UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Celltrion, Inc.

Petitioner,

v.

Genentech, Inc.

Patent Owner

Patent No. 6,407,213

Inter Partes Review No. IPR2017-01373

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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After the Board considered the prior art cited by Petitioner and granted institution, PO abandoned its defense of claims 1, 2, 25, 29, 80, and 81 (POR, 18-22), essentially conceding that their limitations did not constitute patentable distinctions over the work of others.[1]

Having made this concession, PO falls back to the position that certain elements distinguish a handful of remaining claims from the prior art: (1) the use of a "human consensus sequence" as the human framework (claims 4, 33, 62, 64 and 69), (2) "lack of immunogenicity as compared to a non-human parent antibody" (claim 63), (3) "up to 3-fold more" binding affinity than the parent antibody (claim 65), and (4) binding to $p185^{HER2}$ (claim 30). (POR, 1-4.) PO also alleges that even if some of the claimed substitutions were explicitly disclosed in the prior art, not all of them were. (POR, 3-4.) These elements do not make the otherwise-obvious claims patentable, however.

Elements (1)-(4) above affect only a small number of claims. PO's arguments do not change the fact that each element was explicitly disclosed in, or obvious from, the prior art.

PO's allegation that not all of the claimed residues are explicitly disclosed in the prior art ignores all that the prior art teaches, as well as the limitations of what

[1] Therefore, this Reply addresses the remaining challenged claims: 4, 12, 30, 31, 33, 42, 60, 62-67, 69, and 71-79.

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the patent teaches. The patent does not teach that *all* of the claimed substitutions and possible combinations thereof will work to improve the binding of *all* of the huge number of antibodies that could fall within the claims. Indeed, as the patent and prior art make clear, the substitutions needed to optimize antigen binding will vary from mAb to mAb. In fact, the patent does not teach that *any* specific substitution will work in *any* specific mAb falling within the claims, other than the handful of examples provided. Instead, the patent teaches that a POSA must conduct extensive modeling to determine which of the claimed substitutions might possibly improve binding in a given project, and then use serial mutagenesis—making mAbs with different substitutions and then testing them—to confirm which precise combination of possibilities optimizes that binding. But there is no material difference between this method and the humanization roadmap laid out in Queen-1989 and -1990. PO's expert Dr. Wilson conceded that each of the steps required would have been routine to a POSA, and thus PO cannot credibly dispute that a POSA would have been able to identify the claimed substitutions when developing humanized mAbs that require them for optimal binding affinity. In fact, if this is not the case, the claims are not enabled.

In addition, PO misconstrues the law when it comes to the laundry lists of substitutions recited in the *Markush* groups of claims 4, 12, 30, 31, 33, 42, 60, 62, 63, 65-67, 69, and 71-78. As the Board found in its institution decision, a POSA

applying the roadmap in Queen-1989 or -1990 would have identified at least *some* of the residues in each of claims 4, 30, 31, 33, 62, 63, 64 65, 66, 67, 69, and 78 as likely candidates for substitution during humanization. (Institution Decision, 16) (A POSA "would have identified nine positions in the light chain and eleven in the heavy chain as candidates for substitution, including those recited in the challenged claims."). Since the claimed *Markush* groups merely require "one or more" of the recited substitutions, this is sufficient to render them obvious. *See, e.g.*, *Ecolochem, Inc. v. S. Cal. Edison Co.*, 91 F.3d 169, 1996 WL 297601, *2 (Fed. Cir. 1996) ("[I]f utilizing one element of the [*Markush*] group is anticipated or obvious, the patentee is precluded from arguing that the claim is valid."). In addition, as the Board found, a POSA would have identified *all* of the substitutions in claims 12, 42, 60 and 71-79 (Institution Decision, 16), which means they, too, are invalid.

PO's attempt to avoid invalidity through antedating also fails. The evidence of record is not corroborated and does not satisfy PO's burden to prove an earlier invention date. Moreover, PO only attempts to establish an earlier invention date of claims 12, 42, 60, 65, 71, 73-74, and 79, and therefore concedes that it cannot antedate Petitioner's prior art for claims 4, 30-31, 33, 62-64, 66-67, 69, 72, and 75-78.

