No. 20-1074

IN THE

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

AMGEN INC., AMGEN MANUFACTURING, LIMITED, 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, in No. 1:14-cv-01317-RGA

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FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

Amgen Inc., et al. **v.** Sanofi, et al.

Case No. 20-1074

CERTIFICATE OF INTEREST

Counsel for the:
☐ (petitioner) ■ (appellant) ☐ (respondent) ☐ (appellee) ☐ (amicus) ☐ (name of party)

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10% or more of stock in the party
Amgen Inc.	None	None
Amgen Manufacturing, Limited	None	Amgen Inc.
Amgen USA, Inc.	None	Amgen Inc.

4. The names of all law firms and the 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 **(and who have not or will not enter an appearance in this case)** are:

Please see attached.

FORM 9. Certificate of Interest **Form 9**
Rev. 10/17

5. The title and number of any case known to counsel to be pending in this or any other 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 47.5(b). (The parties should attach continuation pages as necessary).

None.

2/21/2020
Date

/s/ Jeffrey A. Lamken
Signature of counsel

Please Note: All questions must be answered

Jeffrey A. Lamken
Printed name of counsel

cc: All counsel by ECF

Reset Fields

CERTIFICATE OF INTEREST

Appellants Amgen Inc., Amgen Manufacturing, Limited, and Amgen USA, Inc. (collectively "Amgen") state that the following partners or associates have appeared on their behalf before the district court or are expected to appear in this Court:

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[1] Michelle M. Ovanesian no longer practices with Young Conaway Stargatt & Taylor LLP and is not expected to enter an appearance on behalf of Amgen in this appeal.

[2] Eric W. Hagen, Terry W. Ahearn, Shane G. Smith, Michael V. O'Shaughnessy, Esther E. Lin, and Evan Boetticher no longer practice with McDermott Will & Emery LLP and are not expected to enter appearances on behalf of Amgen in this appeal.

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[4] Daryl L. Joseffer and Adam M. Conrad no longer practice with King & Spalding LLP and are not expected to enter appearances on behalf of Amgen in this appeal.

[5] Joshua Mack is no longer employed by Amgen, Inc., and is not expected to enter an appearance on behalf of Amgen in this appeal.

[6] In the prior appeal in this case (No. 17-1480), Christopher R. Healy, Merritt E. McAlister, and Joshua N. Mitchell from King & Spalding LLP appeared before this Court on behalf of Amgen. Those attorneys are not expected to enter appearances on behalf of Amgen in this appeal.

TABLE OF CONTENTS

Page

INTRODUCTION 1

JURISDICTIONAL STATEMENT 4

STATEMENT OF THE ISSUE 4

STATEMENT OF THE CASE 5

I. Factual Background 5

A. Amgen Invents Antibodies To Treat Heart Disease by Dramatically Lowering LDL Cholesterol 5

B. Amgen's Patents Claim a Class of PCSK9 Antibodies That Bind the "Sweet Spot" 10

C. Amgen's Patents Provide a Detailed Roadmap for Making the Claimed Antibodies 13

D. Amgen's Patents Disclose a Prior-Art Method of Making "Variants" 16

II. Proceedings Below 18

A. First Trial and Appeal 18

B. Second Trial and the District Court's JMOL Decision 19

1. Written Description 19

2. Enablement 20

SUMMARY OF ARGUMENT 26

STANDARD OF REVIEW 30

ARGUMENT 31

I. Substantial Evidence Showed—and *Wands* Confirms—That Amgen's Claims Are Enabled 32

A. Amgen's Patents Contain a Roadmap for POSAs To Practice the Invention's Full Scope 32

B. *Wands* Confirms That Amgen's Claims Are Enabled 34

C. Sanofi-Regeneron's Failure To Show Any Difficult-To-Make Embodiments Confirms Enablement 37

II. The Jury Was Not Required To Accept Sanofi-Regeneron's Theory That the Genus Encompasses Millions of Antibodies That Would Need To Be Tested 39

A. The Evidence Showed That the Claims' Scope Is Narrow 40

B. The Possibility of "Conservative Substitutions" Does Not Yield Millions of Antibodies That Must Be Tested 42

1. Table 1 Substitutions Do Not Yield Millions of Distinct Antibodies—Just Minor Variants That Are All Enabled 43

2. Table 1 Variants Do Not Require Testing for Binding PCSK9's Sweet Spot 46

C. The District Court's Invocation of "Random Mutations" Is Unsupported 49

III. The District Court's Analysis of Other *Wands* Factors Also Defies JMOL Standards 51

A. Predictability: The Jury Reasonably Could—and Implicitly Did—Find the Art Predictable 51

1. Ample Evidence Showed the Disclosed Methods for Obtaining Claimed Antibodies Were Predictable 52

2. The District Court's Rationale Departs from the Purpose of the Predictability Inquiry and Misconceives the Antibody Arts....54

3. The Court Erred in Finding Conservative Substitutions "Unpredictable" as a Matter of Law....56

4. The Jury Was Entitled To Find That Any Confirmatory Processes Were Quick and Routine....60

B. Amount of Guidance: The District Court's Analysis of Guidance Disregards the Patents' Roadmap Based on an Erroneous Comparison....61

IV. The District Court's Interpretation of the "Full Scope" Requirement Contravenes Longstanding Enablement Law....63

CONCLUSION....69

TABLE OF AUTHORITIES

Page(s)

CASES

ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.,
694 F.3d 1312 (Fed. Cir. 2012) 55

AK Steel Corp. v. Sollac, 344 F.3d 1234 (Fed. Cir. 2003) 46, 64, 67

Amgen Inc. v. Sanofi, 872 F.3d 1367 (Fed. Cir. 2017) .....*passim*

In re Angstadt, 537 F.2d 498 (C.C.P.A. 1976) 66, 69

Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.,
876 F.3d 1350 (Fed. Cir. 2017) 30, 51

Atlas Powder Co. v. E.I. du Pont De Nemours & Co.,
750 F.2d 1569 (Fed. Cir. 1984) 66, 67

Battin v. Taggert, 58 U.S. (17 How.) 74 (1854).....30

Bio-Tech. Gen. Corp. v. Genentech, Inc., 267 F.3d 1325
(Fed. Cir. 2001).....*passim*

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.,
320 F.3d 1339 (Fed. Cir. 2003) 30

CEATS, Inc. v. Cont'l Airlines, Inc., 526 F. App'x 966
(Fed. Cir. 2013).....57

Centocor Ortho Biotech, Inc. v. Abbott Labs., 636 F.3d 1341
(Fed. Cir. 2011).....53, 62

Core Wireless Licensing S.A.R.L. v. LG Elecs., Inc.,
880 F.3d 1356 (Fed. Cir. 2018) 30

Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.,
276 F. Supp. 3d 629 (E.D. Tex. 2017), *aff'd*, 739 F. App'x 643
(Fed. Cir. 2018) (mem.).....67

Fireman's Fund Ins. Co. v. Videfreeze Corp., 540 F.2d 1171 (3d Cir. 1976).....30

In re Halleck, 422 F.2d 911 (C.C.P.A. 1970).....66

Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986).....56

Idenix Pharm. LLC v. Gilead Scis. Inc., 941 F.3d 1149 (Fed. Cir. 2019).....67, 68

Invitrogen Corp. v. Clontech Labs., Inc., 429 F.3d 1052 (Fed. Cir. 2005).....55

Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342 (Fed. Cir. 1998) 38, 56, 62, 67

Kinetic Concepts, Inc. v. Smith & Nephew, Inc., 688 F.3d 1342 (Fed. Cir. 2012) 31, 38, 51, 60

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398 (2007) 69

Lucent Techs., Inc. v. Gateway, Inc., 580 F.3d 1301 (Fed. Cir. 2009).....50

MagSil Corp. v. Hitachi Glob. Storage Techs., Inc., 687 F.3d 1377 (Fed. Cir. 2012) 31, 34, 64

Marra v. Phila. Hous. Auth., 497 F.3d 286 (3d Cir. 2007) 31

Martek Biosciences Corp. v. Nutrinova, Inc., 579 F.3d 1363 (Fed. Cir. 2009).....31, 51

Minerals Separation, Ltd. v. Hyde, 242 U.S. 261 (1916).....64, 65, 66, 69

In re Moore, 439 F.2d 1232 (C.C.P.A. 1971).....66

MorphoSys AG v. Janssen Biotech, Inc., 358 F. Supp. 3d 354 (D. Del. 2019) 48, 64

Mowry v. Whitney, 81 U.S. 620 (1872) 65

Nautilus, Inc. v. Biosig Instruments, Inc., 572 U.S. 898 (2014).....69

Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075 (Fed. Cir. 2008).....52

Starceski v. Westinghouse Elec. Corp., 54 F.3d 1089 (3d Cir. 1995).....30

Trs. of Bos. Univ. v. Everlight Elecs. Co., 896 F.3d 1357 (Fed. Cir. 2018).....30

In re Wands, 858 F.2d 731 (Fed. Cir. 1988).....*passim*

Wood v. Underhill, 46 U.S. (5 How.) 1 (1846).....30, 65

Wyeth & Cordis Corp. v. Abbott Labs., 720 F.3d 1380 (Fed. Cir. 2013).....67, 68

STATUTES

28 U.S.C. § 1295(a)(1).....4

28 U.S.C. § 1331.....4

28 U.S.C. § 1338(a).....4

35 U.S.C. § 112.....19

35 U.S.C. § 112(a).....32, 46

STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, Plaintiffs-Appellants Amgen Inc., Amgen Manufacturing, Limited, and Amgen USA, Inc. note that:

(a) There has been a prior appeal to this Court in this case.

(1) The title and number of that earlier appeal are: *Amgen Inc., Amgen Manufacturing Limited, Amgen USA, Inc. v. Sanofi, Aventisub LLC, Regeneron Pharmaceuticals Inc., Sanofi-Aventis U.S., LLC*, No. 17-1480.

(2) The appeal was decided on October 5, 2017.

(3) The panel consisted of Chief Judge Prost and Circuit Judges Taranto and Hughes.

(4) The opinion was published as *Amgen Inc. v. Sanofi*, 872 F.3d 1367 (Fed. Cir. 2017).

(b) There are no other cases pending in this or any other court that will directly affect or be directly affected by this Court's decision in this appeal.

INTRODUCTION

Two juries have rejected Sanofi-Regeneron's enablement challenge to Amgen's patents, and with good reason: The patents contain a wealth of enabling disclosures that allow persons skilled in the art ("POSAs") to obtain all the claimed antibodies. Despite refusing to grant Sanofi-Regeneron's motion for judgment as a matter of law after the first trial, the district court granted that motion after the second trial. But the court's rationale misconceives antibody science, departs from the patents' disclosure, ignores evidence, and invents new enablement requirements that defy Supreme Court precedent. The court repeatedly acknowledged conflicting evidence, but reweighed the evidence for itself. And the court ultimately based its decision on speculation about what "could be" or "might be"—which falls far short of proof that any reasonable juror would be required to accept as clear-and-convincing evidence of invalidity.

The patents describe and claim a breakthrough invention—***antibodies*** that dramatically lower levels of LDL (or "bad") cholesterol linked to heart disease. Those antibodies bind to a small region—the "sweet spot"—on a protein called "PCSK9." They thereby block PCSK9 from binding to "LDL receptors" that are responsible for removing cholesterol from the bloodstream. The inventors showed that blocking PCSK9 from binding to LDL receptors frees them to remove more LDL cholesterol. The patents characterize 26 antibodies representing the full

structural diversity of the claimed genus. And they provide a detailed "roadmap" that teaches POSAs how to obtain the other antibodies within the claims. Amgen's expert, Dr. Rees, testified that POSAs following the patents' teachings would "make all the antibodies within the scope of the claims." Appx3908(757:12-14); *see* Appx3909(762:14-20). Despite having obtained a remand so it could argue invalidity based on post-priority-date antibodies, Sanofi-Regeneron failed to identify a single, actual antibody that could not be produced quickly and easily using the patents' roadmap. The jury was entitled to find that failure of proof dispositive.

The district court nonetheless made its own findings—that the claim scope is vast, that the art was unpredictable, and that the patents provide no meaningful guidance to POSAs in making additional antibodies. The court then speculated that it would require undue experimentation to make ***every*** antibody covered by the claims. But that is not the test. And the court's "findings" contradict witness testimony saying the opposite, backed by evidence and science.

On scope of claims, Amgen showed the genus is small—a reasonable fact-finder could find it to be in the range of 400 distinct antibodies. Because the "sweet spot" on PCSK9 is a small region with a unique structure, only a limited number of antibodies have the physical and chemical structure to bind there. The restricted immune response of super-immunized mice producing antibodies to the PCSK9 antigen confirms that small number. So does the limited number of actual

antibodies produced at trial. The jury was entitled to credit that evidence and, on JMOL, the court was bound to accept it.

Instead, the court ignored that evidence and accepted Sanofi-Regeneron's effort to artificially inflate the number of antibodies, invoking the patents' discussion of how to make "variants" of antibodies through "conservative substitutions." Accepting the calculations of Sanofi-Regeneron's expert, the court stated that it "appear[ed]" to be uncontested that conservative substitutions would yield "millions" of "potential candidates" that must be tested to see if they still bind PCSK9. But all of that was contested. A reasonable juror could easily have rejected Sanofi-Regeneron's argument. The jury certainly was not compelled to accept it as clear and convincing.

