No. 2020-1074

IN THE

United States Court of Appeals
for the Federal Circuit

AMGEN INC., AMGEN MANUFACTURING, LTD., and AMGEN USA, INC.

Plaintiffs-Appellants,

v.

SANOFI, AVENTISUB LLC, fka AVENTIS PHARMACEUTICALS INC., REGENERON PHARMACEUTICALS INC., and SANOFI-AVENTIS U.S. LLC,

Defendants-Appellees.

On Appeal from
the United States District Court for the District of Delaware
No. 14-cv-01317-RGA, District Judge Richard G. Andrews

CORRECTED BRIEF OF STANLEY D. LIANG AS AMICUS CURIAE IN SUPPORT OF APPELLEES

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June 12, 2020

CERTIFICATE OF INTEREST

Stanley D. Liang certifies the following:

1. The full name of every party or amicus represented by me is: **STANLEY D. LIANG**

2. The name of the real party in interest is: **NONE.**

3. All parent corporations and any publicly held companies that own ten percent or more of the stock of the party or *amicus curiae* represented by me are: **NONE.**

4. The names of all law firms and partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are: **STANLEY D. LIANG**

5. The title and number of any case known to counsel to be pending in this or any court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and R. 47.5(b).: **NONE.**

Date: June 12, 2020

/s/ *Stanley D. Liang*
Stanley D. Liang

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STATEMENT UNDER RULE 29

Pursuant to Federal Rule of Appellate Procedure 29(c)(5)(A)–(C), I, amicus curiae Stanley D. Liang, confirm that no party's counsel involved in the litigation below authored this brief, in whole or in part. I confirm that, while I am, and have been for the last 5-6 years, counsel for Party Regeneron on other matters, I am not counsel in the present matter. The Regeneron matters in which I have been involved are confidential and are protected by attorney-client privilege. The only Regeneron matter that includes a publicly available filing of mine is the Opposition proceedings for EP 2 550 363 ("ADAM6 Mice"), relating to certain genetic modifications in mice that allow the male mice to generate offspring, in which I submitted a declaration. I also confirm that no party or party's counsel, or any other person other than me, contributed money that was intended to fund preparing or submitting this brief.

Pursuant to Federal Circuit Rule 27(a)(5), counsel for amici curiae contacted counsel for the parties to ascertain whether the parties would consent or oppose this motion. Appellees do not oppose the motion and do not intend to file a response. Appellants oppose the motion and intend to file a response.

Pursuant to Federal Rule of Appellate Procedure 29(a)(3), I, amicus curiae Stanley D. Liang, move the Court for leave to file this *amicus curiae* brief. A Motion For Leave to File Amicus Curiae Brief accompanies this brief.

STATEMENT OF INTEREST OF *AMICUS CURIAE*

The amicus is Stanley D. Liang. I am a member of the patent bar and hold a doctorate in biochemistry and molecular biology. I have been counsel for parties participating in proceedings before the Patent Trial and Appeal Board and litigation at the district court and appellate level. I have also represented clients in patent prosecution related to biological and chemical subject matter. Accordingly, I am keenly interested in this Court's decisions on patent validity requirements and, in particular, that these decisions are founded on accurate scientific bases.

This Court's interpretation of the enablement requirement for functionally-claimed biologic patents is of particular concern to patent practitioners and the patent system. New biologics are needed to treat life-threating diseases and, given these stakes, striking the appropriate quid-pro-quo balance between disclosure and the monopoly is crucial. While it is important to reward inventors for medical innovation, granting an overbroad, unfair monopoly would undermine this incentive structure.

This brief is meant to assist the Court in determining an appropriate balance rooted in fundamental scientific principles. Accordingly, this brief describes the scientific background necessary to understand the scope of the claims at issue and to determine patent enablement.

INTRODUCTION

This Court's determination of whether a genus claim is enabled often hinges on the question, how many *potential* species of a genus must be tested to determine the set of *actual* species in the genus? In the biologics context, and particularly for functional claims, this question has arisen frequently. Scientists generally cannot predict which structures will exhibit functionally claimed attributes and, instead, must test *all* species *potentially* in a functional genus to identify the *actual* species in that genus. Whether undue experimentation is required to identify the members of a functionally-claimed biologic genus, therefore, often depends on the number of species potentially in that genus. This brief estimates that number.

Unsurprisingly, this Court has requested estimates of the number of potential genus candidates frequently. Judge Prost immediately posed this question to counsel for Idenix in oral arguments for *Idenix v. Gilead*: "Can you talk to me about the numbers? What is your number in terms of the potential compounds here?"[1] Likewise, when this case first reached this Court, Judge Taranto questioned counsel about limitations on the size and scope of the genus, noting that without limitations,

[1] Oral Argument of *Idenix Pharm. LLC v. Gilead Scis. Inc.*, 2018-1691, at 1:41–47 (Fed. Cir. Sep. 7, 2019), *decided* 941 F.3d 1149 (Fed. Cir. 2019).

the genus of antibodies would grow to include "every possible numerical combination" of amino acids, "an extremely large number."[2]

Other biotech companies also appear to agree that the large potential scope of a functionally-claimed, biologic genus renders it unpatentable. In its recent dispute with Eli Lilly, for example, Genentech voluntarily dismissed infringement claims that were based on a patent with broad functional claims to antibodies binding a particular dimer.[3] Relying heavily on the reasoning from this Court's previous decision in this matter and the subsequent determination on remand, Genentech conceded that when Judge Andrews invalided Amgen's remaining claims, it "cast considerable doubt over whether Genentech would succeed in defending the validity of [its] patent claims," especially "in view of the similar arguments presented by the defendant in that case" and "evolving decisional law."[4]

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[2] Oral Argument of *Amgen Inc. v. Sanofi*, 2017-1480, at 5:50–6:30 (Fed. Cir. June 6, 2017), *decided* 872 F.3d 1367 (Fed. Cir. 2017); *see also id.* at 6:53, 10:45, 27:41, and 32:35.