I. All Challenged Claims Would Have Been Obvious over Queen-1989 or Queen-1990 and the PDB Database, Optionally in Light of Tramontano and/or Kabat-1987 and/or Hudziak

A. Claims 12, 42, 60, 65-67, and 71-79 are Obvious Over Queen-1989 or Queen-1990, in Combination with the PDB

1. A POSA Following the Teachings of the Prior Art Would Have Identified the Claimed Residues for Substitution

PO faults the Queen references as leading POSAs "to a broad genus of potential framework substitutions," and alleges incorrectly that "Petitioner has provided no reason why a skilled artisan would have selected the specific framework substitutions recited in the challenged claims." (POR, 46.) PO does not deny that a POSA following the prior art would identify the residues in claims 12, 42, 60, 65-67, and 71-79 as candidates for substitution, only that a POSA would not *limit* the candidates to those specific residues. But this does not save the claims.

The '213 patent purports to identify a laundry list of murine framework residues that can be substituted for the corresponding human framework residues to improve binding affinity. However, the patent does not tell a POSA which of these residues to substitute in a *specific* humanized mAb project beyond huMAb4D5, anti-CD3, and anti-CD18. (Ex. 1143, ¶4.) And as Figures 5-6 and Table 3 of the patent make clear, each humanized mAb requires a different set of substitutions to optimize binding affinity. (Ex. 1001; Ex. 1143, ¶20.) While the

patent claims a laundry list of possible substitutions to try, the only guidance in the '213 patent concerning how to select specific substitutions that will work in mAbs beyond the examples is, as PO's expert Dr. Wilson acknowledged, remarkably similar to the guidance in Queen-1989 and Queen-1990. The patent requires a POSA to construct a computer model, identify the residues that, because of their positions within the V_H and V_L domains, could alter binding affinity, and then conduct trial-and-error mutagenesis to see which substitutions improve binding. (Ex. 1138, 116:1-122:1; *compare* Ex. 1050, 12:17-17:24 *with* Ex. 1001, 20:41-21:3; Ex. 1142, 76:19-80:13.) Dr. Wilson further conceded that it would have required nothing more than routine skill and experimentation to use these methods to identify specific residue(s) that would work in a given humanization project. (Ex. 1138, 116:1-122:1; *see also* Ex. 1142, 97:14-98:22.)

As discussed in the Petition regarding Ground 1, a POSA following the Queen-1989 roadmap and using the PDB would have identified the substitutions at 4L, 58L, 66L, 67L, 69L, 73L, 2H, 45H, and 69H using concededly routine skill. Since claims 4, 12, 30, 31, 33, 42, 60, 62, 63, 65-67, 69, 71-75, and 78 each merely require that "one or more" of the listed residues be selected for substitution, they are invalid. *See Ecolochem*, 1996 WL 297601, *2 ("[I]f utilizing one element of the [*Markush*] group is anticipated or obvious, the patentee is precluded from

arguing that the claim is valid.").[2]

PO's complaint that POSAs would have been faced with a large list of residues to choose from ignores that the patent likewise requires a POSA to choose the particular substitutions needed for a given humanization project from the large list of possibilities recited in the patent. PO has conceded that this kind of selection would have involved nothing but routine skill, thus it does not weigh against obviousness. *See, e.g., KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

The fact that a POSA would have understood from the cited prior art references that additional residues were also candidates for substitution is also immaterial. A POSA would have understood that a given humanization project may require substitutions not described in the patent, and thus that the list of possible substitutions in the patent is incomplete. (Ex. 1143, ¶¶8-12.) Indeed, Perjeta® (pertuzumab)—which PO states was made using methods disclosed in the patent—contains substitutions not described in the patent. (Ex. 1138, 253:18-254:21.) PO offers no rationale why the selection process required by the patent is any less complex than the selection process disclosed in the prior art.

[2] Dr. Wilson's opinions applied an improper legal standard, requiring every recited framework substitution to be obvious. (Ex. 1138, 91:3-92:14.)