Conservative substitution variants are more than 99% identical to the reference antibody, differing from the original only through replacement of one or two amino acids with others that have similar characteristics. The evidence showed that POSAs would not view minor changes through conservative substitutions as creating a new and different antibody with unpredictable activity. Sanofi-Regeneron's own witnesses testified that POSAs would expect such minor variants to bind and block like the original. Sanofi-Regeneron did not identify a single example of conservative substitution to a claimed antibody that stopped it from binding PCSK9 and blocking the interaction with LDL receptors.

The district court's finding that "any reasonable factfinder would conclude that the patent does not provide significant guidance or direction" is unfounded. The patents disclose not merely the inventors' success in generating dozens of antibodies that bind the "sweet spot" on PCSK9—and block it from interfering with LDL receptors—but also detail the techniques that achieve success.

The enablement test, moreover, does not concern the effort required for POSAs to make every single claimed antibody, as the court supposed. The question is whether POSAs following the disclosure can practice the full scope of the invention. Here, the roadmap enabled POSAs to easily make any antibody within the claims' scope. Under Supreme Court precedent and this Court's cases alike, that is enablement.

JURISDICTIONAL STATEMENT

The district court had jurisdiction under 28 U.S.C. §§1331 and 1338(a). Final judgment was entered on October 3, 2019. Appx36. Amgen timely appealed on October 23, 2019. Appx4394. This Court has jurisdiction under 28 U.S.C. §1295(a)(1).

STATEMENT OF THE ISSUE

Whether the district court erred in holding that any reasonable juror was required to find that Sanofi-Regeneron established non-enablement by clear-and-convincing evidence.

STATEMENT OF THE CASE

I. FACTUAL BACKGROUND

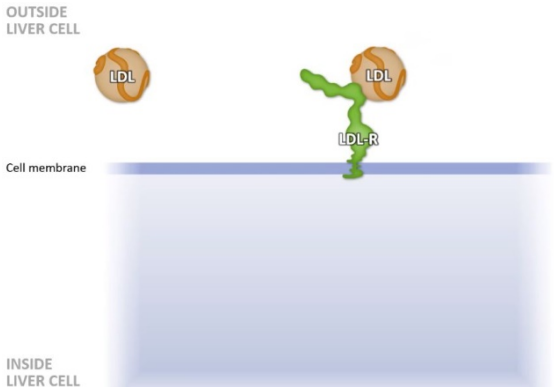
A. Amgen Invents Antibodies To Treat Heart Disease by Dramatically Lowering LDL Cholesterol

High LDL cholesterol levels lead to heart disease—the leading cause of death in the United States—and increase the risks of strokes and other illnesses. Appx3793(487:24-488:4); Appx3678(179:24-180:12). For many patients, traditional medicines, like statins, are insufficient. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1371 (Fed. Cir. 2017).

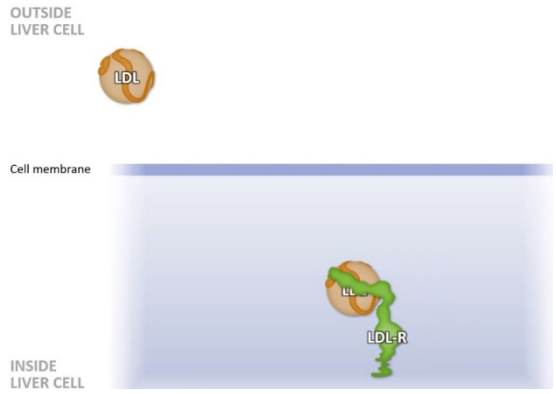
This case concerns Amgen's trail-blazing invention to treat heart disease—a novel class of antibodies that dramatically lower LDL (or "bad") cholesterol. Appx3804(529:4-6). Amgen invested 10 years researching and developing its invention. Appx3793(488:8-12). The result of those efforts was Amgen's Repatha®, which provides a highly effective therapy for patients with high LDL. *Id.*; Appx3804(529:7-20).

Amgen's efforts began in 2005, when Dr. Simon Jackson and his team studied a protein in the body called PCSK9. Appx3795(493:21-494:6). At the time, PCSK9 was thought to affect LDL levels, but no one understood how. Appx3795(495:9-13); Appx3796(500:18-24). Dr. Jackson was the first to discover that PCSK9 binds "directly" to "LDL receptors" that otherwise remove cholesterol from the bloodstream. Appx3795(494:19-495:13); Appx3796(497:17-498:4).

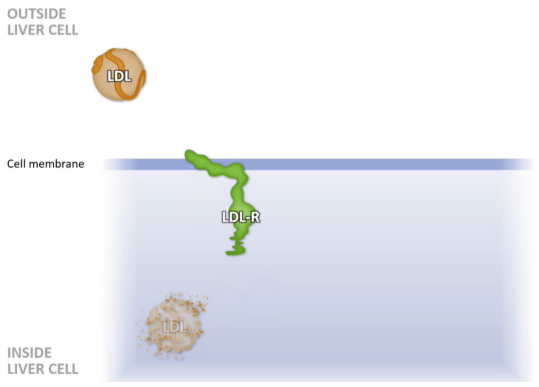
Located on the surface of liver cells, LDL receptors ordinarily "bind" to LDL cholesterol—they capture it.



Appx4073. That process is animated at PDXR24.1 (attached to appendix). The cholesterol-receptor complex is then internalized into the cell.

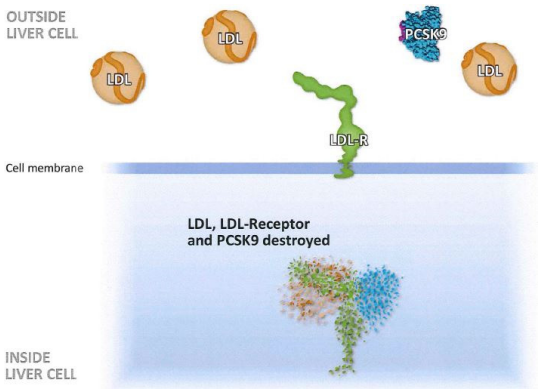


Appx4073. The cholesterol is released inside the cell and destroyed; the receptor then recycles to the surface to capture more cholesterol.



Id.; Appx3678-3679(180:16-181:22); Appx3796(499:10-18). That process is animated at PDXR24.1 (attached to appendix).

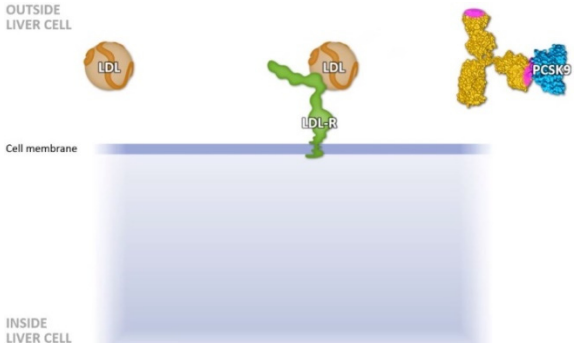
When PCSK9 binds to LDL receptors, however, it causes the LDL, PCSK9, ***and the receptors*** to be destroyed.



Appx4040; Appx3800(513:3-14); Appx3679(181:23-182:20). The diminution of LDL receptors available to remove LDL causes LDL levels to rise. Appx3679(181:23-182:20).

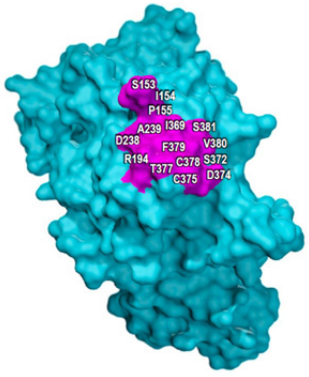
Dr. Jackson "hypothesiz[ed]" that he could develop antibodies that "bind to PCSK9 in the special region" that PCSK9 uses to bind LDL receptors—a region now dubbed the "sweet spot." Appx3796(498:16-499:2); Appx3799(509:9-13).

He also hypothesized—and later confirmed—that, by binding there, the antibodies would block PCSK9 from binding LDL receptors. Appx3796(498:21-499:2); Appx3799(509:20-510:3).



Appx4075. That process is animated at PDXR24.3 (attached to appendix).

PCSK9's sweet spot turns out to be tiny, comprising just 15 of PCSK9's 700 amino acids or "residues." Appx3802(524:10-11); Appx3875(625:5-6); Appx3900(724:15-16); Appx247(100:5-10); Appx180(Fig. 21D).



Appx4152 (purple region shows the sweet spot's 15 amino acids). It also has a "unique" three-dimensional structure and "distinct" "chemical characteristics." Appx3880(644:4-10); Appx3788(467:16-468:7). Consequently, only a limited number of structures can fit its "topology"—its "hills and valleys."

Appx3880(644:4-10); Appx3900(726:4-14); Appx3901-3902(730:21-731:3); Appx3788(467:16-23). But antibodies with the right shape and chemical complementarity to bind PCSK9's sweet spot will block PCSK9 from binding LDL receptors. Appx3876(628:12-629:21).

To create blocking antibodies, Dr. Jackson's research team developed a specialized protocol for super-immunizing mice to generate hybridomas, as well as optimized assays to isolate the antibodies that bind and block—all disclosed in the patents, as explained below (at 13-16).[1] Of the 3,000 antibodies they generated that bound PCSK9, 384 blocked the interaction between PCSK9 and LDL receptors "well," and 85 blocked the interaction by "greater than 90%," Appx236(77:66-78:7); Appx237(80:22- 37); Appx3797-3798(504:4-9, 505:9-15). Following favorable in vitro experiments, Appx242(Ex. 12); Appx3799(510:11-511:14), animal experiments proved for the "first time" that "the antibodies would work just the way [Amgen] wanted them to," lowering LDL, Appx3799(511:20-512:14); Appx242-244(Exs. 13-16).

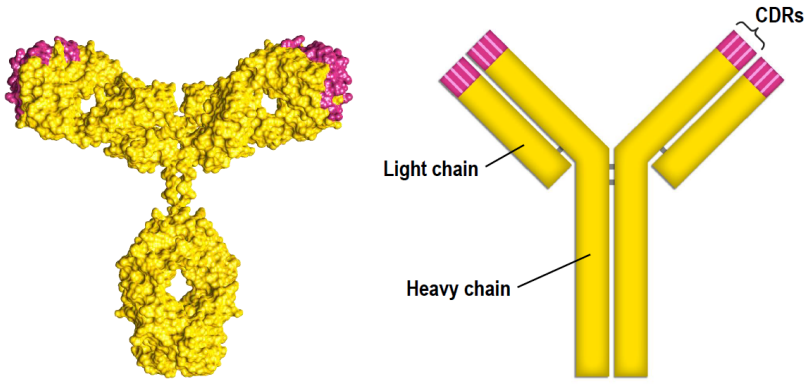
[1] In the antibody arts, POSAs isolate the cells that make antibodies, culturing them as "hybridomas." Appx3797(503:9-17). Hybridomas generate antibodies that can be sorted for ability to bind PCSK9. Appx3797(503:9-504:16).

B. Amgen's Patents Claim a Class of PCSK9 Antibodies That Bind the "Sweet Spot"

Amgen obtained patents on the novel class of PCSK9 antibodies that it invented. *See* U.S. Patent No. 8,829,165 ("'165 Patent"), Appx37-420; and No. 8,859,741 ("'741 Patent"), Appx421-806.[2] Amgen's patents are a "rich handbook" that provides POSAs a "wealth of information." Appx3910(763:1-12). As explained below, they describe techniques that generated the hundreds of blocking antibodies, and provide extensive binning, binding, and blocking data, sequence information, and crystal structures. *See* Appx234-238(Exs. 1-3); Appx240-244(Exs. 9-16); Appx245-249(Exs. 24-31).

The specification discloses the amino-acid sequences of 26 representative antibodies, including sequence information for their complementary determining regions ("CDRs"). Appx51-116(Figs. 2A-3JJJ); Appx240(85:9-12, 85:35-43); Appx3800(513:15-22); Appx3868(598:21-23). The CDRs (in pink below) are the tips of the antibodies, where they bind with PCSK9.

[2] The '165 and '741 Patents share a specification. For convenience, only the '165 Patent is cited.



Appx4134. CDRs are "where all the action is"—they determine whether the antibody has the shape and chemical "complementarity" to "fit," and therefore bind, an antigen like PCSK9. Appx3680(186:9-24); Appx214(33:25-33); Appx3761-3762(360:18-361:14); *see* Amgen's Resp. Br. 7-9, No. 17-1480 (Fed. Cir.), Doc. 120 (explaining antibody science); Appx3876(629:10-15). The CDRs are "what make[ ] one antibody different from another one"—the rest of the antibody simply serves as a "scaffold" that holds the CDRs "in the right place." Appx3680(186:11-24). Of an antibody's six CDRs, "CDR3" of the "heavy chain" is the "most important." Appx3680(187:21-188:5).

The inventors conducted x-ray crystallography studies on two of the 26 exemplary antibodies—"21B12" and "31H4." Appx169-171(Figs. 19A-19B, 20A); Appx174-176(Figs. 20D-20F); Appx247-249(Exs. 28-31); Appx3800(514:25-516:13).[3] X-ray crystallography provides an atomic-level picture of where the antibodies bind. Appx3897(712:19-714:5); Appx247-249(Exs. 29-30). Figure

[3] 21B12 is the basis for Amgen's Repatha product. Appx3800(513:23-514:2).

