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.: IPR2017-02139

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 anticipated and/or obvious over the prior art.

For the sake of completeness and efficiency, the present petition is a practical copy of the petition in IPR2017-01488. A Motion for Joinder with IPR2017-01488 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
Dimitrios T. Drivas White & Case LLP 1221 Avenue of the Americas New York, New York 10020 Tel: (212) 819-8200 Fax: (212) 354-8113 ddrivas@whitecase.com USPTO Reg. No. 32,218	Scott T. Weingaertner White & Case LLP 1221 Avenue of the Americas New York, New York 10020 Tel: (212) 819-8200 Fax: (212) 354-8113 scott.weingaertner@whitecase.com USPTO Reg. No. 37,756

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 with 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. § 102 and/or 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 IPR2017-01488. 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 IPR2016-01488, 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 IPR2017-01488, 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, 25, 29, 63, 66, 67, 71, 72, 75, 76, 80, and 81 are anticipated by Kurrle
2	Claims 1, 2, 4, 29, 62, 63, 64, 80, and 81 are anticipated by Queen 1990
3	Claims 1, 2, 4, 25, 29, 62-64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81 are obvious over Kurrle and Queen 1990
4	Claim 12 is obvious over Kurrle and Queen 1990 in view of Furey
5	Claims 73 and 77 are obvious over Kurrle and Queen 1990 in view of Chothia & Lesk
6	Claim 74 is obvious over Kurrle and Queen 1990 in view of Chothia 1985
7	Claims 79 and 65 are obvious over Kurrle and Queen 1990 in view of Chothia & Lesk and Chothia 1985
8	Claims 30, 31, 33, and 42 are obvious over Queen 1990 in view of Hudziak
9	Claim 42 is obvious over Queen 1990 in view of Hudziak and Furey
10	Claim 60 is obvious over Queen 1990 in view of Chothia & Lesk 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

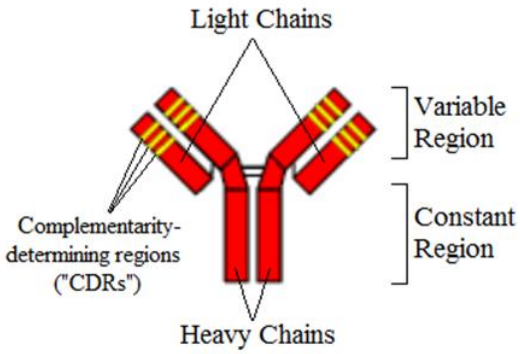
¶¶29–32; 1004 ¶¶30–33; 1190 ¶¶29-32; 1191 ¶¶29-32) Such a person would have the educational background above with experience in common laboratory techniques in molecular biology. (*Id.*) Such experience can include three dimensional computer modeling of protein structures, domain and sequence manipulation 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

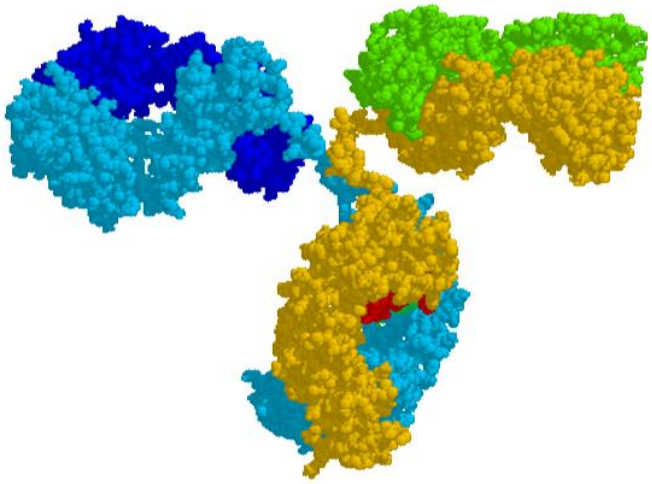
A. Antibodies and Humanization

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 antibodies 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. Kurrle

EP 0 403 156 A1 ("Kurrle") (Ex. 1071) published on December 19, 1990, and is therefore prior art to the '213 patent under at least 35 U.S.C. § 102(a).

Kurrle described the humanization of a mouse monoclonal antibody, called BMA 031, which bound the human alpha/beta T-cell receptor. (*Id.* at Abstract, 8:8-8:31) Kurrle taught skilled artisans that refining the framework region was important. In particular, Kurrle taught skilled artisans to ensure that "amino acids necessary for antigen binding are maintained murine" while the remainder of the framework takes the identity of a human framework region. (*Id.* at 3:9-10) Residues that may remain murine include those adjacent to the CDRs. Kurrle taught:

> A refinement to this basic civilized version can advantageously be made in the sequence immediately before and after the CDRs. The CDRs are assigned based on sequence homology data. Molecular models of antibodies have shown that the actual CDR loops can contain amino acids up to 4 amino acids away from the 'Kabat' CDRs. Therefore, maintaining at least

> the major amino acid differences (in size or charge) within 4 amino acids of the CDRs as murine may be beneficial.

(*Id.* at 8:27-29) (internal citations omitted) Thus, Kurrle taught a skilled artisan to make "essentially a human antibody with a much lower immunogenicity in patients." (*Id.* at 3:10-12)

Kurrle further taught that complex computer modeling to determine which framework residues to substitute as murine was unnecessary; simplified computer models "based on sequence homology to other antibodies with solved structures" could be used in the development of humanized antibodies. (*Id.* at 8:33-34) Such models were useful "to judge proximity of framework amino acids to the CDRs." (*Id.* at 8:34-35)

Kurrle made four humanized antibodies: CIV-1, CIV-2, CIV-3, and CIV-4. (*See id.* at 25-26, Tables 6A and 6B) In each, Kurrle substituted certain framework residues with non-human, *i.e.*, murine, residues. In humanized antibody CIV-4, for example, Kurrle substituted residues 27H, 28H, 30H, 38H, 40H, 48H, 66H, 67H, 69H, 71H, 73H, 76H, 83H, 89H, 90H, 91H, and 94H in the heavy chain and 1L, 3L, 4L, 42L, 46L, 47L, 48L, 50L, 70L, 71L, 72L, 80L, and 81L in the light chain, when using Kabat numbering. (*See id.*) Residues 4L, 69H, 71H, 73H, and 76H are among the residues recited in the Challenged Claims.

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. Furey

W. Furey Jr., *et al., Structure of a Novel Bence-Jones Protein (Rhe) Fragment at 1.6 Å Resolution*, 167 J. Mol. Biol 661-692 (1983) ("Furey") (Ex.

1125) published in 1983, and is therefore prior art to the '213 patent under 35 U.S.C. § 102(b).

Furey taught the structural importance of framework residues that established tight hydrogen bonding with residues in the CDRs, including at position 66L in the light chain variable domain, which maintains CDR2 conformation, and forms a hydrogen bond with CDR residue 52L.

TABLE 4

Side chain–side chain hydrogen bonds

Donor	Acceptor	*d* D–A (Å)	D–H–A (°)	C–O–H (°)
Q6NE2	T105OG1	3·005	174	114
R17NH2	S77OG	3·166	152	171
T27OG1	S25OG	3·209	155	140
T27OG1	N93OD1	3·148	164	99
N32ND2	D94OD2	3·115	178	102
R62NH1	D83OD1	2·830	174	123
R62NH2	D83OD2	2·994	169	121
K67NZ	N52OD1	2·912	172	103
N93ND2	D28OD1	2·858	169	119
S95OG	N93OD1	2·682	172	123
Q112NE2	E84OE2	3·254	156	96
Mean		3·016	167	119
Standard deviation		0·181	9	22

(*See id.* at Table 4 (residue 67 is residue 66L when using Kabat numbering)) Furey therefore taught that residue 66L, as a residue that interacted with the CDRs, was a potential candidate for substitution with a non-human residue.

