No. 21-757

In the Supreme Court of the United States

AMGEN INC., ET AL.,

Petitioners,

v.

SANOFI, ET AL.,

Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF SIR GREGORY PAUL WINTER AND INTERESTED SCIENTISTS AS *AMICI CURIAE* IN SUPPORT OF RESPONDENTS

Sophie F. Wang
Counsel of Record
Eric J. Marandett
Jillian L. Gately
Olivia L. Campbell
Timothy J. Conklin
CHOATE HALL & STEWART LLP
Two International Place
Boston, MA 02110
(617) 248-5000
swang@choate.com

FEBRUARY 10, 2023 *COUNSEL FOR AMICI CURIAE*

SUPREME COURT PRESS ♦ (888) 958-5705 ♦ BOSTON, MASSACHUSETTS

TABLE OF CONTENTS

TABLE OF CONTENTS – Continued

TABLE OF AUTHORITIES

Page

CASES

STATUTES

TABLE OF AUTHORITIES – Continued

Page

OTHER AUTHORITIES

INTEREST OF THE AMICI CURIAE

Amici are world-renowned scientists, professors, and researchers who have dedicated their careers to researching innovative ways to treat and prevent disease.[1] In particular, Amici are experienced in the fields of antibody science, chemistry, and the development of novel pharmaceutical drugs.

Sir Gregory Paul Winter CBE FRS FMedSci, is a Nobel Prize-winning English molecular biologist best known for his work on the therapeutic use of monoclonal antibodies. In 1982, he was the first to design and make mutants in proteins to explore the role of individual amino acids in protein function. In 1986, he invented methods commonly called CDR grafting to humanize mouse monoclonal antibodies for therapy. From 1989 to 1991, he invented methods for making fully human recombinant antibodies by antibody phage display technology, using combinatorial gene repertoires, which earned him the 2018 Nobel Prize in Chemistry, shared with Frances Arnold and George Smith. Dr. Winter's work is behind several of the world's top-selling human antibody drugs, including pembrolizumab (Keytruda®), a humanized monoclonal antibody for treatment of cancer, and adalimumab (Humira®), the first fully human monoclonal antibody drug, and used for treatment of rheumatoid arthritis,

---

[1] Amici have no financial interest in any party or the outcome of this case. This brief was neither authored nor paid for, in whole or in part, by any party. Respondents submitted to the Clerk of the Court its blanket consent on November 29, 2022 and Petitioners did the same on December 1, 2022.

psoriasis, and inflammatory bowel diseases. In addition to holding numerous patents for his work, Dr. Winter has also founded several successful biotechnology businesses over the years to put his techniques into practice.

Dr. Winter received his PhD in 1977 from Medical Research Council Laboratory of Molecular Biology, Cambridge, UK–where he continued his research until 2012. He then served as Master of Trinity College, Cambridge, UK, from 2012 to 2019, was elected as a Fellow of the Royal Society in 1990, and in 2011 the Society awarded Dr. Winter the Royal Medal for his work in protein engineering and therapeutic monoclonal antibodies.

Dr. Timothy Springer, PhD, is the Latham Family Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School and Boston Children's Hospital, as well as the Principal Investigator in the Program of Cellular and Molecular Medicine, Division of Hematology/Oncology, Department of Medicine at Boston Children's Hospital. He is best known for his pioneering work in the discovery of integrins, a class of adhesion receptors that allow immune system molecules to adhere to their targets. His work on these receptors has advanced to characterizing their interactions and allosteric transitions by x-ray crystallography, electron microscopy, and laser tweezers force spectroscopy. Dr. Springer's work has resulted in the development of numerous novel treatments for a variety of diseases.

Dr. Springer received his PhD in 1976 from Harvard University and completed a fellowship with César Milstein in Cambridge, UK. He has published over 500 articles in the field of immunology and is

the recipient of the 2022 Albert Lasker Basic Medical Research Award. Dr. Springer is also an investor in Selecta Bioscience since its B round, founder and investor in Scholar Rock and Morphic Therapeutics, and a founding investor in Moderna Therapeutics and Editas Medicine.

Dr. Robert Kamen, PhD, is an advisory partner at Third Rock Ventures focused on the formation and development of biologics companies. Dr. Kamen has over 35 years of leadership experience in the pharmaceutical and biotechnology industries, including as the former president of Abbott Bioresearch Center, where he oversaw the discovery and production of Humira®, the first fully human monoclonal antibody drug approved for market. Dr. Kamen also previously served as the president of BASF Bioresearch Corporation until it was acquired by Abbott Laboratories in 2001. Throughout his career, Dr. Kamen has founded and served as a director or advisor to numerous biopharmaceutical companies. He received his PhD in biochemistry and molecular biology from Harvard University.

Dr. Andrew Griffiths, PhD, is a Professor of Biochemistry at École Supérieure de Chimie Industrielles de Paris (ESPCI Paris) in Paris and formerly the holder of a Chaire d'Excellence from the Ministère pour la Recherche, France, at the Institut de Science et d'Ingénierie Supramoléculaires in Strasbourg. After receiving his PhD from the University of Leicester in 1988, he joined Dr. Winter at the MRC Laboratory of Molecular Biology, Cambridge, UK, where he co-developed phage display for the selection of human antibodies for therapy. This work led directly to the creation of two companies, Cambridge

Antibody Technology and Domantis, and several blockbuster drugs including Humira® and Benlysta®. Subsequently, he pioneered the use of systems for directed evolution, high-throughput screening for drug discovery, single-cell analysis and diagnostic applications, in which reactions are compartmentalized in microscopic droplets, in particular in microfluidic systems (droplet microfluidics). He has co-founded five start-ups: RainDance Technologies, HiFiBiO Therapeutics, Design Pharmaceuticals (formerly Biomillenia), Cyprio, and Minos Biosciences.

