UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC. and
SAMSUNG BIOEPIS CO., LTD.,[1]
Petitioners,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01488
Patent 6,407,213

PETITIONERS' REPLY TO PATENT OWNER RESPONSE

[1] Samsung Bioepis Co. Ltd.'s IPR2017-02139 has been joined with this proceeding. (IPR2017-02139, Paper 42.) Emphasis added unless otherwise noted.

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I. BACKGROUND AND ARGUMENT SUMMARY

The '213 patent does ***not*** "provide[] a broadly-applicable humanization platform" (POR_1), but rather claims vast genuses of humanized antibodies PO never made or tested, which are indistinguishable from the prior art. PO ***concedes*** claims 1-2, 25, 29, and 80-81 are invalid. The remaining claims also are invalid.

PO's expert and inventors concede it was known ***before*** the patent that:

- "overexpression of the HER2 protein led to a poor prognosis in cancer, including breast cancer";
- "work had been done to identify murine antibodies that would target the HER2 receptor," with "4D5" shown "to have the…greatest effect of relative cell proliferation";
- "[t]here was a concern that you might get a reaction against a mouse antibody if you give it to a human";
- scientists had succeeded in "humanizing" monoclonal antibodies by "taking…the CDRs, from the mouse monoclonal antibodies and placing them in [a] human antibody framework" to reduce their immunogenic potential;
- "[i]n some cases, humanizing an antibody by placing the CDRs from the mouse antibody into the human framework" would "retain some binding

affinity toward the original antigen…but it was hard to regain, often, the original affinity";

- "one approach to try to regain the binding affinity that was lost…was to make additional substitutions back to mouse in the human framework";
- investigators had set forth "criteria" to identify framework residues to substitute back, including (1) "to look for framework residues that were likely to contact the antigen," (2) "to look for framework residues that were in contact with or in close proximity to the CDR residues," and (3) "to identify framework residues that may impact the binding affinity of humanized antibody by looking at residues that were known to affect the conformation of the antibody";
- a POSITA could "use 3-D structures of known antibodies identified in the protein data bank in computer modeling to predict which framework residues were likely to contact antigen or contact or be in close proximity to CDR residues"; and
- "framework residues that introduced a glycosylation site could impact binding of antigen," and "residues that participate in the interactions between the light and the heavy chain of an antibody could affect the

confirmation of the antibody" by "impact[ing] the folding of an antibody into the shape needed to bind antigen."[2]

PO's claims merely adopt these known humanization techniques, while reciting arbitrary numbers of FR substitutions either previously-identified or readily-identifiable through known methods. The only aspects of PO's claims even ***allegedly*** new are: (1) humanization of ***anti-HER2*** antibodies (claims 30-33, 42, 60); (2) "***consensus***" human frameworks (claims 4, 62, 64); (3) specific recited FR substitution (all claims); and (4) antibodies that have "up to three-fold more" binding affinity than their parents (claims 63, 65). (Exs.1199(Presta)_84:3-128:23; 1197(Wilson)_19:7-31:4, 49:25-56:17, 104:2-17; 196:22-199:6). PO cannot establish patentability.

First, PO does not dispute that "a skilled artisan would have been motivated to make a humanized version of the murine 4D5 antibody (which binds $p185^{HER2}$) based upon Hudziak." (POR at 62.) This motivation is clear. HER2-overexpressing cancer was being intensely researched, anti-HER2 mouse antibodies showed promising anti-tumor activity, and mouse antibodies were known to need

[2] Ex.1197(Wilson)_19:7-23:15, 24:11-28:8, 51:3-53:13, 54:6-13, 55:19-56:17; Exs.1198(Carter)_22:13-24:7, 24:13-26:15, 27:7-28:20; 1199(Presta)_22:18-23, 23:19-25:23, 67:6-70:3, 70:11-25, 71:8-23, 72:9-21, 75:17-76:18, 156:24-159:10; 1001_1:58-4:23; 1021_8, 14, abstract; 1034_3-7; 1003¶¶97-120; 1004¶¶38-43, 56-67; 2041¶¶35-37, 46-63; 1202¶¶35-58.

"humanization" for therapeutic use. Humanization of the 4D5 antibody was simply a matter of applying known humanization techniques. (Exs.1202¶¶3-12, 57; 1197(Wilson)_258:3-263:21; 264:9-267:18; 267:24-268:12; 1199(Presta)_92:9-93:9; 115:1-116:17.) That, in fact, is all the named inventors allegedly did.

Second, the "consensus" technique upon which PO relies was disclosed in the prior art, including Queen-1990.[3] Moreover, the '213 patent does not claim processes, and the consensus process confers no patentable distinction from humanized antibodies made using other approaches. *In re Kubin*, 561 F.3d at 1356 (differences in prior art and patent processes irrelevant to product claims' obviousness).

Third, to the extent recited FR substitutions were not explicitly identified in the prior art, they necessarily would have been identified by following the prior art teachings. PO's criteria for identifying candidates are ***the same*** as in the prior art. Dr. Presta admitted that "once you have the candidate list, the sequences that you're ultimately going to test is determined by whether the framework residue…and the mouse sequence differ at a given position," requiring a POSITA

[3] As described below (§III.B), PO's antedation attempt fails; PO's claims are unsupported by the parent '272 application, and its evidence is unreliable and does not show invention of the ***claimed*** antibodies.