20A from the patents shows where antibodies 21B12 and 31H4 (in yellow) bind to the sweet spot (in blue).

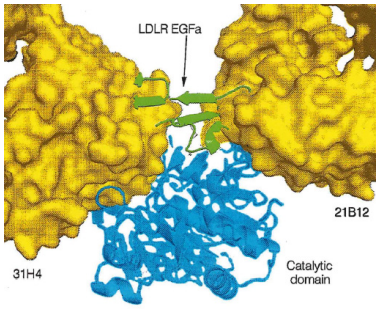


FIG. 20A

Appx171(Fig. 20A).

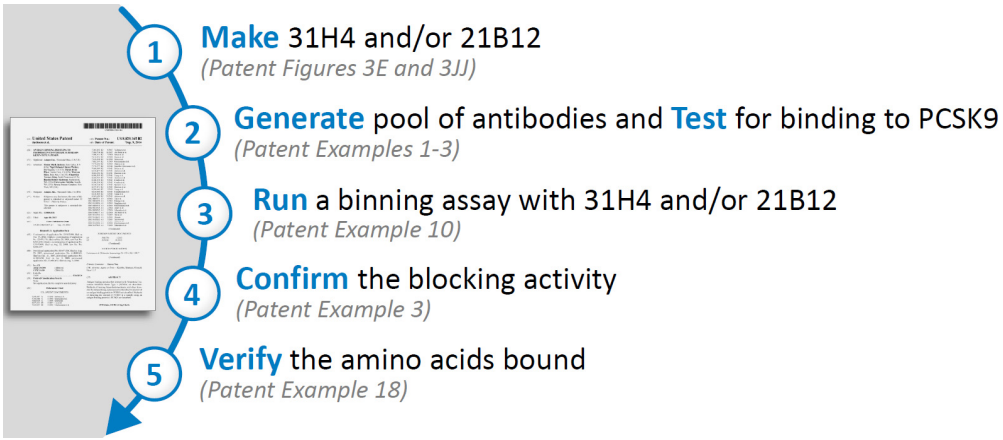
Those two antibodies bind across the sweet spot—one on each side. *See* Appx3876(630:19-25). Consequently, as explained below, POSAs can use 21B12 and 31H4 as "anchors" to identify other antibodies that bind anywhere on PCSK9's sweet spot. Appx3904(742:6-13). The crystal structures in the patents also disclose the atomic structure of the 15 amino acids of PCSK9's sweet spot as it binds to LDL receptors. Appx247(100:5-10); Appx249(Ex. 31); Appx3801(518:16-519:5).

Amgen's patents claim classes of antibodies that bind to one (or more) of the 15 amino acids or "residues" that constitute PCSK9's sweet spot, blocking PCSK9 from binding to LDL receptors. Appx411-412(427:46-430:23); Appx3801(517:2-518:6); Appx247(100:18-27). For example, independent claim 1 of the '165 Patent recites "[a]n isolated monoclonal antibody, wherein, when bound to PCSK9, the

monoclonal antibody binds to at least one" of 15 amino acids comprising the sweet spot, "and wherein the monoclonal antibody blocks binding of PCSK9 to LDL[receptors]." Appx411(427:47-52). Dependent claim 19 covers "[t]he isolated monoclonal antibody of claim 1 wherein" the antibody "binds to at least two" of those amino acids. Appx412(429:7-11).

C. Amgen's Patents Provide a Detailed Roadmap for Making the Claimed Antibodies

The patents also disclose detailed directions for quickly and easily making the claimed antibodies. Appx3903(736:1-7); Appx3908(757:12-14); Appx3909(762:14-20). That "roadmap" leverages the inventors' discovery of 21B12 and 31H4 by using those "anchor" antibodies as a short-cut to obtain the other PCSK9 antibodies. *See* Appx3904(742:6-13). The patents' roadmap thus starts where the inventors' experiments finished.



Appx4123.

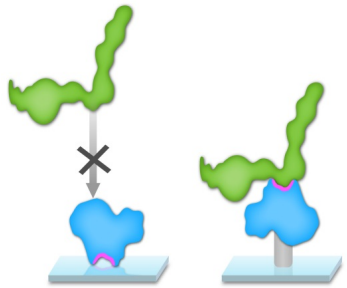
First, POSAs make either 21B12 or 31H4—antibodies ***already demonstrated*** by the patents to bind to the claimed residues and block PCSK9's interaction with LDL receptors. Appx3903(737:12-738:6); Appx3876(630:20-25); Appx3881(649:20-650:14). POSAs can easily make those antibodies. *See* Appx238-239(Exs. 4.1-5); Appx59(Fig. 3E); Appx90(Fig. 3JJ); Appx3903(737:12-738:10).

Second, by applying Amgen's super-immunization protocol to transgenic mice—mice genetically engineered to produce human antibodies—POSAs generate a pool of PCSK9 antibodies. Appx234-235 (Ex. 1); Appx3797(501:2-502:15); Appx3904(739:15-740:14). When the "extensive schedule" of immunizations disclosed in Table 3 of the patents is used, Appx3904(739:21-740:2); Appx3797(501:2-502:15); Appx234(Tbl. 3), the mice maximize production of the "full spectrum" of PCSK9 antibodies, Appx3904(739:24-740:11).[4]

The patents explain how to use Amgen's enhanced assays to identify the mouse-produced antibodies that bind PCSK9. *See* Appx236-238(Ex. 3). Those assays are "optimize[d]" to "find[ ] the antibodies that were binding in that specific region where PCSK9 binds to the LDL receptor" (the "sweet spot"). Appx3904(740:22-741:5); Appx3797(503:18-504:3); Appx3905(744:3-19). The

[4] The patents teach that, alternatively, phage displays—a non-animal means of generating antibodies, Appx3896(709:2-10)—can be used, Appx223(52:23-42); Appx224(53:27-29); Appx225(55:1-5); *see* Appx3909(759:7-17).

optimized assay orients PCSK9 (in blue below) so that its sweet spot (pink)—which "interact[s] with the LDL receptor" (green)—is "accessible to the antibodies" for binding. Appx3797(503:19-23); Appx3904(740:16-741:9).



The binding assays are high-throughput, allowing POSAs to screen hundreds of antibodies at once. Appx3797(504:10-18); Appx3898(718:3-23).

Third, the patents teach using one of the "anchor" antibodies from step one—21B12 or 31H4—to identify the mouse- (or phage-) produced antibodies that bind residues of PCSK9's sweet spot. POSAs conduct "binning" assays to identify which antibodies "compet[e]" with the anchor antibody to bind the same area. Appx3904(741:10-742:13); *see* Appx241-242(Ex. 10). Antibodies that bind to the same or overlapping regions are in the same "bin." Appx3767(382:8-11); Appx3798(507:18-508:23). If a generated antibody competes with an anchor antibody, POSAs have "a very good idea" that the new antibody binds the "sweet spot" and falls within the claims. Appx3904(741:24-742:5). Binning assays are high-throughput. *See* Appx241(88:34-47); Appx3898(718:3-23); Appx3909(761:1-762:1).

Fourth, the patents teach running Amgen's optimized blocking assay to confirm whether, and, if desired, to what extent, the antibodies that co-bin with 21B12 or 31H4 (or both) block PCSK9's interaction with LDL receptors. Appx3904-3905(742:14-743:17); *see* Appx3798(505:2-8). ***Fifth***, the patents explain that POSAs can, if they wish, "verif[y] . . . exactly which amino acids . . . [the] antibodies are binding to." Appx3905(744:20-745:12). POSAs can conduct alanine scanning, Appx244(Ex. 18), which takes only a couple of days, Appx3906(748:3-16).

D. Amgen's Patents Disclose a Prior-Art Method of Making "Variants"

In addition to the roadmap, the patents explain how to make "variants" of claimed antibodies "using well-known techniques" involving "conservative" amino-acid substitutions. Appx221(48:21-23, 48:29-33). Because amino acids "can be divided into classes based on common . . . properties," Appx211(27:32-39), some can be substituted for others while "retain[ing] a similar biological activity," Appx211(27:60-62, 28:1-3, Tbl. 1). POSAs would not make every possible substitution; they instead would selectively choose one or two "conservative" substitutions to achieve a desired goal (referred to as "intelligent" substitutions). *See* Appx3902(732:19-733:22); Appx3907(753:1-20); *see also* Appx220(46:55-64); Appx222(49:55-60).

Well-known since the 1980s, Appx3902(733:12-22); Appx3907(753:1-20), conservative substitutions are "a standard protocol and method . . . that all antibody scientists use," Appx3917(792:23-793:3). Variants made through conservative substitutions with one or two changes are over 99% similar to the original antibody.[5] Indeed, Sanofi-Regeneron's expert Dr. Eck characterized even antibodies with up to ten amino-acid differences in the heavy-chain variable region as "essentially copies of each other"; they share "common structural features." Appx3788(467:7-15).[6] Sanofi-Regeneron's Dr. Boyd similarly characterized antibodies that are "very close in sequence" as "the same antibody" since they bind in the same way. Appx3763(368:9-15). "Conservative" substitutions are made without "substantially chang[ing] the structural characteristics of the parent sequence," Appx222(49:65-50:1), and thus "without destroying activity" of the antibodies, Appx221(48:23-33).

[5] For example, antibody 31H4's heavy chain is 123 amino acids long (Appx288 at SEQ ID No. 67), and its light chain is 111 amino acids long (Appx267 at SEQ ID No. 12), for a total of 234 amino acids. As explained below, Sanofi-Regeneron's expert Dr. Boyd suggested making two substitutions to the heavy chain. Appx3688(219:18-220:7). That yields an antibody that is 232 of 234 amino acids identical to 31H4, or 99.1% the same.

[6] The referenced testimony concerned a "set of 12 antibodies" Dr. Eck described as "very close variants of each other." Appx3788(465:1-11). Sanofi-Regeneron presented a demonstrative that, Dr. Eck explained, showed the "sequences" of "the heavy chain variable" region of those antibodies. Appx3778(425:23-426:5). Comparison of the sequences of 25A7 and 21B12, for example, showed 10 amino-acid differences in that region. *See* Appx4317.

II. PROCEEDINGS BELOW

In 2014, Amgen sued Sanofi-Regeneron in the District of Delaware, Appx2, alleging that Sanofi-Regeneron's drug Praluent® infringes its '165 and '741 Patents, *Amgen*, 872 F.3d at 1371-72. Like Amgen's Repatha, Praluent is an antibody that targets PCSK9's sweet spot; it thereby prevents PCSK9 from binding to, and causing the destruction of, LDL receptors. *Id.* at 1372. Sanofi-Regeneron stipulated to infringement. Appx2058-2059. But Sanofi-Regeneron asserted invalidity defenses—written description, enablement, and obviousness.

A. First Trial and Appeal

After a five-day trial, the jury rejected Sanofi-Regeneron's written-description and enablement challenges, and the district court denied Sanofi-Regeneron's motion for JMOL. Appx2061-2065; Appx2885. The court granted Amgen's motion for JMOL of non-obviousness. *See Amgen*, 872 F.3d at 1379-80.

On appeal, this Court affirmed the district court's grant of JMOL of non-obviousness, but ordered a new trial on written description and enablement. 872 F.3d at 1379-82. The Court ruled that the district court had erred in categorically excluding evidence of PCSK9 antibodies developed after the patents' January 2008 priority date. *Id.* at 1375. The Court also held that the district court had given erroneous jury instructions on written description, identifying the "correct[]" instructions for remand. *Id.* at 1375-79.

B. Second Trial and the District Court's JMOL Decision

At the second trial, Sanofi-Regeneron presented post-priority-date antibodies—including Praluent (alirocumab) and antibodies created by Merck (1DO5 and AX132) and Pfizer (J16)—as evidence that Amgen's patents lacked written-description and enablement. *See, e.g.*, Appx3681(191:9-15); Appx3753(326:25-327:18); Appx3878(635:23-636:10). The jury again found for Amgen.[7] On JMOL, the court upheld the jury's verdict on written description, Appx7-11, but overturned the jury's verdict on enablement, Appx11-25.

1. *Written Description*

The district court upheld the jury's finding that Amgen's patents satisfied §112's written-description requirement. Appx9. It acknowledged testimony by Amgen's experts that "three-dimensional structure"—not amino-acid sequence—"was the appropriate metric for compari[ng]" antibodies within the claimed genus. *Id.* And there was "substantial evidence of similarity in the three-dimensional structure of the antibodies disclosed in the patent[s] and the Competitor Antibodies." *Id.* Thus, the court held, "substantial evidence . . . supports the jury verdict of validity under the representative species test." Appx10.

[7] Amgen selected claims 7, 15, 19, and 29 of the '165 Patent and claim 7 of the '741 Patent for retrial. Appx3631-3632. The jury rejected Sanofi-Regeneron's enablement challenge to all claims and its written-description challenge to claim 7 of the '741 Patent and claims 19 and 29 of the '165 Patent. Appx3.

