UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD., Petitioner,

v.

GENENTECH, INC., Patent Owner.

United States Patent No. 6,407,213
Title: Method for Making Humanized Antibodies

Case No.: IPR2017-02140

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,407,213

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Exhibit 1184C	*Preliminary Refinement and Structural Analysis of the FAB Fragment from Human Immunoglobulin New at 2.0 Angstroms Resolution*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/obsolete.do?obsoleteId=3FAB
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Exhibit 1184I	*Structure of a Novel Bence-Jones Protein (Rhe) Fragment at 1.6 A Resolution*, RCSB Protein Data Bank, http://www.rcsb.org/pdb/explore/explore.do?structureId=2RHE
Exhibit 1185	Miller, *To Build a Better Mousetrap, Use Human Parts*, 90(1) J. NAT'L CANCER INST. 1416 (1998) ("Miller '98")
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Exhibit No.	**Document Description**
Exhibit 1189	U.S. Patent No. 5,859,205
Exhibit 1190	Declaration of Diljeet S. Athwal, Ph.D.
Exhibit 1191	Declaration of Mark Gerstein, Ph.D.
Exhibit 1192	S. Roberts, *et al.*, *Generation of an antibody with enhanced affinity and specificity for its antigen by protein engineering*, 328 NATURE 731-34 (Aug. 1987)

I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Samsung Bioepis Co., Ltd. ("Bioepis" or "Petitioner") petitions for *inter partes* review of claims 1, 2, 4, 12, 25, 29-31, 33, 42, 60, 62-67, 69, 71-81 (the "Challenged Claims") of United States Patent No. 6,407,213 (the "'213 patent") (Ex. 1001). Concurrently filed with the petition is a power of attorney pursuant to 37 C.F.R. § 42.10(b).

The Challenged Claims of the '213 patent are directed to humanized antibodies with non-human residues in the Complementarity Determining Regions ("CDRs") as well as in the framework region at certain, specified positions. This petition shows, by a preponderance of the evidence, that the Challenged Claims are unpatentable as obvious over the prior art.

For the sake of completeness and efficiency, the present petition is a practical copy of the petition in IPR2017-01489. A Motion for Joinder with IPR2017-01489 is being filed concurrently with this petition.

II. MANDATORY NOTICES

A. Petitioner and Real Party in Interest (37 C.F.R. § 42.8(b)(1))

Bioepis is the Real Party in Interest. Bioepis is a corporation organized and existing under the laws of the Republic of Korea, having its principal place of business at 107, Cheomdan-daero, Yeonsu-gu, Incheon 21987, Republic of Korea.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Bioepis is unaware of any litigation related to the ’213 patent.

Bioepis is concurrently filing an additional petition related to the ’213 patent. Bioepis is also aware of six previously filed petitions related to the ’213 patent. Mylan Pharmaceuticals Inc. filed two petitions: IPR2016-01693 and IPR2016-01694. On March 10, 2017, the Board terminated both proceedings in response to the parties’ joint motion to terminate. *See* IPR2016-01693, Paper 24; IPR2016-01694, Paper 23. Celltrion, Inc. filed two petitions: IPR2017-01373 and IPR2017-01374, both of which are active. Pfizer Inc. also filed two petitions: IPR2017-01488 and IPR2017-01489, both of which are active.

Bioepis is otherwise unaware of any judicial or administrative proceedings that would either affect or be affected by a decision regarding this petition.

C. Counsel and Service Information (37 C.F.R. § 42.8(b)(3) and (4))

Bioepis identifies its lead and backup counsel as shown below.

Lead Counsel	Backup Counsel
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Please address all correspondence to lead and backup counsel. Bioepis consents to service by email at the following addresses: ddrivas@whitecase.com and scott.weingaertner@whitecase.com.

III. FEES (37 C.F.R. § 42.15(a))

Bioepis authorizes the United States Patent and Trademark Office to charge the fees enumerated in 37 C.F.R. § 42.15(a) regarding this Petition and any additional fees that may be due in connection to this Petition from Deposit Account No. 50-3672.

IV. REQUIREMENTS UNDER 37 C.F.R. § 42.104

A. Grounds for Standing (37 C.F.R. § 42.104(a))

Bioepis certifies that the ’213 patent is available for *inter partes* review, and that Bioepis is not barred or estopped from requesting an *inter partes* review of the Challenged Claims on the grounds identified in this petition.

B. Statement of relief requested (37 C.F.R. § 42.104(b))

Bioepis respectfully requests *inter partes* review, under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.100-42.123, for the cancellation of the Challenged Claims of the ’213 patent as being unpatentable under 35 U.S.C. § 103. Petitioner’s full statement of the reasons for the relief requested is set forth in detail in §§ V-IX below. In accordance with 37 C.F.R. § 42.6(c), copies of the exhibits are filed herewith. Bioepis supports its challenges with the Declaration of Jefferson Foote, Ph.D, (Ex. 1003), the Declaration of Timothy Buss, (Ex. 1004),[1] the Declaration of Diljeet (“Dee”) Athwal (Ex. 1190), and the Declaration of Mark Gerstein, Ph.D (Ex. 1191).

[1] The Foote and Buss Declarations are exact copies of the declarations submitted by Dr. Foote and Mr. Buss in IPR2017-01489. These declarations are cited in this petition to avoid unnecessary cost and to advance efficiency in this instance. As mentioned above, this petition is presented along with a motion to join IPR2017-01489, and by using the same declarations, Bioepis has eliminated the need for analysis of another declaration or a new expert report. To the extent Dr. Foote or Mr. Buss become unavailable in IPR2017-01489, however, Bioepis will rely upon the Declarations of Drs. Athwal and/or Gerstein.

The Challenged Claims relate to humanized antibody technology and are unpatentable on the following grounds:

Ground	Claims and Basis
1	Claims 1, 2, 12, 25, 29, 63, 64, 67, and 71-81 are obvious over Queen 1989 and PDB Database
2	Claims 1, 2, 4, 12, 25, 29, 62-64, 66, 67, 69, and 71-81 are obvious over Queen 1990 and PDB Database
3	Claims 75-77, 79, and 65 are invalid as obvious over Queen 1989 in view of PDB Database and Tramontano
4	Claims 75-77, 79, and 65 are obvious over Queen 1990 in view of PDB Database and Tramontano
5	Claims 4, 62, 64, and 69 are obvious over Queen 1989 in view of PDB Database and Kabat 1987
6	Claims 30, 31, 42, and 60 are obvious over Queen 1989 in view of PDB Database and Hudziak
7	Claims 30, 31, 33, 42, and 60 are obvious over Queen 1990 in view of PDB Database and Hudziak

V. THE LEVEL OF ORDINARY SKILL IN THE RELEVANT ART

The alleged invention relates to humanizing non-human antibodies, *e.g.*, mouse monoclonal antibodies. A skilled artisan would have held a Ph.D. or equivalent (for example, knowledge gained through 4–5 years of work experience) in molecular biology, immunology, biochemistry or a closely related field, and may work as a member of a team. A team member or advisor or consultant would have an M.D. with clinical experience in the disease or disease area (*e.g.*, oncology) for which the antibody development is intended. (*See, e.g.*, Exs. 1003 ¶¶29–32; 1004 ¶¶30–33; 1190 ¶¶29-32; 1191 ¶¶29-32) Such a person would have the educational background above with experience in common laboratory

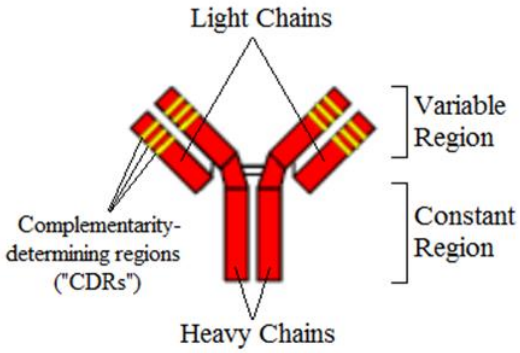
techniques in molecular biology. (*Id.*) Such experience can include three dimensional computer modeling of protein structures, domain and sequence manipulation and swapping, construction and expression of recombinant proteins, antibody binding assays (for specificity and affinity), immunogenicity testing and the like. (*Id.*) Such person may have consulted with one or more team members or experienced professionals to develop a humanized monoclonal antibody for therapeutic use, including consulting with others to select non-human monoclonal antibodies (such as a mouse monoclonal antibody) for humanization, as well as subsequent testing of the humanized antibody and its intermediates. (*Id.*) Such a person would also have been well-versed in the world-wide literature that was available as of the priority date. (*Id.*)

VI. THE SCOPE AND CONTENT OF THE PRIOR ART

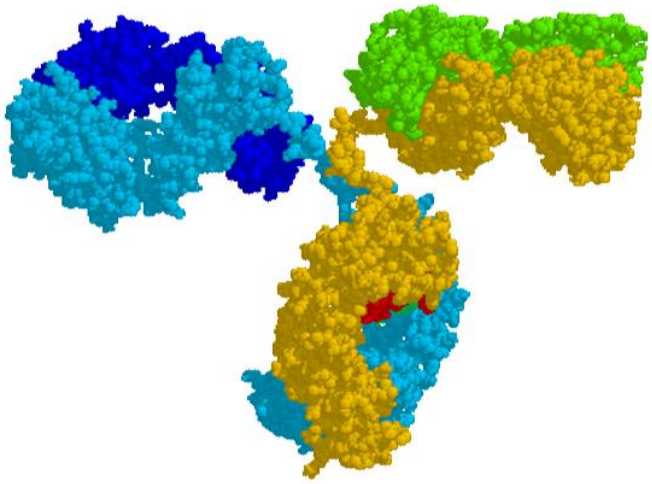
A. Antibodies and Humanization

Antigens are molecules that provoke an immune response in humans and animals. A natural response to the presence of an antigen is the production of antibodies, proteins that bind to antigens and may facilitate a complex immune response to neutralize any potential threat by the antigen or the organism of which it is a part. Antibodies are "Y" shaped proteins with several different components. Antibodies are composed of two heavy chains and two light chains. Antibodies further consist of a "variable region" and a "constant region." The variable region

includes the complementarity-determining regions ("CDRs"), the portion of the antibody that binds to an antigen and determines the antibody's specificity. They are typically depicted as follows:



Typical "Y" antibody depiction



A more realistic antibody depiction, where the two heavy chains are yellow and light blue and the two light chains are green and dark blue.

In the mid-1970's, researchers developed a method of producing monoclonal antibodies. Monoclonal antibodies are a homogenous population of antibody, which binds a particular antigen. Köhler and Milstein published the seminal paper on this topic, which disclosed the ability to grow monoclonal antibodies in a culture. (Ex. 1022) Such antibodies were useful mainly as a means of purifying proteins of interest and, to a limited extent, as therapeutics.

