THE ANTIBODY PATENT PARADOX

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ABSTRACT

Antibodies constitute a staggering $145 billion annual market—an amount projected to almost double by 2026. Consequently, patents covering antibodies are among the most valuable in the patent system. But antibody patents are being struck down left and right, victims of the Federal Circuit's recent shift to strengthen two doctrinal areas of patent law—enablement and the written description requirement. For each, the Federal Circuit has heightened requirements that patentees disclose or teach how to make and use the "full scope" of their inventions.

There are good reasons to be skeptical of the Federal Circuit's attack on genus claims in chemistry generally. But it seems to be a particular problem for antibodies. Applying the Federal Circuit's reinvigorated written description and enablement requirements to antibodies and their chemical structure fits poorly with the science underlying the molecules themselves. Immune receptor production—a semi-random and galactically expansive process—produces antibodies that are startingly different in both structure and function. There is no way to genus claims to antibodies that satisfy the court's current tests. The science simply doesn't allow it. At the same time, this change in the Federal Circuit's jurisprudence is a legitimate reaction to some of the problems with the long-standing (and long-permitted) practice of claiming antibodies in functional terms. Functional claiming can lead to overbroad patents that stifle future innovation, as it has done in the software industries. Perhaps the Federal Circuit is wary of a similar result in biotechnology.

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Fortunately, we think there is a middle ground—a new (or, really, quite old) form of patent claim drafting that gives inventors effective control over true substitutes without giving them the power to block real improvements: means-plus-function claims and infringement by the equivalents. Those doctrines limit patentees to claiming only the specific structural features of antibodies they both possessed and described, but also entitle them to assert their patents against antibodies with equivalent functions but different structural characteristics. If the economics of intellectual property center on balancing a need for protection beyond the literal invention and allowing improvements, this seems a step in the right—or, at least doctrinally permissible and economically sensible—direction.

Whether patentees go for such a solution remains to be seen. Recent empirical evidence on antibody claims has yet to document such a shift. Patent attorneys may need to get over their historical reluctance in writing their claims in such a fashion. Our solution won't give patentees everything they want. But they just might find it gives them what they need.

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INTRODUCTION

Antibodies are the backbone of modern biotechnology. They are the workhorses of molecular biology research, the principal component in numerous diagnostic tests, and the heart of both the immunity provided by COVID-19 vaccines and of the single most effective COVID therapy.[1] But long before antibodies became a household word with the COVID-19 pandemic, engineered antibodies were central to many of the most important and most valuable medical tests and therapies of the past thirty years.[2] Annual revenue from just the top six best-selling antibody drugs in 2021 reached $75.3 billion—almost double that of the global market for movies and music, combined.[3]

Patent law has long given antibodies broad protection, allowing an inventor who identifies an antibody that targets a particular antigen of interest to claim ownership over not just the particular antibody they developed, but over a genus of antibodies attracted to the same antigen.[4] An inventor who created an antibody that bound to, say, tumor necrosis factor alpha (TNF-α)—the basis of three of the top six selling antibody therapies—could claim that antibody and almost all other antibodies that bound to it.[5] In part, this claim practice was one of necessity. Scientists had long identified antibodies not by their precise molecular structure—as was the case with typical "small molecule" drugs—but by what they *did*.[6] Indeed, characterizing antibodies atom-by-atom

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[1] Amanda C. Freise & Anna M. Wu, *In Vivo Imaging with Antibodies and Engineered Fragments*, 67 MOLECULAR IMMUNOLOGY 142, 142 (2015) ("The precise discrimination offered by antibodies has formed the basis of workhorse assays used in research labs worldwide."); Carl A.K Borrebaeck, *Antibodies in Diagnostics—From Immunoassays to Protein Chips*, 21 IMMUNOLOGY TODAY 379, 379 (2000); Peter J. Hotez et al., *COVID-19 Vaccines: Neutralizing Antibodies and the Alum Advantage*, 20 NATURE REV. IMMUNOLOGY 399, 399 (2020).

[2] Borrebaeck, *supra* note 1, at 379; Nicholas APS Buss et al., *Monoclonal Antibody Therapeutics: History and Future*, 12 CURRENT OPINION IN PHARMACOLOGY 615, 615 (2012).

[3] Lisa Urquhart, *Top Product Forecasts for 2021*, 20 NATURE REV. DRUG DISCOVERY 10, 10 (2021); Patrick Frater, *Global Box Office in 2021 Hit $21.4 Billion, Says Analyst*, VARIETY (Jan. 6, 2022) https://variety.com/2022/film/box-office/global-box-office-2021-1235148732/ [https://perma.cc/65TU-T7YR]; IFPI, GLOBAL MUSIC REPORT 2021 (2021), https://gmr2021.ifpi.org/assets/GMR2021_State%20of%20the%20Industry.pdf [https://perma.cc/K4Z3-J8RH].

[4] *See, e.g.*, Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342 (Fed. Cir. 1998); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986); In re Wands, 731 F.2d 731 (Fed. Cir. 1988).

[5] *See* Centocor Ortho Biotech, Inc. v. Abbott Laboratories, 636 F.3d 1341, 1352 (Fed. Cir. 2011) (describing the "newly characterized antigen" test); *see also* Asher Mullard, *FDA Approves 100th Monoclonal Antibody Product*, 20 NATURE REV. DRUG DISCOVERY 491, 492 (2021) (noting the popularity of TNF-α as a target).

[6] *See, e.g.*, Lionel Crawford & Ed Harlow, *Uniform Nomenclature for Monoclonal Antibodies Directed Against Virus-Coded Proteins of Simian Virus 40and Polyoma Virus*, 41 J. VIROLOGY 709, 709 (1982) (establishing nomenclature system for antibodies based on antigen).

was both impractical and pointless—akin to describing a fighter jet by listing every nut and bolt.[7] "Functional claiming"—ownership of "[a] thing that performs [a] function" was not only permitted but a norm for antibody patents.[8] The form of patent claims thus followed their function.

Things have changed. In the laboratory, it is now easier to identify the physical sequence of a newly-discovered antibody.[9] But in the courts, no antibody patent in over a decade has survived a challenge based on overbreadth and inadequate disclosure at the U.S. Court of Appeals for the Federal Circuit,[10] with the court regularly throwing out billion dollar jury verdicts in favor of those patents.[11] Mainly, the patents have fallen victim to patent law's "written description" requirement, the doctrine that requires patentees to disclose "enough" examples of what they invented to show a person having skill in the art (the PHOSITA, or a reasonable expert) that the inventor was in possession of the invention.[12] That doctrine is intended to prevent a patentee from "gun jumping"—filing for a patent application before they have actually nailed down the invention.[13] Emboldened, perhaps, by this expansion of the written description doctrine, the Federal Circuit has also invalidated antibody patents on a related doctrinal ground—enablement—even though the technology is now easier to find and apply.[14]

Because the written description doctrine prevents inventors from filing patent applications too early, the doctrine has long operated with the conceit that the more knowledge a PHOSITA possesses about the field, the less a patent must show to demonstrate possession of that invention.[15]

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[7] *See* W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1026 (2016) ("In terms of size and rough complexity, if an aspirin were a bicycle, a small biologic would be a Toyota Prius, and a large biologic would be an F-16 fighter jet. ").

[8] Mark A. Lemley, *Software Patents and the Return of Functional Claiming*, 2013 WISC. L. REV. 905, 923; Colin G. Sandercock & Ulrich Storz, *Antibody Specification Beyond the Target: Claiming a Later-Generation Therapeutic Antibody by its Target Epitope*, 30 NATURE BIOTECHNOLOGY 615, 618 (2012).

[9] Lena Meyer et al., *A Simplified Workflow for Monoclonal Antibody Sequencing*, 14 PLOS ONE e0218717 (2019).

[10] *See infra* Part II.C. Section 112(a) of the patent statute requires that a patentee provide both a "written description" of the invention as claimed and enable the person having skill in the art in how to make and use the invention. 35 U.S.C. § 112(a) (2021). Some patents have survived in cases that presented other types of challenges, typically to the novelty or nonobviousness of the invention, but did not present enablement or written description issues. *E.g.*, Immunex Corp. v. Sandoz, Inc., 964 F.3d 1049 (Fed. Cir. 2020).

[11] *E.g.*, Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021) ($1.1 billion); Centocor Ortho Biotech, Inc. v. Abbott Laboratories, 636 F.3d 1341 (Fed. Cir. 2011) ($1.67 billion); *see also* Amgen Inc. v. Sanofi, 987 F.3d 1080 (Fed. Cir. 2021) (jury verdict overturned before damages assessment).

[12] Timothy R. Holbrook, *Possession in Patent Law*, 59 SMU L. REV. 123, 127 (2006).

[13] Dmitry Karshtedt, Mark A. Lemley & Sean B. Seymore, *The Death of the Genus Claim*, 35 HARV. J.L. & TECH. 1, 61-62 (2021).

[14] *Amgen*, 987 F.3d at 1080.

[15] *See* Capon v. Eshhar, 418 F.3d 1349, 1357 (Fed. Cir. 2005) ("The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.") ("The descriptive text needed to meet these requirements

With antibodies, though, a paradox has emerged. In the early days of the industry, when scientists often knew little about antibodies' precise molecular and genetic structures—and lacked tools to easily find them—the law permitted broad patents covering any antibody that bound to a particular target with a certain specificity; identifying those characteristics was the only practical way to describe newly discovered antibodies.[16] Now that scientists understand the chemical structure antibodies better—including an appreciation for just how genetically diverse antibodies are, even those that bind to a single target—functional patent claims to antibodies' antigens are routinely being held invalid for failing the written description doctrine.[17] Today, scientists know that the discovery of one or even dozens of antibodies that bind to a particular target with a particular specificity doesn't exclude the possibility that many other antibodies with different structures do the same.[18] Instead of requiring scientists to disclose more information when their colleagues start out knowing less, patent law now requires them to disclose more information about each invention when their colleagues know *more*. This cuts against patent law's precept that "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement."[19] We call this the antibody patent paradox.

The antibody paradox may be part of a broader shift in patent doctrine, what one of us has called "the death of genus claims."[20] Or it may be an extension of the concerns about the abuse of functional claiming in other areas like software.[21] Or it could be the result of trying to fit one of the most complex biological molecules we know in a single, convoluted sentence that is a patent claim.[22] Or perhaps it's simply the result of a strange and possibly unique factual circumstance in which learning more about a field—essentially, coming to understand just how complex it is—

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varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence."); Chiron Corp. v. Genentech, Inc., 363 F.3d 1247, 1254 (2004) ("As noted above, a patent disclosure need not enable information within the knowledge of an ordinarily skilled artisan. Thus, a patentee preferably omits from the disclosure any routine technology that is well known at the time of application.").

[16] *See, e.g.*, Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1369 (Fed. Cir. 1986) (describing the state of the art).

[17] *Juno Therapeutics*, 10 F.4th at 1330; *Amgen*, 987 F.3d at 1080; *Centocor*, 636 F.3d at 1341.

[18] Joel Finney et al., *Germinal Center Responses to Complex Antigens*, 284 IMMUNOLOGICAL REV. 42, 46-47 (2018) (measuring genetic diversity of antibodies specific to a given antigen).

[19] Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written Description"' Requirement; Request for Comments, 64 Fed. Reg. 71427, 71435 (Dec. 21, 1999) [hereinafter Revised Interim § 112 Guidelines].

[20] Karshtedt, Lemley & Seymore, *supra* note 13, at 1.

[21] *See* Lemley, *supra* note 8, at 907–908.

[22] *See* Dan L. Burk & Mark A. Lemley, *Fence Posts or Sign Posts? Rethinking Patent Claim Construction*, 157 U. PA. L. REV. 1743, 1745 (2009) ("[I]t may simply be impossible to cleanly map words to things.").

means we have only come to appreciate our ignorance, and need to update our definitions accordingly.[23] We explore all these possibilities.

Regardless of the explanation, though, the antibody paradox lies at the heart of several critical questions in patent policy: how broad patent claims should be to encourage invention; whether patent law is and should be technology-specific; and how we accommodate follow-on innovation after an initial, pioneering disclosure.[24] If we get those questions wrong, we may end up with a second antibody paradox—how the patent-fueled success of antibody technology made it impossible to get the very kinds of patents that drove innovation in the first place. As a matter of innovation policy, we think the end of functional antibody claims is a problem, though as we will show, the likely innovation effects are complicated. We suggest some possible middle ground that may save narrower antibody genus claims.

In Part I, we explain the science of antibodies, how it has changed, and why antibodies are so complex. In Part II, we discuss the parallel history of the law, beginning with broad protection for functional antibody claims and ending with the current period of hostility to antibody patents. Part III considers a number of possible explanations for this shift, none completely satisfactory. In Part IV, we explain how the antibody paradox is central to many of the current policy debates in patent law, and we offer some guidance as to how to resolve the paradox. We conclude by suggesting broader implications for the written description doctrine and patent claims for other complex technologies.

I. THE SCIENCE OF ANTIBODIES

A. Antibodies and the Immune System

The human immune system is dynamically adaptive: it can respond, in real time, to both unknown and unforeseen foreign invaders, like novel pathogenic bacteria and viruses.[25] The key to this adaptive immune system is the body's ability to quickly and precisely flag such threats—to recognize them as being potentially harmful even though the immune system hasn't encountered them before.[26] Once a threat is identified, the immune system also needs the tools to neutralize and dispose of it, and to do so without otherwise harming healthy tissue or commandeering too many

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[23] *Cf.* Jacob S. Sherkow, *The Natural Complexity of Patent Eligibility*, 99 IOWA L. REV. 1137, 1142–1143 (2014) (suggesting courts redefine the doctrine patentable subject matter based on the complexity of articulating "natural laws").

[24] *See* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1592–1595 (2003) (describing such concerns as policy levers in patent law).

[25] Enkelejda Miho et al., *Computational Strategies for Dissecting the High-Dimensional Complexity of Adaptive Immune Repertoires*, 9 FRONTIERS IN IMMUNOLOGY 224 (2018).

[26] William H. Robinson, *Sequencing the Functional Antibody Repertoire—Diagnostic and Therapeutic Discovery*, 11 NATURE REV. RHEUMATOLOGY 171, 171 (2015).

of the body's resources.[27] Overaggressive policing by the immune system risks harming the body by attacking foreign but benign material—essentially, a hyperactive allergic reaction.[28] An apathetic immune response risks yielding the body to systemic infections.[29] More than anything, functional adaptive immune systems need precision without sacrificing flexibility.[30]

While the immune system is famously complex, this marriage of precision and flexibility is largely mediated a class of complex proteins known as immune receptors, namely, antibodies and T cell receptors.[31] These are produced by two types of immune system cells—B cells and T cells, respectively—that circulate throughout the blood and the lymphatic system.[32] Antibodies and T cell receptors jut out from the surface of their respective cells until they eventually come in contact with a complementary large molecule, known as an antigen.[33] This causes the particular immune cell carrying the immune receptor to both proliferate—that is, to divide and make copies of itself—and signal other components of the immune system to and bind to the offending material.[34] The upshot of this interaction is that more immune receptors specific to the particular antigen will be produced and that interactions between B cells and T cells will allow the body to "remember" the offending antigen if it attacks the body again.[35] In this way, the immune system can continually adapt to new threats without entirely forgetting past battles.

Importantly, antibodies and T cell receptors are not monolithic proteins. To the contrary, they are wildly diverse, with a given individual likely having tens of billions of different variations of immune receptors circulating in their blood at any given time.[36] This poses a genetic conundrum: how can so many different immune receptors be made without the genome—the sum total of DNA in an individual—being infinitely long?[37] The answer lies in how immune receptors

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[27] David H. Raulet & Russell E. Vance, *Self-Tolerance of Natural Killer Cells*, 6 NATURE REV. IMMUNOLOGY 520, 520 (2006).

[28] Hannah J. Gould et al., *The Biology of IgE and the Basis of Allergic Disease*, 21 ANN. REV. IMMUNOLOGY 579, 580 (2003).

[29] Sudhir Gupta & Ankmalika Gupta Louis, *Tolerance and Autoimmunity in Primary Immunodeficiency Disease: A Comprehensive Review*, 45 CLINICAL REV. ALLERGY & IMMUNOLOGY 162, 162 (2013).

[30] Doreen E. Szollosi et al., *Modulation of the Adaptive Immune System*, *in* PHARMACOLOGY OF IMMUNOTHERAPEUTIC DRUGS, 68 (Clinton B. Mathias et al. eds., 2020).

[31] *See* Felix Breden et al., *Reproducibility and Reuse of Adaptive Immune Receptor Repertoire Data*, 8 FRONTIERS IN IMMUNOLOGY 1 (2017).

[32] Miho et al., *supra* note 25, at 224.

[33] Clinton B. Mathias, *Overview of the Immune System 1 and Its Pharmacological Targets*, *in* PHARMACOLOGY OF IMMUNOTHERAPEUTIC DRUGS, 17–19 (Clinton B. Mathias et al. eds., 2020).

[34] *Id.* at 21-23.

[35] *Id.*

[36] Wenzhao Meng et al., *An Atlas of B-Cell Clonal Distribution in the Human Body*, 35 NATURE BIOTECHNOLOGY 879, 879 (2017).

[37] Miho et al., *supra* note 25, at 2.

are made. Antibodies, for example, consist of four "chains" of proteins—two heavy chains and two light chains—that come together in what is classically represented as a Y-shaped structure.[38] The tips of this Y-shaped structure—known as the complementary dependent region (CDR)—are the portion of the antibody that interact with the antigen.[39] Both of these chains are produced, incredibly, by only three genes—*V*, *D*, *J*—each of which contains multiple smaller "cassettes," e.g., V1, V2, V3, and so on.[40] Naïve B cells—that is, B cells that have never come in contact with an antigen—randomly combine these cassettes from each of the three genes and then further alter the genetic makeup of the combination, producing a novel antibody.[41] T cells create their receptors through a similar mechanism.[42] This random recombination system has the potential to produce an almost limitless number of different immune receptors. Some researchers have estimated that the theoretical number of different types of antibodies, for example, is on par with the number of stars in the galaxy.[43]

Antibodies' galactic diversity means that multiple different antibodies are likely to target the same antigen, albeit in potentially different ways. Multiple antibodies specific to a particular antigen may nonetheless bind to it in different places.[44] The specific place on an antigen to which an antibody binds is known as the "epitope."[45] Even multiple antibodies specific to a single epitope may bind more or less strongly to it, an antibody's "affinity" in immunological parlance.[46] And even multiple antibodies with similar epitopes and affinities may nonetheless possess differences in how stable the interaction is—that is, how *long* the interaction lasts, a measurement of an antibody's "avidity."[47] Because of the way antibodies are produced, however—that is, through the *V(D)J* recombination mechanism—all have different genetic sequences; at a molecular level, all are different antibodies.[48]

Immune receptors are of immense biologic value, the "central feature" of the adaptive immune system as a whole.[49] This is because the CDR of antibodies have the potential to bind to

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[38] See Szollosi et al., *supra* note 30, at 70-71.

[39] Robinson, *supra* note 26, at 171.

[40] Fumihiko Matsuda et al., *The Complete Nucleotide Sequence of the Human Immunoglobulin Heavy Chain Variable Region Locus*, 188 J. EXPERIMENTAL MED. 2151, 2151 (1998).