2. *Enablement*

Instructed on the factors in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), *see* Appx2906-2907, the jury found for Amgen on enablement. Despite repeatedly acknowledging that there was "conflicting testimony" regarding many factors, *e.g.*, Appx17, the court held Amgen's claims not enabled, Appx25.

State of the Art and Skill in the Field. The parties' experts agreed on several *Wands* factors, including nature of the invention, state of the art, and skill of those in the field. *See* Appx19-20. They concurred that antibody arts were well-established by the January 2008 priority date. *See* Appx3758(347:9-22); Appx3902(734:3-15); Appx3909(761:1-762:4). They agreed that techniques for making antibodies were well-developed, automated, and routine. *See* Appx3909(761:1-762:4); Appx3897(712:1-714:6). POSAs thus "would be familiar with the techniques disclosed in the patent[s]." Appx20. The other *Wands* factors, however, were hotly contested.

Breadth of the Claims. Amgen's experts, Dr. Petsko and Dr. Rees, testified that the claims are "very narrow" and that "the genus of antibodies that bind the sweet spot and block is small." Appx3883(658:1-5); Appx3910(763:20-22). Dr. Petsko, a structural biologist, Appx3872(613:17-20), explained that PCSK9 has a tiny sweet spot of just 15 amino-acid residues, Appx3875(625:5-6). In addition, as both sides' experts explained, its biochemical properties and shape are "unique."

Appx3880(644:4-14); Appx3788(467:16-468:7). Consequently, only a limited number of antibodies can have the structural shape and chemical complementarity to fit the sweet spot. Appx3900(724:20-725:5); Appx3901-3902(730:21-731:3). Dr. Rees, an antibody scientist, further explained that the immune system has a "restricted" response that produces only a limited number of antibodies that can bind PCSK9's sweet spot. Appx3902(732:9-18).

The jury heard evidence from which it could conclude that the number of distinct antibodies within the claims was around 400. The patents disclose that Amgen isolated 384 antibodies that bound PCSK9 and blocked the interaction with LDL receptors "well." Appx237(80:22-23); Appx3798(505:10-12). Of those, 85 blocked the interaction by "greater than 90%." Appx237(80:35-37); Appx3798(505:12-15). At trial, Sanofi-Regeneron introduced evidence of only Praluent and three antibodies from other companies falling within the claims. Appx3760(353:6-22). And Regeneron's CEO admitted that, beyond Praluent, Regeneron had generated only "five or so" additional antibodies within the claims. Appx3766(379:1-11). Although Sanofi-Regeneron's expert speculated that there "could potentially be millions" of antibodies within Amgen's claims, Appx3688(218:9-16), the evidence of ***actual*** antibodies was around 400, at most.

The district court nevertheless ruled that the claim scope is "vast." Appx16. The court did not find that a large number of antibodies meet the claim limitations.

It stated that "there does not appear to be a genuine dispute" that there are "millions of ***candidates***" that "would need to be tested to determine whether they fell within the claims." *Id.* (emphasis added). The court relied on Dr. Boyd's testimony that, if a POSA made two conservative amino-acid substitutions listed in the patents' Table 1, at ***each*** position in the heavy chain of one of the representative antibodies, the result would be "97,000 antibodies that she would then have to test to see whether they bound to PCSK9 and blocked binding to LDL receptors." Appx15-16; *see* Appx3688(219:18-220:7). Performing those same substitutions for each of the 26 representative antibodies would yield "millions." Appx16. The court cited no evidence that POSAs actually would make all those changes; nor did it dispute testimony they would not. *See* Appx3902(733:2-7).

The court did not address the fact that Dr. Boyd's posited substitutions yield variants that are more than 99% ***identical*** to the reference antibody. *See* p. 17 & n.5, *supra*. Testimony from Sanofi-Regeneron's own experts indicated that even antibodies with up to ***10*** amino-acid differences in the heavy-chain variable region should be considered "essentially copies of each other" and would bind in the same way. *See* p. 17 & n.6, *supra*; Appx3788(467:7-15). The patents explained that the point of "conservative amino acid substitutions" was that replacing amino acids with similar alternatives yields variants "without destroying the biological activity." Appx221(48:29-33). The opinion does not mention that Sanofi-

Regeneron identified not one conservative substitution that destroyed the claimed biological activity.

Predictability. Sanofi-Regeneron's experts acknowledged that similar antibodies are likely to bind to an antigen in the same way and thus could be considered "the same antibody." Appx3763(368:9-15); *see* Appx3787-3788(464:9-465:5). But Dr. Boyd insisted that the art was unpredictable because scientists cannot tell, in the first instance, whether an antibody will bind by examining its amino-acid sequence alone. Appx3749(309:5-11). Amgen's Dr. Rees rejected that perspective. "[A]ntibody scientists," he explained, "focus on structure," not sequence. Appx3910(765:10-766:12). He explained that scientists create antibodies using mice or phage displays, Appx3896(709:2-10); Appx3909(759:11-17), which predictably produce antibodies within the claims—and do so based on structure, not amino-acid sequence, Appx3909(762:15-20); Appx3910-3911(766:13-767:15); Appx4138.

The court acknowledged "conflicting testimony as to the predictability of the art," and that Amgen's Dr. Rees had testified the art was "'highly predictable.'" Appx17-18. Accepting Sanofi-Regeneron's "sequence" theory over Dr. Rees's testimony, however, the court found the art was "unpredictable" as a matter of law. Appx17, Appx19. The court did not reconcile that approach with its acknowl-

edgement, for written description, that what matters is "structure," not sequence. Appx9.

The court dismissed Dr. Rees's testimony that variants using Table 1 substitutions would not need to be tested for activity, Appx18—that variants from conservative substitutions to an antibody that already binds and blocks do not "lose" those characteristics, Appx3902(733:2-22). The court did not mention testimony from Sanofi-Regeneron's own experts that antibodies that are so similar are effectively "copies" that will bind similarly. *See* Appx3763(368:9-15); Appx3787-3788(464:9-465:5); Appx3788(467:7-15); *see* p. 17 & n.6, *supra*.

Guidance and Examples. Amgen's Dr. Rees explained that the patents' roadmap will "generate the antibodies" covering the full scope of the claims with "certainty." Appx3908(756:8-20, 757:12-14); Appx3909(762:14-20). Sanofi-Regeneron's antibody expert, Dr. Ravetch, opined that POSAs using "well established," prior-art techniques would "inevitabl[y]" get the antibodies "claimed by Amgen." Appx3896-3897(709:2-711:11).

The district court, however, ruled that Amgen's patents did not "provide significant guidance or direction." Appx22. The court dismissed the patents' roadmap for making antibodies, beyond the 26 representative antibodies, deeming it "significant[ly] similar[]" to Dr. Jackson's original research process. Appx20-21. The court did not explain why that comparison was legally relevant. Nor did it

mention the differences between the original research and the ensuing roadmap, which ***starts*** with two working antibodies the inventors created and characterized in the patents.

Quantity of Experimentation Necessary. At trial, Amgen presented evidence that the generation and isolation of claimed antibodies using the roadmap is routine, cheap, and quick. Restricted immune response means that the number of unique antibodies generated, even by super-immunizing mice, will be limited. Appx3902(732:9-18). Sorting the ones that bind and block as the patents require was routine. Appx3903(737:3-11); Appx3897(711:22-712:15). High-throughput techniques and "advanced" robotic technology allow antibodies in "thousands of wells" to be processed simultaneously using the assays the patents disclose; as a result, the claimed antibodies can be isolated "in a very short space of time." Appx3898(718:3-23).

Sanofi-Regeneron introduced no evidence of any actual antibody that would not be quickly made using the roadmap. Dr. Boyd speculated that scientists "***could be*** immunizing mice for a hundred years" without being certain they had found every embodiment. Appx3754(330:18-22) (emphasis added). While recognizing that the "parties dispute how much experimentation is needed" to practice the claims, Appx22, the court credited Dr. Boyd's speculation that "'[t]here ***might*** be'" a hypothetical antibody POSAs would not identify using the roadmap,

Appx23 (emphasis added). The court thus concluded that "enabl[ing] the full scope of the claims would take a substantial amount of time and effort." Appx24.

The Court's Conclusion. "In light of" its own "factual conclusions" on the *Wands* factors, the court "determine[d] as a matter of law that undue experimentation would be needed to practice the" claims' "full scope." Appx24-25. The court thus granted JMOL "for lack of enablement." Appx25.

SUMMARY OF ARGUMENT

I. A. Amgen's patents provide POSAs a wealth of enabling information. Witness after witness testified about the 26 representative antibodies within the claims that the patents characterize and the "roadmap" that allows POSAs to produce all other claimed antibodies. As Dr. Rees explained: If "you applied . . . what you have revealed in the patent plus the road map you would be certain to make all of the claim's antibodies." Appx3909(762:14-20); *see* Appx3908(757:12-14).

B. This Court's seminal enablement decision, *Wands*, demonstrates that Amgen's patents are enabled. The disclosures in *Wands*—also an antibody case—were dwarfed by the disclosures here, and were based on a state of technology now decades past. Yet this Court held the patent enabled. The jury here was amply justified in finding that Sanofi-Regeneron failed to clearly and convincingly prove the patents' rich disclosures were not enabling. The district court's contrary holding defies *Wands*.

C. Sanofi-Regeneron failed to identify a single, actual antibody that could not be made following the patents' roadmap. The jury could find that failure, by the party with a steep burden of proof, compelling. Sanofi-Regeneron's expert and the opinion below speculated that "'[t]here ***might be kind of*** an antibody'" out there waiting to be found. Appx23 (emphasis added). Such speculation is not clear-and-convincing proof of non-enablement that any reasonable juror would be required to accept.

II. The evidence showed that Amgen's claims are narrow. The district court, however, adopted Sanofi-Regeneron's argument that applying every possible conservative substitution described in Table 1 yields a "vast" genus or "millions" of candidates that must be tested. A reasonable jury was not required to accept that theory.

A. Viewing the evidence most favorably to the verdict, the jury could find the genus was around 400 antibodies (Amgen having found 384 that blocked PCSK9's interaction with LDL receptors "well"). At trial, the parties identified at most 35 distinct antibodies shown to bind residues in the sweet spot, 26 of which were characterized in Amgen's patents. Amgen's witnesses explained the scientific reason the genus was small: PCSK9's tiny sweet spot and unique topology. POSAs would recognize that relatively few antibodies would have the structural and chemical complementarity to bind to that small, unique region.

B. The jury was not required to accept Sanofi-Regeneron's effort to inflate the genus based on Table 1's list of "conservative substitutions," which defies how POSAs would understand and apply Table 1. Conservative substitution ***begins*** with an antibody within the claims and replaces just one or two amino acids with another known to be chemically and structurally similar. It thus does not produce distinct antibodies, but 99% identical "variants" of the original. Sanofi-Regeneron described antibodies with far more differences as mere "copies" of each other. The patents teach, and evidence showed, that POSAs understood that such substitutions do not destroy the antibody's binding to PCSK9. While Sanofi-Regeneron cited snippets of testimony about "testing," that was not in the context of applying Table 1. It cannot compel jurors to find non-enablement by clear-and-convincing evidence.

C. The district court speculated there "could" be antibodies discoverable only by "random mutation." The court never explained what it meant and cited no evidence for a random-mutation approach. Insofar as "random mutations" are relevant, the jury heard that the processes in the roadmap would account for them, producing the full structural diversity of antibodies across the entire genus.

III. The court's remaining *Wands* analysis was similarly flawed.

A. On predictability, the jury heard extensive testimony that the art was predictable because antibody-production techniques—*e.g.*, immunizing transgenic

mice—were well established in 2008 and the skill level was high. The jury heard evidence that the roadmap predictably and reliably generates claimed antibodies. The court reached the wrong result by asking the wrong question. The court asked whether POSAs can predict an antibody's activity in the abstract by looking at amino-acid sequence alone. But antibody scientists do not make antibodies based on amino-acid sequences in the abstract. They use the techniques disclosed in the patents—including transgenic mice and phage displays—to reliably generate antibodies.

B. Downplaying the patents' rich guidance, the opinion below declared that the patents' roadmap "do[es] not improve a [POSA's] ability to discover non-disclosed antibodies" and "does not provide significant guidance or direction." Appx20; Appx22. But the opinion ignores that the patents provide the guidance that matters: Following the patents' roadmap produces claimed antibodies—every time.

IV. The opinion evaluated enablement by examining the effort required for POSAs to discover and make ***each and every possible*** antibody within the claims. This Court and the Supreme Court have long rejected that view as contrary to the Patent Act and good policy. The disclosure must be "commensurate" with the claimed invention—a standard the jury could and did find met here.

STANDARD OF REVIEW

"[G]ranting judgment as a matter of law for the party carrying the burden of proof is generally 'reserved for extreme cases' . . . ." *Core Wireless Licensing S.A.R.L. v. LG Elecs., Inc.*, 880 F.3d 1356, 1364 (Fed. Cir. 2018); *see Fireman's Fund Ins. Co. v. Videfreeze Corp.*, 540 F.2d 1171, 1177 (3d Cir. 1976). Because Sanofi-Regeneron had the burden of proving non-enablement by clear-and-convincing evidence, its burden on JMOL was "doubly high: it must show that no reasonable jury could have failed to conclude that [its non-enablement] case had been established by clear and convincing evidence." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1353 (Fed. Cir. 2003).