Dr. Royston Jefferis, PhD, is Professor Emeritus in the Institute of Immunology and Immunotherapy within the College of Medical and Dental Sciences at the University of Birmingham, UK. After completing his PhD in chemistry, Dr. Jefferis began his tenure of research into the structure and function of antibody molecules. His work has included investigation into the engineering and design of antibody therapeutics. Dr. Jefferis has published over 300 articles in his field and has received numerous awards, including an honorary Doctor of Science degree from the University of Birmingham and being elected as a Member of the Royal College of Physicians and a Fellow of the Royal College of Pathologists.

Dr. Nick Ray, PhD, is the Chief Scientific Officer of a UK drug discovery company, C4X Discovery. Dr. Ray received his PhD in Organic Chemistry from the University of Birmingham, UK, in 1989 and completed his postdoctoral research at Dartmouth College in 1991. He has more than thirty years' experience leading key drug development programs at multiple multi-national companies including Rhône-Poulenc, Celltech and Argenta/Charles River in the therapeutic

areas of oncology, respiratory diseases, inflammation, central nervous system, pain and metabolic disease. Dr. Ray is a named inventor on over 75 patents and has published numerous papers and presentation abstracts.

***Dr. David M. Manuta, PhD, FAIC*,** is a Fellow and current Board Chair of the American Institute of Chemists (AIC). He received his BS in Chemistry from the State University of New York (SUNY) at Oneonta and his PhD in Inorganic Chemistry from SUNY Binghamton. He was named a Distinguished Alumnus at both universities in 2014. AIC is a national, non-profit organization founded in 1923 for emphasizing and promoting the relevance of the chemical profession and its practitioners to society at large. AIC's mission is to advance the chemical professions in the US, to promote and protect the public welfare by establishing and enforcing high professional standards of practice for these professions, and to promote the professional, social, and economic interests of its members for the benefit of society at large.

This case hinges on basic scientific questions concerning antibody design and development and what it means to enable the making and using of patented scientific innovations. As some of the world's leading antibody scientists, chemists, and innovators, Amici have a strong interest in advising the Court about basic principles of antibody design and how overbroad patent claims like Amgen's create enormous barriers to scientific innovation across a variety of fields.

SUMMARY OF ARGUMENT

The development of antibodies for the treatment of disease—particularly for auto-immune inflammatory diseases and cancers—has revolutionized the pharmaceutical industry. Many patients throughout the world rely on antibody drugs to treat serious and life-threatening diseases.

This case involves antibody drugs that treat high cholesterol by binding to a naturally occurring protein, PCSK9, and blocking it from interfering with natural "LDL receptors" that remove cholesterol from the bloodstream. Amgen's primary assertion appears to be that because it was the first to determine the identity of the amino acids that make up the natural site on PCSK9 where LDL receptors bind—the alleged "sweet spot"—it should be entitled to patents covering any and all antibodies that bind there. But Amgen did not invent the natural binding site, nor did Amgen even use its discovery of that alleged "sweet spot" to make its own two lead antibodies. Rather, Amgen's claimed "invention" is simply a hindsight characterization of that which existed naturally. Amgen's attempt to monopolize the natural PCSK9 binding site by reciting the specific amino acid residues of that site, without providing any teaching as to how to make and use antibodies that specifically bind to those residues, is fundamentally at odds with the patent bargain and principles of scientific advancement and innovation.

This amicus brief provides information and scientific perspectives concerning several issues at

the heart of this case, namely, (1) the unpredictability of antibody design and engineering, including methods of generating and testing antibodies for a particular function; (2) the lack of guidance provided by Amgen's patents, and indeed, the additional hurdles created by Amgen's claims to make and use the claimed class of antibodies; and (3) the devastating impact of over-broad, purely functional claims like Amgen's on antibody development and innovation for pharmaceutical drugs.

First, it is a fundamental tenet of basic antibody science that an antibody's structure, as determined by its sequence, further determines its function. It is equally fundamental that the reverse is not true. That is, simply knowing an antibody's function (*e.g.*, what it binds to, or where it binds specifically) does not tell an antibody scientist about its structure (*i.e.*, what it *is*).

Second, Amgen's patents are not directed to a narrow class of specific antibodies. Rather, Amgen's patents broadly claim any and all antibodies (of unspecified and unknown structure) that bind to a natural antigen at its natural interface with natural receptors. Indeed, by further requiring that the claimed antibodies bind to specific residues—which can only be determined by performing additional, onerous testing of each generated antibody—Amgen has actually increased the burden on scientists, forcing them to engage in undue experimentation in order to make, test, and characterize each one of potentially billions of antibodies to determine whether they are covered by Amgen's claims.

Finally, using this case to vitiate the Federal Circuit's long-standing enablement standard would permit an applicant to effectively patent a natural interface on a target of interest. Doing so would stifle

innovation and set a dangerous precedent for the scientific and pharmaceutical community at large.

ARGUMENT

I. ANTIBODY DESIGN IS UNPREDICTABLE.

A. Overview of Antibodies.

Antibodies are a critical part of our natural defense against infections. When a foreign agent (an "antigen") such as a virus enters our bodies, the immune system generates a diverse range of antibodies to target and bind to the antigen, stopping it before it can cause us harm.

Although nature created antibodies to protect against infectious disease, over the last few decades, scientists have developed and evolved antibodies for the treatment of non-infectious diseases such as auto-immune conditions and cancer.[2] In these situations, the antigens targeted by antibodies are not viruses or foreign agents but rather our own proteins, receptors, and ligands. While naturally occurring in our bodies, these molecules can also be involved in inflammatory disorders, uncontrolled cell growth, or other biological pathways that may be associated with disease.

Antibodies are proteins that are made up of basic building blocks called amino acids. Different amino acids are made of different configurations of atoms.

---

[2] Gregory Winter & César Milstein, *Man-made Antibodies*, 349 NATURE 293, 293-99 (1991).

See D. Ct. Dkt. 864, Tr. 400-01.[3] At a high level, all IgG antibodies have the same basic Y-shaped structure, as shown below, made up of four tightly associated chains of linked amino acids—two identical heavy chains and two identical light chains.

