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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01373
Patent 6,407,213

PATENT OWNER'S RESPONSE

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I. INTRODUCTION

U.S. Patent No. 6,407,213 claims humanized antibodies with amino acid substitutions at specific positions. Unlike prior art humanized antibodies—which required handpicking a unique human framework sequence for each antibody—the claimed antibodies could be produced from a single human "consensus" sequence, which is a composite of all human antibody framework sequences of a particular subclass or subtype. The '213 invention thus provides a broadly-applicable humanization platform, which has produced numerous successful drugs, including treatments for cancer, asthma, and macular degeneration.

In its preliminary response, Patent Owner identified several deficiencies in Petitioner's proof for all challenged claims. However, to narrow the issues, Patent Owner now focuses on a subset of the challenged claims and presents specific reasons why Petitioner has failed to carry its burden for those claims. Patent Owner's response is supported by new evidence obtained from cross-examination of Petitioner's declarants Dr. Lutz Riechmann (Ex-2039) and Dr. Robert Leonard (Ex-2040), as well as the declaration of Dr. Ian Wilson (Ex-2041) submitted herewith.

First, the Board should confirm the patentability of claims 12, 42, 60, 65, 71, 73-74, and 79[1] because the inventors conceived and actually reduced to practice those claims prior to the publication of Queen-1990 and Tramontano. That prior reduction to practice is corroborated by several non-inventors whose contemporaneous notebooks confirm that the inventors made humanized antibodies embodying the claims and verified that they would work for their intended purpose before July 26, 1990. In addition, although Petitioner purport to rely upon Queen-1989 for Grounds 1, 3, and 6, Petitioner's obviousness theory in those grounds actually rests on Queen-1990 (which Petitioner's expert explicitly cites as the basis for his analysis). If the Board finds Queen-1990 antedated, then it should also reject Petitioner's challenge to those claims in Grounds 1, 3, and 6.

Second, the Board should confirm the patentability of claims 12, 42, 60, 65-67, and 71-79, Petitioner's analysis of the Queen references combined with the PDB database discloses numerous potential framework substitutions. In fact, the record now shows that applying Petitioner's own analysis of the PDB structures encompasses many more framework substitutions than the selective subset that

[1] Many claims have been challenged in multiple grounds. Patent Owner explains below (§VII) how the issues summarized in this introductory section correspond with the instituted grounds.

Petitioner cited in its petition. That broad disclosure does not render obvious claims 12, 42, 60, 65-67, and 71-79, which narrowly require at least one and up to five specific framework substitutions. Nor would those specific claimed framework substitutions have been obvious to try. What Petitioner cites is not a "small" or "easily traversed" number of possibilities in the context of antibody humanization, particularly as of 1991 when the field was still nascent. And the record also confirms that the high degree of unpredictability of making framework substitutions, where even a single substitution can affect antigen binding in unpredictable ways.

Third, Petitioner has failed to show that Queen-1990, or Queen-1989 alone or combined with Kabat-1987, teaches the "consensus" sequence limitations of claims 4, 33, 62, 64, and 69. As the Board recognized in its institution decision, the '213 patent expressly defines "consensus" sequence, as a sequence generated from "***all*** human immunoglobulins of any particular subclass or subunit structure." Queen-1990, however, describes "a consensus framework from ***many*** human antibodies," not "all." Dr. Wilson explains that a skilled artisan would understand that Queen-1990's "consensus framework" is referring to a sequence generated from a subset of antibodies, which differs from what the '213 patent requires. Queen-1989 does not even mention a consensus sequence, and Dr. Wilson explains

that Petitioner's proposed combination with Kabat-1987 in Ground 5 would not have led to the consensus sequence of the '213 patent.

Fourth, claims 30-31, 33, 42, and 60 require an antibody with the recited substitutions that binds a specific antigen called "$p185^{HER2}$." Petitioner has not shown that such an antibody would have been obvious. Petitioner merely cites the general disclosure of references involving humanized antibodies for different antigens and presents no evidence that those general techniques would result in the claimed substitutions when applied to an antibody that binds $p185^{HER2}$.

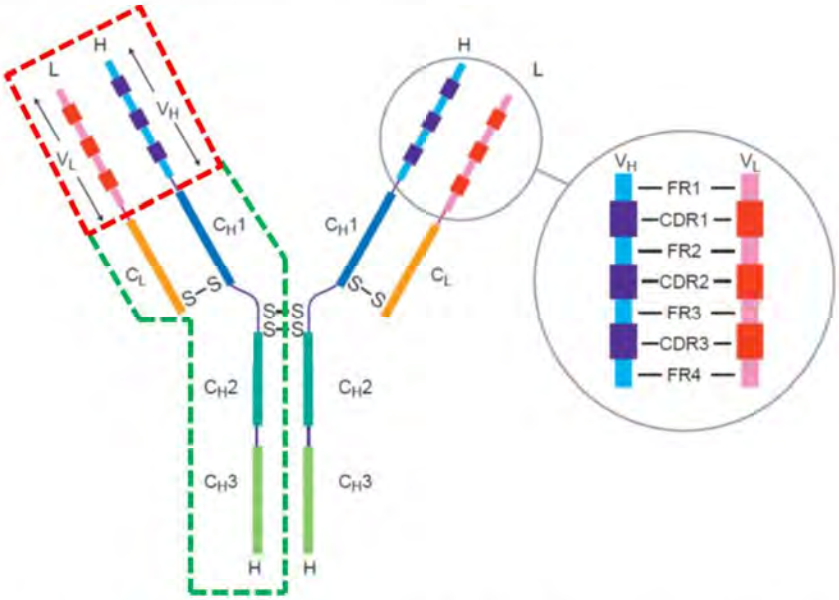
Finally, claims 63 and 65 contain additional limitations requiring that the antibody "lacks immunogenicity" or has "up to 3-fold more" binding affinity as compared with the parent non-human antibody. Petitioner presented no evidence of any antibody disclosed in the asserted references that has those properties. And the record now confirms that these properties are highly unpredictable and that a skilled artisan would not have had a reasonable expectation of success in achieving those specific claim limitations.

II. TECHNOLOGY BACKGROUND

A. Antibody "Variable" And "Constant" Domains

The immune system defends against foreign substances called "antigens," by producing antibodies. Antibodies are proteins that bind to antigens. (Ex-2041 ¶33;

Ex-1082 at 160.) A typical antibody, or "immunoglobulin," has two identical heavy chains and two identical light chains:



(Ex-2041 ¶33; Ex-2023 at 10 (annotated); Ex-1001, 1:17-20.) Each chain contains a "variable" domain (red box above) and "constant" domains (green box above). (Ex-2041 ¶35; Ex-1001, 1:20-27.) The heavy chain (V_H) and light chain (V_L) variable domains are illustrated above in blue and pink, respectively.

Variable domains directly bind to the antigen. (Ex-2041 ¶37; Ex-1001, 1:35-37.) Each variable domain contains three "complementarity determining regions," or "CDRs," (Ex-2041 ¶38; Ex-1001, 1:35-50), shown as CDR1, CDR2, and CDR3 in the enlarged portion above. Variable domains also contain four "framework regions," or "FRs"—one on either side of each CDR—shown as FR1, FR2, FR3, and FR4 in the same enlarged portion. The framework regions form a

core structure from which the CDRs extend and form a binding site for the antigen. (Ex-2041 ¶40; Ex-1001, 1:47-50.) Unlike the CDRs, which generally contain unique amino acids (or "residues") for a particular antigen, the framework regions typically share more amino acid sequences in common (*i.e.*, the same amino acids at the same positions) across other antibodies. (Ex-2041 ¶39; Ex-1001, 1:37-44.)

The constant domains are not directly involved in antigen binding and typically have similar amino acid sequences across all antibodies within a subclass. (Ex-2041 ¶36; Ex-2016 ¶15.)

B. "Humanized" Antibodies

Before the '213 patent, antibodies targeting a specific antigen could be obtained from animals (*e.g.*, mice). (Ex-2041 ¶48; Ex-1001, 1:52-58.) Those non-human antibodies, however, had limited use therapeutically because the human immune system would over time identify them as antigens and attack them—known as an "immunogenic" response. (Ex-2039, 159:5-11; Ex-2041 ¶50; Ex-1001, 1:55-58.) An immunogenic response had adverse clinical consequences, including diminished efficacy and allergic reactions. (Ex-2041 ¶51.)

Scientists developed several techniques seeking to address immunogenicity. One involved "chimeric" antibodies that combined a non-human variable domain with a human constant domain. (Ex-2041 ¶53; Ex-1001, 1:59-2:19.) However, immunogenicity could still result because chimeric antibodies retained a significant

portion of the non-human antibody sequence. (Ex-2039, 242:3-20; Ex-2041 ¶54; Ex-1001, 2:12-19; Ex-2022 at 2156.)

Scientists also created "humanized" antibodies containing a human variable domain substituted with the amino acid sequence of the non-human CDRs. (Ex-2041 ¶55; Ex-1001, 2:20-52.) But that approach could reduce the antibody's ability to bind to specific antigens. (Ex-2041 ¶61; Ex-1034 at 10033.)

Scientists pursued techniques for making humanized antibodies that balanced strong binding with low immunogenicity. (Ex-2041 ¶61.) For example, Queen-1989 (Ex-1034) chose an existing human framework that was "as homologous as possible to the original mouse antibody to reduce any deformation of the mouse CDRs." (Ex-1034 at 10033.) The humanized sequence was then further refined using computer modeling "to identify several framework amino acids in the mouse antibody that might interact with the CDRs or directly with antigen, and these amino acids were transferred to the human framework along with the CDRs." (*Id.*) That technique became known as the "best-fit" approach because it started from an existing human sequence with the closest match to the non-human antibody. (Ex-2041 ¶¶56-60; Ex-2024 at 4184.)

Even using the best-fit approach, however, it still was difficult to produce an antibody with both strong binding and low immunogenicity. (Ex-2041 ¶¶68; Ex-1001, 3:50-52.) The best-fit approach also was inefficient because it required

identifying a new human framework sequence for each different humanized antibody. (Ex-2041 ¶¶85, 261-62.)

III. '213 PATENT

A. Invention

Beginning in the late 1980s, the inventors of the '213 patent—Drs. Paul Carter and Leonard Presta at Genentech—developed a new approach to humanizing antibodies that solved the prior art binding and immunogenicity problems. Rather than starting from the most homologous human sequence of an actual antibody, the inventors developed an artificial "consensus human sequence"—*i.e.*, "an amino acid sequence which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." (Ex-1001, 11:32-38.) That "consensus" sequence provided a single human sequence for ***any*** humanized antibody of a particular subclass or subunit structure (*e.g.*, light chain κ1). (*Id.*, 54:66-56:57.)

The '213 inventors developed a multi-step process for their approach. First, they added the non-human CDRs to the human consensus sequence. (*Id.*, 20:12-31.) Next, they evaluated the differences between the framework regions of the non-human antibody and the human consensus sequence to determine whether further modifications to the consensus sequence were needed. (*Id.*, 20:32-40.)

