UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC., and
SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

GENENTECH, INC,
Patent Owner.

Case IPR2017-01489[1]
Patent 6,407,213 B1

Before SHERIDAN K. SNEDDEN, ZHENYU YANG, and ROBERT A. POLLOCK, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

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[1] Case IPR2017-02140 has been joined with this proceeding.

ORDERS

Denying-in-Part and Dismissing-in-Part Petitioner's Motion to Exclude
37 C.F.R. § 42.64(c)

Denying Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Dismissing Patent Owner's Motion to Strike
37 C.F.R. § 42.5

Denying Petitioner's Motions to Seal without Prejudice to Patent Owner
37 C.F.R. § 42.55

Granting Patent Owner's Motion to Seal
37 C.F.R. § 42.55

Modifying Previous Order Granting Patent Owner's Motions to Seal
37 C.F.R. § 42.55

INTRODUCTION

Pfizer, Inc. ("Petitioner") filed a Petition (Paper 1 ("Pet.")) for an *inter partes* review of claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–67, 69, and 71–81 of U.S. Patent No. 6,407,213 B1 (Ex. 1501, "the '213 patent"). Genentech, Inc. ("Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp."). We instituted trial to review patentability of the challenged claims. Paper 27 ("Dec.").

Thereafter, Patent Owner filed a Response to the Petition (Paper 42, "PO Resp."), and Petitioner filed a Reply (Paper 53). The parties also briefed whether certain exhibits should be excluded from the record. Papers 60, 65, 67, 69, 71, 72. Patent Owner further sought to strike certain evidence and argument, and the parties briefed the issue. Papers 58, 70. In addition, Patent Owner filed a motion for observation on the cross-examination of Petitioner's declarant (Paper 61), and Petitioner filed an opposition thereto (Paper 68).

An oral hearing for this proceeding was held on July 16, 2018. *See* Paper 81.

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons provided below, we conclude Petitioner has established by a preponderance of the evidence that claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–64, 66, 67, 69, 71, 73, 74, 78, 80, and 81 of the '213 patent are unpatentable. Petitioner, however, has not met its burden to show the unpatentability of claims 65, 72, 75–77, and 79.

Related Proceedings

Samsung Bioepis Co., Ltd. submitted a petition presenting substantially the same challenges as set forth in Pfizer's Petition and moved to join this case. We granted that petition and the joinder motion. Paper 40.

Petitioner also filed IPR2017-01488, challenging the same claims of the '213 patent based on different prior art references. Concurrently with this Decision, we issue a final written decision in that case.

In addition, the '213 patent is the subject of IPR2017-01373 and IPR2017-01374. Concurrently with this Decision, we issue final written decision in those cases.

Four other *inter partes* reviews involving the '213 patent have been terminated. In IPR2016-01693 and IPR2016-01694, the parties settled before institution, whereas in IPR2017-02031 and IPR2017-02032, petitioner in those cases sought adverse judgement after institution.

The parties further identified several district court cases involving the '213 patent. Paper 82, 3–4; Paper 83, 1–2.

The '213 Patent and Relevant Background

The '213 patent issued from an application that is a continuation-in-part of an application filed on June 14, 1991. Ex. 1501, (63). The '213 patent relates to "methods for the preparation and use of variant antibodies and finds application particularly in the fields of immunology and cancer diagnosis and therapy." *Id.* at 1:12–14.

A naturally occurring antibody (immunoglobulin) comprises two heavy chains and two light chains. *Id.* at 1:18–20. Each heavy chain has a variable domain (V_H) and a number of constant domains. *Id.* at 1:21–23.

Each light chain has a variable domain (V_L) and a constant domain. *Id.* at 1:23–24.

The variable domains are involved directly in binding the antibody to the antigen. *Id.* at 1:36–38. Each variable domain "comprises four framework (FR) regions, whose sequences are somewhat conserved, connected by three hyper-variable or complementarity determining regions (CDRs)." *Id.* at 1:40–43. The constant domains are not involved directly in binding the antibody to an antigen, but are involved in various effector functions. *Id.* at 1:33–34.

Before the '213 patent, monoclonal antibodies targeting a specific antigen, obtained from animals, such as mice, had been shown to be antigenic in human clinical use. *Id.* at 1:51–53. The '213 patent recognizes efforts to construct chimeric antibodies and humanized antibodies in the prior art. *Id.* at 1:59–2:52. According to the '213 patent, chimeric antibodies are "antibodies in which an animal antigen-binding variable domain is coupled to a human constant domain" (*id.* at 1:60–62), whereas "humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies" (*id.* at 2:32–35).

The '213 patent also acknowledges the following as known in the prior art:

1. In certain cases, in order to transfer high antigen binding affinity, it is necessary to not only substitute CDRs, but also replace one or several FR residues from rodent antibodies for the human CDRs in human frameworks. *Id.* at 2:53–61.

2. "For a given antibody[,] a small number of FR residues are anticipated to be important for antigen binding" because they either directly contact antigen or "critically affect[] the conformation of particular CDRs and thus their contribution to antigen binding." *Id.* at 2:62–3:8.

3. In a few instances, a variable domain "may contain glycosylation sites, and that this glycosylation may improve or abolish antigen binding." *Id.* at 3:9–12.

4. The function of an antibody is dependent on its three-dimensional structure, and amino acid substitutions can change the three-dimensional structure of an antibody. *Id.* at 3:40–43.

5. The antigen binding affinity of a humanized antibody can be increased by mutagenesis based upon molecular modelling. *Id.* at 3:44–46.

Despite such knowledge in the field, according to the '213 patent, at the time of its invention, humanizing an antibody with retention of high affinity for antigen and other desired biological activities was difficult to achieve using then available procedures. *Id.* at 3:50–52. The '213 patent purportedly provides methods for rationalizing the selection of sites for substitution in preparing humanized antibodies and, thereby, increasing the efficiency of antibody humanization. *Id.* at 3:53–55.

Illustrative Claim

Among the challenged claims, claims 1, 30, 62–64, 66, 79, and 80 are independent. Claim 1 is illustrative and is reproduced below:

> 1. A humanized antibody variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprising a Framework Region (FR) amino acid substitution at a site selected from the

group consisting of: 4L, 38L, 43L, 44L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, and 92H, utilizing the numbering system set forth in Kabat.

Reviewed Grounds of Unpatentability

We instituted *inter partes* review of the following grounds of unpatentability:

Ground	Claims	Basis	References
1	1, 2, 12, 25, 29, 63–67, and 71–81	§ 103	Queen 1989[2] and Protein Data Bank (PDB database)
2	1, 2, 4, 12, 25, 29, 62–67, 69, and 71–81	§ 103	Queen 1990[3] and PDB database
3	65, 75–77, and 79	§ 103	Queen 1989, PDB database, and Tramontano[4]
4	65, 75–77, and 79	§ 103	Queen 1990, PDB database, and Tramontano
5	4, 62, 64, and 69	§ 103	Queen 1989, PDB database, and Kabat 1987[5]

[2] Queen et al., *A Humanized Antibody that Binds to the Interleukin 2 Receptor*, 86 PRO. NAT'L ACAD. SCI. 10029–33 (1989) (Ex. 1534).
[3] Queen, et al., International Publication No. WO 1990/07861, published July 26, 1990 (Ex. 1550).
[4] Tramontano, A. et al., *Framework Residue 71 is a Major Determinant of the Position and Conformation of the Second Hypervariable Region in the V_H Domains of Immunoglobulins*, 215 J. MOL. BIOL. 175–82 (1990) (Ex. 1551).
[5] Kabat, et al., Sequences of Proteins of Immunological Interest, Tabulation and Analysis of Amino Acid and Nucleic Acid Sequences of Precursors, V-Regions, C-Regions, J-Chain, T-Cell Receptor for Antigen, T-Cell Surface Antigens (National Institutes of Health, Bethesda, MD, 4th Ed. 1987) (Ex. 1552).

Ground	Claims	Basis	References
6	30, 31, 42, and 60	§ 103	Queen 1989, PDB database, and Hudziak[6]
7	30, 31, 33, 42, and 60	§ 103	Queen 1990, PDB database, and Hudziak

Pet. 5–6; Dec. 25–26; Paper 14, 2–3.

In support of its patentability challenges, Petitioner relies on the Declarations of Dr. Jefferson Foote (Exs. 1503, 1702) and Mr. Timothy Buss (Ex. 1504).

Patent Owner relies on the Declarations of co-inventors Dr. Leonard G. Presta (Ex. 2016) and Dr. Paul J. Carter (Ex. 2017), research technician Mr. John Ridgway Brady (Ex. 2018), and expert witness Dr. Ian A. Wilson (Ex. 2041).

ANALYSIS

Principles of Law

To prevail in this *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying

[6] Hudziak et al., *p185^{HER2} Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor*, 9 MOL. CELL BIOL. 1165–72 (1989) (Ex. 1521).

factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The strength of each of the *Graham* factors must be weighed in every case and must be weighed en route to the final obviousness determination. *See, e.g., Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983) (instructing that evidence of secondary considerations, when present, must always be considered in determining obviousness).

A party that asserts obviousness of a claim must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016). An obviousness analysis, however, "need not seek out precise teachings directed to the specific subject matter of the challenged claim" because we "can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. Moreover, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420.

We analyze the instituted grounds of unpatentability in accordance with these principles.

Level of Ordinary Skill in the Art

In the Decision to Institute, we found the parties' proposed definitions of a person of ordinary skill for the '213 patent are similar. Dec. 7 (citing

Pet. 16; Prelim. Resp. 17). We adopted Patent Owner's proposed definition that "[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." *Id.*

During trial, Patent Owner points out that Petitioner's proposed definition "encompasses persons without advanced degrees but who have 'knowledge gained through 4–5 years of work experience.'" PO Resp. 17. A person of ordinary skill in the art is a hypothetical person who is presumed to know the relevant prior art. *Custom Accessories, Inc. v. Jeffrey–Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986). The artisan may gain such knowledge through either formal education or extensive work experience. Thus, we do not discern an appreciable difference in the parties' respective definitions of the level of ordinary skill in the art, and any perceived distinction does not impact our Decision. Having considered the complete record developed at trial, we see no reason to change our assessment.