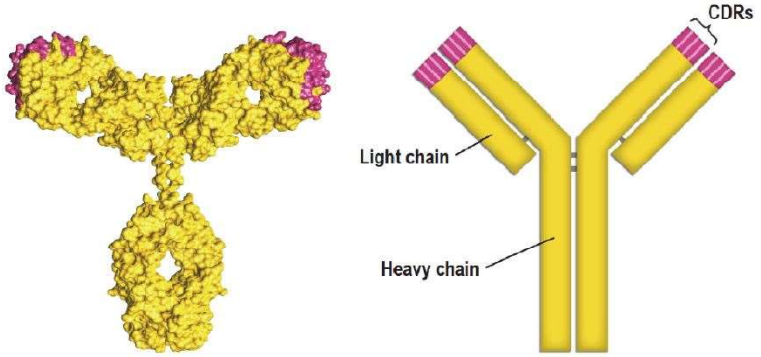

Figure 1. The basic structure of an antibody.[4]

Each antibody chain has a constant region and a variable region. Each variable region has three complementarity-determining regions ("CDRs"), which are shown in pink on Figure 1. As Amgen noted, these CDRs are "where all the action is"—these loops of variable sequences of amino acids are responsible for an individual antibody's specific ability to target and bind to antigens. Pet. Br. 10; *see* C.A. App. 3680 (186:21-22, 187:3-7). Human antibody CDRs can have practically unlimited diversity potential—that is, there are effectively endless possibilities as to the structure of these CDRs and what they can bind to.

---

[3] "D. Ct. Dkt." refers to district court docket entries, No. 14-cv-1317 (D. Del.).

[4] Reproduced from Pet. Br. 10.

The location on an antigen where a given antibody binds[5] is called an "epitope." *See Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1291 (2014). An epitope on a protein can be comprised of several amino acids, and antigens have many possible epitopes. Furthermore, like a lock with billions of possible keys, there are "a practically infinite combination of antibody structures [that] bind to an epitope." D. Ct. Dkt. 865, Tr. 672:1-8.

B. Basics of Antibody Structure and Function.

When scientists refer to an antibody's "structure," they may be referring to several related concepts, all of which describe what an antibody *is*. At the most basic level, the linear amino acid sequence of an antibody is also referred to as its "primary structure." C.A. App. 3890. In the case of Amgen's patents, for example, this would be reflected by, *e.g.*, SEQ ID NO: 67. *See* U.S. Patent No. 8,829,165 ("the '165 patent"), Fig. 3E:

Amino acid sequence of heavy chain variable region:
EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYISY
ADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYFCARDYDFWSAYYDAFDVWGQGT
MVTVSS **(SEQ ID NO: 67)**

But antibodies are not simply two-dimensional, linear sequences, as the atoms of the amino acids in the chains interact with each other, causing the chains to "fold up." This creates a complex three-dimensional shape referred to as the "tertiary structure." *See* C.A. App. 3910 (766:5-9).

---

[5] The district court construed "[b]inds to residues" to mean "[i]nteracts with residues and contributes to the affinity of the PCSK9-antibody interaction." *Amgen Inc., v. Sanofi et al.*, C.A. No. 14-1317-SR, 2015 WL 6159114, at *2 (D. Del. Oct. 20, 2015).

The precise shape of an antibody will depend on the sequence of amino acids in the antibody. And the shape will in turn dictate the antibody's "function," including whether it can bind to the target antigen, and whether it can block the binding of another molecule to the same antigen. For example, the fact that an antibody binds to one part of an antigen does not necessarily mean the antibody will also block the binding of another molecule to a different part. Indeed, Amgen itself disclosed that although it was able to generate approximately 3,000 antibodies that bound to PCSK9, only 384 blocked LDL receptors from binding to PCSK9, and a mere 85 were considered "strong" blockers. *See* Pet. Br. 13; *Amgen, Inc. v. Sanofi*, 872 F.3d 1367, 1372 (Fed. Cir. 2017); '165 patent, 73:39, 78:4-6, 80:22-37.[6]

For an antibody to bind to an antigen, the two surfaces have to fit together and contact each other at multiple points. The tightness with which an antibody binds to an antigen will depend on many factors, including how well the two surfaces fit together. It will also depend on whether the amino acids at the contacts can make strong bonds across the interface with each other.[7] As the shapes of the antibody binding

---

[6] Amgen's patents further provide an example of an antibody that "can bind to PCSK9 without blocking the PCSK9 and LDLR binding interaction" and yet still be "useful" in neutralizing PCSK9. *See* '165 patent, 123:23-29 (Example 41).

[7] For example, "plus" charged amino acid residues such as arginine, lysine, and histidines can make strong electrostatic bonds to "minus" charged residues such as glutamic acid and aspartic acid. Likewise, polar residues, such as serine and threonine, are capable of making strong hydrogen bonds to the polypeptide backbone if orientated correctly.

sites and the locations of the different amino acids vary greatly, different antibodies can bind to different regions of the antigen and with a great range of binding affinities and blocking capabilities.

By way of example, Amgen, Sanofi and Regeneron, Pfizer, and Merck all made antibodies with varying structures that bind to PCSK9 and block binding to LDL receptors, but they do so in notably different ways. As shown in Figure 2 below, these different antibodies make different contacts to different numbers and combinations of amino acid residues within the alleged "sweet spot" epitope on PCSK9.