The human immune system normally does not raise antibodies against antigens that the human body itself produces, for example a normal human subject

will not produce antibodies to human $p185^{HER2}$. Indeed, such a response would constitute an autoimmune disease. To target such human-produced antigens, researchers raise antibodies in another species. Because the human body's immune system often targets non-human proteins, such as non-human antibodies (*e.g.*, the Human Anti-Mouse Antibody or "HAMA" response), the approach published by Köhler and Milstein, though useful for generating antibodies, is problematic. To alleviate this limitation, researchers developed antibodies raised in non-human species, but which contain less non-human protein.

The first such antibodies are known as chimeric antibodies. Chimeric antibody technology was first published in November 1984. (*See* Ex.1031) In this paper, researchers described the creation of antibodies with mouse-derived variable regions and human-derived constant regions. Despite containing a majority of human-derived protein, these antibodies maintained the antigen-binding specificities generated in mice. Chimeric antibodies are produced by cells that have been genetically-engineered to contain DNA from two different species. Although chimeric antibodies consist of less non-human proteins than murine monoclonal antibodies, a patient to whom a chimeric antibody has been repeatedly administered is likely to produce a HAMA response. While chimeric antibodies are an improvement over monoclonal antibodies, further advancements were necessary to eliminate the HAMA response.

The next important advancement for therapeutic antibodies was the development of humanized antibodies. The first publication to describe a humanized antibody appeared in 1986 from the laboratory of Dr. Winter. (*See* Ex. 1033) In this first humanized antibody publication, non-human residues are present only in a small portion of the variable region – specifically, in the antigen binding CDR region. The humanized antibodies of this publication had an entirely human framework region. (*See id.*) Humanized antibodies contain far less non-human residues than chimeric antibodies.

In 1988, the field again progressed with the first publication of a "reshaped" humanized antibody, *i.e.*, a humanized antibody with some substitutions in the framework region made to retain the three-dimensional structure of the non-human CDR. (*See* Ex. 1069) By mimicking the three-dimensional structure of the murine protein's hypervariable regions through specific point mutations in the framework region, these "reshaped" humanized antibodies maintained high-specificity binding to a human antigen using a mostly human antibody without the risk of an immune response against the antibody itself.

B. Prior Art Cited in this Petition

Bioepis relies on the following patents and printed publications in this petition:

1. Queen 1989

Cary Queen, *et al.*, *A humanized antibody that binds to the interleukin 2 receptor*, 86 Proc. Nat'l Acad. Sci. USA 10029-10033 (Dec. 1989) ("Queen 1989") (Ex. 1034) published more than one year before the earliest priority date of the '213 patent (June 14, 1991), and is therefore prior art to the '213 patent under at least 35 U.S.C. § 102(b).

Queen 1989 (published December 1989) disclosed humanized antibodies which, to reduce immunogenicity, retained only the mouse CDRs. To preserve the structure of the mouse CDRs, Queen 1989 targeted specific residues in the human framework region to switch back to mouse, thus restoring the mouse CDRs' affinity and optimizing the antibody for long-term therapy. (Exs. 1034 at 3; 1003 ¶¶126–30; 1190 ¶¶102-06) The result was a humanized version of an anti-Tac antibody. (Exs. 1003 ¶126; 1190 ¶102)

Queen 1989 provided guidelines for humanizing mouse antibodies, particularly focusing on antibodies' framework regions. (Ex. 1034 at 3, Abstract) These guidelines included three concepts:

1) select a human antibody framework sequence homologous to the mouse to minimize distorting the existing shape and positioning of the mouse CDRs; (*id.* at 5);

2) use computer modeling to identify mouse amino acid residues in the framework likely interacting with either (a) mouse antibody CDRs or (b) antigen, to better preserve the overall conformation of the mouse CDRs; (*id.* at 5-6); and

3) substitute a rare or unusual amino acid in the human framework region if the corresponding location in the mouse antibody's framework region "actually has a residue much more typical of human sequences," *i.e.*, is common or conserved in humans. (*Id.* at 6)

This methodology generated a "combination of mouse and human sequence elements that would reduce immunogenicity while retaining high binding affinity." (*Id.* at 3) Queen 1989 thought their "ideas…may have wider applicability" beyond Queen 1989's anti-Tac antibody. (*Id.* at 7)

2. Queen 1990

WO90/007861 ("Queen 1990") (Ex. 1050) published on July 26, 1990, and is therefore prior art to the '213 patent under at least 35 U.S.C. § 102(a). Queen 1990 teaches four criteria useful for the production of humanized antibodies.

Criterion I teaches skilled artisans which human – or human "consensus" – framework to use:

> 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.

(*Id.* at 12:17-20)

Criterion II teaches skilled artisans to substitute "common" non-human (*e.g.*, murine) residues at positions that have "rare" – or uncommon – human residues:

> 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.

(*Id.* at 13:22-32) (underlining in original)

Criterion III teaches skilled artisans to substitute non-human residues at positions near the CDRs:

> Criterion III: In the positions immediately adjacent to the 3 CDR's in the humanized immunoglobulin chain, the donor

> amino acid 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.

(*Id.* at 14:1-12) (internal citations omitted)

Criterion IV teaches skilled artisans to identify framework residues that have atoms within 3 Å, and thus likely to contact the CDR, as possible candidates to substitute with non-human residues:

> 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. Computer programs to create models of proteins such as antibodies are generally available and well known to those skilled in the art[.]

(*Id.* at 14:14-28) Queen 1990 also teaches deriving these "contact" residues from known antibody structures. (*Id.*) Such framework residues are more likely to be important in influencing how CDRs interact with the antigen.

3. PDB Database

In 1971, the PDB Database identified by Queen 1990 was established as "a computer archival service…managed by the Brookhaven National Laboratory." (*See* Exs. 1003 ¶140 (citing to Ex. 1080); 1190 ¶116) An electronic publication such as an on-line database or Internet publication is considered to be a "printed publication" within the meaning of 35 U.S.C. 102 so long as the "publication was accessible to persons concerned with the art to which the document relates." MPEP 2128. Further, "[p]rior art disclosures on the Internet or on an on-line database are considered to be publicly available as of the date the item was publicly posted." *Id.* The PDB Database and its contents is a printed publication under 35 U.S.C. §102(b). *See In re Hall*, 781 F.2d 897, 898 (Fed. Cir. 1986)

("printed publication" includes "ongoing advances in the technologies of data storage, retrieval, and dissemination.").

The PDB Database was "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it and recognize and comprehend therefrom the essentials of the claimed invention without need of further research or experimentation." *In re Wyer*, 655 F.2d 221, 226 (C.C.P.A. 1981). In fact, "[t]he purpose of the Bank is to collect, standardize, and distribute atomic co-ordinates and other data from crystallographic studies." (Exs. 1080 at 3; 1003 ¶140; 1190 ¶116)

As early users of the PDB Database well prior to June 1991, Dr. Foote, in connection with IPR2017-01489, and Dr. Athwal describe the PDB Database as "a repository of protein crystal atomic co-ordinates available to the public....Skilled 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." (Exs. 1003 ¶140; 1190 ¶116)

Drs. Foote and Athwal also detail the organization and data uniformity of entries in the PDB Database: "Entries in the PDB included verified co-ordinate information as well as specific information regarding the entry itself." (Ex. 1003

¶141 quoting Ex. 1080 at 537–540, (describing the entry for protein ribonuclease S); Ex. 1090 ¶117)

In order to apply Queen 1989 and Queen 1990's instructions to use computer programs "to create models of proteins such as antibodies," including "known antibody structures, which are available from the *Brookhaven Protein Data Bank*," (Ex. 1050 at 16:25–36), solved murine monoclonal antibodies and Bence-Jones proteins that were available in the PDB database prior to June 1991 were identified: HYHEL-5, KOL, NEWM, J539, 4–4–20, McPc603, HYHEL-10, 1REI and 2RHE. (Exs. 1003 ¶¶261–62; 1190 ¶¶261-62)

The atomic coordinates and sequence information from the PDB Database as it would have existed in June 1991 for these molecules were taken, and then the Queen 1989 and Queen 1990 methodologies (including the computer modeling step) were applied, to identify which amino acid residues a skilled artisan would have reverted back to murine in a human framework. (Exs. 1003 ¶¶261–66; 1190 ¶¶261-66) Each solved structure was available pre-June 1991, as their release dates confirm. (*See, e.g.,* Exs. 1084 ¶¶4–21; 1003F, 1084A (HYHEL-5; October 16, 1987), 1003G, 1084B (KOL; July 28, 1983), 1003H, 1684C (NEWM; December 8, 1981), 1003I, 1084D (J539; July 15, 1990), 1503J, 1084E (McPc603; January 2, 1985), 1003K, 1084F (4–4–20; July 15, 1990), 1003L, 1084G

(HYHEL-10; July 12, 1989), 1003M, 1684H (1REI; May 19, 1976) and 1003N, 1084I (2RHE; September 15, 1983); 1190, exhibits F-N)

As Drs. Foote and Athwal explain, evaluating each existing sequence and calculating interatomic distances between each framework residue and CDR region, just as a POSITA would have done, produced a list of amino acid residues in the light and/or heavy chains that correspond to the patent claims. (Exs. 1003 ¶¶263, 266; 1190 ¶¶263, 266)

4. Tramontano

A. Tramontano, *et al.*, *Framework Residue 71 is a Major Determinant of the Position and Conformation of the Second Hypervariable Region in the VH Domains of Immunoglobulins*, 215 J. Mol. Biol. 175-182 (1990) (Ex. 1051) ("Tramontano"), and is therefore prior art to the '213 patent under, at least, 35 U.S.C. § 102(a).

Tramontano analyzed amino acid residues important for maintaining the conformation of heavy chain CDR2. (Ex. 1051, Abstract) Tramontano analyzed systemic differences in the position and main chain conformation of known antibody structures, reporting that "the major determinant of the position of H2 is the size of the residue at site 71, a site that is in the conserved framework of the V_H domain." (*Id.*) Tramontano taught that "[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.*) As such, Tramontano emphasized the importance of residue 71H in maintaining a CDR conformation, *i.e.*, CDR2 in the heavy chain. Such a position was therefore a necessary target for substitution with a non-human residue in humanized antibodies.

5. Kabat 1987

E. Kabat, *et al.*, SEQUENCES OF PROTEINS OF IMMUNOLOGICAL INTEREST (4th ed. 1987) (Ex. 1052) ("Kabat 1987") is prior art to the '213 patent under at least 35 U.S.C. § 102(b).