4. Chothia & Lesk

C. Chothia & A. Lesk, *Canonical Structures for the Hypervariable Regions of Immunoglobulins*, 196 J. Mol. Biol. 901-917 (1987) ("Chothia & Lesk") (Ex. 1062) published in 1987, and is therefore prior art to the '213 patent under 35 U.S.C. § 102(b).

Chothia & Lesk taught that certain framework residues were important for maintaining antibody structure. Chothia & Lesk disclosed that "[t]he major determinants of the tertiary structure of the framework are the residues buried within and between the [V_L and V_H] domains." (*Id.* at 4) Chothia & Lesk summarized these findings in Table 4:

Table 4

Residues commonly buried within V_L and V_H domains

V_L domains			V_H domains		
Position	Residues in known structures	A.S.A.[a] (Å^2)	Position	Residues in known structures	A.S.A.[a] (Å^2)
4	L,M	6	4	L	14
6	Q	12	6	Q,E	16
19	V	11	18	L	21
21	I,M	1	20	L	0
23	C	0	22	C	0
25	G,A,S	13	24	S,V,T,A	8
33	V,L	3	34	M,Y	4
35	W	0	36	W	0
37	Q	30	38	R	13
47	L,I,W	8	48	I,V	1
48	I	24	49	A,G	0
62	F	11	51	I,V,S	4
64	G,A	13	69	I,V,M	13
71	A,F,Y	2	78	L,F	0
73	L,F	0	80	L	0
75	I,V	0	82	M,L	0
82	D	4	86	D	2
84	A,S	11	88	A,G	3
86	Y	0	90	Y	0
88	C	0	92	C	0
90	A,S,Q,N	7	104	G	11
97	V,T,G	18	106	G	19
99	G	3	107	T,S	17
101	G	11	109	V	2
102	T	1			
104	L,V	2			

[a] Mean accessible surface area (A.S.A.) of the residues in the Fab structures NEWM, MCPC603, KOL and J539 and in the V_L structures REI and RHE.

(*Id.* at 7) (red boxes added) These residues help maintain tertiary structure of the framework and overlap with important CDR contact residues disclosed in other prior art and with known highly conserved residues. Such residues suitable for substitution include, *inter alia*, residues 4L, 62L, 73L, 4H, 36H, 69H, 78H, and 92H which are claimed in the ’213 patent.

5. Chothia

C. Chothia, *et al.*, *Domain Association in Immunoglobulin Molecules*, 186 J. Mol. Biol. 651-663 (1985) ("Chothia 1985") (Ex. 1063) published in 1985, and is therefore prior art to the '213 patent under 35 U.S.C. § 102(b). Chothia 1985 teaches certain "buried" framework residues involved in the "packing of the VL and VH β-sheets in the conserved 'framework' . . ." (*Id.* at Abstract) Chothia 1985 explains:

> When the VL and VH domains pack together, residues from these edge strands form the central part of the interface and give what we call a three-layer packing: i.e. there is a third layer composed of side-chains inserted between the two backbone side-chain layers that are usually in contact. This three-layer packing is different from previously described β-sheet packings. The 12 residues that form the central part of the three observed VL-VH packings are absolutely or very strongly conserved in all immunoglobulin sequences.

(*Id.*) One such important "buried" residue – and thus a candidate for substitution – is claimed residue 93H. (*Id.* at 660)

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 by 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 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. *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, however, 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).

Queen 1990 described the importance of substituting non-human residues in the framework regions near the CDRs. (*See* Ex. 1050). Kurrle applied similar logic and created a number of humanized antibodies with such substitutions, including one called CIV-4. (*See* Ex. 1071 at 25-26, Tables 6A and 6B) Both references teach that humanized antibodies will maintain – or improve upon – the affinity of the parent, non-human antibody and will display reduced immunogenicity. Furey, Chothia & Lesk, and Chothia 1985 complement the teaching of Queen 1990 and Kurrle by citing additional framework residues of

particular interest for substitution. Hudziak provided a motivation to skilled artisans to create anti-p185^{HER2} humanized antibodies. In light of this prior art, the Challenged Claims are unpatentable as anticipated and/or obvious.

A. Ground 1: Kurrle anticipates claims 1, 2, 25, 29, 63, 66, 67, 71, 72, 75, 76, 80, and 81

1. Independent claim 1 and dependent claims 2, 25, and 29

Independent claim 1 recites "[a] humanized antibody variable domain comprising," the elements (1) "non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen incorporated into a human antibody variable domain," and (2) FR substitutions 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."

The "humanized antibody variable domain" element is disclosed in Kurrle, which taught "humanised and civilised versions of [mouse monoclonal] antibodies." (Exs. 1071 at 1, Abstract; 1003 ¶¶155-56; 1190 ¶¶156-57) Kurrle also disclosed "non-human Complementarity Determining Region (CDR) amino acid residues which bind an antigen" and "a Framework Region (FR) amino acid substitution" incorporated into a human antibody variable domain, referring to the "civilised" antibodies as those where "[o]nly the *complementarity determining regions* and *selected framework amino acids* necessary for antigen binding are

maintained *murine*." (Exs. 1071 at 3:9–10 (emphasis added); 1003 ¶¶156–58; 1190 ¶¶157-59)

Further, Kurrle substituted several corresponding murine amino acids for human framework residues under Kabat's numbering system, including 4L and 69H, as found in claim 1. (*See* Ex. 1071 at 25–26, Tables 6A and 6B; Ex. 1003 ¶¶155–58, Exhibit B; Ex. 1190 ¶156-59) Claim 1 is anticipated.

Claim 2 depends on claim 1, and 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 precisely what Kurrle did. (*See* Ex. 1071 at 8:45–47 ("In one position…the human consensus sequence is the same as [in the mouse sequence]. One could rationalize changing [the human acceptor antibody residue] back to [mouse], so this change was incorporated…")) This is a basic step in the humanization process taught by Kurrle. (*See* Exs. 1003 ¶159; 1190 ¶160) Claim 2 is also anticipated.

Claim 25 depends on claim 1, and recites "wherein the residue at site 69H has been substituted." Because framework residue 69H was substituted with the murine residue in Kurrle's humanized anti-T-cell receptor antibody, (*see supra* §IX.A.1), Kurrle anticipates claim 25. (Exs. 1003 ¶160; 1190 ¶161)

Claim 29 depends on claim 1, and recites "[a]n antibody comprising the humanized variable domain of claim 1." Kurrle created an antibody comprising

the humanized variable domain: "The resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients." (Ex. 1071 at 3:11–12; *see also* 2:2–4; Ex. 1003 ¶161; 1190 ¶162) Kurrle anticipates Claim 29.