Where the non-human antibody framework sequence differed from the human consensus sequence, the inventors used computer modeling to identify whether the different non-human amino acid (i) "non-covalently binds antigen directly"; (ii) "interacts with a CDR"; (iii) "participates in the V_L-V_H interface," *i.e.*, the interface between variable domains of the heavy and light chains, or (iv) is a glycosylation site outside the CDRs that is likely to affect "antigen binding and/or biological activity." (*Id.*, 20:32-21:36, 54:64-56:57.) The inventors believed that those positions were important to maintaining binding affinity. (*Id.*, 20:32-35.) If any of those requirements was met, that position in the consensus sequence could be substituted with the amino acid at the same position in the non-human antibody. Otherwise, the sequence of the human consensus sequence was retained. (*Id.*, 20:66-21:8.)

The '213 claims reflect the inventors' novel consensus sequence approach. They require a "humanized" antibody or variable domain that contains non-human CDRs that bind antigen when incorporated into the human framework sequence and certain specified framework substitutions that the inventors determined were important to antibody binding in their consensus sequence. (Ex-2016 ¶31.)

B. Advantages Of '213 Invention

Antibodies containing the '213 patent's consensus sequence were a significant advance over the prior art.

First, the '213 patent's consensus sequence addressed the immunogenicity problems of other humanization techniques. (Ex-1002 at 456-58, ¶¶2-9; Ex-2041 ¶83.) At the same time, humanized antibodies embodying the '213 invention retained strong binding affinity, or even have improved binding over the original non-human antibody. (Ex-1001, 4:24-28, 51:50-53; Ex-2041 ¶83.)

Second, unlike the prior art best-fit approach that used a unique human sequence for each antibody, the '213 patent provided a single human sequence that could be applied to a wide variety of antibodies. (Ex-1002 at 456-58, ¶¶2-9; Ex-2041 ¶85.) That broadly-applicable platform is reflected in the '213 patent's claims that specifically require a consensus sequence or that recite framework substitutions derived from that consensus sequence. (Ex-2041 ¶85.) Genentech has used the '213 invention to develop numerous drugs, including Herceptin® (breast and gastric cancer), Perjeta® (breast cancer), Avastin® (colon, lung, ovarian, cervical, kidney, and brain cancer), Lucentis® (macular degeneration), and Xolair® (asthma). (Ex-2017 ¶4; Ex-2016 ¶5.)

C. Prosecution History

The '213 patent is a continuation-in-part of an application filed on June 14, 1991. (Ex-1001 at 1.) The challenged claims issued over hundreds of references considered during prosecution, including every reference in the instituted grounds. (Ex-1001 at 1-6.)

During prosecution, the applicants successfully antedated U.S. Patent No. 5,693,762, which had a filing date of September 28, 1990. (Ex-1002 at 710-11, 721.) As detailed below, the record in this proceeding further confirms that certain challenged claims were also invented before the publication of either Queen-1990 (July 26, 1990) or Tramontano (September 5, 1990).

IV. ASSERTED REFERENCES

A. Queen-1989

Queen-1989 describes the humanization of a murine anti-Tac antibody. (Ex-1034 at 10029.) Unlike the '213 patent, Queen-1989 does not disclose or suggest the use of a generalized "consensus" sequence. (Ex-2041 ¶109.) Instead, Queen-1989 used a best-fit approach, which involved (i) identifying a framework sequence of an actual human antibody that was "as homologous as possible to the original mouse antibody" (Ex-1034 at 10033); and (ii) incorporating the murine CDRs into that human sequence (Ex-1034 at 10033). (Ex-2041 ¶¶107, 109.)

Queen-1989 then identified additional locations in the human framework to substitute with murine residues. If the human framework contained "atypical" residues, Queen-1989 substituted them with more commonly-occurring amino acids from the murine antibody. (Ex-1034 at 10032.) Queen-1989 also used a computer model of the murine antibody "to identify several amino acids which, while outside the CDRs, are likely to interact with the CDRs or antigen." (Ex-

1034 at 10029.) Using those techniques, Queen-1989 made a humanized antibody with 15 framework substitutions—none of which fall within the scope of the challenged claims. (Ex-1034 at 10031-32; Ex-2041 ¶105.)

B. Queen-1990

Queen-1990 is a PCT application published July 26, 1990. It is not prior art to certain challenged claims. (*Infra* §VIII.A.)

Queen-1990 used a best-fit approach to produce a humanized antibody. (Ex-1050, 26:5-33:25; Ex-2041 ¶¶110-11.) Queen-1990 identified four general criteria for designing humanized antibodies. (Ex-2041 ¶¶111-19.)

Criterion I: Queen-1990 emphasized the importance of choosing the human sequence most similar to the non-human antibody to reduce the possibility of distorting the binding site formed by the CDRs. (Ex-1050, 12:17-35.) Queen-1990 mentioned "a consensus framework from many human antibodies" (*id.*, 12:19-20), but included no details of what that "consensus framework" might be or how it might be used to make a humanized antibody. (Ex-2041 ¶¶113.) Indeed, Petitioner's expert, Dr. Riechmann conceded that the term as used in Queen-1990 was "ambiguous." (Ex-2039, 284:10-13.)

Criterion II: After selecting a best-fit human framework sequence, Queen-1990 provided that "unusual" or "rare" amino acids could be replaced with more common amino acids from the non-human sequence. (Ex-1050, 13:22-32.) This

step was intended to eliminate residues that may "disrupt the antibody structure" by replacing them with non-human residues commonly found in other human antibody sequences. (*Id.*, 13:32-37.)

Criterion III: Queen-1990 disclosed that non-human residues may be used immediately adjacent to CDRs to help maintain binding affinity. (*Id.*, 14:1-12.) But as Petitioner's expert Dr. Riechmann confirmed, substituting residues at these positions is "optional, not mandatory." (Ex-2039, 289:20-22.) Queen-1990 provides no guidance on which of these residues should be substituted for any given antibody. Indeed, as Dr. Riechmann noted, "[t]hat would not be a sensible thing to do" because substitutions would vary according to the particular antibody to be humanized, and "the structural components in each case are different." (Ex-2039, 291:22-292:10.)

Criterion IV: Queen-1990 used computer modeling, "typically of the original donor antibody," to identify other residues that "have a good probability of interacting with amino acids in the CDR's [sic] by hydrogen bonding, Van der Waals forces, hydrophobic interactions, etc." (Ex-1050, 14:14-19.) Non-human residues "may [or] may not" be substituted at those positions that may interact with CDRs "depending on the particular antibody that you're trying to humanize." (Ex-2039, 294:5-8; Ex-1050, 14:19-21.) Amino acids satisfying this criterion

"generally have a side chain atom within about 3 angstrom units of some site in the CDR's [sic]." (Ex-1050, 14:22-25.)

Queen-1990 disclosed a humanized antibody sequence produced using its technique. (*Id.*, Fig. 2.) That antibody contained 15 framework substitutions—none of which correspond with the '213 claims. (Ex-2041 ¶122.) Queen-1990 states that the antibody produced using its technique had a binding affinity ***within*** about 3- to 4-fold of the parent murine antibody, but does not indicate any ***improvement*** in binding affinity for the humanized antibody. (Ex-2041 ¶123; Ex-1050, 31:33-37.) Queen-1990 does not describe or report any testing of immunogenicity for this humanized antibody. (Ex-2041 ¶123.)

C. Protein Data Bank

The Protein Data Bank ("PDB") "was established in 1971 as a computer-based archival file for macromolecular structures." (Ex-1080 at 535.) As of 1991, the PDB included structural information for only a small number of antibodies or antibody fragments, whose crystal structure had been solved—a process that at the time could take several years for a single antibody. (Ex-2041 ¶154.) As a database, the PDB does not describe the humanization of antibodies, let alone what substitutions may be relevant for any particular antibody. (Ex-2041 ¶155.)

Petitioner cites data from nine antibody crystal structures available in the PDB database prior to August 1989. (Ex-1003C, Riechmann Exs. D-L.) As

discussed below, Petitioner contends that those crystal structures would have supposedly led to numerous possible framework substitutions.

D. Tramontano

Tramontano (Ex-1051) was published on September 5, 1990. (Ex-2027 (showing date).) Tramontano is not prior art to certain claims. (*Infra* §VIII.A.)

Tramontano analyzed several antibody structures and found that "the major determinant" of the position of one of the CDRs "is the size of the residue at [heavy chain] site 71." (Ex-1051 at 175.) Tramontano discussed potential "applications to antibody engineering," explaining that "[f]or the binding site of the synthetic product to be the same as that in the original antibody, the frameworks should have the same residues at those sites important for the positions and conformations of the hypervariable regions." (Ex-1051 at 181.) Tramontano, however, never suggested that substitutions at position 71H were desirable. (Ex-2041 ¶149.)

Instead, Tramontano discussed humanized antibodies reported in Jones (Ex-1033), Verhoeyen (Ex-1068), and Riechmann (Ex-1069). (Ex-1051 at 181; Ex-2041 ¶150.) Jones had the same residue at 71H as the parent antibody and "had the same affinity … as the original mouse antibody." (Ex-1051 at 181; Ex-2041 ¶150.) By contrast, Verhoeyen (Ex-1068) included a different residue at 71H than the murine antibody and saw a 10-fold reduction in binding affinity. (Ex-1051 at

181; Ex-2041 ¶150.) Finally, Riechmann (Ex-1069) had a different residue at 71H, but maintained a binding affinity "close to that of the rat original." (Ex-1051 at 181; Ex-2041 ¶151.) Tramontano had no explanation for those divergent results. (Ex-1051 at 181; Ex-2041 ¶¶150-51.)

E. Kabat-1987

Kabat-1987 (Ex-1052) is a reference book of antibody sequences that includes statistics on the most common amino acids for a given type of immunoglobulin. (*Id.* at 8; Ex-2041 ¶156.)

Kabat-1987 does not describe antibody humanization or discuss substitutions that may be beneficial when humanizing an antibody. (Ex-2041 ¶157.) Rather, Kabat-1987's tabulation of the "most common" amino acids was intended to help scientists evaluate whether their sequence for a given antibody was likely to be correct. (Ex-2026 at 3 ("It is also possible, by examining the numbers of sequences at the end of each table and the summary tables, to evaluate the probability that a given amino acid at a given position may not be correct.").)

F. Hudziak

Hudziak (Ex-1021) is a 1989 publication that studied human breast cancer cells overexpressing the cellular receptor called "$p185^{HER2}$." Hudziak prepared a murine monoclonal antibody ("4D5") that binds to the extracellular domain of $p185^{HER2}$ and found that it "inhibit[ed] in vitro proliferation of human breast tumor

cells overexpressing $p185^{HER2}$." (Ex-1021 at 1165.) Hudziak does not describe antibody humanization or discuss substitutions that may be beneficial to antibody humanization. (Ex-2040, 149:9-20, 150:20-151:3; Ex-2041 ¶146.)