Kabat 1987 compiled known antibody sequences, derived through protein and gene sequencing, and identified the most common amino acids occurring at each position in antibody variable and constant domains groups by class, *i.e.*, consensus sequence. (Ex. 1052) Kabat 1987 provided the occurrences of the most common amino acids at each position in human kappa variable light chain subgroup I and human variable heavy chain III. (*Id.* at 13, 22) Kabat 1987 also disclosed boundaries of antibody domains within the heavy and light chain variable domains, including framework and CDR boundaries. (*Id.* at 9 (with lines separating the four framework regions and three CDRs))

6. Hudziak

R. Hudziak, *et al.*, *p185^{HER2} Monoclonal Antibody Has Antiproliferative Effects In Vitro and Sensitizes Human Breast Tumor Cells to Tumor Necrosis Factor*, 9(3) Mol. & Cell. Biol. 1165-1172 (Mar. 1989) ("Hudziak") (Ex. 1021) published in 1989, and is therefore prior art to the '213 patent under 35 U.S.C. § 102(b).

Hudziak confirmed p185^{HER2}'s role in carcinoma development. (*Id.* at Abstract) Hudziak "prepared monoclonal antibodies against the extracellular domain of p185" and chose antibody 4D5, which was then "characterized in more detail and was shown to inhibit in vitro proliferation of human breast tumor cells overexpressing p185^{HER2} and, furthermore, to increase the sensitivity of these cells to the cytotoxic effects of TNF-α." (*Id.*) Growth inhibition studies showed "[m]aximum inhibition was obtained with monoclonal antibody 4D5, which inhibited cellular proliferation by 56%." (*Id.*) Table 1 from Hudziak, entitled "Inhibition of SK-BR-3 proliferation by anti-p185^{HER2} monoclonal antibodies," is set forth below:

TABLE 1. Inhibition of SK-BR-3 proliferation by anti-p185^{HER2} monoclonal antibodies[a]

Monoclonal antibody	Relative cell proliferation[b]
7C2	79.3 ± 2.2
2C4	79.5 ± 4.4
7D3	83.8 ± 5.9
4D5	44.2 ± 4.4
3E8	66.2 ± 2.4
6E9	98.9 ± 3.6
7F3	62.1 ± 1.4
3H4	66.5 ± 3.9
2H11	92.9 ± 4.8
40.1.H1	105.8 ± 3.8
4F4	94.7 ± 2.8

[a] SK-BR-3 breast tumor cells were plated as described in Materials and Methods. Following adherence, medium containing 5 μg of either anti-p185^{HER2} or control monoclonal antibodies (40.1.H1 and 4F4) per ml were added.

[b] Relative cell proliferation was determined by crystal violet staining of the monolayers after 72 h. Values are expressed as a percentage of results with untreated control cultures (100%).

(*Id.* at 1168) (red box added) Hudziak further taught that "the combination of TNF-α and monoclonal antibody 4D5 reduced the tumor cell number to a level below that initially plated," which "indicated the induction of a cytotoxic response." (*Id.* at 6) Hudziak concluded that "[m]onoclonal antibodies specific for p185^{HER2} may therefore be useful therapeutic agents for the treatment of human neoplasias, including certain mammary carcinomas, which are characterized by the overexpressing of p185^{HER2}." (*Id.* at 1171)

VII. THE '213 PATENT

The '213 patent is entitled, "Method for Making Humanized Antibodies." (Ex. 1001) It issued on June 18, 2002 from U.S. Application No. 08/146,206 (the "'206 application"), filed June 15, 1992. (*Id.*) The '206 application is a

continuation-in-part of U.S. Application No. 07/715,272, filed on June 14, 1991, now abandoned. (*Id.*) Thus, the '213 patent purports to claim an earliest effective filing date under 35 U.S.C. § 120 of June 14, 1991.

The '213 patent has 82 claims. Claims 1, 30, 62-64, 66, 79, and 80 and independent claims, each of which recite: (1) a "humanized antibody variable domain," a "humanized antibody," a "humanized variant of a non-human parent antibody," and/or a "humanized heavy chain variable domain," (2) a "non-human" CDR, and (3) a "Framework Region (FR) amino acid substitution" at one of several specific positions. Other limitations include an antibody which "bind[s] p185HER2" (*e.g.*, claim 30), "lacks immunogenicity compared to a non-human parent antibody" (claim 63), and "(a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another" (claim 80).

'206 Application Prosecution. The '213 patent issued from Application No. 08/146,206 (the "'206 application"). During prosecution, the PTO rejected the '206 application's claims for anticipation, obviousness, lack of written description, lack of enablement, indefiniteness, and obviousness-type double patenting. The examiner allowed the claims on December 18, 2001.

Interference with Application No. 11/284,261. Applicants for U.S. Application No. 11/284,261 ("Adair") requested an interference with the '213 patent. After declaring an interference, the Board found that Adair's request was barred under 35 U.S.C. § 135(b)(1). (*See* Ex. 1095). The Federal Circuit then affirmed the Board. *See Adair v. Carter*, 668 F.3d 1334 (Fed. Cir. 2012).

VIII. CLAIM CONSTRUCTION

Bioepis assumes that the Challenged Claims possess their broadest reasonable construction ("BRI"). *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (finding "broadest reasonable construction" standard appropriate for IPRs). Under such a construction, Bioepis assumes that these claim terms have the following meanings:

Claims	Claim Term	Broadest Reasonable Construction
1, 30, 62-64, 66, 79, 80 and all dependent claims	• "humanized antibody variable domain" • "humanized antibody" • "humanized variant of a non-human parent antibody" • "humanized heavy chain variable domain"	A skilled artisan would understand "a humanized antibody" to include an antibody or antibody fragment that has been humanized, *i.e.*, made more human-like. A skilled artisan would also understand that none of the claims relate to a single, specific antibody or antibody fragment. Even in claim 30, where the phrase "[a] humanized antibody" is modified with "which binds p185$_{HER2}$," the claim is not limited to a particular antibody.

Claims	Claim Term	Broadest Reasonable Construction
1, 30, 62, 63, 66, 79, and 80 and all dependent claims	"a Framework Region (FR) amino acid substitution at a site selected from the group consisting of"	Independent claims 1, 30, 62, 63, 66, 79 and 80 include a Markush Group list of amino acid residues from which a framework region substitution is chosen. Markush Group members are accorded functional equivalency status for purposes of claim construction. *See Ecolochem, Inc. v. S. Cal. Edison Co.*, 1996 U.S. App. LEXIS 13330, at *6 (Fed. Cir. June 5, 1996) ("By claiming a Markush group . . . members of the claimed group are functionally equivalent."); *see also In re Skoll*, 523 F.2d 1392, 1397 (C.C.P.A. 1075) ("By the presentation of the Markush group, appellant has made a representation that for the purpose of the claimed invention the elements of the group are equivalents."). As none of the claims are limited to a specific antibody, and all Markush Group members are functional equivalents of each other for the purpose of creating a humanized antibody, the BRI would be that any of the recited residues can be equally substituted for any given antibody. Thus, it is assumed for the purposes of claim construction in this proceeding that each of the recited substitutions is available for humanization of an antibody.

Claims	Claim Term	Broadest Reasonable Construction
1, 30, 62, 63, 66, 79, and 80 and all dependent claims	"numbering system set forth in Kabat"	Independent claims 1, 30, 62, 63, 66, 79 and 80 recite "utilizing the numbering system set forth in Kabat." The '213 patent specifically ties its numbering system to two references: Kabat 1987 (Ex. 1052) and Kabat 1991 (Ex. 1055). (*See* Ex. 1001 at 10:45–49) As noted, the Kabat 1987 and 1991 data derives from a database of publicly available antibody sequences, formatted to display the sequences in alignment with each other and in a numerical sequence order. Kabat 1987 and 1991 also show boundaries of known antibody regions, including the three CDRs and four FRs in each antibody chain variable domain. The BRI of "utilizing the numbering system set forth in Kabat" encompasses the Kabat 1987 and Kabat 1991 designations, including the amino acid residue positions set forth in Kabat and the boundary designations for CDR and FR structures.
65 & 79	"up to 3-fold more"	Claim 65, which depends from claim 79, requires a "humanized variant...bind[ing] the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." The BRI of this claim includes all binding affinity values "up to" 3-fold more, *i.e.*, any value no matter how small and greater than zero "up to" 3-fold more.

Bioepis reserves the right to advance a different claim construction in any subsequent proceedings.

IX. DETAILED STATEMENT OF GROUNDS FOR INVALIDITY

Prior to the earliest priority date of the ’213 patent, the prior art contained detailed instructions regarding the humanization and “reshaping” of antibodies. Indeed, it was well-recognized that chimeric and fully murine antibodies, while useful, had several drawbacks as therapeutics, including immunogenic concerns (*i.e.*, the HAMA response). As such, research groups around the world were seeking ways to maintain – or improve – antibody-antigen affinity, while reducing the amount of non-human protein sequence to alleviate the HAMA response. At least four different research groups, in fact, had already published in this field, including: Celltech (Ex. 1189), the Medical Research Council (*e.g.*, Exs. 1033 and 1069), Protein Design Labs (*E.g.*, Exs. 1034 and 1050), and Genzyme Corporation (Ex. 1071).

Detailed instructions for humanizing murine monoclonal antibodies were widely available before the earliest possible priority date. Queen 1989 (Ex. 1034) and Queen 1990 (Ex. 1050), for example, taught humanization methods which relied on reverting select human framework residues back to mouse in order to preserve the original mouse CDRs’ binding affinity. (*See* Exs. 1034 at 3, Abstract; 1050 at 1, Abstract; 1003 ¶¶125–37; 1190 ¶¶101-13) While other techniques (chimeric antibodies and CDR grafting) were available, the field recognized that those antibodies often exhibited poor binding or resulted in immunogenicity. (*See*

Exs. 1050 at 3:30–33; 1073 at 8:12–19; 1003 ¶¶97–100; 1004 ¶¶38–39; 1190 ¶¶73-76; Ex. 1191 ¶¶37-38)

Queen 1989 and 1990 addressed these issues by providing skilled artisans with the best of both worlds: (1) human FR regions to reduce immunogenicity; with (2) restoration of binding affinity through preservation of mouse CDRs and key mouse residues in the FR that support or maintain CDR conformation.

Queen 1989 provided the following roadmap:

1) Use a human framework structurally closest to the non-human (mouse) monoclonal antibody or a consensus sequence; and

2) Target FR residues within the human sequence that (a) are close enough to influence CDR conformation; (b) interact directly with the antigen; and/or (c) are more 'human' in the mouse or donor immunoglobulin at the same-positioned residue in the human antibody variable domain; and convert them back to the donor residue.