This Court reviews enablement de novo as "a question of law," *Trs. of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1361 (Fed. Cir. 2018), although the Supreme Court has held that enablement is a question of fact for the jury, *see Battin v. Taggert*, 58 U.S. (17 How.) 74, 85 (1854); *Wood v. Underhill*, 46 U.S. (5 How.) 1, 5-6 (1846).[8] The verdict's factual underpinnings are reviewed "for substantial evidence"; the Court presumes that the jury resolved each dispute in support of its verdict. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1358, 1364 (Fed. Cir. 2017); *see Starceski v. Westinghouse Elec. Corp.*, 54 F.3d 1089, 1100 (3d Cir. 1995). The record evidence "must be considered in

[8] Amgen notes this discrepancy for preservation purposes.

the light most favorable to the jury's verdict, drawing reasonable factual inferences and resolving issues of credibility in favor of the verdict." *Bio-Tech. Gen. Corp. v. Genentech, Inc.*, 267 F.3d 1325, 1329 (Fed. Cir. 2001); *see Marra v. Phila. Hous. Auth.*, 497 F.3d 286, 300 (3d Cir. 2007).

ARGUMENT

The enablement requirement is satisfied if the specification teaches POSAs "how to make and use the full scope of the claimed invention without 'undue experimentation.'" *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012). The jury was entitled to reject Sanofi-Regeneron's enablement challenge. Ample evidence showed that Amgen's patents disclose a "roadmap" for making all antibodies within the claims. Reasonable jurors could find that Sanofi-Regeneron failed to prove the opposite by clear-and-convincing evidence. Indeed, Sanofi-Regeneron did not identify a single, actual antibody that could not be made quickly and easily using the roadmap.

Overturning the verdict, the district court ignored evidence the jury could have credited, reweighed conflicting testimony, credited unsupported speculation by Sanofi-Regeneron's experts, and embarked on its own fact-finding in violation of Rule 50. *See Bio-Tech.*, 267 F.3d at 1329. That is reason enough to reverse, as this Court has held time and again. *See, e.g.*, *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1368-69 (Fed. Cir. 2012); *Martek Biosciences Corp.*

v. Nutrinova, Inc., 579 F.3d 1363, 1378-79 (Fed. Cir. 2009). But the court also adopted an erroneous legal standard—one measured in terms of the effort required to "discover[]" and make "every" "embodiment[] of the claims"—that is contrary to precedent from the Supreme Court and this Court. Appx15. For that reason, too, the decision below cannot stand.

I. SUBSTANTIAL EVIDENCE SHOWED—AND *WANDS* CONFIRMS—THAT AMGEN'S CLAIMS ARE ENABLED

Section 112(a) requires that the patent's specification "enable" POSAs "to make and use" the claimed invention. 35 U.S.C. § 112(a). Properly instructed on the factors articulated in *In re Wands*, 858 F.2d 731 (1988), the jury found that Sanofi-Regeneron failed to prove, by clear-and-convincing evidence, Amgen's claims are not enabled. *Wands*—which itself concerned the antibody arts—confirms that finding.

A. Amgen's Patents Contain a Roadmap for POSAs To Practice the Invention's Full Scope

There was no dispute that Amgen's patents characterize 26 antibodies that meet the claims' requirements of binding to specified residues on PCSK9's sweet spot and blocking PCSK9's interaction with LDL receptors. *See* pp. 10-13, *supra*. Those antibodies were found to be "representative of the structural diversity of the genus." Appx9; *see* Appx10. The patents extensively characterize two of those antibodies—21B12 and 31H4—providing their sequence and crystal structure. *See*

pp. 11-12, *supra*. The patents tell POSAs precisely how to make those antibodies. *See* pp. 13-16, *supra*. And the evidence showed that the patents provide POSAs with detailed instructions—a "roadmap"—for using those two antibodies to make the full scope of "antibodies that satisfy the claims." Appx3903(735:20-736:7); Appx3908(757:12-14).

The roadmap begins by directing POSAs to make either 21B12 or 31H4. Appx3903(737:12-738:6). So POSAs start with antibodies ***proven*** to work. As Amgen's expert Dr. Rees explained, the roadmap teaches POSAs to start with those two "anchor" antibodies and, following Amgen's super-immunization protocol and carefully designed binding, binning, and blocking assays, easily produce and isolate other antibodies within the claims. *See* pp. 13-16, *supra*.

While the patents teach significant enhancements (*e.g.*, super-immunization and optimal orientation of the PCSK9 antigen, *see* pp. 13-16, *supra*), the district court agreed that "the methods disclosed in the patent for making the invention were routine and well-known in the prior art." Appx19. POSAs thus "would be familiar with the techniques disclosed in the patent," including "immunizing mice," "binning," and "alanine scanning." Appx20. ***This Court*** recognized that such "methods for obtaining and screening monoclonal antibodies were well known" 30 years before the priority date of Amgen's patents. *Wands*, 858 F.2d at 736.

Sanofi-Regeneron never disputed that following Amgen's roadmap generates claimed antibodies ***every time***, just as it did for Amgen. *See* pp. 24-25, *supra*. That is "not . . . trial and error." Appx3908(756:8-20). And Dr. Rees testified that POSAs following the roadmap "would be ***certain*** to make ***all*** of the claim's antibodies." Appx3909(762:14-20) (emphasis added); *see* Appx3908(757:12-14).

Amgen's specification is thus the epitome of enabling disclosure. A specification that discloses Amgen's discoveries and inventions—including 21B12 and 31H4—and provides a roadmap for using those inventions to make all other claimed antibodies, plainly "teach[es] those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *MagSil*, 687 F.3d at 1380.

B. *Wands* Confirms That Amgen's Claims Are Enabled

Comparison to *Wands*—this Court's seminal enablement decision—confirms that Amgen's claims are enabled. Like the invention here, the invention in *Wands* relied on a class of antibodies that bound a specific antigen. 858 F.2d at 733. The PTO found certain method and compound claims not enabled because "production of" such "antibodies is unpredictable and unreliable, so that it would require undue experimentation . . . to make the antibodies." *Id.* at 735.

The Court explained that the inquiry was whether "undue experimentation" is required "to obtain antibodies needed to practice the claimed invention." 858

F.2d at 740. The Court explained that "[t]he nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics." *Id.* The patent, it continued, "provide[d] a detailed description of procedures for immunizing a specific strain of mice" with the relevant antigen. *Id.* at 737. The mice produced antibodies, which were "assayed to determine whether [they] bind[ ] to the [target] antigen." *Id.* at 737-38. "[B]y screening enough" antibodies—"often hundreds at a time"—those with the "desired characteristics" were found. *Id.* at 738, 740. The evidence showed that, each of three times the inventor performed the "entire procedure," he "was successful . . . in making at least one antibody that satisfied all of the claim limitations." *Id.* at 740.

The Court held the claims enabled. "Practitioners of this art," it explained, "are prepared to screen negative hybridomas in order to find one that makes the desired antibody." 858 F.2d at 740. In the antibody arts, "screening of a single hybridoma" is not considered an "'experiment.'" *Id.* Although the patent required screening a pool of mouse-produced antibodies to identify claimed antibodies, that was not undue experimentation. *Id.*

Wands compels a finding of enablement here. Amgen's patents concern the same antibody art found predictable and reliable in *Wands*—but with the benefit of 30 years of advances and Amgen's disclosed optimizations. As in *Wands*, the

patents here provide a "detailed" procedure for "immunizing . . . mice," 858 F.2d at 737—including an "extensive schedule" for "super-immuniz[ing]" transgenic mice with Amgen's specified 11 immunization "boost[s]," Appx3904(739:21-740:2); Appx234(Tbl. 3). As in *Wands*, the patents here also call for "screening" mouse-produced antibodies ("hybridomas") to isolate those "with desired characteristics," using "assay[s]" to identify those that "bind[ ] to the [target] antigen." 858 F.2d at 737-38, 740; *see* pp. 9 & n.1, 13-16, *supra* (patents' disclosures for sorting antibodies to identify those that bind to PCSK9's sweet spot). In *Wands*, this Court recognized that the process for producing the antibodies is one "[p]ractitioners of this art are prepared" to perform and thus not undue experimentation. 858 F.2d at 740. The same is true here. And critically, as in *Wands*, there is no dispute that POSAs following the patents obtain antibodies that "satisf[y] all of the claim limitations." *Id.* The district court never suggested otherwise.

The district court dismissed *Wands*' guidance on "enable[ment] in the context of antibody technology" because "the claim at issue" supposedly "was a method claim rather than a genus claim." Appx17 n.8. That is wrong. The "claims on appeal" in *Wands* included claims drawn to a genus of monoclonal antibodies against "HBsAg determinants." 858 F.2d at 741 (Newman, J., concurring in part, dissenting in part); *see id.* at 734 (majority opinion). Even so, the district court never explained why that putative distinction matters. It does not. In

Wands, the "sole issue" was whether "undue experimentation" would be required to "produce" the antibodies. *Id.* at 736 (majority opinion). The steps POSAs are "prepared to" undertake to make and isolate the "desired antibod[ies]" are the same, whether the patent claims antibodies for use in a detection method or for blocking PCSK9. *Id.* at 740. And *Wands* holds that the steps for making the antibodies were not undue experimentation. To uphold the decision below—which found non-enablement as a matter of law—would overrule *Wands*.

C. Sanofi-Regeneron's Failure To Show Any Difficult-To-Make Embodiments Confirms Enablement

After Sanofi-Regeneron lost the first trial, this Court overturned the district court's categorical exclusion of post-priority-date evidence, affording Sanofi-Regeneron the opportunity to introduce evidence of post-priority-date antibodies to disprove enablement. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1375 (Fed. Cir. 2017). At trial, Sanofi-Regeneron invoked four—its own Praluent product and three antibodies from Merck and Pfizer, Appx3681(191:2-21)—arguing they disproved enablement, Appx3989-3990(912:21-913:7).

The jury had ample reason to reject Sanofi-Regeneron's position. The evidence showed that POSAs could make Praluent (alirocumab) and the other competitor antibodies through the patents' teachings. Appx3908-3909(757:12-760:21); Appx3918-3919(798:25-799:5). Amgen's expert observed that Praluent likely was among the 384 antibodies Amgen itself initially produced. Appx3918-

3919(798:25-799:5). After years of litigation, despite ample opportunity and incentive, Sanofi-Regeneron failed to identify a single actual antibody not enabled by Amgen's patents. Not one. The jury was entitled to find that failure of proof, by the party with a steep evidentiary burden, persuasive. It was not compelled to find non-enablement proved by clear-and-convincing evidence. This Court has rejected enablement challenges, with far greater evidence of difficulty making the antibody genus, as insufficient as a matter of law. *See Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1359-61 (Fed. Cir. 1998).

Rather than identify a hard-to-make antibody, the district court credited speculation. The court cited testimony from Sanofi-Regeneron's expert that "'you ***could be*** immunizing mice for a hundred years,'" but "'[t]here ***might be kind of*** an antibody that you didn't come up with in that time period.'" Appx23 (emphasis added). But the jury heard zero evidence of ***any*** antibody that could not be made, or required undue experimentation to make, using super-immunized mice or phage displays and the techniques disclosed in the patents. It cannot be that every juror was compelled to disregard the evidence that the roadmap makes all the claimed antibodies—much less accept, as clear-and-convincing proof, speculation that there "might be" or "could be" some hypothetical, but nowhere specified, antibody the roadmap would not generate easily. *Kinetic Concepts*, 688 F.3d at 1367.

II. THE JURY WAS NOT REQUIRED TO ACCEPT SANOFI-REGENERON'S THEORY THAT THE GENUS ENCOMPASSES MILLIONS OF ANTIBODIES THAT WOULD NEED TO BE TESTED

Faced with evidence that the roadmap generates every member of the claimed genus, Sanofi-Regeneron invoked additional disclosures in the patents' Table 1—on how to make "variants" of functioning antibodies—as somehow defeating enablement. Table 1 of the patents, Appx211, lists potential "conservative amino acid substitutions" that POSAs can make to working antibodies, replacing amino acids with similar amino acids, to generate "variants" of working antibodies that remain within the claims. Appx221(48:21-33). The district court accepted Sanofi-Regeneron's position that application of Table 1's teachings yields "millions of candidates" that "need to be tested to determine whether they fell within the claims," deciding that "there does not ***appear*** to be a genuine dispute" on that issue. Appx16 (emphasis added). But that issue—which drove the court's analysis—was disputed. Moreover, the evidence showed that Table 1 provides ***additional enabling disclosure*** that allows POSAs to make variants of antibodies within the claims, secure in the knowledge that they work like the original. The court largely ignored that evidence, as well as myriad other reasons the jury could find Sanofi-Regeneron's theory unpersuasive, and certainly less than clear and convincing.

A. The Evidence Showed That the Claims' Scope Is Narrow

The patents teach that the genus of claimed antibodies can be generated from immunizing mice or using a phage-display library. *See* p. 14 & n.4, *supra*. The jury heard ample testimony, including from Amgen's expert Dr. Rees, that the number of claimed antibodies generated is "small" and that the genus is "narrow." Appx3902(731:16-17). Far from being "conclusory," Appx15, that testimony was backed by science.