2. Independent claim 63

Independent claim 63 is drawn to an antibody with structural components substantially identical to those of claim 29, *i.e.*, the same "humanized antibody" incorporating the same claimed non-human CDRs and completely overlapping substituted framework residues as in claim 1. (*See supra* § IX.A.1) Accordingly, because the structural components are the same, the same function (*i.e.*, "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") is also present. *See Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) ("'[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.'"). (Exs. 1003 ¶¶162–66; 1190 ¶¶163-65)

Not only is lacking immunogenicity compared to a non-human parent an inherent aspect of the claimed humanized antibodies, this is explicitly stated in Kurrle. (*See* Exs. 1071 at 3:8–12 ("A further refinement involves humanization of

the variable regions…the resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients."); 1003 ¶¶162–63; 1190 ¶¶163-64) One of ordinary skill in the art would thus know that Kurrle's humanized antibodies would "lack immunogenicity compared to a non-human parent antibody upon repeated administration…" Claim 63 is anticipated.

3. Independent claim 66 and dependent claims 67, 71, 72, 75, 76, and 78

Independent claim 66 shares elements with claims 1 and 63, which are met by Kurrle as demonstrated above. (*See supra* §§ IX.A.1 & 2; Exs. 1003 ¶¶165–66; 1190 ¶¶166-67) Claim 66 requires an "amino acid substitution at a site selected from the group consisting of: 24H, 73H, 76H, 78H, and 93H," under Kabat's numbering system. As Kurrle substituted residues 73H and 76H, (Exs. 1003D; Exs. 1003 ¶¶165–66; 1190 ¶¶166-67), it anticipates claim 66.

Claim 67 depends from claim 66 and recites "wherein the substituted residue is the residue found at the corresponding location of the nonhuman antibody from which the non-human CDR amino acid residues are obtained." Kurrle taught this limitation. (*See* Ex. 1071 at 8:45–47 ("In one position…the human consensus sequence is the same as [in the mouse sequence]. One could rationalize changing [the human acceptor antibody residue] back to [mouse], so this change was incorporated…"); *see also* § IX.A.1 (claim 2); Exs. 1003 ¶167; 1190 ¶168)

Dependent ***claims 71, 72, 75 and 76*** recite the humanized variable domain of claim 66 "wherein the residue at site 73H has been substituted" (*claim 71*), "wherein the residue at site 76H has been substituted" (*claim 72*), "which further comprises an amino acid substitution at site 71H" (*claim 75*), and "which further comprises amino acid substitutions at sites 71H and 73H" (*claim 76*). Kurrle substituted amino acid residues 71H, 73H and 76H in their humanized anti-T-cell receptor monoclonal antibody. (*See* Exs. 1071 at 26, Table 6B; 1003D; 1003 ¶168; 1190 ¶169) Accordingly, and in view of the discussion for claims 1 and 66, (*see supra* §§ IX.A.1 & 2; Exs. 1003 ¶¶155–58, 168; 1190 ¶¶156-59, 169), Kurrle anticipates claims 71, 72, 75 and 76.

4. Independent claim 80 and dependent claim 81

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." Claim 80 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…" Claim 80 then recites "the substituted FR residue is 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, 24H, 36H, 39H, 43H, 45H, 69H, 70H, 73H, 74H, 76H, 78H, 92H and 93H, utilizing the numbering system set forth in Kabat." As discussed above, Kurrle substituted residues 4L, 69H, 73H and 76H. **(***See supra* §§ IX.A.1 & 2)

The additional recited elements, which are noted functions of the substituted residues, do not add anything new to the claim. (*See supra* § IX.A.2 (claim 63); Exs. 1003 ¶¶162–164; 1190 ¶¶163-65) S*ee also Atlas Powder Co.*, 190 F.3d at 1347. Even if the inherency of these functions were discounted (they should not be), Kurrle teaches interaction of the framework residues with the CDR as a reason for substitutability. (*See* Exs. 1071 at 8:28–29, 32–40 (use of a "simplified computer model" to determine whether or not FR residues were close enough to CDRs to influence binding); 1003 ¶¶169–171; 1190 ¶¶170-72) Accordingly, Kurrle at least teaches substitution of a framework residue that "interacts with a CDR," *i.e.*, limitation "(b)" from claim 80, and therefore anticipates claim 80.

Claim 81 depends on claim 80, and further recites, "wherein the substituted residue is the residue found at the corresponding location of the nonhuman antibody from which the non-human CDR amino acid residues are obtained." As discussed above, this is taught by Kurrle. (*See supra* § IX.A.1 (claim 2); Exs. 1071 at 25–26, Tables 6A and 6B; 1003 ¶¶162–64, 172; 1190 ¶¶163-65, 173) Kurrle anticipates claim 81.

B. Ground 2: Queen 1990 anticipates claims 1, 2, 4, 29, 62, 63, 64, 80, and 81

1. Independent claim 1 and dependent claims 2, 4, and 29

The first part of claim 1, "[a] humanized antibody variable domain," is disclosed in Queen 1990. Queen 1990 disclosed creating "a humanized antibody variable domain" by not only swapping CDRs, but also manipulating the framework region of the variable domain, as claim 1 of the '213 patent recites. Queen provided "novel methods for designing humanized immunoglobulins having one or more complementarity determining regions (CDR's) from a donor immunoglobulin and a framework region from a human immunoglobulin . . ." (Exs. 1050 at 1, Abstract; 1003 ¶174; 1190 ¶175)

Queen 1990 further provided a detailed roadmap with specific criteria that could be used in making humanized immunoglobulins. (Exs. 1050 at 12:11–12; 1003 ¶¶173–183; 1190 ¶¶174-184) For example, Queen 1990 emphasized the importance of framework positions adjacent to the CDR: "Each humanized immunoglobulin chain may comprise about 3 or more amino acids from the donor immunoglobulin in addition to the CDR's, *usually at least one of which is immediately adjacent to a CDR in the donor immunoglobulin*…" (Ex. 1050 at 1, Abstract) A skilled artisan could have readily envisioned such locations. (*See* Exs. 1003 ¶¶177–79; 1190 ¶¶178-79)

Queen 1990 encapsulated this rule in Criterion III, which states:

> *In the positions immediately adjacent to one or more of the 3 CDR's in the humanized immunoglobulin chain, the donor [mouse] amino acid(s) rather than acceptor [human] amino acid may be selected.* These amino acids are particularly likely to interact with the amino acids in the CDR's and…[m]oreover, 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.

(Exs. 1050 at 14:1–12 (citations omitted); 1003 ¶178; 1190 ¶179)

Dr. Foote, in connection with IPR2017-01488, and Dr. Athwal explained that "one of ordinary skill in the art at the time of the '213 patent…would have readily understood that Queen 1990 (specifically Criterion III) explicitly taught the substitution of framework sites immediately adjacent to CDRs." (Exs. 1003 ¶179; 1190 ¶180) Using the numbering system set forth by Kabat 1987, claimed framework residues 98L and 36H are "immediately adjacent" to CDRs. (*See* Exs. 1003 ¶¶173–83; 1190 ¶¶174-84)

Thus, Queen 1990's teaching to substitute CDR-adjacent framework region amino acid positions would inevitably include substitutions at claimed amino acid residues 98L and 36H. Queen 1990 thus anticipates claim 1.

Claim 2 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," which is also disclosed by Queen 1990. (*See* Exs. 1050 at 5:36–6:2 ("substitutions of a human framework amino acid of the acceptor (*i.e.*, human) immunoglobulin with a corresponding amino acid from a donor (*i.e.*, non-human) immunoglobulin"); 1003 ¶184; 1190 ¶185) Queen 1990 anticipates claim 2.

