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UNITED STATES PATENT AND TRADEMARK OFFICE

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**BEFORE THE PATENT TRIAL AND APPEAL BOARD**

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PFIZER, INC. AND
SAMSUNG BIOEPIS CO., LTD.
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

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Case IPR2017-01488
Patent 6,407,213

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# 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 Petitioners' 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 Petitioners have failed to carry their burden for those claims. Patent Owner's response is supported by new evidence obtained from cross-examination of Petitioners' declarants Dr. Jefferson Foote (Ex-2039) and Mr. Timothy Buss (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 Kurrle and Queen-1990. 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.

***Second***, the challenged claims require that resulting humanized antibodies bind an antigen. Petitioners have failed to offer any proof that this limitation is satisfied for antibodies having the substitutions recited in claims 66-67, 71-72, 75-76, and 78. Kurrle contains ***no*** binding data for the only antibody (EUCIV-4) that discloses the substitutions recited in claims 66-67, 71-72, 75-76, and 78. And Queen-1990 discloses no antibody sequence containing the claimed framework substitutions—let alone data showing that such an antibody binds antigen. At their depositions, Petitioners' declarants confirmed that the only way to know whether a

[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.

particular humanized antibody has binding affinity at all is to test it—yet Petitioners have presented no evidence of such testing here.

***Third***, Petitioners have failed to show that Queen-1990 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.

***Fourth***, claims 12, 42, 60, 65-67, and 71-79 recite at least one and up to five specific framework substitutions. Petitioners assert that these claims would have been obvious in view of the broad genus of potential framework substitutions purportedly disclosed in the asserted references—which essentially encompasses every framework position. Missing from the asserted references (or anywhere in the petition) is a ***reason*** why a person of ordinary skill would have chosen the specific framework substitutions recited in those claims. On the contrary, applying the same general criteria relied upon by Petitioners, Queen-1990 produced a humanized antibody with 15 substitutions—***none*** of which correspond with the

claims. If Queen-1990 itself did not obtain ***any*** of the claimed substitutions, it surely would not have been obvious to a skilled artisan to do so applying those same rules. Nor would those specific claimed framework substitutions have been obvious to try. What Petitioners cite 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.

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

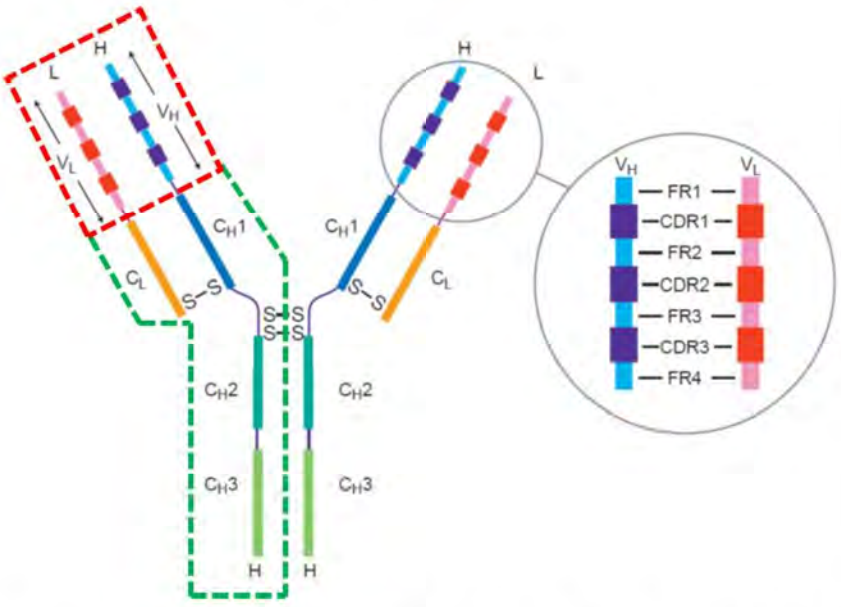
***Finally***, claims 63 and 65 contain additional limitations requiring that the antibody "lacks immunogenicity" or has "up to 3-fold more" binding affinity as compared with the parent non-human antibody. Petitioners presented no evidence of any antibody disclosed in Kurrle and/or Queen-1990 that has 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 ¶32; 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-2041 ¶50; Ex-1001, 1:55-58.) An

immunogenic response had adverse clinical consequences, including diminished efficacy and allergic reactions. (Ex-2041 ¶51; Ex-2039, 190:25-191:8.)

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-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.)

Scientists pursued techniques for making humanized antibodies that balanced strong binding with low immunogenicity. (Ex-2039, 55:5-9; 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 ¶¶61-68; 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, 264-65.)

## 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 3439-41, ¶¶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 3439-41, ¶¶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.) The examiner did not make any rejection based upon any reference underlying the instituted grounds.

Petitioners assert that Kurrle (Ex-1071), Chothia & Lesk (Ex-1062), and Chothia-1985 (Ex-1063) were not considered during prosecution. (Paper 1 at 14.) That is incorrect. Each is cited on the face of the patent. (*See* Ex-1001 at 1 (Kurrle: "EP 403156"); *id.* at 2 (Chothia & Lesk: right column, ninth from top); *id.* (Chothia-1985: right column, twelfth from top).) And Chothia & Lesk and Chothia-1985 are discussed in the '213 specification. (*Id.*, 1:27-30 (Chothia-1985); *id.*, 3:1-3, 3:32, 7:7-8, 7:45, 10:38, 20:22-23, 20:29-30, 47:42-43, 48:66-67 (Chothia & Lesk).)