"to test approximately ten different variants" regardless of the criteria for identifying candidates. (Ex.1199(Presta)__99:6-20, 98:25-99:5.) Notably, PO asserts that the relevant level of ordinary skill is even higher than Petitioner proposes, yet identifies no aspect of the claimed invention under either side's definition a POSITA would not know how to do.

Indeed, all of PO's attempts to distinguish the prior art—including "failure" to disclose specific sequences, substitutions, and binding data—cannot be reconciled with the '213 patent's specification, which provides ***no*** sequences, substitutions, or binding data for the vast majority of the innumerable combinations it attempts to monopolize. It also explicitly admits that identifying antibodies that bind antigen is "***per se routine and well within the ordinary skill of the art***." (Ex.1001_10:28-34.)

Finally, the prior art teaches antibodies that "lack immunogenicity" with "up to 3-fold more" affinity than their parent. Immunogenicity ***data*** cannot be necessary, as the patent provides none for ***any*** antibody.

The challenged claims are unpatentable.

II. CLAIM CONSTRUCTION

For this IPR, Petitioners adopt PO's definitions of "consensus human variable domain" ("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") and "lacks immunogenicity" (this "refer[s] to a humanized antibody having reduced immunogenicity in a human patient as compared to its non-humanized parent antibody").

III. ARGUMENT

A. Claims 1-2, 25, 29, 80-81 Are Unpatentable

The Petition demonstrated these claims are unpatentable because they are (i) anticipated by Kurrle, (ii) anticipated by Queen-1990, and (iii) obvious over Queen-1990/Kurrle. (Pet._28-30, 33-45, 50-51; Ex.1003¶¶155-232.) The POR does not rebut these grounds, and Dr. Wilson admitted he did "not consider those claims." (Ex.1197(Wilson)_61:4-16.) PO, apparently interested in keeping the claims it is not willing to defend, did not do the right thing and disclaim them. The Board should rule these claims unpatentable.

B. Grounds 1, 3-10: Kurrle And Queen-1990 Are Prior Art

PO only seeks to antedate these references for claims 12, 42, 60, 65, 71, 73-74, and 79. (POR_24.) Its attempt fails.

1. No priority to the '272 application

For priority, a parent application must "reasonably convey to those skilled in the art that as of the claimed priority date the inventor was in possession of the later claimed subject matter." *Los Angeles Biomedical Research Inst. Harbor-UCLA Med. Ctr. v. Eli Lilly & Co.*, 849 F.3d 1049, 1057(Fed. Cir. 2017). That is not the case here.

Each challenged claim recites ***any*** humanized antibody or variable domain comprising CDR residues from ***any*** non-human antibody (or anti-HER2 antibody for claims 42, 60) incorporated into a human framework, comprising one or more substitutions at ***up to 28*** different positions. But the '272 application does not show the inventors were in possession of any claimed antibody or variable domain, much less the full scope.

The '272 application identifies only eight humanized antibody variants made by the inventors—huMAb4D5-1 through 8. (Ex.2032_93.) Yet, each variant has CDRs with both human and mouse residues, notwithstanding Dr. Presta testified that the claims require the ***entire*** CDRs to be from mouse. (Exs.1001_48:52-49:1; 1202¶¶85-86; 1199(Presta)_86:20-87:7.) Furthermore, each variant with FR substitutions has at least one ***outside*** the recited Markush groups. (Ex.1202¶¶87-89.) PO previously conceded these claims "recite *Markush* groups of framework substitutions." (Paper 7_35.) Thus, it is presumed with respect to the substitution element that "th[e] claim element is 'closed' and therefore 'exclude[s] any elements…not specified in the claim.'" *Shire Dev., LLC v. Watson Pharm., Inc.*, 848 F.3d 981, 984(Fed. Cir. 2017). Notably, PO's expert admitted he did ***not*** consider the Markush groups to be closed. (Ex.1197(Wilson)_77:17-81:21, 162:7-168:10.) In arguing priority, PO contends antibodies with non-recited FR substitutions embody the claims. (POR_36-39; Ex.2041¶¶88-95.) Because PO has

not rebutted the presumption the Markush groups are closed, the variants fall outside the claims and cannot demonstrate possession. *Shire*, 848 F.3d at 984.

Thus, the '272 application does not show possession of any ***claimed*** embodiment. *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1350-51(Fed. Cir. 2011)(no possession where patent "does not describe a single antibody that satisfies the claim limitations").

Even if one or more variants was within the claims, the claims also encompass countless other variants with any combination of recited substitutions, most being unrepresented in any '272 embodiment. (Exs.2032_93; 1202¶90.) The only other working examples were added to the ***later*** application, which PO's expert and inventor admitted was critical to generalize the claimed invention beyond the described 4D5 variants. (Exs.2041¶89; 1197(Wilson)_75:5-77:13, 97:19-101:18, 137:21-138:20, 143:1-144:24; 1198(Carter)_89:18-94:7, 110:6-129:8.) The '272 application therefore certainly fails to show possession of the ***full claim scope***. *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1253(Fed. Cir. 2004)("[P]rior application must enable…[POSITA] to practice the ***full scope*** of the claimed invention.").

Thus, Kurrle and Queen-1990 are §102(b) art and cannot be antedated.

2. No antedation in any event

PO's flawed antedation argument rests on its assertion that its "inventors

conceived and ***actually reduced to practice*** prior to the publication of" the prior art. (POR_2) But that is not borne out by the evidence. "To demonstrate reduction to practice, a party must prove that the inventor: (1) constructed an embodiment or performed a process that met all the limitations and (2) determined that the invention would work for its intended purpose." *In re Omeprazole Patent Litig.*, 536 F.3d 1361, 1373(Fed. Cir. 2008). Testimony from the inventors must be independently corroborated. *See Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 999(Fed. Cir. 2009).