First, the characteristics of PCSK9's sweet spot narrowly circumscribe the range of antibodies that can bind there. The "sweet spot" is a small target, consisting of only 15 of PCSK9's 700 amino acids. Appx3802(524:10-11); Appx3875(625:5-6); Appx3900(724:15-16); Appx247(100:5-10). POSAs thus would know that only a small group of (otherwise large) antibodies will have the structure to bind that restricted target. *See* Appx3900(724:20-725:5); Appx3901-3902(728:13-15, 730:1-731:3). The experts also agreed that the sweet spot has a "unique" "topology" and "distinct" "chemical characteristics." Appx3880(644:4-10); Appx3788(467:16-23). Only antibodies with CDRs with the necessary shape and chemical complementarity can "fit" that tiny and uniquely shaped sweet spot. Appx3876(628:12-629:21); Appx3900(726:4-727:4); Appx3910(764:8-765:3).

Second, "restricted immune response" confirms the genus's narrow scope. Appx3902(732:9-18). As Dr. Rees explained, the immunization protocol yields

only a limited number of antibodies: "[W]hen you put a particular antigen" (like PCSK9) "into a mouse, for example, you don't get this enormous response of antibodies." Appx3902(732:14-16). Instead, the immune system produces a "restricted group of antibodies that respond to that particular antigen." Appx3902(732:14-18). The injected antigen selects only the limited number of antibodies having the structure that allows them to bind. Appx3910-3911(766:15-767:15).

Third, actual experience proved those scientific explanations correct. At trial, the parties identified only a small number of antibodies meeting the claim limitations. Amgen found ***384*** antibodies that block the interaction between PCSK9 and LDL receptors "well." Appx237(80:22-23); Appx3798(505:10-12). Of those, 85 block the interaction by "greater than 90%." Appx237(80:35-37); Appx3798(505:12-15). Amgen's patents characterize 26 representative antibodies in a manner that shows they meet the claims' limitations. Appx3883(656:8-657:20); Appx3759-3760(352:18-353:1). Regeneron's CEO conceded that, beyond Praluent, Regeneron had produced only "five or so" antibodies that, according to him, fall within the genus. Appx3766(379:1-11). At trial, Sanofi-Regeneron identified only three antibodies from competitors (Merck and Pfizer). Appx3681(191:2-21). That paltry showing is telling: This Court remanded for a new trial to allow Sanofi-Regeneron to introduce evidence of antibodies developed

after the patents' 2008 priority date. *See* 872 F.3d at 1375. Despite having every incentive to show an expansive number of members of the genus, it mustered only a handful.

Having heard that evidence, a reasonable juror could infer the genus was limited, consisting of around 400 distinct antibodies—or fewer—but certainly not millions. And, as explained above, there was ample evidence that following the patents' roadmap would lead POSAs to all of the limited number of claimed antibodies. *See* pp. 32-34, *supra*. Thus, even if one were to examine the effort required for POSAs to "discover[]" and make "every antibody within the scope of the claims," Appx15, a reasonable jury could have found that would not require undue experimentation here. Viewed in the light most favorable to the verdict, and drawing all reasonable inferences in its favor—as this Court must—the evidence amply supports the verdict. *Bio-Tech.*, 267 F.3d at 1329.

B. The Possibility of "Conservative Substitutions" Does Not Yield Millions of Antibodies That Must Be Tested

The district court hardly addressed the concrete, empirical, and scientific evidence that the claims are narrow and that undue effort is not required to practice their full scope. Instead, it adopted testimony, from Sanofi-Regeneron's Dr. Boyd, concerning conservative amino-acid substitutions disclosed by the patents' Table 1. *See* Appx15-16. Conservative-substitution variants are made by replacing one or two amino acids from the original antibody with other amino acids that have

similar characteristics. Appx221(48:21-33); Appx211(27:32-39, Tbl. 1). Sanofi-Regeneron's Dr. Boyd calculated that, if a POSA made ***every*** potential substitution in Table 1, at ***every position*** in the ***heavy chain*** (not just CDRs) of an antibody, replacing "two amino acids at a time," that would yield 97,000 additional antibodies. Appx3688(219:18-220:7). Performing those substitutions on each of the 26 representative antibodies in the patent, Dr. Boyd claimed, would produce "millions" of antibodies to PCSK9, each of which "would need to be tested to determine whether they fell within the claims." Appx16. But the jury was entitled to reject Dr. Boyd's mathematical calculation as misleading. And even if the jury accepted his calculation, the jury was also entitled to conclude that all the antibodies are enabled.

1. *Table 1 Substitutions Do Not Yield Millions of Distinct Antibodies—Just Minor Variants That Are All Enabled*

The patents describe how, after POSAs have a claimed antibody in hand, they can make "***variants***" of that antibody by making "conservative amino acid substitutions" to certain amino acids. Appx221(48:21-33) (emphasis added); *see* Appx225(56:13-19); Appx222(49:55-64); pp. 16-17, *supra*. POSAs might wish to make variants to "modify" certain properties, such as "reduc[ing] susceptibility to oxidation" or "alter[ing] binding affinities." Appx222(49:55-60); *see* Appx220(46:55-64); Appx3907(753:1-13). The patents explain that the technique of conservative substitution—"well-known" in the prior art—involves replacing

selected amino acids in the antibody with alternative amino acids known to share "common . . . properties." Appx221(48:21-33); Appx211(27:32-42); Appx3902(733:12-22).

Table 1 discloses "[e]xemplary amino acid substitutions." Appx211(28:10-25, Tbl. 1). While those substitutions can alter certain properties, Appx3907(753:1-15); Appx220(46:55-64); Appx222(49:55-60), the variant is expected to "still retain a similar biological activity," Appx211(27:60-62). The disclosure of how to make "variants" cannot disprove enablement, for multiple reasons.

First, Dr. Boyd's numbers were hypothetical—he never suggested a POSA ***would*** perform the millions of substitutions he posited. Nothing in the patents instructs POSAs to make every possible substitution under Table 1, much less target the entire heavy chain. Amgen's Dr. Rees explained that POSAs do not make rote substitutions to see what happens, but make selective, "intelligent" substitutions—*i.e.*, minor changes made with a specific goal. Appx3902(732:19-733:22); Appx3907(753:1-15); *see* Appx220(46:55-64); Appx222(49:55-50:4).

Second, Table 1's conservative substitutions do not produce "new" antibodies with unknown properties. The evidence shows that such substitutions produce virtually identical "variants" of the reference antibodies. Dr. Boyd's approach to substitution—changing two amino acids at a time—yields variants that

are more than 99% ***identical*** to the original antibody. *See* p. 17 & n.5, *supra*. Dr. Boyd told the jury that antibodies with small differences in sequence are considered "***the same*** antibody" that "bind in the [same] way." Appx3763(368:6-15) (emphasis added). Indeed, attempting to downplay the antibodies disclosed in the patent for written-description purposes, Sanofi-Regeneron's expert Dr. Eck testified that the identified antibodies—which differ by as many as ***10*** amino-acids in the variable region—are "essentially copies of each other." Appx3788(467:7-15); *see* p. 17 & n.6, *supra*. Such "close variants," he explained, will have "common structural features," and thus "are likely to interact with PCSK9 in the same way." Appx3788(465:9-20, 467:7-15); *see* Appx3787(464:7-16) ("They'll share a common structure function relationship."). Having heard that testimony on written description, the jury was not required to accept Sanofi-Regeneron's about-face on enablement—that replacing just ***two*** amino acids with other highly similar amino acids somehow creates "new" antibodies that must be tested.

Third, even if Table 1 "variants" were deemed distinct embodiments, the patents' disclosure is commensurate with that scope, because the patents teach POSAs how to make them. *See* pp. 16-17, *supra*. As Sanofi-Regeneron's Dr. Boyd conceded, the patents and Table 1 "***give[] the rules for generating*** additional antibody sequences" through conservative substitution. Appx3688(219:1-9, 21) (emphasis added); Appx3919(802:12-14). The additional disclosure thus does not

defeat enablement but enhances it: Whatever embodiments can be produced through conservative substitutions, the patents give the rules for "mak[ing] and us[ing]" them. 35 U.S.C. § 112(a). The potential for variants, within the skill of ordinary artisans, cannot defeat enablement. *See AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

For that reason, Dr. Rees's testimony that "'if the millions of antibodies that Dr. Boyd described . . . continued [] to bind and block . . . they would [] fall within the claims,'" Appx15 (alterations in original) (quoting Appx3902(733:2-7)), does not support the district court's conclusions.[9] If following the patents' teachings on substitutions results in additional antibodies within the scope of the claims, that proves enablement, not non-enablement. Indeed, because conservative substitutions can be made to ***any*** antibody, accepting the district court's theory would render ***all*** antibody genus claims—including Sanofi-Regeneron's, *e.g.*, D. Ct. Dkt. 662 at 11-14, 19-20—invalid.

2. *Table 1 Variants Do Not Require Testing for Binding PCSK9's Sweet Spot*

Variants made pursuant to Table 1 need not be tested to see if they bind the sweet spot and block. POSAs start with antibodies already shown to block PCSK9

[9] Nor was the jury required to accept that testimony as "tacitly admitt[ing]" the existence of "'millions of antibodies.'" Appx15. Dr. Rees merely answered a question that assumed Dr. Boyd's hypothetical calculation.

from binding to LDL receptors by binding at PCSK9's sweet spot and then make small substitutions, replacing amino acids with similar ones. *See* pp. 16-17, *supra*. Table 1 thus does not set POSAs searching for antibodies that work. It allows them to tinker with those that already have the structure and chemical complementarity to bind and block at the sweet spot. The court was thus wrong in finding there was no "genuine dispute" that Table 1 substitutions would yield "millions of candidates" that "would need to be tested." Appx16. That was fully disputed, and reasonable jurors could reject Sanofi-Regeneron's theory as unconvincing—and certainly not clear and convincing.

For one thing, Dr. Boyd inflated his figure by hypothesizing substitutions along the "heavy chain" of a reference antibody, Appx3688(219:18-220:7); *see* Appx3921(809:21-810:3), which spans around 120 amino acids, *see* Appx288. As Dr. Boyd testified elsewhere, the much smaller CDR region is "what makes one antibody different from another one," Appx3680(186:9-14), because CDRs "determine what the antibody will bind to," Appx3680(187:3-8); *see* Appx3761-3762(360:18-361:14); pp. 10-11, *supra*. Sanofi-Regeneron's expert testified that an even smaller part of the CDR, the "CDR3 loop," is what is "most important for determining what the antibody is going to bind to." Appx3692(233:17-20). That section can be only 9 amino acids. Appx3691(231:19-24). Thus, the vast majority of substitutions Dr. Boyd hypothesized would be made to portions of the antibody

that are just a "scaffold," Appx3680(186:20-22), and do not affect binding, *see* pp. 10-11, *supra*.[10] The jury was not required to accept a calculation premised on the (erroneous) assumption that substitutions outside the binding area create uncertainty whether the variant still binds PCSK9's sweet spot.

Even for substitutions within critical areas, Table 1 substitutions by design do not "substantially change the structural characteristics of the parent" antibody so as to jeopardize binding—which is why they are "conservative" substitutions. Appx222(49:65-50:1). The patents explain that "even areas that can be important for biological activity or for structure can be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure." Appx221(48:29-33). The patents explain that POSAs can "review structure-function studies" to "predict" which amino acids are "important for activity" and "opt for chemically similar amino acid[s]" when making substitutions. Appx221(48:34-42); *see* Appx246(98:27-32) (patent Figs. 13A-13J "present a large amount of guidance as to the importance of particular amino acids . . . and which amino acid positions can likely be altered."). The

[10] While the decision below invokes the District of Delaware's decision in *MorphoSys AG v. Janssen Biotech, Inc.*, 358 F. Supp. 3d 354 (D. Del. 2019), Appx24, *MorphoSys* acknowledges that a POSA would understand that, where substitutions are made "within the framework regions of an antibody"—outside the CDRs—the variant "would be 'reasonably expected' to be effective even without screening," 358 F. Supp. 3d at 370, 372.

"well-known technique[]" of conservative substitutions, Appx221(48:23), preserves structure and function by replacing amino acids only with others that are similar, Appx211(27:32-39, 27:60-62). Table 1 reflects those "Exemplary Substitutions." Appx211(Tbl. 1).

Dr. Rees thus testified that variants he created through "conservative substitutions" had "the same properties" as the unmodified antibody. Appx3914(779:21-780:11). Where the substitution is limited to replacing amino acids with others that are structurally and chemically similar, as the patents instruct, the modified antibodies won't "lose their binding to their target." Appx3902(733:12-22). They instead remain "antibodies to PCSK9 having [the] functional and chemical characteristics" of the unmodified antibody. Appx225(56:13-19).

Sanofi-Regeneron never identified a single variant, produced following Table 1, that lost its ability to bind PCSK9 and block its interaction with LDL receptors. Not one. That failure of proof speaks volumes. Nothing compelled the jury to find that POSAs would think every Table 1 variant "need[s] to be tested to determine whether" it still "fell within the claims" like the original. Appx16.