We further note that, in this case, the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown") (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

Claim Construction

In an *inter partes* review, the Board interprets a claim term in an unexpired patent according to its broadest reasonable construction in light of the specification of the patent in which it appears. 37 C.F.R. § 42.100(b) (2017); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under that standard, and absent any special definitions, we assign claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention, in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In the Decision to Institute, we agreed with Patent Owner that the '213 patent expressly defined "consensus human variable domain," which appears in claims 4, 33, 62, and 69, to 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." Dec. 9–10; Ex. 1501, 11:32–38. During trial, the parties did not argue otherwise, and we see no reason to change our position as to claim construction. *See* PO 17–18; Reply 5.

We, however, clarify that "all" in the consensus of "all human immunoglobulins" is not in the literal sense. In fact, Patent Owner does not appear to argue otherwise.[7] Dr. Wilson, the expert witness for Patent

[7] In a parallel proceeding involving the same patent, counsel for Patent Owner acknowledged that the term "all human immunoglobulins" refers to

Owner, testified that the consensus sequence of the '213 patent was "derived from 'all' *known* antibody sequences of any particular subclass or subunit structure." Ex. 2041 ¶ 210 (emphasis added); *see also* PO Resp. 52 (arguing the same); Ex. 1698, 59:22–60:1 (Dr. Carter testifying that the consensus sequence, as defined in the '213 patent, "only describes what was known at that time or it's only available sequences at that -- at that time"); Ex. 1699, 35:9–16 (Dr. Presta explaining that the consensus sequence of the '213 patent had the most common residue at every position "for the sequences that were available").

And evidence of record shows that at the priority date of the '213 patent, the sequences that were listed in Kabat 1987 "were the sequences available." Ex. 1699, 35:9–20; *see also* Ex. 2016 ¶ 25 (Kabat 1987 "collected known sequence data of antibodies"); Ex. 1698, 60:13–25 (Dr. Carter explaining the consensus sequence was derived from Kabat 1987, which is what was available at the time of the '213 patent); Ex. 1699, 27:19–25 (Dr. Presta stating that "Elvin Kabat had taken all known human/mouse/rabbit antibody sequences, published them in a government publication, and that there were human subgroups of sequences within the heavy and the light chains").

Thus, although we reiterate our previous construction of "consensus human variable domain," we clarify that "all human immunoglobulins of

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"all reasonably available[,] all known at the time of the invention." IPR2017-01373, Paper 83, 47:21–48:5.

any particular subclass or subunit structure" in the '213 patent refers to those immunoglobulins set forth in Kabat 1987.[8]

In the institution decision of the companion case IPR2017-01488, the same panel stated that the term "lacks immunogenicity," as recited in claim 63, refers to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody. For the purpose of this Decision, we adopt the same interpretation, which neither party disputes. *See* PO Resp. 18; Reply 5–6.

For the purpose of this Decision, we see no need to expressly construe any other claim terms. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (stating claim terms need only be construed to the extent necessary to resolve the controversy).

Disclosures of the Asserted Prior Art

Queen 1989

Queen 1989 teaches constructing a humanized antibody by combining the CDRs of a murine antibody with human framework and constant regions. Ex. 1534, Abstract, 3–4. According to Queen 1989, "[f]or the humanized antibody, sequence 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." *Id.* at 3. In Queen 1989, the human framework regions were chosen to maximize

[8] Because an *inter partes* review is limited to challenges based "only on the basis of prior art consisting of patents or printed publications," we do not address whether the challenged claims would satisfy the written description and/or enablement requirement under 35 U.S.C. § 112 if "all human immunoglobulins" were not limited as set forth in Kabat 1987.

homology with the murine antibody sequence. *Id.* at Abstract, 5. In addition, based on a computer model, Queen 1989 identified "several amino acids which, while outside the CDRs, are likely to interact with the CDRs or antigen. These mouse amino acids were also retained in the humanized antibody." *Id.* at Abstract, 5. Further, Queen 1989 teaches substituting an unusual amino acid in the human framework region if the corresponding positions in the murine antibody "actually has a residue much more typical of human sequences." *Id.* at 6.

Queen 1990

Queen 1990 teaches the following four criteria for designing humanized antibodies that "have a very strong affinity for a desired antigen":

> Criterion I: As acceptor, use a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized, or use a consensus framework from many human antibodies . . . .
>
> . . . .
>
> Criterion II: If an amino acid in the framework of the human acceptor immunoglobulin is unusual (i.e. "rare", which as used herein indicates an amino acid occurring at that position in no more than about 10% of human heavy (respectively light) chain V region sequences in a representative data bank), and if the donor amino acid at that position is typical for human sequences (i.e. "common", which as used herein indicates an amino acid occurring in at least about 25% of sequences in a representative data bank), then the donor amino acid rather than the acceptor may be selected . . . .
>
> Criterion III: In the positions immediately adjacent to one or more of the 3 CDR[]s in the primary sequence of the humanized immunoglobulin chain, the donor amino acid(s) rather than acceptor amino acid may be selected. These amino

> acids are particularly likely to interact with the amino acids in the CDR[]s and, if chosen from the acceptor, distort the donor CDR[]s and reduce affinity. Moreover, the adjacent amino acids may interact directly with the antigen . . . and selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody.
>
> Criterion IV: A 3-dimensional model, typically of the original donor antibody, shows that certain amino acids outside of the CDR[]s are close to the CDR[]s and have a good probability of interacting with amino acids in the CDR[]s by hydrogen bonding, Van der Waals forces, hydrophobic interactions, etc. At those amino acid positions, the donor amino acid rather than the acceptor immunoglobulin amino acid may be selected. Amino acids according to this criterion will generally have a side chain atom within about 3 angstrom units of some site in the CDR[]s and must contain atoms that could interact with the CDR atoms according to established chemical forces, such as those listed above.

Ex. 1550, 14:9–16:25. According to Queen 1990, "[w]hen combined into an intact antibody, the humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen." *Id.* at 8:21–25.

PDB Database

According to Petitioner, the Protein Data Bank (PDB) database was established in 1971 as a computer archival service managed by the Brookhaven National Laboratory. Pet. 23; Ex. 1503 ¶ 140 (citing Ex. 1580). The purpose of the Bank is to "collect, standardize, and distribute atomic co-ordinates and other data from crystallographic studies." Ex. 1580, 3. Dr. Foote testified that the PDB database "is a repository of protein crystal atomic co-ordinates available to the public." Ex. 1503 ¶ 140. According to

Dr. Foote, "[s]killed artisans relied on and contributed to the PDB database, retrieving computer-readable data that could be directly input into distance calculation and graphic programs for use in visualization and comparison studies, before the earliest priority date of the '213 patent." *Id.*

Tramontano

Tramontano teaches that "the major determinant of the position of H2 [i.e., CDR2 of the heavy chain] is the size of the residue at site 71, a site that is in the conserved framework of the V_H domain." Ex. 1551, Abstract. According to Tramontano, "[u]nderstanding the relationship between the residue at position 71 and the position and conformation of H2 has applications to the prediction and engineering of antigen-binding sites of immunoglobulins." *Id.*

Kabat 1987

Kabat 1987 is a compilation of known antibody sequences. Ex. 1552. For a given type of immunoglobulin, Kabat 1987 identifies the most common amino acids occurring at each position. *See, e.g., id.* at 13. It also teaches the FR and CDR boundaries within the variable domains. *See, e.g., id.* at 9.

Hudziak

Hudziak teaches $p185^{HER2}$'s role in carcinoma development. Ex. 1521, Abstract. Hudziak shows that 4D5, "a monoclonal antibody directed against the extracellular domain of $p185^{HER2}$ specifically inhibits the growth of breast tumor-derived cell lines overexpressing the *HER2*/c-*erbB*-2 gene product." *Id.* In addition, Hudziak reports that "resistance to the cytotoxic effect of tumor necrosis factor alpha, which has been shown to be a consequence of *HER2/c-erbB*-2 overexpression, is significantly reduced in

the presence of this antibody." *Id.* Hudziak states that "[m]onoclonal antibodies specific for $p185^{HER2}$ may therefore be useful therapeutic agents for the treatment of human neoplasias." *Id.* at 14.

Unpatentability of Claims 1, 2, 25, 29, 80, and 81

Petitioner challenges claims 1, 2, 25, 29, 80, and 81 as obvious over the combination of the PDB database with either Queen 1989 or Queen 1990. Pet. 31–40, 52–53. Patent Owner states it "does not defend the patentability of" those claims. PO Resp. 19 n.2. We adopt Petitioner's obviousness analysis of claims 1, 2, 25, 29, 80, and 81 (Pet. 31–40, 52–53), and conclude Petitioner has shown by a preponderance of the evidence that those claims are unpatentable.

Alternatively, we interpret Patent Owner's express decision not to defend the patentability of claims 1, 2, 25, 29, 80, and 81 as a request for adverse judgment as to those claims. A party may request judgment against itself at any time during a proceeding. 37 C.F.R. § 42.73(b). Thus, we enter judgment adverse to Patent Owner and with respect to those claims.

Ground 1: Obviousness over Queen 1989 and PDB Database

Petitioner argues that claims 1, 2, 12, 25, 29, 63–67, and 71–81 would have been obvious over the combination of Queen 1989 and the PDB Database. Pet. 26–49. Because we dispose of claims 1, 2, 25, 29, 80, and 81 above, we only need to address the patentability of claims 12, 63–67, and 71–79 as challenged under this ground. After reviewing the entire record, we determine that Petitioner has established by a preponderance of the evidence that claims 12, 63, 66, 67, 71, 73, 74, and 78 are unpatentable. We, however, conclude that Petitioner has not met its burden to show the unpatentability of claims 64, 65, 72, 75–77, and 79.

> Relying on the Declaration of Dr. Foote, Petitioner asserts that
>
> Queen 1989 taught that framework residues that (1) are close enough to influence CDR conformation; (2) interact directly with the antigen; and/or (3) are more 'human' in the mouse or donor immunoglobulin than the residue at the same position in human antibody variable domain (i.e., conserved) are suitable for substitution.

Pet. 31–32 (citing Ex. 1534, 5–6; Ex. 1503 ¶ 254). According to Petitioner, an ordinary artisan "would have used those simple rules to determine which residues in a human FR region could be switched back to mouse." *Id.* at 32 (citing Ex. 1503 ¶¶ 255–259).