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 4432-33, 4443.) As detailed below, the record in this proceeding further confirms that

certain challenged claims were also invented before the publication of either Kurrle (December 19, 1990) or Queen-1990 (July 26, 1990).

## IV. ASSERTED REFERENCES

### A. Kurrle

Kurrle is a European Patent Application published on December 19, 1990. Kurrle is not prior art to certain challenged claims. (*Infra* §VIII.A.)

Unlike the '213 patent's consensus sequence approach, Kurrle used a best-fit approach for antibody humanization. (Ex-2041 ¶129.) Starting from the murine antibody sequence, Kurrle searched for "the most homologous human antibody" to provide the variable domain. (Ex-1071, 8:16-18.) Kurrle incorporated the CDRs from the mouse antibody into the human antibody sequence (*id.*, 3:8-11), and then made further substitutions of murine residues "in the sequence immediately before and after the CDRs" and "up to 4 amino acids away" (*id.*, 8:25-29).

Kurrle's technique thus involved making substitutions in any of up to 24 different positions per antibody chain—*i.e.*, 4 amino acids on either side of the 3 CDRs—or 48 potential substitutions in total. (Ex-2041 ¶131; Ex-2039, 298:25-299:5.) Kurrle provided no guidance on which substitutions may be beneficial for any given antibody. (Ex-2041 ¶133.) Kurrle also highlighted the unpredictable and "potential[ly] adverse consequences" of modifying the human antibody

sequence to incorporate amino acids from the murine antibody. (Ex-1071, 8:40-43 ("[E]xtreme caution must be exercised to limit the number of changes.").)

Kurrle disclosed the sequence for four humanized antibodies: EUCIV1, EUCIV2, EUCIV3, and EUCIV4. (*Id.*, Tables 6A-B; Ex-2041 ¶134 (identifying substitutions in Kurrle's antibodies).) EUCIV1 and EUCIV2 lacked binding affinity to the target antigen. (Ex-1071, 9:1-14; Ex-2041 ¶135.) EUCIV3 had binding affinity for the target antigen, but it was less than the murine parent antibody. (Ex-1071, Table 7; Ex-2041 ¶135.) EUCIV4 is the only antibody sequence reported in Kurrle with substitutions at 71H, 73H, and/or 76H. (Ex-2041 ¶136.) However, Kurrle provides no binding affinity data for EUCIV4, and the corresponding scientific publication to Kurrle makes no mention of EUCIV4. (Ex-2041 ¶136; Ex-2033.)

### 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 ¶¶113-14.) Queen-1990 identified four general criteria for designing humanized antibodies. (Ex-2041 ¶¶114-122.)

***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 ¶¶115-16.)

***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. (Ex-1050, 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 Petitioners' expert Dr. Foote confirmed, substituting residues at these positions is optional, "not obligatory." (Ex-2039, 238:24-239:4.) Queen-1990 "doesn't specify … a certain method for choosing these [residues]" and "does not prioritize any particular one." (Ex-2039, 246:3-12, 246:25-247:4.)

***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 be substituted at those positions that may interact with CDRs. (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.) But Dr. Foote admitted that Criterion IV "doesn't give a formula for when or when not to replace them. [It] mainly giv[es] the list that you would consider replacing." (Ex-2039, 253:9-16.)

Queen-1990 disclosed a humanized antibody sequence produced using its technique. (Ex-1050, Fig. 2.) That antibody contained 15 framework substitutions—none of which correspond with the '213 claims. (Ex-2041 ¶125.) 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 ¶126; Ex-1050, 31:33-37.) Queen-1990 does not describe or report any testing of immunogenicity for this humanized antibody. (Ex-2041 ¶126.)

### C. Furey

Furey (Ex-1125) is a 1983 publication describing the crystal structure of a Bence-Jones protein fragment. A Bence-Jones fragment is different from a typical antibody structure. It consists of two antibody light chains, instead of two light chains and two heavy chains. (Ex-2041 ¶125.) Furey does not describe antibody humanization or discuss substitutions beneficial when humanizing an antibody, let

alone describe how its analysis of a Bence-Jones fragment would be applicable to typical antibody structures. (Ex-2041 ¶147.)

Furey identified "11 side chain-side chain hydrogen bonds" of which 6 "may be common to all $V_L$ domains." (Ex-1125 at 673-74.) According to Furey, the "most important" of those six hydrogen bonds "seem to be the two involved in the salt-bridge" between 61L (Arg62) and 82L (Asp83). (*Id.*; Ex-2041 ¶146.)[2]

### D. Chothia & Lesk

Chothia & Lesk (Ex-1062) is a 1987 publication that analyzed known antibody structures to identify positions "primarily responsible for the main-chain conformations observed in the hypervariable regions." (Ex-1062 at 902.) Chothia & Lesk does not describe antibody humanization or discuss substitutions beneficial when humanizing an antibody. (Ex-2041 ¶141.)

Chothia & Lesk noted that "[t]he major determinants of the tertiary structure of the frameworks are the residues buried within and between the domains." (Ex-

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[2] This shorthand follows Kabat's convention, which assigns standardized numbers to the amino acid positions in antibody heavy ("H") and light ("L") chains. (Ex-1001, 10:46-57; *see* Ex-2041 ¶33.) For example, "61L" refers to the 61st position in the light chain. Furey identifies these positions using a different numbering convention (*i.e.*, Arg62).

1062 at 903.) Table 4 identifies 50 positions "commonly buried within $V_L$ and $V_H$ domains"—26 from the light chain and 24 from the heavy chain. (*Id.* at 906.) Chothia & Lesk does not indicate that any of those 50 positions has more importance than any other to determine antibody structure. (Ex-2041 ¶¶140-41.)