C. The District Court's Invocation of "Random Mutations" Is Unsupported

The court acknowledged that Dr. Rees, explaining why "'the genus . . . would be narrow,'" testified that "antibody scientist[s] would not engage in random mutations to the disclosed antibodies." Appx14 (ellipsis in original). But it

declared that "[a]n antibody scientist's refusal to engage in random mutations does not mean that there ***could*** not be embodiments of the claims that ***could*** only be discovered by performing a random mutation." Appx15 (emphasis added). If the court was not referring to Dr. Boyd's testimony about making two conservative amino-acid substitutions to known antibodies, *see* pp. 42-43, *supra*, it is unclear what the court meant. And Sanofi-Regeneron produced no evidence of any embodiment achievable only through "random mutation." Sheer speculation that there "could" be some unidentified hypothetical variant, achievable only through some unspecified "random mutation," cannot justify overturning the jury's verdict. Such "speculation does not" even "constitute substantial evidence." *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1327 (Fed. Cir. 2009) (quotation marks omitted).

Insofar as "random mutations" might be relevant, the jury was entitled to find, based on the evidence, that super-immunized mice (or phage displays) account for them. Sanofi-Regeneron's Dr. Boyd acknowledged that, in response to antigens like PCSK9, "the immune system" produces various antibodies through a "randomized process." Appx3754(329:2-13); *see* Appx3754(331:13-19); Appx17 (randomness "best serves the immune system"). And there was ample testimony that the roadmap "make[s] all the antibodies within the scope of the claims." Appx3908(757:12-14); Appx3909(762:14-20); *see* pp. 32-34, *supra*. The specter of "random mutations" cannot defeat enablement here.

III. THE DISTRICT COURT'S ANALYSIS OF OTHER *WANDS* FACTORS ALSO DEFIES JMOL STANDARDS

On JMOL, courts must view the evidence and draw all inferences in the light most favorable to the verdict, *Bio-Tech.*, 267 F.3d at 1329, and presume the jury resolved each dispute in support of its verdict, *Arctic Cat*, 876 F.3d at 1358, 1364. On the remaining *Wands* factors, however, the district court again displaced jury findings with its own "factual conclusions." Appx24. For example, the court held that "a reasonable factfinder could only find that the art is unpredictable," Appx19—notwithstanding "conflicting testimony" on the issue, Appx17, and this Court's finding in *Wands* that the antibody arts were predictable 30 years earlier. The district court held that "the patent does not provide significant guidance or direction" as a matter of law, Appx22—even though it was undisputed that the patents teach POSAs how to make claimed antibodies. Reversal is warranted. *See, e.g.*, *Kinetic Concepts*, 688 F.3d at 1346, 1368-71; *Martek*, 579 F.3d at 1378-79; *Bio-Tech.*, 267 F.3d at 1327, 1331-32.

A. Predictability: The Jury Reasonably Could—and Implicitly Did—Find the Art Predictable

While acknowledging "conflicting testimony as to the predictability of the art at the time of the 2008 patent application," Appx17, the decision below declared the antibody arts "unpredictable" as a matter of law, Appx19. The court's finding, however, was not based on techniques described in the patents and that

antibody scientists employ—*e.g.*, generating antibodies using transgenic mice or phage displays. Those are concededly predictable and routine. *Id.* Instead, the court focused on something POSAs do not do: It asked whether POSAs can predict whether an antibody will bind PCSK9 by looking at its amino-acid sequence alone. And the court misconstrued and re-weighed the evidence concerning the predictability of conservative substitutions following Table 1.

1. *Ample Evidence Showed the Disclosed Methods for Obtaining Claimed Antibodies Were Predictable*

The predictability inquiry must consider "the specific area of science or technology" POSAs use to make the invention. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008). Both parties presented evidence the antibody arts were well established by the 2008 priority date, s*ee* Appx3758(347:9-22); Appx3909(761:1-762:4); Appx3902(734:8-15), and that the techniques for making antibodies with required binding properties were well-developed, automated, and routine, *see* Appx3909(761:1-762:4); Appx3897(712:1-714:6). Dr. Rees testified that the antibody arts are "highly predictable." Appx3908(757:2-11). The court acknowledged that POSAs "would be familiar with the techniques disclosed in the patent[s]"—including "immunizing mice," "binning," "alanine scanning," and "making amino acid substitutions"—and could practice them to obtain antibodies within the claims. Appx19-20.

This Court has found that the "methods for obtaining and screening monoclonal antibodies were well known" by "1980." *Wands*, 858 F.2d at 736. It has found that, after the inventor fully characterizes the relevant antigen and proves its antigenicity—as Amgen did here—producing antibodies is routine. *See Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1351-52 (Fed. Cir. 2011). Antibody scientists reliably generate antibodies by "immuniz[ing] a mouse" or using a phage library. Appx3683(197:1-10); Appx3903(736:20-737:11); Appx3909(759:11-17). The resulting pool includes the desired antibodies, which can be isolated through standard binding, binning, and blocking assays. *See* pp. 13-16, *supra*; *Wands*, 858 F.2d at 740.

Sanofi-Regeneron's expert, Dr. Ravetch, testified that standard methods would "inevitabl[y]" yield the antibodies "claimed by Amgen." Appx3896-3897(709:2-711:11). *A fortiori*, the advanced techniques disclosed by Amgen would too. Dr. Rees repeatedly testified that a POSA utilizing the advantages and shortcuts provided by the roadmap, *see* pp. 13-16, *supra*, "would be certain to make all of the claim's antibodies," Appx3909(762:14-20); *see* Appx3908(757:12-14) ("road map [can] be used to make all the antibodies within the scope of the claims").

2. *The District Court's Rationale Departs from the Purpose of the Predictability Inquiry and Misconceives the Antibody Arts*

The decision below deems antibody science "unpredictable" because POSAs cannot "predict from an antibody's sequence" alone "whether it will bind to specific [PCSK9] residues." Appx19-20. That makes no sense. When addressing written description, the district court held there was "substantial evidence" that antibody scientists would not view amino-acid ***sequence*** as "the appropriate . . . metric" for comparing the "disclosed species" to the claimed "genus." Appx9. The court never explained why that same rejected metric—looking at amino-acid sequence alone—governs predictability for enablement purposes. Appx19-20.

Neither the antibody arts, nor the patents' enabling disclosures, ask POSAs to predict whether an antibody works by looking at its amino-acid sequence alone. Sanofi-Regeneron's Dr. Boyd conceded that antibody scientists do not "sit down and say, I think I'll design an antibody" by "writ[ing] out the amino acid sequence." Appx3683(197:2-10). Antibody scientists reliably produce antibodies as taught in the patent—by immunizing transgenic mice and using assays to isolate those that bind and block as claimed.

The court thus erred by declaring that Dr. Rees "admitted that a person of ordinary skill would not know the exact substitutions needed in the amino acid sequence to alter the residues of PCSK9 to which the antibody will bind." Appx18 (citing Appx3917(792:12-20, 793:5-13, 794:6-16)). That misunderstands the testi-

mony and the antibody arts. In the cited testimony, Dr. Rees responded to a question about "mak[ing] substitutions to ***Repatha*** to arrive at an antibody that binds to the same amino acids in PCSK9 as ***Praluent***." Appx3917(792:3-8) (emphasis added). As Dr. Rees explained, POSAs would not attempt to make substitutions to Repatha to convert it into Praluent. Appx3917(792:16-21); Appx3917-3918(794:17-795:2). POSAs would instead reliably produce Repatha, Praluent, and other antibodies that bind the same amino-acid residues by following the patents' roadmap. Appx3908(757:12-758:6); Appx3918-3919(798:25-799:5).

Dr. Rees's testimony on predictability cannot be dismissed as "conclusory." Appx18. An expert's opinion is "conclusory" only where he fails to "provide[] any factual basis for his assertions." *ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012). Dr. Rees explained in detail why the "maturity of the antibody arts" rendered this area "highly predictable," and that POSAs, using known "methods" in "combination with the disclosures in the patent," Appx3908(757:2-14), "would be ***certain*** to make ***all*** of the claim's antibodies." Appx3909(762:14-20) (emphasis added); *see* pp. 32-34, *supra*. The court ignored that testimony.

The court's focus on sequence alone fails for another reason. A claim is enabled if the specification "'enables any mode of making and using the invention.'" *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1071 (Fed. Cir.

2005). Even assuming a POSA might try to create antibodies by assembling amino acids into different sequences, there was no requirement that Amgen enable that method. The jury heard evidence that the ***relevant art*** as actually practiced by POSAs—using transgenic mice to generate antibodies—is highly predictable and that they would generate all the antibodies, including Praluent, using the patents' roadmap. Appx3908(757:12-758:6); Appx3919(799:3-5); *see* pp. 32-34, *supra*. The jury was not compelled to find that Sanofi-Regeneron proved the relevant art unpredictable, contrary to decades of precedent. *See Wands*, 858 F.2d at 740; *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Johns Hopkins*, 152 F.3d at 1351 n.14.

3. *The Court Erred in Finding Conservative Substitutions "Unpredictable" as a Matter of Law*

The district court theorized that conservative substitutions yield unpredictable outcomes that require validation. *See* Appx18. For the reasons discussed above, the jury was not required to credit that theory, much less find it proved by clear-and-convincing evidence. Conservative substitution ***begins*** with a claimed antibody with the structure and chemical complementarity that binds PCSK9. It allows POSAs to replace amino acids with highly similar ones to obtain a desired attribute, making minor variants that still bind and block like the original. *See* pp. 46-49, *supra*. The court faulted Dr. Rees for not providing "explicit testimony" that further screening is unnecessary. Appx18 n.10. But the JMOL standard

rejects any "explicit testimony" requirement. Courts must draw all reasonable ***inferences*** in support of the verdict. *Bio-Tech.*, 267 F.3d at 1329. Here, the jury could infer from the evidence that testing is not required because conservative substitution predictably produces variants that retain the structure of the original antibody and thus its claimed binding and blocking. *See* pp. 46-49, *supra*; *CEATS, Inc. v. Cont'l Airlines, Inc.*, 526 F. App'x 966, 969 (Fed. Cir. 2013).

The opinion below asserts that it was undisputed that variants produced by conservative substitution must be tested. Appx16. The testimony it cites from Dr. Rees says no such thing. The first citation is to testimony about screening the larger "pool of antibodies" mice produce as a result of "the super immunization process." Appx3904(740:15-21); *see* pp. 14-15, *supra*. That reference to the road-map's step of producing antibodies has nothing to do with whether ***variants*** of working antibodies, produced under Table 1, have to be "screened" again. In the second passage, Dr. Rees stated only that "unknown" antibodies must be screened. Appx3914(779:15-20). Table 1 variants are not "unknown"—they are variants of antibodies already demonstrated to satisfy the claims. *See* pp. 46-49, *supra*. In the testimony that immediately follows, when Dr. Rees discusses "conservative substitutions," he confirmed that variants would "still have . . . the same properties" as the original. Appx3914(779:23-780:11).

If Dr. Rees's testimony was "contradicted by other testimony," Appx18, that at most creates a jury issue. The court's effort to resolve the conflict itself, moreover, rests on findings the jury was not required to make. For example, the court invoked Dr. Boyd's testimony that the amino-acid sequences of antibodies are unpredictable because unpredictability serves the immune system. Appx17 (citing Appx3690(225:9-17)). But that testimony is unrelated to making conservative amino-acid substitutions to antibodies ***demonstrated*** to bind PCSK9. The immune system's unpredictability is why antibody scientists rely on the immune system itself—as opposed to random sequences—to generate antibodies. Appx3749(311:12-15); Appx3751(317:6-16): Appx3754(331:13-19); *see* p. 14, *supra*. The jury heard testimony (some from Sanofi-Regeneron witnesses) that, once you have antibodies with particular sequences that bind and block as required, variants with very similar sequences will bind and block similarly. *See* pp. 46-49, *supra*. The court did not mention that evidence.

Nor did Dr. Mehlin, one of the inventors, contradict Dr. Rees. Appx17-18. Dr. Mehlin testified that "conservative mutations" to a protein generally "are going to be better tolerated by a protein than nonconservative mutations." Appx3768(388:21-23). He did say that he had "been surprised in the past," and that "the only way to know in the end is to test it." Appx3768-3769(388:24-389:8). But that testimony was not in the context of Table 1 or the claimed anti-

bodies. And it applies a level of scientific certainty—empirically proven knowledge—not imposed by *Wands*' "predictability" factor. Dr. Mehlin's patents state that, once POSAs know which amino-acid residues "are important for activity or structure," they can "predict" "amino acid substitutions" that will retain that activity or structure. Appx221(48:29-42). The jury could credit the patents; it did not have to twist Dr. Mehlin's testimony into contradicting them.

The court's citation of Dr. Petsko's purported testimony that "testing would be required to ensure that a substitution does not alter the binding and blocking functions," Appx18 (citing Appx3891(688:21-689:10)), similarly misses the mark. Dr. Petsko was not addressing ***conservative*** substitutions or Table 1. He was testifying about the "theoretical[]" impact that random changes to "a single amino acid in an antibody's sequence" could have on "that antibody's function." Appx3891(688:21-23). Predictability is about the effects of changes the art employs (like conservative substitution of one amino acid for another similar one), not remote theoretical outcomes from random methods.

Significantly, Sanofi-Regeneron produced ***no evidence*** of any conservative substitution that yielded an unpredictable result. It identified no conservative change to any working antibody that made it stop binding and blocking like the original. It did not even try. Appx3921(810:4-20). For that reason alone, the jury was entitled to reject the notion that the ability to produce variants under Table 1

renders the art unpredictable—or at least find that Sanofi-Regeneron's speculation fell short of clear-and-convincing proof. *Kinetic Concepts*, 688 F.3d at 1367.