Here, PO relies on inventor declarations, supported primarily by their notebooks. But the inventors' testimony lacks credibility because they could not even agree on key aspects of the alleged invention story, such as who first suggested the "consensus" approach. (Exs.1199(Presta)_26:7-27:13; 1198(Carter)_50:17-51:11.) Moreover, the inventors rely on their notebooks, but they are ***unwitnessed*** and, on some pages, ***unsigned***, despite clear instructions to [redacted] (Exs.2001_4, 13-90; 2002_13-68; 2003_4, 13-110; 2004_4, 13-109; 1198(Carter)_169:14-173:14, 174:9-13; 175:3-10; 1199(Presta)_63:12-64:10, 65:1-67:5, 180:16-181:24.) Dr. Presta even admitted he ***changed dates*** without following PO's procedures. (Ex.1199(Presta)_178:24-

179:6, 179:14-180:15.) Both inventors admittedly understood the importance of PO's notebook procedures, including potential use in patent proceedings, yet chose to ignore them anyway. (Exs.1198(Carter)_169:14-173:14, 174:9-13; 175:3-10; 1199(Presta)_65:13-67:5.) Such undated, unwitnessed notebooks ***cannot*** corroborate invention. *Medichem S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1170(Fed. Cir. 2006)(unwitnessed notebook alone insufficient to support reduction to practice); *Procter & Gamble*, 566 F.3d at 998-99(same).

The only other evidence PO presents is a declaration from lab technician John Ridgeway, and his and other technicians' notebooks describing testing of antibody variants. (POR_24-41; Exs. 2005-8, 2018.) Yet none corroborates the ***design*** (*e.g.*, Markush selection of framework residues) of the tested antibodies, which was known only by individuals who did ***not*** provide evidence here. (Exs.1201(Ridgeway)_9:1-12:12; 1198(Carter)_141:12-145:13.) Thus, no corroboration evidence shows the tested antibodies embody the claims. *Medichem*, 437 F.3d at 1172(corroboration evidence must show the ***claimed invention***).[4]

[4] PO produced notebook copies scanned in late 2016, rather than the original microfilmed versions. (Ex.1200(Loeffler)_15:1-12.) PO's records manager testified that storage and access to the notebooks was the responsibility of the individuals to whom they were assigned, and she had no knowledge of how

(continued…)

Furthermore, none of the variants made by the inventors is an "embodiment" that meets "all the limitations." (*See* Section 1 *supra*.) PO provides no expert testimony comparing the inventors' work to the claims, nor did the inventors perform such analysis. (Exs.1197(Wilson)_255:20-257:3; 1198(Carter)_37:19-39:15; 1199(Presta)_84:3-85:2.) Unsubstantiated attorney argument is insufficient. *Zimmer Tech. Inc. v. Howmedica Osteonics Corp.*, 476 F. Supp. 2d 1024, 1049(N.D. Ind. 2007).

Finally, the inventors had ***not*** established any variant "would work for its intended purpose." *Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery*, 514 F. Supp. 2d 351, 360(D. Conn. 2007). The "intended purpose" was to treat humans, requiring both sufficient binding ***and*** reduced immunogenicity. (Exs.1198(Carter)_29:17-32:15; 1199(Presta)_110:21-111:22; 1197(Wilson)_101:19-103:5; 1001_4:24-40.) PO shows no immunogenicity testing

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they were filled out, where and how they were stored during the decades since they were assigned, or if the original entries had been altered. (*Id.*_18:2-20:6, 21:1-22:7, 23:18-27:24, 28:2-38:11, 41:18-42:4, 46:14-50:3.) The remaining notebooks (Exs.2007–09) were not authenticated by their assignees, and the other documents (Exs.2010-15; 2003_74-77) cannot corroborate because they were not authenticated by any non-inventor. (Ex.1200(Loeffler)_38:20-39:2.)

of ***any*** variant, despite asserting such data is necessary for obviousness. (Exs.1198(Carter)_112:7-112:19; 1199(Presta)_109:24-112:21; 1202¶¶91-93.) PO's antedation argument fails for this additional reason.

C. Grounds 1 And 2: Claims 1-2, (25),[5] 29, 63, 66-67, 71-72, 75-76, and 80-81 Are Anticipated By Kurrle And Queen-1990

The Petition showed both Kurrle and Queen-1990 teach each limitation of these claims. PO's contrary arguments fail. Notably, indisputably invalid claims 1-2, 25, 29, and 80-81 recite humanized antibodies comprising non-human CDRs incorporated into human frameworks, with FR substitutions at any one or more of ***29 different positions***, including 66L, 73H, 78H and 93H, with the remaining claims differing in only insignificant and unpatentable ways.

1. Kurrle and Queen-1990 disclose "bind[ing] an antigen"

Kurrle teaches methods for making "civilised" (humanized) antibodies where "[o]nly the ***complementarity determining regions*** and ***selected framework amino acids <u>necessary for antigen binding</u>*** are maintained murine." (Pet._29; Ex.1071_3:9-10.) Queen-1990 teaches its antibodies will "retain substantially the ***same affinity*** as the donor immunoglobulin to the antigen." (Pet._41; Ex.1050_Abstract.) And PO does not dispute that Kurrle's and Queen-1990's criteria for identifying FR substitutions necessarily identifies recited positions,

[5] Only Kurrle is argued to anticipate claim 25.

including ***4L***, ***69H***, ***71H***, ***73H*** and ***76H*** (Kurrle), and ***4L***, ***98L***, ***36H***, ***69H***, ***71H***, ***73H***, and ***76H*** (Queen-1990). (Ex.1003¶¶33-38, 121-137, 155-199.)