Performing Queen 1989's methodology on antibody structures known and publicly available prior to the '213 patent through the PDB database, Petitioner continues, Dr. Foote was able to confirm the CDR-contacting framework residues that were targets for substitution. Pet. 32–34 (citing Ex. 1503 ¶¶ 261–66). These include nine residues in the light chain (4L, 58L, 62L, 66L, 67L, 69L, 73L, 85L, and 105L), and 11 residues in the heavy chain (2H, 24H, 39H, 45H, 69H, 71H, 73H, 76H, 78H, 93H, and 103H). *Id.*

Of the '213 patent, claims 12, 71, 73, and 74 recite a substitution at 66L, 73H, 78H, and 93H, respectively; claim 63 recites a substitution at 4L, 58L, 62L, 66L, 67L, 69L, 73L, 85L, 2H, 39H, 45H, or 69H; each of claims 66, 67, and 78 recites a substitution at 24H, 73H, 78H, or 93H. Thus, Petitioner argues these claims would have been obvious over the combination of Queen 1989 and the PDB database. Pet. 38–39, 41–47.

Claims 12, 71, 73, and 74

Patent Owner argues that Queen 1989 does not disclose a 3.3 angstrom cutoff, the distance Petitioner relies on to identify CDR-contacting

framework residues. PO Resp. 44–45. According to Patent Owner, Petitioner's obviousness analysis under this Ground in fact relies on the teachings of Queen 1990, which is not prior art to claims 12, 42, 60, 65, 71, 73, 74, and 79. *Id.* (citing Ex. 1503 ¶ 263). We are not persuaded.

Dr. Foote testified that, in his opinion, "it would have been routine for one of ordinary skill in the art in 1991 to take an antibody sequence and perform the same analysis done in Queen 1989." Ex. 1503 ¶¶ 259, 260. He noted that Dr. Eduardo A. Padlan, an expert witness for the petitioner in IPR2016-01693 and IPR2016-01694, "used known variable domain structures that were published in the PDB database to demonstrate the roadmap set forth in Queen 1989." *Id.* ¶ 261. Dr. Foote stated that he agreed with Dr. Padlan's analysis[9] and had used the same procedure to humanize antibodies. *Id.* For the analysis,

> First, the atomic coordinates on the PDB database for each antibody above were extracted, each of the atoms of the main and

[9] Patent Owner argues that Dr. Foote "simply adopted" the opinion of Dr. Padlan without confirming the calculations. PO Resp. 46 (citing Ex. 2039, 261:10–262:6, 264:3–265:14, 268:25–269:5, 276:15–277:22, 279:3–280:9). Dr. Foote, however, testified that his reliance on Dr. Padlan's opinion "is really the way a peer-reviewed paper would work." Ex. 2039, 280:10–281:10. He stated that he had known Dr. Padlan "by reputation for quite a long time" as "someone who's contributed . . . loads of findings to the antibody field," and "had great respect for him." *Id.* at 29:3–9. Dr. Foote also explained that he trusted Dr. Padlan's analysis because Dr. Padlan gave his opinion under the penalty of perjury and "could go to jail for faking some of this if it turned out he had manipulated the numbers." *Id.* at 281:1–10. In addition, Dr. Wilson, Patent Owner's expert, agreed that Dr. Padlan "was certainly . . . an expert in antibody structures" with "a good reputation." Ex. 1697, 236:13–237:1. Under these circumstances, we find it reasonable for Dr. Foote to rely on Dr. Padlan's opinion.

> side chains of each amino acid in the framework region was evaluated, and the Euclidean distance to the atoms of the main and side chain of the contacted CDR amino acid residue was calculated.

Id. ¶ 263. The interatomic distance calculations are summarized in Exhibit O, and the "identity of framework residue atoms which contact the respective CDRs as demonstrated by their proximity (i.e., within about 3 Å in one or more known antibody structures) for each known and solved antibody structure available prior to June 1991" is listed in Exhibit Q. *Id.* (footnote omitted).

In a footnote, Dr. Foote explained the 3 Å cutoff:

> *See, e.g.*, Queen 1990 at 14:21–25 (Ex. 1550 at 16) ("Amino acids according to this criterion will generally have a side chain atom within about 3 angstrom units of some site in the CDR's and must contain atoms that could interact with the CDR atoms according to established chemical forces, such as those listed above."). In my experience, the term "about" generally means a +/– 10% variance from the claimed value. Accordingly, any distance of 3.3 Å or less will fall under this distance threshold set by Queen 1990 (Ex. 1550).

Id. n.19.

Patent Owner takes issue with the citation to Queen 1990. PO Resp. 44–45. According to Patent Owner, the inventors of the '213 patent conceived and actually reduced to practice claims 12, 42, 60, 65, 71, 73, 74, and 79 before July 26, 1990, and thus, Queen 1990 is not prior art to those claims. *Id.* at 23–43. We do not need to resolve the issue of antedation here, because even without considering Queen 1990, we are persuaded that an ordinary artisan, with the teachings of Queen 1989 and the PDB database, as

well as knowledge in the field, would have identified the candidates for substitution, as recited in claims 12, 42, 60, 71, 73, and 74.[10]

Dr. Foote testified that, in his opinion, in addition to the 3D modeling used in Queen 1989, "one of ordinary skill in the art could have also measured distances between atom pairs in protein crystal structures to obtain boundaries by which a framework residue for a specific antibody was close to or contacted a CDR." Ex. 1503 ¶ 258. According to Dr. Foote,

> Using atomic distances to characterize various types of contacts was a well-known technique in the art. For example, the PDB database contained the x, y and z coordinates for any two atoms for solved crystal structures. From this information, a skilled artisan could have determined whether the atomic distance between atoms of residues in a three-dimensional structure fell within a threshold using standard geometrical formulas.

Id.

Dr. Wilson testified that an ordinary artisan would have recognized a cutoff of 4 angstroms, and thus, would have considered more amino acid positions for substitution than when using a 3.3-angstrom cutoff, as Dr. Foote suggested. Ex. 2041 ¶ 187 (citing Ex. 2045). Dr. Wilson opined that "a combination of references that would lead a person of ordinary skill in the art to consider a substitution at every single amino acid position" does not suggest a humanized antibody with specific substitutions. *Id.* We are not persuaded.

First, even with the 4-angstrom cutoff, we are not persuaded an ordinary artisan would have to consider a substitution at "every single amino

[10] Petitioner does not challenge claims 42 and 60 under Ground 1. We discuss claims 65 and 79 in a later section separately.

acid position," as Dr. Wilson stated. Indeed, as Patent Owner points out, in Queen 1989, "[g]raphic manipulation shows that a number of amino acid residues outside of the CDRs are in fact *close* enough to them to either influence their conformation or interact directly with antigen." Ex. 1534, 5 (emphasis added). Thus, even though "Van der Waals and hydrophobic interactions can occur at distances of 3.5 to 4 Angstroms" (Ex. 2041 ¶ 187), an ordinary artisan would have chosen amino acid residues with closer proximity to CDRs than the upper limit of 4 angstroms.

Second, Dr. Foote explained that even among the candidates identified based on the interatomic distances, the number of substitutable residues is "in reality, even more limited given the highly conserved nature of antibodies." Ex. 1503 ¶ 265. Queen 1989 supports this testimony. *See* Ex. 1534, 5 (substituting only "[w]hen these residues differ between the anti-Tac and Eu antibodies"). And Dr. Presta confirms it too. *See* Ex. 1699, 99:6–20.

Third, we recognize a 4-angstrom cutoff likely will result in more amino acid positions for substitution. But as the Supreme Court instructed,

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR, 550 U.S. at 421. Here, Queen 1989 recognizes the need to substitute framework residues in order to "reduce immunogenicity while retaining high binding affinity." *See* Ex. 1534, 3. Thus, even if Queen 1990 is not available as prior art, we find that an ordinary artisan would have identified

the candidates for substitution, as recited in claims 12, 42, 60, 71, 73, and 74. Indeed, Dr. Wilson testified that he performed a "good analysis" and identified 19 amino acid positions in the light chain and 19 in the heavy chain, including 66L (recited in claims 12 and 42), 73H (recited in claim 71), 78H (recited in claims 60 and 73), 93H (recited in claim 74). Ex. 1697, 242:4–6; Ex. 2041 ¶ 186, Appendix 1.

Claims 12, 66, 67, 71, 73, 74, and 78

Patent Owner contends that Petitioner's argument that an ordinary artisan "would have analyzed published PDB crystal structures to arrive at a list that 'includes' 20 different framework positions" fails "for several reasons." PO Resp. 45. We address Patent Owner's reasons in turn.

First, Patent Owner argues that Queen 1989 does not teach using the PDB database as Petitioner uses it. *Id.* But evidence of record shows otherwise. Queen 1989 teaches identifying framework substitutions by "construct[ing] a plausible molecular model of the anti-Tac V domain . . . based on homology to other antibody V domains with known crystal structure and on energy minimization." Ex. 1534, 5. Dr. Presta testified that, at the time of the '213 patent, "if [ordinarily skilled artisans] needed an antibody structure, they either would have to get those coordinates from the Protein Data Bank or ask the authors themselves to send the coordinates." Ex. 1699, 157:5–17. Thus, an ordinary artisan would have known to resort to the PDB database even though Queen 1989 does not expressly teach so.

Second, Dr. Wilson, in applying Dr. Padlan's calculations, identified 38 potential framework substitutions, more than the 20 identified by Petitioner. Ex. 2041 ¶¶ 184–186. Patent Owner argues that Petitioner's analysis would have led to "literally millions of potential combinations and

permutations of framework substitutions," and that Petitioner has "provided no reason a skilled artisan would have selected the specific framework substitutions recited in the challenged claims." PO Resp. 46. Assuming Dr. Wilson identified the correct number (38) of potential substitutions, we are not persuaded that it materially changes the analysis or the ultimate conclusion on obviousness.

Take claim 12 as an example. Claim 12 recites a humanized antibody variable domain *comprising* a framework amino acid substitution at site 66L. As Patent Owner acknowledges, this claim is open-ended in nature, and thus does not exclude substitutions at positions in addition to the specifically recited site 66L. PO Resp. 49. Applying Patent Owner's reasoning, which is not faulty, claim 12 encompasses millions of species. What is faulty is Patent Owner's argument suggesting we must determine if one species out of a genus of millions would have been obvious. The question, properly framed, is not whether an ordinary artisan would have selected one sequence with a substitution at 66L out of millions of possibilities, but whether an ordinary artisan would have selected from this genus, any of the millions of possibilities that contains a substitution at 66L, as encompassed by claim 12. Or put more plainly, whether an ordinary artisan would have selected 66L out of the 38 possible substitutions. And the answer to that question is yes.