[3] *See Genentech, Inc. v. Eli Lilly and Co.*, 18-cv-01518-JLS, Dkt. 1 (S.D. Cal., July 2, 2018) (asserting that Eli Lilly's antibody, Taltz, infringed U.S. Patent No. 10,011,654, which broadly claims antibodies binding to the IL-17A/F dimer); *see also Genentech, Inc. v. Eli Lilly and Co.*, 18-cv-01518-JLS, Dkt. 73 (S.D. Cal., Feb. 26, 2020) (voluntarily dismissing litigation and attaching "Request for an Adverse Judgment" filed in the associated post grant review).

[4] *Genentech, Inc. v. Eli Lilly and Co.*, 18-cv-01518-JLS, Dkt. 82, at *1, *13–14 (S.D. Cal., Apr. 30, 2020).

This brief provides the Court with scientifically-based estimates of the number of potential genus members for the claims-at-issue using three methods. The first method calculates the theoretical number of potential genus members using experimentally-obtained data regarding human antibody diversity and antigen binding frequency. The second method calculates the number of genus members that, as taught by the patents, a person of ordinary skill would likely consider, using the patents' method for generating new antibodies through amino acid substitution. The final method calculates the number of functional classes of antibodies satisfying relevant claim limitations to determine the number of classes of antibodies that must be tested.

While no method calculates with absolute precision, these estimates provide a scientific basis for the enablement analysis so that the difficulty of ascertaining and practicing the full scope of the claims-at-issue can be assessed. All these methods are consistent with Judge Andrews's findings of a "vast" potential genus size,[5] and as a result, indicate that undue experimentation would be required to identify and practice the full scope of the claims.

[5] *See Amgen Inc. v. Sanofi*, 1:14-cv-01317-RGA, 2019 U.S. Dist. LEXIS 146305, at *23, *35 (D. Del., Aug. 28, 2019) [hereinafter *Amgen II*].

SCIENTIFIC AND PATENT BACKGROUND

To provide reasonable estimates of the number of potential claimed genus members, this brief relies upon scientific properties of antibodies as well as functional limitations present in the claims-at-issue. This relevant background is detailed below

I. Scientific Background Related to Antibody Structure and Variation

Antibodies are proteins and are part of the human immune system.[6] They are composed of long chains of the twenty possible amino acids and their role in the immune system is to bind to antigens (foreign or toxic substances in the body) so that these antigens may be eliminated.[7] The likelihood of a particular antibody binding to a given antigen is low; current conservative estimates indicate that, on average, any particular antigen is bound by only one of every 10^6 antibodies.[8] On the other hand, the body naturally creates an enormous number and variety of

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[6] *The Structure of a Typical Antibody Molecule, in* Immunobiology: The Immune System in Health and Disease 113–15 (Charles A. Janeway, Jr. et al. 5th ed., 2001) [hereinafter, Janeway, *Structure of Antibody*].

[7] *See id.*; *see also The Chemistry of Amino Acids*, The Biology Project | Biochemistry, http://www.biology.arizona.edu/biochemistry/problem_sets/aa/aa.html.

[8] *See* Veronika I. Zarnitsyna et al., *Estimating the Diversity, Completeness, and Cross-reactivity of the T Cell Repertoire*, Frontiers in Immunology (Dec. 26, 2013) at 7.

antibodies. Accordingly, while many antibodies must be tested to identify even one that binds a particular antigen, the full number of antibodies binding an antigen is often quite large.