[41] Breden et al., *supra* note 31, at 2.

[42] Miho et al., *supra* note 25, at 2.

[43] *Id.* at 1.

[44] *See, e.g.*, Lihong Liu et al., *Potent Neutralizing Antibodies Against Multiple Epitopes on SARS-CoV-2 Spike*, 584 NATURE 450 (Aug. 2020).

[45] Mathias, *supra* note 33, at 17–18.

[46] *Id.* at 22–23.

[47] *Id.*

[48] Meng et al., *supra* note 36, at 879.

[49] Max D. Cooper & Matthew N. Alder, *The Evolution of Adaptive Immune Systems*, 124 CELL 815, 815 (2006).

almost any other large molecule, extant or yet to be conceived.[50] But the interaction of any *particular* CDR is incredibly specific; generally speaking, each antibody binds to only a single epitope.[51] Scientists have long likened this specificity to a "lock and key" model, whereby an antibody can be "unlocked" by only a single epitope on a single antigen.[52] Today, researchers appreciate there is some "fuzziness" to this lock-and-key model, more accurately describing it not as a "lock and key" but an "induced fit."[53] But even with molecularly large antigens, antibodies can recognize atomic—and in extreme cases, subatomic—differences in epitopes.[54] As noted above, this pairing is not unique; while a given antibody can bind to only a single antigen, a single antigen can—and frequently does—bind with multiple, slightly different, antibodies.[55] To extend the lock-and-key metaphor, while each antibody is specific to only a single antigen key, any given key can unlock several—and often many—antibody locks. While exceptions to this lock and key model do exist and are the subject of ongoing research, this specificity is a hallmark of immune receptors and few other biologic molecules that have similar properties.[56]

B. Applications of Antibodies

Antibodies' specificity makes them useful in multiple applications, including research tools, therapies, and diagnostics. As research tools, antibodies are the workhorses of any molecular biology lab, "among the most frequently used tools in basic science research and in clinical assays."[57] Antibodies can be used, for example, to assess whether a specific antigen exists in a large mixture of proteins, like a powerful magnet to find a needle in a haystack.[58] This also allows researchers to isolate a specific protein from an undifferentiated mass for further study.[59] Researchers can further modify this technique to assess whether one protein interacts with one

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[50] Anthony R Rees, *Understanding the Human Antibody Repertoire*, 12 MABS 1729683, at *1 (2020).

[51] *See* Alkistis N. Mitropoulou et al., *Structure of a Patient-Derived Antibody in Complex with Allergen Reveals Simultaneous Conventional and Superantigen-Like Recognition*, 115 PROC. NAT'L ACAD. SCI. USA E8707, E8708 (2018) (calling "one-antibody-one-epitope" a "dogma").

[52] Abner Louis Notkins, *Polyreactivity of Antibody Molecules*, 25 TRENDS IN IMMUNOLOGY 174 (2004) (challenging this view, but nonetheless noting it has "has long dominated immunological thinking").

[53] Ping Zhang et al., *Capturing Transient Antibody Conformations with DNA Origami Epitopes*, 11 NATURE COMMUNICATIONS 3114, at *1 (2020).

[54] *Id.*

[55] *See, e.g.*, Liu et al., *supra* note 44, at 450.

[56] Cooper & Alder, *supra* note 49, at 815.

[57] Mathias Uhlen et al., *A Proposal for Validation of Antibodies*, 13 NATURE METHODS 823, 823 (2016).

[58] *Id.* at 824 (describing Western blots).

[59] Yiling Gao et al., *A Brief Review of Monoclonal Antibody Technology and its Representative Applications in Immunoassays*, 39 J. IMMUNOASSAY & IMMUNOCHEMISTRY 351, 358–359 (2018) (describing immunoprecipitation).

another, or whether a given protein interacts with another molecule of interest.[60] This includes research into how certain proteins, or other large molecules, bind to DNA—instrumental in investigating how genes function.[61] Antibodies can also be used to separate living cells from one another, giving researchers the ability to investigate molecular and genetic changes at the level of individual cells.[62] The use of antibodies as research tools is a large market unto itself, clocking in $3.4 billion per year in 2020.[63]

Relatedly, antibodies can also be used as diagnostics—tools used to diagnose diseases or other health conditions.[64] Antibodies can be paired with fluorescent or other color-providing molecules, for example, to "glow" when they come into contact with a particular antigen, a diagnostic technique known as immunochromatography.[65] This is the principle behind some of the most popular at-home diagnostics for COVID-19, such as Abbott Laboratories' BinaxNOW test, which uses antibodies "tagged" with a color-giving fluorophore to test for the presence of a protein on the shell of the SARS-CoV-2 virus.[66] A variation on the technique tags the antibody not with a fluorescent molecule but an enzyme that detectably reacts when then antibody is bound to it, a technique known as an enzyme linked immunoassay or ELISA.[67] This is the primary technique used to detect a number of diseases including, influenza and rotavirus.[68] Other diagnostics test for the presence of antibodies themselves in the blood to determine whether a patient has been exposed to a particular infection.[69] Antibodies can also be used to detect the presence of certain proteins typically produced by cancer cells, an important technique in cancer diagnoses known as

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[60] Shane C. Masters, *Co-Immunoprecipitation from Transfected Cells*, in PROTEIN-PROTEIN INTERACTIONS: METHODS AND APPLICATIONS 337 (Haian Fu ed., 2004) (describing co-immunoprecipitation).

[61] Philippe Collas, *The Current State of Chromatin Immunoprecipitation*, 45 MOLECULAR BIOTECHNOLOGY 87, 87 (2010) (describing chromatin immunoprecipitation).

[62] Gao et al., *supra* note 59, at 356–358.

[63] Jan L.A. Voskuil et al., *The Antibody Society's Antibody Validation Webinar Series*, 12 MABS 1794421, at *2 (2020).

[64] Definitions 21 CFR 809.3 (Jan. 27, 2022) (defining "in vitro diagnostic devices" as "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions").

[65] Gao et al., *supra* note 59, at 359–361.

[66] Garrett A. Perchetti et al., *Analytical Sensitivity of the Abbott BinaxNOW COVID-19 Ag Card*, 59 J. CLINICAL MICROBIOLOGY (2021).

[67] Gao et al., *supra* note 59, at 355–356.

[68] Karen Leirs et al., *Bioassay Development for Ultrasensitive Detection of Influenza A Nucleoprotein Using Digital ELISA*, 88 ANALYTICAL CHEMISTRY 8450, 8450 (2016); T. Anand et al., *Development of Dot-ELISA for the Detection of Human Rotavirus Antigen and Comparison with RNA-PAGE*, 32 LETTERS IN APPLIED MICROBIOLOGY 176, 176 (2001).

[69] *E.g.*, Eleftherios Mylonakis et al., *Laboratory Testing for Infection with the Human Immunodeficiency Virus: Established and Novel Approaches*, 109 AM. J. MED. 568, 568–570 (2000) (HIV).

immunohistochemistry.[70] Like research tools, antibody-based diagnostics are big business too, yielding their manufacturers roughly $20 billion per year.[71]

Antibodies' specificity also makes them useful as therapies. By binding to particular antigens in the body, antibodies can precisely target certain cellular pathways gone awry. The cellular protein tumor necrosis factor alpha (TNF-α), for example, is responsible for driving a powerful inflammatory response.[72] Antibodies that bind to TNF-α, in turn (i.e., anti-TNF-α antibodies), disrupt this pathway and are immensely useful in regulating an overstimulated inflammatory response.[73] This is the mechanism of three of the top-selling antibody therapies in the world, Humira, Enbrel, and Remicade.[74]

Antibodies can similarly be used as therapies to signal biologic targets to other systems in the body, including other components of the immune system. Vascular endothelial growth factor A (VEGF-A) is a protein known to be overexpressed in certain cancers.[75] Modified antibodies that precisely target VEGF-A can then be used to recruit other components of the immune system to attack the offending tumor; this is the basis for two antibody therapies currently on the market, Avastin and Lucentis.[76]

Lastly, antibodies can be used to precisely to target certain cells in order to deliver drugs chemically attached to them. These antibody–drug conjugates are designed such that their CDR region is specific to only a certain cellular antigen, while their "tail" (also known as the "constant region") is attached to a therapeutic drug.[77] When the conjugate binds to a target cell, it is effectively "eaten" by the cell and subsequently releases its drug payload; this is the basis for the breast cancer therapy Enhertu.[78]

Because antibodies are so specific to their targets, they are increasingly preferred, in many therapeutic contexts, over older, "small molecule" drugs that may have unwanted side effects on

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[70] Atsuko Kitamura et al., *Immunohistochemical Detection of EGFR Mutation Using Mutation-Specific Antibodies in Lung Cancer*, 16 CLINICAL CANCER RES. 3349, 3349 (2010).

[71] *Diagnostic Specialty Antibodies Market Insights, New Innovations, Research and Growth Factor Till 2027*, BIOSPACE (Nov. 30, 2021) https://www.biospace.com/article/diagnostic-specialty-antibodies-market-insights-new-innovations-research-and-growth-factor-till-2027/.

[72] Michael A. Palladino et al., *Anti-TNF-α Therapies: The Next Generation*, 2 NATURE REV. DRUG DISCOVERY 736, 736 (2003).

[73] *Id.* at 737.

[74] *Id.* at 738–739.

[75] S. Lien and H.B. Lowman, *Therapeutic Anti-VEGF Antibodies*, in THERAPEUTIC ANTIBODIES 132 (Yuti Chernajovsky & Lucienne Chatenoud eds., 2008).

[76] *Id.* at 131.

[77] Alexis Q. Dean et al., *Targeting cancer with Antibody-Drug Conjugates: Promises and Challenges*, 13 MABS (2021).

[78] *Id.* at *3–*7.

other body systems.[79] Today, six of the top ten selling therapies in the U.S. are antibodies or fragments of antibodies, generating a total of roughly $75 billion of revenue per year.[80]

C. The History and Development of Antibody Research

Antibodies' present-day power belies a long and difficult development history. While researchers have generally known about the existence of antibodies since the nineteenth century, the immune receptors' size and complexity defied scientists' ability to molecularly characterize them for almost seventy years.[81] But finding an antibody that bound to the right antigen was only the first step. Isolating enough antibodies specific to an antigen for systematic research initially proved elusive if not impossible.[82] In 1975, César Milstein and Georges Köhler first published a paper on producing monoclonal antibodies—antibodies derived from a single B cell "clone"—at something approaching a large-enough scale for research purposes.[83] Their method—fusing a single B cell with a specific type of cancer cell—allowed the resulting "hybridoma" to continuously propagate and produce the starting B cell's particular antibody.[84] Milstein and Köhler's efforts—as well as efforts of numerous researchers on the path to discovering antibodies—yielded numerous Nobel Prizes.[85]

Despite Milstein and Köhler's success, for decades generating antibodies was still a laborious and error-prone process.[86] To develop an antibody specific to a particular protein target, researchers used model animals, such as laboratory mice.[87] Researchers would inject a model animal with the particular target protein and wait several weeks for the animal to develop

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[79] *See, e.g.*, Kohzoh Imai & Akinori Takaoka, *Comparing Antibody and Small-Molecule Therapies for Cancer*, 6 NATURE REV. CANCER 714, 722-723 (2006) (comparing adverse events in small molecule drugs versus monoclonal antibody therapies).

[80] Urquhart, *supra* note 3, at 10.

[81] Alison Farrell, *Serum Power*, in NATURE MILESTONES IN VACCINES S8 (Sept. 28, 2020), https://www.nature.com/collections/hcajdiajij; Gerald M. Edelman, *Dissociation of γ-globulin*, 81 J. AM. CHEMICAL SOC'Y 3155, 3155 (1959); R. R. Porter, *The Hydrolysis of Rabbit γ-globulin and Antibodies with Crystalline Papain*, 73 BIOCHEMICAL J. 119, 119 (1959). von Behring, Edelman, and Porter all won Nobel Prizes for their work.

[82] G. Köhler & C. Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 NATURE 495, 495 (1975).

[83] *Id.* at 497.

[84] *Id.*

[85] *Nobel Prizes and the Immune System*, THE NOBEL PRIZE, https://www.nobelprize.org/prizes/themes/nobel-prizes-and-the-immune-system/ [https://perma.cc/72VM-TMEU].

[86] Harold F. Stills, *Polyclonal Antibody Production*, in THE LABORATORY RABBIT, GUINEA PIG, HAMSTER, AND OTHER RODENTS 16 (2012).

[87] Gerald Corbitt & Christopher C. Storey, *Monoclonal Antibodies—Current Techniques and Applications*, 11 BIOCHEMICAL EDUCATION 125, 125 (1983).

antibodies against the target. Afterwards, researchers would then extract large quantities of blood or tissue from the animal—and then "fuse" this blood with cancer cells to yield hybridomas.[88] In early variations, these hybridomas were then grown in Petri dishes for more than six weeks before they were validated to see if they, in fact, reacted to the original target.[89] Only then could antibodies be extracted for research purposes. But failure was common, with some steps in the process yielding failure rates of as high as 97%.[90]

This gave us a crude method for manufacturing antibodies that targeted a specific antigen. But it still posed numerous problems. It was, back then, difficult if not impossible to determine whether two antibodieswere from the same line of B cells (i.e., monoclonal) or different ones (i.e., polyclonal).[91] It was also difficult to determine to whether an antibody was truly specific to the target antigen or simply "cross-reactive" with something else.[92] Batch variation was also a problem.[93] Hybridomas also rapidly picked up numerous mutations as they proliferated, virtually guaranteeing that a cellular source of a particular antibody would subtly change over time.[94] And, given the random nature of antibody production—the V(D)J recombination process discussed earlier—this procedure was in no way replicable from animal to animal or laboratory to laboratory.[95] Even today "validating" antibodies to ensure they are similar enough to be considered the "same" remains a persistent and significant challenge in the field.[96]

For these reasons, researchers—at least back in antibody research's early days—had almost no way of comparing one set of antibodies to another. Two antibodies specific to the same antigen could derive from the same clone or might come from an entirely different genetic sequence.[97] As a consequence, even after Köhler and Milstein, researchers thought of and named antibodies not by their molecular features but solely by which antigen they bound to.[98] Thus, a variety of

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88 *Id.*

89 *Id.* at 126.

90 Köhler & Milstein, *supra* note 82, at 496.

91 Corbitt & Storey, *supra* note 87, at 125 ("Even consecutive bleeds from the same animal can yield sera of different immunological reactivity.")

92 O. T. Schönherr & E. H. Houwink, *Antibody Engineering, A Strategy for the Development of Monoclonal Antibodies*, 50 ANTONIE VAN LEEUWENHOEK 597, 608 (1984).

93 *Id.* at 613.

94 Sandra J. Kromenaker & Friedrich Srienc, *Stability of Producer Hybridoma Cell Lines after Cell Sorting: A Case Study*, 10 BIOTECHNOLOGY PROGRESS 299, 307 (1994) (noting that this was a rare albeit measurable event).

95 Corbitt & Storey, *supra* note 87, at 125–126.

96 Uhlen et al., *supra* note 57, at 823.

97 Corbitt & Storey, *supra* note 87, at 125–126.

98 *E.g.*, Lionel Crawford & Ed Harlow, *Uniform Nomenclature for Monoclonal Antibodies Directed Against Virus-Coded Proteins of Simian Virus 40and Polyoma Virus*, 41 J. VIROLOGY 709 (1982).

antibodies specific to the protein CD3 were called "anti- CD3 antibodies."[99] Today, despite major advances in molecular biological techniques, researchers continue to use this nomenclature, even if they can define antibodies more specifically by identifying which epitope on the antigen they bound to and with what specificity.[100] But these, too, are observed characteristics of the antibody, not something specific to its molecular structure. Researchers—then and now—define antibodies not by what they *are* but by what they *do*. At best, in Köhler and Milstein's time, some more sophisticated efforts appended numbers or letters after the target antigen to differentiate hybridomas.[101] But there was still no way to assess precisely what the molecular differences were.[102]

Today, molecular biology is quite more advanced and obtaining the precise genetic sequence of an antibody from a single B cell clone is routine.[103] Antibodies can also be reengineered in a variety of ways to better or more poorly fit their epitopes.[104] There are even efforts to design immune receptors from scratch and to predict what an immune receptor binds to without validation experiments.[105] But older notions of characterizing antibodies by their function, i.e., what they bind to, and how well, are still prevalent in the field.[106]

II. THE DEATH OF ANTIBODY PATENT CLAIMS

A. The Science of Patenting Antibodies

In a field that prizes molecular characterization—like patent law—patenting antibodies has long presented several technical and strategic challenges. Describing a complex molecule like an antibody, atom by atom, has been likened to describing a F15 fighter jet by its every nut and bolt,

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[99] W. Holter et al., *Analysis of T Cell Activation with a Non-Mitogenic anti-CD3 Antibody and the Phorbol Ester TPA*, 62 Clin. Exp. Immunol. 600, 600 (1985).

[100] *E.g.*, Xin-Lin Zhang et al., *Safety and Efficacy of Anti-PCSK9 Antibodies: A Meta-Analysis of 25 Randomized, Controlled Trials*, 13 BMC MEDICINE 123 (2015) (referring to a variety of antibodies as "anti-PCSK9" antibodies because they bind to PCSK9).

[101] *E.g.*, Crawford & Harlow, *supra* note 98, at 709.

[102] P. M. Alzari, M.-B. Lascombe & R. J. Poljak, *Three-Dimensional Structure of Antibodies*, 6 ANN. REV. OF IMMUNOLOGY 555, 555 (1988) (noting that "understanding of the structural bases of specifciity physicochemical characterization of antibody action at the molecular level are only beginning").

[103] Cristina Parola, Daniel Neumeier & Sai T. Reddy, *Integrating High-Throughput Screening and Sequencing for Monoclonal Antibody Discovery and Engineering*, 153 IMMUNOLOGY 31, 31 (2018) ("[I]t has now become more routine to perform high-throughput sequencing on antibody reper- toires to also directly discover antibodies").

[104] *Id.* at 33.

[105] William D. Chronister et al., *TCRMatch: Predicting T-Cell Receptor Specificity Based on Sequence Similarity to Previously Characterized Receptors*, 12 FRONTIERS IN IMMUNOLOGY 640725 (2021).

[106] *E.g.*, Zhang et al., *supra* note 53, at 123.

an exercise of equal utility as Borges' map of the globe at a 1:1 scale.[107] For this reason, among others, patent law has long allowed inventors of complex biologic materials to deposit those materials in a public depository to, at a minimum, demonstrate possession of the invention.[108] At the same time, the mere act of deposit isn't dispositive; courts must still engage in a case-by-case, factual determination as to whether the deposit was "sufficient" to demonstrate possession, "representative of the scope of those claims."[109]

The alternative for patentees who want to claim a genus has therefore been to characterize, with increasing precision, the functional relationship between an antibody (or a class of antibodies) and their targets. At the highest level of abstraction, one could claim an antibody simply by characterizing the antigen, as did the junior party for some of the claims at issue in a 2004 Federal Circuit case, *Noelle v. Lederman.*[110] But such claims were potentially risky. They were, in both a scientific and patent law sense, wildly expansive: claims specific to nothing more than a single antigen would encompass *every* antibody that happened to bind to it, even though—based on antibodies' generation through the random rearrangement of *VDJ* cassettes—this could be potentially thousands if not millions of molecules.[111] They were also almost purely functional and therefore possibly invalid on several grounds.[112] Moreover, claims directed solely to an antibody's antigen made no distinction among different antibody clones—a potential trap for patent law's "novelty" requirement.[113]

Beside this "newly characterized antigen" strategy, one could claim an antibody by how it bound to its particular epitope.[114] While this claiming strategy significantly circumscribed the universe of antibodies encompassed by the claims, the technique still claimed the antibody by its function, albeit a more specific function.[115] Nonetheless, the Patent Office routinely granted

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[107] Price & Rai, *supra* note 7, at 1026; *On Exactitude in Science*, in JORGE LUIS BORGES, COLLECTED FICTIONS 325 (1999).