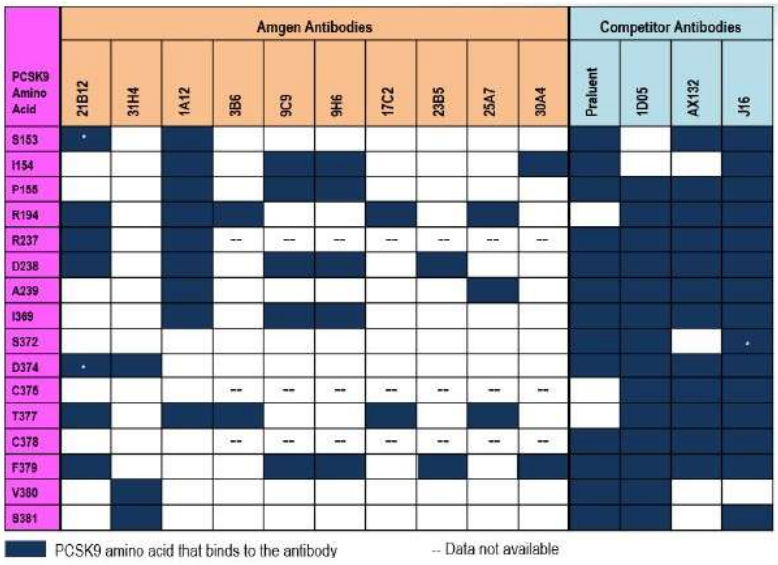

Figure 2. Comparing the claimed PCSK9 contact residues at the binding sites of the Amgen blocking antibodies and competitor antibodies.[8]

---

[8] Most of the Amgen antibodies make contact to only 2-3 residues of the "sweet spot" (and no more than 9). By contrast, the competitor antibodies (Praluent, 1D05, AX132, and J16) make contact with nearly all of the residues. C.A. App. 4283 (reproduced); *see id.* at

Furthermore, as shown in Figure 3 below, while Sanofi and Regeneron's antibody, Praluent, binds to the middle area of PCSK9 (*i.e.*, sitting directly on top), thus contacting nearly all of the amino acid residues in the "sweet spot," Amgen's exemplified "anchor" antibodies, 21B12 and 31H4, only make contact to each side of the epitope and less than half of the claimed residues.[9]

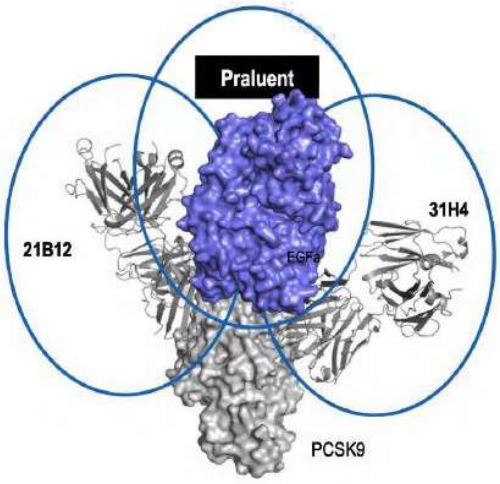

Figure 3. A view of PCSK9 (grey surface), including the portion recited in Amgen's claims, and where Amgen's antibodies, 21B12 and 31H4 (grey sticks), bind (on the sides) as compared with Sanofi and Regeneron's antibody, Praluent (blue surface).[10]

3776 (crystal structures for 21B12, 31H4, 1A12, and Competitor Antibodies); C.A. App. 3884-85 (alanine scanning for 9H6, 25A7, 17C2, 30A4, 23B5, 9C9, 3B6).

[9] It appears Amgen's own scientists agreed at the time that it would be "tricky to find" an antibody that could bind to this middle region and referred to it as a "missing epitope." Resp. C.A. Br. 13-14; C.A. App. 3782-83 (444:13-445:13).

[10] C.A. App. 4377 (reproduced).

C. Structure Determines Function, But Not Vice Versa.

It is well understood in antibody science that an antibody's amino acid sequence is its "recipe," which determines both the antibody's structure (what it *is*) and, accordingly, its function (what it *does*, *e.g.*, what it binds or blocks). The precise order of amino acids dictates how they will interact, how the chains will fold and arrange, and, additionally, which amino acids will comprise the CDR loops that ultimately interact with antigens. *See* C.A. App. 3748. Changing even one amino acid in the entire sequence can alter an antibody's 3D structure and function.[11] *See, e.g.*, *id.* at 3767. In fact, as Amgen's expert testified at trial, it is possible that changing a single amino acid in an antibody's sequence could turn an antibody that binds to an antigen into an antibody that does not bind to that same antigen. *See id.* at 3891 (688:21-689:4).

That being said, it is not well understood in antibody science even today precisely *how* a particular change in the amino acid sequence (*e.g.*, substituting one amino acid for another) will affect the antibody's structure and function. *See, e.g.*, *id.* at 3910 (765:10-19) (Amgen's expert agreeing, "[t]he way in which you get from sequence to that three-dimensional

---

[11] Similarly, in the chemical arts, the chemical formula of a compound determines its function. The substitution of a single moiety in the structure of a chemical compound could alter entirely the compound itself and its associated function. *See, e.g.*, *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1161 (Fed. Cir. 2019) (finding that the art was unpredictable given expert testimony that "the smallest change can have a dramatic effect not only on the activity of that compound but on the toxicity of the compound").

structure isn't fully understood today. It's going to get a Nobel Prize for somebody at some point, but translating that sequence into a known three-dimensional structure is still not possible."); *id.* at 3911 (770:12-16) (Amgen's expert further agreeing that even if antibody sequences were "similar," that "doesn't tell you whether or not—whether an antibody binds to a particular region on a particular protein"). Thus, while it can be fairly said that an antibody's sequence determines its structure, which determines its function, an antibody scientist is unable to predict the function of an antibody from its sequence. Furthermore, an antibody scientist is unable to accurately predict how a change in the amino acid sequence of an antibody of known function may affect that function. The only way to know the function of a given antibody is to test it once it has been made. *See, e.g.*, *id.* at 3914 (779:10-14).

For these reasons, Amgen's reliance on the utility of so-called "conservative substitutions" is misplaced. Amgen claims that a scientist could use the "conservative substitutions" depicted in Table 1 of its patents to modify its two exemplified antibodies to identify other antibodies covered by its claims. Pet. Br. 14-15. But the principle of conservative substitution does not render antibody design predictable or ensure that the created antibodies have the requisite binding and blocking functions.