Third, Patent Owner points out that the challenged claims require that the CDRs incorporated into the human antibody sequence bind to an antigen.[11] PO Resp. 49. Patent Owner emphasizes "the unpredictable

[11] There are two different groups of claims with respect to the language surrounding the antigen-binding limitation in the challenged claims.

effects of making even a single framework substitution on antigen binding." *Id.* at 49–50 (citing Ex. 1571, 8:41–42; Ex. 2039, 310:2–10; Ex. 2041 ¶¶ 235–236). According to Patent Owner, Petitioner has not presented any evidence that an ordinary artisan "would have had a reasonable expectation of success that humanized antibodies containing the claimed substitutions would achieve that result." *Id.* at 49. We are not persuaded.

Petitioner argues, and Dr. Wilson, Patent Owner's expert, agrees, that following the roadmap of Queen 1989, an ordinary artisan would have identified the candidate positions for substitution, including those recited in claims 12, 66, 67, 71, 73, 74, and 78. *See* Pet. 38–39, 41–47; Ex. 2041 ¶ 186, Appendix 1. It is true that Petitioner presents no binding affinity data. But, binding affinity is an inherent property of an antibody. *See* Ex. 1534, 4 (reporting the binding affinity under "Properties of Chimeric and Humanized Antibodies").

Although "inherency may supply a missing claim limitation in an obviousness analysis," we recognize that the use of inherency in the context

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Independent claim 1 recites a humanized antibody variable domain "comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain." Each of independent claims 30, 62, 63, 66, and 80 recites a similar requirement. On the face of these claims, thus, the antigen-binding requirement is directed to the CDR residues. Independent claim 79, however, recites "[a] humanized variant of a non-human parent antibody which binds an antigen." When inquired about this during the hearing, counsel for Patent Owner explained that the Specification of the '213 patent requires the humanized antibody to bind the antigen. Tr. 33:23–34; Ex. 1501, 8:11–14. In any event, the parties do not appear to dispute whether the CDR residues bind the antigen. Thus, we do not address that issue further in this Decision.

of obviousness must be carefully circumscribed. *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014). "What is important regarding properties that may be inherent, but unknown, is whether they are unexpected." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1355 (Fed. Cir. 2017).

Here, as the '213 patent acknowledges,

> Since it is not entirely possible to predict in advance what the exact impact of a given substitution will be it may be necessary to make the substitution and assay the candidate antibody for the desired characteristic. These steps, however, are per se routine and well within the ordinary skill of the art.

Ex. 1501, 10:28–33. Thus, after identifying a claimed substitution, an ordinary artisan would, through routine tests, determine the binding affinity of the humanized antibody.

The '213 patent cites Queen 1989 to demonstrate that "[i]t ha[d] previously been shown that the antigen binding affinity of a humanized antibody can be increased by mutagenesis based upon molecular modelling." *Id.* at 53:45–47 (citing Ex. 1534). Queen 1989 teaches constructing a humanized antibody "that would reduce immunogenicity while retaining high binding affinity." Ex. 1534, 3. And as the '213 patent makes clear, the humanized antibody with the claimed substitution binds the antigen. Just as "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations," *PAR Pharm.*, 773 F.3d at 1195, an otherwise obvious antibody does not become nonobvious merely because it, as expected, binds the antigen. "To hold otherwise would allow any formulation—no matter

how obvious—to become patentable merely by testing and claiming an inherent property." *Id.*

Fourth, Patent Owner warns us that accepting Petitioner's obviousness theory "would have sweeping consequences," because it "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." PO Resp. 50–51. We are not persuaded. Elsewhere in this Decision, we uphold claims that recite more than one framework substitution. Each of the claims we determine to be obvious recites a humanized antibody *comprising* a single substitution of a residue suggested by prior art, with no other meaningful limitation. As Petitioner correctly points out, "[t]he claims are obvious because PO claims vast genuses of humanized antibodies that would be identified as a matter of course following the prior art, having tested only a handful while relying on 'routine' skill to fill in the gaps." Reply 16.

Finally, we empathize with Patent Owner that scientists toiled in the field; but in patent law, labor-intensive and time-consuming efforts do not necessarily translate into non-obviousness. *See* PO Resp. 48. Instead, when there is a design need and "a finite number of identified, predictable solutions," an ordinary artisan would pursue the known options. *KSR*, 550 U.S. at 421. "If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.*

Claim 63

Claim 63 recites a humanized antibody "which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a

human patient." As explained above, this claim refers to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody.

Petitioner contends that generating a humanized antibody that lacks immunogenicity "is the goal of all monoclonal antibody humanization projects, including that of Queen 1989." Pet. 41 (citing Ex. 1503 ¶¶ 273–274). Dr. Foote points out that the "functional recitation" of lacking immunogenicity "is the only difference to the language between claims 1 and 63." Ex. 1503 ¶ 273. According to Dr. Foote, "claims 1 and 63 recite the same structural limitations, including the substituted amino acid residue. Thus, in the absence of any other difference in structural elements, antibodies that have the same structural limitations will also have the same functional effect," in this case "lack[ing] immunogenicity." *Id.*; *see also id.* ¶ 163 (testifying that the humanized antibodies of claims 1, 29, and 63 "would necessarily have the same function" of lacking immunogenicity because they have "identical structure"). Thus, Dr. Foote concludes that claims 1 and 63 would have been obvious for the same reasons. *Id.* ¶ 274.

Patent Owner argues Petitioner has cited "no data showing that an antibody produced according to Queen-1989 . . . 'lacks immunogenicity,' as required by claim 63." PO Resp. 60. Patent Owner points to Queen 1989 for stating that "[t]he extent to which humanization eliminates immunogenicity will need to be addressed in clinical trials." *Id.* at 61 (citing Ex. 1534, 7). According to Patent Owner, Dr. Foote admitted (1) "any humanized antibody can provoke an immunogenic response—just like the parent non-human antibody—because the humanized antibody contains non-human CDRs;" and (2) absent testing, "you can't tell" whether a given

patient will have an immune response to a particular humanized antibody. *Id.* at 60–61 (citing Ex. 2039, 180:7–10, 181:16–23). "Given that it was unpredictable whether any humanized antibody would be any less immunogenic than its non-human parent antibody," Patent Owner contends, "the aspirational statement in the Queen references that the authors hoped to address the problem of immunogenicity does not make it obvious how to achieve that result." *Id.* at 61 (citing Ex. 2041 ¶ 205).

We find Petitioner's arguments more persuasive. As Dr. Wilson testified, "[t]he goal of humanization is to retain binding affinity and reduce immunogenicity." Ex. 1697, 103:3–5; *see also id.* at 26:13–18 (agreeing that "one further solution to the immunogenicity problem that was known before the '213 patent invention was to 'humanize the monoclonal antibody"). Dr. Presta also agreed that "the fact that there were fewer mouse residues in the humanized variant versus the parent led to an expectation that it would lack immunogenicity compared to the parent." Ex. 1699, 112:16–21; *see also id.* at 112:5–9 ("From what I learned about the immune system and the immunogenicity of murine and chimeric antibodies, I not only hoped, but expected, that a humanized antibody would in fact be less immunogenic than the parental antibodies.").

The record evidence, thus, demonstrates that an ordinary artisan would have expected humanization would make the antibody less immunogenic. Indeed, as Petitioner correctly points out, the '213 patent "includes ***no*** immunogenicity data for ***any*** humanized antibody." Reply 22 (citing Ex. 1697, 245:22–246:19); *see also* Ex. 2017 ¶ 19 (Dr. Carter testifying that he believed that the consensus-sequence approach of the '213 patent "would reduce the possibility of an immunogenic response by

avoiding the unique variations introduced by relying on published antibody sequences obtained from a single individual").

In addition, Dr. Wilson testified that immunogenicity is determined by "[p]utting the antibody into a human and seeing whether you got some sort of measurable response that would be regarded as being immunogenic." Ex. 1697, 244:9–21. In other words, immunogenicity, or a relative lack thereof, is an inherent property of an antibody. As discussed above in relation to the limitation of "bind[ing] an antigen," the important question in analyzing inherency in the context of obviousness is whether the property is unexpected. *Honeywell Int'l Inc.*, 865 F.3d at 1355.

Here, an ordinary artisan, following the roadmap of Queen 1989, would necessarily have identified the framework substitution recited in claim 63.[12] Because we agree with Dr. Foote that antibodies with the same sequence and structure would necessarily have the same property (Ex. 1503 ¶ 273), we determine an antibody produced according to Queen 1989 would necessarily have the same property as an antibody of claim 63, and thus, would lack immunogenicity. *See* Ex. 1501, 52:55–57 (stating, without supporting data, that "it is anticipated that the optimal MAb4D5 variant molecule for therapy will have low immunogenicity"). Even if, as Patent Owner argues, the statement in Queen 1989 is merely aspirational, "the discovery of a previously unappreciated property of a prior art composition,

[12] Twenty-four of the amino acid residues recited in the Markush group of claim 63 are also recited in the Markush group of claim 1. As explained above, Petitioner has shown the unpatentability of claim 1 by a preponderance of the evidence. Alternatively, Patent Owner has sought adverse judgment against itself as to claim 1.

or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Claims 64, 65, 72, 75–77, and 79

Although claim 64 is listed as obvious over Queen 1989 and the PDB database (Pet. 5, 41), Petitioner does not provide any analysis on this claim. *See id.* at 41–42, 44 (analyzing obviousness of claim 64 only over Queen 1990 and the PDB database). Thus, we conclude Petitioner has not shown claim 64 obvious over Queen 1989 and the PDB database.

Claim 72 specifies that "the residue at site 76H has been substituted." Citing Dr. Foote's Declaration, Petitioner argues that Queen 1989 in view of the PDB database teaches substitution at 76H. Pet. 46 (citing Ex. 1503 ¶ 284); *see also* Ex. 1503 ¶¶ 263–66 (identifying 76H as one of 20 candidates for substitution). Dr. Wilson, after the same analysis, however, did not identify 76H as a candidate. Ex. 2041 ¶ 186, Appendix 1. In this *inter partes* review, Petitioner must prove unpatentability of the challenged claims by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). Because the record evidence for this claim is at an equipoise, we hold that Petitioner has not met its burden to show the unpatentability of claim 72.