Additionally, PO does not point to any evidence that the particular substitutions listed in claims 12, 42, 60, 65-67, and 71-79 are critical to the claimed invention. The prior art identified a range of potential residues to be substituted in a humanization project, including the claimed residues. As a result, these residues are *prima facie* obvious, and the patentee must establish "that the [claimed residue] is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (quoting *In re Geisler*, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997)). PO has not made any such showing, and therefore, the selection of the residues listed in claims 12, 42, 60, 65-67, and 71-79 would have been obvious. (Ex. 1143, ¶¶26-27; Ex. 1001, Table 3; Ex. 1142, 131:10-132:5.)

2. A POSA Would Have Used The PDB As Dr. Riechmann Did

PO incorrectly argues that "the Queen references do not teach using the PDB database as Petitioner uses it." (POR, 45.) PO does not dispute that the Queen references teach the use of computer modeling to identify residues that influence the conformations of the murine CDRs or interact directly with the antigen. (*See* Ex. 1003, ¶¶249, 260; Ex. 1034, 10031; Ex. 1050, 14:32-36.) The prior art teaches the use of the PDB data to do this. (*See, e.g.*, Ex. 1050, 14:32-36; Ex. 1062, 902). Indeed, a POSA would have had to use data like that contained in the PDB to create an accurate molecular model. (Ex. 1143, ¶5.) Although PO points out that

the Queen references describe modeling the murine antibody versus the humanized antibody, PO ignores that the modeling in Queen-1989 also considered "other antibody V domains with known crystal structure" when constructing the model (Ex. 1034, 10031), and Queen-1990 disclosed using "known antibody structures" in the PDB as rough models (Ex. 1050, 16). PO also does not allege that this distinction would alter the analysis in any respect, and a POSA would have recognized that the Queen method is a reliable means of identifying framework residue substitutions that would improve binding. (Ex. 1143, ¶¶6-7.)

3. A POSA Would Have Expected the Resulting Humanized mAb to Bind the Target Antigen

PO incorrectly argues that there is no evidence that a POSA would have expected a humanized mAb to bind an antigen.[3] The claim language "bind an antigen" encompasses binding *to any degree*. PO's expert admitted that in a humanization project "one approach to try to regain the binding affinity . . . was to make additional substitutions back to mouse in the human framework." (Ex. 1138, 28:2-8.)

PO's argument ignores all of the prior art discussing successful

[3] PO makes similar arguments with respect to claims 4, 33, 62, and 69. (POR, 56-57.) The arguments presented in this section apply with equal weight to those claims.

humanization projects. For example, Queen-1989's humanized anti-Tac mAb bound the target antigen with high affinity. (Ex. 1034, 10029, 10033 ("The resulting humanized antibody has a high affinity, $3 \times 10^9 M^{-1}$, for its antigen.").) Dr. Riechmann's humanized CAMPATH mAb similarly had high binding affinity. (Ex. 1069, 3.) A POSA using the methodology set forth in Queen-1990 would have understood that the prior art methods for humanization had been successfully used to achieve mAbs with high binding affinity. (Ex. 1050, Abstract (disclosed antibodies "retain the same affinity as the donor immunoglobulin to the antigen").) A POSA using prior art methods would have had a reasonable expectation of achieving results at least as good as those disclosed in the prior art. (Ex. 1138, 104:12-105:5.) Additionally, the binding affinity of any antibody made according to the teachings of the prior art would be an inherent property of an obvious combination and cannot impart patentability. *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009).

Furthermore, the '213 patent provides no binding affinity data for most of the residue substitutions identified in the claims, which indicates either that a POSA would reasonably have expected antibodies with those substitutions to bind the target antigens, or that the patent lacks sufficient written description.

4. Holding the Challenged Claims Invalid Would Not Have "Sweeping Consequences"

PO's hyperbole that finding the challenged claims obvious over the Queen references and the PDR would remove "patent protection for most if not all humanized antibodies" is baseless. (POR, 51.) The challenged claims are not directed to the primary sequences of the handful of specific humanized mAbs that the named inventors allegedly created. And PO already obtained a patent covering the variable domain sequences of its humanized 4D5 mAb, but that patent expired. (Ex. 1144, Claim 15; Ex. 1143, ¶29.) In this patent, PO is trying to reach far beyond the humanized mAbs the named inventors actually made, to grasp essentially huge numbers of mAbs made using basic prior-art humanization techniques pioneered by others. There is no evidence of record to support PO's allegation that holding these over-reaching claims obvious would impact the patentability of different claims to novel humanized mAbs. Regardless, the only issue before the Board here is the invalidity of the challenged claims.