Claim 4 further recites "wherein the human antibody variable domain is a consensus human variable domain." Queen 1990 expressly teaches this by disclosing in Criterion I that "[a]s acceptor…use a *consensus framework* from many human antibodies." (*See* Exs. 1050 at 12:17–20 (Criterion I); 1003 ¶¶132, 184; 1190 ¶185) Queen 1990 anticipates claim 4.

Claim 29 further recites "[a]n antibody comprising the humanized variable domain of claim 1." As Drs. Foote and Athwal explain, the goal of antibody humanization programs was to create antibodies with humanized variable domains. (*See, e.g.*, Exs. 1050 at 4:21–25 ("mouse complementarity determining regions, with or without additional naturally-associated mouse amino acid residues, can be used to produce human-like antibodies…"); 1003 ¶186; 1190 ¶187) A skilled artisan would thus recognize that Queen 1990 teaches creating therapeutic-quality antibodies with a humanized variable domain in order to maintain a high level of

binding and affinity. (Exs. 1003 ¶186; 1190 ¶187) Queen 1990 anticipates claim 29.

2. Independent claim 62

Independent Claim 62 is identical to claim 1 except that it requires the amino acid residues "bind an antigen incorporated into a consensus human variable domain" and adds residues 46L, 75H, 76H and 78H to claim l's list of FR substitutable residues list. As discussed above for claim 1, (*see supra* § IX.B.1), Queen 1990 discloses claimed residues 98L and 36H as inevitably requiring substitution. As with claim 1, claim 62 only requires substitution at one of the recited list of residues.

Regarding the "consensus human variable domain," Queen 1990 disclosed in Criterion I that "[a]s acceptor…use *a consensus framework* from many human antibodies." (*See* Exs. 1050 at 12:17–20; 1003 ¶¶187–88; 190 ¶¶188-89 *supra* § IX.B.1) Queen 1990 anticipates claim 62.

3. Independent claim 63

Independent Claim 63 differs from claim 62 by reciting "[a] humanized antibody" (as opposed to claim 62's "humanized antibody variable domain") and by describing the claimed humanized antibody as lacking "immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient."

As above, lacking immunogenicity compared to a non-parent antibody is a non-patentable distinction. (*See* § IX.B.2, citing to *Atlas Powder Co.*, 190 F.3d 1342; Exs. 1003 ¶176; 1190 ¶177) Regardless, Queen 1990 taught: "When combined into an intact antibody, the humanized immunoglobulins of the present invention *will be substantially non-immunogenic* in humans…." (Exs. 1050 at 1, Abstract; 1003 ¶¶189–91; 1190 ¶¶190-92) Further, Queen 1990 taught a humanized antibody. (*Id*.) Claim 63 is also anticipated by Queen 1990.

4. Independent claim 64

Independent Claim 64 recites "[a] humanized variant of a non-human parent antibody which binds an antigen; comprising 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."

Queen 1990 anticipates claim 64. As with claims 1, 4 and 29, Queen 1990 disclosed an antibody incorporating a humanized variable domain with a consensus sequence (*i.e.*, "most frequently occurring amino acid residues at each location in all human immunoglobulins of a human heavy chain immunoglobulin subgroup"). (*See supra* §§ IX.B.1 & 2; Exs. 1003 ¶¶192–94; 1050 at 12:17–20; 1190 ¶¶193-95)

While the remaining limitations are merely inherent functions of the humanized antibody, Queen 1990 disclosed at least functions (a) and (b) above in Criterion III: "immediately adjacent…amino acids are *particularly likely to interact with the amino acids in the CDR's*….Moreover, *the adjacent amino acids may interact directly with the antigen*…." (Exs. 1050 at 14:1-12; 1003 ¶194) Because Queen 1990 teaches to substitute "immediately adjacent" residues 98L and 36H, (*see supra* § IX.B.1), and because Queen 1990 teaches those residues "are particularly likely to interact with the amino acids in the CDR's and…may interact directly with the antigen," Queen 1990 anticipates claim 64. (Exs. 1003 ¶¶192–94; 1190 ¶¶193-95)

5. Independent claim 80 and dependent claim 81

Independent Claim 80 is also anticipated by Queen 1990. As discussed with claims 1 and 64, Criterion III of Queen 1990 explicitly teaches the selection of framework residues immediately adjacent to CDRs for substitution—this would include claimed residues 36H and 98L. (*See supra* §§ IX.B.1 & 4; Exs. 1003E;

1003 ¶¶195–98 (citing Ex. 1050 at 14:4–8); 1190 ¶¶196-99) Queen 1990 explains that "selecting these amino acids from the donor may be desirable to keep all the antigen contacts that provide affinity in the original antibody." (Exs. 1050 at 14:9–12; 1003 ¶196; 1190 ¶197)

Moreover, Criterion IV teaches "interact[ion] with a CDR" by disclosing 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." (Exs. 1050 at 14:15–19; 1003 ¶197; 1190 ¶198) Queen 1990 anticipates Claim 80.

Claim 81 (dependent on claim 80) is also taught by Queen 1990, which disclosed "substitutions of a human framework amino acid of the acceptor (*i.e.*, human) immunoglobulin with a corresponding amino acid from a donor (*i.e.*, nonhuman) immunoglobulin." (*See* Exs. 1050 at 5:36–6:2; 1003 ¶199; 1190 ¶200) Queen 1990 anticipates Claim 81.

C. Ground 3: Claims 1, 2, 4, 25, 29, 62-64, 66, 67, 69, 71, 72, 75, 76, 78, 80, and 81 are obvious over Kurrle and Queen 1990

1. Independent claim 1 and dependent claims 2, 4, 25, and 29

Queen 1990 disclosed a detailed pathway for humanizing non-human monoclonal antibodies, with the expectation that the resulting humanized antibodies "will be substantially non-immunogenic in humans and retain

substantially the same affinity as the donor immunoglobulin to the antigen . . . ," including:

- Criterion I: Choose an acceptor human framework antibody, including one that is "unusually homologous to the donor immunoglobulin to be humanized, or use a consensus framework from many human antibodies." (Exs. 1050 at 12:17–13:20; 1003 ¶¶132, 203; 1190 ¶¶108, 204);
- Criterion II: Once the human antibody is selected, evaluate whether amino acid residues in the framework of the human acceptor antibody are "rare" amongst human antibodies. If the residue is "rare" and the donor [mouse] antibody is more "typical for human sequences," choose the donor residue. Criterion II "helps ensure that an atypical amino acid in the human framework does not disrupt the antibody structure" (Exs. 1050 at 13:22–37; 1003 ¶¶133–34, 203; 1190 ¶¶109-10, 204);
- Criterion III: "In the positions immediately adjacent to the 3 CDR's in the humanized immunoglobulin chain, the donor [mouse] amino acid rather than acceptor [human] amino acid may be selected." (Exs. 1050 at 14:1–12; Exs. 1003 ¶¶135, 203; 1190 ¶¶111, 204); and
- Criterion IV: Generate a 3-dimensional model of the original donor antibody, and select amino acid positions where:

> [C]ertain 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….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.