### E. Chothia-1985

Chothia-1985 (Ex-1063) is a 1985 publication that analyzes "the structure of the interface between VL and VH domains in three immunoglobulin fragments." (Ex-1063 at 651.) Chothia-1985 does not describe antibody humanization or discuss substitutions beneficial when humanizing an antibody. (Ex-2041 ¶144.)

Table 4 of Chothia-1985 identifies 20 positions at the $V_L$-$V_H$ interface. (Ex-1063 at 660.) Chothia-1985 does not indicate that any of those 20 positions has more importance than any other to determine antibody structure. (Ex-2041 ¶143-44.)

### 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, 134:11-25; Ex-2041 ¶149.)

## 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 27 at 8.)

Petitioners' proposed definition encompasses persons without advanced degrees but who have "knowledge gained through 4-5 years of work experience" (Paper 1 at 15-16), which is an attempt to fit their expert, Mr. Timothy Buss, within the definition of a person of ordinary skill. Patent Owner disagrees that Mr. Buss was a person of ordinary skill at the time of the '213 invention and believes that he lacks the qualifications to offer the opinions in his declaration. The Board should give his testimony no weight. (*Infra* pp. 63-64.)

## 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.) 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 27 at 10.) Patent Owner submits that this continues to be the correct result.

Petitioners have proposed constructions of several terms. (Paper 1 at 16-18.) As the Board recognized in its institution decision, no construction of those terms is necessary. (Paper 27 at 10.)

For purposes of this proceeding, Patent Owner does not dispute the Board's construction of "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." (Paper 27 at 10-12.)

## 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) claim 71 because Kurrle has been antedated (*infra* §VIII.A); (2) claims 66-67, 71-72, and 75-76 because the "bind antigen" limitation is not anticipated by Kurrle (*infra*

§VIII.B); and (3) claim 63 because there is no evidence that any antibody disclosed in Kurrle "lacks immunogenicity compared to [its] non-human parent antibody" (*infra* §VIII.E). 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 4, 62, and 64 because Queen-1990 does not disclose a "consensus" sequence as defined by the '213 patent (*infra* §VIII.C); and (2) claim 63 because there is no evidence that any antibody disclosed in Queen-1990 "lacks immunogenicity compared to [its] non-human parent antibody" (*infra* §VIII.F). Patent Owner does not defend the patentability of claims 1-2, 29, and 80-81.

**Ground 3:** The Board should confirm the patentability of (1) claim 71 because Kurrle and Queen-1990 have been antedated (*infra* §VIII.A); (2) claims 4, 62, and 64 because Queen-1990 does not teach a "consensus" sequence as defined by the '213 patent (*infra* §VIII.C); (3) claims 66-67, 71-72, 75-76, and 78 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.D); and (4) claim 63 because, given the unpredictability of immunogenicity, it would not have been obvious that an antibody produced according to Kurrle or Queen-1990 "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 4:** The Board should confirm the patentability of claim 12 because (1) Kurrle and Queen-1990 have been antedated (*infra* §VIII.A); and (2) 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.D).

**Ground 5:** The Board should confirm the patentability of (1) claim 73 because Kurrle and Queen-1990 have been antedated (*infra* §VIII.A); and (2) claims 73 and 77 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.D).

**Ground 6:** The Board should confirm the patentability of claim 74 because (1) Kurrle and Queen-1990 have been antedated (*infra* §VIII.A); and (2) it would not have been obvious to select 93H 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.D).

**Ground 7:** The Board should confirm the patentability of (1) claims 65 and 79 because Kurrle and Queen-1990 have been antedated (*infra* §VIII.A); (2) claims 65 and 79 because it would not have been obvious to select 71H, 73H, 78H, and 93H 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.D); 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.F).

**Ground 8:** The Board should confirm the patentability of (1) claim 42 because Queen-1990 has been antedated (*infra* §VIII.A); (2) claim 33 because Queen-1990 does not teach a "consensus" sequence as defined by the '213 patent (*infra* §VIII.C); (3) claim 42 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.D); and (4) claims 30, 31, 33, and 42 because it would not have been obvious that an antibody with the recited framework substitutions would bind $p185^{HER2}$ (*infra* §VIII.G).

**Ground 9:** The Board should confirm the patentability of claim 42 because (1) Kurrle and Queen-1990 have been antedated (*infra* §VIII.A); (2) 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.D); and (3) it would not have been obvious that an antibody with a framework substitution at 66L would bind $p185^{HER2}$ (*infra* §VIII.G).

**Ground 10:** The Board should confirm the patentability of claim 60 because (1) Kurrle and Queen have been antedated (*infra* §VIII.A); (2) it would not have been obvious to select 78H 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.D); and (3) it would not have been obvious that an antibody with a framework substitution at 78H would bind $p185^{HER2}$ (*infra* §VIII.G).

## VIII. ARGUMENT

### A. Grounds 1, 3-10: The Board Should Confirm The Patentability Of Claims 12, 42, 60, 65, 71, 73-74, And 79 Because Neither Kurrle Nor Queen-1990 Is Prior Art.

Each instituted ground rests on Kurrle and/or Queen-1990. In its preliminary response, Patent Owner presented antedation evidence for every challenged claim. (Paper 6 at 20-43.) The Board, however, declined to deny

institution because (i) Petitioners had not yet had an opportunity to test that antedation evidence; and (ii) in the Board's view, it was not clear whether that antedation evidence applied to certain claimed substitutions. (Paper 27 at 15.)

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 Kurrle or Queen-1990.