[108] *See* Donald Levy & Lucile Burd Wendt, *Microbiology and a Standard Format for Infra-Red Absorption Spectra in Antibiotic Patent Applications*, 37 J. PATENT OFF. SOC'Y 855 (1955) (first describing the practice).

[109] Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956 (Fed. Cir. 2002).

[110] Noelle v. Lederman, 355 F.3d 1343 (Fed. Cir. 2004).

[111] *See* Centocor Ortho Biotech, Inc. v. Abbott Laboratories, 636 F.3d 1341, 1352 (Fed. Cir. 2011) (describing the relationship as "a [key] ring with *a million* keys on it").

[112] *See Noelle*, 355 F.3d at 1349 (discussing deficiencies in functional claiming for antibodies).

[113] *See* Nichols Institute Diagnostics, Inc. v. Scantibodies Clinical Laboratory, Inc., 195 F. App'x 947, 951–952 (2006) (concluding that claims directed to antibody derived from well-known anti-serum containing other antibodies was anticipated).

[114] *See Noelle*, 355 F.3d at 1349 ("If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the ''fully characterized' antigen.").

[115] *See Centocor*, 636 F.3d at 1352 ("Claiming antibodies with specific properties, e.g., an antibody that binds to human TNF-a with A2 specificity, can result in a claim that does not meet written description even

patents to epitope-specific antibody claims.[116] As antibody technology progressed through the 1990s and beyond, inventors could further claim antibodies by their affinity—how tightly they bound to their targets—or their avidity—the stability of the antibody-antigen interaction.[117] While these were even more specific, to the point of likely narrowing down a gargantuan class of antibodies to only hundreds or even a dozen or so,[118] they were all still *functional* claiming strategies, claiming what antibodies *did*, not their constituent components or genetic makeup.

Historically, the Patent Office has been aware of these technical challenges. In its 1999 interim guidelines on written description, the Patent Office noted that "there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement."[119] But it seemingly carved out an exception for antibodies, allowing "[a]n applicant [to] also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention . . . [including] functional characteristics when coupled with a known or disclosed correlation between function and structure."[120] For antibodies, these functional characteristics included "binding affinity, binding specificity, molecular weight, and length."[121] The Patent Office generally allowed such functional claims when coupled with the applicant's deposit of antibody-producing cells in a public depository to demonstrate evidence of possession.[122]

All of these strategies, though, served as substitutes for disclosing antibodies by their structure: work-arounds aimed at disclosing *enough* functional characteristics to overcome patent law's presumptions against purely functional claiming. *Truly* structural claims to antibodies would have to center on their underlying genetic sequences and their 3D folding structure, if not the

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if the human TNF-a protein is disclosed because antibodies with those properties have not been adequately described.").

[116] *E.g.*, U.S. Patent No. 5,703,213 (claiming an anti-AF-20 antibody with a specific epitope profile); U.S. Patent No. 5,700,649 (claiming a method of using an anti-UTAA antibody with particular epitope locations); U.S. Patent No. 5,688,918 (claiming an anti-p53as antibody with an epitope "within the final 50 carboxyl terminal amino acids of p53as").

[117] *See* In re Wands, 731 F.2d 731, 738 n.26 (Fed. Cir. 1988) (explaining this practice).

[118] *See, e.g.*, Rhys M Adams et al., *Measuring the Sequence-Affinity Landscape of Antibodies with Massively Parallel Titration Curves*, 5 eLIFE e23156, at *10 (2016) (screening 18 antibody clones using tight affinity controls).

[119] Revised Interim § 112 Guidelines, *supra* note 19, at 71435.

[120] *Id.*

[121] *Id.* at 71439.

[122] *Id.* at 71432. This practice was consecrated by *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956 (Fed. Cir. 2002).

atom-by-atom approach of smaller chemical compounds.[123] But defining antibodies by their underlying genetic sequence has only recently become practical with the routinization of high-throughput genetic sequencing methods beginning in the mid-1990s—a full twenty years after the advent of antibodies as molecular biological tools and therapies.[124]

Even so, claiming antibodies solely by genetic sequence presents several strategic problems for patent applicants. Narrow claims to specific antibody sequences are easy to design around. A potential infringer could simply change a few bases here and there to escape infringement, making such claims economically worthless.[125] And disclosing such information in a patent application is likely to defeat whatever trade secret protection may have otherwise existed on the same antibodies protected by more functional claims.[126]

Applicants had, in the past, attempted to write patents to cover these trivial changes by claiming "homology percentages"—e.g., antibodies with an 80% similarity to the claimed sequence—but the Patent Office's guidance made clear that any such claims would still need to satisfy the written description requirement.[127] That is, claims to a group of sequences that share homology would need to disclose the variations of the sequences in the patent application's specification.[128] The problem is that slight changes in antibodies' sequences were likely to yield non-functional embodiments—antibodies that didn't bind to the particular antigen disclosed—thus risking Patent Office rejections on other doctrines.[129] For all of these reasons, as antibody technology progressed, applicants tended to avoid claims directed primarily to antibodies'

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[123] *Cf.* Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) (requiring, for written description purposes, claims to genes to include "structure, formula, chemical name, or physical properties," such as DNA sequences).

[124] *See* Ruei-Min Lu, Yu-Chyi Hwang, I-Ju Liu, Chi-Chiu Lee, Han-Zen Tsai, Hsin-Jung Li & Han-Chung Wu, *Development of Therapeutic Antibodies for the Treatment of Diseases*, J. BIOMED. SCI. 27 (2020) (discussing the history of phase display technology).

[125] *See* Biogen Idec, Inc. v. GlaxoSmithKline LLC, 713 F.3d 1090, 1094 (Fed. Cir. 2013) (affirming district court's noninfringement ruling because competitor's antibody had slightly different sequence and affinity profile).

[126] *See* Water Techs. Corp. v. Calco, Ltd., 50 F.2d 660, 670 (Fed. Cir. 1988) (noting that a formula described in a patent could not therefore be a trade secret); Mark A. Lemley, *The Surprising Virtues of Treating Trade Secrets as IP Rights*, 61 STAN. L. REV. 311, 313 (2008) (noting that trade secret protection on "self-disclosing" products is meaningless).

[127] Christopher M. Holman, *Protein Similarity Score: A Simplified Version of the Blast Score as a Superior Alternative to Percent Identity for Claiming Genuses of Related Protein Sequences*, 21 SANTA CLARA COMPUTER & HIGH TECHNOLOGY LAW JOURNAL 55, 71–72 (2004).

[128] *Id.* at 64–66; Amgen, Inc. v. Chugai Pharm., 927 F.2d 1200 (Fed. Cir. 1991).

[129] Novozymes A/S v. DuPont Nutrition Biosciences APS, 723 F.3d 1336 (Fed. Cir. 2013) (affirming rejection of a patent for including such nonfunctional embodiments in the claims).

sequences. Instead, they filed patents on some combination of functional elements, including an antibody's antigen, its epitope, and the binding affinity and avidity of the antibody to its target.[130]

B. Functional Claiming of Antibodies: 1986–2002

The Federal Circuit for years regularly allowed a patentee to describe and claim a new antibody by reference to its functional characteristics—the particular epitope or binding site to which it attached on an antigen of interest and the strength or specificity with which it bound to that epitope.[131] Antibody claims with functional limitations specific to the antibody's antigen were consistent with other cases in which a patentee invented something new but didn't know exactly what it was made of or precisely how it worked.[132] Even before antibodies, patent law had long allowed so-called "product-by-process" claims, in which the patentee claimed to own the thing produced by applying a certain process to certain starting materials even though they may not know exactly how to describe the resulting product. [133] So long as the inventor could teach others how to replicate the process—that is, making and using the product from the disclosed process—the fact that the inventor didn't know how to describe the structure of the resulting product didn't matter.[134]

Early antibiotics derived from naturally occurring bacteria were a prime example. In the 1950s, analytic organic chemistry was still such a nascent science that "the analytical techniques of the chemists [may have been] inadequate to determine the structural formula" of a given antibiotic.[135] But they knew how to make it, and they knew what the resulting chemical did. As a result, antibiotic chemists typically relied on product-by-process claims with functional limitations—the isolated chemical compound's ability to absorb certain wavelengths of infra-red

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[130] *See* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2001) ("An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . [such as] complete or partial structure, other physical and/or chemical properties, functional characteristics . . . or some combination of such characteristics.").

[131] *See, e.g.*, Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004).

[132] Laura R. Ford, *Alchemy and Patentability: Technology, "Useful Arts," and the Chimerical Mind-Machine*, 42 CAL. WESTERN L. REV. 49, 60 (2005) (reviewing limits of functional claims on "devices or mechanisms that the patentee might not even be familiar with or understand").

[133] Michael J. Meurer & Craig Allen Nard, *Invention, Refinement and Patent Claim Scope: A New Perspective on the Doctrine of Equivalents*, 93 GEO. L.J. 1947, 1975 (2005 ("Patent law accommodates inventors who have an incomplete understanding of their invention, for example by allowing product-by-process claims. Such a claim may be used by an inventor who cannot characterize a new compound, but who can describe the process that produces the compound."). For a history, see Dmitry Karshtedt, *Limits on Hard-To-Reproduce Inventions: Process Elements and Biotechnology's Compliance with the Enablement Requirement*, 3 HAST. SCI. & TECH. L.J. 109 (2011).

[134] Meurer & Nard, *supra* note 133, at 1975.

[135] Levy & Wendt, *supra* note 108, at 859-862.

light.[136] These supplanted more structural claims, including for oxytetracycline and chlortetracycline, "the structures of [which] were determined only years after the patents on these compounds issued."[137] While they didn't know the atomic structure of their creations, the inventors had still given the world something of value.

Early antibody claims operated on a similar principle. The patentee had identified an antibody with certain characteristics, and—by describing the structure of the antigen and the antibody's relationship to it—taught others how to identify and make similar antibodies and how to use them.[138] Concerns related to written description aside, so long as the PHOSITA could replicate the process without "undue experimentation"—that is, that the claims satisfied patent law's enablement requirement—the Federal Circuit largely held that the patent had disclosed enough.[139] This was, in fact, the basis for the Federal Circuit's first decision on monoclonal antibody technology in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*.[140] There, Hybritech's patent claimed the use of a novel monoclonal antibody assay to detect an antigen of a hepatitis virus.[141] Because structurally characterizing antibodies was, back then, virtually impossible, Hybritech's patent disclosed the method of producing the antibody using hybridoma technology, along with certain binding characteristics, including affinity.[142] Monoclonal Antibodies defended on various grounds, including a lack of enablement—an argument it won at trial.[143] But the Federal Circuit reversed, calling the district court's decision an "utterly baseless determination."[144] The Federal Circuit, noting that the claims centered on Hybritech's antibodies' affinity, concluded that the patent disclosed "the necessary characteristics, including affinity, of the monoclonal antibodies used in the invention."[145] This was true even if "those calculations [pertaining to affinity] are not precise."[146] The patent "reasonably apprise[d] those skilled in the art and [is] as precise as the subject matter permits. . . . [N]o court can demand more."[147]

This reasoning was extended by the Federal Circuit in *In re Wands*, an appeal of a Patent Office rejection of the applicant's claims directed to the diagnostic use of a novel anti-hepatitis B-

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[136] *Id.*

[137] *Id.* at 859.

[138] *See, e.g.,* Scripps Clinic and Research Foundation v. Genentech, Inc., 927 F.2d 1565, 1583–1584 (Fed. Cir. 1991); In re Wands, 858 F.2d 731, 736–740 (Fed. Cir. 1988); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986).

[139] *Wands*, 858 F.2d at 736–740.

[140] 802 F.2d 1367 (Fed. Cir. 1986).

[141] *Id.* at 1377.

[142] *Id.* at 1370.

[143] *Id.* at 1368.

[144] *Id.* at 1384.

[145] *Id.*

[146] *Id.* at 1385.

[147] *Id.*

surface antigen antibody defined by binding affinity.[148] In *Wands*, the applicants had deposited the relevant hybridomas with a depository (American Type Culture Collection) and taught, in their specification, how to screen for the relevant antibodies—that is, based on affinity—from their deposit.[149] This screening, the Federal Circuit concluded, was not "undue experimentation" in violation of patent law's enablement requirement.[150] No additional description was required.[151] Indeed, the Federal Circuit understood that "[w]here an invention depends on the use of living materials . . . it may be impossible to enable the public to make the invention (i.e., to obtain these living materials) solely by means of a written disclosure."[152] But that impossibility wouldn't prevent the court from upholding a patent.

The first cracks in this analysis began to appear, however, in 2002, in *Enzo Biochem, Inc. v. Gen-Probe Inc.*[153] *Enzo*—a patent case not about antibodies but genetic probes (short snippets of DNA that matched other pieces of DNA)—was decided against a backdrop of a new invigoration of the written description doctrine.[154] In *Enzo*, the Federal Circuit clarified that § 112 of the patent statute "required a 'written description' of an invention separate from enablement."[155] The court also noted that where "a gene material has been defined only by a statement of function or result . . . such a statement alone did not adequately describe the claimed invention."[156] But, relying on the Patent Office's 1999 Guidelines, it carved out an exception for antibodies.[157] There, the Federal Circuit adopted the Guidelines' approach that it would "find compliance with 112, 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well-defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well

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148 858 F.2d 731 (Fed. Cir. 1988).

149 *Id.* at 736.

150 *Id.* at 740.

151 *Id.* In a separate opinion, however, Judge Newman presciently noted:

"As the science of biotechnology matures the need for special accommodation, such as the deposit of cell lines or microorganisms, may diminish; but there remains the body of law and practice on the need for sufficient disclosure, including experimental data when appropriate, that reasonably support the scope of the requested claims. That law relates to the sufficiency of the description of the claimed invention, and if not satisfied by deposit, must independently meet the requirements of Section 112."

Id. at 741 (Newman, J., concurring-in-part and dissenting-in-part).

152 *Id.* at 735.

153 323 F.3d 956 (Fed. Cir. 2002).

154 *See, e.g.*, Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997); Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharma. Co., 927 F.2d 1200 (Fed. Cir. 1991).

155 *Enzo*, 323 F.3d at 963.

156 *Id.*

157 *Id.* at 964.

developed and mature."[158] At the time, this "antibody exception" seemed to cut against prevailing winds in favor of a more robust written description requirement, including several cases in which functional description of DNA-based claims were being struck down.[159] But it reinforced the idea that antibodies were special.[160]

C. The Rejection of Functional Claiming for Antibodies: 2004–Today

That relief was to prove short-lived, however. Starting in 2004 and continuing to the modern day with *Amgen Inc. v. Sanofi*[161] and *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*,[162] the Federal Circuit has rejected its earlier antibody exceptionalism. The court no longer permits patentees to claim antibodies by functional claims directed to the antigen. Nor, as a practical matter, does it permit patentees to claim a broad class of antibodies at all, even if they are robustly enabled and sufficiently described. While the Federal Circuit's earlier jurisprudence mostly centered on enablement, this turn away from antibodies' earlier claiming practices have fallen along two lines: enablement and written description.

1. Enablement

The court took the first step towards invalidating antibody claims in *Chiron Corp. v. Genentech, Inc.*[163] There, the Federal Circuit affirmed the invalidation of Chiron's antibody patent, claiming "[a] monoclonal antibody that binds to human c–erbB–2 antigen";[164] erbB-2, now known as HER2, is a cellular marker of many breast cancers.[165]

To be fair, the claims in that case were dubious. The asserted patent's prosecution history was complex but was ultimately based on a series of continuations-in-part over a 15-year period, the earliest of which disclosed murine (i.e., mouse) antibodies that bound to erbB-2, but not human or chimeric (that is, hybrid mouse-human) ones.[166] To satisfy § 112, the patentee also deposited a hybridoma line that produced the mouse antibodies at the American Type Culture Collection ("ATCC").[167] Beaten to the finish line by Genentech in producing an antibody cancer therapy that

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158 *Id.*

159 *See, e.g.*, *Regents of Univ. of Cal.*, 119 F.3d at 1562; *Fiers*, 984 F.2d at 1171; *Amgen*, 927 F.2d at 1203.

160 On the industry- and technology-specific nature of patent law, see generally DAN L. BURK & MARK A. LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT (2009).

161 872 F.3d 1367 (Fed. Cir. 2017); *Amgen Inc. v. Sanofi*, 987 F.3d 1080 (Fed. Cir. 2021).

162 10 F.4th 1330 (Fed. Cir. 2021).

163 Chiron Corp. v. Genentech, Inc., 363 F.3d 1247 (Fed. Cir. 2004). Full disclosure: one of us (Lemley) represented Genentech in this case.

164 *Id.* at 1250.

165 Yosef Yarden & Mark X. Sliwkowski, *Untangling the ErbB Signalling Network*, 2 NATURE REV. MOLECULAR CELL BIOLOGY 127, 127 (2001).

166 *Chiron*, 363 F.3d at 1251–1252.

167 *Id.* at 1250 n.1.

targeted HER2, Chiron then sued Genentech for infringement by Herceptin (trastuzumab), Genentech's humanized antibody product.[168]

The primary issues at trial were whether Chiron's broad claims—read as covering *any* monoclonal antibody that bound to HER2—satisfied the enablement or written description requirements.[169] A jury disagreed and found the patent invalid for failing to comply with § 112.[170] On appeal, the Federal Circuit, relying on its "full scope jurisprudence" for enablement, stated that the boundaries of any claims must be commensurate with specification's disclosure.[171] While the court recognized that "a patent disclosure need not enable information within the knowledge of an ordinarily skilled artisan," nascent technology must be fully enabled with "a specific and useful teaching."[172] This was problematic for Chiron, however, because the disclosure of its earliest application dated back to 1985—the dawn of recombinant antibody technology, and an era that required significant experimentation.[173] While the patent enabled *murine* antibodies, the Federal Circuit concluded that it did not enable the production of chimeric let alone fully human ones because the breadth of the claims did not "provide a 'specific and useful teaching' . . . of all antibodies within the scope of the claim."[174]

In addition, the court took issue with Chiron's definition of a "monoclonal antibody" in its specification, tethering the term to antibodies produced from a single hybridoma line—again, a throwback to the early days of antibody technology.[175] Further, the specification included an additional disclaimer that the term "monoclonal" meant all antibodies produced from the same source—even if they possessed functional variations.[176] This definition meant that the specification, in combination with Chiron's ATCC deposit, disclosed antibodies produced from a single hybridoma source—a disclosure "not broad enough to encompass chimeric antibodies" made by other means.[177]

Chiron may be particular to a unique set of facts at a unique time and to the extraordinary breadth of Chiron's claims. Chiron's patents claimed priority to continuations-in-part that straddled the invention and development of chimeric antibodies.[178] But it sought to apply those

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[168] *Id.* at 1252.