(Exs. 1034 at 5–6; 1003 ¶¶127, 130; 1190 ¶¶103, 106)

Queen 1990 went further, instructing targeting residues which, in the original mouse antibody, possessed side chain atoms within about 3Å of the CDR residues and "could interact with the CDR atoms according to established chemical forces." (Ex. 1050 at 14:21–25)

Based on the teachings of Queen 1989 or Queen 1990, a skilled artisan could have reasonably expected to identify the most important framework positions in any donor antibody to target for substitution. (*Id*. at 14:2, 14–15) By at least 1991, the prior art therefore provided a detailed roadmap to optimize the humanization of non-human monoclonal antibodies for therapeutic use which would "be substantially non-immunogenic and retain substantially the same affinity as the donor immunoglobulin to the antigen." (*See id.* at 1, Abstract; Ex. 1003 ¶¶125–37; 1190 ¶¶101-03)

A. Grounds 1 and 2: Claims 1, 2, 4, 12, 25, 29, 62-67, 69, and 71-81 are obvious over Queen 1989 (Ground 1) or Queen 1990 (Ground 2) in view of the PDB Database

1. Ground 1: Claim 1 is obvious over Queen 1989 in view of the PDB Database

Independent claim 1 is drawn to "[a] humanized antibody variable domain" comprising "non-human" (*e.g.*, mouse) CDRs.

As discussed above, Queen 1989 disclosed making "a humanized antibody variable domain" comprising "non-human CDR amino acid residues which bind an antigen incorporated into a human antibody variable domain." (*See* Ex. 1034, Abstract ("We have therefore constructed a 'humanized' antibody by combining the complementarity determining regions (CDRs) of the anti-Tac antibody with human framework and constant regions."); Ex. 1003 ¶¶126, 253; 1190 ¶¶102, 254)

Claim 1's humanized antibody "further compris[es] 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."

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. (Exs. 1034 at 5–6; 1003 ¶254; 1190 ¶255) A skilled artisan would have used those simple rules to determine which residues in a human framework region could be substituted for a mouse residue. (Ex. 1003 ¶¶255–59; 1190 ¶¶256-60)

Queen 1989 did exactly this for the anti-Tac antibody, using programs to compare known antibody structures to show that "a number of amino acid residues…are in fact close enough to [CDRs] to either influence their conformation or interact directly with antigen." (Exs. 1034 at 5; 1003 ¶¶255–56; 1190 ¶¶256-57) Queen 1989 then substituted these framework positions with the mouse residue. (Exs. 1034 at 5; 1003 ¶¶255–56; 1190 ¶¶256-57) Queen 1989 taught that such

steps "may have wider applicability" to humanize other antibodies. (Exs. 1034 at 7; 1003 ¶128; 1190 ¶104)

A skilled artisan would have applied the same methodology prior to 1991. Many private and public research institutions, including Genzyme Corporation (*see, e.g.*, Ex. 1071), Protein Design Labs (*see, e.g.*, Ex. 1050), the Winter Lab and the Medical Research Council (*see, e.g.*, Ex. 1073), and his laboratory at the National Institutes of Health, were very active in the field of humanization as of June 1991. (Exs. 1003 ¶110; 1190 ¶86)

Skilled artisans used publicly available tools such as the PDB Database, (*see supra* § VI.B.4), and computer programs, to measure interatomic distances and create three-dimensional graphical models. "In order to ensure the preservation of antigen-binding properties, when an antibody is 'humanized' by CDR-grafting, *all the framework residues, that could influence the structure of its combining site, must be retained*." (*Id*.) These tools helped skilled artisans identify such residues. Thus, a skilled artisan engaged in antibody humanization would have followed Queen 1989's guidance to identify the framework region residues close enough to influence CDR conformation or interact directly with the antigen. Moreover, where the acceptor and donor sequences are known, a residue by residue comparison of the human framework region sequences against the mouse donor sequence would have revealed whether there are unusual residues in the human framework that

should be substituted to a common or conserved residue if present in the mouse donor. (Exs. 1034 at 5–6 (residues that "are more 'human' in the mouse or donor immunoglobulin at the same-positioned residue in the human antibody variable domain" should be converted back to the donor residue); 1003 ¶265; 1190 ¶265)

Queen 1989's methodology was performed on antibody structures known and publicly available prior to 1991 through the PDB Database. (*See* Exs. 1003 ¶¶261–63; 1190 ¶¶261-63) The atomic coordinates of each of the known and available solved antibody structures (*i.e.*, HYHEL-5, KOL, NEWM, J539, MCPC603, 4–4–20, HYHEL-10, 1REI and 2RHE) were extracted, which contained distance calculations between framework and CDR amino acid residues. (*Id.* at ¶¶262–63) Then, the interatomic (Euclidean) distances between the atom pairs of the framework residue and the CDR residues were determined, a practice that was considered routine as of 1991. (*Id.* at ¶¶262–66; Ex. 1003O (interatomic distance calculations); 1190 ¶¶262-66 and exhibit O) Using this information, framework residue side chains that were in contact with the CDRs were identified. (*See* Exs. 1003 ¶¶262–66; 1003O and 1003Q; 1190 ¶¶262-66 and exhibits O and Q)

Following the teachings of Queen 1989, the primary amino acid sequence of each of the antibody structures were aligned according to the Kabat numbering system, (*see* Ex. 1003P; 1190, exhibit P), and identified contact residues that were

targets for substitution were identified. (*See* Exs. 1034 at 3–4 and Figure 3; 1003 ¶¶263–66; 1003O and 1003P; 1190 ¶¶263-66) It was found that 9 light (L) chain residues (4L, 58L, 62L, 66L, 67L, 69L, 73L, 85L and 105L) and 11 heavy (H) chain residues (2H, 24H, 39H, 45H, 69H, 71H, 73H, 76H, 78H, 93H and 103H) were readily identified as in contact with CDRs, according to the numbering system of Kabat 1987. (Ex. 1052; s*ee* Exs. 1003 ¶263; 1003O (interatomic distance calculations), P (antibody alignment), and Q (contact summary); 1190 ¶263 and exhibits O-Q) Of these, claim 1 recites residues 4L, 58L, 66L, 67L, 69L, 73L, 2H, 45H and 69H. (*See* Ex. 1003 ¶266; 1190 ¶266) As Drs. Foote and Athwal explain, a skilled artisan could easily and quickly identify at least 9 claimed residues that one would have had on a list of substitutable residues following Queen 1989's roadmap.

The '213 patentees followed Queen's roadmap. The specification states the purported invention involved obtaining a donor antibody and a consensus sequence, (Ex. 1001 at 4:47–49), importing CDRs from the donor into the consensus, (i*d*. 4:50–54), identifying any residues in the framework that differ, (*id.* at 4:59–61), determining whether the residue where the difference lies is involved in CDR interaction and/or antigen binding, (*id.* at 4:62–67), and if so, substituting in the donor residue (mouse) for the human residue, (*id*. at 5:1–5). In other words,

they predictably identified residues already ripe for substitution by following the roadmap of Queen 1989.

The specification provides further evidence that the '213 patentees simply followed the teachings of Queen 1989 and 1990:

- "Step 1 . . . crystal structures from the Brookhaven Protein Data Bank were used . . ." (Ex. 1001 at 16:30-32);
- "Step 2 . . . the structures were superimposed on one another using the INSIGHT computer program . . ." (*id.* at 17:15-19);
- "[m]odels of a humanized, import or human antibody sequence are used . . . [to] show residues which may be important in antigen binding, or for maintaining the conformation of the antibody . . ." (*id.* at 19:58-64).

Given the teachings in Queen 1989 and the readily available structures on the PDB Database, it would have been obvious to humanize an antibody with a framework residue substitution at 4L, 58L, 66L, 67L, 69L, 73L, 2H, 45H or 69H. A skilled artisan would have been motivated to "reduce immunogenicity while retaining high binding affinity" in the original non-human (*e.g.*, murine) monoclonal antibody, (Exs. 1034 at 3; 1003 ¶¶36, 254; 1190 ¶35, 255), and would have had a reasonable expectation of success in humanizing the antibodies on the PDB Database based on the broad teachings of Queen 1989. (*Id.* at ¶266) A skilled artisan considering Queen 1989 would have been directed to antibody

structures in the PDB Database by Queen 1989's own disclosure. For these reasons, claim 1 is obvious.

2. Ground 2: Claim 1 is obvious over Queen 1990 in view of the PDB Database

Queen 1990 also disclosed making "a humanized antibody variable domain" comprising "non-human CDR amino acid residues which bind an antigen incorporated into a human antibody variable domain." Queen 1990 encompassed a human antibody variable domain comprising CDRs from a mouse (donor) monoclonal antibody. (Exs. 1050 at Abstract ("[n]ovel methods for designing humanized immunoglobulins having one or more complementary [sic] determining regions (CDR's) from a donor immunoglobulin and a framework region from a human immunoglobulin comprising...."); 1003 ¶¶132, 267; 1190 ¶¶108, 267)

Further, Queen 1990 provided 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)). (Exs. 1050 at 14:1–36; 1003 ¶¶135–36, 267–68; 1190 ¶¶111-12, 267-68) Queen 1990 also disclosed detailed information for decreasing immunogenicity by maintaining conserved residues in the human acceptor framework (Criterion II (*i.e.*, conserved or rare)). (Exs. 1050 at 13:22–37; 1003 ¶133 (adopting definition of >90% conservation of residue according to Kabat 1987 as a target for substitution); 1190 ¶109)

Queen 1990 thus provided a detailed rationale for substituting particular amino acids and *how* to choose these amino acids in an objective way. Queen 1990 explicitly instructed a skilled artisan to look to the "Brookhaven Protein Data Bank" (*i.e.*, the PDB Database), (Exs. 1003 ¶137; 1190 ¶113), to identify the framework residues that: "could interact with the CDR atoms" (Criterion IV; Ex. 1050 at 14:14–15:2); were conserved (Criterion II; *id.* at 13:22–37); or were adjacent to CDRs (Criterion III; *id.* at 14:1–12). (Exs. 1003 ¶¶133–36, 267; 1190 ¶¶109-12, 267)

A skilled artisan following Queen 1990's roadmap would have quickly determined that 19 light (L) chain and 23 heavy (H) chain residues were readily identified for substitution:

- 4L, 58L, 62L, 66L, 67L, 73L, 85L, and 105L (CDR contact residues);
- 23L, 25L, 33L, 35L, 49L, 53L, 57L, 88L, 90L, 98L (Kabat and Chothia adjacent residues);
- 2H, 24H, 39H, 45H, 69H, 71H, 73H, 76H, 78H, and 103H (CDR contact residues); and
- 25H, 30H, 33H, 36H, 49H, 52H, 56H, 66H, 94H, 95H, 102H, and 103H (Kabat and Chothia adjacent residues).

This includes positions 4L, 58L, 66L, 67L, 69L, 73L, 98L, 2H, 36H, 45H and 69H recited in claim 1. (*See supra* § IX.A.1; Exs. 1003 ¶268; 1003E (adjacent

residues), O (interatomic distance calculations), P (alignment) and Q (contact summary); 1190 ¶268 and exhibits E, O-Q) It therefore would have been obvious to have substituted an amino acid at least at one of these positions.