### 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])[3]

**b) Humanized 4D5 antibody sequences**

[redacted]

[3] 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]

[redacted]

**c) Production and testing of humanized 4D5 antibodies**

[redacted]

[redacted]

[redacted]

**(i) First humanized 4D5 variable domain fragment**

[redacted]

[redacted]

[redacted]

**(ii) First humanized 4D5 full-length antibody**

[redacted]

[4] [redacted]

[redacted]

**(iii) Other humanized 4D5 variants**

The '213 inventors made five other humanized 4D5 antibodies with different substitutions.[5] [redacted]

[5] 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]

6 [redacted]

### 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*, 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-2006 at 47, 51; Ex-2008 at 6.)<br><br>Before July 26, 1990, the inventors had made | 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.)<br><br>Before July 26, 1990, the inventors had made HuMAb4D5-8 (Variant 6 with "c" light and heavy |

[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 |
|---|---|---|
| | 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.) | 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 numbering system set forth in Kabat. | 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, 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.

***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.

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[8] Neither Kurrle nor Queen-1990 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 Kurrle and/or Queen-1990.

**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. 24-34.)

**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.[9] (*Supra* pp. 24-34.) 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,

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[9] Petitioners' own expert, Dr. Foote, who knows Dr. Carter because they both worked in Dr. Gregory Winter's laboratory, testified that he has "no reason to think of Paul Carter as being sloppy or dishonest" (Ex-2039, 159:15-16), which reinforces that the veracity of the contemporaneous records kept by Genentech scientists working on this project.

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.").

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

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

Kurrle and Queen-1990 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-2032, p.9 (3:21-23), p.35-36 (29:11-30:6), p.107 (claim 1), p.109 (claim 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.81-88 (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. (Ex-2032, 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-2032, p.15 (9:12-19), p.96 (90:1-18), p.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-2032, p.88-89 (82:31-83:8), 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 3 specifically identifies the framework substitutions in HuMAb4D5-5 and

HuMAb4D5-8, which correspond with the framework substitutions recited in those eight claims. (Ex-2032, 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-2032, 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-2032, 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.*, p.88-89 (82:31-83:3), p.91 (85:24-32), 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 Kurrle and Queen-1990 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.

### B. Grounds 1, 3: Claims 66-67, 71-72, 75-76, and 78 Are Not Anticipated Or Obvious Because The Asserted References Fail To Teach Non-Human CDRs "Which Bind Antigen Incorporated Into A Human Antibody Variable Domain."

Claim 66 recites "[a] humanized antibody heavy chain variable domain comprising non-human [CDRs] ***which bind antigen*** incorporated into a human antibody variable domain" that includes framework substitutions at 24H, 73H, 76H, 78H, and/or 93H. Claims 67, 71-72, 75-76, and 78 depend from claim 66. Petitioners assert that these claims are anticipated by Kurrle (Ground 1) or would have been obvious over the combination of Kurrle and Queen-1990 (Ground 3). (Paper 1 at 31-32, 48-50.) Both grounds fail, however, because Petitioners have not shown that the prior art taught a humanized antibody heavy chain variable domain with the recited substitutions that incorporates non-human CDRs "which bind antigen."

The sole evidence that Petitioners cite for that claim limitation is Kurrle's disclosure of the humanized antibody called EUCIV4, which is the only antibody sequence disclosed in Kurrle that contains substitutions (71H, 73H, 76H) corresponding with claim 66-67, 71-72, 75-76, and/or 78. (Ex-1003 ¶¶165-168; Ex-2041 ¶167.) Kurrle, however, contains ***no*** data demonstrating that the CDRs incorporated into that human antibody sequence "bind antigen," as required by claims 66-67, 71-72, 75-76, and 78. (Ex-1071, 9:10-31; Ex-2041 ¶¶163-66.)

Absent binding data for EUCIV4, Kurrle does not teach the "bind antigen" limitation. Kurrle states that other humanized antibodies incorporating the ***same*** CDRs were unable to bind antigen. (Ex-1071, 9:17 ("The BMA-EUCIV1 and BMA-EUCIV2 antibodies were unable to bind to T cells.").) Furthermore, EUCIV4 contains ***34*** substitutions—a large number that makes it unpredictable whether the CDRs would have any binding affinity when incorporated into the human sequence, as Kurrle itself makes clear and Dr. Foote confirmed. (Ex-1071, 8:42-43 ("[E]xtreme caution must be exercised to limit the number of changes."); Ex-2041 ¶¶130-34; Ex-2039, 310:2-10.) And the scientific publication corresponding with the Kurrle patent application never mentions EUCIV4, further suggesting that the CDRs incorporated into that antibody sequence were unable to bind antigen. (Ex-2033 at 4366; Ex-2041 ¶136, 166.) Accordingly, Petitioners have not demonstrated that the "bind antigen" limitation is taught expressly or inherently by Kurrle, and the Board should confirm the patentability of 66-67, 71-72, 75-76, and 78 over Ground 1.

Petitioners' obviousness theory in Ground 3 fails for similar reasons. Again, the only evidence that Petitioners cite supporting its challenge to these claims in Ground 3 is Kurrle's disclosure of EUCIV4. (Ex-1003 ¶¶223-227; Ex-2041 ¶¶163-68.) But it would not have been obvious that the CDRs could "bind antigen" when incorporated into a humanized antibody sequence containing the

framework substitutions recited in claims 66-67, 71-72, 75-76, and 78. As just discussed, Kurrle's failure to include binding data for the only antibody sequence containing those substitutions is a strong indication the CDRs incorporated into those sequences do ***not*** "bind antigen." Accordingly, the Board should confirm the patentability of 66-67, 71-72, 75-76, and 78 with respect to Ground 3.