[169] *Id.*

[170] *Id.* Interestingly, "[t]he verdict form, however, did not require the jury to specify the particular requirement of § 112 left unfulfilled by each disclosure of the priority applications." *Id.*

[171] *Id.* at 1253.

[172] *Id.* at 1254.

[173] *Id.* at 1253.

[174] *Id.* at 1255.

[175] *Id.* at 1257.

[176] *Id.* at 1257–1258.

[177] *Id.*

[178] *Id.* at 1257.

patents to cover humanized antibody technology that didn't exist—at all—at the time it made its mouse-derived antibodies.[179]

It very well may be the case that the *Chiron* court got things correct as matter of innovation policy; how broad an "optimal" claim would have been for Chiron's technology is impossible to say, but it should not have extended to what Genentech did. But even though it reached the right result, *Chiron* was troubling as a doctrinal matter, beginning a series of cases where the Federal Circuit increasingly juxtaposed the enablement and written description requirements in the context of antibodies. In *Chiron*, the court emphasized that the two doctrines, despite originating from the same sentence of the same statute, were two different requirements, an interpretation later confirmed by the court, en banc, in *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*[180] As applied to antibodies, however, this laid a trap for the unwary: even as recombinant antibody technology became more routine, and thus easier to enable, the galactic variation in antibodies specific to a given antigen became more difficult to sufficiently describe.

2. Written Description

Much of the recent change in antibody law has happened in the written description doctrine. Again, the purpose of the written description doctrine is two-fold: to prevent "gun jumping" (filing for a patent before the inventor has actually identified the invention) and "late claiming" (changing claims during prosecution to cover something the inventor hadn't actually invented at the time).[181]

Some of the cases that began this written description revolution for antibodies did so in factual circumstances that fit pretty well into those traditional (and reasonable) purposes. In *Noelle v. Lederman*, an appeal of an interference proceeding before the Patent Office, the Federal Circuit cast doubt on some of Noelle's broad claims to any antibodies—human, mouse, chimeric, or otherwise—that bound to CD40CR, a portion of an important protein in the inflammatory response.[182] Like Chiron, Noelle had only disclosed the murine sequence but claimed the later-developed, far-more-valuable chimeric, humanized, and fully human sequences.[183] The Federal Circuit concluded that "a patentee of a biotechnological invention cannot necessarily claim a genus

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[179] *Id.* at 1257–1258.

[180] 598 F.3d 1336 (Fed. Cir. 2010) (en banc).

[181] *See* Jorge L Contreras, *Patent Reality Checks: Eliminating Patents on Fake, Impossible and Other Inoperative Inventions*, 102 J. PATENT & TRADEMARK OFF. SOC'Y 2, 7 (2021); Holbrook, *supra* note 12, at 161–162 (referring to the prevention of late claiming as a "priority policing" function); Karshtedt, Lemley & Seymore, *supra* note 13, at 61–62 (discussing "gun jumping" in the context of genus claims); Mark A. Lemley, *Ready for Patenting*, 96 B.U. L. REV. 1171, 1191 (2016) (remarking on "gun jumping"); Lemley, *supra* note 8, at 940 (discussing the problems of "late claiming" for functional claims); Mark A. Lemley et al., *Life After* Bilski, 63 STAN. L. REV. 1315, 1331 (2011) (noting preventing "gun jumping" is a "subsidiary goal" of § 112); *see also Ariad*, 598 F.3d at 1336.

[182] 355 F.3d 1343, 1350 (Fed. Cir. 2004); Robert D. Stout & Jill Suttles, *The Many Roles of CD40 in Cell-Mediated Inflammatory Responses*, 17 IMMUNOLOGY TODAY 487, 487 (1996).

[183] *Noelle*, 355 F.3d at 1345–1348.

after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."[184] As a consequence, Noelle lost a number of claims on written description grounds.[185]

As a general matter, the Federal Circuit's description of genus-species claims is a true statement.[186] But the *Noelle* court was the first to apply this understanding directly to antibodies and in the written description context.[187] Noelle unsuccessfully argued that "because antibodies are defined by their binding affinity to their antigens, not their physical structure, he sufficiently described [the claimed antibody] by stating that it binds to [the] human CD40CR antigen."[188] While this was standard black-letter law in the 1980s, the Federal Circuit rejected the argument because "Noelle failed to disclose the *structural* elements of [the] antibody or antigen in his earlier [patent] application."[189] The court distinguished Noelle's circumstance from *Enzo*—the case that established the "fully characterized antigen" test—because Noelle had not "fully characterized" *human* CD40CR.[190] Without disclosing the structure for the claimed antibody *or* its antigen, the court held that the contested claims had not satisfied the written description requirement.[191] Notably, however, the antigen was well known at the time; Noelle simply hadn't described its *structure* in his specification.[192] The Federal Circuit, by changing *Enzo*'s focus from "structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository"[193] to structure alone, limited the universe of cases in which the patentee could rely on characterization of the antigen to provide written description for the antibody.

This universe was further circumscribed in *Centocor Ortho Biotech, Inc. v. Abbott Laboratories* in 2011,[194] a case that even more also likely involved an instance of late claiming and an effort to expand a patent on one genus of antibodies to cover a different and better invention by the defendant. But the change in the Federal Circuit's articulation of the legal standard was dramatic—nixing the Patent Office's previous reliance on satisfying written description for antibody claims even if the antigen was "fully characterized." *Centocor* consequently marked a

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184 *Id.* at 1350.

185 *Id.* at 1353.

186 *See* Karshtedt, Lemley & Seymore, *supra* note 13, at 14–17 (reviewing other cases supporting this).

187 The Federal Circuit addressed this issue in *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998) in a slightly different context—claim construction—but ultimately declined to address it directly for written description because not addressed at the district court.

188 *Noelle*, 355 F.3d at 1349.

189 *Id.* (emphasis added).

190 *Id.*

191 *Id.* at 1350.

192 *Id.* at 1349.

193 Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (2002).

194 636 F.3d 1341 (Fed. Cir. 2011).

bright-line shift towards the Federal Circuit's "full-scope" view of written description law for antibodies akin to what it was doing in other fields at the same time.[195]

The claims in *Centocor* involved antibodies to TNF-α, the overproduction of which can lead to inflammatory conditions like arthritis.[196] Originally, Centocor and Abbott separately embarked on different research programs to develop antibodies for use in human patients.[197] Centocor focused on adapting murine antibodies to TNF-α for use in humans with the goal of producing a chimeric antibody, one with a mouse CDR (to bind to TNF-α) but a human constant region (to "trick" the human immune system into not attacking the antibody as a foreign intruder.)[198] Centocor filed a patent application disclosing mouse and chimeric antibodies in 1991 and filed various continuations-in-part until 1994.[199]

Abbott pursued a different research strategy, however, and filed a patent application in 1996 an antibody that was fully "humanized," with both a human constant region and a human CDR; the patent issued in 2000.[200] Abbott's fully humanized antibodies were far more successful than chimeric ones; Abbott, now AbbVie, used the technology to create Humira (adalimumab), now the world's most valuable therapy.[201] After Abbott obtained regulatory approval on Humira, Centocor filed additional claims to fully-human antibodies.[202] Centocor's chimeric antibody patents were still pending in 2002, so Centocor filed the new claims as part of that patent family and claimed priority to its 1994 applications.[203] Centocor then sued Abbott on this late patent and won a $1.67 billion jury verdict.[204]

The Federal Circuit invalidated Centocor's claims under an invigorated approach to written description.[205] The court reiterated that written description required an applicant to "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention."[206] Yet Centocor's 1994 application, in the Federal Circuit's view, did not adequately disclose a fully-human antibody to TNF-α; the application disclosed,

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195 Karshtedt, Lemley & Seymore, *supra* note 13, at 62-63.

196 *Centorcor*, 636 F.3d at 1344–1345.

197 *Id.* at 1344.

198 *Id.* at 1345.

199 *Id.* at 1346.

200 *Id.*

201 Urquhart, *supra* note 3, at 10.

202 *Centorcor*, 636 F.3d at 1346.

203 *Id.* at 1347-1348.

204 *Id.* at 1343-1344.

205 *Id.* at 1350-1351.

206 *Id.* at 1348 (quoting *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008)).

instead, only a *chimeric* one.[207] And although human antibodies and human TNF-α were mentioned in the specification, it only provided amino acid sequences for a single mouse CDR.[208] The Federal Circuit concluded that this amounted to "nothing in the specification that conveys to one of skill in the art that Centocor possessed fully-human antibodies . . . within the boundaries of the claims."[209]

Moreover, the court rejected Centocor's arguments that the Patent Office's guidelines allowed the disclosure of a fully characterized antigen structure to show constructive possession of antibodies that bind to them.[210] The court explained that while in some simple situations possessing a protein makes it trivially easy to secure a complementary antibody,[211] this was not so for TNF-α.[212] Indeed, anti- TNF-α antibodies were already in the prior art.[213] The challenge instead was finding an efficient and therapeutically tolerable antibody that bound to TNF-α in the desired way. But finding one required, essentially, a canvassing of all possible CDR sequences that met such requirements.[214] Centocor's patent was therefore not like claiming a lock to be opened by a single, known key, but claiming a lock with "a ring with *a million* keys on it."[215] Centocor's claims were consequently invalid for lacking sufficient written description.[216]

The door to claiming antibodies from their antigens closed further in *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*[217] Here, unlike prior cases, the patentee wasn't seeking to stretch its claims to cover a different form of technology it hadn't invented.

In *AbbVie*, the patents at issue were directed towards human antibodies that bind to the human protein interleukin 12 ("IL-12").[218] AbbVie's specification described amino acid sequences of about 300 antibodies with a range of binding affinities.[219] Importantly, though, the patent described only one type of heavy and light chains, which shared "90% or more amino acid sequence similarity in the variable regions [i.e., the CDR]."[220] While the accused product had different heavy and light chains with only 50% sequence similarity to AbbVie's disclosed sequences, it was

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207 *Id.* at 1347–1348.

208 *Id.* at 1349.

209 *Id.* at 1351.

210 *Id.* at 1351.

211 *Id.* at 1352.

212 *Id.* at 1352–1353.

213 *Id.* at 1352.

214 *Id.*

215 *Id.* (quoting Abbott's expert, Dr. Jochen Salfeld).

216 *Id.* at 1353.

217 759 F.3d 1285 (Fed. Cir. 2014).

218 *Id.* at 1291.

219 *Id.*

220 *Id.*

nonetheless covered by AbbVie's claims.[221] This is because AbbVie's claims were predicated on the antibodies' *functionality*—how *strong* the antibodies bound to IL-12 by a measure of its disassociation rate from the antigen.[222] And there the defendant's antibodies were essentially indistinguishable from the plaintiffs.[223]

This mix of some disclosed structure and functional claims—typical of antibody patents filed under the governing law at the time—still failed the written description requirement.[224] The Federal Circuit noted that when a patentee claims a genus, they must disclose "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."[225] The court found "no evidence to show any described antibody to be structurally similar to, and thus representative of, [the accused product]" and "no evidence to show whether one of skill in the art could make predictable changes to the described antibodies to arrive at" antibodies like the accused product.[226]

AbbVie argued that its disclosure, in describing a substantial number of antibodies with a range of binding affinities, had disclosed species representative of what it claimed, which was, after

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[221] *Id.* at 1292–1294.

[222] *Id.* at 1292 (quoting U.S. Patent No. 6,914,128 col. 386 ll.55-59 (filed Mar. 24, 2000)).

[223] *Id.* at 1293.

[224] *Id.* at 1297–1302.

[225] *Id.* at 1299 (quoting Ariad Pharm. Inc. v. Eli Lilly & Co., 598 F.3d 1336, 1350 (Fed. Cir. 2010)) (internal quotation mark omitted).

[226] *Id.* at 1298. The court wrote:

> AbbVie argues that each of the asserted claims is limited to a small genus of antibodies that are rare and difficult to obtain and that its patents describe a representative number of antibodies commensurate with the scope of the claims. . . .
>
> Here, the claimed invention is a class of fully human antibodies that are defined by their high affinity and neutralizing activity to human IL–12, a known antigen. AbbVie's expert conceded that the ′128 and ′485 patents do not disclose structural features common to the members of the claimed genus.
>
> All of the antibodies described in AbbVie's patents were derived from Joe–9 and have VH3 type heavy chains and Lambda type light chains. Although the described antibodies have different amino acid sequences at the CDRs, they share 90% or more sequence similarity in the variable regions and over 200 of those antibodies differ from Y61 by only one amino acid. The patents describe that other VH3/Lambda antibodies may be modified to attain IL–12 binding affinity. However, the patents do not describe any example, or even the possibility, of fully human IL–12 antibodies having heavy and light chains other than the VH3 and Lambda types. In contrast, Centocor's Stelara, which falls within the scope of the claimed genus, differs considerably from the Joe–9 antibodies described in AbbVie's patents. Stelara has VH5 type heavy chains and Kappa type light chains. The variable regions of Stelara only share a 50% sequence similarity with the Joe–9 antibodies, which is far lower than the 90% sequence similarity shared among the Joe–9 antibodies described in AbbVie's patents. . . .

all, antibodies with a range of affinities and not antibodies with a range of structures.[227] The court called this an "inapposite attempt[]" which "merely" recited "a desired result, rather than the actual means for achieving that result."[228] The court warned that functionally defined genus claims were "inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus."[229]

AbbVie represented a fundamental shift away from the functional characterization of antibodies—a rejection in spirit if not letter of the Federal Circuit's allowance of such claims in *Wands*, *Hybritech*, *Enzo* (albeit in dicta), and the Patent Office's previous guidelines. In *AbbVie*, the antigen *was* fully characterized, and AbbVie provided hundreds of examples of antibodies that bound to its target antigen at particular places with particular affinity.[230] This would have clearly met the standard in *Enzo* that written description could be satisfied by claiming functional definitions alongside disclosures of an antigen's structural characteristics, especially where "the antibody technology is well developed and mature."[231] After *AbbVie*, this has been no longer enough; the Federal Circuit has come to fundamentally reject functional claiming of antibodies in a demand for structure.

3. Today: The Death of the Antibody Claim

The most dramatic evidence of this demand for structure comes in two recent cases, *Amgen Inc. v. Sanofi* and *Juno Therapeutics v. Kite Pharmaceuticals*.[232] In *Amgen*, the Federal Circuit held that the disputed claims were invalid under the enablement requirement because Amgen's claims were broad functional claims that provided little guidance on how to recreate the full scope of the invention—that is, anti-PCSK9 antibodies—without undue experimentation.[233] And in *Juno*, the Federal Circuit concluded that Juno's claims lacked sufficient written description because even though the patent included working examples of Juno's engineered immune receptor, the fact that other functional receptors existed—and were not disclosed in the patent—made the disclosure not "representative" of the scope of the claims.[234]

In *Amgen*, Amgen's '165 and '741 patents, asserted against Sanofi's product Praluent (alirocumab), describe antibodies which bind to proprotein convertase subtilisin/kexin type 9

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[227] *Id.* at 1298.

[228] *Id.* at 1301.

[229] *Id.* (citations omitted).

[230] *Id.* at 1291.

[231] Enzo Biochem, Inc. v. Gen-Probe Inc., , 323 F.3d 956, 964 (Fed. Cir. 2002).

[232] Amgen Inc. v. Sanofi, 987 F.3d 1080 (Fed. Cir. 2021); Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330 (Fed. Cir. 2021).

[233] *Amgen*, 987 F.3d at 1080.

[234] *Juno*, 10 F.4th at 1330.

enzymes ("PCSK9"), enzymes important in the processing of cholesterol.[235] By binding to PCSK9, these antibodies prevent the enzymes from binding to low-density lipoprotein ("LDL") receptors, ultimately lowering LDL cholesterol (or "bad cholesterol") levels.[236] The specification lists partial amino acid sequences for the CDRs of twenty-six antibodies and claims antibodies that bind at least one of fifteen amino acids on the PCSK9 protein.[237]

At the first trial, the jury and the district court found the patents not invalid and the court ordered a permanent injunction.[238] But on an emergency appeal from the injunction order, the Federal Circuit reversed the underlying validity determination.[239] It refused to permit Amgen to characterize a class of antibodies by reference to detailed knowledge of the antigen—even when coupled with a partial description of the antibodies' genetic structure.[240] The Federal Circuit pointedly took issue with the district court's jury instructions on § 112.[241] Consistent with prior law, the district court had instructed the jury that:

> In the case of a claim to antibodies, the correlation between structure and function may also be satisfied by the disclosure of a newly characterized antigen by its structure, formula, chemical name, or physical properties if you find that the level of skill and knowledge in the art of antibodies at the time of filing was such that production of antibodies against such an antigen was conventional or routine.[242]

This, the Federal Circuit stated, would lead a jury to "naturally understand the instruction to permit it to deem any antibody within the claim adequately described merely because the antibody could easily be 'produc[ed]' (and, implicitly, used as an antibody)."[243] This could not be the case, according to the appellate court, because the language of the district court's instruction "does not even require any *particular* antibody to be easily made; all it requires is that 'production of *antibodies*'—some, not all—'against [a newly characterized] antigen'—be conventional or routine."[244]

This instruction "ran afoul" of the written description requirement in the Federal Circuit's view.[245] "We cannot say," the Federal Circuit stated, "that this particular context, involving a 'newly characterized antigen' and a functional genus claim to corresponding antibodies, is one in which

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235 *Amgen*, 987 F.3d at 1082–1083.

236 *Id.* at 1083 (citing U.S. Patent Nos. 8,859,741 and 8,829,165).

237 *Id.*

238 *Id.* at 1084.

239 Amgen Inc. v. Sanofi, 872 F.3d 1367, 1371 (Fed. Cir. 2017).

240 *Id.* at 1376–1378.

241 *Id.* at 1378.

242 *Id.* at 1376.

243 *Id.* at 1377.

244 *Id.* at 1377–1378.

245 *Id.* at 1378.

the underlying science establishes that a finding of 'make and use' (routine or conventional production) actually does equate to the required description of the claimed products."[246]

On remand, a second jury once again found that Sanofi had not proven the patents invalid.[247] The district court, however, ultimately granted Sanofi's motion for judgment as a matter of law for lack of enablement.[248] On a second appeal, the Federal Circuit now upheld the district court's invalidity ruling.[249] At the Federal Circuit, Amgen argued that a person of ordinary skill in the art could make "make all antibodies within the scope of the claims by following a roadmap using anchor antibodies and well-known screening techniques as described in the specification or by making conservative amino acid substitutions in the twenty-six examples."[250] Indeed, under the *Wands* factors, Amgen argued, its claimed invention required only routine experimentation—made all the more routine due to the development of antibody science in the intervening thirty-three years since *Wands* was decided.[251]

The court, however, disagreed—not so much with Amgen's factual assertions, but with prior Federal Circuit law itself.[252] The Federal Circuit noted that "although *Wands* gave birth to its eponymous factors, *Wands* did not proclaim that all broad claims to antibodies are necessarily enabled."[253] The functional claim limitations here "did not enable preparation of the full scope of these double-function claims without undue experimentation."[254] Amgen's claims were "far broader in functional diversity than [its] disclosed examples" and—despite the progress in the field—were still situated in an "unpredictable field of science."[255] A person of ordinary skill in the art, the appellate court concluded, could only discover the claimed embodiments through massive trial-and-error or accidentally discovering new ones themselves.[256] The Court saw broad functional claims coupled with narrow guidance—so much so that no reasonable jury could find "anything but 'substantial time and effort' would be required to reach the full scope of claimed embodiments."[257]

This seeming repudiation of *Wands*—and by extension, genus claims in the life sciences and chemical fields—reflects a fundamental reorientation of § 112 jurisprudence, imposing a new

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246 *Id.*

247 Amgen Inc. v. Sanofi, 987 F.3d 1080, 1084 (Fed. Cir. 2021).

248 *Id.*

249 *Id.* at 1088.