5. Petitioner's Arguments Regarding Queen-1989 Do Not Rely on Queen-1990

PO is incorrect that Petitioner's arguments in Grounds 1, 3, and 6 rely on Queen-1990 and not Queen-1989 because Dr. Riechmann used a 3.3 Å cutoff for identifying residues in contact with one another. (POR, 44-45.) Queen-1989 states that "a number of amino acid residues outside of the CDRs are in fact close enough

to them to either influence their conformation or interact directly with antigen." (Ex. 1034, 10031.) As explained by Dr. Riechmann,[4] a POSA reading Queen-1989 would have known that the operative distance would be approximately twice the interatomic distance—that is, approximately 3.3 Å for most protein atoms. (Ex., 1003, ¶255 n.17; Ex. 1143, ¶23; Ex. 1145, 261.) PO's expert agreed, acknowledging that a POSA would have known that "Van der Waals and hydrophobic interactions can occur at distances of 3.5 to 4 Angstroms." (Ex. 2014, ¶184; Ex. 2045.)

6. Queen-1990 and Tramontano Further Support Petitioner's Position

PO wrongly states that Tramontano "never suggested that substitutions at position 71H were desirable." (POR, 15.) Tramontano explicitly disclosed that residue 71H is likely a "major determinant of the conformation of" the H2 CDR, thus it would have been obvious to a POSA to consider this residue for substitution where the murine and human framework residues differed at this position. (Petition, 7-8, 22, 50; Ex. 1003, ¶132; Ex. 1051, Abstract.)

[4] PO's arguments that Dr. Riechmann "simply adopted the opinions" of Dr. Padlan are misplaced. (POR, 46-47.) Dr. Riechmann conducted his own thorough review of the relevant art and the '213 patent and formed his own opinions regarding the '213 patent. (Ex. 1003, ¶10; Ex. 2039, 29:12-47:2; Ex. 1143, ¶36.)

B. The Consensus Sequence Limitation of Claims 4, 33, 62, 64, and 69 Was Taught By the Prior Art

As discussed in the Petition, Queen-1990 explicitly discloses the use of a consensus sequence as the human framework in a humanization project. (Petition, 36-37.) In arguing that Queen-1990's disclosure of using "many human antibodies" to make a consensus is different than the claimed approach of using "all human antibodies," PO offers no evidence that Queen's approach was any different than [redacted] (Ex. 1142, 27:14-28:13, 32:17-20, 35:9-20.) Moreover, a POSA would have been motivated to use as many different known antibody structures as possible, to make the sequence as much of a consensus as possible. (Ex. 1143, ¶13-14.) A POSA would not have understood Criterion I as instructing a POSA to consider only a subset of human antibodies, since it does not explain what that subset is.

PO's argument that the Queen-1990 consensus sequence is different than that disclosed in the '213 patent is also wrong. PO relies on a passage in Queen-1990 regarding "a representative collection" of human heavy chains, but this passage is taken out of context. This quote from Queen-1990 does not refer to the consensus sequence human framework, but relates to the other potential framework Queen-1990 describes. (Ex. 1050, 13:3-11; Ex. 1143, ¶15.)

PO is also incorrect that a POSA would have understood the "rare" amino acids language in Criterion II of Queen-1990 as applying to the consensus sequence in Criterion I. (POR, 53.) Queen-1990 is clear that each of the criteria may be used separately. (Ex. 1050, 12:12-15 ("These criteria may be used singly, or when necessary in combination, to achieve the desired affinity or other characteristics."); Ex. 1143, ¶16.)