### C. Grounds 2-3, 8: Claims 4, 33, 62, 64, and 69 Are Not Anticipated Or Obvious.

#### 1. The Asserted References Do Not Teach The Consensus Sequence Limitations.

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 27 at 10.)

Petitioners have not demonstrated anticipation or obviousness of the "consensus" limitations of claims 4, 33, 62, 64, and 69 under the specific definition provided in the patent. At the institution stage, the Board declined to credit Patent Owner's preliminary response with respect to the "consensus" limitations because Patent Owner had not yet proffered its evidence on this issue. (Paper 27 at 26.) However, the record now contains the testimony of Dr. Wilson, who explains that

the "consensus framework" referred to in Queen-1990 does not disclose a "consensus" sequence as defined by the '213 patent.

As Dr. Wilson explains, a skilled artisan 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 ¶210.) Such a consensus sequence would not necessarily be derived from "all" known sequences, as described in the '213 patent. (*Id.*) And although Queen-1990 does not have any examples using a "consensus framework," the text of the reference makes clear that it is not referring to a "consensus" sequence generated from ***all*** antibody sequences of any particular subclass or subunit structure. Rather, Queen-1990 describes "a consensus framework from ***many*** human antibodies," not ***all*** as in the '213 patent. (Ex-1050, 12:19-20; Ex-2041 ¶211.)

The remainder of Queen-1990 reinforces that its "consensus framework" is not generated from all antibody sequences. For example, the next paragraph in Queen-1990 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 person of ordinary skill 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 ¶211.)

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, as Dr. Foote admits. (Ex-2041 ¶213; Ex-2039, 222:12-17.) 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 the set of ***all*** antibodies. (Ex-2041 ¶213.) 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 ¶¶208-14.)

**2. Queen-1990 does not teach any antibody with the framework substitutions of claims 4, 33, 62, 64, and 69 that incorporates non-human CDRs that bind antigen.**

Queen-1990 does not expressly disclose an antibody with the claimed framework substitutions with non-human CDRs that "bind an antigen" as required by claims 4, 33,[10] 62, 64, and 69. (Ex-2041 ¶171.) And this limitation is not inherent to Queen-1990. Indeed, Dr. Foote admitted that antigen binding is unpredictable, such that even a single framework substitution may eliminate

[10] The antigen in claim 33 is "$p185^{HER2}$."

antigen binding. (Ex-2039, 310:2-10; Ex-2041 ¶177.) For this reason, it was "standard practice in antibody engineering" to test the affinity of any humanized antibody. (Ex-2040, 132:18-133:6.) Yet Petitioners cite no actual antibody sequence that meets this limitation, let alone binding affinity data for that sequence.

Petitioners' obviousness argument in Grounds 3 and 8 fails for similar reasons. 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, ¶¶177-78.) Indeed, the lack of binding affinity for several of the humanized antibodies disclosed in Kurrle confirms that a person of ordinary skill would not have had a reasonable expectation of success in achieving the claimed binding limitations. (*Supra* pp. 45-47.)

The Board should confirm the patentability of claims 4, 33, 62, 64, and 69 over Grounds 2, 3, and 8.

### D. Grounds 3-10: Claims 12, 42, 60, 65-67, And 71-79 Would Not Have Been Obvious From The Broad Genus Of Potential Substitutions Allegedly Disclosed In The Asserted References.

Claims 12, 42, 60, 65-67, and 71-79 recite at least one and up to five specific framework substitutions. Petitioners' only challenge to these claims is on obviousness grounds based upon a broad genus of potential framework

substitutions supposedly disclosed by the asserted references. However, a broad genus does not demonstrate obviousness where, as here, the claims recite a specific species and "there is nothing in the disclosure of [the reference] suggesting that one should select" the claimed species. *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994).

Queen-1990 is the primary reference underlying Ground 3-10. Under Petitioners' obviousness theory, Queen-1990's Criterion III alone discloses 23 different positions that could be substituted. (Ex-1003 ¶179.) Dr. Foote admits that Queen-1990 provides no guidance on which of those 23 substitutions may be important for any given antibody. (Ex-2039, 246:25-247:4 ("It does not prioritize any particular one.").) And those 23 different positions do not include the potential substitutions under Queen-1990's other criteria—for example, the 19 substitutions that Petitioners assert would be CDR contacts under Criterion IV. (IPR2017-01489, Paper 1 at 37; Ex-1003 ¶268; Ex-2041 ¶231.)

The other references underlying Grounds 3-10 also disclose many potential framework substitutions. Kurrle (Grounds 3-7) discloses 48 potential substitutions, as Dr. Foote admits. (Ex-2039, 295:14-21, 297:14-19; Ex-2041 ¶131.) Chothia & Lesk (Grounds 5, 7, 10) identifies 50 amino acid positions "commonly buried within $V_L$ and $V_H$ domains." (Ex-1062 at 906; Ex-2041 ¶140.) Chothia-1985 (Grounds 6-7) identifies 20 amino acid positions at the $V_L$-$V_H$ interface. (Ex-1063

at 660; Ex-2041 ¶143.) And Furey (Grounds 4, 9) identifies "11 side chain-side chain hydrogen bonds" of which 6 "may be common to all $V_L$ domains." (Ex-1125 at 674; Ex-2041 ¶147.) There are only 75 to 85 framework region amino acids in the light or heavy chain of a typical antibody (Ex-1050, 11:6-7; Ex-2041 ¶64.) Petitioners' theory is essentially that a substitution at ***any*** of those positions would have been obvious.