V. PERSON OF ORDINARY SKILL

A person of ordinary skill for the '213 patent would have had a Ph.D. or equivalent in chemistry, biochemistry, structural biology, or a closely related field, and experience with antibody structural characterization, engineering, and/or biological testing, or an M.D. with practical academic or industrial experience in antibody development. (Ex-2041 ¶96.) The Board adopted this definition in its institution decision. (Paper 16 at 10-11.)

VI. CLAIM CONSTRUCTION

For purposes of this proceeding, "consensus human variable domain" (claims 4, 33, 62, and 69) should mean "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." That construction comes from an express definition provided in the '213 patent (Ex-1001, 11:32-38) and is consistent with Petitioner's expert's understanding of the term (Ex-2040, 116:13-117:1.) Under principles of lexicography, that express definition controls. *Sinorgchem Co. v. Int'l Trade Comm'n*, 511 F.3d 1132, 1136

(Fed. Cir. 2007). The Board adopted this construction in its institution decision. (Paper 16 at 7-8.) Patent Owner submits that this continues to be the correct result.

Petitioner has proposed constructions of several terms. (Paper 2 at 13-15.) As the Board recognized in its institution decision, no construction of those terms is necessary. (Paper 16 at 7.)

In a related proceeding, the Board construed "lacks immunogenicity" in claim 63 "as referring to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody." (IPR2017-01488, Paper 27 at 12.) For purposes of this proceeding, Patent Owner does not dispute that construction.

VII. SUMMARY OF ARGUMENT

The instituted grounds involve overlapping claims and issues. To facilitate the Board's review, the following summary identifies the basis for confirming the patentability of the claims challenged in each ground.

Ground 1: The Board should confirm the patentability of (1) claims 12, 65, 71, 73-74, and 79 because, although Petitioners purport to rely upon Queen-1989, their obviousness theory actually rests on Queen-1990, which has been antedated (*infra* §VIII.B); (2) claims 12, 65-67, and 71-79 because it would not have been obvious to select the specific claimed framework substitutions from the broad genus of potential framework substitutions supposedly disclosed in the asserted

references with a reasonable expectation of success that the resulting antibody would bind antigen (*infra* §VIII.C); (3) claim 65 because it would not have been obvious that an antibody substitutions with substitutions at 71H, 73H, 78H, and 93H would have "up to 3-fold more" binding affinity than the parent antibody (*infra* §VIII.E); and (4) claim 63 because, given the unpredictability of immunogenicity, it would not have been obvious that an antibody produced according to Queen-1989 "lacks immunogenicity compared to [its] non-human parent antibody" (*infra* §VIII.F). Patent Owner does not defend the patentability of claims 1-2, 25, 29, and 80-81.

Ground 2: The Board should confirm the patentability of (1) claims 12, 65, 71, 73-74, and 79 because Queen-1990 has been antedated (*infra* §VIII.A); (2) claims 12, 65-67, and 71-79 because it would not have been obvious to select the specific claimed framework substitutions from the broad genus of potential framework substitutions supposedly disclosed in the asserted references with a reasonable expectation of success that the resulting antibody would bind antigen (*infra* §VIII.C); (3) claims 4, 62, 64, and 69 because Queen-1990 does not teach a "consensus" sequence as defined by the '213 patent (*infra* §VIII.D); (4) claim 65 because it would not have been obvious that an antibody substitutions with substitutions at 71H, 73H, 78H, and 93H would have "up to 3-fold more" binding affinity than the parent antibody (*infra* §VIII.E); and (5) claim 63 because, given

the unpredictability of immunogenicity, it would not have been obvious that an antibody produced according to Queen-1989 "lacks immunogenicity compared to [its] non-human parent antibody" (*infra* §VIII.F). Patent Owner does not defend the patentability of claims 1-2, 25, 29, and 80-81.

Ground 3: The Board should confirm the patentability of (1) claims 65 and 79 because Tramontano has been antedated (*infra* §VIII.A) and because, although Petitioners purport to rely upon Queen-1989, their obviousness theory actually rests on Queen-1990, which has been antedated (*infra* §VIII.B); (2) claims 65, 75-77, and 79 because it would not have been obvious to select the specific claimed framework substitutions from the broad genus of potential framework substitutions supposedly disclosed in the asserted references with a reasonable expectation of success that the resulting antibody would bind antigen (*infra* §VIII.C); and (3) claim 65 because it would not have been obvious that an antibody substitutions with substitutions at 71H, 73H, 78H, and 93H would have "up to 3-fold more" binding affinity than the parent antibody (*infra* §VIII.E).

Ground 4: The Board should confirm the patentability of (1) claims 65 and 79 because Queen-1990 and Tramontano have been antedated (*infra* §VIII.A); (2) claims 65, 75-77, and 79 because it would not have been obvious to select the specific claimed framework substitutions from the broad genus of potential framework substitutions supposedly disclosed in the asserted references with a

reasonable expectation of success that the resulting antibody would bind antigen (*infra* §VIII.C); and (3) claim 65 because it would not have been obvious that an antibody substitutions with substitutions at 71H, 73H, 78H, and 93H would have "up to 3-fold more" binding affinity than the parent antibody (*infra* §VIII.E).

Ground 5: The Board should confirm the patentability of claims 4, 62, 64, and 69 because Queen-1989 and Kabat-1987 do not teach a "consensus" sequence as defined by the '213 patent (*infra* §VII.D).

Ground 6: The Board should confirm the patentability of (1) claims 42 and 60 because, although Petitioners purport to rely upon Queen-1989, their obviousness theory actually rests on Queen-1990, which has been antedated (*infra* §VIII.B); (2) claims 42 and 60 because it would not have been obvious to select 66L from the broad genus of potential framework substitutions supposedly disclosed in the asserted references with a reasonable expectation of success that the resulting antibody would bind antigen (*infra* §VIII.C); and (3) claims 30, 31, 42, and 60 because it would not have been obvious that an antibody with the recited framework substitutions would bind $p185^{HER2}$ (*infra* §VIII.G).

Ground 7: The Board should confirm the patentability of (1) claims 42 and 60 because Queen-1990 has been antedated (*infra* §VIII.A); (2) claims 42 and 60 because it would not have been obvious to select 66L from the broad genus of potential framework substitutions supposedly disclosed in the asserted references

with a reasonable expectation of success that the resulting antibody would bind antigen (*infra* §VIII.C); and (3) claims 30, 31, 42, and 60 because it would not have been obvious that an antibody with the recited framework substitutions would bind $p185^{HER2}$ (*infra* §VIII.G).

VIII. ARGUMENT

A. Grounds 2-4, 7: The Board Should Confirm The Patentability Of Claims 12, 42, 60, 65, 71, 73-74, And 79 Because Neither Queen-1990 Nor Tramontano Is Prior Art.

Grounds 2-4 and 7 rest on Queen-1990 and/or Tramonanto. In its preliminary response, Patent Owner presented antedation evidence for every challenged claim. (Paper 9 at 19-42.) The Board, however, declined to deny institution because Petitioner had not yet had an opportunity to cross-examine Patent Owner's witnesses regarding the antedation evidence. (Paper 16 at 10.)

To simplify the issues, Patent Owner now focuses its antedation contentions only on claims 12, 42, 60, 65, 71, 73-74, and 79. As demonstrated by declarations of inventors Drs. Paul Carter (Ex-2017) and Leonard Presta (Ex-2016), and corroborated by the declaration of Mr. John Brady (Ex-2018) and contemporaneous records from several non-inventors, the '213 inventors conceived and actually reduced to practice those eight claims before the publication of Queen-1990 or Tramontano.

1. The inventors made and tested HuMAb4D5-5 and HuMAb4D5-8 before July 26, 1990.

a) Consensus sequence

In 1989, Genentech scientists Drs. Paul Carter and Leonard Presta began pursuing a new technique for humanizing antibodies. (Ex-2017 ¶¶3-4; Ex-2016 ¶¶5, 22-23.) At that time, no one had successfully developed a therapeutic humanized antibody. In fact, many scientists were skeptical of using antibodies therapeutically because they could provoke an immunogenic response. (Ex-2017 ¶19; Ex-2016 ¶¶16-21.)

Drs. Carter and Presta, however, conceived of a novel strategy for minimizing immunogenicity. Rather than starting from the sequence of another human antibody, as done in the prior art best-fit approach, they sought to develop an artificial human "consensus" sequence consisting of the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure. (Ex-2017 ¶¶19-20; Ex-2016 ¶¶23-24.) They believed that this approach would reduce immunogenicity by avoiding reliance on a specific human antibody sequence, which may contain unique variations that might result in immunogenicity. (Ex-2017 ¶19; Ex-2016 ¶24.) They also hoped to provide a more efficient platform by using a single sequence as the starting point for antibody humanization. (Ex-2017 ¶19; Ex-2016 ¶24.)

Drs. Carter and Presta decided to apply that novel concept to humanize a murine antibody called "4D5," which binds to a cellular receptor ($p185^{HER2}$) associated with an aggressive form of breast cancer. (Ex-2017 ¶21.) Genentech scientists had previously studied the murine 4D5 antibody and observed in preclinical *in vitro* cell studies that it could inhibit the growth of tumors overexpressing $p185^{HER2}$. (Ex-1021 at 1165.)

[redacted]

[redacted])[2]

b) Humanized 4D5 antibody sequences

[redacted]

[2] Irene Loeffler, Genentech's records custodian for laboratory notebooks, establishes the authenticity and admissibility of the notebooks discussed herein as business records. (Ex-2019 ¶¶3-7.)

[redacted]

[redacted]

c) Production and testing of humanized 4D5 antibodies

[redacted]

[redacted]

(i) First humanized 4D5 variable domain fragment

[redacted]

[redacted]

(ii) First humanized 4D5 full-length antibody

[redacted]

[redacted][3] [redacted]

[redacted]

[redacted]

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[3] [redacted]

(iii) Other humanized 4D5 variants

The '213 inventors made five other humanized 4D5 antibodies with different substitutions.[4] [redacted]

[4] The other variants are HuMAb4D5-3, HuMAb4D5-4, HuMAb4D5-6, HuMAb4D5-7, and HuMAb4D5-8 in the '213 patent. (Ex-2017 ¶¶67, 76; Ex-2016 ¶50.)