4. *The Jury Was Entitled To Find That Any Confirmatory Processes Were Quick and Routine*

Even if POSAs choose to confirm activity, substantial evidence showed that was predictable and easy. Decades ago, this Court found that "[p]ractitioners of this art are prepared to screen" pools of antibodies "to find . . . the desired antibody." *Wands*, 858 F.2d at 740. Consistent with that, Dr. Rees testified that "'automated high-throughput techniques'" can "'test[] a large number of antibodies'" to determine whether they fall within the claims "'quickly, efficiently, and cheaply.'" Appx23. As *Wands* recognizes, that is not undue experimentation. *See* pp. 34-37, *supra*.

The court disregarded Dr. Rees's testimony as "conclusory." Appx23. It was not. Dr. Rees provided detailed testimony about the systems that efficiently and cheaply make and screen thousands of antibodies at a time. Appx3898(718:3-23); Appx3909(761:1-762:1). Assays for desired characteristics like blocking were "fully automated" since the 1980s and "very advanced" by the priority date. Appx3898(718:3-23). Scientists "process . . . thousands of wells, hundreds of these plates in a very short space of time," and for minimal cost—less than $300 for as many as 10,000 antibodies. *Id.*; Appx3909(761:1-762:1). POSAs would not consider such rapid and inexpensive processes "undue experimentation."

Appx3909(761:6-13). Even Sanofi-Regeneron's expert, Dr. Ravetch, agreed the patent called for "[v]ery straightforward," "standard techniques." Appx3896(709:6-10, 710:8-14); Appx3897(712:13). A reasonable jury was not compelled to find otherwise.

B. Amount of Guidance: The District Court's Analysis Disregards the Patents' Roadmap Based on an Erroneous Comparison

In perhaps its most obvious error, the district court held that "the specification and the examples do not improve a [POSA]'s ability to discover non-disclosed antibodies within the scope of the claims." Appx20-21. The court dismissed the patents' roadmap—the process by which POSAs make additional claimed antibodies—as "significant[ly] similar[]" to Dr. Jackson's initial "'research plan'"; it requires, the court insisted, "'essentially the same amount of work as the inventors'" "to obtain a claimed antibody" not exemplified in the patents or a "variant of a disclosed antibody." Appx21. That fails, legally and factually.

Legally, enablement does not require that the disclosed techniques depart from those the inventor used in making his discovery. In *Wands*, the patent disclosed the inventors' own "procedure for immunizing mice," the inventors' "use of lymphocytes from these mice to produce" antibodies of the invention, and the "well known" "screening techniques used by [the inventors]." 858 F.2d at 734, 738. That did not mean the patents were not enabled. *See* pp. 34-37, *supra*; *see*

also Johns Hopkins, 152 F.3d at 1351 & n.14, 1361 (finding antibody claims enabled where patent disclosed the inventors' "methodology").

Factually, the decision below ignores the significant advances and success taught by the patents' roadmap. The roadmap ***starts*** where Dr. Jackson's research ***ends***. Dr. Jackson had to discover that the small spot on PCSK9 that binds LDL receptors—the sweet spot—is antigenic, and he had to invent the first antibodies that bind there. Appx3796(498:21-499:2); Appx3798(505:24-506:3); Appx3804(532:12-15). Making those discoveries is the hardest part of antibody science. *See, e.g.*, *Centocor*, 636 F.3d at 1351-52. Dr. Jackson created dozens of antibodies that bind PCSK9 and block its interaction with LDL receptors before anyone knew that was possible. *See* Appx3802(523:25-524:11); Appx3796(498:5-500:24). The patents fully characterize 26 representative antibodies. The patents further disclose, by way of x-ray crystallography images, the three-dimensional structures of two of those antibodies and precisely which amino acids interact with PCSK9. And they disclose techniques and tools the inventors had to invent. *See* pp. 13-16, *supra*.

The court's "comparison" to the inventors' "steps" omits all of that. *See* Appx21. The court acknowledged that "[s]tep 1" of the roadmap involves "[m]ak-[ing] a known antibody binding" a PCSK9 sweet-spot residue. *Id.* There was no such "known antibody" when Dr. Jackson started out. The roadmap teaches

POSAs how to use two anchor antibodies ***Dr. Jackson invented*** and disclosed (21B12 and 31H4) to make others that bind in the same areas and thus have the same blocking effect. Appx3904(741:10-742:5); p. 14, *supra*. The patents also disclose Amgen's super-immunization protocol for transgenic mice, and Amgen's specially optimized assays. *See* pp. 14-16, *supra*. Amgen had to develop those advances as part of Dr. Jackson's research, while POSAs simply benefit from them. The opinion ignores those, too.

Dr. Jackson's research, moreover, started with only a "hypothesi[s]." Appx3796(498:16-499:2). POSAs following the patents' roadmap start with the certainty of producing claimed antibodies. The court did not mention that either. Only by disregarding the patents' extensive disclosures and the trial evidence can one say that the inventors' "research plan" and the "roadmap" require "essentially the same amount of work." Appx21 (quotation marks omitted). While the court ignored proof of the specification's enabling disclosures, the jury was not required to do so. For those reasons too, the decision below cannot stand.

IV. THE DISTRICT COURT'S INTERPRETATION OF THE "FULL SCOPE" REQUIREMENT CONTRAVENES LONGSTANDING ENABLEMENT LAW

The trial record alone is reason enough to reinstate the jury's verdict. To reach the contrary result, however, the opinion below also had to adopt an enablement standard that is contrary to precedent—from this Court and the Supreme Court. Construing this Court's requirement that the specification teach

POSAs "'how to make and use the ***full scope*** of the claimed invention without undue experimentation,'" Appx11 (quoting *MagSil*, 687 F.3d at 1380), the decision below initially stated that the requirement is not met "'when there is ***an embodiment*** within the claim's scope that a [POSA], reading the specification, would be unable to practice without undue experimentation,'" Appx12 (emphasis added) (quoting *MorphoSys*, 358 F. Supp. 3d at 368-69). But the opinion quickly shifted to a different approach—it considered the experimentation required to "discover[]" and make "***every antibody*** within the scope of the claims." Appx15 (emphasis added).[11]

This Court, however, has already explained that the "full scope of the claimed invention" standard does ***not*** require the patent to "describe how to make and use every possible variant." *AK Steel*, 344 F.3d at 1244. Enablement focuses instead on whether the specification "guide[s] those skilled in the art to" the "successful application" of "the invention." *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 271 (1916). The disclosure must provide "reasonable enablement" of the claims' "scope." *AK Steel*, 344 F.3d at 1244.

The Supreme Court's *Minerals Separation* decision makes that clear. In *Minerals Separation*, the invention allowed metallic ores to be separated from

[11] For the reasons given above (at 32-34), the jury could find Sanofi-Regeneron's proof insufficient even under that test.

other minerals using a fraction of the oil required by prior-art methods; it achieved that result by exploiting the "buoyancy of the air bubbles introduced" by "agitation." 242 U.S. at 268. The defendants argued that the claims were not enabled because "[t]he composition of ores varies infinitely, each one presenting its special problem." *Id.* at 271. Skilled artisans were required to perform "preliminary tests" to employ the invention for each of those "infinit[e]" ore varieties. *Id.* at 270-71. The Supreme Court rejected the effort to require inquiry into ***every*** conceivable implementation. *Id.* The law, it explained, requires only "reasonable" disclosures sufficient "to guide those skilled in the art to its successful application." *Id.*

A host of Supreme Court cases reach similar conclusions. *See, e.g.*, *Wood v. Underhill*, 46 U.S. (5 How.) 1, 4-6 (1846) (rejecting enablement challenge to patent for "manufacturing bricks" through mix of coal dust and clay, even though proportions vary for each type of clay); *Mowry v. Whitney*, 81 U.S. 620, 644-46 (1872) (rejecting enablement challenge to method of cooling metal wheels, even though temperature required for each embodiment was "left to the judgment of the operator"). The district court's attempt to evaluate enablement in terms of the effort required to "discover[]" and make "every" theoretical "embodiment[] of the claims," Appx15, cannot be reconciled with that precedent.

Following *Minerals Separation*, this Court's predecessor likewise eschewed inquiries into the effort required to make every conceivable embodiment. It asked

instead "whether the scope of enablement provided to one of ordinary skill in the art by the disclosure is such as to be ***commensurate*** with the scope of protection sought by the claims." *In re Moore*, 439 F.2d 1232, 1236 (C.C.P.A. 1971) (emphasis added). Thus, in *In re Angstadt*, 537 F.2d 498 (C.C.P.A. 1976), the court held the claimed process for catalytically oxidizing a genus of hydrocarbons was enabled even though it was "unpredictable" and the inventor had "not disclosed ***every*** catalyst which will work" of "'thousands'" of possibilities. *Id.* at 502. Patent protection ought not require inventors to conduct "a prohibitive number of actual experiments" to catalogue every embodiment. *Id.* at 502-03; *see In re Halleck*, 422 F.2d 911, 914 (C.C.P.A. 1970) (similar).

Invoking *Minerals Separation*, this Court's seminal enablement case—*Wands*—similarly explains that "undue experimentation" is "a standard of reasonableness" that requires "weighing many factual considerations." 858 F.2d at 737 & n.19. *Wands* focused on the "experimentation" necessary "to obtain antibodies needed to practice the claimed invention"—not to obtain ***every*** antibody within the claims. *Id.* at 740. In *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569 (Fed. Cir. 1984), this Court found claims enabled even where the specification listed "numerous salts, fuels, and emulsifiers that could form thousands of" embodiments. *Id.* at 1576-77. Reasoning that POSAs would learn from "'failures,'" the Court found enablement because the disclosure allowed POSAs to

make working embodiments on most (even if not all) attempts. *Id.*; *see Johns Hopkins*, 152 F.3d at 1360-61.

None of those cases define undue experimentation in terms of the effort to discover and make every conceivable embodiment. *AK Steel* rejected any requirement that the specification "describe how to make and use every possible variant." 344 F.3d at 1244. The contrary approach would require patent disclosures that are many times longer, with redundant experiments that would teach POSAs no additional information. In a first-to-file patent system, inventors would struggle to produce all possible embodiments within a short period of time. Very few inventors would have the resources to do so. As Judge Bryson has observed, it would be a "fundamental error[]" to require that "a skilled artisan can practice the entire scope of the invention within a short period of time." *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 661 (E.D. Tex. 2017) (Bryson, J.), *aff'd*, 739 F. App'x 643 (Fed. Cir. 2018) (mem.).

Insofar as the district court derived a contrary rule from *Wyeth* or the then-district court decision in *Idenix*, it erred. Appx25. This Court's *Idenix* decision reiterates that the touchstone for enablement is "disclosure" "'commensurate in scope with the claim.'" *Idenix Pharm. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1160 (Fed. Cir. 2019). The small-molecule claims in *Idenix* and *Wyeth* "encompassed 'millions of [candidate] compounds,'" which had to be "'made by

varying the substituent groups'" on a molecule, "while only a 'significantly smaller' subset of those compounds would have the claimed 'functional effects.'" *Id.* at 1162 (quoting *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013)). The Court found the patents provided no guidance or methodology for "'how to get from a large number of candidate compounds to a relatively speaking small number of effective compounds.'" *Id.* (brackets omitted).

The Court did not define enablement in terms of the effort required to "discover[]" each and every potential "embodiment[] of the claims," as the opinion below put it. Appx15. The Court viewed the specification as leaving POSAs to "search[] for a needle in a haystack" to find ***any*** embodiments beyond specifically disclosed examples. *Idenix*, 941 F.3d at 1162. That stands in stark contrast to this case. The specification discloses numerous representative antibodies, together with a roadmap for how—using those antibodies and super-immunized mice—to produce all other antibodies within the claims. It provides techniques for creating structurally and thus functionally similar variants through conservative substitutions. It thus provides explicit instructions for successfully making the "needles," the working antibodies. There is no "haystack" to be searched.

* * *

The district court's requirement that POSAs easily "discover[]" each and every potential "embodiment[] of the claims," Appx15, defies the "standard of

reasonableness" the Supreme Court, this Court, and its predecessor court have long applied. *Wands*, 858 F.2d at 737. The Supreme Court has repeatedly rejected efforts to replace flexible and historically grounded tests like "reasonableness" with rigid tests for patent validity. *See, e.g.*, *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901, 910 (2014) (rejecting "'insolubly ambiguous'" test for indefiniteness in favor of "reasonable certainty" test); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415, 419 (2007) (rejecting "rigid" "teaching, suggestion, or motivation" test for obviousness in favor of "expansive and flexible" inquiry).

Enablement does not require the "impossible"; disclosure must be "reasonable, having regard to [the claims'] subject-matter." *Minerals Separation*, 242 U.S. at 270-71. Measuring enablement as the effort required for POSAs to make every conceivable embodiment—indeed, all hypothetical variants no matter how inconsequential—defies those precedents. *Wands*, 858 F.2d at 737; *Angstadt*, 537 F.2d at 502-03. For that reason, too, reversal is warranted.

CONCLUSION

The district court's judgment should be reversed.

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Respectfully submitted,

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