and therapeutic strategies for treatment of human malignancies." Ex. 1047 at 4; Ex. 1004 at ¶55; Ex. 1003 at ¶324.

Given the understanding that an antibody must be humanized before use as a therapeutic agent, the published accounts regarding other monoclonal antibody humanization efforts, and the strength of 4D5 as a clinical target, the logical and necessary next step would have been to humanize 4D5. Ex. 1004 at ¶62; Ex. 1003 at ¶324. The 4D5 investigators urged artisans to follow precisely this path:

> The muMAb *4D5 also serves as a template for antibody engineering efforts to construct humanized versions* more suitable for chronic therapy or other molecules which may be directly cytotoxic for tumor cells overexpressing the HER2 protooncogene.

Ex. 1048 at 10; Ex. 1004 at ¶60 (emphasis added).

Queen 1990 provided the detailed steps for humanizing mouse monoclonal antibodies, such as 4D5, and represented the state of the art of antibody humanization by 1991, teaching humanization of antibody variable domains having non-human CDR amino acid residues that bind to an antigen and are incorporated into a human antibody variable framework domain. Ex. 1003 at ¶¶120–26, 333. Further, Queen 1990 explicitly disclosed that a POSA would have had a reasonable expectation that such a humanized antibody would be capable of binding to $p185^{HER2}$. *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 ¶333. Queen 1990, thus, provided the explicit motivation to make framework substitutions that would, for example, be more representative of a human residue (Criterion II; *id.* at 15:22–37), residues that are "immediately adjacent" to CDRs that "likely [] interact with ... the CDR's..." (Criterion III; *id.* at 16:1–12), and residues that are "in contact", *i.e.*, within about 3Å of a CDR (Criterion IV; *id.* at 14:14–15:2). Ex. 1003 at ¶¶120–26.

Hudziak provided explicit motivation to develop 4D5 for therapeutic use, disclosing "monoclonal antibodies specific for $p185^{HER2}$ (e.g., 4D5) [as] useful therapeutic agents for the treatment of human neoplasias." *See* Ex. 1021 at 7; Ex.

1003 at ¶¶320–24, 332; Ex. 1004 at ¶55. POSAs would have recognized in June 1991, that 4D5 required humanization before clinical use and therefore would have been motivated to combine the teachings of Queen 1990 and Hudziak. *See* Ex. 1048 at 10 ("4D5 also serves as a template for antibody engineering efforts to construct humanized versions more suitable for chronic therapy ..."); Ex. 1003 at ¶¶322–24, 332–33, 336; Ex. 1004 at ¶60. As discussed in §§V.E.2 & 3, and H.1, *supra*, the particular residues to modify would have included at least **98L** and **36H** which likewise appear in claim 30. Claims 30 is obvious over Queen 1990 and Hudziak.

<u>Claim 31</u>. Claim 31 recites that "the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained." Queen 1990 explicitly disclosed this limitation. *See* Ex. 1050 at 5:36–6, Ex. 1003 at ¶¶120–26, 333. Claim 31 is also obvious over Queen 1990 and Hudziak.

<u>Claim 33</u>. Claim 33 further adds that "the human antibody variable domain is a consensus human variable domain," which Queen 1990 explicitly discloses. *See* Ex. 1050 at 12:17–20 ("As acceptor ... use a consensus framework from many human antibodies."); Ex. 1003 at ¶¶120–26, 334. For at least these and the reasons for claim 30, claim 33 is also obvious over Queen 1990 and Hudziak.

M. Ground 7: Claim 42 is Obvious Over Queen 1990 in view of Furey and Hudziak

Claim 42, which depends on claim 30, recites "wherein the residue at site 66L has been substituted." As discussed above, claim 30 is obvious in light of Queen 1990 and Hudziak. *See* §V.L. The art also the art taught individual residues to target for humanization for additional reasons. For example, Furey disclosed that residue 66L forms a hydrogen bond contact with CDR2 of the light chain. *See* Ex. 1125 at Table 4; Ex. 1003 at ¶¶335–37. Following the detailed roadmap of Queen 1990; recognizing Furey's particular emphasis on **66L** to improve binding affinity; and in light of the teachings of Hudziak motivating a POSA to target p185*HER2* with an antibody, particularly 4D5, Ex. 1003 at ¶¶335–37, Ex. 1004 at ¶55, a POSA would have placed residue **66L** on a short list of substitutable residues. Ex. 1003 at ¶¶335–37. Claim 42 is obvious over Queen 1990, and further in view of Furey and Hudziak.

N. Ground 8: Claim 60 is Obvious Over Queen 1990 In view of Chothia & Lesk and Hudziak

Claim 60, which also depends on claim 30, recites "wherein the residue at site 78H has been substituted." As discussed above, claim 30 is obvious in light of Queen 1990 and Hudziak. *See* §V.L. Chothia & Lesk disclosed a small universe of residues which are "primarily responsible for the main-chain conformations of the hypervariable regions" (*i.e.*, maintaining CDR conformation as Queen 1990 taught), including residue **78H**. *See* Ex. 1062 at Abstract, Table 4; Ex. 1003 at ¶¶335–37. Following the detailed roadmap of Queen 1990, a POSA would have looked to Chothia & Lesk and identified FR positions that could interact with or influence CDR conformation, and antigen binding and specificity, including residue **78H**. Ex. 1003 at ¶¶335–37. Claim 60 is obvious over Queen 1990, in view of Chothia & Lesk.

O. Secondary Considerations Cannot Preclude 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); *see also Torrent Pharms. Ltd. v. Novartis AG*, IPR2014-00784 at 12 (PTAB Sep. 24, 2015) ("If objective indicia of nonobviousness are due to an element in the prior art, no nexus exists."). Nor can Patent Owner show 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 (P.T.A.B. Apr. 29, 2015). Celltrion nonetheless preliminarily 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 2:63–3:8; Ex. 1003 at ¶¶339–40. Given the extensive prior art, successful antibody humanization was readily achievable, not surprising, or unexpected. Ex. 1003 at ¶¶339-40; Ex. 1004 at ¶¶33–40. More specifically, successfully humanizing an antibody using a consensus sequence would have been expected. Ex. 1003 at ¶339. As Dr. Riechmann 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.

Additionally, the data allegedly showing enhanced (allegedly 3-times more) target binding does not show unexpected improvement. Ex. 1003 at ¶340. As Dr. Riechmann 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*.

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 scope of the challenged claims include antibodies other than antibody 4D5. Therefore, any need that this antibody filled is not commensurate in scope with the challenged claims.

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, 882–83 (Fed. Cir. 2012). The ’213 patent’s purported problem was that “[m]ethods are needed for rationalizing the selection of sites for substitution in preparing [humanized] antibodies,” and 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 1990, Kurrle and others had already described this process—they 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 ¶¶339-343.

3. No nexus/commercial success to Herceptin.

Any commercial success experienced with Herceptin[7] 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, and only 1 of the 13 heavy chain residues (78H) cited in claims 30, 62 and 63 is modified in Herceptin. *Second*, any alleged success is not commensurate in scope with the challenged claims because they are not limited to any particular antibody or class of antibodies. Ex. 1003 at ¶343. Even claim 30, which recites that the antibody binds $p185^{\mathit{HER2}}$, is limited to any specific anti-$pl85^{\mathit{HER2}}$ antibody. 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.

Dated: May 8, 2017

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

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, May 8, 2017 on the Patent Owner's correspondence address of record for the subject patent as follows:

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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 13,915 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: May 8, 2017

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