[redacted]

[5] [redacted]

[6] Petitioner's expert, Dr. Leonard, confirmed that as of 1991, "there was skepticism" among skilled artisans as to "whether or not antibodies would ultimately prove useful for the treatment of solid tumor cancers." (Ex-2040, 65:11-19.) At the time, humanization was "still in its early stages," and scientists and clinicians "did not know about the potential for humanizing which emerged during that time." (Ex-2040, 51:17-52:10.) Petitioners' experts recognized "a whole list of" challenges associated with antibody-based cancer therapies at the time, including antibodies not being "sufficiently cytotoxic" or "not adequately harness[ing] the patients' own effector mechanisms." (Ex-2040, 143:16-144:21; *see id.*, 139:13-141:7; Ex-2039, 191:14-193:7, 195:7-197:9; Ex-2059 at 647; Ex-2060 at 732.) That the inventors created the first FDA-approved humanized monoclonal antibody for cancer therapy in the face of such skepticism makes the

2. HuMAb4D5-5 and HuMAb4D5-8 demonstrate actual reduction to practice of claims 12, 42, 60, 65, 71, 73-74, and 79 before July 26, 1990.

To antedate a reference under 35 U.S.C. § 102(a), an inventor must show, "with sufficient documentation, that [he] was in possession of the later-claimed invention before the effective date of the reference." *In re Steed*, 802 F.3d 1311, 1316 (Fed. Cir. 2015). Such prior invention can be shown with evidence that the inventor actually reduced the invention to practice prior to the publication of the reference. *Id.*

"To demonstrate an actual reduction to practice, the applicant must have: (1) constructed an embodiment or performed a process that met all the limitations of the claim and (2) determined that the invention would work for its intended purpose." *Id.* at 1318. An inventor's testimony establishing prior invention must be corroborated, applying a "rule of reason" analysis. *In re NTP, Inc.*, 654 F.3d 1279, 1291 (Fed. Cir. 2011). "Under the rule of reason, the evidence 'must be considered as a whole, not individually.' Thus, an inventor's conception can be corroborated even though 'no one piece of evidence in and of itself' establishes that fact, and even through circumstantial evidence." *NFC Tech., LLC v. Matal*,

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'213 patent invention all the more remarkable. (Ex-2053 at 56; Ex-2039, 90:16-19, 189:17-20.)

871 F.3d 1367, 1372 (Fed. Cir. 2017) (citations omitted). As detailed below, the inventors' work preparing and testing HuMAb4D5-5 and HuMAb4D5-8 demonstrates actual reduction to practice of claims 12, 42, 60, 65, 71, 73-74, and 79 before July 26, 1990. (*See* Ex-2017 ¶79; Ex-2016 ¶53.)

a) HuMAb4D5-5 and HuMAb4D5-8 embody claims 12, 42, 60, 65, 71, 73-74, and 79.

Claims 12, 42, 60, 65, 71, 73-74, and 79 require at least three elements: (i) a "humanized" antibody or variable domain, which binds to an antigen; (ii) "non-human" CDRs; and (iii) one or more specified framework substitutions. HuMAb4D5-5 and HuMAb4D5-8 embody those limitations, as shown below for representative claim 79.[7]

Claim Language	HuMAb4D5-5	HuMAb4D5-8
79. A humanized variant of a non-human parent antibody, which binds to an antigen,	HuMAb4D5-5 is a humanized variant of the murine 4D5 antibody, which binds to the antigen $p185^{HER2}$. (Ex-2016 ¶¶45-48; Ex-2017 ¶¶58-66, 76; Ex-2018 ¶¶13-17; Ex-2003 at 97; Ex-2004 at 44-46; Ex-2005 at 73; Ex-	HuMAb4D5-8 is a humanized variant of the murine 4D5 antibody, which binds to the antigen $p185^{HER2}$. (Ex-2016 ¶¶45-48, 50-51; Ex-2017 ¶¶67-68, 75-77; Ex-2018 ¶¶14-15, 22-24; Ex-2006 at 84-85; Ex-2009 at 7-8.)

[7] Other humanized 4D5 antibodies prepared and tested before July 26, 1990 also meet these limitations. For simplicity, Patent Owner focuses on HuMAb4D5-5 (the first humanized 4D5 antibody) and HuMAb4D5-8 (Herceptin®).

Claim Language	HuMAb4D5-5	HuMAb4D5-8
	2006 at 47, 51; Ex-2008 at 6.) Before July 26, 1990, the inventors had made HuMAb4D5-5 (Variant 1 with "a" light and heavy chains) and confirmed that it binds p185^{HER2}, as corroborated by the binding assay results reported in Mr. Hotaling's and Mr. Brady's laboratory notebooks. (Ex-2017 ¶¶58-66, 76; Ex-2018 ¶¶13-17; Ex-2003 at 97; Ex-2004 at 44-46; Ex-2005 at 73; Ex-2006 at 47, 51; Ex-2008 at 6.)	Before July 26, 1990, the inventors had made HuMAb4D5-8 (Variant 6 with "c" light and heavy chains) and confirmed that it binds p185^{HER2}, as corroborated by the binding assay results reported in Mr. Brady's and Ms. Carver's laboratory notebooks. (Ex-2017 ¶75; Ex-2018 ¶¶13-15, 22-24; Ex-2006 at 84-85; Ex-2009 at 7-8.)
wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-human antibody incorporated into a human antibody variable domain,	HuMAb4D5-5 contains the non-human CDRs from the murine 4D5 antibody, which are incorporated into a human antibody variable domain—here, the human consensus sequence. (Ex-2016 ¶¶45-48; Ex-2017 ¶¶23-27, 68, 76; Ex-2018 ¶¶13-15.)	HuMAb4D5-8 contains the non-human CDRs from the murine 4D5 antibody, which are incorporated into a human antibody variable domain—here, the human consensus sequence. (Ex-2016 ¶¶45-48, 51; Ex-2017 ¶¶23-27, 68, 76-77; Ex-2018 ¶¶13-15.)
and further comprises Framework Region (FR) substitutions at heavy chain positions 71H, 73H, 78H and 93H, utilizing the	HuMAb4D5-5 includes framework substitutions at Kabat heavy chain positions 71H, 73H, 78H, and 93H. (Ex-2016 ¶¶45-48; Ex-2017 ¶¶23-27, 68, 76; Ex-2018 ¶¶13-15.)	HuMAb4D5-8 includes framework substitutions at Kabat heavy chain positions 71H, 73H, 78H, and 93H. (Ex-2016 ¶¶45-48, 51; Ex-2017 ¶¶23-27,

Claim Language	HuMAb4D5-5	HuMAb4D5-8
numbering system set forth in Kabat.		68, 76-77; Ex-2018 ¶¶13-15.)

HuMAb4D5-5 and HuMAb4D5-8 embody claims 12, 42, 60, 65, 71, and 73-74 for similar reasons.

Claim 12 requires "a humanized antibody variable domain" and non-human CDRs "which bind an antigen," which HuMAb4D5-5 and HuMAb4D5-8 satisfy as discussed above for claim 79. Claim 12 further requires a framework substitution at 66L, which both HuMAb4D5-5 and HuMAb4D5-8 contain. (Ex-2016 ¶¶45-48, 51; Ex-2017 ¶¶23-27, 68, 76-77; Ex-2018 ¶¶13-15.)

Claim 42 contains the same limitations discussed above for claims 12 and 79, including a framework substitution at 66L. The only additional limitations of claim 42 are that the antibody and non-human CDRs must bind "$p185^{HER2}$," which HuMAb4D5-5 and HuMAb4D5-8 satisfy. (Ex-2016 ¶¶45-48, 50-51; Ex-2017 ¶¶23-27, 65-68, 75-77; Ex-2018 ¶¶13-15, 17-24; Ex-2004 at 44-46; Ex-2005 at 73; Ex-2006 at 47, 51, 84-85; Ex-2008 at 6; Ex-2009 at 7-8.)

Claim 60 has the same limitations as claim 42, except that the only required framework substitution is at 78H. HuMAb4D5-5 and HuMAb4D5-8 satisfy those limitations for the reasons discussed above for claims 79 and 42.

Claim 65 (as corrected by a certificate of correction) depends from claim 79 and further requires that the humanized antibody "binds the antigen up to 3-fold

more in the binding affinity than the parent antibody binds antigen." HuMAb4D5-8 embodies claim 65. (Ex-1001, 51:48-53 ("[HuMAb4D5-8] binds the $p185^{HER2}$ ECD 3-fold more tightly than does muMAb4D5 itself.").)[8]

Claim 71 requires a "humanized antibody heavy chain variable domain," non-human CDRs "which bind antigen," and a framework substitution at 66L, which HuMAb4D5-5 and HuMAb4D5-8 satisfy for the reasons discussed above for claims 12 and 79.

Claim 73 is the same as claim 71, except that it requires a framework substitution at 78H. HuMAb4D5-5 and HuMAb4D5-8 embody claim 73 for the reasons discussed above for claims 71 and 79.

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[8] Neither Queen-1990 nor Tramontano contains data showing that any disclosed antibody has up to 3-fold more binding affinity. Because antedation only requires "priority with respect to so much of the claimed invention as the reference happens to show," *In re Clarke*, 356 F.2d 987, 991 (C.C.P.A. 1966), it is not necessary to show that the studies confirming that HuMAb4D5-8 has 3-fold more binding affinity were completed before the publication of Queen-1990 and/or Tramontano.

Claim 74 is the same as claim 71, except that it requires a framework substitution at 93H. HuMAb4D5-5 and HuMAb4D5-8 embody claim 74 for the reasons discussed above for claims 71 and 79.

b) The inventors determined that HuMAb4D5-5 and HuMAb4D5-8 would work for the intended purpose of the claims before July 26, 1990.

The inventors had sufficiently characterized HuMAb4D5-5 and HuMAb4D5-8 before July 26, 1990 to know they would work for the intended purpose of the claims. By then, they had already confirmed that the expression vectors contained the correct DNA sequence to produce their humanized 4D5 antibodies. (Ex-2017 ¶¶62-63, 75; Ex-2018 ¶22; Ex-2003 at 69-71, 78-81, 95-97; Ex-2004 at 41, 43, 44, 46; Ex-2006 at 83, 85; Ex-2009 at 5, 7-8.) And they had already expressed and purified HuMAb4D5-5 and HuMAb4D5-8, and performed experiments to confirm that they had produced humanized antibodies with the expected size and sequence. (Ex-2017 ¶¶63-65, 75; Ex-2018 ¶¶13, 16-24; Ex-2003 at 97; Ex-2004 at 44-46; Ex-2005 at 73; Ex-2006 at 47, 51, 83, 85; Ex-2008 at 6, 44-45; Ex-2009 at 5, 7-8.) In addition, the inventors established before July 26, 1990 that HuMAb4D5-5 and HuMAb4D5-8 bind the antigen called "p185^{HER2}." (*Supra* pp.23-33.)

c) Contemporaneous records from non-inventors corroborate the inventor's actual reduction to practice before July 26, 1990.