250 *Id.* at 1085.

251 *Id.*

252 *Id.*

253 *Id.* at 1086.

254 *Id.*

255 *Id.*

256 *Id.* at 1088.

257 *Id.*

requirement that a patentee teach the PHOSITA how to identify every working claim in the genus rather than just teaching people how to find working examples in the genus. It is at odds with the rule in other countries.[258] It has been subject to academic criticism, including from one of the authors, who claim it represents "the death of the genus claim."[259] On a petition for rehearing en banc in *Amgen*, Judge Lourie took the unusual step of writing a concurrence to the panel's own denial of rehearing, perhaps to address such criticism. There, Judge Lourie asserted that, despite arguments to the contrary, there was no change in the law; patentees could still obtain genus claims provided they showed enough working examples.[260]

Notably, however, there were 26 working examples in *Amgen* and 300 working examples in *AbbVie*.[261] In *Amgen*, that still was not sufficient for written description for the Federal Circuit despite a jury finding to the contrary.[262] Nor did the jury's factual findings that PHOSITAs could identify other working antibodies in both cases move the court.[263] While the immaturity of the art was the central inquiry in *Wands* and earlier cases, *Amgen* and *AbbVie* suggest that scientific advances in the area and the realities of "undue experimentation" are irrelevant. The requirement to disclose structure is entrenched as a matter of law. To put it more bluntly: It doesn't matter how many antibodies the patentee discloses, or how much of a roadmap the patent gives to finding other embodiments. Without proof of something that the science just doesn't support—evidence that antibodies that bind to particular epitopes with particular affinity must have parallel structures—it isn't possible for a functionally-defined antibody claim to survive. Indeed, it does not seem that a single antibody case from the modern era has survived *Amgen*'s approach to enablement or written description.

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[258] The same parties litigated in Japan, where the IP High Court held that Amgen's functional claims were permissible. *See* Alix Vermulst, *Sufficiency of Disclosure for Monoclonal Antibodies: A Comparative Study* (working paper January 2022).

[259] Karshtedt, Lemley & Seymore, supra note 13, at 1; *see also* Jeffrey A. Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 BERK. TECH. L.J. 1141, 1210 (2008) (noting that written description's "possession inquiry" cannot support this "full scope" requirement); Jonathan S. Masur, Regulating Patents, 2010 SUP. CT. REV. 275, 324 n.196 (2010) (suggestion the "full scope" requirement is "inconsistent with the admonition against reading limitations from the specification into the claims"); Sean B. Seymore, *The Enablement Pendulum Swings Back*, 6 NW. J. TECH. & INTELL. PROP. 278, 286 (2008) (discussing this in the context of *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371 (Fed. Cir. 2007)); Comment, Guang Ming Whitley, *A Patent Doctrine without Bounds: The "Extended" Written Description Requirement*, 71 U. CHI. L. REV. 617, 628–630 (2004) (noting that the requirement suffers from "unclear boundaries"); S. Sean Tu & Christopher M. Holman, *Technology Changes Drive Legal Changes for Antibody Patents: What Patent Examiners Can Teach Courts About the Written Description and Enablement Requirements* (forthcoming 2022) (measuring prosecution changes in response to this shift in doctrine).

[260] Amgen Inc. v. Sanofi, 850 F. App'x 794, 795–796 (Fed. Cir. 2021) (Lourie, J., concurring in denial of panel rehearing).

[261] Amgen Inc. v. Sanofi, 987 F.3d 1080, 1083 (2021); AbbVie Deutschland GmbH v. Janssen Biotech, Inc., 759 F.3d 1285, 1291 (Fed. Cir. 2014).

[262] *Amgen*, 987 F.3d at 1084.

[263] *Id.*; *AbbVie*, 759 F.3d at 1305.

Juno Therapeutics, Inc. v. Kite Pharma, Inc., cements the court's structural turn.[264] *Juno* concerned a remarkable application of immune receptors—re-engineering patients' T cells to produce chimeric antibodies that specifically target patients' unique blood cancers.[265] The technology—chimeric antigen receptor T cell therapy, or "CAR-T"—is arguably the first true gene therapy approved by FDA.[266]

Although Kite Pharma was the first across FDA's finish line, Juno Therapeutics, in conjunction with Sloan Kettering Institute for Cancer Research, had conducted early research in the area, and patented its innovations. These concerned novel ways of linking the engineered antibodies' CDR and constant regions together in a manner that further stimulated the immune system to fend off cancer.[267] Juno subsequently sued Kite Pharma, Inc. for infringing its patents with Kite's Yescarta (axicabtagene ciloleucel) product.[268] A jury found that the claims were adequately described.[269]

On appeal, however, the Federal Circuit reversed, finding that Juno's patent for nucleic acids encoding chimeric T cell receptors was invalid for lack of written description as a matter of law.[270] The patent included dependent claims that covered the technology as used in single-chain antibody-variable fragments (scFvs)—a structural genus of the antibody claims, writ broadly.[271] Nonetheless, the court held that for the claimed genus, the asserted patent failed to disclose "representative species or common structural features to allow a person of ordinary skill in the art to distinguish between scFvs that achieve the claimed function and those that do not."[272] This was so even though the '190 patent disclosed two working examples of scFvs, albeit without disclosing the amino acid sequence of either.[273] The court noted that the amino acid sequences not being disclosed would not have been fatal if the patent had "provided other means of identifying which scFvs would bind to which targets, such as common structural characteristics or shared traits."[274] But that seemed unlikely given that the court's definition of the functional genus—anything scFvs that that bound to their targets—claimed potentially quadrillions of candidates.[275]

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264 10 F.4th 1330 (Fed. Cir. 2021).

265 *Id.* at 1333-1334.

266 Jacob S. Sherkow, Patricia J. Zettler & Henry T. Greely, *Is It "Gene Therapy"*?, 5 J.L. & BIOSCIENCES 786, 786–787 (2018).

267 *Juno*, 10 F.4th 1333–1334.

268 *Id.* at 1334.

269 *Id.*

270 *Id.* at 1332.

271 *Id.* at 1333-1334 (discussing claims 3 and 9 of U.S. Patent No. 7,446,190).

272 *Id.* at 1342.

273 *Id.* at 1333.

274 *Id.* at 1337.

275 *Id.* at 1336.

Remarkably, the scFv fragments were not even the inventive part of the patent—the point of novelty was, again, the double-inclusion of the ζ chain and the costimulatory region.[276] Nonetheless, the Federal Circuit required the specification to demonstrate possession of all possible variants of *all* elements of the claimed invention, not merely its novel elements.[277]

D. Antibody Claims in the Courts Today

Very few if any functional antibody patents are going to survive *Amgen*'s and *Juno*'s revolutions on enablement and written description. Post-*Amgen*, the enablement standard for antibodies has become, if not an impossible barrier, at least an impractical one—especially for the myriad antibody claims issued before *Amgen* was decided. Because of the science of antibodies, any antibody claim centered on functional elements—even narrow ones, like those directed to a precise affinity or avidity—will likely encompass antibodies beyond those disclosed in the specification. And, if the Federal Circuit's math on antibody diversity is accurate, they will cover *many* undisclosed antibodies.[278] It no longer seems to matter, as the *Wands* test suggests, whether identifying these other antibodies or even a "representative" subset of them would require undue experimentation.[279] Rather, in the words of Judge Lourie, the standard now is "not simply that the claimed genus was numerous—[but whether] it was so broad, extending far beyond the examples and guidance provided."[280] Given what we now know about antibody science, no robust specification could possibly encompass all possible examples of functionally claimed antibodies. Although enablement—not just for antibodies, but all technologies—has long been satisfied by linking the scope of claims to instructions for their use, for antibodies at least post-*Amgen*, "one cannot claim everything that works."[281]

Things are even worse when it comes to written description. The written description requirement is now satisfied only if the specification enumerates "representative species or common structural features to allow a person of ordinary skill in the art to distinguish between [inventions] that achieve the claimed function and those that do not."[282] But, again, the science of antibodies has made the legal standard impossible; similar *functions* for antibodies do not mean

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[276] *Id.* at 1334.

[277] *Id.* at 1337-38.

[278] *See* Centocor Ortho Biotech, Inc. v. Abbott Laboratories, 636 F.3d 1341, 1352 (Fed. Cir. 2011) (suggesting the number is "millions"). We note, though, that the precise number of undisclosed antibodies is potentially calculable for each given case and, depending on the patent's affinity constraints, could be as few as a dozen-and-a-half undisclosed examples. *See* Adams et al., *supra* note 118, at *10 (finding only 18 antibodies from a universe of thousands that met the experimental binding affinity constraints).

[279] In re Wands, 858 F.2d 731, 736–740 (Fed. Cir. 1988).

[280] Amgen Inc. v. Sanofi, 850 F. App'x 794, 796 (Fed. Cir. 2021) (Lourie, J., separate opinion).

[281] *Id.* at 797.

[282] Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1336 (Fed. Cir. 2021).

similar *structures*.[283] Antibodies are made, naturally at least, through semirandom rearrangement of the *VDJ* cassettes.[284] They can be further selected for based on their function, i.e., to which antigens they bind—but their utility and inventiveness is based on these functions, not their underlying structure. Less abstractly put, researchers have little interest in the particular DNA sequence that gives rise to a particular antibody; they are interested, instead, in what the antibody does and how it does it. This means that although *function* can make an antibody representative of a class—that is, by establishing a group of molecules by what they bind to and how—this class may have no "common structural features." This representative structure standard is, if not scientifically impossible, textually impractical—roughly equivalent to demanding that a software patent identify individual strings of computer code that *every* implementation must have in common, even if slight variations do the exact same thing.

One can see this future in a recently decided district court case, *Baxalta Inc. v. Genentech, Inc.*[285] In *Baxalta*, Judge Timothy B. Dyk, a Federal Circuit judge sitting by designation in District of Delaware, determined that Baxalta's claims to bispecific antibodies—in which one arm of CDR's Y-shape binds to one antigen, and the other arm, to another antigen—were invalid for lack of enablement.[286] Baxalta's claims were indeed broad, e.g., "An isolated antibody or antibody fragment thereof that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa."[287] But the specification of the asserted patent nonetheless provided much of the antibodies' underlying DNA sequences and eleven working examples of antibodies that fell within the scope of the claims. Nonetheless, this combination of functional claims and structural disclosure were not enough to overcome the enablement hurdles set forth in *Amgen*. The claims, even in combination with the disclosed sequences, did not "describe what structural or other features of the disclosed antibodies cause them to bind to Factor IX/IXa or to increase the procoagulant activity of Factor IXa" even though the specification provided working examples.[288] The issue instead was that "potential candidates number in the millions."[289] And routine experimentation or not, "the only way to practice the teachings of the patent," according to Judge Dyk, "is by trial-and-error; i.e., by screening tens of thousands, if not millions, of candidate antibodies to determine whether they satisfy the limitations of the asserted claims."[290] This failed

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[283] *See supra* notes 44–48 and accompanying text; *see also* Adams et al., *supra* note 118, at *1 ("Despite the central role that antibodies play in the adaptive immune system and in biotechnology, much remains unknown about the quantitative relationship between an antibody's amino acid sequence and its antigen binding affinity.").

[284] *See supra* notes 40–43 and accompanying text.

[285] Baxalta Inc. v. Genentech, Inc., 1:17-cv-00509 (D. Del. Jan. 13, 2022) (Dkt. No. 573-1).

[286] *Id.* at 47.

[287] *Id.* at 8 (reciting U.S. Patent No. 7,033,590).

[288] *Id.* at 5.

[289] *Id.* at 29.

[290] *Id.* at 5.

to satisfy the enablement standard.[291] But, given the breadth of antibody diversity, it is difficult to imagine antibody claims with functional limitations that do not suffer from similar deficiencies.

While Judge Dyk did not address written description, it is difficult to imagine—post-*Juno*—that the patent satisfied the requirement. If the standard now requires the specification to demonstrate possession of every, or almost every, structural variation of the claimed invention, not merely its novel elements, then no functionally claimed antibody patents could withstand the challenge. In *Baxalta*, for example, Judge Dyk noted that the specification gave "no specific direction as to the structure" and "no assurance that, once [any] modifications are made, the antibody will retain the same functional qualities much less that making it bispecific would enhance its properties."[292] Such an assurance, of course, would be technically and legally impossible—an empty promise for almost all functional antibody claims.

III. WHAT'S GOING ON HERE?

What's behind this rather dramatic shift in the law of antibody patenting? And is it truly specific to antibodies or part of broader currents at work in the Federal Circuit? We can imagine at least four underlying narratives to explain this revolution in the Federal Circuit's jurisprudence. Each explanation has a certain amount of truth to it although none, considered alone, is perfectly satisfying.

The first is to take at face value the court's assertion that, when it comes to molecules, structure is king. That is, independent of the technical nuances of biology, perhaps patent law prefers claims covering "atoms"—i.e., things—over, say, "variable domains"—which is a combination of a thing and what it does. A second explanation is that the court is concerned with the problems of functional claiming *generally* or specifically in the *software* context; antibody patents have simply found themselves in the wrong place at the wrong time. A third possibility is that the court's changing jurisprudence reflects advances in the science of antibodies. As scientists have learned the extent of antibodies' complexity, the same genus claim to a given antibody has, with hindsight, expanded, and the Federal Circuit is now restricting them in kind. A fourth explanation is that the Federal Circuit is simply responding to politics concerning the drug industry—doing what they can do, within the confines of some particular narrow doctrines in patent law, to curb patents that are responsible, in part, for exorbitantly expensive drugs.

A. The Primacy of Structure

The simplest narrative for the Federal Circuit's restriction on antibody claims is the one the court offers itself in the cases just discussed: patent law is concerned with chemistry, and chemistry is all about molecular structure.[293] Pithily: antibodies are molecules and so they are

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[291] *Id.*

[292] *Id.* at 43.

[293] *See* Elizabeth Bailey, *Products of Human Ingenuity: The Isolation and Purification of Genes Under the Product of Nature Doctrine*, 32 TEMPLE J. SCI., TECH. & ENVTL. L. 25, 41 (2013) ("[S]tructure is a large component of the issuance of molecular patents, and any small variance in the structure of a molecule in

chemistry, albeit chemistry on a scale large enough that atomic identity is impractical.[294] On this theory, now that researchers can somewhat routinely identify the structure of a particular antibody, the only question relevant to claim scope is whether other antibodies within a given claim share the same structure. If they don't, you can't claim a genus of them. And even if some do, it is still the *structural* homology that matters, even if that structure isn't particularly connected to function. So, a defendant whose antibody structurally looks different *shouldn't* be infringing and a patent that too broadly covers other variants *shouldn't* be valid.

This explanation—simplistic though it is—has the virtue that it's what the Federal Circuit says it's actually doing. And it is consistent with the law in other patent life science doctrines. Others have remarked on the Federal Circuit's obsession with structural identity in chemical and biotechnological cases.[295] And the court has coupled that focus with the repeated incantation that chemistry and biotechnology are "unpredictable" arts, which—to the court, at least—means that we can't know what even small structural changes will do.[296] For antibodies, the unpredictability of the connection between structure and function largely remains true, though that doesn't mean the science as a whole is unpredictable.[297]

But a structural story can't explain why the Federal Circuit allowed antibodies to be patented in purely functional terms in the first few decades of their existence. Perhaps the answer to this mystery is that the Federal Circuit has, in fact, become *more* obsessed with structure over time. Indeed, that obsession with structure in the chemical realm is one explanation for the growth of the written description doctrine generally. As noted above, the doctrine has useful purposes in

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chemistry could result in a whole new, and patentable, invention."); Dan L. Burk, *Tailoring Patent Policy to Specific Industries*, 7 MARQ. INTELL. PROP. L. REV. 1, 9 (2003) ("[Computer chips are] not like a chemical structure where the structure is the invention and the product and the invention are sort of coterminous."); Burk & Lemley, *supra* note 24, at 1684–1686 (discussing the relationship between molecular structure and inventiveness).

294 *See supra* notes 107–109 and accompanying text.

295 Dan L. Burk, *Biotechnology in the Federal Circuit: A Clockwork Lemon*, 46 ARIZ. L. REV. 441, 442-444 (2004); Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERK. TECH. L.J. 1155, 1174-1175 (2002).

296 Dan L. Burk & Mark A. Lemley, *Biotechnology's Uncertainty Principle*, 54 CASE WEST. RES. L. REV. 691, 704 (2004). For criticism that the Federal Circuit takes an excessively formalist view in its jurisprudence, preferring bright lines to more flexible standards, see, e.g., DAN L. BURK & MARK A. LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT, 79-94 (2009); Timothy R. Holbrook, *The Supreme Court's Complicity in Federal Circuit Formalism*, 20 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1, 1–2 (2003); Lucas S. Osborn, *Instrumentalism at the Federal Circuit*, 56 ST. LOUIS U. L.J. 419, 425–26 (2012); Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1102–22 (2003); John R. Thomas, *Formalism at the Federal Circuit*, 52 AM. U. L. REV. 771 (2003). For a more favorable view of the Federal Circuit's formalism, see Peter Lee, *Patent Law and the Two Cultures*, 120 YALE L.J. 2, 27–29 (2010).

297 *See, e.g.*, Chronister et al., *supra* note 105, at 1 (partially predicting antibody function based on sequence).

preventing gun-jumping and late claiming, but it has been applied more broadly in the life sciences as a sort of "super-enablement" requirement.[298]

The result of this newfound obsession has been what one of the authors has called "the death of the genus claim" in the pharmaceutical industry in recent years.[299] That obsession, along with the idea that biotechnology is inherently unpredictable, has increasingly caused the court to allow patents only for individual species that are proven to work.[300] This has allowed the Federal Circuit to reject genus claims even where, as in *Juno Therapeutics*, the genus identified is, once disclosed, both well-understood and predictably specific to a large class of antibodies.[301] Simply put, if antibody claims written in functional form are, in some senses, the ultimate genus claims, a Federal Circuit intent on such claims' demise would render such antibody claims invalid under this recent doctrinal shift. On this theory, the Federal Circuit's U-turn on antibody claims isn't about antibodies in particular, but about chemical structure more generally. Antibody claims just happened to get swallowed by the system's larger reaction.

If this is the explanation, though, it would be particularly ironic, because the evolving lesson of antibody science is that structure *isn't* everything. There are many paths to bind to an antigen, some of them quite structurally different from one another.[302] Limiting antibody patents to only a single molecule (or even a representative one) would narrow antibody claims, but not in any logical or meaningful way—nor in any way that parallels laboratory practice or biologic significance.