(Exs. 1050 at 14:14–15:2; 1003 ¶¶136, 203; 1190 ¶¶112, 204)

Queen 1990 concludes that when the humanized variable regions are "combined into an intact antibody, the humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen…" (Exs. 1050 at 6:21–26; 1003 ¶204; 1190 ¶205) Queen 1990 thus provided motivation to humanize monoclonal antibodies along with a detailed roadmap for production of humanized monoclonal antibodies. (Exs. 1003 ¶¶203–04; 1190 ¶¶204-05)

Kurrle employed a similar roadmap to obtain a "humanized antibody variable domain" as claimed in claim 1, including the steps of: choosing the most similar human acceptor sequence (Criterion I of Queen 1990, Ex. 1050 at 12:17–13:21; *see* Ex. 1071 at 8:16–18); accounting for the adjacent residue rules of

Queen 1990 (Criterion III of Queen 1990, Ex. 1050 at 14:1–12; *see* Ex. 1071 at 8:25–31); substituting CDR-contact residues using computer models based on solved structures (Criterion IV of Queen 1990, Ex. 1050 at 14:16–15:2; *see* Ex. 1071 at 8:32–36); and substituting "rare" amino acids in the human acceptor framework for "common" (consensus) amino acid residues (Criterion II of Queen 1990, Ex. 1050 at 13:22–37; *see* Ex. 1071 at 8:36–40). (Exs. 1003 ¶¶121–124, 205; 1190 ¶¶97-100, 206)

Using these guidelines, Kurrle made a total of 13 substitutions in the light chain framework region and 18 substitutions in the heavy chain framework region according to the Kabat numbering system, including claimed residues 4L and 69H. (*See supra* §§ VI.B.1 & IX.A.1; Exs. 1003D; 1003 ¶¶155–58, 206; 1190 ¶¶156-60, 207)

A skilled artisan considering Kurrle would have looked to other references disclosing the successful humanization of non-human antibodies, including Queen 1990, in order to gather as much information as they could to guide their selection of specific residues for substitution in order to maintain the affinity and strength of a particular non-human antibody. Kurrle and Queen 1990 were published less than six months apart. (Exs. 1071 at 1; 1050 at 1) International Publication No. WO 92/05274, published on April 2, 1992, lists both references in the International Search Report. (Ex. 1183 at 71, 73) Additionally, the International Search Report

for both Kurrle and Queen 1990 include International Publication No. WO 89/01783 entitled "Recombinant Antibody and Method." (Exs. 1071 at 44; 1050 at 48; 1182 at 1) Given the interrelated teachings of Kurrle and Queen 1990, it would have been obvious to a skilled artisan to have incorporated the teachings of Queen 1990 when humanizing the antibody of Kurrle in order to ensure successful humanization. (Exs. 1003 ¶207; 1190 ¶208)

The combination of Queen 1990 and Kurrle provided ample motivation and a reasonable expectation of success that a humanized monoclonal antibody could be obtained with "a much lower immunogenicity in patients", (Ex. 1071 at 3:11–12), while maintaining the binding affinity and specificity of the donor monoclonal antibody. Claim 1 is obvious over Queen 1990 and Kurrle. (Exs. 1003 ¶¶203–07; 1190 ¶¶204-08)

Claim 2 is also taught by Queen 1990 and Kurrle. As discussed above, claim 2 recites a basic step in humanization, followed by many in the field, including Queen 1990, (Ex. 1050 at 5:36–6:2), and Kurrle, (Ex. 1071 at 8:28–29). (*See supra* §§ IX.A.1 & IX.B.1; Exs. 1003 ¶209; 1190 ¶210) Claim 2 is obvious over Queen 1990 and Kurrle.

Claim 25 recites "wherein the residue at site 69H has been substituted." Residue 69H was substituted in Kurrle's humanized anti-T-cell receptor antibody.

(*See supra* § IX.A.1; Exs. 1003 ¶210; 1190 ¶211) Accordingly, claim 25 is also obvious over Queen 1990 and Kurrle.

Claim 29 recites "[a]n antibody comprising the humanized variable domain of claim 1." Queen 1990 and Kurrle created antibodies comprising a humanized variable domain. (Ex. 1050 at 6:21–26 ("the humanized light and heavy chains of the present invention will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen"); *see also* Exs. 1071 at 3:26–28, 2:2–4; 1003 ¶211; 1190 ¶212) Claim 29 is also obvious over Queen 1990 and Kurrle.

Claim 4 further recites: "wherein the human antibody variable domain is a consensus human variable domain." Queen 1990 teaches the use of a human consensus variable domain as the human acceptor framework antibody, (*see* Ex. 1050 at 12:17–20 ("As acceptor…use a consensus framework from many human antibodies.")), which would have motivated a skilled artisan to use the human "acceptor" framework together with the humanization methods of Kurrle. (Exs. 1003 ¶¶132, 212; 1190 ¶¶108, 213) Claim 4 is also obvious over Queen 1990 and Kurrle.

2. Independent claim 62

As discussed above, claim 62 differs from claim 1 by adding that the human variable domain is a "consensus human variable domain." (*See supra* § VIII.C.1)

Queen 1990 discloses the use of a consensus human variable domain in Criterion I. (Exs. 1050 at 12:17–20 ("As acceptor…use *a consensus framework* from many human antibodies."); 1003 ¶¶213–14; 1190 ¶¶214-15) As discussed above, this would have motivated a skilled artisan to use the human "acceptor" framework together with the humanization methods of Kurrle. (*See supra* § IX.C.1) Queen 1990 and Kurrle provided both the motivation and a reasonable expectation of success to make and use the remaining limitations, including substituting at claimed positions 98L and 36H (Ex. 1050; *supra* § IX.C.1) and 4L, 69H and 76H (Ex. 1071; *supra* § IX.B.l). Exs. 1003 ¶214; 1190 ¶215) Claim 62, like claims 1 and 4, (*see supra* § IX.C.1), is obvious over Queen 1990 and Kurrle.

3. Independent claim 63

As discussed above, claim 63 differs from claim 62 by reciting "[a] humanized antibody" and by describing the claimed humanized antibody as lacking "immunogenicity compared to a non-human parent antibody upon repeated administration to a human patient." Both Queen 1990 and Kurrle disclose these features. (*See, e.g.*, Exs. 1050 at 1, Abstract ("the humanized immunoglobulins of the present invention *will be substantially non-immunogenic in humans*…"); 1071 at 3:11–12 ("The resulting mAb of the present invention is thus essentially a human antibody with a much lower immunogenicity in patients."); 1003 ¶¶215-18; 1190 ¶¶216-19) Claim 63 is obvious over Queen 1990 and Kurrle.

4. Independent claim 64

Queen 1990 and Kurrle also disclose the limitations of claim 64. Queen 1990 discloses an antibody incorporating a humanized variable domain comprising a consensus sequence. (*See supra* §§ IX.B.1 & 4; Exs. 1050 at 12:17–20 ("As acceptor…use *a consensus framework* from many human antibodies."); 1003 ¶¶219–22; 1190 ¶¶220-23) Both Queen 1990 and Kurrle also taught humanized antibodies containing a non-human CDR and substituted FR residues. (*See*, *e.g.*, Exs. 1071 at 3:9–11 ("Only the complementarity determing [sic] regions and selected framework amino acids necessary for antigen binding are maintained murine. The remaining framework regions are converted to human sequences."); 1003 ¶219; 1190 ¶220) While the remaining limitations are merely stated functions of the humanized antibody, (*see supra* §§ IX.A.2 & IX.B.4), both Queen 1990 and Kurrle disclosed that certain framework residues were important because of their proximity to neighboring CDRs. (*See* Ex. 1050 at 14:1–12 ("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."); *see also* Exs. 1071 at 8:27–29; 1003 ¶220; 1190 ¶221) Queen 1990 and Kurrle provided the motivation and reasonable expectation of success to make the claimed "humanized variant of a non-human parent antibody." Claim 64 is obvious over Queen 1990 and Kurrle.