The inventors carefully documented their progress developing HuMAb5D5-5 and HuMAb4D5-8, and contemporaneous records from several non-inventors, including John Brady, Ann Rowland, Tim Hotaling, and Monique Carver, confirm all aspects of the invention before July 26, 1990, including the expression, purification, and characterization of $p185^{HER2}$ binding affinity for HuMAb4D5-5 and HuMAb4D5-8. (*Supra* pp.23-33.) That is more than sufficient corroboration. *See Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998) (finding sufficient corroboration where the evidence of reduction to practice did not "depend solely on statements or writings by the inventor himself"); *Green Cross Corp. v. Shire Human Genetic Therapies*, IPR2016-00258, Paper 89 at 12-13 (Mar. 22, 2017) (accepting patent owner's antedation and corroborating evidence); *Nintendo of Am., Inc., v. iLife Tech., Inc.*, IPR2015-00109, Paper 40 at 24-30 (Apr. 28, 2016) (same). To the extent that any individual piece of evidence is insufficient to substantiate the inventors' prior invention standing on its own, the totality of the evidence—where several non-inventors created contemporaneous corroborating records—overwhelming confirms the prior invention of claims 12, 42, 60, 65, 71, 73-74, and 79. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1170 (Fed. Cir. 2006) ("Sufficiency of corroboration is determined by using a 'rule of reason'

analysis, under which all pertinent evidence is examined when determining the credibility of an inventor's testimony.").

Queen-1990 and Tramontano therefore are not prior art under 35 U.S.C. § 102(a) to claims 12, 42, 60, 65, 71, 73-74, and 79.

3. Queen-1990 and Tramontano are not § 102(b) prior art.

Queen-1990 and Tramontano are also not prior art to claims 12, 42, 60, 65, 71, 73-74, and 79 under 35 U.S.C. § 102(b) because those claims properly have priority to U.S. Patent Application No. 07/715,272 ("the '272 application"), filed on June 14, 1991—*i.e.*, within one year of these references.

As a continuation-in-part of the '272 application, the '213 claims have priority to that earlier application so long as it provides written description and enablement support for the claims. 35 U.S.C. § 120. As described below, the '272 application describes all limitations of claims 12, 42, 60, 65, 71, 73-74, and 79, provides step-by-step instructions to prepare humanized antibodies embodying those claims, and discloses data characterizing humanized antibodies that embody those claims (including HuMAb4D5-5 and HuMAb4D5-8). Dr. Wilson identifies in a chart on a claim-by-claim basis how the '272 application contains written description and enablement support for claims 12, 42, 60, 65, 71, 73-74, and 79. (Ex-2041 ¶¶88-95.) That evidence is summarized below for each claim limitation.

"Humanized" antibody or variable domain. The '272 application describes humanized antibodies and variable domains. (Ex-2037, p.9 (3:21-23), pp.35-36 (29:11-30:6), p. 107 (claim 1), p.109 (claims 9).) It also describes step-by-step how the inventors humanized the murine 4D5 antibody (Example 1) and provides a generalized scheme for humanizing any non-human antibody (Example 2). (*Id.*, p.81-99 (75:31-93:19).) Example 1 contains binding affinity data and other experimental results for humanized 4D5 antibodies, including HuMAb4D5-5 and HuMAb4D5-8, which confirms that the inventors were in possession of those humanized antibodies at that time. (*Id.*, p.87-90 (81:20-84:21); Ex-2041 ¶91.)

"Non-human" CDRs. The humanized antibodies described in the '272 application include non-human CDRs, which bind to the antigen. (Ex-2037, p.15 (9:12-19), p.96 (90:1-18), pp.2-3 (Figs. 1A-1B); Ex-2041 ¶92.) In fact, Example 1 describes creating humanized 4D5 antibodies by "installing the muMAb4D5 CDRs into the consensus human sequences" and contains binding affinity data showing that those CDRs bind antigen when incorporated into the human sequence. (Ex-2037, pp.88-89 (83:31-83:8, p.93 (Table 1).)

Framework substitutions. The '272 application discloses the framework substitutions recited in claims 12, 42, 60, 65, 71, 73-74, and 79. For example, Table 1 specifically identifies the framework substitutions in HuMAb4D5-5 and

HuMAb4D5-8, which correspond with the framework substitutions recited in those eight claims. (Ex-2037, p.93 (Table 1); Ex-2041 ¶93.)

Claims 42 and 60. The '272 application describes humanized antibodies that $p185^{HER2}$ and contain non-human CDRs that bind $p185^{HER2}$. (Ex-2037, p.87 (81:11-14, p.88 (82:25-27), p.93 (Table 1); Ex-2041 ¶94.) Example 1 describes creating humanized 4D5 antibodies by "installing the muMAb4D5 CDRs into the consensus human sequences." (Ex-2037, p.89 (83:4-5).) And the '272 application describes the tight binding affinity of huMAb4D5-8 for $p185^{HER2}$. (*Id.*, p.91 (85:18-86:1).)

Claim 65. The '272 application explains that HuMAb4D5-8 binds the target antigen 3-fold more tightly than the parent murine antibody. (*Id.*, pp.88-89 (82:31-83:3), p.91 (85:24-27, 85:29-32), p.93 (Table 1); Ex-2041 ¶94.)

Based upon the detailed experimental disclosure in the '272 application, a person of ordinary skill could make and use the invention claimed in claims 12, 42, 60, 65, 71, 73-74, and 79 without undue experimentation and would understand that the inventors were in possession of the invention. (Ex-2041 ¶95.)

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Because Queen-1990 and Tramontano are not prior art, they cannot invalidate claims 12, 42, 60, 65, 71, 73-74, and 79. The Board should thus confirm

the patentability of claims 12, 42, 60, 65, 71, 73-74, and 79 over Grounds 2-4 and 7.

B. Grounds 1, 3, 6: Petitioner's obviousness theory for Queen-1989 actually rests on Queen-1990, which is not prior art to claims 12, 42, 60, 65, 71, 73-74, and 79.

For Grounds 1, 3, and 6, Petitioner purports to rely upon Queen-1989 combined with the PDB database. (Paper 2 at 26-49, 52-57.) To arrive at the claimed framework substitutions, Petitioner analyzed certain PDB structures to determine which framework residues were within 3.3 angstroms of a CDR. (Ex-1003 ¶255.) However, the only support that Petitioner cites for that 3.3-angstrom cutoff is ***Queen-1990***, not Queen-1989. (Ex-1003 ¶255 n.17 ("Accordingly, any distance of 3.3 Å or less will fall under this distance threshold ***set by Queen-1990*** (Ex-1050).").)

Queen-1989 does not disclose a 3.3-angstrom cutoff. Queen-1989 suggests identifying positions that "are in fact close enough to [the CDRs] to either influence their conformation or interact directly with antigen." (Ex-1034 at 10031.) As Dr. Wilson explains, that broad description would include residues that are further than 3.3 angstroms from the CDRs—for example, those within 4

angstroms could interact with the CDRs via van der Waals forces.[9] (Ex-2041 ¶184.) Petitioner has presented no evidence explaining how Queen-1989 would have led to the 3.3-angstrom cutoff that is the basis for its obviousness theory.

If the Board determines that Queen-1990 has been antedated, it should also confirm the patentability of claims 12, 42, 60, 65, 71, 73-74, and 79 over Grounds 1, 3, and 6.

C. Grounds 1-4, 6-7: The Queen references combined with the PDB database would not have led to the invention of claims 12, 42, 60, 65-67, and 71-79 with a reasonable expectation of success.

Claims 12, 42, 60, 65-67, and 71-79 recite at least one and up to five specific framework substitutions. Petitioner argues that a skilled artisan would have analyzed published PDB crystal structures to arrive at a list that "includes" 20 different framework positions. (Paper 2 at 33 (listing "CDR contact residues"), 34-36, 41-49, 52-57.) That argument fails for several reasons.

As an initial matter, the Queen references do not teach using the PDB database as Petitioner uses it. The Queen references describe modeling the ***parent murine antibody*** to identify residues that may interact with the CDRs. (*E.g.*, Ex-1050, 14:14-19 ("A 3-dimensional model, ***typically of the original donor***

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[9] As a point of comparison, the '213 inventors used a 6-angstrom cutoff. (*Supra* p. 26.)

antibody…."); Ex-1034 at 10031 ("A computer program was used to construct a plausible molecular model of the ***anti-Tac V domain*** ….").) As Dr. Wilson explains, using the parent murine antibody as the model makes sense; such a model would indicate the framework residues important to the structure of the ***murine CDRs***. (Ex-2041 ¶180.) Petitioner's obviousness theory takes the opposite approach by analyzing a collection of ***human*** sequences. (Ex-1003 ¶¶250-274; Ex-2041 ¶178-80.) That approach, however, makes no sense because it does not relate to the structure of the CDRs of the antibody to be humanized. (Ex-2041 ¶178.)

In any case, Petitioner's analysis would have led to a broad genus of potential framework substitutions, and Petitioner has provided no reason why a skilled artisan would have selected the specific framework substitutions recited in the challenged claims. In fact, as Dr. Wilson explains, applying Petitioner's analysis to the PDB database generates a list of 38 potential framework substitutions, not the 20 positions that Petitioner identified. (Ex-2041 ¶181-83.) Petitioner's list selectively focused on the framework substitutions that appear in the '213 claims, but ignores 18 other framework substitutions that would be identified following the same analysis that fall outside the scope of the claims. (Ex-2041 ¶181.) Dr. Riechmann does not deny this. He simply adopted the opinions of another expert in a prior proceeding challenging the '213 patent and

did not confirm himself whether the list of 20 framework substitutions in the petition was accurate or complete. (Ex-2039, 313:5-314:6 (Exhibit M (summary of atomic distance calculations) was "work that was done by Dr. Padlan"), 318:16-319:1 (Exhibit N (alignment of each analyzed antibody according to its Kabat numbering)), 320:11-321:2 (Exhibit O (identity of framework residue atoms which contact the respective CDRs as demonstrated by their proximity)).)

The 37 potential substitutions applying Petitioner's analysis of PDB structures also does not account for other potential substitutions disclosed in the references. For example, both Queen references disclose a humanized antibody with 15 framework substitutions, ***none*** of which correspond with the '213 patent's claims. (Ex-2041 ¶187; Ex-1034 at 10031-32; Ex-1050, 26:18-27:16.)[10] In addition, Petitioner argues that Queen-1990 would have led a person of ordinary skill to 24 potential framework substitutions by applying Criterion III—for a total

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[10] In its institution decision, the Board stated that Queen-1989 discloses a substitution at 93H. (Paper 16 at 16.) Respectfully, that is incorrect. The amino acid positions in Queen-1989 use a different numbering convention; what Queen-1989 calls position 93 in the heavy chain is 89H under Kabat's numbering convention. (Ex-2041 ¶105.)

of 42 substitutions supposedly disclosed between Criteria III and IV (after accounting for overlapping positions). (Paper 2 at 33-34.)[11]

Given the large number of potential framework substitutions, there are literally millions of potential combinations and permutations of framework substitutions the combination of the Queen references with the PDB database. (Ex-2041 ¶187-88.) Yet claims 12, 42, 60, 65-67, and 71-79 recite at least one and up to five very specific substitutions. For example, claims 65 and 79 require substitutions at each of 71H, 73H, 78H, and 93H. Petitioner offers no reason (other than hindsight) why a person of ordinary skill would have chosen the specific framework substitutions recited in claims 12, 42, 60, 65-67, and 71-79 from among the numerous possibilities allegedly disclosed in the asserted references.