3. Grounds 1 and 2: Claims 2, 12, 25, and 29 are obvious over Queen 1989 and the PDB Database or Queen 1990 and the PDB Database

Claims 2, 12, 25 and 29 are also obvious in view of either Queen 1989 or Queen 1990 and the PDB Database. (Exs. 1003 ¶¶269–70; 1190 ¶¶296-70) Claims 2, 12, 25, and 29 depend from claim 1. As discussed above, claim 1 is obvious in view of Queen 1989 or Queen 1990, in view of the PDB Database. (*See supra* §§ IX.A.1 & 2)

Queen 1989 and Queen 1990, in view of the PDB Database, additionally disclosed "wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained," as recited in claim 2, (*see* Exs. 1034 at 3; 1050 at 5:36–6:1), "wherein the residue at site 66L has been substituted," as recited in claim 12**,** (*see* Ex. 1003 ¶269; *supra* IX.A.1 & 2 (framework residue 66L within 3 Å of CDR); 1190 ¶269), "wherein the residue at site 69H has been substituted" as recited in claim 25, (*see* Ex. 1003 ¶269, *supra* §§ IX.A.1. & 2 (69L is a contact residue); 1190 ¶269), and "[a]n antibody comprising the humanized variable domain of

claim 1," as recited in claim 29. (*See* Exs. 1034 at 5; 1050 at 4:21–25; 1003 ¶269; 1190 ¶269)

Both Queen 1989 and Queen 1990 provide express motivation to evaluate proteins in the PDB. (Ex. 1003 ¶¶137, 258, 268; 1190 ¶¶113, 259, 268) In view of the discussion above, claims 2, 12, 25 and 29 are obvious over Queen 1989 or Queen 1990, in view of known antibody structures available on the PDB Database.

Claim	**Queen 1989 + PDB Database (Ground 1)**	**Queen 1990 + PDB Database (Ground 2)**
Claim 2: "wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained."	*See* claim 1; Exs. 1034 at 3 ("When these residues differ between the anti-Tac and Eu antibodies, the residue in the humanized antibody was chosen to be [mouse] rather than [human].)"; 1003 ¶¶269-70; 1190 ¶¶269-70)	*See* claim 1; Exs. 1050 at 5:36–6:2 ("substitutions of a human framework amino acid of the [human] acceptor immunoglobulin with a corresponding amino acid from a [mouse] donor immunoglobulin will be made at positions.)"; 1003 ¶¶269-70; 1190 ¶¶269-70)
Claim 12: "wherein the residue at site 66L has been substituted."	*See* claim 1; Exs. 1003O and Q (66L substitutable as a conserved residue and in contact with CDR); 1003 ¶¶269-70; 1190 ¶¶269-70, exhibits O and Q)	*See* claim 1; Exs. 1003O and Q (66L substitutable as a conserved residue and in contact with CDR—Queen 1990 Criteria IV); 1003 ¶¶269-70; 1190 ¶¶269-70, exhibits O and Q)

Claim	Queen 1989 + PDB Database (Ground 1)	Queen 1990 + PDB Database (Ground 2)
Claim 25: "wherein the residue at site 69H has been substituted."	*See* claim 1; Exs. 1003O and Q (69H substitutable as a conserved residue and in contact with CDR); 1003 ¶¶269-70; 1190 ¶¶269-70, exhibits O and Q)	*See* claim 1; Exs. 1003O and Q (69H substitutable as a conserved residue and in contact with CDR—Queen 1990 Criteria IV); 1003 ¶¶269-70; 1190 ¶¶269-70, exhibits O and Q)
Claim 29: "An antibody comprising the humanized variable domain of claim 1."	*See* claim 1; Exs. 1034 at 5 ("The CDRs in the humanized antibody were of course chosen to be identical to the anti-Tac CDRs."); 1003 ¶¶269-70; 1190 ¶¶269-70)	*See* claim 1; Exs. 1050 at 6:21–26 ("When 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 immuno-globulin . . ."); 1003 ¶¶269-70; 1190 ¶¶269-70)

4. Ground 2: Claim 4 is obvious in view of Queen 1990 and PDB Database

Claim 4 depends from claim 1 and recites "wherein the human antibody variable domain is a consensus human variable domain." As discussed above, claim 1 is obvious over Queen 1990 and the PDB Database. (*See supra* § IX.A.2)

Further, Queen 1990 disclosed using a "consensus human variable domain." (*See* Exs. 1050 at 12:19–20; 1003 ¶271; 1190 ¶271) Accordingly, claim 4 is also obvious over Queen 1990, in view of known antibody structures available on the PDB Database.

5. Ground 2: Claim 62 is obvious in view of Queen 1990 and PDB Database

Independent claim 62 is nearly identical to claim 1, but adds that the human variable domain is a "consensus human variable domain." For the same reasons as for claims 1 and 4, claim 62 is also obvious. (*See supra* § IX.A.2)

Queen 1990 teaches substituting amino acid residues that contact or interact with a CDR, or are conserved. A skilled artisan following Queen 1990's criteria would readily identify at least claimed residues 4L, 58L, 66L, 67L, 73L, 2H, 36H, 45H, and 69H. (*See supra* §§ IX.A.2; Ex. 1003 ¶272; 1190 ¶272) Queen 1990 also taught using a "consensus human variable domain" in the humanization process. (Exs. 1050 at 12:17–20; 1003 ¶272; 1190 ¶272) Claim 62 is thus obvious over Queen 1990 and the PDB Database.

6. Grounds 1 and 2: Claims 63, 64, and 66 are obvious over Queen 1989 or Queen 1990 and the PDB Database

Independent claim 63 differs from claim 1 by further reciting that the claimed antibody "lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a

chronic disease in that patient . . ." This is the goal of all monoclonal antibody humanization projects, including that of Queen 1989 and Queen 1990, in which the disclosed humanized immunoglobulins "will be substantially non-immunogenic in humans...." (Exs. 1034 at 3; 1050 at Abstract; 1003 ¶¶273–74; 1190 ¶¶273-74) Accordingly, as for claim 1 above, (*see supra* §§ IX.A.1 & 2), claim 63 is obvious over Queen 1989 or Queen 1990 in view of the PDB Database. (*Id*.)

Independent claim 64 recites a "humanized variant of a non-human parent antibody which binds an antigen;" a "human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup"; non-human CDRs; and, rather than require a FR substitution at one of a variety of locations (*cf.* claims 1, 62, 63), recites *functional* elements of the substituted FR residue: "(a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another."

Listing such properties 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). Instead, such elements reflect inherent humanized antibody properties. Even so, Queen 1990 stated amino acids "immediately adjacent" to the CDRs "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." (Exs. 1050 at 14:1–12; 1003 ¶¶276–77; 1190 ¶¶276-77) This satisfies at least limitations (a) and (b).

Further, Queen 1990 disclosed humanized antibodies which bind an antigen and comprise a human variable domain with a "consensus framework from many human antibodies." (*See supra* § IX.A.4; Ex. 1003 ¶277; 1190 ¶277) Queen 1990, given the PDB database, renders claim 64 obvious.

Claim 66: Independent claim 66 is similar to claim 1, but requires an amino acid substitution "selected from the group consisting of 24H, 73H, 76H, 78H and 93H" under Kabat's numbering system. Queen 1989 and Queen 1990 teach residues that are substitutable in a human FR region by identifying amino acid positions that: 1) contact a CDR; or 2) are adjacent to a CDR. (*See supra* §§ IX.A.1; Ex. 1003 ¶280; 1190 ¶280) Given Queen 1989 and Queen 1990 disclosures teaching computer modeling and comparison with known antibody structures from the PDB Database, a skilled artisan would have readily recognized that all of the claimed FR options (24H, 73H, 76H, 78H, and 93H) satisfy Queen's criteria. (*See id.*; 1003C, Exhibit O (interatomic distance calculations), Exhibit Q (Contacts Summary); 1190, exhibits C, O, Q) Claim 66 is therefore obvious over Queen 1989 or Queen 1990 and the PDB database.

Claim	Queen 1989 + PDB Database (Ground 1)	Queen 1990 + PDB Database (Ground 2)
Claim 63: "A humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient in order to treat a chronic disease in that patient, wherein the humanized antibody comprises non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain, and further comprises an amino acid substitution at a site selected from the group consisting of: 4L, 38L, 43L, 44L, 46L, 58L, 62L, 65L, 66L, 67L, 68L, 69L, 73L, 85L, 98L, 2H, 4H, 36H, 39H, 43H, 45H, 69H, 70H, 74H, 75H, 76H, 78H and 92H, utilizing the numbering system set forth in Kabat"	*See* discussion of claims 1 and 29 for "humanized antibody" comprising non-human...CDR; and claimed substituted amino acids 4L, 58L, 66L, 67L, 73L, 2H, 36H, 45H and 69H. (*See supra* §§ IX.A.1; *see also* Exs. 1034 at 1; 1003 ¶¶273-74; 1190 ¶¶273-74)	*See* discussion of claims 1 and 29 for "humanized antibody" comprising non-human...CDR; and claimed substituted amino acids 4L, 58L, 66L, 67L, 73L, 2H, 36H, 45H and 69H. (*See supra* §§ at IX.A.2 & 3; *see also* Exs. 1050 at Abstract ("the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans…."); 1003 ¶¶273-74; 1190 ¶¶273-74)

Claim	Queen 1989 + PDB Database (Ground 1)	Queen 1990 + PDB Database (Ground 2)
Claim 64: "A humanized variant of a non-human parent antibody which binds an antigen and comprises a human variable domain comprising the most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup wherein amino acid residues forming Complementarity Determining Regions (CDRs) thereof comprise non-human antibody amino acid residues, and further comprises a Framework Region (FR) substitution where the substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; (c) introduces a glycosylation site which affects the antigen binding or affinity of the antibody; or (d) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with respect to one another."		*See* discussion of claim 1 for "humanized antibody variable domain comprising non-human...CDR; (*See supra* §§ IX.A.1 & 2; Ex. 1003 ¶¶275-78; 1190 ¶¶275-78; s*ee also* for "the most frequently occurring amino acid residues at each location in all human immunoglobulins," (Ex. 1050 at 12:17–20 ("As acceptor...use a consensus framework from many human antibodies.")) For functional limitations (a), (b) and (c), *see id*. at 14:4–12 ("These amino acids are particularly likely to interact with the amino acids in the CDR's...[and] interact directly with the antigen."))