5. Independent claim 66 and dependent claims 67, 69, 71, 72, 75, 76, and 78

Regarding independent claim 66, both Queen 1990 and Kurrle disclose the claimed "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," which is also essentially recited in claims 1 and 62. (*See supra* §§ IX.C.1 & 2) Claim 66 further requires a framework substitution of one of residues 24H, 73H, 76H, 78H and 93H. Kurrle, using Queen 1990's roadmap, substituted FR amino acids at claimed positions 73H and 76H, rendering the humanized antibody "essentially a human antibody with a much lower immunogenicity in patients." (Exs. 1071 at 3:11–12; 1003 ¶¶223–24; 1190 ¶¶224-25)

Both Queen 1990 and Kurrle provide the motivation and a reasonable expectation of success to make "a humanized antibody variable domain" as in claim 66. (Exs. 1003 ¶224; 1190 ¶225) Claim 66 is also obvious over Queen 1990 in view of Kurrle.

Claim 67, which depends from claim 66, 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." Both Queen 1990 and Kurrle disclosed this additional limitation. (*See, e.g.*, Exs. 1050 at 5:36–6:2 (disclosing "substitutions of a human framework amino acid of

the acceptor (*i.e.*, human) immunoglobulin with a corresponding amino acid from a donor (*i.e.*, non-human) immunoglobulin."); 1003 ¶225; 1190 ¶226) Claim 67 is also obvious over Queen 1990 and Kurrle.

Claim 69 is dependent on claim 66, and further recites "the human antibody variable domain is a consensus human variable domain." Queen 1990 teaches using a consensus sequence as the human acceptor framework antibody. (Exs. 1050 at 12:17–20; 1003 ¶228; 1190 ¶229) As discussed above, this would have motivated a skilled artisan to use the human "acceptor" framework together with the humanization methods of Kurrle. (*See supra* § IX.C.1) Claim 69 is also obvious over Queen 1990 and Kurrle.

Claims 71, 72, 75 and 76 recite "wherein the residue at site 73H has been substituted" (***claim 71***), "wherein the residue at site 76H has been substituted" (***claim 72***) "which further comprises an amino acid substitution at site 71H" (***claim 75***), and "which further comprises amino acid substitutions at sites 71H and 73H" (***claim 76***). Kurrle substituted the murine amino acid residues at claimed positions **71H**, **73H** and **76H**. (Exs. 1003 ¶226; 1190 ¶227) Thus, claims 71, 72, 75 and 76 are also obvious over Queen 1990 in view of Kurrle.

Claim 78 recites an antibody "comprising the humanized variable domain of claim 66." The goal of humanization, including Queen 1990 and Kurrle was to create a therapeutic antibody comprising a humanized variable domain: "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 immunoglobulin to the antigen." (*See* Exs. 1050 at 6:21–26; 1071 at 3:26–28; 1003 ¶227; 1190 ¶228) Indeed, both Queen 1990 and Kurrle created humanized antibodies. Claim 78 is obvious over Queen 1990 and Kurrle.

6. Independent claim 80 and dependent claim 81

Claim 80 recites the same "humanized antibody variable domain" as claim 1 (*i.e.*, "comprising non-human CDR amino acid residues which bind an antigen…and further comprising a Framework Region (FR) amino acid substitution" at residues which completely overlap with claim 1). Like claim 64, claim 80 further recites functional aspects of the humanized antibody, including: (a) noncovalently binds antigen directly; (b) interacts with a CDR; or (c) participates in the VL-VH interface . . ." (Exs. 1003 ¶¶169–171, 229–231, 219–222; 1190 ¶¶170-72, 230-32, 220-23)

The additional recited elements, which are functions of the substituted residues, do not add anything new to the claim. (*See supra* § IX.C.4 (claim 64); Exs. 1003 ¶219; 1190 ¶220) S*ee Atlas Powder Co.*, 190 F.3d at 1347. Even assuming one could discount the inherency of these functions (which Bioepis disagrees with), both Queen 1990 and Kurrle teach interaction of the framework

residues with the CDR as a reason for substitution. (*See* Exs. 1050 at 14:4–8; 1071 at 8:28–29, 32–40; 1003 ¶¶229–231; 1190 ¶¶230-32) For the same reasons as claims 1 and 64 above, (*see supra* §§ IX.C.1 & 4), including the disclosure of framework region substitutions at 4L, 69H, 73H and 76H (*see supra* §§ IX.A.1, IX.A.2, & IX.C.1), as provided by Kurrle, as well as the explicit motivation and reasonable expectation of success provided by both Queen 1990 and Kurrle (*see supra* §§ IX.A.1 & IX.B.l), claim 80 of the '213 patent is obvious over Queen 1990 and Kurrle.

Claim 81 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." Both Queen 1990 and Kurrle teach this. (*See* Exs. 1050 at 6:21–26; 1071 at 3:26–28; 1003 ¶232; 1190 ¶233) Claim 81 is also obvious over Queen 1990 and Kurrle.

D. Ground 4: Claim 12 is obvious over Queen 1990 and Kurrle in view of Furey

When humanizing an antibody, a skilled artisan would have been motivated to identify residues important for antibody binding, *e.g.*, CDR contact residues and residues involved in V_L-V_H interaction. (Exs. 1003 ¶¶108-09, 233–234; 1190 ¶¶84-85, 234-35)

Claim 12, which depends on claim 1, recites "wherein the residue at site 66L has been substituted." Furey disclosed the importance of residue 66L in

maintaining antigen binding and specificity. (*See* Exs. 1125 at 3, Abstract; 1003 ¶¶233–235; 1190 ¶¶234-36) Specifically, Furey identified 66L as interacting with CDR2 of the light chain. (Exs. 1125 at 16, Table 4; 1003 ¶234; 1190 ¶235)

This directly ties to Queen 1990's and Kurrle's teachings, which provided a skilled artisan the motivation and reasonable expectation of success to substitute framework region positions that are close enough to interact directly with antigen, as Furey identified with residue 66L, which a skilled artisan would have understood as being on a list of substitutable residues in order to maintain antigen binding and specificity. (*See* Exs. 1125 at 16, Table 4; 1003 ¶234; 1190 ¶235) A skilled artisan looking to humanize an antibody according to the teachings of Queen 1990 and Kurrle (including identifying residues close enough to interact with antigen) would have looked to Furey because it disclosed residues that are close enough to interact directly with antigen. Claim 12 is thus obvious over Queen 1990 and Kurrle, and further in view of Furey.