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[11] Moreover, Petitioner interpreted "about" 3 angstroms to mean 3.3 angstroms. (Ex-1003 ¶255 n.17.) But it is not clear from Queen-1990 why that should be the case. Queen-1990, for example, instructs to look at amino acids that could interact with the CDRs through "Van der Waals forces." (Ex-1050, 14:14-19.) As Dr. Wilson explains, a skilled artisan would understand that residues within 4 angstroms could interact with the CDRs via Van der Waals forces, which would include even more framework positions. (Ex-2041 ¶184.)

In its institution decision, the Board acknowledged the number of substitutions supposedly disclosed by the asserted references, but nevertheless was not persuaded that the breadth of that disclosure defeats obviousness because the number of identified substitutions was "finite." (Paper 16 at 17.) Respectfully, that does not accurately describe the complexity of the problem solved by the '213 patent. Antibody humanization is labor-intensive and time-consuming. (Ex-2041 ¶172; Ex-2039, 73:11-74:5 (humanizing anti-CAMPATH-1 antibody took almost two years).) And given the state of the biotechnology field as of 1991 (when the '213 patent was filed), each new antibody sequence was itself a significant undertaking to make. (Ex-2041 ¶172.) It would not have been feasible to identify the specific framework substitutions recited in claims 12, 42, 60, 65-67, and 71-79 by ticking through a list of dozens of potential substitutions. (Ex-2041 ¶228-30.)

The open-ended nature of the claims—which do not exclude substitutions in addition to those specifically recited—does not relieve Petitioner of its burden to identify a reason a person of ordinary skill would have chosen the specific framework substitutions required by the claims. Indeed, Petitioner's own cited references warn that "extreme caution must be exercised to limit the number of changes" (Ex-1071, 8:42-43) and suggest making "about 3 or more" substitutions (Ex-1050 at 1.) A skilled artisan would not have been motivated to try

combinations of many substitutions when Petitioner's own references caution against doing so. (Ex-2041 ¶¶232-33.)

In any case, claims 12, 42, 60, 65-67, and 71-79 require that the CDRs incorporated into the human antibody sequence bind to an antigen. Petitioner has presented no evidence that a person of ordinary skill would have had a reasonable expectation of success that humanized antibodies containing the claimed substitutions would achieve that result. Nor could it. Dr. Riechmann concedes—and Petitioner's own references reflect—the unpredictable effects of making even a single framework substitution on antigen binding. (Ex-2039, 349:21-350:19 ("if you change one [amino acid residue] in a protein, that can have an effect…on everything"); Ex-1071, 8:41-42 ("Changing an amino acid in one chain may cause changes in the interactions with other amino acids of that chain as well as with amino acids in the other chain."); *see also* Ex-2041 ¶¶232-33.)

Nor were claims 12, 42, 60, 65-67, and 71-79 among "a finite number of identified, predictable solutions," *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). (*See* Paper 16 at 17.) What is a "small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness" depends upon "the context of the art." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). And the record now makes clear that the dozens of framework substitutions supposedly identified in the

asserted references would not have been considered "small or easily traversed"—particularly as of 1991. (Ex-2041 ¶¶228-34.) Moreover, as just discussed, the effect of even a single framework substitution on the properties of the resulting antibody was highly unpredictable, taking this case outside the realm of those that might support a conclusion of obviousness to try. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (invention not obvious to try where "the solution was not predictable").

Finally, accepting Petitioner's obviousness theory would have sweeping consequences. Because Petitioner has offered no reason to choose the specific claimed substitutions, its obviousness theory would render obvious ***any*** humanized antibody that contains one or more of the dozens of framework substitutions supposedly disclosed in the asserted references—effectively foreclosing patent protection for most if not all humanized antibodies. That untenable result confirms the flaws underlying Petitioner's obviousness theory, and no case would support that result based upon the generalized teachings of the asserted references here.

The Board should confirm the patentability of claims 12, 42, 60, 65-67, and 71-79.

D. Grounds 1-2, 5, 7: Claims 4, 33, 62, 64, And 69 Would Not Have Been Obvious Because The Asserted References Do Not Teach The "Consensus" Sequence Limitations.

1. The asserted references do not teach the "consensus" sequence limitation.

The '213 patent provides a specific definition of the claimed human "consensus" sequence, "which comprises the most frequently occurring amino acid residues at each location in all human immunoglobulins of any particular subclass or subunit structure." (Ex-1001, 11:32-38.) The Board adopted this claim construction in its institution decision. (Paper 16 at 7-8.)

Petitioner has not demonstrated the obviousness of the "consensus" limitations of claims 4, 33, 62, 64, and 69 under the specific definition provided in the patent.

a) Queen-1990 (Grounds 2, 7)

For Grounds 2 and 7, Petitioner asserts that Queen-1990's discussion of a "consensus human framework from many antibodies" discloses the claimed consensus sequence limitations. (Paper 2 at 40-45, 60.) However, as Dr. Wilson explains, a person of ordinary skill at the time would have understood that a "consensus" sequence simply refers to sequence that reflects the most common amino acids at each position from a group of antibodies. (Ex-2041 ¶207.) Such a consensus sequence would not necessarily be derived from "all" known sequences, as in the '213 patent. (*Id.*) In fact, the only description in Queen-1990 refers to "a

consensus framework from ***many*** human antibodies," not ***all*** as in the '213 patent. (Ex-1050, 12:19-20; Ex-2041 ¶208.)

The remainder of Queen-1990 reinforces that its "consensus framework" is not generated from all antibody sequences. For example, the next paragraph recommends using "a representative collection of a least 10 to 20 distinct human heavy chains" and a "similar[]" number of light chain sequences when selecting a human framework sequence. (Ex-1050, 13:3-11.) A skilled artisan would understand that this "representative collection of at least 10 to 20" sequences could be used to generate Queen-1990's "consensus framework from many human antibodies." (Ex-2041 ¶208.)

Moreover, Queen-1990's "Criterion II" specifically pertains to "unusual" or "rare" amino acid residues, which occur "in no more than about 10%" of human sequences. (Ex-1050, 13:22-32.) Criterion II would be inapplicable to a consensus sequence generated from "all" antibody sequences, since it would include ***no*** "unusual" or "rare" residues. (Ex-2041 ¶210.) However, "a consensus framework from many human antibodies" as described in Queen-1990 might nevertheless contain "unusual" or "rare" residues, since it was not generated from ***all*** antibodies. (Ex-2041 ¶210.) Criterion II thus further demonstrates that the "consensus framework" mentioned in Queen-1990 differs from the '213 patent's definition of a consensus sequence. (Ex-2041 ¶210.)

b) Queen-1989 (Ground 5)

Petitioner asserts that Queen-1989 in combination with Kabat-1987 and the PDB database (Ground 5) discloses the claimed consensus sequence limitations. However, the record now shows that is incorrect.

The combination of Queen-1989, Kabat-1987, and the PDB database does not render obvious the "consensus" sequence claims challenged in Ground 5 (claims 4, 62, 64, and 69). The term "consensus" sequence does not appear anywhere in Queen-1989. (Ex-2041 ¶213.) And Queen-1989 uses a human sequence that contains "unusual residues," which is different than the '213 patent's consensus sequence containing "the most frequently occurring amino acid residues." (Ex-1001, 11:32-38; Ex-1034 at 10032; Ex-2041 ¶217.)

Petitioner nevertheless argues that Queen-1989 "taught moving towards a consensus framework region, observing that replacing amino acid residues with ones that are 'more typical' and common would make the resulting antibody more human and less immunogenic." (Paper 2 at 51.) But ***modifying*** a sequence to include "more typical" residues is not the consensus sequence of the '213 patent. (Ex-2041 ¶215.) The '213 patent's consensus sequence starts with "the most frequently occurring amino acid residues at each location" (Ex-1001, 11:32-40) and adds ***less common*** residues from the non-human sequence (*id.*, 20:41-21:3). (Ex-2041 ¶¶74-75.)

The result of Queen-1989's approach is also not a "consensus" sequence as defined by the '213 patent. Queen-1989 describes substituting those "unusual residues" with the ***murine*** residue at that position, not the ***human*** residue like the '213 patent's consensus sequence. (Ex-1034 at 10032; Ex-2041 ¶215.) In addition, Queen-1989 describes adding "more typical" residues, not the "most commonly occurring residues" as the '213 patent requires. (Ex-1034 at 10032; Ex-2041 ¶215.)

Kabat-1987 does not cure Queen-1989's deficiencies. Petitioner argues that a skilled artisan would look to Kabat-1987 to identify human residues to substitute into a human framework sequence. (Paper 2 at 51-52; Ex-1003 ¶¶309-310.) All substitutions in Queen-1989, however, added ***murine*** amino acids, not ***human*** amino acids. (Ex-1034 at 10032 ("At these positions, we therefore chose to use the anti-Tac residue rather than the Eu residue in the humanized antibody."); Ex-2041 ¶104.) That makes sense. Adding the murine residues would help maintain the proper conformation of the transplanted murine CDRs, whereas adding human residues would not. (Ex-2041 ¶62.) Petitioner has not explained why a person of ordinary skill would ignore Queen-1989's teaching to add ***murine*** residues and add ***human*** residues instead.

Moreover, Kabat-1987 is a reference book of antibody sequences; it does not disclose any techniques for humanizing an antibody. (Ex-2041 ¶¶156-57.) Kabat-

1987's tabulation of the "most common" amino acids was simply to assist scientists evaluate "the probability that a given amino acid at a given position may not be correct" when sequencing an antibody. (Ex-2026 at 3; Ex-2041 ¶157.) Nothing in Kabat-1987 suggests using that information to engineer ***entirely new*** antibody sequences. (Ex-2041 ¶216.)

Finally, in some instances, Kabat-1987 identifies more than one amino acid for each position where there are several amino acids that frequently occur at a given position. (*E.g.*, Ex-1052 at 10 (residues 1, 3, 6, 17, etc.); Ex-2016 ¶25.) There is thus no reason a skilled artisan would have been led from Kabat-1987 to a "consensus" sequence consisting only of the single "most frequently occurring amino acid residues at each location." (Ex-1001, 11:32-40; Ex-2041 ¶¶117-18.)

2. The asserted references do not teach any antibody with the framework substitutions of claims 4, 33, 62, and 69 that incorporates non-human CDRs that bind antigen.