B. A Rejection of Functional Claiming

A second explanation is that the demise of antibody patents reflects a broader rejection of functional claiming. Almost no antibody patents claim a specific chemical, or even a series of steps for making a chemically-defined antibody. Rather, most claim the effect of the antibody itself—binding to a given antigen. But antibody patents are not alone in defining their claims functionally. Software patent lawyers have been writing patent claims in broad, functional terms for decades.[303] The resulting functional software patents (many of which are wildly overbroad) overlap and create patent thickets that have been widely identified as a significant problem in the software and

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[298] Burk & Lemley, *supra* note 24, at 1653–1654; Christopher M. Holman, *Is* Lilly *Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of* Eli Lilly *and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1, 4 (2007); Karshtedt, Lemley & Seymore, *supra* note 13, at 39' Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 BERKELEY TECH. L.J. 615, 617 (1998) (coining that term).

[299] Karshtedt, Lemley & Seymore, *supra* note 13, at 1.

[300] *Id.* For a contrary interpretation of the same, see Christopher M. Holman, *Is the Chemical Genus Claim Really "Dead" at the Federal Circuit?: Part I*, 41 BIOTECH. L. REP. 4, 5 (2022). Holman does not deny the cases we identify, but points to other genus patents that survived. Most of those cases, however, were ones in which enablement and written description were not actually raised.

[301] *See supra* notes 270–277 and accompanying text.

[302] Adams et al., *supra* note 118, at *10 (listing antibody clones with the same function but different structure); *supra* notes 36–43 and accompanying text (describing the V(D)J arrangement process).

[303] Lemley, *supra* note 8, at 923.

information technology fields.[304] The Federal Circuit may view antibody patents in this same vein today.

Patent law has faced functional claims before. They were quite common in the early twentieth century.[305] The Wright brothers, for instance, notoriously claimed the idea of creating a warped-wing "aeroplane," however implemented.[306] The Supreme Court ultimately rejected such broad functional claiming in the 1940s as inconsistent with the purposes of the patent statute.[307] When Congress rewrote the Patent Act in 1952, it adopted a compromise position: patentees could write their claim language in functional terms, but when they did so the patent would not cover the goal itself, but only the particular means of implementing that goal described by the patentee and equivalents thereof. These "means-plus-function" claims permitted the patentee to use functional language to describe an element of their invention, but did not permit them to own the function itself regardless of how it was implemented.[308]

A second possible explanation, then, is that the Federal Circuit is simply bringing antibody claims in line with the general strictures on functional claiming. The court's en banc reaffirmation of the written description doctrine in *Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.* has some of this

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[304] *Id.* Portions of this paragraph and the next are adapted from Lemley, *supra* note 8.

[305] Among the early cases permitting functional claiming, see *Morley Sewing Mach. Co. v. Lancaster*, 129 U.S. 263, 283–84, 289–90 (1889). That view was then ensconced in PTO practice in Commissioner's decisions such as *Ex parte Pacholder*, 1889 Dec. Comm'r Pat. 55, 61; *Ex parte Halfpenny*, 1895 Dec. Comm'r Pat. 91, 92; and *Ex parte Knudsen*, 1895 Dec. Comm'r Pat. 29, 32. *See also* Lemley, *supra* note 8 at 919-922 (collecting cases).

[306] *Wright Co. v. Herring-Curtiss Co.*, 211 F. 654, 655 (2d Cir. 1914); *Wright Co. v. Paulhan*, 177 F. 261, 264 (C.C.S.D.N.Y. 1910) (holding the Wrights' patent to be pioneering and so entitled to broad scope). The Wrights successfully enforced their patent to defeat all alternative aircraft, including many that surpassed the technical achievement of the Wrights. *See Glenn Curtiss and the Wright Patent Battles*, U.S. CENTENNIAL OF FLIGHT COMM'N, https://www.centennialofflight.net/essay/Wright_Bros/Patent_Battles/WR12.htm [https://perma.cc/NM47-JYE4]. For more detailed discussion of this history, see, Mark A Lemley, *The Myth of the Sole Inventor*, 110 MICH. L. REV. 709, 725–726 (2012).

[307] 329 U.S. 1 (1946). *See also General Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 368–74 (1938) (rejecting claim to lighting filament claimed in functional terms: "comparatively large grains of such size and contour as to prevent substantial sagging and offsetting"); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 133 (1948) (Frankfurter, J., concurring) (arguing that claims to groups of bacteria "not identified and identifiable only by their compatibility" should be rejected because similar efforts to claim by function in other areas are impermissible). Rejections of functional claims actually go back a century earlier, to 1840. *Wyeth v. Stone*, 30 F. Cas. 723 (C.C.D. Mass. 1840) (No. 18,107) (Story, J.).

[308] July 19, 1952, c. 950, 66 Stat. 798, Pub. L. 593:

An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

This has since been codified at 35 U.S.C. § 112(f).

flavor.[309] The patentee in *Ariad* wrote its claim in functional terms, seeking to cover any later-discovered drug that bound to an important inhibitory molecule in the inflammation pathway, NF-κB.[310] The Federal Circuit rejected such an attempt as "a vague functional description and an invitation for further research [that] does not constitute written disclosure of a specific inhibitor."[311] One could, perhaps, look at antibody claims and say something similar.[312]

But if that is the explanation, it presents a different irony than the one on structure. For many of the modern problems with functional claiming seem largely confined to the software realm. Most perniciously, functional claiming is frequently used by patent trolls who claim the idea of solving a problem but have never actually made a product, and who sue those who actually do solve the problem.[313] To date, at least, most antibody cases don't present similar worries—both because antibody patentees have almost invariably discovered and actually made new antibodies and because function can still be defined at a much lower level of abstraction.[314] Even if claims directed to binding to a particular antigen are like "ring[s] with a million keys on [them],"[315] that's still a significantly smaller subset than functional software claims, some of which are akin to claiming the very concept of "unlocking"—unlocking *anything*.[316] Despite this, the Federal Circuit has actually done relatively little to rein in functional claiming in software, where it is generally overbroad, is causing significant social harm,[317] and where the patentees who employ it add little

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[309] 598 F.3d 1336 (Fed. Cir. 2010) (en banc).

[310] *Id.* at 1340.

[311] *Id.* at 1356.

[312] But only by squinting quite a lot. The real problem in *Ariad* was gun-jumping. The patentee claimed the idea of solving a problem but hadn't actually come up with any drugs at all that solved it. Indeed, it took Ariad *thirty-one years* to get its first drug approved by FDA—decades after it filed its first patents on the technology at-issue. Julie M. Donnelly, *Ariad Wins Its First FDA approval—Leukemia Drug Iclusig*, BOSTON BUS. J. (Dec. 14, 2012), https://www.bizjournals.com/boston/news/2012/12/14/ariad-wins-first-fda-approval-for.html [https://perma.cc/CYC4-EVES]. That is very different from antibody patents where the patentee has a working antibody with particular epitopes and binding specificity (or, in many cases, dozens of such working examples) and uses those characteristics to define the invention.

[313] Lemley, *supra* note 8 at 908.

[314] To be clear, some of the early cases occasioning this shift do involve overclaiming. *See, e.g.*, Centocor Ortho Biotech, Inc. v. Abbott Laby's, 636 F.3d 1341 (Fed. Cir. 2011); Chiron Corp. v. Genentech, Inc., 363 F.3d 1247 (Fed. Cir. 2004). But the problem is not functional claiming; it's the effort to capture new technology never contemplated in the patent.

[315] *Centocor*, 636 F.3d at 1352.

[316] One of the challenges of regulating functional claiming in computer software is that software can be claimed at different levels of abstraction, and arguably software (as distinguished from computer hardware) is entirely about function even at the lowest level of implementation. Kevin Emerson Collins, *Patent Law's Functionality Malfunction and the Problem of Overbroad, Functional Software Patents*, 90 WASH. U. L. REV. 1399, 1440 (2013) (noting that software is "functional all the way down"). *Compare* Lemley, *supra* note 8, at 961 (arguing that courts can nonetheless usefully limit claims to own the result however it is achieved).

[317] Lemley, *supra* note 8.

social value.[318] Indeed, two 2022 decisions essentially endorse pure functional claiming in software, undermining *Williamson v. Citrix*.[319] But it has been hypervigilant in preventing functional claiming for antibodies—extending this vigilance even past the point of novelty in *Juno*.

With Dan Burk, one of the authors has argued that patent law is technology-specific, allowing the law to adapt to different technologies and market conditions.[320] The Federal Circuit periodically denies any such differences, even in the doctrines that most exhibit those differences—for example, antibodies and software.[321] But in stepping in to restrict functional claiming, the Federal Circuit seems to be not only creating technology-specific patent law, but is arguably doing it in a way that is "exactly backwards."[322]

C. The Law is Following Changes in the Science

A third possible explanation is that the change in the validity of functional antibody claims reflects changes in scientific knowledge about antibodies. On this theory, neither patent owners nor the law ever really intended to claim all possible antibodies that bound to a particular antigen. Rather, in the early days of antibody research, inventors did the best they could practically do in describing the valuable new thing they had discovered; the best they could do was to identify the antibody by defining an antibody as "the thing that attaches to this antigen we have identified."[323] The Federal Circuit allowed those claims, not because it intended to give ownership over a vast, poorly defined genus of molecules, but out of pragmatism. *Function* was the only practical touchstone researchers could use to describe a particular antibody that the patentee had in fact identified. As the science advanced, however, it became easier to identify the attributes of a given antibody in greater detail—its three-dimensional structure, the particular epitope to which it bound to the antigen, the specificity with which it bound, and so on. Those attributes were introduced into claims as they were discovered, further narrowing the particular antibodies an

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[318] *See* Lemley, *supra* note 8, at 962-963. To some extent the doctrine of patentable subject matter has stepped in to police functional software claims by treating them as an unpatentable abstract idea, as one of us (Lemley) warned might happen. *See, e.g.*, Alice Corp. v. CLS Bank Int'l, 573 U.S. 208 (2014). But the cases are all over the map, and many cases allow functional software claims under § 101. T. Vann Pearce, Jr. & Christopher Higgins, *The Effect of Alice and Its Progeny in 2020 on Software and 3D Printing Patents*, ORRICK, https://www.orrick.com/Articles/The-Effect-of-the-Alice-Decision-on-Software-and-3D-Printing-Patents [https://perma.cc/42BK-A9MG] (reviewing cases).

[319] Dyfan LLC v. Target Corp., No. 2021-1725 (Fed. Cir. Mar. 24, 2022) (holding that the mere use of the term "code" satisfied the requirement to show particular structure to implement a computer program); VDPP LLC v. VIZIO, Inc., No. 2021-2040, 2022 WL 885771 (Fed. Cir. Mar. 25, 2022) (same for "a storage").

[320] BURK & LEMLEY, *supra* note 296, at 49–65; Burk & Lemley, *supra* note 24, at 1589–1595.

[321] Ariad Pharma., Inc. v. Eli Lilly and Co., 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc).

[322] Burk & Lemley, *supra* note 296, at 692.

[323] See Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "'Written Description'" Requirement; Request for Comments, 64 Fed. Reg. 71427, 71439 (Dec. 21, 1999) (noting that "identifying characteristics" of an antigen "may be sufficient to show possession of the claimed invention to one of skill in the art").

inventor had identified. But now that researchers can routinely identify the underlying DNA sequence of a particular antibody, patent claims—under this account—should be limited accordingly.

This theory has the virtue of aligning the Federal Circuit's recent work in the area with its older cases. Defining antibody claims as narrowly as the science allows avoids the problem of broad genus claims of indeterminate scope. It narrows functional claiming to its smallest, practical, and specific factual circumstance while still allowing claims to be written in functional terms when necessary. It is analogous, perhaps, to how courts have historically treated product-by-process claims. Courts historically allowed claims that cover a chemical product to be written in the form of "the product produced by process *X*" when all that is known about the product is how it is made. Those claims traditionally covered the product as a whole, however made, but the Federal Circuit has more recently read them to cover the product only when made by that specific process.[324] There, too, courts might be responding to changes in the science, allowing a patentee to describe their claims by the manufacturing process when that was all they knew about the product, but narrowing claims as the science advanced and they could describe the product directly. Such a theory also offers an alternative to an outright reversal in Federal Circuit doctrine—an explanation of why the Federal Circuit might transition over time from allowing functional antibody claims to soundly rejecting them.

There's a problem with this theory, though: there's no indication that this is what the Federal Circuit thinks it's doing. To the contrary, the court's statements all suggest that it is concerned—and has always been concerned—with identifying molecular structure. Nothing has changed, at least according to Judge Lourie: "It has always been, or at least has been since the Patent Act of 1870, that a patent applicant must enable one's invention, whatever the invention is. . . . What is new today is not the law, but generic claims to biological materials that are not fully enabled. "[325]

Perhaps. But from that perspective, the shift is paradoxical: potentially broad antibody genus claims were permissible when we knew virtually nothing about the molecules, but the more we *learn* about them—including what to do with them—the less we can claim. This is this article's titular paradox and the opposite of how both the enablement and written description doctrines normally work.

This may mean that despite the enormous economic value of new antibodies there can no longer be a valid genus claim covering them. We know now that there is no simple relationship between the molecular structure of different antibodies capable of binding to the same epitope in similar ways, so claims covering functional outcomes will necessarily cover widely different gene sequences. On this story, the conceptual work of antigen identification and antibody discovery is but a first step—not the invention of a genus. Rather, the inventive act, today, is homing in on a specific, common genetic structure of practical use.

Nor are we likely to see structure-based antibody genus claims in the future. Antibodies are composed of *billions* of different proteins, more than the number of genes in the genome—*ten*

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[324] Abbott v. Sandoz, 566 F.3d 1282 (Fed. Cir. 2009) (en banc); Meurer & Nard, *supra* note 133, at 1975. For a history of this development, see Karshtedt, *supra* note 133, at 109.

[325] Amgen Inc. v. Sanofi, 850 F. App'x 794, 795 (2021) (Lourie, J., separate opinion).

million times over.[326] Pathbreaking innovation decades ago—like Köhler and Milstein's Nobel Prize winning work—allowed researchers simply to identify and produce antibodies *generally*. Pathbreaking biologics innovation today concerns sequencing and optimizing a single one.[327] And there is no clear relationship between the structure of any of those billions of proteins and the binding function they perform. There simply cannot be a valid claim to a structural genus under this theory. While the Federal Circuit (and Judge Lourie) have promised that claims directed to antibody genera are not dead if the patentee just discloses enough structural similarity, that promise has so far proven illusory. And as a matter of advancing science, there is good reason to think it will always be illusory.

D. The Drug Pricing Backlash

A fourth possible explanation for restricting antibody patents is grounded in the *realpolitik* of drug development. Wry-eyed court watchers may suggest that the Federal Circuit's doctrinal turn for antibody patents is in response to public ire over pharmaceutical patents and drug pricing.[328] Antibody therapies are, of course, enormously expensive. Humira, the world's best-selling antibody therapy, stickers for $77,586, per patient, every year—about a Tesla-and-a-half.[329] Globally, antibody therapies net their manufacturers about $157.33 billion per year.[330] And while the relationship between patents and prices for biologics is complex—especially given the fractured

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[326] *See* Iakes Ezkurdia et al., *Multiple Evidence Strands Suggest that There May Be as Few as 19,000 Human Protein-Coding Genes*, 23 HUMAN MOLECULAR GENETICS 5866, 5866 (2014).

[327] *See, e.g.*, Stefan Schreiber et al., *Physicochemical Analysis and Biological Characterization of FKB327 as a Biosimilar to Adalimumab*, 8 PHARMACOLOGY RESEARCH & PERSPECTIVES e00604, at *1 (2020) (comparing the sequence of Humira to a biosimilar of Humira in an prospective therapeutic assessment).

[328] The reports on the public's wrath over patents and drug-prices is leviathan. For but one recent example, see Patents Kill, https://www.patents-kill.org. *See also* GlaxoSmithKline LLC v. Teva Pharma. USA, Inc., 7 F.4th 1320, 1342 (Fed. Cir. 2021) (Prost, C.J., dissenting) (criticizing majority opinion for not encouraging generic access).

[329] *Compare* Committee on Oversight and Reform, U.S. House of Representatives, Drug Pricing Investigation: Abbvie—Humira and Imbruvica (2021), https://oversight.house.gov/sites/democrats.oversight.house.gov/files/Committee%20on%20Oversight%20and%20Reform%20-%20AbbVie%20Staff%20Report.pdf?_sm_au_=iVVQtWnMtkJWjk7QvMFckK0232C0F [https://perma.cc/3TWP-T9P7], *with $35,000 Tesla Model 3 Available Now*, TESLA, https://www.tesla.com/blog/35000-tesla-model-3-available-now [https://perma.cc/BD3E-NEY3].

[330] *Monoclonal Antibody Therapy Market Size, Analysis, Development, Revenue, Future Growth, Business Prospects and Forecast to 2027,* MARKETWATCH, https://www.marketwatch.com/press-release/monoclonal-antibody-therapy-market-size-analysis-development-revenue-future-growth-business-prospects-and-forecast-to-2027-2022-01-03 [https://perma.cc/C4T3-BF9L].

U.S. healthcare system[331]—patents are certainly a significant component in that equation.[332] The public has digested this information and turned its bile on drug manufacturers who are routinely vilified in the press and, increasingly, Capitol Hill.[333] It is difficult to imagine that the judges on the Federal Circuit—sitting two miles from the halls of Congress in a famously clubby town—have failed to notice.

There is no reason to think politics are driving the court's decision, though. The political story doesn't explain why the appellate court upholds some biologics patents but not others.[334] Nor is there an easy trendline between cost of antibody drugs (or profits reaped by their developers) and which franchises suffer invalidated patents. The anti-PCSK9 antibody therapies at issue in *Amgen v. Sanofi*—Repatha (evolucumab) and Praluent (alirocumab)—are cheap, all things considered.[335] But the Federal Circuit invalidated Amgen's claims regardless.[336] Humira, by contrast, is wildly expensive—and getting more expensive still—and its patents have largely been upheld.[337] Lastly, such a political explanation doesn't address why, of all provisions in the patent statute, the Federal Circuit chose to make its stand on § 112, the source of the written description and enablement requirements. Other sections, like obviousness under § 103 for example, are available in virtually every litigated antibody case; a court interested in burying outcome-focused decisions has much better and more surreptitious ways of doing so.

And such political explanations are a bit too thin—not so much a portrait of judicial realism but a landscape of judicial nihilism. For all our criticisms, the Federal Circuit seems *legitimately* troubled by the scope of antibody claims. Ignoring such realities entirely would better serve claims to judicial realism than grappling with them in case after case. And the court has not, traditionally at least, radically shifted patent doctrines on gross policy analyses, famously going out of its way,

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[331] Robin Feldman, *Perverse Incentives: Why Everyone Prefers High Drug Prices-Except for Those Who Pay the Bills*, 57 Harv. J. on Legis. 303 (2020).