In protein science, the terms conservative replacement, conservative mutation, or conservative substitution[12] are typically used in the context of studying

[12] Amgen also uses the term "intelligent substitution," which is not a term that Amici, who include leaders and pioneers in antibody science, understand to be commonly used in the field.

evolutionary changes in proteins. Specifically, scientists often examine proteins that evolve from each other and identify patterns of similar amino acids that tend to be more interchangeable, *e.g.*, that have similar biochemical properties and thus may be better tolerated. In doing so, scientists seek to understand what properties are favored and/or conserved by evolutionary pressures.

While understanding such conservative substitutions may be useful in protein research, they are by no means a "shortcut" in antibody engineering for therapeutics. Rather, the impact of such substitutions remains highly unpredictable. Even purportedly conservative changes to amino acid sequences can have a large impact on an antibody's structure and associated binding properties—which in turn can impact blocking ability. As one of Amgen's own inventors noted, "I have been surprised in the past where sometimes what you think is a conservative substitution is not conservative at all . . . in terms of protein function." C.A. App. 3768 (388:24-389:2); *see also id.* at 3878 (638:8-9) (Amgen's expert agreeing, "small changes in sequence can make big changes in structure and in some cases function"). There is also no way to predetermine that a substitution *will* change how an antibody specifically binds, such as, *e.g.*, whether the modified antibody will bind to other residues within the epitope.

Moreover, some of the allegedly conservative substitutions reflected in Table 1 of Amgen's patents would not necessarily be considered conservative by an antibody scientist, especially since it may depend on where in the antibody's sequence the substitution is made. For example, Table 1 describes replacing tyrosine ("Tyr") with phenylalanine ("Phe") as a

"preferred substitution." '165 patent, 28:49 (Table 1). But an antibody scientist would be wary of such a substitution, particularly within the CDRs of an antibody, because doing so could remove a hydrogen bond important for binding to an antigen.[13] The only sure way to determine whether the function of an antibody tolerates an amino acid substitution is to make the substitution and test the resulting antibody. *See* C.A. App. 3768-69; *id.* at 3913-14 (778:24-779:14) (Amgen's expert admitting "you'd have to test" antibodies to know whether they fell within the scope of Amgen's claims). This process would be unduly cumbersome, and indeed, no antibody scientist would ever construct an experiment in this way in order to generate antibodies with a desired function.

Thus, it is well understood that the relationship between an antibody's structure and its function is unpredictable. While knowing the sequence of an antibody would allow a scientist to make and use that particular antibody, it does not allow the scientist to change the sequence with any degree of confidence that doing so would result in a given function, particularly where that function requires binding to specific amino acid residues of an identified epitope.

Similarly, simply knowing what an antibody does (*e.g.*, its function) does not inform an antibody scientist as to what the sequence or structure of such an antibody would be. *See* C.A. App. 3769 (389:25-391:3) ("it would be challenging to determine the amino acid sequence of something binding your antigen just

---

[13] *See, e.g.*, Alan Fersht et al., *Hydrogen Bonding and Biological Specificity Analysed by Protein Engineering*, 314 NATURE 235 (1985).

know[ing] where it binds because of the wide variety of ways that it could be bound"). Indeed, antibodies with similar structures may bind to entirely different epitopes, or bind through different residues within the same epitope. Different antibodies also may bind to the same epitope but exhibit different degrees of binding and blocking. At the end of the day, an antibody scientist must engage in extensive experimentation to identify and develop antibody candidates for any therapeutic application.

D. Generating and Testing Antibodies That Bind to Specific Residues of an Epitope and Exhibit Desired Blocking Functions Requires Undue Experimentation.

There are several ways for scientists to generate large quantities of monoclonal antibodies that bind to a particular antigen. One involves immunizing a mouse (or other mammal) with the target antigen to provoke an immune response and then harvesting the antibody-producing cells from the mouse to create essentially antibody factories that can be grown in culture. *See* C.A. App. 3690. Alternatively, scientists can use an antibody library approach such as phage display, which harnesses the power of bacteriophages (viruses that infect and replicate within bacteria) to produce vast libraries of millions of potential antibody candidates.

Regardless of the method used to make antibodies, however, scientists must screen them for binding ability. None of the antibody-making techniques can guarantee the creation of antibodies that necessarily bind to specific sets of amino acid residues. As discussed above, the generated antibodies could bind to

anywhere on the epitope of a target antigen, or to different epitopes on the same target. In order to identify the specific amino acid residues of the target antigen that each antibody contacts, it would be necessary to undertake further experiments on each of the randomly generated antibodies.

These experiments would typically include x-ray crystallography, as described in Amgen's patents, which can identify the precise contacts between an antibody's CDRs and the specific amino acid residues of an epitope. As of 2007, when Amgen's patents were filed, performing these experiments for every antibody generated would have required a significant amount of time, cost, and effort. *See also* C.A. App. 3902 (733:2-11) (Amgen's expert agreeing that this "is not actually something that an antibody scientist would do" and that it would require an "enormous amount of work" to make the "millions of antibodies" that could be covered by the claims).

Moreover, the determination of whether any specific residue of PCSK9 "binds to" an antibody would require yet further experimentation, for example by mutation of that residue in PCSK9 and observing the effect on binding affinity. Indeed, the inventors themselves highlight the lack of predictability of these experiments, noting, for example, "while there were approximately a dozen mutants that could have been expected to have an effect on binding (based upon the crystal structure), the present experiment demonstrated that, surprisingly, they did not." '165 patent, 121:41-44.

As such, rather than being useful to an antibody scientist, the identification of the interface residues between an antigen and a natural ligand, and the

demonstration that each antibody binds to a specific set of those interface residues, would require an antibody scientist to engage in much more, not less, experimentation, and perhaps even then to be unsure whether he had made the antibody as claimed.

II. AMGEN'S HINDSIGHT "INVENTION" IS NOT COMMENSURATE IN SCOPE WITH ITS CONTRIBUTION TO THE FIELD.

A. Amgen Did Not Discover the PCSK9 Pathway.

PCSK9 (proprotein convertase subtilisin/kexin type 9) is a naturally occurring protein that can bind to low-density lipoprotein (LDL) receptors and interfere with their ability to remove cholesterol from our bloodstream. Buildup of LDL cholesterol in our arteries can cause clots that lead to heart attack and stroke.