Claim	Queen 1989 + PDB Database (Ground 1)	Queen 1990 + PDB Database (Ground 2)
Claim 66: "A humanized antibody heavy chain variable domain comprising non-human Complementarity Determining Region (CDR) amino acid residues which bind 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: 24H, 73H, 76H, 78H, and 93H, utilizing the numbering system set forth in Kabat"	*See* discussion of claim 1 for "humanized antibody variable domain comprising non-human...CDR; and claimed substituted amino acids. (*See supra* §§ at IX.A.1 & 2; *see also* Exs. 1003 ¶¶279-83; 1003O and Q, for substitution of residues 24H, 73H, 76H, 78H and 93H; 1190 ¶¶279-83, exhibits O and Q**)**	*See* discussion of claim 1 for "humanized antibody variable domain comprising non-human...CDR; and claimed substituted amino acids. (*See supra* §§ at IX.A.1 & 2; *see also* Exs. 1003 ¶¶279-83; 1003O and Q, for substitution of residues 24H, 73H, 76H, 78H and 93H; 1190 ¶¶279-83, exhibits O and Q)

7. Ground 2: Claim 69 is obvious in view of Queen 1990 and PDB Database

Claim 69 depends from claim 66 and recites "wherein the human antibody variable domain is a consensus human variable domain." As discussed above, claim 66 is obvious over Queen 1990 and the PDB Database. (*See supra* § IX.A.6) Further, Queen 1990 disclosed using a "consensus human variable domain". (*See supra* § IX.A.4; Exs. 1050 at 12:19–20; 1003 ¶132; 1190 ¶108) For these reasons,

claim 69 is also obvious over Queen 1990, in view of known antibody structures available on the PDB Database.

8. Grounds 1 and 2: Claims 67, 71-74, and 78 are obvious in view of Queen 1989 or Queen 1990 and PDB Database

Claims 67, 71–74 and 78 depend from claim 66, and further recite "wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained" (*claim 67*), "wherein the residue at site 73H has been substituted" (*claim 71*), "wherein the residue at site 76H has been substituted" (*claim 72*), "wherein the residue at site 78H has been substituted" (*claim 73*), "wherein the residue at site 93H has been substituted" (*claim 74*) and "[a]n antibody comprising the humanized variable domain of claim 66" (*claim 78*).

Each of 73H, 76H, 78H and 93H are CDR contact residues as disclosed by Queen 1989, (Ex. 1034), and Queen 1990, (Ex. 1050), in view of the PDB Database,[2] and thus would have been readily identified for reverting to the mouse residue in any humanization project. (*See supra* §§ IX.A.1 & 2; Exs. 1003 ¶284;

[2] Dr. Foote, in connection with IPR 2017-01489, and Dr. Athwal point to antibody 4–4–20 (available 1989) with a cluster of close (<3.0Å) contacts at 73H, 76H, 78H and 93H, emphasizing the relative importance of these residues for maintaining antibody conformation. (Ex. 1003 ¶¶280-81; 1190 ¶¶280-81)

1003Q; 1190 ¶284 and exhibit Q) Moreover, like claims 2 and 29, claims 67 and 78 are also obvious. (*See supra* § IX.A.3; Ex. 1003 ¶284; 1190 ¶284) For these reasons, claims 67, 71–74 and 78 are also obvious over Queen 1989 or Queen 1990, in view of known antibody structures in the PDB Database.

9. Grounds 1 and 2: Claims 75-77 and 79 are obvious in view of Queen 1989 or Queen 1990 and PDB Database

Claim 75 depends from independent claim 66, and recites a humanized variable domain "which further comprises an amino acid substitution at site 71H." As discussed above, Queen 1989 and Queen 1990 teach substituting framework residues that: 1) contact a CDR; or 2) are adjacent to a CDR. (*See supra* §§ ix.a.1 & 2; Ex. 1003 ¶¶127, 135–36; 1190 ¶¶103, 111-12) Moreover, based on Queen 1989 and Queen 1990's teachings of computer modeling and comparison with known antibody structures from, *e.g.*, the PDB Database, (*see* Exs. 1050 at 14:14–15:2 (Criterion IV); 1003 ¶¶128, 137, 258; 1190 ¶¶104, 113, 259), a skilled artisan would have readily identified FR position 71H for substitution. (*See* Ex. 1003 ¶288; Ex. 1003O (interatomic distance calculations) and Q (contact summary); 1190 ¶288 and exhibits O and Q) Accordingly, claim 75 is also obvious over Queen 1989 or Queen 1990, given known antibody structures available in the PDB Database. (Exs. 1003 ¶288; 1190 ¶288)

Claims 76–77 depend from independent claim 66 and recite the additional limitations of "amino acid substitutions at sites 71H and 73H" (***claim 76***) and

"amino acid substitutions at sites 71H, 73H and 78H" (***claim 77***). ***Claim 79*** is an independent claim, and recites "[a] humanized variant of a non-human parent antibody which binds an antigen, wherein the humanized variant comprises Complementarity Determining Region (CDR) amino acid residues of the non-human parent antibody incorporated into a human antibody variable domain, and further comprises Framework Region (FR) substitutions at heavy chain positions 71H, 73H, 78H and 93H" using Kabat's numbering system.

As noted above, residues 71H, 73H, 78H and 93H are among those that would have been targeted for substitution in view of Queen 1989, (Ex. 1034), or Queen 1990, (Ex. 1050), and the PDB Database. (*See supra* §§ at IX.A.1 & 2; Exs. 1003 ¶¶263, 268; 1003O (interatomic distance calculations) and Q (contact summary); 1190 ¶¶263, 268 and exhibits O and Q) Therefore, it would have been obvious to have had "amino acid substitutions at sites 71H and 73H" of claim 76, "amino acid substitutions at sites 71H, 73H and 78H" of claim 77 and "substitutions at heavy chain positions 71H, 73H, 78H and 93H" of claim 79, given the limited set of residues already targeted for substitution. (Exs. 1003 ¶281; 1190 ¶281)

Further, the substitutability of residues 71H, 73H, 78H and 93H would not have been surprising or unexpected to a skilled artisan. The importance of heavy chain residue 71H was well-known by those in the field, including patentees. (*See*

supra Exs. 1001 at 3:1–8 (recognizing framework residues that "critically affect[] the conformation of particular CDRs and thus their contribution to antigen binding," (citing Ex. 1051)); 1003 ¶295 n.23; 1190 ¶295 n.15) Drs. Foote and Athwal also cite to antibody 4–4–20 (4Fab) which has a cluster of close contacts (less than 3Å) at 73H, 78H and 93H, which "emphasizes the relative importance of these contacts made . . . in maintaining antibody conformation." (Exs. 1003 ¶281; 1190 ¶281)

Moreover, the typical scenario was that more than one framework substitution was often needed to restore function and antigen binding of the resultant humanized antibody. (Exs. 1003 ¶297; 1190 ¶297) This is exemplified in Queen 1989 and Queen 1990, which both describe humanizing antibodies with multiple FR substitutions. Specifically, Queen 1989 taught 15 mouse substitutions. (*See* Exs. 1034 at 5, Fig. 2; 1003 ¶297; 1190 ¶297) Similarly, Queen 1990 states that the Queen CDR-contact criterion can be "used singly, or when necessary in combination" with other criteria to "achieve the desired affinity or other characteristics." (*See* Exs. 1050 at 12:9–15; 1003 ¶297; 1190 ¶297)

Further, a substitution's value can be limited given the antibody sequence itself. For example, comparing the mouse monoclonal antibody 4D5 sequence,[3]

[3] 4D5 was made available for use by outside investigators prior to June 1991 (Kumar *et al.*, 11(2) MOLECULAR CELLULAR BIOLOGY 979–86 (1991) (Ex. 1088); Soomro *et al.*, 44 J. CLINICAL PATHOLOGY 211–14 (1991) (Ex. 1089)),

and a human consensus amino acid sequence from Figures 1A and IB of the ’213 patent, (*see* Ex. 1001 at 7–8), and using the knowledge readily derived from the PDB Database and the Queen references, a skilled artisan would have arrived at a short list of light and heavy chain amino acid residues for substitution: 66L, 71H, 73H, 76H, 78H, 93H, and V_L:V_H contacts 43L, 73L, 85L and 43H, all of which are claimed in the ’213 patent. (*See* Exs. 1003 ¶¶299–302; 1003O–Q; 1190 ¶¶299-302, exhibits O-Q)

Applying Queen 1990’s Criterion IV, a skilled artisan would have thus targeted claimed residues 71H, 73H, 78H and 93H given the differences in size and/or characteristics of these residues in the mouse and human positions. (*See, e.g.*, Ex. 1003 ¶301 (71H); ¶302 (73H (polar to charged: aspartic acid in human acceptor vs. threonine in mouse 4D5)); ¶302 (78H (small to large: leucine in human acceptor vs. alanine in mouse 4D5)); ¶302 (93H (polar to hydrophobic: alanine in human acceptor vs. serine in mouse 4D5)); 1190 ¶¶301-02) Thus, a skilled artisan in view of Queen 1989 or Queen 1990 and known available antibody structures in the PDB Database, would have been motivated to substitute framework residues at least at 71H, 73H, 78H and 93H (*i.e.*, claims 75, 76, 77 and

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allowing a skilled artisan to obtain the amino acid sequence of the variable domain through routine protein sequencing. *See, e.g.*, Wilson & Goulding (Ex. 1090); Ex. 1003 ¶301 n.26) Many sequences present in the Kabat database (Ex. 1052) were obtained through routine protein sequencing. (*Id*, citing to Ex. 1091; Ex. 1092)

79) for the humanization of mouse 4D5 using a human consensus sequence as the acceptor antibody. (*See* Exs. 1050 at 12:19–20; 1003 ¶¶302–03; 1190 ¶¶302-03) A skilled artisan would have had a reasonable expectation of success given the teachings of Queen 1989 and Queen 1990 that the resultant humanized antibody would be "substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin . . ." (Exs. 1050 at Abstract; 1003 ¶¶302–03; 1190 ¶¶302-03) For these reasons, claims 75–77 and 79 were obvious in view of Queen 1989 or Queen 1990, and the PDB Database.