Queen-1989 also teaches the use of a consensus sequence as the human framework. Queen-1989 describes further humanizing a human antibody framework by replacing residues that are "unusual" in human antibodies with "residue[s] much more typical of human sequences . . . to make the antibody more generically human." (Ex. 1034, 10032.) A POSA following that teaching, and informed by the sequence data in Kabat-1987 identifying the residues that are most "typical" in human immunoglobulins of particular subclasses and subunits, would have swapped out unusual residues with consensus residues until he or she ended up with a human consensus framework. (Petition, 51-52; Ex. 1003, ¶310; Ex. 1143, ¶17-18.)

PO's argument that Queen-1989 does not teach a POSA to *start* with a consensus sequence is irrelevant. The '213 patent claims do not require that a particular method be used to obtain the human consensus sequence.

PO's complaint that Queen-1989 replaces unusual human framework

residues with *murine* residues is also misplaced. Queen-1989 describes how human antibodies exhibit "strong amino acid homology outside of the CDRs," but that there are occasionally atypical residues. (Ex. 1034, 10031-32.) During humanization of anti-Tac, several atypical residues were identified, including 93H, 95H, 98H, 106H, 107H, 108H, and 110H, as well as 47L and 62L, which were back-mutated to the murine residue. (Ex. 1034, 10032.) According to Queen-1989, back mutation to the murine residue only occurs when the murine antibody "has a residue much more typical of human sequences than does" the human framework. (Ex. 1034, 10032.). This was not done, as PO suggests, to maintain the confirmation of the murine CDRs, but instead "to make the antibody more generically human." (Ex. 1034, 10032.)

That Queen-1989 does not use the word "consensus" is irrelevant. Queen-1989 renders obvious all that it teaches a POSA, regardless of the terminology Queen et al. chose to use. *See In re Applied Materials, Inc.*, 692 F.3d 1289, 1298 (Fed. Cir. 2012) ("A reference must be considered for everything that it teaches").

Similarly, PO is incorrect that Kabat-1987 was only a reference to check the veracity of a potential sequence. A POSA would have used the information in Kabat-1987 to determine whether a particular residue was common. (Petition, 22-23, 51-52; Ex. 1003, ¶309; Ex. 1143, ¶19; Ex. 1142, 30:5-13, 57:23-58:6, 178:18-179:14; Ex. 1140, 60:3-12.)

Finally, PO ignores that prior to the earliest possible priority date of the alleged invention, scientists had already created humanized antibodies using consensus sequences. (Ex. 1193, 106; Ex. 1138, 196:5-197:6 (discussing Genentech's admission during EU patent proceedings that Dr. Riechmann used Foote's consensus sequence in humanizing CAMPATH).) This is compelling evidence that it would have been obvious to use human consensus sequences in the human framework.

C. The "Up to 3-Fold More Binding Affinity" Limitation of Claim 65 Was Taught By the Prior Art

The language "up to 3-fold more binding affinity" in claim 65 means just that: *any* improvement up to 3-fold more binding affinity, no matter how small. (Ex. 1138, 103:23-104:1; Ex. 1142, 118:8-17.) As explained in the Petition, a POSA optimizing binding affinity through mutagenesis would reasonably have expected to achieve a humanized antibody with an affinity around that of the parent antibody, i.e., an affinity that was slightly less or slight more than the parent. (*E.g.*, Petition, 47-48.) A POSA also would have known that mutagenesis could lead to improved binding. Indeed, as Table 3 of the patent shows, one residue substitution can increase the binding affinity during humanization. (Ex. 1001, Table 3; Ex. 1143, ¶26). While the specific binding properties of a humanized antibody can only be confirmed by testing, such mutagenesis would

have been a routine part of antibody humanization. (Ex. 2039, 271:15-17; Ex. 1142, 101:24-102:19; Ex. 1143, ¶20.)