E. Grounds 5-7: Claims 73, 74, 77, 79, and 65 are obvious over Queen 1990 and Kurrle in view of Chothia & Lesk and Chothia 1985

1. Ground 5: Dependent claims 73 and 77

Claims 73 and 77, which both depend on claim 66, recite "wherein the residue at site 78H has been substituted" (*claim 73*), and "which further comprises amino acid substitutions at sites 71H, 73H and 78H (*claim 77*). As discussed

above, claim 66 is obvious in view of Queen 1990 and Kurrle. (*See supra* § IX.C.5) Further, Chothia & Lesk and Queen 1990 taught residue 78H was already known as important for maintaining antibody conformation, and thus antigen binding and specificity. (*See* Exs. 1062 at 3, Abstract; 1003 ¶236; 1190 ¶237) Chothia & Lesk found that "[t]he major determinants of the tertiary structure of the framework are the residues buried within and between the [V_L and V_H] domains," including residue 78H. (Exs. 1062 at 5, 8, Table 4; 1003 ¶¶237–38; 1190 ¶¶238-39)

The Background of the '213 patent also recognized the importance of Chothia & Lesk's findings. (*See* Ex. 1001 at 3:1–8 (citing to Chothia & Lesk for determining residues "critically affecting the conformation of particular CDRs and thus their contribution to antigen binding.")) The inventors of the '213 patent did not discover the importance of residue 78H for maintaining antigen binding. (Exs. 1003 ¶237; 1190 ¶238)

In view of the known importance of 78H (*i.e.*, the teachings of Queen 1990 and Chothia & Lesk), it would have been obvious for a skilled artisan to have included 78H as a substitutable residue. (Exs. 1003 ¶238; 1190 ¶239) Claim 73 is obvious over Queen 1990, Kurrle, and Chothia & Lesk.

Further, adding residue 78H to the combination of residues 71H and 73H does not confer patentability. (*Id*.) These residues were substituted (71H and 73H)

in Kurrle, or would have been substituted (78H) if necessary. (*Id*.) Claim 77 is also obvious over Queen 1990, Kurrle, and Chothia & Lesk.

2. Ground 6: Dependent claim 74

Claim 74, which also depends on claim 66, recites "wherein the residue at site 93H has been substituted." As discussed above, claim 66 is obvious in view of Queen 1990 and Kurrle. (*See supra* § IX.C.5) Further, Chothia 1985 identified residue 93H as important for maintaining V_L-V_H interactions. (*See* Exs. 1063 at 12, Table 4; 1003 ¶¶239–40; 1190 ¶¶240-41) The inventors of the '213 patent and others recognized the importance of residues that maintain V_L-V_H interface contact. (*See supra* Ex. 1001 at 3:1–8; *see also* Ex. 1050 at 16:1–2 (recognizing the importance of "residues essential for inter-chain interactions")) Thus, Kurrle and Queen 1990 provided the explicit motivation as well as reasonable expectation of success to substitute residue 93H for the non-human (*e.g.*, murine) residue. (Exs. 1003 ¶¶239–40; 1190 ¶¶240-41) Claim 74 is obvious over Queen 1990, Kurrle and Chothia 1985.

3. Ground 7: Independent claim 79 and dependent claim 65

Claim 79 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, utilizing the numbering system set forth in Kabat."

As above, Kurrle already substituted positions 71H and 73H and it would have been obvious to a skilled artisan to have incorporated the teachings of Queen 1990 when humanizing the antibody or Kurrle in order to ensure successful humanization. (*See* Exs. 1071 at 26, Table 6B; 1003 ¶242, 1003D; 1190 ¶243; *supra* § IX.C.1) Chothia 1985 disclosed residue 93H as important for maintaining V_L:V_H interactions. (Exs. 1063 at 12, Table 4; 1003 ¶¶242–243, 243; 1190 ¶¶243-44) Finally, Chothia & Lesk disclosed residue 78H as one specifically and independently important for maintaining antigen binding. (Exs. 1062 at 8, Table 4; 1003 ¶¶242–43; 1190 ¶¶243-44) It would have been obvious to a skilled artisan to have made substitutions at 71H, 73H, 78H and 93H, as taught by Queen 1990, Kurrle, Chothia & Lesk and Chothia 1985. (*See supra* §§ IX.A.3, IX.C.1 & IX.C5; Exs. 1003 ¶¶241–46; 1190 ¶¶242-27) Claim 79 is obvious over Queen 1990 and Kurrle, and further in view of Chothia & Lesk and Chothia 1985.

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 (emphasis added)) 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 § 2144.05. (Exs. 1003 ¶¶247–251; 1190 ¶¶248-52)

Moreover, Drs. Foote and Athwal explain that to a skilled artisan, "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 unexpected that at least a moderate improvement in affinity would be achieved when humanizing some antibodies." (Exs. 1003 ¶308; 1190 ¶308) Drs. Foote and Athwal further explain that "it was not unexpected [that in this process] one could go beyond the parent antibody's original affinity, *i.e.*, an increase in affinity as claimed in claim 65." (Exs. 1003 ¶309; 1190 ¶309) Claim 65 is obvious over Queen 1990 and Kurrle, and further in view of Chothia & Lesk and Chothia 1985.

F. Ground 8: Claims 30, 31, 33, and 42 are obvious over Queen 1990 in view of Hudziak

Independent Claim 30 of the '213 patent recites "[a]n antibody which binds p185*HER2* and comprises a humanized antibody variable domain, wherein the

humanized antibody variable domain comprises non-human Complementarity Determining Region (CDR) amino acid residues which bind $p185^{HER2}$ incorporated into a human antibody variable domain and further comprises a Framework Region (FR) 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." ***Claim 42*** depends from claim 30, and further recites "wherein the residue at site 66L has been substituted."

Claim 30 is similar to claim 1, differing in the recitation that the CDRs (and antibody) also bind to $p185^{HER2}$. Claim 30 also includes additional framework sites for substitution at positions 46L, 75H, and 76H.

Antibody humanization was developed for a single purpose: realizing the "therapeutic promise of monoclonal antibodies for the treatment of human diseases." (Exs. 1003 ¶330; Exs. 1004 ¶¶35–45; 1190 ¶330; 1191 ¶¶34-44) While murine monoclonal antibodies were capable of targeting antigens (*e.g.*, proteins) in a highly specific manner, immunogenicity issues severely limited the applicability of this technology to human therapeutics. (*See* Exs. 1003 ¶330; Exs. 1004 ¶37; 1190 ¶330; 1191 ¶36)

A prime molecular target was HER*2/c-erbB-2*, whose amplification in breast cancer patients was correlated with poor prognosis and high relapse rate. (*See* Exs.

1021 at 8, Abstract; 1004 ¶¶46–69; 1003 ¶¶331–32; 1190 ¶¶331-32; 1191 ¶¶45-68) With respect to the HER*2/c-erbB-2* gene product p185*HER2*, Hudziak reported that:

- p185*HER2* was amplified in about 30% of breast cancer tumors; (Exs. 1021 at 8; 1004 ¶50; 1003 ¶331; 1190 ¶331; 1191 ¶49);
- p185*HER2* "correlated with a negative prognosis and high probability of relapse"; (Exs. 1021 at 8; 1004 ¶50; 1003 ¶331; 1190 ¶331; 1191 ¶49);
- Increased expression of HER-2/*neu* resulted in cellular transformation of the cells and tumorigenesis when the transformed cells were implanted in athymic mice, (Exs. 1021 at 8; 1004 ¶52; 1003 ¶331; 1190 ¶331; 1191 ¶51); and
- High levels of HER-2 gene expression resulted in the cells forming anchorage-independent colonies in soft agar and at low density in low serum concentration, which are characteristics of a transformed phenotype, (Exs. 1021 at 8; 1004 ¶58; 1003 ¶331; 1190 ¶331; 1191 ¶57).