Given the large number of potential framework substitutions, there are literally millions of potential combinations and permutations of framework substitutions based upon the references underlying Grounds 3-10. (Ex-2041 ¶¶231-33.) Yet claims 12, 42, 60, 65-67, and 71-79 recite at least one and up to five specific substitutions. For example, claims 65 and 79 (Ground 7) require substitutions at each of 71H, 73H, 78H, and 93H. Petitioners offer 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. Indeed, Queen-1990 itself applied those same rules to create an antibody sequence with 15 framework substitutions—***none*** of which correspond with the challenged claims. Petitioners can hardly contend that it would have been obvious to arrive at the specific substitutions claimed in the '213 patent when Queen-1990 obtained none of them following its own criteria.

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 27 at 30.) 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 ¶234.) 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. (*Id.*) 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. (*Id.*)

The open-ended nature of the claims—which do not exclude substitutions in addition to those specifically recited—does not relieve Petitioners of their burden to identify a reason a person of ordinary skill would have chosen the specific framework substitutions required by the claims. Indeed, Petitioners' 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 Petitioners' own references caution against doing so. (Ex-2041 ¶235.)

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. Petitioners have 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. Foote concedes—and Petitioners' own references reflect—the unpredictable effects of making even a single framework substitution on antigen binding. (Ex-2039, 310:2-10 ("[A] single amino acid change can take you from an antibody that you want to try in a patient to one that you wouldn't try in a patient."); 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 ¶¶236-37.)

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 27 at 30.) 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 ¶¶231-37.) 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").

The full record now confirms that Kurrle and Queen-1990 did not provide a "detailed roadmap" (Paper 27 at 30) to arrive at the claimed invention. For example, Dr. Foote himself admitted that Queen-1990 "does not prioritize any particular" substitution and "is mainly giving the list that you would consider replacing." (Ex-2039, 246:3-247:4, 253:9-16.) In other words, the asserted references here provide "only general guidance as to the particular form of the claimed invention or how to achieve it," which is insufficient to support an obvious-to-try theory. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1073 (Fed. Cir. 2012).

The only "roadmap" underlying Petitioners' obviousness theory is the improper use of the '213 invention itself "as a roadmap to find its prior art components." *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1337 (Fed. Cir. 2005). For example, to identify the specific framework substitutions in claims 65 and 79 (71H, 73H, 78H, 93H) in Ground 7, Petitioners

combine the teachings of four different references for no other reason than to reconstruct the claimed substitutions. (Paper 1 at 54-56.) The Board should reject this hindsight-driven reasoning.

Finally, accepting Petitioners' obviousness theory would have sweeping consequences. Because Petitioners have 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 Petitioners' 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 over Grounds 3-10.

### E. Ground 7: Claim 65's "Up To 3-Fold More" Binding Affinity Limitation Would Not Have Been Obvious.

Claim 65 requires the humanized antibody to have a binding affinity "up to 3-fold more" than the parent non-human antibody. Petitioners point to no data showing that ***any*** antibody produced according to Kurrle and/or Queen-1990 had "up to 3-fold more" binding affinity. Instead, Petitioners argue that this limitation

is obvious over Queen-1990 and Kurrle in view of Chothia & Lesk and/or Chothia-1985 because Queen-1990 states 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 1 at 55-56; Ex-1050, 6:26-28.)

This argument fails. 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-2033 at 1 ("about 2.5 times lower"); Ex-2041 ¶257.) And two of Kurrle's humanized antibodies did not even bind the antigen. (Ex-1071, 9:17-19; Ex-2041 ¶257.) Nothing in the record demonstrates that Queen-1990's analogous technique would increase binding affinity as required by claim 65.

Moreover, Petitioners have 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. Foote's initial opinion was equivocal at best on this issue. He stated that "it would not have been surprising that at least a moderate 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 ¶308.) Moreover, what may occur "in some cases" is

insufficient to carry Petitioners' burden because it does not address the invention of claim 65, which recites four specific framework substitutions. And Dr. Foote 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, 310:2-10; Ex-2041 ¶258.)

The Board should confirm the patentability of claim 65.

### F. Grounds 1-3: Claim 63's "Lacks Immunogenicity" Limitation Is Not Anticipated Or Obvious.

In Grounds 1-3, Petitioners challenge claim 63, which requires "[a] humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient." In its institution decision, the Board construed this claim "as referring to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody." (Paper 27 at 12.) The Board then concluded that Petitioners had demonstrated a reasonable likelihood of success with respect to claim 63 because Kurrle discloses antibody sequences with three overlapping substitutions with claim 63 (4L, 69H, 76H) and states that "[t]he resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients." (Paper 27 at 19-20.)

However, the record now confirms that Kurrle does not disclose any humanized antibody with reduced immunogenicity as compared with the non-human parent. Dr. Foote confirmed at his deposition that ***any*** humanized antibody can provoke an immunogenic response—just like the parent non-human antibody—because the humanized antibody contains non-human CDRs that "could be attacked by the immune system." (Ex-2039, 180:7-10; Ex-2041 ¶199.) Dr. Foote also admitted that "you can't tell" whether a particular humanized antibody will provoke an immunogenic like the parent non-human antibody without administering the antibody to patients. (Ex-2039, 181:16-23.)