[332] **Error! Hyperlink reference not valid.**Evidence from small molecule drugs suggests that prices decline 80-85% once several generics enter. Robin Feldman, *May Your Drug Price Be Evergreen*, 5 J.L. & BIOSCIENCES 590, 601 (2018).Biosimilars may occasion a smaller drop in price, given that they are harder to make and get approval for, but an unpatented antibody drug will undoubtedly cost a good deal less than a patented one. Victor L. Van de Wiele et al., *The Characteristics of Patents Impacting Availability of Biosimilars*, 40 NATURE BIOTECHNOLOGY 22 (2022).

[333] *See* Committee on Oversight and Reform, *supra* note 329.

[334] *Compare, e.g.*, Amgen Inc. v. Sanofi, , 987 F.3d 1080 (Fed. Cir. 2021) (invalidating Amgen's anti-PCSK9 antibody patent) *with* Eli Lilly & Co. v. Teva Pharma. Int'l GmbH, 8 F.4th 1331 (Fed. Cir. 2021) (upholding Teva's anti-CGRP antibody patents).

[335] Gregg C. Fonarow et al., *Updated Cost-Effectiveness Analysis of Evolocumab in Patients With Very High-Risk Atherosclerotic Cardiovascular Disease*, 4 JAMA CARDIOLOGY 691, 694 (2019) (concluding that "[a]t its current list price, the addition of evolocumab [Amgen's therapy] to standard background therapy meets accepted cost-effectiveness thresholds across a range of baseline [cardiovascular] event rates").

[336] Amgen Inc. v. Sanofi, 987 F.3d 1080 (Fed. 2021).

[337] *See* In re Humira Antitrust Litig., 465 F. Supp. 3d 811 (N.D. Ill. 2020) (noting that most Humira patents have survived challenges); Committee on Oversight and Reform, *supra* note 329.

instead, to deny such motivations from time to time.[338] If anything, rather, the court has a political reputation for *protecting* the patent system.[339] It would seem odd, therefore, that a political explanation for this doctrinal shift ends up destroying the some of the patent system's most valuable assets.

IV. RESOLVING THE PARADOX

Is the game up for antibody patents? Should it be? Envisioning a future for antibody patent claims requires a mix of theory and pragmatism, an understanding of what role, if any, genus claims will continue to play in antibody patenting, and an investigation into strategies about what to do next.

A. Do We Still Need Genus Antibody Claims?

Post-*Amgen* and *Juno*, it seems fair to say that the inventor of an antibody is limited to claiming only specific antibodies enumerated in the claims and disclosed in the specification as having a particular structure. More broadly, antibody patentees will be limited to *species* claims rather genera of antibodies with similar functions. The patent office still issues functional genus claims, but those claims are unlikely to survive in court. Recently, work by S. Sean Tu and Christopher M. Holman suggest that patentees are taking this lesson to heart; an increasing number of patents directed to antibodies are directed to individual species.[340] Some are definitely narrow—limited to particular CDR sequences of particular antibodies.[341] Others attempt to create narrow genus claims out of a specified group of CDR sequences.[342]

Is that truly a problem? It's unclear. Perhaps we have now reached the point where antibody innovation—at least, creating new antibodies from specific antigens—is more routine and, consequently, does not need broad, functional patent protection. If so, such a shift in patenting strategy seems to be a routine development in many fields. It is often the case that early innovations get broad patents because they are opening up a new field and there is not much prior art to

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[338] *See, e.g.*, Ass'n Molecular Pathology v. USPTO, 689 F.3d 1303 (Fed. Cir. 2012) ("[I]t is important to state what this appeal is not about. . . . [It] is not about, that patents on life-saving material and processes, involving large amounts of risky investment, would seem to be precisely the types of subject matter that should be subject to the incentives of exclusive rights."). More broadly, one early study found no connection between the political affiliations of Federal Circuit judges and how they vote on patent cases. John R. Allison & Mark A. Lemley, *How Federal Circuit Judges Vote in Patent Cases*, 27 FLA. STATE UNIV. L. REV. 745, 745 (2000).

[339] JORGE L. CONTRERAS, THE GENOME DEFENSE 215 (2021) (noting the Federal Circuit's "pro-patent" reputation).

[340] S. Sean Tu & Christopher M. Holman, *Technology Changes Drive Legal Changes for Antibody Patents: What Patent Examiners Can Teach Courts About the Written Description and Enablement Requirements* (forthcoming 2022) (manuscript at 24–27).

[341] *Id.*

[342] *Id.* at 22–24.

constrain them.[343] The law used to speak of such patents as "pioneering" and therefore entitled to broad scope, especially in the old days of central rather than peripheral claiming.[344] But as a field of research matures, it gets more crowded and the inventions get more incremental. It therefore makes sense that claims should be constrained accordingly.

Perhaps something analogous is going on with antibodies. As the science matures, improvements—even the discovery of new antibodies—become less of a pioneering act and more a humdrum extension of ordinary innovation; narrower patents are accordingly appropriate, too. And there are also efforts to adopt a commons model—notably the Structural Genomics Consortium—to antibody-antigen identification.[345] If so, the Federal Circuit's change in policy might be a good thing. Antibody treatments are notoriously expensive, and anything that increases competition seems beneficial. The complexities surrounding biosimilars notwithstanding,[346] eliminating antibody genus patents will allow noninfringing alternatives—namely, antibody therapies that bind to the same antigen, but have different structures. In *Amgen*, for example, Amgen's and Sanofi's anti-PCSK9 antibodies are not structurally identical, but they bind to the

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[343] *See, e.g.*, Jacob S. Sherkow, *Law, History and Lessons in the CRISPR Patent Conflict*, 33 NATURE BIOTECHNOLOGY 256, 256–257 (2015) (describing this for several biotechnological inventions); Samantha Zyontz & Cassidy Pomeroy-Carter, *Mapping of the Research, Innovation and Diffusion Activity of CRISPR Across Countries* (2021) (describing this in the context of genome editing technologies).

[344] For discussion of the pioneer patents doctrine, see, e.g., *Miller v. Eagle Mfg. Co.*, 151 U.S. 186, 207 (1894) ("If the invention is broad or primary in its character, the range of equivalents will be correspondingly broad, under the liberal construction which the courts give to such inventions."); *Perkin-Elmer Corp. v. Westinghouse Elec. Corp.*, 822 F.2d 1528, 1532 (Fed. Cir. 1987) ("A pioneer invention is entitled to a broad range of equivalents."); Meurer & Nard, *supra* note 133, at 2004 (arguing that pioneer inventions are deserving of greater protections because of the inherent difficulty of anticipating how a uniquely new invention might be imitated); John R. Thomas, *The Question Concerning Patent Law and Pioneer Inventions*, 10 HIGH TECH. L.J. 35, 37 (1995) ("Courts construe pioneer patent claims . . . to encompass a broader range of so-called 'equivalents' during an infringement determination."). *But see* Brian J. Love, *Interring the Pioneer Invention Doctrine*, 90 N.C. L. REV. 379 (2012) (arguing that most "pioneering" inventions are in fact merely improvements). The Court of Customs and Patent Appeals, the predecessor to the Federal Circuit, applied the pioneer patent doctrine. *See Autogiro Co. v. United States*, 384 F.2d 391, 400–01 (Ct. Cl. 1967). And the Supreme Court continues to talk about patent scope under the doctrine of equivalents as a function of how pioneering the patent is. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.,* 520 U.S. 17, 27 n.4 (1997).

In fact, however, the pioneer patents doctrine made sense in a world of central or signpost claiming, where the patent identified the thing the patentee had built. It makes less sense in the modern world of peripheral or fencepost claiming, because the point of the claim is to define the breadth of the legal right. Burk & Lemley, *supra* note 22, at 1745; Lemley, *supra* note 8, at 910.

[345] *See, e.g.*, SGC | Structural Genomics Research Consortium, https://www.thesgc.org.

[346] Price & Rai, *supra* note 7, at 1026.

same antigen and compete in the same market for lowering persistently high cholesterol. That competition can lower prices, which is a good thing.[347]

But we're skeptical of the more general claim that we no longer need effective patent protection for antibodies—or, more narrowly, that the means to invalidating antibody claims under § 112 is the right move. First, the fact that we know more about antibodies generally, or even can routinely create some of them from known antigens, doesn't mean we have anything close to a systematic way of generating antibodies with particular characteristics—and therapeutic effect—from scratch. Even in 2020, a systematic review of the computational antibody design compared the technique to "arduous experimental approaches that are the current standard in antibody discovery."[348] To the contrary, what we've learned is that different structures may produce similar effects, and vice versa. We know more about the antibodies we make, but that doesn't mean making them has become routine. Generating effective, high-affinity, high-specificity, therapeutically tolerable, scalable, soluble, non-immunogenic antibodies remains a challenge.[349] And failures still abound. Biogen's recent efforts to develop antibodies that target an Alzheimer's-related protein have been not just a dud but the subject of mockery.[350] There is still good reason to encourage investment in the task of identifying new antibodies, even with the regulatory protections associated with developing new biologics, as seen in *Amgen v. Sanofi* and the development of anti-PCSK9 antibodies. Species patents that turn out to be easy to evade may not encourage that investment.

Second, while at least some diagnostic antibodies have been around for decades, the move into the more promising—and lucrative—field of therapeutics is much newer. The hurdles to FDA approval for antibody therapies remain, despite major successes, stubbornly high with failure still routine.[351] This suggests we are far from the point of diminishing returns of encouraging investment in antibody innovation. Even if antibody generation from a known antigen is much simpler today than it was, say, in 1984 (when Chiron first applied for patents covering its antibody), that doesn't mean getting such a therapy across FDA's finish line has gotten substantially easier.[352] Instead, broader patents covering multiple embodiments likely give larger pharmaceutical

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[347] Ned Pagliarulo & Jacob Bell, *Amgen Cuts US Repatha Price 60% Amid Market Pressure*, BIOPHARMA DIVE (Oct. 24, 2018), https://www.biopharmadive.com/news/amgen-cuts-us-repatha-price-60-amid-market-pressure/540517/ [https://perma.cc/3VY6-B46X].

[348] Richard A. Norman et al., *Computational Approaches to Therapeutic Antibody Design: Established Methods and Emerging Trends*, 21 BRIEFINGS IN BIOINFORMATICS 1549, 1549 (2020).

[349] *Id.*

[350] And perhaps rightfully so. *See* Adam Feuerstein and Damian Garde, *Biogen's Reckoning: How the Aduhelm Debacle Pushed a Troubled Company and Its Fractured Leadership to the Brink*, STAT NEWS (Dec. 8, 2021), https://www.statnews.com/2021/12/08/biogen-aduhelm-al-sandrock-michel-vounatsos-company-reckoning/ [https://perma.cc/9WGH-JGQS].

[351] *See, e.g., id.*

[352] Angelika Batta, Bhupinder Singh Kalra & Raj Khirasaria, *Trends in FDA Drug Approvals Over Last 2 Decades: An Observational Study*, 9 J. FAMILY MED. & PRIMARY CARE 105, 105 (2020) (noting that the approval rate for biologics—while increasing—remains under 20%).

developers some solace that they'll have the time (and exclusivity) to optimize antibody candidates.[353] Narrowing claiming strategies to only a few embodiments of an early-stage antibody molecule may cause some to abandon the race. And it's not obvious that a patent limited to the particular species the inventor discovered will necessarily provide effective protection.[354] Advances in antibody science now make it significantly easier to evade species claims by using a structurally different antibody with similar if not identical effects.

At the same time, there are good reasons to worry about pure functional claiming because it forecloses not just easy equivalents but potentially very different antibodies that might have different practical—and therapeutically important—effects. Enbrel, Humira, and Remicade all target the same antigen, for example, but have different indications.[355] And the substitution of humanized for murine antibodies in *Chiron v. Genentech*, for example, was a radical improvement that eliminated serious health risks and introduced a new technology that rapidly became the industry standard.[356] Claims that are too broad—even if a good incentive to encourage such work—would allow such patentees to control dramatic improvements to therapies directed to the same antigens.

So: do we still need antibody genus claims? We think so. Genus claims encourage the broad ranging research needed for antibody development, "prevent[ing] competitors from capturing the benefit of an invention while avoiding infringement by making a minor change to one aspect of it."[357] Given the uncertain—and costly road—from antigen identification to therapeutic development, companies that develop new therapeutic antibodies need some form of effective protection. But expansive functional claims to "newly discovered antigens" or simple recitations to antibodies affinity, without more, are another matter.

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[353] Importantly, this additional time need not come from patents; it could just as well come from regulatory exclusivities. *See, e.g.*, Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 348 (2007) ("Indeed, as the role of the patent system in drug development has become more complex and ambiguous, drug regulation has become an increasingly important source of market exclusivity for innovating firms."); John R. Thomas, *The End of "Patent Medicines"? Thoughts on the Rise of Regulatory Exclusivities*, 70 FOOD & DRUG L.J. 39, 39 (2015) ("From the perspective of brand-name firms, exclusivities have always been superior to patents in view of ease of enforcement and effective lack of contestability.").

[354] *See* Robert A. Bohrer, *It's the Antigen, Stupid: A Risk/Reward Approach to the Problem of Orphan Drug Act Exclusivity for Monoclonal Antibody Therapeutics*, 5 COLUM. SCI. & TECH. L. REV. 1, 17 (2003) (making this point in the context of FDA exclusivities).

[355] Palladino et al., *supra* note 72, at 736.

[356] *See* Tu & Holman, *supra* note 337.

[357] Karshtedt, Lemley & Seymore, *supra* note 13, at 3.

B. Practical Alternatives to Functional Antibody Claims

Perhaps there is a middle ground in patent law—a way to get some of the benefits of genus claims for antibodies even in a world where the Federal Circuit is unlikely to uphold them.[358] One solution—sequence "homology" or "structure-plus" claims tried in other areas of biotechnology—is unlikely to work for antibodies because broad changes in genetic structure are likely to affect their function.[359] Means-plus-function claiming is another possibility, depending on how broadly the courts apply it. Lastly, patentees could rely on the doctrine of equivalents, an alternative theory of patent infringement, to expand species claims, a possibility that—perhaps oddly—best parallels the science of antibodies.

1. Sequence Homology and "Structure-Plus" Claims

One possible way to salvage antibody genus claims would be to add enough structural elements to traditional functional antibody claims to overcome the hurdles imposed by *Amgen* and *Juno*. This could include, for example, identifying both some structure of a given antibody and its epitope or affinity, for instance.[360] Tu and Holman provide some evidence of this occurring—claims directed to a combination of function and *some* sequence to the claimed antibodies' CDRs.[361] The problem, however, is that because there's not a direct relationship between structure and functional binding characteristics, such a strategy wouldn't create a genuinely broad genus claim, only a loose subset of particular antibody species the patentee has identified. Other antibodies with the same binding characteristics but slight variations in CDR sequences would likely escape infringement just as if the claim were purely structural. And many chemicals included in the genus wouldn't function as antibodies, creating a potential enablement problem as well.

Nor is adding sequence homology to the full antibody sequence—a limitation that includes a "percent match" to an antibody's DNA sequence—likely to be effective.[362] First, we don't know whether other similarly binding antibodies will have mostly the same sequence structure as the claimed one—and indeed, given the science surrounding antibody diversity, we can virtually guarantee otherwise.[363] Homology claims for antibodies might be easy to evade. And in any event, it's not even clear sequence homology claims would avoid condemnation in the Federal Circuit's war on genus claims. The Federal Circuit has been invalidating claims to chemical genera coupled with functional limitations because the court—wrongly, in our view—requires the patentee to

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[358] At this writing it is also possible that the Supreme Court will intervene to restore life science genus claims more generally, though it is less likely that they will rule in favor of functional claims in particular.

[359] Holman, *supra* note 127, at 65-68 (noting problems with this approach historically); Tu & Holman, *supra* note 340, at 36-38 (noting problems with this approach today).

[360] Tu & Holman, *supra* note 340, at 24–26.

[361] *Id.*

[362] Holman, *supra* note 127, at 65-68.

[363] *See supra* notes 36–48 and accompanying text.

describe and enable the "full scope" of the claimed genus.[364] The court today interprets this to mean that patentees must disclose, for all species in a claimed genus, which ones will perform a given function and which ones won't—an impossibility for antibodies and indeed for most chemical genera.[365] A variation on this, functional claims to an antibody coupled with a method of treatment limitation, are likely to face the same fate.[366] Adding one function to another doesn't seem to avoid the "full scope" problem that has invalidated almost all life science genus claims in the last two decades.

Perhaps patentees in other life science areas outside antibodies can save their genus claims if they take the functional elements *out* of their claims, replacing them with purely structure limitations, e.g., a claim simply to "Genus *Q*," with no mention of other functional limitations like efficacy or achieving a particular result. That would be an odd result if it worked; the Federal Circuit would be holding that *narrower* claims (i.e., those with functional limitations) require *more* proof on enablement and written description than broad claims that encompass any use of the genus. But even if such a strategy works elsewhere in the chemical industries, it is unlikely to work for antibodies, a science where the relationship between structure and function is weak or nonexistent.

2. Means-Plus-Function Claiming and the Doctrine of Equivalents

The key to saving some antibody genus claims, rather, may lie in how Congress actually treated functional claiming when it passed the Patent Act of 1952. Patent owners a century ago often wrote claims in purely functional terms.[367] After permitting those claims for a period of time, particularly for pioneering inventions, the Supreme Court cracked down on them in the 1940s, prohibiting the use of functional language as a substitute for a specific definition of the invention at the point of novelty.[368] In *Halliburton Oil Well Cementing Co. v. Walker*, the Supreme Court invalidated a patent claiming a resonator added to gas tubing that doubled as a "tuned acoustical means which performs the functions of a sound filter"—a functional effect.[369]

Congress reversed *Halliburton* in the 1952 Patent Act by explicitly allowing "means-plus-function" claims—claims that that used functional language when coupled with a means of

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[364] Karshtedt, Lemley & Seymore, *supra* note 20, at 49–50.

[365] *Id.*

[366] Tu & Holman, *supra* note 340, at 43–44.

[367] *See supra* notes 305–314 and accompanying text.

[368] Halliburton Oil Well Cementing Co. v. Walker, 329 U.S. 1 (1946). The Court held that the patent claim was indefinite because it did not specify how the patent performed the function or limited the invention to the particular means the patentee actually invented. Substituting broad functional language at the very point of novelty, the Court said, did not sufficiently put the world on notice of what the patentee was removing from the world.

[369] *Id.* at 7.

achieving the result.[370] This was so even if the means was the only novel part of the invention.[371] The new statute, then § 112 ¶ 6, did not simply permit unfettered functional claiming, however. Instead, § 112 ¶ 6 provides:

> An element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.[372]

This new means-plus-function claiming represented a significant departure from the normal rules of patent claim construction. Patent claim construction starts with the plain meaning of the claim language. While the description of the invention can be read to help understand what the claims mean, the fundamental rule of patent claim construction is that the claim terms are not to be limited to what the patentee actually invented or described.[373] A patentee can, for example, claim a group of chemicals without having described, much less tested, all or even very many of the chemicals in the group. That's why a patent claim to an antibody that binds to a specific antigen in a specific way will literally cover *any* antibody that does so, even if it isn't one the patentee discovered and even if it structurally looks quite different than the one the patentee disclosed.