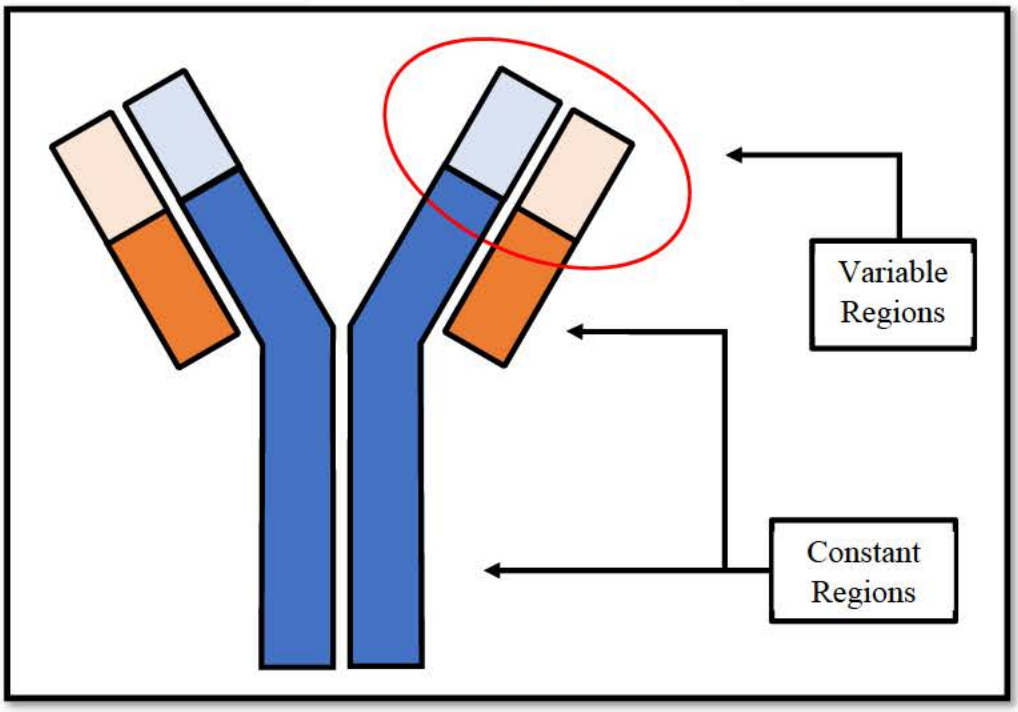
As shown below, antibodies have a "Y"-shaped structure.[9] They are comprised of two identical heavy chains (depicted below in blue) and two identical light chains (depicted below in orange).[10] Within each of the heavy and light chains is a constant region (depicted below in dark blue and dark orange coloring for the heavy and light chains, respectively), and a variable region that binds to antigens (depicted below in light blue and light orange coloring for the heavy and light chains, respectively).[11] The constant regions have limited amino acid sequence variation, while the variable regions can exhibit wide sequence variation from one antibody to the next.

[9] *See* Janeway, *Structure of Antibody* at 113–15.

[10] *See id.*

[11] *See id.*

Basic Antibody Structure



Each variable region is composed of three complementarity-determining regions ("CDRs") that have extensive or "hyper" variability, interspersed within four framework regions that have modest variability.[12] While the CDRs directly bind to antigens,[13] the framework regions mainly provide structural support for the CDRs,[14] although some framework-region amino acids may be involved in antigen binding.

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12 *See Antibody Structure*, The Biology Project | Immunology, http://www.biology.arizona.edu/immunology/tutorials/antibody/structure.html.

13 *See id.*

14 *See id.*

The heavy and light chains of antibodies are encoded by specific gene segments in the DNA that rearrange to form the genes that encode the antibody amino acid sequences.[15] Heavy chain variable regions are encoded by three gene segments, where one is from each of the "V" (variable), "D" (diversity), and "J" (joining) groups.[16] The heavy chain V, D, and J gene segments are localized at a particular locus within the genome, such that all of the V gene segments are together at one locus, and so on.[17]

Similarly, light chain variable regions are encoded by two gene segments, one from each of the light chain V and J gene segments.[18] The light chain V and J gene segments are also localized at a particular locus within the genome, however the light chain has two distinct sets of V and J segments, with one set localized at the kappa locus and one set localized at the lambda locus.[19] The heavy chain V/D/J loci

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15 *See The Generation of Diversity in Immunoglobulins*, *in* Immunobiology: The Immune System in Health and Disease 138–39 (Charles A. Janeway, Jr. et al. 5th ed., 2001) [hereinafter, Janeway, *Generation of Diversity*].

16 *See id.*

17 *See id.* at 139–51.

18 *See id.*

19 *See id.*

and each of the light chain V/J kappa and lambda loci are all different and are found on separate chromosomes.[20]

In practice, the number of varieties of the components of antibodies are relatively well known. There are nine types of heavy chain constant regions,[21] and five total types of light chain constant regions (including those encoded at both the kappa and lambda loci).[22] Human heavy chains have approximately fifty-one varieties of framework regions and light chains have approximately seventy-two varieties.[23] The number of combinations of these various segments constitutes a substantial amount of antibody diversity, as set forth in the calculations below.

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[20] *See* O. Wesley McBride et al., *Chromosomal Location of Human Kappa and Lambda Immunoglobulin Light Chain Constant Genes*, 155(5) J. Experimental Medicine 1480–90 (1982).

[21] There are five isotypes of constant regions for heavy chains, labeled M, D, E, G, and A. *See* Janeway, *Structure of Antibody* at 113–15. The G isotype, however, has four subclasses and the A isotype has two subclasses. *See Structural Variation in Immunoglobulin Constant Regions*, in *Immunobiology: The Immune System in Health and Disease* (Charles A. Janeway, Jr. et al. 5th ed., 2001). Accordingly, there are nine total varieties of heavy chain constant region.

[22] The lambda type light chain constant region has four subtypes and the kappa type light chain constant region has one subtype. *See* Thomas J. Kindt et al., *Kuby Immunology* 87 (6th ed., 2004). Thus, there are five varieties of light chain constant regions.