That Kurrle presents no binding data for EUCIV4 is irrelevant. Petitioners do not rely on EUCIV4 for anticipation. (Exs.1071_25, 26; 1202¶¶122-126) Rather, Kurrle anticipates because, following its criteria for identifying FR substitution candidates—those adjacent in sequence, or in 3D proximity, to CDRs—necessarily identifies substitutions within each claim. (Exs.1003¶¶ 33, 121-24, 155-72; 1199(Presta)_69:10-70:3, 70:11-25, 84:3-128:23, 156:24-159:10; 1197(Wilson)_51:3-52:5, 54:6-13, 258:3-263:21, 264:9-267:18, 267:24-268:12; 1202¶¶126-129.) The same is true of Queen-1990. (Exs.1003¶¶34, 131-37, 173-99; 1197(Wilson)_239:20-25, 240:4-242:6, 242:19-244:7; 1202¶¶130-132.) And both parties' experts admit that POSITAs would not make ***every*** candidate substitution, but rather would test those at positions differing between mouse and human first, one at a time then in combination. (Exs.1197(Wilson)_107:24-114:4, 116:22-135:13, 225:17-231:8, 239:20-25, 240:4-242:6, 242:19-244:7; 2039(Foote)_294:5-299:25, 320:13-326:16; 1199(Presta)_76:19-80:13, 90:1-102:25.) The resulting humanized antibodies necessarily will include those claimed. (Exs.1202¶¶133-134; 1199(Presta)_76:19-80:13, 90:1-102:25.)

That Kurrle and Queen-1990 do not provide "binding data" for ***all*** described antibodies is irrelevant. As noted above, the '213 patent provides no binding data

for the vast majority of FR substitutions in the claims, or indeed for ***any*** antibody meeting the claims. The patent thus necessarily relies on inherent properties of humanized antibodies or routine knowledge and skill. According to that approach, to the extent "bind[ing] an antigen" is not explicitly disclosed, it is inherently disclosed. *In re Kubin*, 561 F.3d at 1357.

2. Kurrle and Queen-1990 disclose the "lacks immunogenicity" limitation of claim 63

Kurrle states that, following "civilization," "the resulting mAb of the present invention is thus essentially a human antibody with a ***much lower immunogenicity in patients***." (Pet._31; Ex.1071_3:8-12.) Queen-1990 teaches that "[w]hen combined into an intact antibody, the humanized immunoglobulins of the present invention ***will be substantially non-immunogenic*** in humans." (Pet._38; Ex.1050_1, Abstract.)

PO argues this limitation nevertheless is not described because the prior art contains "no data indicating that any of its disclosed antibody sequences are any less immunogenic than the parent non-human antibody." (POR_59) This is inconsistent with the '213 patent, which includes ***no*** immunogenicity data for ***any*** humanized antibody. (Ex.1197(Wilson)_244:9-245:15; 245:22-246:19; 1198(Carter)_112:7-112:19.) At most, the patent states "it is anticipated that the optimal MAb4D5 variant molecule for therapy will have low immunogenicity …," providing no more disclosure than the prior art. (Ex.1001_52:54-57.) At least

to the extent the patent provides adequate written description/enablement, Kurrle and Queen-1990 explicitly or inherently disclose this limitation. *In re Kubin*, 561 F.3d at 1357. (Exs.1202¶¶149-155.)