Kurrle contains no data indicating that any of its disclosed antibody sequences are any less immunogenic than the parent non-human antibody. (Ex-2041 ¶203.) Kurrle's statement that "[t]he resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients" (Ex-1071, 3:11-12) is simply a statement of intended result. And so is Queen-1990's statement that "the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans." (Ex-1050 at 1.) Neither Kurrle nor Queen-1990s discloses an actual antibody with less immunogenicity than the non-human parent or make it obvious how to achieve that result, given Dr. Foote's admission that immunogenicity cannot be predicted *ex ante*. (Ex-2039, 181:16-23.)

Nor does the fact that Kurrle disclosed antibody sequences with three substitutions corresponding with claim 63 anticipate or render obvious a humanized antibody with less immunogenicity than the non-human parent. Kurrle's disclosed antibody sequences contain numerous substitutions ***in addition*** to those three. (Ex-2041 ¶¶134, 203 (EUCIV3: 23 substitutions; EUCIV 4: 34 substitutions).)[11] And the greater the number of substitutions, the greater the likelihood of that the humanized antibody will provoke the same immunogenic response as the parent antibody. (Ex-2041 ¶203.) Given the large number of substitutions in Kurrle's antibody sequences, the likelihood of an immunogenic

[11] By contrast, Herceptin® (which embodies claim 63) contains five framework substitutions (66L, 71H, 73H, 78H, 93H) and two CDR substitutions (55L, 102H). (*Supra* pp. 32-33.)

response like the non-human parent antibody is very high. (*Id.*)[12] Accordingly, Petitioners have not shown that the immunogenicity limitation of claim 63 is anticipated or obvious, and the Board should confirm the patentability of claim 63.

### G. Grounds 8-10: It Would Not 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 Kurrle, Queen-1990, Furey, and Chothia & Lesk never mention $p185^{HER2}$. (Ex-2041 ¶259; Ex-2039, 224:23-225:4 (Queen-1990), 312:5-9 (Kurrle).) Kurrle and Queen-1990 describe antibodies for certain T-cell receptors. (Ex-1071, 2:1-4; Ex-1050, 4:11-16.) Furey describes a Bence-Jones protein fragment. (Ex-1125 at 661.) And Chothia & Lesk analyzed a handful of

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[12] The institution decision states that "both Kurrle and Queen-1990 recognize the need to substitute framework residues in order to reduce immunogenicity." (Paper 27 at 30.) Respectfully, that statement is not scientifically accurate. Framework substitutions ***increase*** the potential for immunogenicity by introducing non-human residues into the humanized sequence. (Ex-2041 ¶223.) The purpose of framework substitutions is to improve binding affinity, which must be balanced against the increased risk of immunogenicity, as Drs. Foote and Wilson explained. (Ex-2039, 55:5-9.; Ex-2041 ¶¶83, 223.)

"immunoglobulins of known atomic structure"—none of which bind p185$^{HER}$. (Ex-1062 at 902.) Those four references thus disclose nothing about which substitutions to make for an antibody that binds p185$^{HER2}$. (Ex-2041 ¶¶259-62.)

Petitioners' only asserted reference that even mentions p185$^{HER2}$ is Hudziak.[13] However, it is undisputed that Hudziak "doesn't discuss humanized antibodies" or "any methods for constructing a humanized antibody." (Ex-2040, 134:11-22.) It is also undisputed that "Hudziak does not describe any framework substitutions to humanized murine 4D5" (*i.e.*, a humanized antibody that binds p185$^{HER2}$). (Ex-2040, 134:23-25.)

Petitioners' 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 1 at 57-59.) But that is merely a research goal; it does not make the solution obvious. In particular, Petitioners have presented ***no*** evidence that any of framework substitutions recited in claims 30-31, 33, 42, and 60 would have been obvious ***for an antibody that binds p185$^{HER2}$***. For

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[13] Mr. Buss also discusses Shepard (Ex-1548), 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, 136:4-15.) Indeed, Shepard is not even part of the instituted grounds.

example, Petitioners did not apply the teachings of Kurrle 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.

Petitioners' assertion that "Queen-1990 provided detailed steps for humanizing mouse monoclonal antibodies, such as 4D5" (Paper 1 at 59), 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, Petitioners' reasoning, if accepted, would make obvious a humanized antibody for ***any antigen*** based upon the generalized teachings of Kurrle and/or Queen-1990. This expansive interpretation of Kurrle and/or Queen-1990 is untenable.

Finally, the Board should confirm the patentability of the claims challenged in Grounds 8-10 because Petitioners' obviousness theory rests on opinions from Mr. Buss, which he is unqualified to offer. Mr. Buss opines that the murine 4D5 antibody would have been "a prime candidate for further development as a therapy for breast cancer." (Ex-1004 ¶18.) Mr. Buss, however, is not an oncologist; his background is as laboratory technician. (Ex-2040, 34:15-18, 42:12-13.) Mr. Buss adopted nearly verbatim the opinions of another expert (Dr. Edward Ball), an oncologist retained by Mylan in a prior proceeding challenging the '213 patent.

(Ex-2040, 12:10-14:9; Ex-2058 (redline comparing declarations).) Mr. Buss was not familiar with Hudziak before this case—or most of the other references cited in his declaration, which he admitted that he included only because Dr. Ball had cited them. (Ex-2040, 95:1-8, 125:8-126:21, 127:21-128:3; *see generally id.* at 96:18-125:7 (discussing over 25 references).) And as of 1991, Mr. Buss had not even heard of HER2-positive breast cancer. (Ex-2040, 51:7-11.) Because Mr. Buss is not qualified to opine on whether p185$^{HER2}$ would have been a desirable therapeutic target for breast cancer as of 1991, the Board should disregard his opinions. *See, e.g.*, *Flex-Rest, LLC v. Steelcase, Inc.*, 455 F.3d 1351, 1360 (Fed. Cir. 2006) (affirming exclusion of testimony from unqualified expert).[14]

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

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[14] Patent Owner intends to file a motion to exclude Mr. Buss's opinions.