We also determine that Petitioner has not met its burden to show the unpatentability of claims 65, 75–77, and 79. A proper obviousness inquiry analyzes the differences between the prior art and the claimed invention as a whole. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383 (Fed. Cir. 1986) ("Focusing on the obviousness of substitutions and

differences instead of on the invention as a whole . . . was a legally improper way to simplify the difficult determination of obviousness.").

Here, each of claims 65, 75–77, and 79 requires multiple substitutions: 71H, 73H, 78H and 93H for claims 65 and 79; and a substitution recited in claim 66, plus 71H for claim 75, plus 71H and 73H for claim 76, and plus 71H, 73H, 78H for claim 77. Even though we are persuaded that an ordinary artisan would have substituted residues 71H, 73H, 78H and 93H, individually, Petitioner does not sufficiently explain why an ordinary artisan would have substituted residues at more than one independent positions all at once. In other words, Petitioner has not shown some objective teaching in the prior art or some general knowledge in the art that would have led one of ordinary skill to combine the relevant teachings of the references to arrive at the claimed invention. *See In re Johnston*, 435 F.3d 1381, 1385 (Fed. Cir. 2006). Thus, we reject Petitioner's challenge of claims 65, 76, 77, and 79.

Secondary Considerations

"For objective evidence of secondary considerations to be accorded substantial weight, its proponents must establish a nexus between the evidence and the merits of the *claimed invention*." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (*quoting Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). Where objective indicia "result[ ] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *Id.* "To the extent that the patentee demonstrates the required nexus, his objective evidence of nonobviousness will be accorded more or less weight." *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

Patent Owner argues that the nonobviousness of the challenged claims is supported by secondary considerations, including unexpected results and commercial success. PO Resp. 64–68. According to Patent Owner, the '213 patent provides "a broadly-applicable platform," which "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." *Id.* at 65. The '213 patent's approach also, Patent Owner continues, "results in antibodies with unexpectedly superior properties," including superior binding affinity and reduced immunogenicity, as compared to the original non-human antibody. *Id.* at 66. We are not persuaded.

First, as Patent Owner acknowledges, only claims 4, 33, 62, 64, and 69 recite the consensus limitation. *Id.* at 65. Second, as Petitioner points out, the challenged claims are directed not to a platform or method for humanizing antibodies, but to antibodies with specific framework substitutions. Reply 25.

Third, despite Patent Owner's assertion to the contrary (PO Resp. 7), there is no evidence that the consensus approach has any advantage over the best-fit approach in terms of binding affinity or immunogenicity. Dr. Wilson, Patent Owner's expert, and the two co-inventors, Dr. Presta and Dr. Carter, all agreed that to find out which approach is better, "you would have to do a side-by-side comparison of a consensus approach, say, with a best fit approach." *See, e.g.*, Ex. 1698, 83:7–18. None of them, however, did any such comparison or was aware of anyone else who did the comparison. *See, e.g.*, *id.*; Ex. 1697, 184:16–185:7; Ex. 1699, 36:18–37:5.

Kolbinger, the only record evidence that compared the approaches, concluded there is "no clear advantage to designing reshaped human antibodies based on consensus sequences for human antibodies or on sequences from individual human antibodies," that is, the best-fit approach. Ex. 1694,[13] 9; *see also* Ex. 1702 ¶ 163 (Dr. Foote testifying that "there is no unbridgeable difference between a humanized antibody generated using the 'consensus' and 'best fit' approaches, as the same sequence can arise from both"). Instead, "designing based on consensus sequences may lead to a reshaped human variable region that has unnatural FRs that are the result of averaging many sequences," which "could lead to a higher risk of immunogenicity." Ex. 1694, 9.

Later, Dr. Presta cited Kolbinger[14] in one of his own papers, recognizing that study found "no clear advantage in binding was evident for the consensus antibody versus the 'best-fit' antibody." Ex. 1696,[15] 6, 9. Dr. Presta also stated that even in 1994, "[t]he 'best-fit' method, used first in [Queen] 1989 . . . has remained the more popular method for designing the

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[13] Kolbinger et al., *Humanization of a Mouse Anti-Human IgE Antibody: A Potential Therapeutic for IgE-Mediated Allergies*, 6 PROTEIN ENGINEERING 971–80 (1993).

[14] We recognize that neither Kolbinger nor Dr. Presta's publication citing Kolbinger qualifies as prior art. A post-filing date publication, however, is not automatically excluded from consideration as irrelevant. *See, e.g.*, *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) (approving use of later publications as evidence of the state of art existing on the filing date of an application).

[15] Presta, *Humanized Monoclonal Antibodies*, 29 ANN. REP. IN MED. CHEM. 317–24 (1994).

sequence of the humanized antibody than the later consensus method." *Id.* at 6 (citing Queen 1989).

Fourth, Patent Owner has not established a nexus between the alleged "expectedly superior properties" and the challenged claims. Evidence showing nexus must be "commensurate in scope with the claims which the evidence is offered to support." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 965 (Fed. Cir. 2014). Here, any evidence proffered by Patent Owner to show the alleged superior binding affinity and reduced immunogenicity is limited to a humanized anti-HER2 antibody, huMAb4D5-8 (HERCEPTIN). PO Resp. 66 (citing Ex. 1502, 3439–41); *see also* Ex. 1501, 51:48–53 ("The most potent humanized variant designed by molecular modeling, huMAb4D5-8, contains 5 FR residues from muMAb4D5. This antibody binds the $p185^{HER2}$ ECD 3-fold more tightly than does muMAb4D5 itself."). Thus, it only relates to claims 30, 31, and 33, which are directed to an antibody that binds $p185^{HER2}$. And Patent Owner has failed to establish the requisite nexus, even with regard to claims 30, 31, and 33, for two reasons.

First, HuMAb4D5/Herceptin has substitutions not only in the framework region (71H, 73H, 78H, 93H, and 56L), but also in the CDRs (55L and 102H). Ex. 1501, Table 3. Of the five framework substitutions, only 78H is recited in the Markush group of claim 30, from which claims 31 and 33 depend. Patent Owner presents no evidence that this particular substitution is sufficient, or even necessary, for the allegedly unexpectedly superior properties of huMAb4D5/Herceptin. Conversely, Patent Owner provides no evidence suggesting that substitutions of 102H and 55L in the CDR regions are not required for the unexpected results.

Second, the Markush group of claim 30 encompasses 27 other single site framework substitutions and an unknown number of potential non-human CDRs. Given the large number of species encompassed by the claim, even if Patent Owner had linked the substitution at position 78H to the unexpected superior properties of huMAb4D5/Herceptin, it would not inform the full scope of the claim. *See In re Greenfield*, 571 F.2d 1185, 1189 (CCPA 1978) ("Establishing that one (or a small number of) species gives unexpected results is inadequate proof," because "objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support."). Thus, we find the evidence of unexpected result is insufficient to support the nonobviousness of claims 30, 31, and 33.

We also are not persuaded that Patent Owner has established nexus to support the argument on commercial success. Patent Owner contends that some of its "most successful antibodies embody the '213 claims, including Herceptin®, Perjeta®, Avastin®, Lucentis®, and Xolair®, together generating billions of dollars in revenue annually." PO Resp. 67 (citing Ex. 2029, 2). With the exception of Herceptin, however, Petitioner does little to establish that the recited antibody products embody any claim of the '231 patent. *See, e.g.*, Ex. 1697, 252:12–254:21 (Dr. Wilson admitting that he did not know "what substitutions in addition to those identified by the '213 patent are included in those drugs," or "which substitutions will be necessary in the framework in order to generate a drug that can achieve FDA approval").

For Herceptin, we find Patent Owner has not established nexus for the same reasons as explained above in our discussion of unexpected results. *See Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir.

2018) (stating the commensurate-in-scope test applies to evidence of commercial success).

Furthermore, "evidence related solely to the number of units sold provides a very weak showing of commercial success." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). Here, Patent Owner only presents product sales figures (Ex. 2029, 2) without showing what percentage of the market each drug commanded. As a result, we find the evidence of commercial success presented by Patent Owner is insufficient to support the nonobviousness of the challenged claims.

In sum, after reviewing the entire record, we determine that the combination of Queen 1989 and the PDB database, together with the knowledge of an ordinary artisan, teaches or suggests each limitation of claims 12, 63, 66, 67, 71, 73, 74, and 78, and that a person of ordinary skill in the art would have had a reason to combine the references, and would have had a reasonable expectation of producing humanized antibodies with the substitutions and properties recited in those claims. We further determine that evidence of secondary considerations is not sufficient to outweigh the strong evidence of obviousness associated with the other *Graham* factors. As a result, we conclude that Petitioner has established by a preponderance of the evidence that claims 12, 63, 66, 67, 71, 73, 74, and 78 are unpatentable over Queen 1989 and the PDB database.

We, however, determine that Petitioner has not shown by a preponderance of the evidence the unpatentability of claims 64, 65, 72, 75–77, and 79.

Ground 2: Obviousness over Queen 1990 and PDB database

Petitioner argues that claims 1, 2, 4, 12, 25, 29, 62–67, 69, and 71–81 would have been obvious over the combination of Queen 1990 and the PDB database. Pet. 32–49. Because we conclude above that Petitioner has shown the unpatentability of claims 1, 2, 12, 25, 29, 63, 66, 67, 71, 73, 74, 78, 80, and 81 (Ground 1), we only need to address the patentability of claims 4, 62, 64, 65, 69, 72, 75–77, and 79 as challenged under this Ground. After reviewing the entire record, we determine that Petitioner has established by a preponderance of the evidence that claims 4, 62, 64, and 69 are unpatentable. We, however, conclude that Petitioner has not met its burden to show the unpatentability of claims 65, 72, 75–77, and 79.

Claims 4, 62, 64, and 69

The parties dispute whether Queen 1990 teaches a "consensus" sequence, as recited in claims 4, 62, 64, and 69. We discuss this limitation using claim 4 as an example.