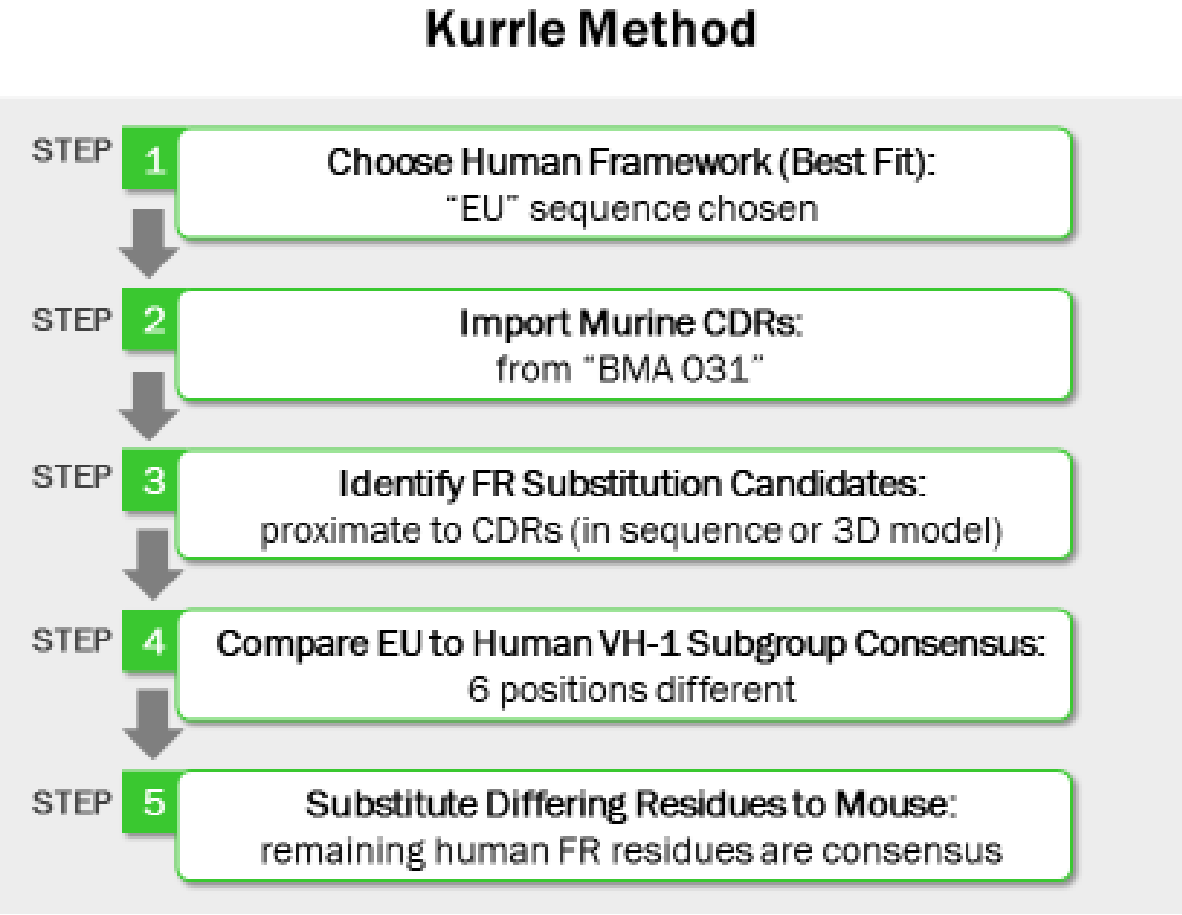
3. Queen-1990 discloses the "consensus human variable domain" limitation

In Criterion I, Queen-1990 teaches POSITAs to use as "acceptor" either a framework identified using the "best fit" approach, ***or*** "a ***consensus framework*** from many antibodies." (Pet._36; Ex.1050_12:17-20.) PO argues the word "many" somehow contradicts the patent definition, which requires a sequence generated from ***all*** antibody sequences of a particular subclass. (POR_47-49.) But a "consensus framework from ***many*** antibodies" necessarily includes one from ***all*** antibodies in a given subclass. Moreover, the "consensus" sequence used for the patent variants was generated using the most common residue at each position identified in ***Kabat(1987)***. (Exs.2016¶¶24-25; 2017¶¶18-19; 1198(Carter)_56:20-61:24; 1199(Presta)_27:14-28:13, 29:25-36:2, 57:1-58:6, 115:7-17, 165:17-169:9; 1001_11:26-12:5.) And Dr. Presta agreed a POSITA looking to use a "consensus" approach would rely on, or recreate, Kabat(1987). (Ex.1199(Presta)_30:5-13, 33:7-34:9; Ex.1202¶¶94-96, 119, 156-163 (POSITA following Queen-1990's "consensus sequence" option would use most common residues of a given subclass from Kabat).) Yet PO's expert and inventors conceded that Kabat(1987) does ***not*** describe ***all*** human antibodies of a given subclass, and not even ***all*** those known.

(Exs.1198(Carter)_56:20-61:24; 1197(Wilson)_33:18-36:7, 183:14-184:4, 212:8-217:22; 1199(Presta)_30:14-32:9.) Rather, it identifies only "***many***" antibodies of each subclass, as Queen-1990 directs. (Ex.1197(Wilson)_33:18-36:32.) To the extent using Kabat(1987) meets the claims as PO asserts, it does so for the prior art as well. *TVIIM, LLC v. McAfee, Inc.*, 851 F.3d 1356, 1362(Fed. Cir. 2017).

Queen-1990's discussion of "a representative collection of at least about 10 to 20 distinct human heavy chains" is in the context of using a "homologous" sequence, *i.e.*, the "best fit" methodology. (Exs.1050_13:3-11; 1202¶158.) The same is true of Queen-1990's Criterion II, which involves identifying "rare" amino acids that would not be present under the "consensus" approach. (Ex.1050_13:22-37; 1202¶¶158.) Queen-1990 makes clear that not all criteria are applicable in all circumstances, and a POSITA would know these applied only to the "best fit" approach. (Ex.1050_12:12-15; 1202¶158.)

Notably, as Dr. Foote explained, there is no meaningful difference between a humanized antibody generated using the "consensus" and "best fit" approaches, as the same sequence can arise from both. This is exemplified in Kurrle, where a "best fit" approach was initially used, but after FR substitutions, the remaining human FR residues were identical to "consensus." (Exs.1071_8; 1197(Wilson)_258:3-263:21, 264:9-267:18, 267:24-268:12; 2039(Foote)_313:7-320:11; 1202¶¶7, 104-106, 160-162, .)



(Ex.1071_8; 1202¶¶7.)

D. Grounds 3-10: Claims 1-2, 4, 12, 25, 30-31, 33, 42, 60, 62-67, 69, 71-81 Are Obvious

As explained in the Petition, each of these claims is obvious over Kurrle and Queen-1990, alone or with one or more of Furey[6], Chothia & Lesk, Chothia 1985,

[6] Contrary to PO's arguments against Furey, its own expert admitted POSITAs used Bence-Jones dimers generally, and Furey's teaching specifically, in

(continued…)

and Hudziak. (Pet._27-68.) PO's contrary arguments fail.