D. The "Lack Immunogenicity Compared to a Non-Human Parent" Limitation of Claim 63 Was Taught By the Prior Art

PO incorrectly implies that claim 63 requires that the humanized antibody produce *no* immunogenic reaction, and uses an out-of-context quote from Dr. Riechmann as support. (POR, 60-61.) But PO does not dispute the Board's construction that "lacks immunogenicity" refers to "a humanized antibody having *reduced immunogenicity* in a human patient as *compared to its non-humanized parent antibody*," (POR, 18 (emphasis added).) As the Queen references state, the expectation that humanizing a murine mAb would reduce its immunogenicity was the very reason why humanization was undertaken in the first place. (Ex. 1034, 10029; Ex. 1050, Abstract; *see also* Ex. 1138, 102:23-103:5 ("the goal of humanization is to retain binding affinity and reduce immunogenicity"); Ex. 1140, 82:22-83:4; Ex. 1142, 111:1-6 ("Q: And in order to make a human therapeutic agent, the humanized antibody would need to lack immunogenicity compared to the nonhuman parent, right? Otherwise, you would just use the mouse? A: Agreed.").) A POSA would thus have expected that making the antibody more human would make the antibody less immunogenic. (Ex. 1142, 112:5-9, 112:16-21 ("Q: So the fact that there were fewer mouse residues in the humanized variant

versus the parent led to an expectation that is would lack immunogenicity compared to the parent, right? . . . A: Yes."); Ex. 1143, ¶24.) Indeed, the patent does not contain any immunogenicity data, which underscores that the named inventors expected that the humanized mAbs would not be as immunogenic as the murine parent mAbs. Moreover, merely testing the immunogenicity of an otherwise obvious mAb does not render it patentable. *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012).

E. The Limitations Related to Binding $p185^{HER2}$ of Claims 30-31, 33, 42, and 60 Was Taught By the Prior Art

PO argues, in essence, that because there is no disclosure in the prior art of a humanized 4D5 mAb, such an antibody cannot be obvious. (POR, 62-63.) This argument misapplies the law of obviousness. PO's expert admitted that, prior to the date of the alleged invention, it was known that overexpression of $p185^{HER2}$ led to a poor prognosis in cancer, and work had been done to identify antibodies that would target $p185^{HER2}$. (Ex. 1138, 19:7-20:1.) Also prior to the alleged invention, Hudziak identified that the murine antibody 4D5 downregulated $p185^{HER2}$. (Ex. 1021, 1169; Ex. 1004, ¶14; Ex. 1140, 22:1-24:7; Ex. 1138, 19:23-20:25, 22:8-12.) This would have motivated a POSA to use the humanization framework of Queen-1989 and apply that framework to 4D5 to make a therapeutic agent that would downregulate $p185^{HER2}$. (Ex. 1004, ¶16; Ex. 1021; Ex. 1143, ¶28.) Dr. Leonard

confirmed that a POSA would have understood 4D5 to be a promising target for humanization, and the prior art taught a POSA how to humanize the antibody to generate a potential therapeutic agent that bound $p185^{HER2}$. (Ex. 1004, ¶¶48-49.) As explained above, the prior art humanization process would have identified the potential residue substitutions identified in the '213 patent, rending claims 30-31, 33, 42, and 60 obvious.

II. PO's Attempts to Establish an Earlier Date of Invention for Claims 12, 42, 60, 65, 71, 73-74, and 79 Are Insufficient

[redacted]

Here, the default date of invention is June 14, 1991. *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000). Ex. 1001. PO bears the burden to establish an earlier invention date. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576-77 (Fed. Cir. 1996).

Evidence of conception must be corroborated by a non-inventor. *Id.* at 1577 (this "rule provides a bright line for both district courts and the PTO to follow in addressing the difficult issues related to invention dates"). PO stresses the "rule of reason," but that "does not dispense with the requirement for some evidence of independent corroboration." *Coleman v. Dines*, 754 F.2d 353, 360 (Fed. Cir. 1985).

Testimony of one co-inventor cannot be used to help corroborate the testimony of another. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1171-72 (Fed. Cir. 2006).

[redacted]

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[redacted]

Additionally, PO has not established that claims 12, 42, 60, 65, 71, 73-74, and 79 are entitled to priority to the '272 application. The only examples in the '272 application are the eight variants of the humanized 4D5 antibody. (Ex. 2032, 93.) These claims, however, are not limited to these variants. If these claims are not rendered obvious by Queen-1989 and the PDB, the examples from a single humanization project do not disclose to a POSA the applicability of these

substitutions to a different antibody. (Ex. 1143, ¶¶31-32; *see also* Ex. 1138, 143:20-144:24.) As a result, the '272 application does not contain sufficient written description for the full scope of the'213 patent claims, and thus these claims are not entitled to claim priority to the '272 application, making Queen-1990 and Tramontano prior art under 35 U.S.C. §102(b). *See Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004).