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 ¶264.) 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 ¶265; Ex-1002 at 3439-41, ¶¶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 ¶¶264-68.)

Petitioners argue that this unexpected result is irrelevant because the claims relate to antibodies, not methods of making them. (Paper 1 at 64-65.) But the broad applicability of the '213 invention is reflected in the claims—for example,

which recite specific framework substitutions that the inventors determined could be used in many different humanized antibodies. (Ex-2017 ¶¶75-79.)

***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-2033 at 4366 (2.5-fold reduction in binding affinity)). (Ex-2041 ¶267.) 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 3439-41, ¶¶2-9; Ex-1001, 51:50-53 ("This antibody binds the $p185^{HER2}$ ECD 3-fold more tightly than does muMAb4D5 itself.").)

Petitioners argue that those unexpected properties are not commensurate with the scope of the claims, since only claims 63 and 65 specifically recite those properties. (Paper 1 at 63-64.) 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-2017 ¶¶75-79; Ex-2016 ¶¶51-53.) 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 ¶¶267-68.) 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).

Petitioners argue that Herceptin®'s commercial success is irrelevant because it contains additional substitutions not recited in the claims. (Paper 1 at 67.) But Petitioners do not dispute that Herceptin® embodies the challenged claims. And Petitioners' argument that Herceptin® somehow is not coextensive with the claimed features because it contains additional unclaimed substitutions is incorrect. (*Id.*) The challenged claims recite ***framework*** region substitutions. The two unclaimed substitutions in Herceptin® (55L and 102H) are in the ***CDRs***. (*See, e.g.*, *id.* at 13 (showing CDRs).) Because Herceptin® is both an embodiment of the claims and coextensive with the claimed features, a nexus between its commercial

success and the challenged claims is presumed. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000).

## 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 13,762 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

/David L. Cavanaugh/
David L. Cavanaugh
Registration No. 36,476

## 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 2039-2045, 2051-2058
- 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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**IPR2017-01488**
**Patent Owner's Exhibit List**

| Patent Owner's Exhibit Number | Exhibit Name |
|---|---|
| 2001 | Genentech, Inc. Laboratory Notebook No. 10098 (Leonard Presta)<br>PROTECTIVE ORDER MATERIAL |
| 2002 | Genentech, Inc. Laboratory Notebook No. 10823 (Leonard Presta)<br>PROTECTIVE ORDER MATERIAL |
| 2003 | Genentech, Inc. Laboratory Notebook No. 11268 (Paul Carter)<br>PROTECTIVE ORDER MATERIAL |
| 2004 | Genentech, Inc. Laboratory Notebook No. 11643 (Paul Carter)<br>PROTECTIVE ORDER MATERIAL |
| 2005 | Genentech, Inc. Laboratory Notebook No. 10840 (John Brady)<br>PROTECTIVE ORDER MATERIAL |
| 2006 | Genentech, Inc. Laboratory Notebook No. 11162 (John Brady)<br>PROTECTIVE ORDER MATERIAL |
| 2007 | Excerpts from Genentech, Inc. Laboratory Notebook No. 11008 (Ann Rowland)<br>PROTECTIVE ORDER MATERIAL |
| 2008 | Excerpts from Genentech, Inc. Laboratory Notebook No. 11297 (Tim Hotaling)<br>PROTECTIVE ORDER MATERIAL |
| 2009 | Excerpts from Genentech, Inc. Laboratory Notebook No. 11568 (Monique Carver)<br>PROTECTIVE ORDER MATERIAL |
| 2010 | Genentech, Inc. Interoffice Memorandum from Paul Carter to Leonard Presta and Dennis Henner<br>PROTECTIVE ORDER MATERIAL |
| 2011 | Genentech, Inc. Interoffice Memorandum from Paul Carter to Leonard Presta<br>PROTECTIVE ORDER MATERIAL |
| 2012 | Genentech, Inc. Synthetic DNA Requests<br>PROTECTIVE ORDER MATERIAL |
| 2013 | Genentech, Inc. Synthetic DNA Requests<br>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 |
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| 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 | File History for U.S. Patent Application No. 07/715,272 *Immunoglobulin Variants* (filed June 14, 1991). |
| 2033 | Shearman, et al. *Construction, expression and characterization of humanized antibodies directed against the human a/b T cell receptor*. J. Immunol. 147(12):4366-4373, (December 15, 1991) |
| 2034 | Declaration of Robert J. Gunther, Jr. in support of Motion for Admission Pro Hac Vice |
| 2035 | Declaration of Daralyn J. Durie in support of Motion for Admission Pro Hac Vice |
| 2036 | Declaration of Lisa J. Pirozzolo in support of Motion for Admission Pro Hac Vice |
| 2037 | Declaration of Kevin S. Prussia in support of Motion for Admission Pro Hac Vice |
| 2038 | Declaration of Andrew J. Danford in support of Motion for Admission Pro Hac Vice |
| 2039 | Deposition Transcript of Jefferson Foote, *Pfizer, Inc. v. Genentech, Inc.* (PTAB), Feb. 4, 2018 |
| 2040 | Deposition Transcript of Timothy Buss, *Pfizer, Inc. v. Genentech, Inc.* (PTAB), Feb. 8, 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 |

| **Patent Owner's Exhibit Number** | **Exhibit Name** |
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| 2048 | Reserved |
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