10. Grounds 1 and 2: Claim 65 is obvious in view of Queen 1989 or Queen 1990 and the PDB Database

Claim 65 depends from claim 79, and recites the humanized variant "binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen." Queen 1990 stated "affinity levels can vary…and may be *within about 4 fold* of the donor immunoglobulin's original affinity to the antigen." (*See* Ex. 1050 at 6:26–28) Queen 1990 thus taught that a humanized antibody would have been expected to be "within about 4-fold," in affinity as the original mouse antibody, disclosing a greater increase in affinity than the 3-fold increase recited in claim 65. The range of increase in affinity disclosed in Queen 1990 therefore encompasses the range recited in claim 65. A prior art reference that discloses a range encompassing a narrower claimed range is sufficient to establish a prima facie case

of obviousness. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003); *see also* MPEP 2144.04. (Exs. 1003 ¶¶306–310; 1190 ¶¶306-10)

Moreover, as explained by Drs. Foote and Athwal, "it was the expectation when humanizing antibodies...that a similar affinity, *i.e.*, slightly better or worse, would be obtained as compared to the parent (mouse) antibody. Thus, it would not have been surprising that at least a moderate improvement in affinity would be achieved" when humanizing some antibodies. (Exs. 1003 ¶308; 1190 ¶308) Thus, any increase in affinity, including small and moderate increases within the scope of claim 65, would have been expected, in view of the humanization techniques disclosed in Queen 1989 and Queen 1990. (Exs. 1050 at 6:26–28; 1003 ¶308; 1190 ¶308) For these reasons, claim 65 is obvious over Queen 1989 or Queen 1990 and the PDB Database.

11. Grounds 1 and 2: Claims 80 and 81 are obvious in view of Queen 1989 or Queen 1990 and the PDB Database

Independent Claim 80 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, and further comprising a Framework Region (FR) amino acid substitution," and further recites the "substituted FR residue: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the V_L-V_H interface by affecting the proximity or orientation of the V_L and V_H regions with

respect to one another...," while reciting a set of FR residues which differ from claim 1 only by *adding* amino acid residues 73H, 76H, 78H and 93H to the list of possible locations. As before, residues 4L, 58L, 66L, 67L, 73L, 2H, 24H, 36H, 45H, 69H, 73H, 76H, 78H and 93H were readily identifiable residues for substitution. (*See supra* §§ IX.A.1 & 2; Exs. 1003 ¶¶312–14; 1003O and Q; 1190 ¶¶312-14)

The additional recited elements—noted functions of the substituted residues—cannot impart novelty. (*See* claim 64, *supra* § IX.A.5 & 6); *see also Atlas Powder*, 190 F.3d at 1347. Even if the inherency of these functions were discounted (they should not be), Queen 1989 and Queen 1990 each explicitly teach interaction of the framework residues with the CDR as a reason for substitutability. (*See* Exs. 1034 at 5; 1050 at 14:32–15:2 (using computer model to assess CDR proximity); 1003 ¶¶312–15; 1190 ¶¶312-15) Accordingly, Queen 1989 or Queen 1990 and the PDB Database, also teaches substitution of a framework residue that "interacts with a CDR," rendering claim 80 obvious.

Claim 81 depends on claim 80, and further recites "wherein the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are obtained." This is taught by Queen 1989 and Queen 1990. (*See* Exs. 1034 at 3 ("selecting a human antibody to provide the variable region framework for the humanized anti-Tac

antibody"); 1050 at 5:36–6:1; 1003 ¶316; 1190 ¶316) Thus, claim 81 is obvious over Queen 1989 or Queen 1990, in view of the PDB Database.

B. Grounds 3 and 4: Claims 75-77, 79, and 69 are obvious over Queen 1989 and/or Queen 1990 in view of PDB Database and Tramontano

While the teachings of Queen 1989 and Queen 1990 in view of the PDB Database would have readily identified residue 71H for substitution based on its CDR contacts, independent work also emphasized the criticality of residue 71H in maintaining CDR conformation. Specifically, Tramontano definitively demonstrated the importance of 71H to maintain the H2 loop and antigen binding. (*See* Ex. 1051) This publication was the first to specifically report that:

> [T]he major determinant of the position of H2 is the size of the residue at site 71, a site that is in the conserved framework of the V_H domain. ***It is likely that for about two thirds of the known V_H sequences the size of the residue at this site is also a major determinant of the conformation of H2***.

(*Id.* at 6, Abstract (emphasis added)) The publication also confirmed Queen's teachings that residues outside of the CDR (*e.g.*, in the FR) help maintain CDR conformation and antigen binding.

The teachings of Queen 1989, (Ex. 1034), or Queen 1990, (Ex. 1050), and Tramontano (definitively demonstrating the importance of framework residue 71H,

see Exs. 1051 at 6, Abstract; 1003 ¶¶143, 289; 1190 ¶¶119, 289), would have motivated a skilled artisan to switch the human residue at position 71H to the mouse residue in order to preserve the conformation of the H2 CDR loop. (*See* Exs. 1051; Ex. 1003 ¶290; 1190 ¶290) Indeed, this would have been an automatic substitution to a skilled artisan. (*Id*.) Thus, together with Queen 1989 or Queen 1990 and the PDB Database, and for the same reasons above with regards to the obviousness of claims 75–77 and 79, (*see supra* §§ IX.A.9), claims 75–77, 79, and 65 are obvious in view of Queen 1989 or Queen 1990, the PDB Database and Tramontano. (Ex. 1051; Ex. 1003 ¶¶291, 304; 1190 ¶¶291, 304)

C. Ground 5: Claims 4, 62, 64, and 69 are obvious over Queen 1989 in view of the PDB Database and Kabat 1987

Claims 4, 62, 64 and 69 are also obvious over Queen 1989 and the PDB Database in view of Kabat 1987. (*See* Exs. 1003 ¶¶317–26; 1190 ¶¶317-26) As Drs. Foote and Athwal explain, the '213 patent's claiming a "consensus" sequence is somewhat misleading because the framework region sequences "are relatively conserved…with respect to both sequence and structure." (Ex. 1003 ¶174; *see also* ¶300 (citing to Ex. 1034 at 5 ("Different human light or heavy chain V regions exhibit strong amino acid homology outside of the CDRs within the framework regions.")); 1190 ¶¶175, 300)

Nevertheless, recognizing the importance of maintaining FR conservation to reduce immunogenicity and "make the antibody more human," Queen 1989 taught

moving toward a consensus framework region, observing that replacing amino acid residues with ones that are "more typical" and common would make the resulting antibody more human and less immunogenic. (*See* Exs. 1034 at 5–6; 1003 ¶320; 1190 ¶320) A skilled artisan considering Queen 1989 would have looked to Kabat 1987 to identify these "more typical" and common residues. Kabat 1987 provided all consensus amino acids at each framework region position. In view of the teachings of Queen 1989 and Kabat 1987, a skilled artisan would have "substitute[d] residues in the framework region itself with the most common amino acid in human antibodies to maximize a reduction in immunogenicity." (Exs. 1003 ¶¶319–20; 1190 ¶¶319-20)

In view of Kabat 1987 and the motivation in Queen 1989 to use a consensus framework region, a skilled artisan would have incorporated "a consensus human variable domain" as the framework region with a reasonable expectation of success. (Exs. 1003 ¶321; 1190 ¶321) As discussed with regards to claim 1 above, a skilled artisan would have readily identified residues 4L, 58L, 66L, 67L, 73L, 2H, 45H and 69H for substitution. (*See id.*; *supra* §§ IX.A.1 & 2) Thus, claims 4, 62, 64 and 69 are obvious in view of Queen 1989, the PDB Database and Kabat 1987.

D. Grounds 6 and 7: Independent claim 30 and dependent claims 31, 33, 42, and 60 are obvious over Queen 1989 (Ground 6) and/or Queen 1990 (Ground 7) in view of the PDB Database and Hudziak

Independent claim 30 differs from claim 1 by requiring the CDRs (and antibody) to bind to $p185^{HER2}$ and includes additional options for the location of the framework residue substitution: 46L, 75H and 76H.

Humanized antibodies were developed for a single purpose: realizing the therapeutic promise of mouse monoclonal antibodies for the treatment of human diseases. (Exs. 1003 ¶330; 1004 ¶36; 1190 ¶330; 1191 ¶35) While mouse monoclonal antibodies were capable of targeting antigens in a highly specific manner, immunogenicity issues severely limited the applicability of this technology in humans. (*See* Exs. 1003 ¶¶97–100; 1004 ¶¶38–45; 1190 ¶73-76; 1191 ¶¶37-44)

Molecular targets of particular interest included HER2/*c-erbB-2*, whose amplification in breast cancer patients correlated with poor prognosis and high relapse rate. (*See* Exs. 1021 at 8, Abstract, 1; 1004 ¶¶46–55; 1003 ¶331; 1190 ¶331; 1191 ¶¶45-54) Hudziak specifically found the HER2/*c-erbB-2* gene product $p185^{HER2}$: (1) amplified in ~30% of breast cancer tumors, (Ex. 1021 at 8); (2) "Correlated with a negative prognosis and high probability of relapse," (*id.*); (3) caused transformation and tumorigenesis when its expression was increased and the transformed cells were implanted in athymic mice, (*id.*; 1004 ¶52; 1191 ¶51);

and (4) caused cells to form anchorage-independent colonies in soft agar and at low density in low serum concentration—characteristics of a transformed phenotype. (Exs. 1021 at 8; 1004 ¶52; 1191 ¶51) Mr. Buss, in connection with IPR2017-01489, and Dr. Gerstein conclude the above findings "strongly suggested that the HER-2/*neu* receptor was a ripe target for therapeutic development." (Exs. 1004 ¶53; 1191 ¶52) Based on the teachings of Hudziak, a skilled artisan would have been motivated to develop a therapeutic monoclonal antibody against $p185^{HER2}$.

A skilled artisan would have also been motivated to develop a therapeutic monoclonal antibody against $p185^{HER2}$ because monoclonal antibodies were known to have the potential for achieving a high degree of specificity, which would allow one to target HER-2 without cross-reactivity with other structurally similar growth factor receptors, including epidermal growth factor receptor (EGFR). (*See* Exs. 1004 ¶¶54–55; 1191 ¶¶53-54) These benefits were demonstrated well prior to June 1991 for 4D5, a well-characterized mouse monoclonal antibody that targeted the $p185^{HER2}$ protein with high affinity, specificity (no binding or recognition of, for example, EGFR) and efficacy in *in vitro* and *in vivo* studies. (*See* Exs. 1004 ¶¶56–58; 1191 ¶¶55-57) The 4D5 investigators insisted it provided a "new potential for diagnostic approaches and therapeutic strategies for treatment of human malignancies." (Exs. 1047 at 6; 1004 ¶52; 1191 ¶51)

Given 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. (Exs. 1004 ¶70; 1003 ¶332; 1191 ¶69; 1190 ¶332) The 4D5 investigators urged artisans to follow precisely this path: "The muMAb *4D5 also serves as a template for antibody engineering efforts to construct humanized versions* more suitable for chronic therapy." (Exs. 1048 at 12 (emphasis added); 1004 ¶67; 1191 ¶66)

As discussed above, Queen 1989 and Queen 1990 provided the detailed roadmap for humanizing mouse monoclonal antibodies, such as 4D5, and represented the state of the art of antibody humanization by 1991. (Exs. 1003 ¶¶332–33; 1190 ¶¶332-33) Further, Queen 1989 and Queen 1990 provided the explicit motivation, and provided a skilled artisan with a reasonable expectation that a humanized antibody, such as 4D5, would be capable of binding to its antigen, in this case $p185^{HER2}$. (*See* Exs. 1050 at 1, Abstract ("When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen …"); 1034 at 3 ("For 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."))