[23] *See* Jaafar N Haidar et al., *A Universal Combinatorial Design of Antibody Framework to Graft Distinct CDR Sequences: A Bioinformatics Approach*, 80(3) Proteins: Structure, Function, and Bioinformatics 896–912 (2012). These values match those reported at the September 9, 2016 United States Patent and Trademark Office roundtable entitled, *Written Description and Antibody Claims: USPTO*

The hyper-variable CDRs have a much larger number of potential variations, much of which results from the natural process of antibody production.[24] A major source of this variability is introduced through V(D)J recombination, the process that assembles the gene sequences encoding heavy and light chains.[25] During this process, the gene sequence encoding a heavy chain is generated by combining a single, randomly selected gene segment from each of the V, D, and J gene segment regions.[26] The light chain variable region is formed through a similar process that includes recombination of a single, randomly selected gene segment from each of the V and J regions.[27] Because the heavy and light chain gene segments for a particular antibody are selected from many potential gene segments, there are many unique combinations of the segments and, therefore, many potential antibody sequences.

Importantly, the joining of these gene segments is often imprecise, resulting in random additions or deletions of DNA nucleotides at the junctions between the

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Policy Roundtable.

[24] *See* Arjun K. Mishra & Roy A. Mariuzza, *Insights into the Structural Basis of Antibody Affinity Maturation from Next-Generation Sequencing*, 9 Frontiers in Immunology 117, at 1–2, 5–8 (Feb. 2018) [hereinafter, Mishra & Mariuzza].

[25] *See* Janeway, *Generation of Diversity* at 139–51.

[26] *See id.*

[27] *See id.*

segments, which creates further diversity.[28] The imprecise combination of these gene segments from non-adjacent portions of the human genome may result in additional sequence variation such that the antibody sequence does not exactly match the sequences in the genome.[29]

Following V(D)J recombination and the imprecise joining of gene segments, amino acid sequences can undergo further diversification through a two-step process known as affinity maturation.[30] The first step of this diversity-adding process is called somatic hypermutation, a process by which random mutations are introduced into the rearranged variable region of the heavy and light chains.[31] Importantly, these mutations occur at a rate several orders of magnitude higher than the average naturally occurring mutation rate in the human genome and generally take place in portions of the sequence corresponding to the CDRs.[32] Therefore, following somatic hypermutation, the CDR amino acid sequences become randomly and significantly different from those produced by V(D)J recombination.[33]

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28 *See* Mishra & Mariuzza at 6–8.

29 *See* Tak E. Mak & Mary W. Saunders, *Immunoglobulin Genes*, The Immune Response, at 179–208 (Elsevier Academic Press 2006).

30 *See* Mishra & Mariuzza at 5–8.

31 *See* Janeway, *Generation of Diversity* at 138–51.

32 *See id.*

33 *See* Masamichi Muramatsu et al., *Class Switch Recombination and Hypermutation Require Activation-Induced Cytidine Deaminase (AID), a Potential RNA Editing Enzyme*, 102 Cell 553–63 (2000).

The second step of the affinity maturation process is called clonal selection. After somatic hypermutation creates new antibody sequences, the immune system can select for antibody clones that bind better than the originally-created antibodies. As this affinity maturation process is repeated, the immune system generates and selects antibodies that bind increasingly better to the antigen.

As a result of these diversity-adding processes, the human body can produce CDRs comprising virtually any sequence of amino acids.[34] Further, because the average combined length of CDRs in a chain is large (approximately thirty-nine amino acids in the heavy chain and thirty-three amino acids in the light chain),[35] CDRs can assume an enormous number of structures. For this reason, an astronomical number of antibody sequences with highly variable structures can be generated that allow antibodies to bind to virtually any antigen that an organism may encounter.

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[34] *Accord* Mishra & Mariuzza at 1.

[35] *See* Yvelise Barrios et al., *Length of the Antibody Heavy Chain Complementarity Determining Region 3 as a Specificity-Determining Factor*, 17(4) J. Molecular Recognition 332–38 (2004).

II. Patent Background Related to Antibody Variation Within the Claimed Genus

Amgen's asserted claims are described by U.S. Patent Nos. 8,829,165 (the " '165 Patent") and 8,859,741 (the " '741 Patent"; collectively, the "Patents") and are directed to a particular genus of antibodies that bind to a specific location on the PCSK9 antigen.[36] This genus is defined using functional limitations based on antibodies' ability to bind to at least two of fifteen amino acid residues in the sequence of PCSK9 and block binding of PCSK9 to low density lipoprotein receptors ("LDLR"). A representative asserted claim is recited below. Notably, the asserted claims do not define any antibody by structure or amino acid sequence.

> *The '165 Patent, Claim 29*: A pharmaceutical composition comprising
> an isolated monoclonal antibody,
> wherein the isolated monoclonal antibody binds to at least two of the following residues S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of PCSK9 listed in SEQ ID NO:3
> and blocks the binding of PCSK9 to LDLR by at least 80%.[37]

The specification of the '165 Patent lists some examples of antibodies that purportedly satisfy the claims and also describes a procedure for generating additional antibodies from the exemplary antibodies. In particular, the specification

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[36] U.S. Patent Nos. 8,829,165 (the "'165 Patent"), claims 19 and 29, and 8,859,741 (the "'741 Patent") claim 17 remain at issue in the instant litigation.