III. Secondary Considerations of Non-Obviousness Do Not Render the Challenged Claims Nonobvious

A. The Use of a Consensus Sequence Would Not Have Been Unexpected

PO incorrectly argues that before the '213 patent, it would have been unexpected that it was "even possible to develop a broadly-applicable platform that could be used to humanize different antibodies from the same sequence." (POR, 64.) Both Foote and Queen-1990 teach use of a consensus sequence in humanizing antibodies. (Ex. 1003, ¶173; Ex. 1050, 12:17-20; Ex. 1143, ¶30; Ex. 1193, 106; Ex. 1138, 196:5-197:6.) Given the previous success in humanizing CAMPATH using Foote's consensus sequence, there was nothing unexpected about the broad-applicability of a consensus sequence. (Ex. 1143, ¶30.) Therefore, PO's position that a POSA would not have expected that a consensus sequence could be used to humanize multiple antibodies is incorrect.

Additionally, PO has provided no data to support its claims of unexpectedly superior properties from using a consensus sequence as defined in the patent, as

compared to other prior art humanization methods. [redacted]

PO provides no evidence of any head-to-head comparison regarding the relative binding affinities for the same antibody humanized using the consensus approach and the most homologous approach. (Ex. 1138, 184:16-185:7.)

B. PO Has Not Established that the Alleged Unexpected Results and Commercial Success Have a Nexus to the Challenged Claims

Even if PO could establish unexpected results or commercial success, there is no evidence that these allegedly unexpected results have any nexus to the claims. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311–12 (Fed. Cir. 2006). To the extent PO is relying on the consensus sequence element, this limits only claims 4, 33, 62, 64, and 69. Therefore, as a matter of law, this evidence can only apply to these claims. *See, e.g.*, *Ex Parte Takeshi Shimono,* Appeal 2013–003410 (PTAB Apr. 29, 2015).

Further, PO relies on data relating to Herceptin to support its claims of enhanced binding and reduced immunogenicity, but PO has not established that

Herceptin is an embodiment of the claims. The '213 patent defines a "consensus human variable domain" as "a human variable domain 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, 11:32-38.) [redacted]

Moreover, the evidence of record indicates that the human framework of Herceptin does not comprise the "most frequently-occurring amino residues at each location *in all human immunoglobulins*." Kabat-1991 added sequences to those listed in Kabat-1987. This caused the consensus for residue 73H to change. (*Compare* Ex. 1054 *with* Ex. 1055; Ex. 1143, ¶34.) This change in Kabat 1991 shows that residue 73H in the framework of Herceptin is not the most frequently-occurring amino acids in all human immunoglobins at that position, and thus does

not fall within the definition of "human consensus variable domain." (Ex. 1143, ¶35.)

PO additionally relies on Perjeta, Avastin, Lucentis, and Xolair as purported evidence of commercial success. PO, however, has not established that any of these antibodies are embodiments of any of the claims of the '213 patent. (Ex. 2041, ¶263; Ex. 1142, 43:24-44:4; Ex. 1140, 36:2-37:3.) Thus, PO has not established the required nexus with the claims.

PO also presents sales figures, without putting them in context of the market as a whole. (POR, 66.) This is insufficient to establish commercial success. *See, e.g.*, *St. Jude Med., Cardiology Division, Inc. v. Board of Regents of the Univ. of Mich.*, IPR2013-00041, Paper 69, 24-28 (PTAB May 1, 2014).

PO has not rebutted the obviousness of the challenged claims of the '213 patent. The Board should, therefore, find all challenged claims invalid as obvious over the prior art.

Dated: May 25, 2018

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WORD COUNT CERTIFICATION

The undersigned certifies that the attached Petitioner's Reply to Patent Owner's Response contains 5,571 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 25, 2018

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 25th day of May, 2018, I caused a copy of this Petitioner's Reply to PO's Response and Exhibits 1133-1136, 1138-1145, and 1193-1196 to be served by email on the lead and back up counsel for Patent Owner at:

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