Petitioner asserts that Queen 1990 teaches (1) "detailed criteria to identify substitutable framework region positions that are adjacent to or can contact the CDRs (Criterion III (i.e., CDR-adjacent) and Criterion IV (i.e., within 3Å of a CDR));" and (2) "detailed information for decreasing immunogenicity by maintaining conserved residues in the human acceptor framework (Criterion II (i.e., conserved or rare))." Pet. 36–37 (citing Ex. 1503 ¶¶ 133, 135–136, 267–268; Ex. 1550, 15:22–37, 16:1–36). Petitioner contends "Queen 1990 thus provided a detailed rationale for substituting particular amino acids, and *how* to do it in a detailed and objective way." *Id.* at 37. Petitioner further points out that Queen 1990 "explicitly instructed" an ordinary artisan to look to the PDB database to

identify candidate framework residues for substitution. *Id.* (citing Ex. 1550, 15:22–37, 16:1–17:2). According to Petitioner, following this roadmap, an ordinary artisan would have identified 19 light chain residues and 23 heavy chain residues as candidates for substitution. *Id.* Among those, 4L, 58L, 66L, 67L, 69L, 73L, 98L, 2H, 36H, 45H, and 69H are recited in claim 1, from which claim 4 depends. *Id.* at 38 (citing Ex. 1503 ¶ 268).

Again, as explained above, Petitioner has shown the unpatentability of claim 1 by a preponderance of the evidence. Alternatively, Patent Owner has sought adverse judgment against itself as to claim 1. Claim 4 depends from claim 1, and further recites that "the human antibody variable domain is a consensus human variable domain." Petitioner asserts that Queen 1990 teaches this limitation. Pet. 40. For this, Petitioner relies on Queen 1990's teaching that "Criterion I: As acceptor, use a framework from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized, *or* use *a consensus framework* from many human antibodies." Ex. 1550, 14:17–20 (emphases added).

Patent Owner disagrees. PO Resp. 52–53. Patent Owner emphasizes that Queen describes the consensus from "many" human antibodies. PO Resp. 52. According to Patent Owner, Queen 1990 teaches generating a consensus using "a representative collection of at least 10 to 20" distinct human heavy or light chains. *Id.* (citing Ex. 1550, 15:3–11). Patent Owner contends that "[s]uch a consensus sequence would not necessarily be derived from 'all' known sequences, as in the '213 patent." *Id.* (citing Ex. 2041 ¶ 210). We are not persuaded by Patent Owner's arguments.

First, as explained in the claim-construction section, in the '213 patent, "all human immunoglobulins," from which a "consensus human

variable domain" is derived, are not "all" in the literal sense, but are those set forth in Kabat 1987. Indeed, Dr. Presta testified that in 1991, the only ways an ordinary artisan could generate the consensus sequence of the '213 patent were either to rely on the sequences disclosed in Kabat 1987, or to recreate Kabat 1987 from independent publications. Ex. 1699, 30:5–13, 33:7–34:9. But as Dr. Wilson, Patent Owner's expert, and the two co-inventors, Dr. Presta and Dr. Carter, all agreed, Kabat 1987 does not include all human antibodies of a given subclass, known at the priority date of the '213 patent. *See, e.g.*, Ex. 1697, 33:18–24, 34:25–36:22; Ex. 1698, 59:17–60:12; Ex. 1699, 30:14–32:9.

In fact, as Dr. Wilson testified, at position 73 of the heavy chain subgroup 3, the consensus sequence derived from the 31 sequences in Kabat 1987 is aspartic acid. Ex. 1697, 214:14–215:7. In 1991, the time of the alleged invention of the '213 patent, the consensus sequence at the same position would have been derived from 84 sequences, and would have been asparagine. *Id.* at 215:8–216:15. Yet, as Dr. Wilson conceded, the '213 patent shows aspartic acid, and not asparagine, as the consensus sequence at the same position. *Id.* at 213:23–214:10, 216:16–217:22; *see also* Ex. 1501, Fig. 1B (the same). Thus, we agree with Petitioner that "[t]o the extent using Kabat(1987) meets the claims as PO asserts [i.e., claims 4, 62, 64, and 69], it also does so for the prior art." Reply 17; *see also* Ex. 1697, 34:11–15 (Dr. Wilson testifying that Kabat 1987 "has *many* sequences in each human subgroup") (emphasis added).

Second, in Queen 1990, Criterion I describes using either a best-fit approach (using homologous sequences) *or* a consensus approach. Ex. 1550, 14:17–20. Queen 1990 observes that "the extent of homology to

different human regions varies greatly, typically from about 40% to about 60–70%." *Id.* at 14:21–26. According to Queen 1990, "[b]y choosing as the acceptor immunoglobulin one of the human heavy (respectively light) chain variable regions that is most homologous to the heavy (respectively light) chain variable region of the donor immunoglobulin, fewer amino acids will be changed in going from the donor immunoglobulin to the humanized immunoglobulin." *Id.* at 14:26–32. It is after this discussion that Queen 1990 continues:

> Typically, one of the 3–5 most homologous heavy chain variable region sequences in *a representative collection of at least about 10 to 20 distinct human heavy chains* will be chosen as acceptor to provide the heavy chain framework, and similarly for the light chain. Preferably, one of the 1–3 most homologous variable regions will be used. The selected acceptor immunoglobulin chain will most preferably have at least about 65% homology in the framework region to the donor immunoglobulin.

Id. at 15:3–11 (emphasis added). Thus, read in context, the discussion of using "a representative collection of at least about 10 to 20 distinct human heavy chains" relates to the best-fit approach using homologous sequences, and not the consensus approach.

Patent Owner further argues that Criterion II of Queen 1990 pertains to rare or unusual amino acids residues, and thus, would be inapplicable to a consensus sequence generated from all known antibody sequences. *Id.* at 53 (citing Ex. 1550, 15:22–33; Ex. 2041 ¶ 213). Patent Owner also cites Dr. Foote's testimony as support. *Id.* (citing Ex. 2039, 232:25–233:9, 237:17–18). Patent Owner's point is not immediately clear to us, because it appears this is not a contested issue. In any event, Petitioner does not dispute, and we agree, that Criterion II of Queen 1990, "which involves

identifying 'rare' amino acids that would not be present under the 'consensus' approach." Reply 17. Indeed, as Dr. Foote testified, "Criterion I gives you two alternatives: the homology matching or consensus. Criterion II is predominantly directed to fixing the problems you might create going with the homology-matching alternative in Criterion I." Ex. 2039, 232:11–15.

In sum, after reviewing the entire record, we determine that the combination of Queen 1990 and the PDB database, together with the knowledge of an ordinary artisan, teaches or suggests each limitation, including the "consensus human variable domain," of claim 4.

In addition to the consensus limitation, independent claim 62 requires a framework substitution at a site selected from a Markush group of 28 residues, including 4L, 58L, 62L, 66L, 67L, 69L, 2H, 4H, 69H, and 78H. Claim 69 depends from claims 66, whose Markush group includes five residues, including 24H, 73H, 78H, and 93H. Both Dr. Foote and Dr. Wilson, following the teachings of Queen 1990, identified these residues as candidates for substitution. Ex. 1503 ¶ 263; Ex. 2041 ¶ 186. The only other limitation in claims 62 and 69 (through dependency from claim 66) is antigen binding. As explained above, binding affinity is an inherent property of the humanized antibody. Again, an ordinary artisan following Queen 1990 would necessarily have identified the claimed substitutions (Ex. 1503 ¶ 263; Ex. 2041 ¶ 186), and humanized antibodies with the same structure would necessarily have the same properties (Ex. 1503 ¶ 163). Because a humanized antibody claimed in the '213 patent binds the antigen, we are persuaded a humanized antibody generated by following Queen 1990 would bind the antigen too.

In sum, after reviewing the entire record, we determine that the combination of Queen 1990 and the PDB database, together with the knowledge of an ordinary artisan, teaches or suggests each limitation, including the "consensus human variable domain," of claims 62 and 69.

In addition to the consensus limitation, the humanized antibody of independent claim 64 "further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR . . . ." Petitioner contends that Queen 1990 teaches these two limitations. Pet. 42. Patent Owner does not dispute this assertion; and we find Petitioner's argument persuasive.

Queen 1990 teaches "the positions immediately adjacent to" the CDRs "are particularly likely to interact with the amino acids in the CDRs and, if chosen from the acceptor, distort the donor CDR[]s and reduce affinity." Ex. 1550, 16:1–6. According to Queen 1990, "the adjacent amino acids may interact directly with the antigen . . . and selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody." *Id.* at 16:7–12. Thus, we determine that the combination of Queen 1990 and the PDB database, together with the knowledge of an ordinary artisan, teaches or suggests each limitation of claim 64.

Claims 65, 72, 75–77, and 79

Petitioner's challenge of claims 65, 72, 75–77, and 79 under Ground 2 (obviousness over the combination of Queen 1990 and the PDB database) is substantially the same as that under Ground 1 (obviousness over the combination of Queen 1989 and the PDB database). Pet. 45–52. As explained above, we determine Petitioner has not shown by a preponderance

of the evidence that claims 65, 72, 75–77, and 79 would have been obvious over the combination of Queen 1989 and the PDB database. Our reasoning there applies with equal force here. Thus, we determine Petitioner has not shown by a preponderance of the evidence that claims 65, 72, 75–77, and 79 would have been obvious over the combination of Queen 1990 and the PDB database.

Having considered the record as a whole, we determine that the combination of Queen 1990 and the PDB database teaches or suggests each limitation of claims 4, 62, 64, and 69, and that a person of ordinary skill in the art would have had a reason to combine the references and would have had a reasonable expectation of producing humanized antibodies with the substitutions and properties recited in those claims. As explained above, we also determine that evidence of the objective indicia of non-obviousness is not sufficient to outweigh the strong evidence of obviousness associated with the other *Graham* factors. Thus, we conclude that Petitioner has established by a preponderance of the evidence that claims 4, 62, 64, and 69 are unpatentable over Queen 1990 and the PDB database. For the same reasons explained under Ground 1, we determine that Petitioner, however, has not shown by a preponderance of the evidence the unpatentability of claims 65, 72, 75–77, and 79.

Other Grounds

Obviousness over Queen 1989/Queen 1990, PDB Database, and Tramontano

Petitioner argues that claims 65, 75–77, and 79 would have been obvious over the combination of Queen 1989 (Ground 3) or Queen 1990

(Ground 4), the PDB database, and Tramontano.[16] Pet. 49–51. As explained above, each of these claims requires multiple substitutions, but Petitioner does not sufficiently explain why an ordinary artisan would have substituted residues at more than one independent position all at once. The addition of Tramontano does not remedy this deficiency. Indeed, Petitioner relies on Tramontano for independently "emphasiz[ing] the criticality of residue **71H** in maintaining CDR conformation." Pet. 53. According to Petitioner, substitution at 71H "would have been an automatic substitution" to an ordinary artisan. *Id.* at 54 (citing Ex. 1503 ¶¶ 143, 289–290).