Amgen did not discover how LDL receptors work, nor did Amgen discover PCSK9 itself. Rather, in the 1970s, researchers Michael S. Brown and Joseph L. Goldstein (both now Directors at Regeneron) at the University of Texas Southwestern first discovered the connection between high LDL cholesterol levels in the blood and a reduced number of LDL receptors.[14] *See* C.A. App. 3680-81. In 2001, scientists at Millennium Pharmaceuticals discovered the gene that encodes PCSK9. *See id*. at 3681. About two years later, Abifadel et al., discovered that point mutations

---

[14] Brown and Goldstein later received the Nobel Prize in Physiology or Medicine in 1985 for this work. *See The Nobel Prize in Physiology or Medicine 1985*, The Nobel Prize, https://www.nobelprize.org/prizes/medicine/1985/summary. Both Brown and Goldstein have been Directors of Regeneron since 1991.

on PCSK9 cause high cholesterol.[15] And in 2006, another group of researchers from the University of Texas Southwestern published research suggesting that the development of antibodies to block PCSK9's interaction with LDL receptors could treat high cholesterol.[16]

Notably, none of these researchers had any connection with Amgen. *See* C.A. App. 3680-81.[17] Indeed, there is no indication that the "discovery" of the identity of the amino acid residues of the naturally occurring "sweet spot" helped anyone in developing PCSK9 antibodies. To the contrary, by December 2008 —well before Amgen even published its discovery of the alleged "sweet spot" in 2009—Sanofi and Regeneron had already made their innovative PCSK9 antibody drug, Praluent. *See, e.g.*, U.S. Prov. Appl. No. 61/122,482 (filed Dec. 15, 2008).

Thus, rather than inventing any class of novel antibodies or discovering anything of actual use, Amgen merely leveraged the work of others and utilized hindsight characterization studies in an attempt to block competition and monopolize the field.

---

[15] Marianne Abifadel et al., *Mutations in PCSK9 Cause Autosomal Dominant Hypercholesterolemia*, 34 NATURE GENETICS 154, 154-56 (2003).

[16] Thomas Lagace et al., *Secreted PCSK9 Decreases the Number of LDL Receptors in Hepatocytes and in Livers of Parabiotic Mice*, 116 J. CLINICAL INVESTIGATION 2995 (2006).

[17] Amgen's unusual suggestion that it was "the first to discover" the LDL/PCSK9 pathway appears to discount the significant work of these pioneers in the field. *See* Pet. Br. 9-10.

B. Amgen's Claimed Invention Is Not a Small Genus.

The two Amgen patents at issue, the '165 patent and U.S. Patent No. 8,859,741 ("the '741 patent") generally relate to antibodies that can target and bind to the alleged "sweet spot" of PCSK9. Claims 19 and 29 of the '165 patent require that antibodies bind to at least two of the listed 15 amino acid residues of the "sweet spot." To meet the binding requirement of these claims, antibodies can bind to any two or more residues, all residues, or some combination thereof. Similarly, Claim 7 of the '741 patent requires that antibodies bind to at least one of two listed residues. *See* '741 patent, Claims 1, 7. To meet the binding requirement of Claim 7, antibodies can bind to one or both of these two residues.

The relevant claims are thus so broad that they "cover the entire genus of antibodies that bind to specific amino acid residues on PCSK9 and block PCSK9 from binding" to the LDL receptors. *Amgen*, 872 F.3d at 1372. Notably, these claims do not include any antibody sequence or other structural feature. Instead, they claim purely by desired function, *i.e.*, what the antibodies bind to. Put differently, the claims are grounded entirely in the sequence and structure of the *antigen,* not the antibodies themselves.[18]

Amgen and its amici repeatedly rely on contrived, overly simplistic analogies in an attempt to downplay the complexities of the applicable technology, the broad

---

[18] This is distinguishable from claims that may recite function but also provide narrowing limitations concerning, *e.g.*, CDR identity or other structural features, which are more likely to be patentable and valid.

scope of Amgen's claimed genus, and the amount of experimentation required to "make and use" its embodiments. For example, Amgen states at one point that while "there are nearly limitless variations of the airplane," including "[d]ifferent materials, wing configurations, body styles, means of propulsion, etc.," "no one would think that skilled aeronautical engineers cannot 'make and use' the airplane simply because one cannot sequentially or simultaneously build and utilize *every* conceivable variation (or improvement) without 'substantial time and effort.'" Pet. Br. 28-29.

This analogy misses the point. Putting aside that there are thousands of patents directed to advancements in aviation technology precisely because no one was able to patent "all airplanes" as broadly as Amgen is trying to do with "all antibodies that block the binding of LDL receptors to PCSK9," Amgen's patents are not limited to a single airplane (*i.e.*, a structure). Instead, even sticking with Amgen's analogy, Amgen's patents are more appropriately characterized as claiming a category of "all things that fly" with certain functional abilities that can only be determined via testing after they are made (*e.g.*, having the ability to reach at least 2 of 15 different altitudes between 1,000 and 30,000 feet). While Amgen's patents disclosed only two examples of things that fly and reach some—but not all—of the claimed altitudes, Amgen's claims are broad enough to cover all helicopters, rockets, spaceships, flying cars, blimps, or drones that could conceivably reach those altitudes. And in order to make such a flying contraption within the scope of Amgen's claims, the artisan would have to engage in undue experimentation to first make a flying object and then determine if it

could reach the desired altitudes, without any guidance in the patent as to what components or features are necessary to achieve that desired, claimed function.

Other attempts to analogize Amgen's claims likewise miss the mark. For example, AbbVie's amicus brief suggests that Amgen's invention is similar to "revolutionary manufacturing processes that render ice cream calorie-free" and because "[t]he flavor makes no difference to the innovative feature of the invention," the inventor thus "ought be entitled to patent claims covering calorie-free ice cream of any flavor, even if the patent only teaches processes making two flavors, vanilla and chocolate." AbbVie Amicus Br. 9. This analogy again is overly simplistic, but even assuming it applies, it is similarly flawed. First, it improperly assumes the critical fact it strives to illustrate—that changing the "flavor" of ice cream does not have any effect on its calorie count. Second, it ignores the fact that Amgen's patents do not claim, or even describe, any such revolutionary process.