[37] '165 Patent, Cl. 29.

lists amino acid sequences for the variable regions of the described antibodies, including for the 12H11 antibody.[38] The specification further asserts that new claimed antibodies can be constructed from the sequences of claimed antibodies by amino acid substitution.[39] Specifically, the sequences for new claimed antibodies can be created by performing certain amino acid substitutions on the sequences for the variable regions of an antibody that already satisfies the claims.[40] The '165 Patent details the acceptable substitutions, explaining that exemplary and preferred "amino acid substitutions are set forth in Table 1," which is reproduced in full below.[41]

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[38] *See id.* at Sheet 59. The amino acid sequence for the 12H11 heavy chain variable region is: QVQLVES GGGVAQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIYYDG INKHYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGLD WGQGTLVTVSS. *Id.* The amino acid sequence for the 12H11 light chain variable region is: DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNSKNYLVWYQQKPGQPP K LLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYSTP WTFGQGTKVEIK. *Id.*

[39] *See id.* at 27:40–28:52.

[40] *See id.*

[41] *Id.* at 28:25.

TABLE 1

Amino Acid Substitutions

Original Residues	Exemplary Substitutions	Preferred Substitutions
Ala	Val, Leu, Ile	Val
Arg	Lys, Gln, Asn	Lys
Asn	Gln	Gln
Asp	Glu	Glu
Cys	Ser, Ala	Ser
Gln	Asn	Asn
Glu	Asp	Asp
Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

Despite this broad method for generating new antibodies, the '165 Patent provides no guarantee that these antibodies will satisfy the claimed limitations. Accordingly, each newly generated antibody must be tested to determine whether it satisfies the claim limitations.

Moreover, the limited experimental data in the '165 Patent provide virtually no restrictions on the number of antibody candidates that can be generated and must

be tested, or on the size or scope of the claimed genus. For example, the '165 Patent indicates that, of 3,104 antibodies that were found to bind to PCSK9, only 384 antibodies blocked binding to LDLR and only 85 blocked binding to LDLR strongly.[42] However, no information about the structural features or representativeness of those initial 3,104 antibodies — or the final 85 that blocked binding to LDLR strongly — is provided.

* * *

Given the uncertain restrictions that functional limitations have on the scope of the claimed genus, and the vast potential antibody diversity, the enablement analysis can be assisted by calculating the potential number of antibodies in the claimed genus (i.e., the number of antibodies that must be tested to determine the size of the claimed genus). Three estimates of this potential genus size are calculated below.

METHODS CALCULATING THE NUMBER OF ANTIBODIES POTENTIALLY WITHIN THE CLAIMED GENUS

The three methods employed by this brief to calculate the potential genus size all support the finding that the number of antibodies that must be tested is vast. The methods investigate (i) the theoretical size of the claim genus; (ii) the members of the claimed genus that, according to the '165 Patent, a person of ordinary skill in the

[42] *See id.* at 77:25–81:34.

art would be likely to consider; and (iii) the number of classes of antibodies that must be tested to determine actual members of the claimed genus. The methods are as follows:

i. ***The Formation Method***. This method estimates the number of potential genus members to be 2.14×10^{91} antibodies by calculating the theoretical number of antibodies that are potentially within the claimed genus. It does so by first calculating the total number of antibodies that can be generated by the immune system, accounting for recombination of variable region gene segments and affinity maturation. It then refines this estimate to apply to the claimed genus using data obtained from experimental testing of antibodies generally, and PCSK9 binding specifically.

ii. ***The Substitution Method***. This method estimates the number of potential genus members to be 4.04×10^{129} antibodies by considering the antibodies that, according to the '165 Patent specification, a person of ordinary skill in the art would be likely to consider as potential members of the claimed genus. In particular, this method uses the '165 Patent's procedure for generating new members of the claimed genus by making "exemplary" or "preferred" substitutions within the disclosed 12H11 amino acid sequences.

iii. ***The Functional Method***. This method defines classes of claimed antibodies based on functional limitations identified by the Patents' claims and then

calculates that, at minimum, there are 32,752 such classes of antibodies that must be tested to determine the genus size.

I. The Formation Method

The *Formation Method* accounts for the diversity producing processes naturally found in human antibody production and then limits the result to apply to antibodies that bind to PCSK9 using experimentally derived data. This method estimates that more than 2.14×10^{91} antibodies would have to be tested to determine the actual members of the claimed genus.

A. Number of Antibodies Capable of Being Produced by the Human Body

The total number of unique antibodies that can be produced by the human body is calculated by counting the possible combinations of the constituent parts of an antibody. An antibody is composed of two identical heavy chains and two identical light chains. Therefore, the total number of potential antibodies is the number of combinations of all the types of heavy and light chains.

$$N_{Total\ Antibodies} = N_{Heavy\ Chains} \times N_{Light\ Chains}$$

The number of types of heavy chains is the product of the number of types of each gene segment region of the heavy chain: constant regions and variable regions. There are nine varieties of heavy chain constant regions. As for the heavy chain

variable region, it is formed through V(D)J recombination and comprises framework regions with three interspersed CDRs. There are fifty-one varieties of framework regions in a heavy chain variable region. The three CDRs combined are approximately thirty-nine amino acids long and, because somatic hypermutation allows virtually any amino acid substitution within the CDRs, any of the twenty amino acids could occur at each position in the sequence of the CDRs.

$$N_{Heavy\ Chains} = N_{Constant\ Regions} \times N_{Variable\ Regions}$$

$$= N_{Constant\ Regions} \times \left(N_{Framework\ Regions} \times N_{CDRs}\right)$$

$$\approx 9 \times (51 \times 20^{39}) = 2.52 \times 10^{53}$$

The number of light chains is calculated using the same procedure. There are five possible constant regions, seventy-two possible framework regions, and the total CDR length is approximately thirty-three amino acids, resulting in 3.09×10^{45} potential light chains.