Even if we agree with Petitioner that Tramontano "definitively demonstrat[es] the importance of framework residue **71H**" (*id.* (citing Ex. 1551, Abstract)), the reference does not explain why an ordinary artisan additionally would have substituted other residues—73H, 78H and 93H for claims 65 and 79; any one of the five choices recited in claim 66 for claim 75; any one of 24H, 76H, 78H, and 93H, plus 73H for claim 76; and any one of 24H, 76H, and 93H, plus 73H, 78H for claim 77—at the same time. *See id.* (arguing the claims are unpatentable here "for the same reasons above" under Grounds 1 and 2). Thus, for the same reasons explained above under Ground 1, we determine that Petitioner has not shown by a preponderance of the evidence the unpatentability of claims 65, 75–77, and 79.

[16] Patent Owner argues that neither Queen 1990 nor Tramontano is prior art to claims 65 and 79. PO Resp. 23–43. We do not need resolve this issue, because our conclusion remains the same even if Queen 1990 and Tramontano qualify as prior art.

Obviousness over Queen 1989, PDB Database, and Kabat 1987

In Ground 5, Petitioner argues that claims 4, 62, 64, and 69 would have been obvious over the combination of Queen 1989, the PDB Database, and Kabat 1987. Pet. 55–56. Because we conclude above that Petitioner has shown that claims 4, 62, 64, and 69 are unpatentable over Queen 1990 and the PDB database (Ground 2), we do not address these claims here.

Obviousness over Queen 1989/Queen 1990, PDB Database, and Hudziak

Claim 30 requires an antibody that binds $p185^{HER2}$. It also requires amino acid substitution at a site selected from a group including, in addition to those sites recited in claim 1, three other substitution candidates: 46L, 75H, and 76H. Each of claims 31, 33, 42, and 60 depends from claim 30.

Petitioner asserts that claims 30, 31, 42, and 60 would have been obvious over the combination of Queen 1989, the PDB database, and Hudziak (Ground 6), and claims 30, 31, 33, 42, and 60 would have been obvious over the combination of Queen 1990,[17] the PDB database, and Hudziak (Ground 7). Pet. 56–61. Patent Owner disagrees. PO Resp. 61–64. We find Petitioner's arguments more persuasive.

Hudziak teaches $p185^{HER2}$ is encoded by HER2/c-erbB-2 gene. Ex. 1521, 8. According to Hudziak, HER2 was amplified in about 30% of breast cancer tumors. *Id.* This amplification "was correlated with a negative prognosis and high probability of relapse." *Id.* Cells with high levels of HER2 expression (high levels of $p185^{HER2}$) were "transformed, i.e., have an

[17] Patent Owner argues that Queen 1990 is not prior art to claims 42 and 60. *Id.* at 23–43. We base our analyses of those two claims on Queen 1989, and thus, do not need to resolve the antedation issue.

altered morphology, are anchorage independent, and will form tumors in athymic mice. *Id.*

Petitioner argues that HER2 "was a ripe target for therapeutic development." Pet. 53. Hudziak confirms this, explicitly stating that "[m]onoclonal antibodies specific for $p185^{HER2}$ may therefore be useful therapeutic agents for the treatment of human neoplasias." Ex. 1521, 14.

Hudziak shows that 4D5, "a monoclonal antibody directed against the extracellular domain of $p185^{HER2}$ specifically inhibits the growth of breast tumor-derived cell lines overexpressing the *HER2/*c-*erbB*-2 gene product." *Id.* at 8. In addition, Hudziak reports that "resistance to the cytotoxic effect of tumor necrosis factor alpha, which has been shown to be a consequence of *HER2/c-erbB*-2 overexpression, is significantly reduced in the presence of this antibody." *Id.*

Petitioner contends that "[g]iven published accounts regarding other monoclonal antibody humanization efforts and the strength of 4D5 as a clinical target, the logical and necessary next step" would have been to humanize 4D5. Pet. 58 (citing Ex. 1503 ¶ 332; Ex. 1504 ¶ 70). Prior art, again, confirms this. *See* Ex. 1548,[18] 12 ("The muMAb 4D5 also serves as a template for antibody engineering efforts to construct humanized versions more suitable for chronic therapy."). According to Petitioner, after identifying 4D5 as a target, an ordinary artisan would have followed the

[18] Shepard et al., *Monoclonal Antibody Therapy of Human Cancer: Taking the HER2 Protooncogene to the Clinic*, 11 J. CLIN. IMMUNOL. 117–27 (1991).

teachings of Queen 1989 or Queen 1990 to carry out the humanization, and necessarily arrive at the alleged invention of claim 30. Pet. 58–59.

Patent Owner argues that none of Queen 1989, Queen 1990, and the PDB database ever mentions $p185^{HER2}$, whereas Hudziak does not discuss humanized antibodies or any methods for constructing a humanized antibody. PO Resp. 62. Non-obviousness, however, cannot be established by attacking references individually where the patentability challenge is based upon the teachings of a combination of references. *See In re Keller*, 642 F.2d 413, 425 (CCPA 1981). Here, an ordinary artisan would have been motivated to humanize 4D5 because of the teachings of Hudziak, and the combination of Queen 1989 or Queen 1990 with the PDB database teaches how to achieve that goal.

As explained above, we agree with Petitioner, and Patent Owner does not dispute, that claim 1 would have been obvious over Queen 1989 and the PDB database. Claim 30 differs from claim 1 in that it has a Markush group with three additional residues, and it requires the humanized antibody to bind $p185^{HER2}$ specifically, instead of "an antigen" in general, as recited in claim 1. Patent Owner argues that Petitioner has presented no evidence to show the humanized antibody with the substitutions recited in claims 30, 31, 33, 42, and 60 would bind $p185^{HER2}$. PO Resp. 63. We are not persuaded.

Queen 1989 states a humanized antibody produced according to its teachings "would reduce immunogenicity while retaining high binding affinity." Ex. 1534, 3. Similarly, Queen 1990 states a humanized antibody produced according to its teachings that "will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen." Ex. 1550, 8:21–25.

As the '213 patent acknowledges, the steps to "assay the candidate antibody for the desired characteristic" are "per se routine and well within the ordinary skill of the art." Ex. 1501, 10:28–33. And as explained above, binding affinity is an inherent property of an antibody. Thus, because a humanized antibody recited in claims 30, 31, 33, 42, and 60 binds $p185^{HER2}$, we are persuaded a humanized antibody generated by following Queen 1989 or Queen 1990 binds $p185^{HER2}$ too.

Patent Owner contends that Petitioner's reasoning, "if accepted, would make obvious a humanized antibody for ***any antigen*** based upon the generalized teachings of the Queen references." PO Resp. 63. But none of the claims challenged is directed to a specific humanized antibody. Instead, with the open-ended language, each of claims 30, 31, 33, 42, and 60 encompasses a large number of humanized antibodies. It is a long-established rule that "claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015), aff'd sub nom. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131 (2016).

In sum, after reviewing the entire record, we determine that the combination of Queen 1989, the PDB database, and Hudziak, together with the knowledge of an ordinary artisan, teaches or suggests each limitation of claims 30, 31, 42, and 60. In addition, the combination of Queen 1990, the PDB database, and Hudziak, together with the knowledge of an ordinary artisan, teaches or suggests each limitation of claims 30, 31, and 33. We also find that a person of ordinary skill in the art would have had a reason to combine the references and would have had a reasonable expectation of

producing humanized antibodies with the substitutions and properties recited in those claims. As explained above, we further determine that evidence of secondary considerations is not sufficient to outweigh the strong evidence of obviousness associated with the other *Graham* factors. As a result, we conclude that Petitioner has established by a preponderance of the evidence the unpatentability of claims 30, 31, 33, 42, and 60.

Motions to Exclude and Strike

Petitioner's Motion to Exclude

Petitioner filed a Motion to Exclude Patent Owner's evidence on secondary considerations, antedation of the prior art, Dr. Wilson's opinion, and the errata to Dr. Carter's and Dr. Wilsons's deposition testimony. Paper 65.

On secondary considerations, Petitioner seeks to exclude paragraphs 5 and 51–53 of the Presta Declaration (Ex. 2016), paragraphs 4 and 77–79 of the Carter Declaration (Ex. 2017), paragraphs 83–87 and 263–268 of the Wilson Declaration (Ex. 2041), and Exhibit 2029 (Excerpt from Roche Finance Report 2016). *Id.* at 4–6. According to Petitioner, these exhibits should be excluded as irrelevant, lacking sufficient reliability for expert testimony, and for failing to show supporting facts and/or data. *Id.* Patent Owner contends that Petitioner's arguments relate, not to any evidentiary objection, but to merits of the unpatentability case: specifically, the nexus between the secondary-considerations evidence and the claimed invention. Paper 69, 12. Our conclusion in this Decision remains the same whether we consider Patent Owner's evidence of secondary considerations, because, as explained above, it is not sufficient to outweigh the strong evidence of

obviousness associated with the other *Graham* factors. Thus, we dismiss this aspect of Petitioner's Motion to Exclude as moot.

Petitioner also seeks to exclude notebooks and internal documents relating to Patent Owner's antedation arguments (Exhibits 2001–2015) and testimony relying thereon. Paper 65, 4. We do not rely on any of these exhibits in rendering this Decision. Thus, we dismiss this aspect of Petitioner's Motion to Exclude as moot.

Petitioner seeks to exclude paragraphs 163–262 of the Wilson Declaration. *Id.* at 13–14. According to Petitioner, at his deposition, Dr. Wilson "admitted that in conducting his validity analysis he applied a standard requiring ***every*** framework region substitution recited in a claim to be disclosed or obvious." *Id.* (citing Ex. 1697, 84:11–15, 91:3–13, 92:3–14, 93:4–12). We decline to exclude Dr. Wilson's opinion because reading his deposition testimony as a whole, it is not clear whether he applied an incorrect standard in the Declaration, misspoke, or was confused by the questioning. *See* Ex. 1697, 82:7–93:12. For example, during that same line of questioning, some of Dr. Wilson's testimony did reflect the proper standard with respect to a Markush group. *See id.* at 84:11–15 (agreeing that "a humanized antibody that has only one of these substitutions listed still would fall within the claims"). Thus, we deny this aspect of Petitioner's Motion to Exclude.