1. Grounds 3-10: Choosing among the candidate FR substitutions taught by the prior art is "per se routine, and well within the ordinary skill in the art"

PO first argues claims 12, 42, 60, 65-67, and 71-79 "would not have been obvious from the broad genus of potential substitutions allegedly disclosed in the asserted references." (POR_50-56.) PO's basic argument is the prior art criteria identify sets of candidate FR substitutions, but provide "no guidance" on which "may be important for any given antibody." (*Id.*_51.) According to PO, given the "unpredictable effects of making even a single framework substitution on antigen binding," there is "no evidence that a [POSITA] would have had a reasonable expectation of success that humanized antibodies containing the claimed substitutions" would "bind to an antigen." (*Id.*_54) But this argument is contradicted by the inventors and the '213 patent itself.

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humanizing antibodies. (Exs.1197(Wilson)_286:10-288:19, 289:2-292:20, 293:8-294:10. 1194(Kolbinger)_972). Furey teaches the importance of 66L in contacting the CDR (meeting Queen/Kurrle's criteria), while the residues PO suggests are more important are involve in inapposite FR-to-FR interactions. (Exs.1125_16; 1003¶138-139; 1202¶¶109-111, 167-171; 1197(Wilson)_231:10-232:14, 233:3-234:2, 234:14-17.)

As an initial matter, the criteria for identifying candidate substitutions in the patent are ***the same*** as the prior art. Two criteria in claim 64—"(a) noncovalently binds antigen directly"; and "(b) interacts with a CDR"—are explicitly identified in Kurrle and Queen-1990. (Exs.1071_8; 1050_14-16; 1197(Wilson)_258:3-263:21; 264:9-267:18; 267:24-268:12; 2039(Foote)_324:13-325:2; 1199(Presta)_92:9-93:9; 115:1-116:17.) And it is undisputed these criteria may identify "a large number" of candidate FR positions for any humanization. (Exs. 1197(Wilson)_112:12-21; 1199(Presta)_76:19-80:13, 90:1-102:25.) Indeed, the patent identifies ***47*** different candidates, with up to ***28*** in certain claims—encompassing millions or more antibodies—yet describes only a handful of variants actually made and tested, with most substitutions unrepresented. (Exs.1001_5:12-6:22, 47:30-60:16, 85:44-90:32; 2039(Foote)_320:13-324:16; 1199(Presta)_96:14-97:13; 1198(Carter)_92:18-94:7.) The patent provides no further guidance on which candidates "may be important for any given antibody" than the prior art. (Ex.1202 ¶¶164-165.)

The patent seeks to traverse this problem, stating although "it is not entirely possible to predict in advance what the exact impact of a given substitution will be," identifying antibodies with the "desired characteristic" (binding antigen) is "***per se routine and well within the ordinary skill of the art***." (Ex.1001_10:28-33.) Dr. Presta agreed. (Ex.1199(Presta)_101:24-102:19.) Indeed, he testified that "once

you have the candidate list, the sequences that you're ultimately going to test is determined by whether the framework residue…and the mouse sequence differ at a given position," which is "a simple comparison of the letters to determine if they differ." (*Id.*_99:6-20.) A POSITA would then "try each of [the substitutions] individually and then in combination" to see if the resulting antibodies are acceptable which, according to Dr. Presta, would require the POSITA "to test approximately ***ten*** different variants," regardless of the criteria for identifying candidates. (*Id.*_98:25-99:5, 100:11-101:23.) According to that approach, if the antibody being humanized happens to differ from the human framework at one or more recited positions, the resulting humanized antibodies will fall within the claims as a matter of course, through nothing more than routine skill. (*Id.*; Ex.1202¶¶166.)[7] Unless the patent is invalid for lack of written description/enablement, identifying working antibodies from the prior art also must be "per se routine." *See Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1567(Fed. Cir. 1997)("[A] description that does not render a claimed invention

[7] In Queen's anti-Tac humanization, the residues at 66L happened to be the same, whereas for the sequences Dr. Presta was reviewing, they were different. (Ex.1197(Wilson)_225:17-229:24; 1202¶¶167-171.) The fact that Queen did not substitute 66L thus does not show it would not be obvious.

obvious does not sufficiently describe that invention for purposes of §112,¶1.").

Notably, PO's contrary arguments rely solely on the opinions of Dr. Wilson, who admitted he applied an incorrect obviousness standard requiring ***every*** recited FR substitution in a claim to be obvious. (Ex.1197(Wilson)_84:11-15, 91:3-13, 92:3-14, 93:4-12.) PO has presented no evidence that humanized antibodies with ***at least one*** recited FR substitution would be non-obvious. *In re Kubin*, 561 F.3d at 1361(obviousness of one embodiment sufficient).

Finally, PO's doomsday warnings about the "sweeping consequences" that would arise from an obviousness finding are meritless. The claims here 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 POSITAs' "routine" skill to fill in the gaps. Petitioners do ***not*** argue that no humanized antibody can ever be patentable.