The number of antibodies that can be produced by the human body is the product of the number of light and heavy chains: 7.80×10^{98} antibodies.

B. Number of Antibodies Narrowed by Experimentally Verified Limitations Related to the Claimed Genus

The result from the previous Subsection can be narrowed to reflect the number of potential members of the claimed genus, rather than all possible antibodies, by accounting for the claimed limitations. There are only two limitations and they are functional. The first limitation requires that each antibody binds to at least two of the fifteen listed PCSK9 amino acid residues. The second limitation requires that each antibody blocks binding of the PCSK9 antigen to LDLR.

The frequency with which antibodies bind to two of the fifteen listed amino acid residues of PCSK9 is not known; estimates of the general frequency with which antibodies bind to any given antigen, however, do exist. These estimates indicate that an antigen is bound by about one of 10^6 antibodies.[43]

The frequency with which antibodies block PCSK9 binding to LDLR, in addition to satisfying the previous limitation, was experimentally tested for the set of antibodies that Amgen generated, and disclosed in the ’165 Patent’s

[43] No theoretical method for predicting or experimental data exists regarding the rate at which antibodies bind to at least two of the fifteen listed residues of PCSK9. The ’165 Patent disclosure relating to PSCK9 binding antibodies provide insufficient information to deduce a general PCSK9 binding frequency for all antibodies. Accordingly, estimating based on the antibody binding rate for antigens generally is the only method available.

specification.[44] Using Amgen's results, only the antibodies that strongly block LDLR binding could be used (85 of 3,104), resulting in a blocking frequency of 2.74%.[45]

Accordingly, the total number of antibodies potentially in the claimed genus can be found by multiplying the total number of antibodies that can be created, by the proportion that bind PCSK9 as claimed, and then by the proportion that also block LDLR. This results in an estimated potential claim genus size of 2.14×10^{91}.

$$N_{Claimed\ Genus} = N_{Total\ Antibodies} \times R_{Bind\ PCSK9} \times R_{Bind\ PCSK9\ \&\ Block\ LDLR}$$

$$\approx 7.80 \times 10^{98} \times \frac{1}{10^{6}} \times 0.0274 = 2.14 \times 10^{91}$$

* * *

Importantly, the number of antibodies that must be tested to identify the actual members of the claimed genus is larger than this estimate. This estimate relies on the estimated statistical prevalence of antibodies likely to satisfy the claim limitations but includes no information about the structure of antibodies in the claimed genus or a method for producing antibodies likely to satisfy these limitations. The number of antibodies that must be tested, therefore, is necessarily

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44 *See* '165 Patent at 77:25–81:34.

45 *See id.* at 79:50–80:37.

larger than the number of antibodies potentially in the genus, because a person of ordinary skill in the art would have to experiment to find these potential candidates.

Nonetheless, testing the number of antibodies calculated by the *Formation Method* would require an enormous amount of experimentation. For each of the 10^{82} atoms estimated to be in the known, observable universe,[46] more than two billion antibodies must be tested to determine the size of the claimed genus.

II. The Substitution Method

The *Substitution Method* employs the procedure that, as described by the '165 Patent, a person of ordinary skill in the art would be likely to use to generate new claimed antibody variable region sequences from reference antibody sequences. Notably, the calculation performed here applies the '165 Patent's procedure on only one reference antibody, the 12H11 antibody. If more reference antibodies were used, the number of potential antibodies generated would increase. This method estimates that more than 4.04×10^{129} antibodies could be generated according to the method described in the specification and would have to be tested to determine the actual members of the claimed genus.

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[46] *See* John C. Villanueva, *How Many Atoms Are There in the Universe*, Universe Today (July 30, 2009), https://www.universetoday.com/36302/atoms-in-the-universe/.

A. Number of Antibodies Generated from the 12H11 Sequences Using All "Exemplary" or "Preferred" Substitutions from the '165 Patent

The total number of unique antibody variable regions that can be generated through "exemplary" or "preferred" substitutions of amino acids in the 12H11 reference sequence is calculated by allowing each possible exemplary or preferred substitution at each position in the 12H11 sequences. This is written formally below where $N_{Amino\ Acid\ 1}$ is the number of possible amino acids that can occupy the first position in a reference sequence (according to Table 1 approved substitutions of the 12H11 sequences) and so on.

$$N_{Variable\ Region\ Sequences} = N_{Amino\ Acid\ 1} \times N_{Amino\ Acid\ 2} \times \cdots$$

The number of amino acids that can occupy each position in the 12H11 variable region sequence is calculated by counting all possible exemplary substitutions listed in Table 1. For example, the 12H11 heavy chain variable region sequence begins with the amino acids Glutamine (Gln) and then Valine (Val). According to Table 1 of the '165 Patent, Glutamine has one exemplary substitution, Asparagine. Therefore, there are two possible amino acids for that position. Table 1 provides six exemplary substitutions for Valine. Therefore, there are seven possible

amino acids for the second position.[47] Applying this analysis to the 115 amino acids in the 12H11 heavy chain variable region sequence generates 2.47×10^{65} potential sequences. Likewise, application to the 114 amino acids in the 12H11 light chain variable region sequence generates 3.63×10^{62} potential sequences.