Against this backdrop, § 112 ¶ 6 (now recodified as § 112(f)) actually represents a significant narrowing of claim scope. While the 1952 Act rejected *Halliburton* and permitted functional claiming, the sort of functional claiming the statutory text allows is far different than the functional claiming that was the norm in 1940. A means-plus-function claim element is not interpreted to cover every means of performing the function. Instead, the courts apply a different rule of claim construction, limiting the scope of these claims to only those disclosed in the patent's specification and equivalents thereof.[374] To take an example, suppose that a patent claim includes, as an element, a "means for processing data."[375] Read literally, without reference to § 112(f), this language would encompass any possible means for processing data, including any computer, but also a calculator, an abacus, pencil and paper, and perhaps even the human mind. Section 112(f) limits the scope of this claim to the particular "means for processing data" actually described in the patent specification—say, an iPad—and, importantly, "equivalents thereof."[376]

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370 *See* July 19, 1952, c. 950, 66 Stat. 798, Pub. L. 593 (now codified at 35 U.S.C. § 112(f)).

371 *See* In re Swinehart, 439 F.2d 210, 212–13 (C.C.P.A. 1971) ("there is nothing intrinsically wrong with defining something by what it does rather than what it is in drafting patent claims."); *see also In re Schreiber*, 128 F.3d 1473 (Fed. Cir. 1997) (relying on the *Swinehart* holding).

372 35 U.S.C. § 112(f) (2012).

373 *See, e.g.,* Becton, Dickinson & Co. v. Tyco Healthcare Group, 616 F.3d 1249, 1253–57 (Fed. Cir. 2010); E.I. du Pont de Nemours & Co. v. Phillips Petroleum, 849 F.2d 1430, 1433 (Fed. Cir. 1988).

374 *See* In re Hyatt, 708 F.2d 712, 713–14 (Fed. Cir. 1983).

375 Another limit on means-plus-function claiming is that it must occur in a combination of elements. "Single means" claims are invalid. *See id.*at 714. If there is more than one element, however, each of the elements can itself be a means-plus-function claim.

376 See, e.g., In re Donaldson Co., 16 F.3d 1189, 1193–94 (Fed. Cir. 1994) (en banc).

For antibodies, the means-plus-function claim format offers an intriguing intermediate possibility between pure functional claims and narrow species claims. If a patent owner claims "means for binding to antigen *X*," that claim would presumably not be invalid under the Federal Circuit's current written description or enablement precedents because it would be interpreted to cover only those means for binding to antigen x that are disclosed in the patent *plus* other means that are equivalent to the ones disclosed.[377] This means such a claim would satisfy written description because it would not "cover an enormous number (millions of billions) of . . . candidates"—only those disclosed in the specification.[378] Nor—in theory—would it suffer from a lack of enablement; if a PHOSITA could make or use the disclosed embodiments, that is all they would need, even though the claim will extend to equivalents.[379] Some but not all antibody claims may meet this current standard, and it would be straightforward to draft antibody claims that intentionally invoked the means-plus-function statute.

The ultimate question, though—equal parts science, philosophy, and claim construction—is, what antibodies are "equivalent" to the ones the inventor disclosed? The formulation typically used for such assessments is not terribly helpful: two limitations are equivalent if the differences between them are "insubstantial."[380] But other tests offer more helpful guidance. Equivalence is normally found when the accused product performs "substantially the same function in substantially the same way to achieve the same result."[381] Some courts even speak of "known interchangeability" between the products.[382] The traditional doctrine of equivalents expressly encompasses later-developed equivalents, which is likely to include most cases of structurally different antibodies with identical functions.[383] Even with massive structural differences between

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[377] The use of the phrase "means for doing x" is standard, but is not required to invoke 112(f). Rather, the question is whether the claim element discloses the function without disclosing structure or material that performs that function. The use of "nonce words" like "module" can also trigger 112(f). Williamson v. Citrix Online LLC, 792 F.3d 1339, 1350 (Fed. Cir. 2015).

[378] Juno Therapeutics, Inc. v. Kite Pharma, Inc., , 10 F.4th 1330, 1336 (2021).

[379] *See* 35 U.S.C. § 112(a) (requiring a patentee to enable a PHOSITA to "make and use" the invention).

[380] Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co., 520 U.S. 17, 39–40 (1997).

[381] *Id.* at 35. Strictly speaking, after *Warner-Jenkinson*, equivalents is tested not by reference to the patent claims as a whole but element by element; each element must be present literally or by equivalents in the accused product. *Id.* at 29–30. That difference is unlikely to matter much in antibody cases, which, unlike mechanical inventions, are not usually claimed in multi-element format.

[382] *Id.* at 36. Strictly speaking, the embodiments disclosed in the specification and equivalents thereof are *literally* infringing a means-plus-function patent claim, per § 112(f). There is a separate "doctrine of equivalents" that applies on top of this literal infringement analysis. For means-plus-function claim terms, though, it primarily applies in two circumstances: (1) where the function as opposed to the structure is similar but not identical, and (2) where the alleged equivalent did not exist at the time the patent issued. Chiuminatta Concrete Concepts, Inc. v. Cardinal Industries, Inc., 145 F.3d 1303, 1307–1308 (Fed. Cir. 1998); Mark A. Lemley, *The Changing Meaning of Patent Claim Terms*, 104 MICH. L. REV. 101, 109 (2005) (noting the cases setting the time at which equivalents is judged under means-plus-function claiming).

[383] *See* Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 731–732 (2002). Means-plus-function equivalence *also* encompasses those later-developed technologies by applying the traditional

them, two antibodies that bind to the same epitope with the same binding affinity and avidity certainly seem to perform substantially the same function in substantially the same way and, presumably, achieve the same result. [384] Thus, an antibody claim written in means-plus-function format should cover other antibodies that achieve the same function even if they are structurally quite different. The structural differences likely don't matter to the function-way-result test, and they avoid the invalidity problems that plagued *Amgen* and *Juno*.[385]

At the same time, such claims are not as broad as the court in those cases feared: antibodies that bind to a different epitope, or do so with different binding characteristics, likely don't work in substantially the same way and so would not be infringing. Interestingly, this is true even if the two antibodies are structurally similar. Thus, equivalents in means-plus-function claiming offers the possibility of antibody claims that are not so broad as to fail the Federal Circuit's new test but sufficiently broad to capture different antibodies that share their functional characteristics.

For this strategy to work, however, the patentee must write claims in means-plus-function format—something that has yet to become popular among patentees.[386] Notably, it appears absent

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doctrine of equivalents on top of the equivalent structures that the law views as literally infringing, creating the possibility of an equivalent (under the doctrine of equivalents) to an equivalent (under § 112(f)). *Chiuminatta*, 145 F.3d at 1307–1308; *see also* Note, John N. Kandara, *Application of the Doctrine of Equivalents to Means Plus Function Claims:* Wms Gaming Inc. v. International Game Technology, 50 DUKE L.J. 887, 916 (2000). Yes, we know that's needlessly confusing and makes no sense. We didn't write the law.

[384] Too broad? Narrowing doctrines, if one is so inclined, include the rules of prosecution history estoppel (preventing a patentee from using the doctrine of equivalents to broaden a claim they narrowed during prosecution), see *Festo*, 535 U.S. at 731; vitiation (preventing the patentee from using the doctrine to ignore a claim limitation altogether), see Cadence Pharmaceuticals Inc. v. Exela PharmSci Inc., 780 F.3d 1364, 1371–1372 (Fed. Cir. 2015); and ensnarement, a ban on expanding claims to cover things in the prior art, see Wilson Sporting Goods Co. v. David Geoffrey & Assoc., 904 F.2d 677, 683 (Fed.Cir.1990).

[385] Holman and Tu suggest using a different doctrine – the reverse doctrine of equivalents – to achieve balance in antibody genus claims. Holman & Tu, *supra* note __. But the reverse doctrine of equivalents applies only if the patent claim is valid and literally infringed, and that is unlikely to be true of genus claims.

[386] For decades patent prosecutors have been discouraging the use of means-plus-function claims because they feared they were too limiting. *See, e.g.,* Note, *Everlasting Software*, 125 HARV. L. REV. 1454, 1460 n.38 (2012) ("[P]atent attorneys often avoid means-plus-function claiming . . . ."). Dennis Crouch finds that the number of claims with "means for" language has declined from 24% in 2001 to only 7% today. Dennis Crouch, *Means Plus Function Claiming*, PATENTLY-O, (Jan. 14, 2013), http://www.patentlyo.com/patent/2013/01/means-plus-function-claiming.html. And that overstates their use, since most of these claims are in patents that also include other claims without that language. For a discussion of the specifics of means-plus-function claiming in software, see Sebastian Zimmeck, *Use of Functional Claim Elements for Patenting Computer Programs*, 12 J. HIGH TECH. L. 168 (2011). Litigators too viewed them as narrower than other alternatives. *See, e.g.,* Ronald L. Lacy et al., *Crafting the Claims*, *in* ELECTRONIC AND SOFTWARE PATENTS: LAW AND PRACTICE (PLI 2d ed. 2011) ("Like method claims, apparatus claims may be afforded a broader scope of interpretation than means-plus-function claims. The apparatus claim is interpreted in light of the specification, but not under Section 112[f]"); Michael A. Molano & Graham (Gray) M. Buccigross, *Traps for the Unwary: Issues Surrounding Means-Plus-Function Claims in the Software Context*, *in* FUNDAMENTALS OF PATENT PROSECUTION 2011: A BOOT CAMP FOR CLAIM DRAFTING AND AMENDMENT WRITING (Practising Law Institute 2011); Ryan Sharp, *Can Beauregard*

from the most recent empirical assessments of antibody claiming practices.[387] We strongly suggest, given the state of the Federal Circuit's jurisprudence, that patentees begin to think about doing so when filing new antibody patents.

But what about existing claims, most of which lack a claim that expressly invokes that format? A possible alternative is to assert a species claim that covers the structure as well as the function of the antibody. As Holman and Tu show, recent patentees are much more likely to have included species claims to particular antibodies as a backstop, at least once it became easy to identify structure.[388] While that claim will not be literally infringed by a different antibody, it may be infringed under the traditional equitable doctrine of equivalents. That doctrine applies the same basic tripartite "function-way-result" test that courts use for means-plus-function claiming, with some differences that broaden its reach and some that narrow it.[389] The traditional doctrine of equivalents also expressly encompasses later-developed equivalents, which is likely to include most cases of structurally different antibodies with identical functions.[390]

What if a patentee just wrote its original claim in the functional format the Federal Circuit used to accept but no longer does? Those older claims face a tougher road, but it might be possible to read a truly functional antibody claim as a means-plus-function claim precisely because it doesn't have structure, at least as the Federal Circuit has redefined that requirement (structure of the antibody rather than the antigen).

3. Policy Implications

Arguably the intermediate scope means-plus-function claiming and the doctrine of equivalents offer is a good result. It permits patent owners to prevent (or profit from) the development of competing technologies that do the same thing or make only trivial improvements. But it also leaves open the possibility of someone else identifying a different antibody that works

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Claims Show You the Money?, 2 CYBARIS: INTELL. PROP. L. REV. 25, 34 (2011) ("[I]t is well known that means-plus-function claims are narrowly construed . . . .") http:// web.wmitchell.edu/cybaris/wp-content/uploads/2011/08/Sharp.pdf; Rudolph P. Hofmann, Jr. & Edward P. Heller, III, *The Rosetta Stone for the Doctrines of Means-Plus-Function Patent Claims*, 23 RUTGERS COMP. & TECH. L.J. 227, 231 (1997) ("Thus, while general claims enjoy a scope as broad as their unambiguous claim language permits, means-plus-function claims are given a different, more limited treatment."). For a dissenting view, see Gregory J. Maier & Bradley D. Lytle, *The Strategic Use of Means-Plus-Function Claims*, 80 J. PATENT & TRADEMARK OFF. SOC'Y 241 (1998); Zimmeck, *supra* note 386, at 228–29 (arguing that means-plus-function claims can be broader than corresponding apparatus claims that disclose structure). But in the modern world since the death of the genus claim, that narrowness may well be the signal virtue of means-plus-function claims.

387 *See generally* Tu & Holman, *supra* note 337 (failing to find such examples).

388 *Id.* at 24–26.

389 Mark A. Lemley, *The Economics of Improvement in Intellectual Property Law*, 75 TEX. L. REV. 989 1005–1007 (1997). Some of this assessment may turn on factual questions about the economic value of given improvements, if any. *Id.*

390 *See supra* notes 383–384 and accompanying text.

in a different way, binding to the antigen at a different site or doing so more effectively—important considerations in antibody development.

We recognize such a claim isn't likely to fully satisfy patent owners used to owning functional antibody genera. Nor is it likely to satisfy challengers who want to be able to sell different molecules that happen to work just like the patented one. But the imperfect competition means-plus-function claiming offers may be as close as we can get to the social optimum in the patent system, at least for antibody claims. It gives patentees some security against the risk of near-perfect substitution, allowing them to recoup their considerable investment. It would prevent broad, functional claims on antibody technologies arising from accidental discoveries or basic research, while tailoring such rights to those more likely to require substantial invest and actual reductions to practice. And certainly it gives patentees more security than the current law does, especially after *Amgen* and *Juno*. But it also has the added virtue of giving challengers an incentive to find new—and, hopefully better—antibodies with different characteristics, balancing incentives for initial inventors against incentives for improvers.[391]

This intermediate level of protection is crucial, in our estimation, for non-therapeutic antibody technologies, often overlooked in discussions surrounding innovation policy. There are a host of possible innovation incentives for therapeutic antibody developers that don't include the blunt instrument of patent protection, such as trade secrecy and regulatory exclusivities provided by FDA.[392] So some might argue that we don't need strong patents at all for those therapeutics.

Unlike their therapeutic brethren, non-therapeutic antibodies—such as those used for diagnostics or research tools—are not protected by any regulatory exclusivities arising out of medicine approval bodies, such as FDA or the European Medicines Agency.[393] Without such protections, copying, as evinced by allegations in a small but increasing spate of patent infringement cases, appears to be an ongoing concern.[394] But the patents in some of these suits are wildly overbroad and subject to invalidation.[395] Means-plus-function claiming seems to strike the

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[391] *See* Lemley, *supra* note 389, at 996-997 (explaining this balancing act).

[392] A substantial literature considers whether and to what extent we need patents in the life sciences industry at all given the robust non-patent exclusivities the law provides, including 12 years of data exclusivity for biologics. John R. Thomas, *The End of "Patent Medicines"? Thoughts on the Rise of Regulatory Exclusivities,* 70 FOOD & DRUG L.J. 39-53 (2015); Rebecca S. Eisenberg, *Patents and Regulatory Exclusivity*, in OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY (2012); Daniel Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. 303 (2013); Mark A. Lemley, Lisa Larrimore Ouellette, & Rachel Sachs, *The Medicare Innovation Subsidy*, 95 N.Y.U. L. REV. 75 (2020). We don't delve further into that debate.

[393] Yaniv Heled, *Regulatory Competitive Shelters in the Area of Personalized Medicine*, 21 B.U. J. SCI. & TECH. L. 287, 288–293 (2015).

[394] *See, e.g.*, Athena Diagnostics, Inc. v. Mayo Collaborative Servs., 915 F.3d 743 (Fed. Cir. 2019) (alleging copying of anti-MuSK antibody diagnostic); Cedars Sinai Medical Ctr. v. Quest Diagnostic Inc., No. 17-cv-5169, 2019 WL 12521480 (C.D. Cal. Aug. 9, 2019) (alleging copying of anti-Cdtb antibody diagnostic); Cleveland Clinic Foundation v. True Health Diagnostics, Case No. 1:17-cv-198, 2017 WL 3381976 (E.D. Va. Aug. 4, 2017) (alleging copying of anti-JUL-1 antibody diagnostic).

[395] *E.g.*, *Athena*, 915 F.3d at 746.

balance of rewarding innovators for what they actually invented while protecting them only against trivial—but not significant—substitutions, without requiring the complexity of having such policy considerations interact with the regulatory system.

But even where regulatory exclusivities are concerned, as they are with therapeutic antibodies under the Biologics Price, Competition, and Innovation Act (BPCIA), we think there is value in this means-plus-function approach. The BPCIA does not provide any regulatory exclusivities for innovators against others using the same antibody target—only against the *same* antibody used as biosimilar. And oftentimes, as with *anti-PCSK9 Patent Infringement*, accused infringers are *not* accused of directly copying a patent holder's technology. Means-plus-function claiming wouldallow innovators of antibody therapies to guard against trivial improvements to their technology, while limiting control over later-developed improvements. Such an approach seems to best tailor patents' rewards to what was actually invented, while allowing—if not encouraging—diversity in the market.

Finally, this intermediate scope framework may turn out to be helpful beyond antibody claims. Other biologics patents are sometimes also written in functional form.[396] And even non-functional genus claims in the more traditional pharmaceutical industry are at risk under the full scope enablement and written description approaches.[397] Means-plus-function claiming may offer alternative claims of intermediate scope that are more appropriate than either broad functional claiming or the rejection of all genus claims.

CONCLUSION

Antibodies constitute a staggering $145 billion annual market—an amount projected to almost double by 2026.[398] Consequently, patents covering antibodies are among the most valuable in the patent system. But antibody patents are being struck down left and right, victims of the Federal Circuit's recent shift to tighten two doctrinal areas of patent law—enablement and the written description requirement. For each, the Federal Circuit has heightened requirements that patentees disclose or teach how to make and use the "full scope" of their inventions.

There are good reasons to be skeptical of the Federal Circuit's attack on genus claims in chemistry generally. But it seems to be a particular problem for antibodies. Applying the Federal Circuit's reinvigorated written description and enablement requirements to antibodies and their chemical structure fits poorly with the science underlying the molecules themselves. Immune receptor production—a semi-random and galactically expansive process—produces antibodies that are startingly different in both structure and function. There is no way to write functional genus claims to antibodies that satisfy the court's current tests. The science simply doesn't allow it. At the same time, this change in the Federal Circuit's jurisprudence is a legitimate reaction to some

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[396] Humira and Opdivo patent portfolios.

[397] Karshtedt, Lemley, & Seymore, *supra* note __.

[398] *Global Antibodies Market Size, Share, Trends, COVID-19 Impact & Growth Analysis Report – Segmented By Product Type, Indication, End User, Application and Region - Industry Forecast (2021 to 2026)*, MARKET DATA FORECAST, https://www.marketdataforecast.com/market-reports/antibodies-market [https://perma.cc/7DM3-JATH].

of the problems with the long-standing (and long-permitted) practice of claiming antibodies in functional terms. Functional claiming can lead to overbroad patents that stifle future innovation, as it has done in the software industries. Perhaps the Federal Circuit is wary of a similar result in biotechnology.

Fortunately, we think there is a middle ground—a new (or, really, quite old) form of patent claim drafting that gives inventors effective control over true substitutes without giving them the power to block real improvements: means-plus-function claims and infringement by the equivalents. Those doctrines limit patentees to claiming only the specific structural features of antibodies they both possessed and described, but also entitle them to assert their patents against antibodies with equivalent functions but different structural characteristics. If the economics of intellectual property center on balancing a need for protection beyond the literal invention and allowing improvements, this seems a step in the right—or, at least doctrinally permissible and economically sensible—direction.

Whether patentees go for such a solution remains to be seen. Recent empirical evidence on antibody claims has yet to document such a shift. Patent attorneys may need to get over their historical reluctance in writing their claims in such a fashion. Our solution won't give patentees everything they want. But they just might find it gives them what they need.