2. Ground 7: Claim 65's "up to 3-fold more" binding affinity limitation would have been obvious

Queen-1990 explains that, for antibodies humanized using its criteria, "affinity levels…may be ***within about 4 fold*** of the donor immunoglobulin's original affinity to the antigen." (Pet._55-56; Ex.1050_6:26-28.) PO asserts this "does not indicate that the humanized antibody's binding affinity is ***more*** than the…parent…." (POR_57.) But the basis for Queen's statement is testing of parent and humanized antibodies in a fluorescence binding assay, finding that both

"decreased the fluorescence to approximately the same degree" (as shown in Figure 10B), which "shows that these antibodies have approximately the same affinity (within 3 to 4 fold)." (Ex.1050_31:28-32:2, Fig._10B.) In other words, Queen's testing showed its humanized antibodies may have 3 to 4 fold ***more*** binding affinity than the parent, within the limits of testing. (Ex.1202¶¶103, 176-177.)

This is consistent with Dr. Wilson's testimony that there were "examples" in the prior art where "using the humanization techniques that were known prior to the '213 patent invention," a POSITA "could achieve about the same binding affinity as the parent" and that "in achieving around about the same binding affinity as the parent, that might include ***a little bit more*** or a little bit less." (Ex.1197(Wilson)_104:12-105:5.) That is all that is required by claim 65. (*Id.*_103:12-25 (agreeing "it could be ***any*** amount more, up to threefold more").)

Moreover, claim 65 encompasses infinite numbers of humanized antibodies with unlimited FR substitutions, while the patent identifies only ***two*** antibody variants able to achieve more binding affinity than the parent, and then only because of one or two ***CDR*** substitutions. (Ex.1001_50:63-54:62, 88:63-65, 90:3-9; 1197(Wilson)_146:9-176:14, 280:24-284:15; 1199(Presta)_117:10-125:15; 1198(Carter)_114:9-129:8; 1202¶¶178.) The patent describes ***no*** embodiment able to achieve this requirement through the claimed ***FR*** substitutions. (Ex.1001_50:63-

54:62, 88:63-65, 90:2-9; 1197(Wilson)_146:9-176:14, 280:24-284:15, 1199(Presta)_117:10-125:15; 1198(Carter)_114:9-129:8; 1202¶¶178.) Again, to the extent claim 65 meets the written description/enablement requirements, identifying humanized antibodies meeting the "desired characteristic" (up to 3-fold more binding affinity), must also be "per se routine and well within the ordinary skill in the art" (Ex.1001_10:28-33) and therefore at the very least obvious. *Regents*, 119 F.3d at 1567.

3. Grounds 8-10: It would have been obvious to make humanized antibodies with the recited FR substitutions that bind $p185^{HER2}$

Although PO asserts that "Hudziak doesn't discuss humanized antibodies," PO does not dispute that POSITAs would have been motivated to humanize Hudziak's 4D5 antibody. Nor could it. Dr. Wilson admitted it was known that "overexpression of the HER2 protein led to a poor prognosis in cancer, including breast cancer," "work had been done to identify murine antibodies that would target the HER2 receptor," with 4D5 shown "to have the…greatest effect of relative cell proliferation," and "[t]here was a concern that you might get a reaction against a mouse antibody if you give it to a human." (Ex.1197(Wilson)_19:7-21:9; *see also* Ex.1003¶¶39-40.)

Thus, any question about qualifications of Timothy Buss (POR_63-64), whose opinions are limited to this issue, is moot. Nevertheless, Mr. Buss testified

that, as of the priority date, he had the "equivalent of a Ph.D." in biochemistry with practical academic experience in antibody development, meeting PO's definition of a POSITA. (Ex. 2040(Buss)_34:19-25, 40:3–6; Ex. 1004¶¶4-6; Paper 27_8.) And in any event, there is no requirement that an expert meet the POSITA definition to provide opinions helpful to the invalidity determination. *Nat'l Oilwell Varco, LP v. Tech. Indus. Inc.*, IPR2017-00860, Paper 34 at 2 (PTAB Apr. 23, 2018).

Once POSITAs decided to humanize 4D5, it was a matter of routine skill to transfer CDRs to a human framework ("consensus" or "best fit"), identify candidate residues following the prior art criteria, narrow to those differing between 4D5 and human framework, substitute FR residues at those positions individually and in combination, and test the few (according to Dr. Presta) resulting variants. (*See* Section III.D.1, *supra*.) This would result in making and testing of humanized antibodies with one or more recited substitutions as a matter of course, with identification of variants with the "desired characteristic" of binding $p185^{HER2}$ being "per se routine and well within the ordinary skill in the art."

That is not to say humanized antibodies for ***any antigen*** would be obvious (POR_63), only that PO's incredibly broad claims, covering countless antibodies that bind ***any*** anti-HER2 antigen comprising any of a multitude of untested

candidate substitutions, are *per se* obvious. *See Application of Mraz*, 455 F.2d 1069, 1072–73(C.C.P.A 1972)("[C]laims are unpatentable when they are so broad as to read on obvious subject matter even though they likewise read on non-obvious subject matter.").

E. "Objective Indicia" Do Not Establish Non-Obviousness

Alleged "objective indicia" (POR_64-68) do not assist PO.

1. No unexpected results

As discussed above, the "results" achieved in humanizing 4D5 following the prior art were in no way "unexpected." The patent does not claim a "broadly-applicable platform that could be used to humanize different antibodies" (POR_64-66), but rather specific antibodies with specific FR substitutions. PO has not even shown the patent's variants fall within the claims. (Section III.B.1, *supra*.) PO certainly has not shown that any other antibodies do so. For example, PO's expert and inventors identify several drugs they claim were designed using "the '213 patent invention," but provided (and performed) no analysis comparing these drugs to the patent claims. (Exs.2016¶5; 2017¶4; 2041¶¶130, 266; 1197(Wilson)_252:12–254:21; 1198(Carter)_32:25–39:15; 1199(Presta)_41:10–44:4.) At most they assert these drugs were designed using the common "consensus" framework from Kabat(1987). (Exs.2016¶5; 2017¶4; 2041¶¶130, 266.) But the "consensus" approach is not even recited in most challenged claims

and, even where it is, the claims include other unmet limitations.