Petitioner seeks to exclude errata to Dr. Carter's and Dr. Wilsons's deposition testimony as improper substantive changes to their testimony. Paper 65, 14–15. We do not rely on any of these errata in rendering this Decision. Thus, we dismiss this aspect of Petitioner's Motion to Exclude as moot.

Patent Owner's Motion to Exclude

Patent Owner filed a Motion to Exclude paragraphs 15, 16, 18, 30–33, 43–35, 53–55, 63, and 69–70 of the Buss Declaration (Ex. 1504), and "the argument and testimony pertaining to it." Paper 60, 1–6. According to Patent Owner, Mr. Buss is not one of ordinary skill in the art, and his opinions are not the product of reliable principles and methods. *Id.* Patent Owner argues that Mr. Buss does not hold an advanced degree in any relevant field and is not an oncologist. *Id.* at 4. Instead, "his purported expertise derives entirely from the on-the-job experience as a lab technician." *Id.* at 4. Patent Owner alleges that Mr. Buss copied nearly verbatim the analysis of Dr. Edward Ball, submitted in *Mylan Pharms. v. Genentech, Inc.*, IPR2016-01694, and performed "no independent research or analysis regarding the subject matter of the '213 patent." *Id.* at 2.

Petitioner responds that Mr. Buss is an "independent consultant in the antibody engineering field" with "more than 25 years of practical and research experience specializing in antibody design, humanization, and expression," was a "Higher Scientific Officer under Sir Gregory Winter at the Cambridge Centre for Protein Engineering," and "had the equivalent of a Ph.D. in molecular biology by 1991." Paper 67, 2. Petitioner concedes that Mr. Buss "based the language in his declaration on that of the declaration of Dr. Edward Ball," but points to Mr. Buss's testimony that he "conducted his own review and performed his own analysis." *Id.* at 3–4.

An expert witness must be qualified as an expert by knowledge, skill, experience, training, or education to testify in the form of an opinion. Fed. R. Evid. 702. Contrary to Patent Owner's assertion, there is no requirement that an expert must qualify as one of ordinary skill in the art. *See* Trial

Practice Guide Update (Aug. 13, 2018),[19] 3 ("A person may not need to be a person of ordinary skill in the art in order to testify as an expert under Rule 702, but rather must be 'qualified in the pertinent art.'") (citing *Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363–64 (Fed. Cir. 2008)).

Here, Petitioner has presented sufficient evidence to show Mr. Buss is qualified to provide, based on his background and experience, expert testimony on the relevant art. Paper 67, 2–15. We also agree with Petitioner that Patent Owner's criticisms of the Buss Declaration go to the weight, and not the admissibility. *Id.* at 12. Thus, we deny this aspect of Patent Owner's Motion to Exclude.

Patent Owner moves to exclude the argument and evidence subject to its Motion to Strike (Paper 58), which relates to allegedly "new and improper" evidence and argument set forth in the Reply. Paper 63, 7–8; Paper 74, 5. A motion to exclude is not a proper vehicle for addressing "arguments or evidence that a party believes exceeds the proper scope of reply." Trial Practice Guide Update (August 13, 2018), 16. Instead, "[i]f a party believes that a brief filed by the opposing party raises new issues, is accompanied by belatedly presented evidence, or otherwise exceeds the proper scope of reply . . . it may request authorization to file a motion to strike." *Id.* at 17. Thus, we deny this aspect of Patent Owner's Motion to Exclude, and address below Patent Owner's redundant argument in its Motion to Strike.

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[19] Available at https://www.uspto.gov/sites/default/files/documents/2018_Revised_Trial_Practice_Guide.pdf.

Patent Owner's Motion to Strike

Patent Owner filed a Motion to Strike (1) Exhibit 1193 and "associated arguments and testimony that rely on this exhibit," and (2) certain portion of the Reply that presents "a new argument that Kurrle (Ex. 1571) discloses a humanized antibody with a 'consensus' sequence," and "the testimony relying on" this "new theory." Paper 58, 1. We do not rely on any of these exhibits, testimony, or arguments in rendering this Decision. Thus, we dismiss Patent Owner's Motion to Strike as moot.

Motions to Seal

There is a strong public policy for making all information filed in an *inter partes* review open to the public, especially because the proceeding determines the patentability of claims in an issued patent and, therefore, affects the rights of the public. Generally, all papers filed in an *inter partes* review shall be made available to the public. *See* 35 U.S.C. § 316(a)(1); 37 C.F.R. § 42.14. Our rules, however, "aim to strike a balance between the public's interest in maintaining a complete and understandable file history and the parties' interest in protecting truly sensitive information." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,760 (Aug. 14, 2012). Thus, a party may move to seal certain information (37 C.F.R. § 42.14); but only "confidential information" is protected from disclosure (35 U.S.C. § 326(a)(7)). Confidential information means trade secret or other confidential research, development, or commercial information. 37 C.F.R. § 42.2.

The standard for granting a motion to seal is "for good cause." 37 C.F.R. § 42.54(a). The party moving to seal bears the burden of proof

and must explain why the information sought to be sealed constitutes confidential information. 37 C.F.R. § 42.20(c).

Confidential information that is subject to a protective order ordinarily becomes public 45 days after final judgment in a trial. Trial Practice Guide, 77 Fed. Reg. at 48761. There is an expectation that confidential information relied upon or identified in a final written decision will be made public. *Id.* A party seeking to maintain the confidentiality of the information may file a motion to expunge the information from the record prior to the information becoming public. 37 C.F.R. § 42.56.

Petitioner's Motions to Seal

In Papers 54 and 63, Petitioner seeks to seal portions of the Transcript of the Deposition of Dr. Paul J. Carter (Ex. 1698), the Transcript of the Deposition of Dr. Leonard G. Presta (Ex. 1699), the Transcript of the Deposition of Ms. Irene Loeffler (Ex. 1700), the Transcript of the Deposition of Mr. John R. Brady (Ex. 1701), the Reply Declaration of Dr. Jefferson Foote (Ex. 1702), and Petitioner's Motion to Exclude (Paper 64).[20]

Petitioner seeks to seal these documents because they "contain references to subject matter filed under seal by Patent Owner." *See, e.g.*, Paper 54, 1. Petitioner does not provide any other justification for why the redacted portions of these documents should be kept confidential and thus, fails to satisfy the good cause requirement. Accordingly, we deny Petitioner's Motions to Seal.

[20] Petitioner also states that it seeks to seal portions of Petitioner's Reply to Patent Owner's Response. Paper 54, 1. It appears, however, no confidential version the Reply was filed.

Patent Owner is invited to file, within 14 days of this Decision, a motion to seal any presently redacted portion of Paper 64 and Exhibits 1698–1701. The motion shall (1) attest that the material sought to be protected is not directly or indirectly relied on in this Decision; or (2) to the extent we rely on any of the material sought to be protected in this Decision, provide sufficient justification that outweighs the heightened public interest in understanding the basis for our decision on patentability. Together with the motion to seal, Patent Owner shall file a narrowly redacted public version of each document sought to be sealed.

In the absence of any action on the part of Patent Owner, at the expiration of 14 days from the date of this Decision, the documents at issue will be made available to the public.

Patent Owner's Motion to Seal

Patent Owner seeks to seal portions of the Patent Owner Response (Paper 41). Paper 43. According to Patent Owner, those portions "contain confidential research and development activities conducted by scientists at Genentech." *Id.* at 2. Patent Owner has filed a redacted version of the Patent Owner Response. Paper 42.

The redacted portions of the Patent Owner's Response relate to the antedation arguments, which we do not rely on in rendering this Decision. Thus, Patent Owner's Motion to Seal is granted.

Modification of Previous Order on Patent Owner's Motion to Seal

We previously granted Patent Owner's Motion to Seal (Paper 6) Exhibits 2001–2015 and the redacted portions of Exhibits 2016–2018. Paper 25.

As explained before, the exhibits sought to be sealed appear to contain confidential business information. *Id.* Insofar as we do not expressly rely on any of the material sought to be protected in this Decision, our decision granting Patent Owner's Motion to Seal remains unchanged. To the extent we rely on any of the material sought to be protected in this Decision, we modify our previous Order (Paper 25). For example, we quote certain language from paragraph 25 of Exhibit 2016, which is currently under seal.

Patent Owner may, within 14 days of this Decision, renew its motion to seal any portion of the presently protected exhibits that are discussed in this Decision. Because the public has a heightened interest in understanding the basis for our decision on patentability, any renewed motion shall provide sufficient justification that outweighs the public interest. Together with the renewed motion to seal, Patent Owner shall file a narrowly redacted public version of each exhibit sought to be sealed.

In the absence of any action on the part of Patent Owner, at the expiration of 14 days from the date of this Decision, the exhibits at issue will be made available to the public.

Redaction of the Final Written Decision

The parties may, within 14 days of this Decision, jointly propose redactions for this Final Written Decision. In the absence of such proposal, at the expiration of 14 days from the date of this Decision, the entirety of the Final Written Decision will be made available to the public.

CONCLUSION

After reviewing the entire record and weighing evidence offered by both parties, we determine that Petitioner has shown, by a preponderance of the evidence, that (1) claims 12, 63, 66, 67, 71, 73, 74, and 78 are

unpatentable over Queen 1989 and the PDB database; (2) claims 4, 62, 64, and 69 are unpatentable over Queen 1990 and the PDB database; (3) claims 30, 31, 33, 42, and 60 would have been obvious over the combination of Queen 1989/Queen 1990, the PDB database, and Hudziak.

Petitioner has not, however, demonstrated by a preponderance of the evidence the unpatentability of claims 65, 72, 75–77, and 79.

ORDER

Accordingly, it is

ORDERED that claims 1, 2, 4, 12, 25, 29–31, 33, 42, 60, 62–64, 66, 67, 69, 71, 73, 74, 78, 80, and 81 of the '213 patent are held unpatentable;

FURTHER ORDERED that claims 65, 72, 75–77, and 79 of the '213 patent have not been shown to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is denied-in-part and dismissed-in-part;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied;

FURTHER ORDERED that Patent Owner's Motion to Strike is dismissed;

FURTHER ORDERED that Petitioner's Motions to Seal (Papers 54, 63) are denied without prejudice to Patent Owner;

FURTHER ORDERED that Patent Owner's Motion to Seal (Paper 43) is granted;

FURTHER ORDERED that Patent Owner may file/renew its request to seal any confidential information as instructed in this Decision; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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