In fact, the scientific realities are similar for antibodies and ice cream. Even small variations in ingredients (*e.g.*, a single amino acid substitution, or a dash of pistachios) could have a large impact on desired function or result (*e.g.*, on binding affinity or caloric value).[19] And without having provided any

[19] Indeed, while most ice cream has the same basic ingredients (*e.g.*, milk, cream, and sugar), there are endless combinations of flavors possible by adding and mixing different ingredients (*e.g.*, vanilla, peanut butter, fudge, pistachios). Substituting one ingredient for another, or changing the ratio of the ingredients, can alter the calorie count and even fundamentally change the texture and taste of the dessert (*i.e.*, replacing dairy with fruit juice would turn ice cream into a sorbet). Moreover, changing how the dessert is made, including how the mixture is churned

novel process for ensuring the desired function or result, the only way to make the claimed antibodies (or ice cream) would be to experiment with different components or ingredients and then test the resulting product. At best, Amgen managed to make two flavors of ice cream (vanilla and chocolate) that it determined, after the fact, to be calorie-free. But rather than patent only those two flavors, Amgen claims to have invented all calorie-free frozen dessert, be it ice cream, sorbet, sherbet, or gelato, and regardless of what flavor it is, what is in it, or how it is made to be calorie-free.

At their core, the Amgen patents are a hindsight attempt to own every possible antibody that binds to the natural site where LDL receptors also bind to PCSK9. *See Amgen*, 872 F.3d at 1372. Amgen's claimed "invention" even includes antibodies that are entirely unknown to Amgen, and that have not yet been discovered or developed. No analogy can mask the breadth of what Amgen seeks to monopolize.

C. Amgen's Patents Do Not Tell an Antibody Scientist How to Make and Use the Claimed Genus of Antibodies Without Undue Experimentation.

Section 112 of the Patent Act requires that a patent specification "enable any person skilled in the art to which it pertains . . . to make and use" the

---

(*i.e.*, how much air is incorporated), could transform ice cream into its Italian cousin, gelato. Yet despite all these variables and lack of predictability as to what combinations could be made to be "calorie-free," Amgen would claim ownership over all such frozen dessert, no matter how original the flavor combination, how novel the ingredients, or how ingenious the churning process.

claimed "invention." 35 U.S.C. § 112. The Federal Circuit has interpreted this as requiring that a patent specification teach a skilled artisan "how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Trs. of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362-64 (Fed. Cir. 2018) (collecting cases).[20] The Federal Circuit analyzes a number of factors to determine whether the amount of experimentation required is "undue," including, but not limited to:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

---

[20] Although Amgen claims this Court's precedent between 1846 and 1916 refutes the Federal Circuit's "full scope" standard, the technology in those cases is highly distinguishable. Indeed, those cases have limited applicability today, particularly in the field of drug discovery and development, as they involved either far simpler objects (*e.g.*, the cotton gin) with specific structural features or actual improved processes for making objects. *See Wood v. Underhill*, 46 U.S. (5 How.) 1 (1846) (patent concerned manufacturing bricks and tiles); *Mowry v. Whitney*, 81 U.S. (14 Wall.) 620 (1872) (patent concerned wheels on rail-cars); *Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261 (1916) (patent concerned metal work). Amgen's claims include no such structural limitations or improved process. In any event, this Court made plain that in cases where "no one could use the invention without first ascertaining by experiment the exact proportion of the different ingredients required to produce the result intended to be obtained," the patents are "void." *Wood*, 46 U.S. at 5.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

Amgen's patents do not come close to teaching an antibody scientist how to make and use antibodies that bind to its claimed specific residues and block binding of LDL receptors. First, Amgen's patents provide no information as to how knowledge of the identity of the "sweet spot" residues can be used to make antibodies. Indeed, as discussed above, this information does not exist.

Second, although Amgen claims to have provided a "roadmap" to scientists in its patents, in reality the patents simply describe Amgen's own trial-and-error experimentation process, including how Amgen injected PCSK9 into genetically engineered mice, repeatedly screened the resulting antibodies for binding and blocking functions, and then performed additional x-ray crystallography studies on just two antibodies, 21B12 and 31H4, to characterize their binding sites with precision. *See Amgen*, 872 F.3d at 1372; *see also* '165 patent, 73:39-54, 78:4-6, 80:22-37; Pet. Br. 13-14. Nowhere in this "roadmap" is any teaching or guidance that provides a practical shortcut to other scientists to make and use the claimed broad genus of antibodies without undue experimentation.

Amgen's heavy reliance on its two exemplified, "anchor" antibodies, 21B12 and 31H4, as part of its purported "roadmap" is misplaced. *See* Pet. Br. 13-14. Amgen's own inventor admitted that the use of these anchor antibodies in the described competition and binning assays "does not give an indication of where on the antigen antibodies are binding." C.A. App. 3767 (383:12-14); *see also id.* at 3769 (391:6-392-10) (another Amgen inventor testifying that "you would not know the exact residues that the antibody binds

[to]" using a competition assay; that antibodies that compete with one another can still have different properties; that as of 2007, it "would be very challenging" to predict the amino acid structure of an antibody that would bind to PCSK9 and block LDR receptors; and that "just de novo trying to make a binding protein knowing the structure of the thing you're trying to bind was in 2007 a real challenge and still is challenging"). Thus, at most, use of the anchor antibodies in competition assays would give a scientist an idea of what antibodies compete with those anchor antibodies. The scientist, however, would still have to run the same experiments to determine whether any of the competing antibodies blocked LDL-receptor binding and bound PCSK9 at the specifically claimed amino acid residues.[21]