Since antibodies contain both variable and constant regions, the total number of antibodies generated must take into account the possible number of constant regions. The number of antibodies can be calculated simply by multiplying the number of variable regions by the number of heavy and light constant regions. This results in 4.04×10^{129} antibodies.[48]

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[47] Rows six and twenty of Table 1 indicate that the substitution for Glutamine is Asparagine (Asn) and the substitutions for Valine are Isoleucine (Ile), Methionine (Met), Leucine (Leu), Phenylalanine (Phe), Alanine (Ala), and Norleucine. Accordingly, there are two potential amino acids for the first position (Glutamine and Asparagine) and seven potential amino acids for the second position.

[48] One possible explanation for the *Substitution Method* generating more potential antibodies than the *Formation Method*, despite relying on only the 12H11 sequences, is the unrestricted amino-acid substitution allowed by the *Substitution Method* throughout the variable region sequence. Specifically, the number of framework regions available for heavy and light chains are known and generally fixed. However, neither the ’165 Patent, nor the *Substitution Method* which it describes, provide any information about portions of the 12H11 variable region sequences that encode framework regions or any prohibitions on portions where substitution is not allowed. Substantial additional experimentation would be necessary to determine these portions and adjust the estimate. *Accord Amgen II*, 2019 U.S. Dist. LEXIS 146305, at *31 (D. Del. Aug. 28, 2019) (“After considering the disclosed roadmap in light of the unpredictability of the art, any reasonable factfinder would conclude that the patent does not provide significant guidance or direction to a person of ordinary skill in the art.”).

$$N_{Claimed\ Genus} = N_{Variable\ Regions} \times N_{Constant\ Regions}$$

$$\approx (2.47 \times 10^{65} \times 3.63 \times 10^{62}) \times (9 \times 5) = 8.98 \times 10^{127} \times (45)$$

$$\approx 4.04 \times 10^{129}$$

B. Number of Antibodies Generated from the 12H11 Sequences Using a Few "Exemplary" or "Preferred" Substitutions from the '165 Patent

A more conservative estimate based on Table 1 substitutions can be performed by counting the number of antibodies generated from the 12H11 sequences when only allowing substitutions in at most two amino acid positions in the heavy chain variable region sequence and two in the light chain variable region sequence.

The number of possible variable region sequences generated by this method for a single chain is calculated by selecting two positions in the 12H11 amino acid sequence, computing the number of sequences that can be generated by allowing all exemplary or preferred substitutions of amino acids in those two positions, and then summing that result together with the results from all other possible pairs of positions in the 12H11 amino acid sequence.

The first steps of the calculation are instructive. There are fourteen potential sequences that can be generated by performing substitutions on only the first two positions of the 12H11 heavy chain sequence (two potential amino acids for the first position multiplied by seven for the second position generate fourteen total

sequences). There are four potential sequences that can be generated from performing substitutions on only the first and third positions of the 12H11 heavy chain sequence (two potential amino acids for the first position multiplied by two for the third position generate four total sequences). The total number of sequences that can be generated is the sum of these numbers over all possible pairings.

Applying this method results in 108,842 potential heavy chain variable region sequences and 100,168 potential light chain variable region sequences. Accordingly, the total number of potential antibodies is the product of the number of heavy and light chain variable region sequences (approximately 1.09×10^{10}) with the number of constant regions (nine heavy chain and five light chain). The number of antibodies generated is therefore:

$$N_{Antibodies} \approx 4.91 \times 10^{11}$$

* * *

Importantly, all of the antibodies generated by the *Substitution Method* must be tested. Unlike in *MorphoSys*, where testimony indicated that the products of substitutions were expected to satisfy the claims without testing,[49] no such

[49] *See MorphoSys AG v. Janssen Biotech, Inc.*, 358 F. Supp. 3d 354, 372 (D. Del. 2019); *see also Amgen II*, 2019 U.S. Dist. LEXIS 146305, at *19.

expectation exists here.[50] Moreover, Amgen cannot subdivide the antibodies resulting from the *Substitution Method* to identify a subset more likely to be considered by a person of ordinary skill. This Court rejected that argument in *Idenix*, concluding that enablement "considers the scope of the claim as written, not just the subset of the claim that a POSA might practice."[51]

The results of the *Substitution Method* furthermore underestimate the number of antibodies that must be tested to determine the actual size of the claimed genus. If variants other than the 12H11 sequences were considered, the number of antibodies that must be tested would grow. As in *MorphoSys*, this substitution method also gives no information about the number of antibodies that satisfy the claims-at-issue but do not result from exemplary or preferred substitutions.[52] As

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[50] *Amgen II*, 2019 U.S. Dist. LEXIS 146305, at *19 ("Even for the suggested substitutions in the ['165 Patent], a person of ordinary skill in the art would still be required to test the newly-generated antibody to see if it meets the functional limitations of the claims.").

[51] *Idenix Pharm. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1162 (Fed. Cir. 2019); *see generally id.* at 1156–64 (analyzing the *Wand* factors and rejecting the argument that only the scope of the claims that a POSITA would consider must be examined).