The Queen references do not disclose ***any*** antibody with the claimed framework substitutions and non-human CDRs in a human consensus framework that "bind an antigen" as required by claims 4, 33,[12] 62, and 69. (Ex-2041 ¶168.) Indeed, Dr. Riechmann admitted that antigen binding is unpredictable, such that even a single framework substitution may eliminate antigen binding. (Ex-2039,

12 The antigen in claim 33 is "$p185^{HER2}$."

270:22-271:17, 349:21-350:19; Ex-2041 ¶186.) This unpredictability manifested in Dr. Riechmann's own work in humanizing the anti-CAMPATH-1 antibody, which initially "bound poorly to the CAMPATH-1 antigen and was weakly lytic." (Ex-1069 at 326.) Yet Petitioner cites no actual antibody sequence with the claimed framework substitutions and non-human CDRs in a human consensus framework, let alone binding affinity data for that sequence.

Without any actual antibody sequence disclosing the claimed substitutions in a human consensus framework, there is no evidence an antibody with the claimed framework substitutions will bind antigen. (Ex-2041 ¶174.) And Petitioner's own cited references disclose humanized antibodies that completely lack binding affinity for the target antigen. (Ex-1071, 9:17.) A skilled artisan therefore would not have had a reasonable expectation of success in achieving the claimed binding limitations.

The Board should confirm the patentability of claims 4, 33, 62, 64, and 69 over Grounds 1-2, 5, and 7.

E. Grounds 2-4: The Asserted References Do Not Render Obvious The "Up To 3-Fold More" Binding Affinity Limitation Of Claim 65.

Claim 65 requires the humanized antibody to have a binding affinity "up to 3-fold more" than the parent non-human antibody. Petitioner points to no data

showing that ***any*** antibody produced according to Queen-1989 and/or Queen-1990 had "up to 3-fold more" binding affinity.

Ground 3: Petitioner cites no disclosure in Queen-1989 that antibodies produced according to its humanization method have improved binding affinity as compared to the non-human antibody. (Paper 2 at 47-48.) Nor could it. Queen-1989 recognizes that humanized antibodies made according to its method may have "significantly less binding affinity for antigen than did the original mouse antibody" and never mentions the possibility of having ***more*** binding affinity than the non-human parent antibody. (Ex-1034 at 10033; Ex-2041 ¶¶252-54.) The only evidence that Petitioner cites for this claim limitation in Ground 3 is Dr. Riechmann's bare assertion that "it would not have been surprising that a small improvement in affinity would be achieved in some cases." (Ex-1003 ¶298.) However, Dr. Riechmann's declaration is inconsistent with Queen-1989, which states that it was "not surprising" that the humanized antibody would have "significantly less binding affinity" because "transferring the mouse CDRs from the mouse framework to the human framework could easily deform them." (Ex-1034 at 10033; Ex-2041 ¶¶60-62.)

Grounds 2, 4: Petitioner argues that Queen-1990 discloses the "up to 3-fold more" limitation by stating that the binding affinity of the humanized antibodies "may be *within about 4 fold* of the donor immunoglobulin's original affinity to the

antigen." (Paper 2 at 47-48; Ex-1050, 6:26-28.) But Queen-1990 does not indicate that the humanized antibody's binding affinity is ***more*** than the non-human parent antibody, as claim 65 requires. The binding affinity could be lower. For example, Kurrle—like Queen-1990—started from a best-fit human antibody sequence and saw a significant ***decrease*** in binding affinity. (Ex-1071, 8:17-19, Fig. 7; Ex-1072 at 4366; Ex-2041 ¶254.) And two of Kurrle's humanized antibodies did not even bind the antigen. (Ex-1071, 9:17-19; Ex-2041 ¶254.) Nothing in the record demonstrates that Queen-1990's analogous technique would increase binding affinity as required by claim 65.

For Grounds 2-4, Petitioner has failed to show a reasonable expectation of success in achieving this binding affinity limitation for a humanized antibody having the four substitutions required in claim 65. Dr. Riechmann's initial opinion was equivocal at best on this issue. He stated that "it would not have been surprising that a small improvement in affinity would be achieved in some cases," not that a skilled artisan would have had a reasonable expectation of success in doing so. (Ex-1003 ¶298.) Moreover, what may occur "in some cases" is insufficient to carry Petitioner's burden because it does not address the invention of claim 65, which recites four specific framework substitutions. And Dr. Riechmann at his deposition admitted that binding affinity is highly unpredictable,

which confirms that a person of ordinary skill would not have had a reasonable expectation of success. (Ex-2039, 350:6-11Ex-2041 ¶255.)

The Board should confirm the patentability of claim 65.

F. Grounds 1-2: Queen-1989 And Queen-1990 Do Not Render Obvious The "Lacks Immunogenicity" Limitation Of Claim 63.

In Grounds 1-2, Petitioner challenges claim 63, which requires "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient."

Petitioner cites no data showing that an antibody produced according to Queen-1989 or Queen-1990 "lacks immunogenicity," as required by claim 63. (Paper 2 at 37-38.) Instead, it merely relies on aspirational statements in both references. (Paper 2 at 38; *e.g.*, Ex-1034 at 10029 ("[S]equence homology and molecular modeling were used to select a combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity."); Ex-1050 at 1 ("[T]he humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans.").)

However, the record now confirms that Queen-1989 and Queen-1990 do not disclose any humanized antibody with reduced immunogenicity as compared with the non-human parent. Dr. Riechmann confirmed that he "would expect some immune response to any antibody given to a human," including a humanized

antibody. (Ex-2039, 242:3-20; Ex-2041 ¶¶69, 196.) Dr. Riechmann also admitted that "[y]ou cannot predict the immune response of any antibody when given to a patient," and as a result, the only way to confirm immunogenicity is to administer the antibody to a patient and observe the response. (Ex-2039, 243:13-244:5.) And Queen-1989 reinforces that whether an antibody is any less immunogenic than the parent antibody is something that can only be determined through clinical trials (which neither Queen-1989 nor Queen-1990 disclose). (Ex-1034, at 10033 ("The extent to which humanization eliminates immunogenicity will need to be addressed in clinical trials ….").) Given that it was unpredictable whether any humanized antibody would be any less immunogenic than its non-human parent antibody, the aspirational statements in the Queen references that the authors hoped to address the problem of immunogenicity does not make it obvious how to achieve that result. (Ex-2041 ¶202.)

The Board should confirm the patentability of claim 63.

G. Grounds 6-7: Petitioner Has Not Shown That It Would Have Been Obvious That A Humanized Antibody With The Framework Substitutions Recited In Claims 30-31, 33, 42, And 60 Would Bind $p185^{HER2}$.

Claims 30-31, 33, 42, and 60 recite humanized antibodies that bind $p185^{HER}$. It is undisputed that Queen-1989, Queen-1990, and the PDB database never mention $p185^{HER2}$. (Ex-2041 ¶256; Ex-2039, 295:1-13 (Queen-1989 and Queen-

1989).) The Queen references describe antibodies for certain T-cell receptors. (Ex-1034 at 10029; Ex-1050, 4:11-16.) And the PDB database is simply a repository of protein structures—none of which at the time of the invention had anything to do with p185^{HER2}. (Ex-2041 ¶256.)

Petitioner's only asserted reference that even mentions p185^{HER2} is Hudziak.[13] However, it is undisputed that Hudziak does not discuss "either humanizing ... or a human version" of the murine 4D5 antibody (*i.e.*, a humanized antibody that binds p185^{HER2}). (Ex-2040, 149:17-151:3.) It is also undisputed that Hudziak does not describe "any type of framework substitutions with respect to the 4D5 antibody." (Ex-2040, 150:20-151:3.)

Petitioner's obviousness theory is simply that a skilled artisan would have been motivated to make a humanized version of the murine 4D5 antibody (which binds p185^{HER2}) based upon Hudziak. (Paper 2 at 52-57.) But that is merely a research goal; it does not make the solution obvious. In particular, Petitioner has presented ***no*** evidence that any of the framework substitutions recited in claims 30-

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[13] Mr. Leonard also discusses Shepard (Ex-1048), but Shepard too does not disclose how to humanize the murine 4D5 antibody, let alone identify framework substitutions that would have been useful for that purpose. (Ex-2040, 154:11-155:16.) Indeed, Shepard is not even part of any of the instituted grounds.

31, 33, 42, and 60 would have been obvious ***for an antibody that binds p185^{HER2}***. For example, Petitioner did not apply the teachings of Queen-1989 or Queen-1990 to the murine 4D5 sequence to determine whether the humanization techniques described in those references would have led to any of the framework substitutions recited in claims 30-31, 33, 42, and 60.

Petitioner's assertion that "Queen 1989 and Queen 1990 provided the detailed roadmap for humanizing mouse monoclonal antibodies, such as 4D5" (Paper 2 at 54), is insufficient to demonstrate that the specific framework substitutions recited in claims 30-31, 33, 42, and 60 would have been obvious for an antibody that binds p185^{HER2}. Indeed, Petitioner's reasoning, if accepted, would make obvious a humanized antibody for ***any antigen*** based upon the generalized teachings of the Queen references. This expansive interpretation of Queen-1989 and/or Queen-1990 is untenable given that, as Dr. Leonard confirms, there were other monoclonal antibodies that were potentially being considered for therapeutic use as of 1991. (Ex-2040, 156:6-12.)

The Board should confirm the patentability of claims 30-31, 33, 42, and 60.

H. Objective Indicia Of Non-Obviousness Confirm The Patentability Of The Challenged Claims.

1. Unexpected results

Unexpected results are powerful evidence of non-obviousness. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Here, the challenged claims reflect at least two unexpected results.

First, it would not have been expected before the '213 patent that it was even possible to develop a broadly-applicable platform that could be used to humanize different antibodies from the same sequence. Before the '213 invention, scientists believed that it was necessary to identify an existing human antibody framework sequence most homologous to the non-human antibody as a starting point. (Ex-2041 ¶261.) For example, Queen-1989 emphasized that choosing an existing human sequence "as homologous as possible to the original mouse antibody to reduce any deformation of the mouse CDRs" was one of its key "ideas that may have wider applicability." (Ex-1034 at 10033.) The '213 patent's consensus sequence approach unexpectedly allowed numerous different antibodies to be humanized from a single consensus sequence—without regard to how similar that consensus sequence is to the original non-human antibody. (Ex-2041 ¶262; Ex-1002 at 456-58, ¶¶2-9.) There is a sufficient nexus between this unexpected result and the challenged claims; indeed, this unexpected result flows directly from the "consensus" limitations of 4, 33, 62, 64, and 69, since it is the consensus sequence generated from ***all*** human antibody sequences of a particular subclass or

subtype that provides a broadly-applicable platform for antibody humanization. (Ex-2041 ¶262.)

Second, the '213 patent's approach results in antibodies with unexpectedly superior properties. For example, prior art humanized antibodies produced immunogenic responses (*e.g.*, Ex-2025 at 751 (3 out of 4 patients suffered immunogenic response)) or had reduced binding affinity (*e.g.*, Ex-1072 at 4366 (2.5-fold reduction in binding affinity)). (Ex-2041 ¶264.) The '213 invention unexpectedly solved both problems. Antibodies embodying the '213 invention lacked immunogenicity even after prolonged use and demonstrated ***superior*** binding affinity to the original non-human antibody. (Ex-1002 at 456-58, ¶¶2-9; Ex-1001, 51:50-53 ("This antibody binds the $p185^{HER2}$ ECD 3-fold more tightly than does muMAb4D5 itself.").)