Thus, while Amgen asserts that its patents provide a "roadmap" and exemplary antibodies to help a scientist make other antibodies that are covered by the claims, in reality, these disclosures put an antibody scientist in no better position to make PCSK9 antibodies than without Amgen's patents. Even worse, rather than teaching a scientist how to make specific antibodies that satisfy the claims, Amgen's patents effectively create *additional* hurdles for those in the art. Following the making and screening of antibodies

---

[21] Indeed, Amgen's patents themselves disclose two antibodies—subclones of an antibody called 27B2—which appeared to "compete" for binding to PCSK9 with Amgen's "anchor antibodies," 21B12 and 31H4. *See* '165 patent, 112:44-66 (Table 37.1). According to Amgen, this would indicate that these antibodies would be excellent therapeutic candidates within the scope of the claims. However, the patents teach that despite competing with the anchor antibodies, 27B2 did not work (it was "non-neutralizing") and thus outside the scope of the claims. *See id.* at 35:37-40.

that bind to PCSK9 and block LDL receptors, scientists would need to perform additional characterization tests for each antibody screened to determine whether the given antibody binds to at least 2 or as many as all 15 (in any combination) of the set of listed residues. Absent any additional guidance as to how to use the identified "sweet spot" residues to make antibodies, and given the complexities and unpredictability of antibody design as previously discussed, Amgen's patents fail to enable the potentially billions of antibodies that it claims to have invented.

III. SWEEPING FUNCTIONAL GENUS PATENTS LIKE AMGEN'S BLOCK INNOVATION AND ACCESS TO NEW MEDICINES.

The patent system is built upon a carefully struck bargain: exclusivity in exchange for, and commensurate with, disclosure. The Federal Circuit's enablement standard, as applied in the decision below, honors this bargain. It requires that a patent disclose enough to the public to allow a skilled artisan to be able to make and use the "full scope" of what is claimed. If patentees only had to teach the public how to make a part of their invention, but received the exclusionary benefits for the full scope of what they claimed, patentees would get to control and own things they did not actually invent. Worse, they could use the patent system to retroactively squeeze other innovators out of the market. That is precisely what Amgen is seeking to do here.

This is not a circumstance where an innovator is losing rights to a true "breakthrough" invention. Amgen did not discover PCSK9, the association between PCSK9 and levels of LDL in the blood, or the knowledge that creating antibodies that bind to PCSK9 and

block its binding to an LDL receptor could treat high cholesterol. At best, Amgen's contribution was identifying the naturally occurring amino acid residues on PCSK9 that contact the LDL receptor, and those that contact two blocking antibodies, 21B12 and 31H4. Amgen did not create or alter any of these natural residues; they existed in nature before Amgen found them.

This should trigger warning bells for the Court and for the field. The natural binding sites on target antigens are wholly unpatentable subject matter under this Court's jurisprudence regarding 35 U.S.C. § 101. *See, e.g.*, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589-90 (2013). But by writing their patent claims so broadly in purely functional terms, Amgen effectively has claimed ownership of the natural binding site of PCSK9 itself. These patents, if upheld, would give Amgen the exclusive right to market antibody therapies blocking PCSK9, despite Amgen not having discovered any of the underlying biology or contributed anything beyond naming the existing residues of the natural binding site.

Indeed, lowering the enablement standard to allow purely functional claims like Amgen's would incentivize companies to use their considerable resources to block access to new therapies by essentially calling "dibs" on anything that binds to a naturally occurring target of interest. Doing so could deny patients access to multiple, differing treatments developed by selecting from a panoply of potential reagents which may have specificity for the same, naturally occurring target. This is particularly important because the repeated administration of one antibody can lead

patients to generate an unwanted response against said antibody, which may require clinicians to turn to other antibodies with different antigen binding regions against the same target for continued treatment. It is therefore desirable for clinicians to have several antibodies available against the same target to allow for long periods of treatment.[22]

For these reasons, Amici are troubled by and disagree strongly with statements of Amgen's amici that suggest that claims like Amgen's somehow promote innovation for, *e.g.*, small companies and researchers. Quite the opposite—an arms race to patent natural interfaces or surfaces of targets involved in key interactions in a disease undermines scientific development and gives an unfair advantage to companies with unlimited resources. Small innovators and scientific researchers will lose the race every time, and they typically do not have the resources to conduct the required "hindsight" testing, as suggested by Amgen's patent, necessary to determine whether their work is covered by a patent.[23] Moreover, when there is no perceived freedom to operate against a target due to

---

[22] Similarly, in the chemical arts, "Best-in-class" drugs often follow "First-in-class" drugs and provide some new advantage (*e.g.*, an improved safety profile). For these "Best-in-class" drugs to be possible requires companies to identify related, but improved compounds and obtain patent coverage for new discoveries. None of this would be attainable if overly broad genus claims have already been granted with little or no exemplification.

[23] Even if a small company managed to obtain a patent with broad functional genus claims, such a patent will likely be vulnerable to multiple challenges and may be of limited practical use, given the time and expense needed to enforce any patent rights against others.

an overly broad claim like Amgen's, smaller companies may not be able to acquire funding for research into that target. Accordingly, many may choose to avoid the space entirely, which would be damning to the discovery of novel compounds, structures, and reagents, which often arise out of coincidental development and free scientific exploration.

In sum, purely functional claims like Amgen's are enormously harmful to scientists who seek to understand, research, and develop new therapies for known targets, particularly where the technology at issue is complex and unpredictable. No entity should be able to contribute only a few drops and claim ownership of the ocean. The current enablement standard protects innovation and limits exclusivity to that which is truly inventive. It should be upheld.

CONCLUSION

For these reasons, Amici respectfully request the Court reject Amgen's attempt to alter the enablement standard.

Respectfully submitted,

Sophie F. Wang
Counsel of Record
Eric J. Marandett
Jillian L. Gately
Olivia L. Campbell
Timothy J. Conklin
CHOATE HALL & STEWART LLP
Two International Place
Boston, MA 02110
(617) 248-5000
swang@choate.com

Counsel for Amici Curiae

February 10, 2023