In reviewing Hudziak (Ex. 1021) and other literature, Mr. Buss, in connection with IPR2017-01488, concluded the above findings "strongly suggested that the HER-2/*neu* receptor was a ripe target for therapeutic development." (Exs. 1004 ¶53; 1003 ¶¶331–32, 342; 1190 ¶¶331-32, 342; 1191 ¶52)

Moreover, a skilled artisan would have been motivated to develop a monoclonal antibody therapeutic against p185^{HER2} because of its structural similarity to other growth factor receptors, including epidermal growth factor receptor (EGFR). (*See* Exs. 1004 ¶56; 1003 ¶333; 1190 ¶333; 1191 ¶55) This similarity was demonstrated well prior to June 1991 for 4D5, a well-characterized mouse monoclonal antibody targeting p185*HER2* protein with high affinity, specificity (no cross-reactivity with, for example, EGFR) and efficacy in *in vitro* and *in vivo* studies. (Exs. 1004 ¶58; 1003 ¶334; 1190 ¶334; 1191 ¶57) The investigators concluded that 4D5 provided "new potential for diagnostic approaches and therapeutic strategies for treatment of human malignancies." (Exs. 1047 at 6; 1004 ¶53; 1003 ¶334; 1190 ¶334; 1191 ¶52)

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 ¶334; 1190 ¶334; 1191 ¶69) Hudziak 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 or other molecules which may be directly cytotoxic for tumor cells overexpressing the HER2 protooncogene.

(Exs. 1048 at 12; 1004 ¶68 (emphasis added); 1191 ¶67)

Queen 1990 provided detailed steps for humanizing mouse monoclonal antibodies, such as 4D5, and represented the state of the art of antibody humanization by 1991, teaching humanization of antibody variable domains having non-human CDR amino acid residues that bind to an antigen and are incorporated into a human antibody variable framework domain. (Exs. 1003 ¶¶131–37, 343; 1190 ¶¶107-13, 343)

Further, Queen 1990 disclosed that a skilled artisan would have had a reasonable expectation that such a humanized antibody would be capable of binding to $p185^{HER2}$. (*See* Exs. 1050 at 1, Abstract ("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…"); 1003 ¶343; 1190 ¶343)

Queen 1990, thus, provided the explicit motivation to make framework substitutions that would, for example, be more representative of a human residue (Ex. 1050 at 13:22–37), residues that are "immediately adjacent" to CDRs that "likely [ ] interact with…the CDR's…" (*id.* at 14:1–12), and residues that are "in contact", *i.e.*, within about 3 Å of a CDR (*id.* at 14:14–15:2). (Exs. 1003 ¶¶131–137; 1190 ¶¶107-13)

Hudziak provided explicit motivation to develop 4D5 for therapeutic use, disclosing "monoclonal antibodies specific for p185*HER2* (*e.g.*, 4D5) [as] useful therapeutic agents for the treatment of human neoplasias." (*See* Exs. 1021 at 14; 1003 ¶¶342–45; 1004 ¶63; 1190 ¶¶342-45; 1191 ¶62) A skilled artisan would have recognized that 4D5 required humanization before clinical use. (*See* Exs. 1048 at 12 ("4D5 also serves as a template for antibody engineering efforts to construct humanized versions more suitable for chronic therapy …"); 1003 ¶¶342–43, 334–36; 1004 ¶68; 1190 ¶¶342-43, 334-36; 1191 ¶67) Therefore, it would have been obvious to humanize 4D5 using the guidelines in Queen 1990. As discussed *supra*, in Sections VI.B.2, VI.B.3, and IX.B.1, the particular residues to modify would have included at least 66L, 98L, and 36H, which likewise appear in claims 30 and 42. Claims 30 and 42 are obvious over Queen 1990 and Hudziak.

Claim 31 recites that "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 1990 disclosed this limitation. (*See* Exs. 1050 at 3:36–4:1; 1003 ¶¶131–37, 344; 1190 ¶¶107-13, 344; *supra* § IX.B.1 (claim 2)) Claim 31 is also obvious over Queen 1990 and Hudziak.

Claim 33 further adds that "the human antibody variable domain is a consensus human variable domain," which Queen 1990 also disclosed. (*See* Exs. 1050 at 12:17–20 ("As acceptor…use a consensus framework from many human

antibodies"); 1003 ¶¶131–37, 345; 1190 ¶¶107-13, 345) Claim 33 is also obvious over Queen 1990 and Hudziak.

G. Ground 9: Claim 42 is obvious over Queen 1990 in view of Hudziak and Furey

Claim 42, which depends on claim 30, recites "wherein the residue at site 66L has been substituted." Claim 30 is obvious in view of Queen 1990 and Hudziak. (*See supra* § IX.F) Furey disclosed that residue 66L forms a hydrogen bond contact with CDR2 of the light chain. (*See* Exs. 1125 at 16, Table 4; 1003 ¶¶346–48; 1190 ¶¶346-48) Following the detailed roadmap of Queen 1990, a skilled artisan would have recognized Furey's particular emphasis on 66L to improve binding affinity would have placed residue 66L on a short list of substitutable residues when humanizing 4D5. (Exs. 1003 ¶¶346–48; 1190 ¶¶346-48) Thus, claim 42 is obvious over Queen 1990, Hudziak, and Furey.

H. Ground 10: Claim 60 is obvious over Queen 1990 in view of Chothia & Lesk and Hudziak

Claim 60, which also depends on claim 30, recites "wherein the residue at site 78H has been substituted." Chothia & Lesk disclosed a small universe of residues which are "primarily responsible for the main-chain conformations of the hypervariable regions" (*i.e.*, maintaining CDR conformation as Queen 1990 taught), including residue 78H. (*See* Exs. 1062 at 1, Abstract, 8, Table 4; 1003 ¶349; 1190 ¶349) Following the detailed roadmap of Queen 1990, a skilled artisan

would have looked to Chothia & Lesk and identified framework positions that could interact with or influence CDR conformation, and antigen binding and specificity, including residue 78H. (Exs. 1003 ¶349; 1190 ¶349) Claim 60 is obvious over Queen 1990, Hudziak and Chothia & Lesk.

I. 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 also 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 recite 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 ¶¶110–16, 280, 347–48; 1190 ¶¶86-92, 280, 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. (Exs. 1003 ¶¶248–50, 307–08; 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 '213 patent's purported problem was that "[m]ethods are needed for rationalizing the selection of sites for substitution in preparing [humanized] antibodies" and 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. (Exs. 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,

/s/ Dimitrios T. Drivas
Dimitrios T. Drivas
USPTO Reg. No. 32,218

Scott T. Weingaertner
USPTO Reg. No. 37,756
White & Case LLP
1221 Avenue of the Americas
New York, New York 10020
T: (212) 819-8200
F: (212) 354-8113
ddrivas@whitecase.com

Counsel for
Samsung Bioepis Co., Ltd.

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 13,353, 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,

/s/ Dimitrios T. Drivas
Dimitrios T. Drivas
USPTO Reg. No. 32,218
Scott T. Weingaertner
USPTO Reg. No. 37,756

Counsel for
Samsung Bioepis Co., Ltd.

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. 6,407,213 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:

Genentech, Inc.
Wendy M. Lee
1 DNA Way
South San Francisco, CA 94080-4990

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.

David L. Cavanaugh
Wilmer Cutler Pickering Hale and Dorr LLP
1875 Pennsylvania Ave., NW
Washington DC 20006

Date: September 29, 2017

Signed,

/s/ Dimitrios T. Drivas
Dimitrios T. Drivas
USPTO Reg. No. 32,218
Scott T. Weingaertner
USPTO Reg. No. 37,756

Counsel for
Samsung Bioepis Co., Ltd.