Petitioner argues that those unexpected properties are not commensurate with the scope of the claims. (Paper 2 at 57-59.) But those properties are a result of the inventors' novel consensus sequence approach, which is reflected in the framework substitutions that are recited in the challenged claims. (Ex-2016 ¶31.) There is no requirement that the unexpected results be recited in the claims themselves. *In re Merchant*, 575 F.2d 865, 869 (C.C.P.A. 1978) (noting "no law requiring that unexpected results relied upon for patentability be recited in the claims").

2. Commercial success

Some of Genentech's most successful antibodies embody the '213 claims, including Herceptin®, Perjeta®, Avastin®, Lucentis®, and Xolair®, together generating billions of dollars in revenue annually. (Ex-2029 at 2.) Their success is attributable, in part, to their unique sequences provided using the '213 patent's consensus sequence approach, which allows good binding affinity while minimizing immunogenicity. (Ex-2041 ¶¶263-64.) This commercial success confirms the non-obviousness of the challenged claims. *See Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1379 (Fed. Cir. 2011).

Petitioner argues that Herceptin®'s commercial success is irrelevant because Herceptin® is supposedly not commensurate with the full scope of the claims—for example, because Herceptin does not contain every framework substitution in the *Markush* groups of independent claims 1, 30, 62, and 63. (Paper 2 at 60.) But there is clearly a nexus to at least claims 12, 42, 60, 65, 71, 73-74, and 79, which only recite framework substitutions contained in Herceptin.® (*Supra* p. 31.) A nexus between Herceptin®'s commercial success and at least those claims is therefore presumed. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). That the claims may encompass other antibodies does not diminish the nexus between Herceptin® and the claim

limitations, given that Herceptin® is both an embodiment of the claims and coextensive with the claimed features.

I. *Inter Partes* Review Is Unconstitutional.

The Board should terminate this proceeding because it violates Patent Owner's constitutional rights. Patent validity must be litigated in an Article-III court, not before an executive agency. *McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898). Adversarial patent challenges—like *inter partes* reviews—are also "suits at common law" for which the Seventh Amendment guarantees a jury trial. U.S. Const. amend. VII; *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 377 (1996). Moreover, even if *inter partes* reviews are constitutional in other circumstances, it is unconstitutional for pre-AIA patents—like the '213 patent.

Patent Owner presents this constitutional challenge to preserve the issue pending the Supreme Court's decision in *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, No. 16-712.

IX. CONCLUSION

The Board should confirm the patentability of claims 4, 12, 30-31, 33, 42, 60, 62-67, 69, and 71-79.

Respectfully submitted,

Date: March 8, 2018

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Response, contains 13,526 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: March 8, 2018

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CERTIFICATE OF SERVICE

I hereby certify that, on March 8, 2018, I caused a true and correct copy of the following materials:

- Patent Owner's Response
- Patent Owner's Motion to Seal
- Patent Owner's Certificate of Compliance
- Exhibits 2037, 2039-2045, 2053-2055, 2059-2063
- Patent Owner's Exhibit List

to be served electronically via File Transfer Protocol (FTP), as previously agreed by the parties, on the following attorneys of record:

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IPR2017-01373
Patent Owner's Exhibit List

Patent Owner's Exhibit Number	Exhibit Name
2001	Genentech, Inc. Laboratory Notebook No. 10098 (Leonard Presta) PROTECTIVE ORDER MATERIAL
2002	Genentech, Inc. Laboratory Notebook No. 10823 (Leonard Presta) PROTECTIVE ORDER MATERIAL
2003	Genentech, Inc. Laboratory Notebook No. 11268 (Paul Carter) PROTECTIVE ORDER MATERIAL
2004	Genentech, Inc. Laboratory Notebook No. 11643 (Paul Carter) PROTECTIVE ORDER MATERIAL
2005	Genentech, Inc. Laboratory Notebook No. 10840 (John Brady) PROTECTIVE ORDER MATERIAL
2006	Genentech, Inc. Laboratory Notebook No. 11162 (John Brady) PROTECTIVE ORDER MATERIAL
2007	Excerpts from Genentech, Inc. Laboratory Notebook No. 11008 (Ann Rowland) PROTECTIVE ORDER MATERIAL
2008	Excerpts from Genentech, Inc. Laboratory Notebook No. 11297 (Tim Hotaling) PROTECTIVE ORDER MATERIAL
2009	Excerpts from Genentech, Inc. Laboratory Notebook No. 11568 (Monique Carver) PROTECTIVE ORDER MATERIAL
2010	Genentech, Inc. Interoffice Memorandum from Paul Carter to Leonard Presta and Dennis Henner PROTECTIVE ORDER MATERIAL
2011	Genentech, Inc. Interoffice Memorandum from Paul Carter to Leonard Presta PROTECTIVE ORDER MATERIAL
2012	Genentech, Inc. Synthetic DNA Requests PROTECTIVE ORDER MATERIAL
2013	Genentech, Inc. Synthetic DNA Requests PROTECTIVE ORDER MATERIAL

Patent Owner's Exhibit Number	Exhibit Name
2014	Genentech, Inc. Protein Engineering of 4D5 Status Report PROTECTIVE ORDER MATERIAL
2015	Genentech, Inc. Interoffice Memorandum re: RCC Minutes and Recommendations PROTECTIVE ORDER MATERIAL
2016	Declaration of Dr. Leonard G. Presta PROTECTIVE ORDER MATERIAL
2017	Declaration of Dr. Paul J. Carter PROTECTIVE ORDER MATERIAL
2018	Declaration of John Ridgway Brady PROTECTIVE ORDER MATERIAL
2019	Declaration of Irene Loeffler
2020	Paul Carter, et al., *Humanization of the Anti-p185 Antibody for Human Cancer Therapy*, 89 PROC. NATL. ACAD. SCI. 4285-4289 (1992)
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2022	Marianne Brüggerman, et al., *The Immunogenicity of Chimeric Antibodies*, 170 J. EXP. MED. 2153-2157 (1989)
2023	Jatinderpal Kalsi, et al., *Structure-function Analysis and the Molecular Origins of Anti-DNA Antibodies in Systemic Lupus Erythematosus*, EXPERT REVIEWS IN MOLECULAR MEDICINE 1-28 (1999)
2024	Scott Gorman, et al., *Reshaping a Therapeutic CD4 Antibody*, 88 PROC. NATL. ACAD. SCI. 4181-4185 (1991)
2025	John Isaacs, et al., *Humanised Monoclonal Antibody Therapy for Rheumatoid Arthritis*, 340 THE LANCET 748-752 (1992)
2026	Elvin Kabat, et al., *Sequences of Proteins of Immunological Interest* 1-23 (4th ed. 1987)
2027	Anna Tramontano, et al., *Framework Residue 71 Is a Major Determinant of the Position and Conformation of the Second Hypervariable Region in the VH Domains of Immunoglobulins*, 215 J. MOL. BIOL. 175-182 (1990)

Patent Owner's Exhibit Number	Exhibit Name
2028	H.M. Shepard, et al., *Herceptin*, *in* THERAPEUTIC ANTIBODIES. HANDBOOK OF EXPERIMENTAL PHARMACOLOGY 183-219 (Y. Chernajovsky & A. Nissim, eds. 2008)
2029	Excerpt from Roche Finance Report 2016
2030	Modified Default Standing Protective Order and Patent Owner's Certification of Agreement to Terms
2031	Modified Default Standing Protective Order – Redline
2032	Declaration of Robert J. Gunther, Jr. in support of Motion for Admission Pro Hac Vice
2033	Declaration of Daralyn J. Durie in support of Motion for Admission Pro Hac Vice
2034	Declaration of Lisa J. Pirozzolo in support of Motion for Admission Pro Hac Vice
2035	Declaration of Kevin S. Prussia in support of Motion for Admission Pro Hac Vice
2036	Declaration of Andrew J. Danford in support of Motion for Admission Pro Hac Vice
2037	File History for U.S. Patent Application No. 07/715,272 *Immunoglobulin Variants* (filed June 14, 1991).
2038	Reserved
2039	Deposition Transcript of Lutz Riechmann, *Celltrion, Inc. v. Genentech, Inc.* (PTAB), Feb. 14, 2018
2040	Deposition Transcript of Robert Leonard, *Celltrion, Inc. v. Genentech, Inc.* (PTAB), Feb. 16, 2018
2041	Expert Declaration of Dr. Ian A. Wilson
2042	U.S. Patent No. 7,375,193
2043	U.S. Patent No. 7,560,111
2044	Leonard Presta, et al., *Humanization of an Antibody Directed Against IgE*, 151 J. IMMUNOLOGY 2623-2632 (1993)
2045	A. Bondi, *van de Waals Volumes and Radii*, 68 J. PHYSICAL CHEMISTRY 441-451 (1964)
2046	Reserved
2047	Reserved
2048	Reserved
2049	Reserved
2050	Reserved

Patent Owner's Exhibit Number	Exhibit Name
2051	Reserved
2052	Reserved
2053	Ole Brekke, et al., *Therapeutic Antibodies for Human Diseases at the Dawn of the Twenty-First Century*, 2 NATURE REVIEWS | DRUG DISCOVERY 52- 62 (2003)
2054	Thomas A. Waldmann, *Monoclonal Antibodies in Diagnosis and Therapy*, 252 SCIENCE 1657-1662 (1991)
2055	Greg Winter, et al., *Antibody-Based Therapy: Humanized Antibodies*, 14 TIPS 139-143 (1993)
2056	Reserved
2057	Reserved
2058	Reserved
2059	Gert Riethmüller, et al., *Monoclonal Antibodies in the Detection and Therapy of Micrometastic Epthelial Cancers*, 4 CURRENT OP. IMMUNOLOGY 647-655 (1992)
2060	Gert Riethmüller, et al., *Monoclonal Antibodies in Cancer Therapy*, 5 CURRENT OP. IMMUNOLOGY 732-739 (1993)
2061	Mark D. Pegram, et al., *Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal Antibody Plus Cisplatin in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer Refractory to Chemotherapy Treatment*, 16 J. CLINICAL ONCOLOGY 2659-2671 (1998)
2062	Redline of IPR2016-01694 Expert Declaration of Dr. Eduardo A. Padlan in Support of Petition for *Inter Partes* Review of Patent No. 6,407,213 and IPR2017-01373 Expert Declaration of Lutz Riechmann, Ph.D., in Support of Petition for *Inter Partes* Review of Patent No. 6,407,213
2063	Corrected Exhibit P of Expert Declaration of Lutz Riechmann, Ph.D., in Support of Petition for *Inter Partes* Review of Patent No. 6,407,213