From Queen 1989 or Queen 1990, together with known antibody structures available in the PDB Database, a skilled artisan would have recognized that claimed framework positions 4L, 58L, 66L, 67L, 73L, 98L, 2H, 36H, 45H and 69H were readily identifiable as residues that: 1) are adjacent to CDRs; or 2) contact CDRs. (*See* Ex. 1003E (adjacent residues), O (distance calculations) and Q (summary); *see also* Ex. 1003 ¶¶333, 335–36; 1190 ¶¶333, 335-46, exhibits E, O, Q; *supra* §§ IX.A.1 & 2)

Further, Queen 1989 and Queen 1990 disclosed that a skilled artisan would have had a reasonable expectation that humanizing a mouse monoclonal antibody, such as 4D5, would have worked. (*See* Exs. 1050 at 1, Abstract ("When combined into an intact antibody, the humanized immunoglobulins of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen..."); 1034 at 3 (expectation that humanized antibodies would "retain[] high binding affinity"); 1003 ¶333; 1190 ¶333) For at least these reasons, claim 30 is obvious over Queen 1989 (Ground 6) or Queen 1990 (Ground 7), in view of known antibody structures available in the PDB Database, and in view of Hudziak.

Claim 31. Claim 31 depends from claim 30 and additionally recites "the substituted residue is the residue found at the corresponding location of the non-human antibody from which the non-human CDR amino acid residues are

obtained." Queen 1989 and Queen 1990 both disclosed this limitation. (*See* Exs. 1034 at 5; 1050 at 5:36–6:1; 1003 ¶337; 1190 ¶337; *see supra* §§ IX.A.3 & 11 (claims 2 and 81)) Therefore, claim 31 is obvious over Queen 1989 or Queen 1990, the PDB Database and Hudziak.

Claims 42 and 60. Claims 42 and 60 depend from claim 30 and recite the residue at site 66L or 78H, respectively, is substituted. For the same reasons as above for claim 30, which details positions 66L and 78H as recognized substitutable positions, claims 42 and 60 are also obvious over Queen 1989 or Queen 1990, the PDB Database and Hudziak. (Exs. 1003 ¶¶338–39; 1190 ¶¶338-39)

Claim 33. Claim 33 depends from claim 30 and recites "the human antibody variable domain is a consensus human variable domain." Queen 1990 disclosed this limitation. (*See* Exs. 1050 at 12:19–20 ("[U]se a consensus framework from many human antibodies."); 1003 ¶¶340–41; 1190 ¶¶340-41) Thus, claim 33 is obvious over Queen 1990, the PDB Database, and Hudziak.

E. Secondary Considerations Cannot Overcome Obviousness

Patent Owner may attempt to assert secondary considerations of nonobviousness, despite no showing of such in the patent. Such evidence would be "insufficient" to "overcome the strong [case] of obviousness" here. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007). Patent Owner cannot show the

required nexus between any purportedly novel feature and any secondary consideration. *See, e.g.*, *Merck & Co. v. Teva Pharms. USA*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Patent Owner cannot show secondary considerations are commensurate with claim scope given the extraordinary breadth of the challenged claims here. *See, e.g.*, *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 666 (D. Del. 2014), *aff'd* 805 F.3d 1112, 1125-26 (Fed. Cir. 2015); *Torrent Pharms. Ltd. v. Novartis AG*, IPR2014-00784, Paper 112 at 12 (PTAB Sept. 24, 2015) ("If objective indicia of nonobviousness are 'due to an element in the prior art, no nexus exists'") (quoting *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1369 (Fed. Cir. 2011)).

In any event, Bioepis addresses secondary considerations below briefly.

1. The Challenged Claims of the '213 patent produced no unexpected results

During prosecution, Genentech argued that the claimed methods achieved unexpected results. (*See, e.g.*, Ex. 1002, Vol. 2 at 3431–37) Specifically, Genentech stated:

> The unexpected properties…include: lack of significant immunogenicity of the claimed humanized antibodies upon repeated administration to a human patient, e.g., to treat a chronic disease in the patient . . .

(*Id.* at 3431)

But Genentech's arguments are not reasonably commensurate with the full scope of the Challenged Claims. *See Cubist Pharms.*, 75 F. Supp. 3d at 666 ("[S]econdary considerations must be commensurate in scope – 'coextensive' – with the claimed features of the invention[.]"). Only Challenged Claim 63 even mentions immunogenicity and none recites a method. (Ex. 1001 at 88:36–38 (claim 63: "humanized antibody which lacks immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient")) Claim 63 does not require a "lack of ***significant*** immunogenicity."

Genentech also argued that:

> The unexpected properties…include…binding affinities superior to those of the non-human parent antibody; and the ability to use the same consensus human variable domain to make many strong affinity antibodies, thus avoiding tailoring each human FR to each non-human antibody to be humanized.

Id. at 3431.

But only challenged dependent claim 65 even mentions binding affinity. *Id.* at 88:63–65 (claim 65: "The humanized variant of claim 63 which binds the antigen up to 3-fold more in the binding affinity than the parent antibody binds antigen."). Further, *no* Challenged Claim requires "use of the same consensus human variable domain" or the making of "many strong affinity antibodies."

Moreover, this argument appears to relate to a *method* of making numerous antibodies as opposed to the *products* recited in the Challenged Claims. *See In re Kubin*, 561 F.3d 1351, 1356 (Fed. Cir. 2009) ("the obviousness inquiry requires this court to review the Board's decision that the claimed sequence, not appellants' unclaimed cloning technique, is obvious").

These properties were also not unexpected based on the teachings of the prior art. The '213 patent, for example, recognizes with respect to affinity that residues important for maintaining CDR conformation and binding were well known prior to June 1991. (*See* Exs. 1001 at 2:63–3:8; 1003 ¶¶110–6, 280, 347–348; 1190 ¶347-48) In addition, Drs. Foote and Athwal observe that a modest increase in binding affinity (which is all claim 65 requires) was not unexpected given the prior art. (Ex. 1003 ¶¶248–250, 307–308; 1190 ¶249-51, 307-08) Indeed, Queen 1990 taught that an increase in affinity would have been expected. (Exs. 1050 at 6:26–28 ("[A]ffinity levels can vary…and may be within about 4-fold of the donor immunoglobulin's original affinity to the antigen.")

Successful antibody humanization was readily achievable, not surprising or unexpected, as of the earliest priority date of the '213 patent. (Exs. 1003 ¶¶350–51; 1004 ¶¶38–45, 68–70; 1190 ¶¶350-51; 1191 ¶¶37-44)

2. The ’213 patent did not satisfy a long-felt, but unmet need

There was no long-felt but unmet need for humanized mouse monoclonal antibody 4D5. First, the full scope of the Challenged Claims exceeds antibody 4D5. Further, if 4D5 satisfied any need, the mouse monoclonal antibody 4D5 disclosures, which claimed and disclosed the original mouse monoclonal antibody, satisfied it. (*See*, *e.g.*, Exs. 1096; 1003 ¶352; 1190 ¶352)

Patent Owner cannot even show the purported invention solved the problem that the specification identified. *See*, *e.g.*, *Norgren Inc. v. ITC*, 699 F.3d 1317, 1324 n.12 (Fed. Cir. 2012) (patent obvious where “[prior art patent] solved similar problems in a similar way.”). The purported problem, according to the ’213 patent, was that “[m]ethods are needed for rationalizing the selection of sites for substitution in preparing [humanized] antibodies,” and applicants claimed their invention could provide methods “for the preparation of antibodies that are less antigenic in humans…but have desired antigen binding.” (Ex. 1001 at 3:53–55, 4:24–35) Queen 1990 and others had already described exactly this process—they set forth why one would desire to humanize and provided detailed roadmaps on how to achieve it. Any problems identified in the ’213 specification had already been solved and addressed by the prior art. (Exs. 1003 ¶¶350–52; 1190 ¶¶350-52)

3. There is no nexus between the commercial success of Genentech drugs and the Challenged Claims of the '213 patent

For evidence of secondary considerations "to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the *claimed invention*." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (emphasis in original) (quoting *In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995)) Indeed, "evidence of commercial success is 'only significant if there is a nexus between the claimed invention and the commercial success.'" *Endo Pharms., Inc. v. Depomed, Inc.*, IPR2014-00652, Paper 38 at 35 (PTAB Sept. 16, 2015) (Final Written Decision) (citing *Ormco Corp. v. Align Tech., Inc.* 463 F.3d 1299, 1311-12 (Fed. Cir. 2006); *see also Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015) (requiring a "nexus" between the alleged unexpected results and the "merits of the claimed invention").

Any commercial success of drugs Genentech sells is not a direct result of the Challenged Claims. Indeed, important features of these drugs are not recited in the Challenged Claims, only three of which include more than a single residue substitution. As an example, Genentech's marketed drug Herceptin® has heavy chain residue substitutions at seven positions: 71H, 73H, 78H, 93H, 55L, 66L, and 102L. None of the Challenged Claims recite substitutions at these seven positions. In fact, positions 55L and 102L do not even appear in the '213 patent. Genentech

will be unable to show that the claimed features resulted in the commercial success of Herceptin®.

Moreover, any alleged commercial success of Genentech's drugs is not commensurate with the full scope of the Challenged Claims because they are not limited to any particular antibody or even any particular class of antibodies. (Ex. 1003 ¶353; 1190 ¶353) Even claim 30—which recites that the antibody binds $p185^{HER2}$—is exceptionally broad and not limited to any specific anti-$p185^{HER2}$ antibodies.

X. CONCLUSION

For the foregoing reasons, Bioepis respectfully requests cancellation of claims 1, 2, 4, 12, 25, 29-31, 33, 42, 60, 62-67, 69, 71-81 of the '213 patent.

Date: September 29, 2017

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. 42.24(d)

Pursuant to 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(d), I hereby certify that the number of words in this Petition is 13,732, excluding the Table of Contents, the Table of Authorities, the Mandatory Notices under § 42.8, Certificate of Service, Certificate of Word Count, signature block, and appendix listing of exhibits.

Date: September 29, 2017

Signed,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6 and 42.105, I hereby certify that on this 29th day of September, 2017, the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,507,213 and accompanying exhibits referenced therein were served via PRIORITY MAIL EXPRESS® for single-day overnight delivery on the Patent Owner at the following correspondence address of record in PAIR:

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The foregoing Petition and accompanying exhibits referenced therein were also served on this 29th day of September, 2017 via PRIORITY MAIL EXPRESS® for single-day overnight delivery on the Patent Owner at an address known to the Petitioner as likely to affect service.

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