[52] *See MorphoSys*, 358 F. Supp. 3d at 372 (observing that "a POS[IT]A attempting to obtain a claimed antibody that is not a variant of a known antibody would have to do essentially the same amount of work as the inventors of the patents-in-suit" (alteration added)); *see also Amgen II*, 2019 U.S. Dist. LEXIS 146305, at *19–21 ("As in *MorphoSys*, a person of ordinary skill in the art 'would have to discover these [non-exemplary and non-preferred variant] antibodies de novo through' super immunization or another technique." (quoting *MorphoSys*,

correctly observed by the district court below, testing to identify antibodies that are not variants of known antibodies would require "essentially the same amount of work as the inventors of the [P]atents[]."[53]

Nonetheless, testing the number of antibodies calculated by the *Substitution Method* would require an enormous amount of experimentation. For each of the 10^{128} neutrons that would be required to fill the entire known universe,[54] more than forty antibodies would have to be tested just to identify 12H11 claimed variants.

III. The Functional Method

The *Functional Method* defines classes of claimed antibodies that must be tested based on the PCSK9 residues to which they bind and then counts the total number of these classes. This is the same analysis performed by Defendants before the district court.[55] This method calculates that 32,752 classes of antibodies must be tested to determine the actual members of the claimed genus.

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358 F. Supp. 3d at 372) (alteration in original)).

53 *See MorphoSys*, 358 F. Supp. 3d at 372.

54 *See* Carl Sagan, *Cosmos* 220–21 (1981).

55 *See* Def.'s Opening Br. In Support of Mot. For J. as a Matter of Law, *Amgen Inc. v. Sanofi*, No. 1:14-cv-01317-RGA, 2019 U.S. Dist. LEXIS 9076, at *3 (D. Del., Mar. 18, 2019). Note, for those familiar with mathematical combinatorics, this method is identical to calculating $\sum_{i=2}^{15}(15 \text{ C } i)$.

Specifically, this method defines a class for each way that an antibody can satisfy the claimed limitations of binding to *at least two of fifteen listed amino acid residues*.[56] Note, calculating this is the same as calculating the total number of ways of binding to any number of the fifteen PCSK9 residues and then subtracting the number of ways of binding to zero or of binding to only one of the residues.

The number of ways an antibody can bind to the fifteen amino acid residues is the product of the number of ways it can bind to each residue. Here, each residue is either bound or unbound; two possibilities. Thus, the total number of ways that an antibody can bind to the fifteen residues is $2^{15} = 32{,}768$.

$$N_{Bind\ Any\ Number\ of\ Residues}$$

$$= N_{Ways\ of\ Binding\ to\ Residue\ 1} \times N_{Residue\ 2} \times \cdots \times N_{Residue\ 15}$$

$$N_{Total} = 2 \times 2 \times \cdots \times 2 = 2^{15} = 32{,}768$$

There is one way that no residue is bound: all residues are unbound; and only fifteen ways where one residue is bound: one way for each of the fifteen residues. Thus, the total number of functional classes is:

[56] Those amino acid residues are S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381. ’165 Patent, Cl. 29.

$$N_{Functional\ Classes}$$

$$= N_{Bind\ Any\ Number\ of\ Residues} - N_{Bind\ 0\ Residues} - N_{Bind\ 1\ Residue}$$

$$= 32{,}768 - 1 - 15 = 32{,}752$$

* * *

The number of antibodies that must be tested to identify the actual genus members from those in the functional classes is many times larger than the number of functional classes. Given the potential variability in antibody structure, it is likely that there are a large number of antibody candidates included in each functional class. All these antibodies must be tested to determine whether the other genus claim limitation is met (i.e., that they block PCSK9 binding to LDLR).

Moreover, extensive experimentation would be required just to identify the members of the functional classes. The Patents contain insufficient structural information to generate all of the antibodies in each functional class or to predict which amino acid residues are bound by an antibody. Instead, the same general and expansive form of testing would have to be performed by a person of ordinary skill in the art that the Patents' inventors should have already performed to identify the scope of the claimed genus. This experimentation, as discussed in the previous Sections, would be enormous.

CONCLUSION

These scientific analyses and calculations demonstrate the vast potential genus size for the claims-at-issue and the undue experimentation that would be required to identify and practice their full scope. The chart below summarizes the methods employed and the potential genus sizes estimates. Hopefully, this will assist the Court in deciding this appeal.

Method	Notes	Result
Formation	Potential antibody genus size is based on diversity generated during antibody formation and narrowed by experimental data. More antibodies must be screened given the lack of structural information identifying antibodies which express claimed binding characteristics.	**2.14×10^{91} antibodies**
Substitution All possible substitutions	Potential antibody genus size generated using the '165 Patent's amino acid substitution method according to Table 1. Additional antibodies could be generated by using reference sequences other than 12H11.	**4.04×10^{129} antibodies**
Substitution Limited substitutions	*See above.*	**4.91×10^{11} antibodies**
Functional	Functional classes of antibodies binding to at least two listed amino acid residues. Each class likely includes a large number of antibodies for screening.	**32,752 functional classes**

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Fed. R. App. P. 29(a)(5) and Fed. R. App. P. 32(a)(7)(B) because this brief contains 6,183 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f).

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/s/ *Stanley D. Liang*
Stanley D. Liang

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I hereby certify that I have electronically filed the foregoing on June 12, 2020. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

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