PO's assertion that the '213 patent's approach results in antibodies with "unexpectedly superior properties"—lacking immunogenicity with "superior binding"—also fails. First, PO's expert and inventors admitted there is no evidence that the "consensus" approach has ***any*** advantage over the "best fit" approach in terms of binding affinity or immunogenicity. (Exs.1197(Wilson)_184:16-185:7, 187:21-193:6; 1199(Presta)_131:10–141:22; 1198(Carter)_83:7-18; 1194.) Indeed, the only publication identified as comparing the two 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," and that the consensus approach "may lead to a reshaped human variable region that has unnatural frameworks that are the result of averaging many sequences" and "***this could lead to a higher risk of immunogenicity***." (Exs.1194(Kolbinger)_979; 1197(Wilson)_187:21-193:6; 1199(Presta)_137:24-141:22; 1002_3:1362.) Dr. Presta himself wrote soon after that "***Dr. Queen's best fit method*** has remained the more popular method for designing the sequence of the humanized antibody than the consensus method" and the two approaches "***both*** may function well with regard to acceptance by the human immune system with perhaps an occasional aberration." (Exs.1196_319-20; 1199(Presta)_131:10-136:14.)

Notably, as PO acknowledged during prosecution, the "prior art humanized antibodies" PO criticizes as immunogenic (POR_66)—described in Riechmann (1988)—***were made using the consensus approach***. (Exs.1002_5:2500 ("Applicants have now learnt that the humanized light chain gene of the CAMPATH-1 antibody in Riechmann *et al.* was converted from an anti-lysozyme construct (see page 108 of Foote, J., *Nova acta Leopoldina* NF **61(269)**:103-110 (1989), of record). Foote's antilysozyme construct was prepared by combining CDR sequences from the kappa light chain of the anti-lysozyme antibody ***with consensus human kappa frameworks (see page 106, third paragraph of Foote, supra)***.")[8]; 1193_106–08; 1197(Wilson)_176:25-178:23; 2039(Foote)_327:12–331:11; 1202¶¶41-43, 79.) Queen's "best fit" antibodies showed ***no*** immunogenicity. (Exs. 1195_45; 1197(Wilson)_218:3–224:13.)

Thus, to the extent the "results" PO identifies were even achieved—which PO has not established—they bear no nexus to the claims. *Merck & Co. Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); IPR2014-00784, Paper 112 at 24 (Sep. 24, 2015) ("If objective indicia of nonobviousness are 'due

[8] Both inventors admitted they received and analyzed Dr. Foote's unpublished sequence during their work on the invention but could not say how they acquired it. (Exs.1198(Carter)_61:25-70:4; 1199(Presta)_159:22 -163:1.)

to an element in the prior art, no nexus exists.'"). They also would not be commensurate with claim scope, as the vast majority of substitutions in countless antibodies encompassed by the immensely broad claims are not represented in ***any*** generated and tested variant, much less ones shown to achieve the alleged "unexpected results." *Ex Parte Takeshi,* Appeal 2013-003410, 2015 WL 1952506 at *4 (PTAB Apr. 29, 2015) ("Evidence of secondary considerations must be reasonably commensurate with the scope of the claims.") (citing *In re Kao,* 639 F.3d 1057, 1068 (Fed. Cir. 2011)).

2. No commercial success

PO's "commercial success" argument similarly fails. Neither PO nor its witnesses provided analysis showing ***any*** identified drug—Herceptin®, Perjeta®, Avastin®, Lucentis®, and Xolair®—actually embodies ***any***, much less all, challenged claims. (Exs.2016¶5; 2017¶4; 2041¶¶130, 266; 1197(Wilson)_252:12–254:21; 1198(Carter)_32:25–39:15; 1199(Presta)_41:10–44:4.) Nor has PO shown any commercial success attributable to this patent. At most, PO identifies the "213 patent's "consensus" approach, which allows good binding affinity while minimizing immunogenicity" but, as discussed above, there is no evidence these alleged advantages are in any way attributable to the "consensus" approach. *Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00652, Paper 68 at 35, ("[E]vidence of commercial success is 'only significant if there is a nexus between the claimed

invention and the commercial success.'"). Nor has PO provided evidence that customers buy these drugs because of the claimed invention, rather than other reasons such as their ability to bind HER-2, as described in the prior art. *Id.* at 35-36 (nexus requires "proof that the sales [of the allegedly successful product] were a direct result of the unique characteristics of the claimed invention—as opposed to other…factors unrelated to the quality of the patented subject matter'").

F. These Proceedings Are Constitutional

This IPR is constitutional. *Oil States Energy Servs. LLC v. Greene's Energy Grp.*, 138 S. Ct. 1365, 1379 (2018).

IV. CONCLUSION

The challenged claims are invalid.

Date: May 25, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

This Reply complies with the type-volume limitations as mandated in 37 C.F.R § 42.24, totaling [5596] words. Counsel has relied upon the word count feature provided by Microsoft Word.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Reply to Patent Owner Response was served on May 25, 2018, via electronic service on lead and back up counsel:

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