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The Antibody Patent Paradox

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 startlingly different in both structure and function. There is no way to describe 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 industry. 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 would give 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 with a desire to allow improvements, this seems a step in the right—or, at least in a 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 to 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 Long before “antibodies” became a household word during 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 ten best-selling antibody drugs in 2019 reached \$79.1 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 six top-selling antibody therapies – could claim that antibody and

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1. See 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, David B. Corry, Ulrich Strych & Maria Elena Bottazzi, Comment, *COVID-19 Vaccines: Neutralizing Antibodies and the Alum Advantage*, 20 *NATURE REVIEWS IMMUNOLOGY* 399, 399 (2020); see also Sharon Amit, Sharon Aleksandra Beni, Asaf Biber, Amir Grinberg, Eyal Leshem & Gili Regev-Yochay, *Postvaccination COVID-19 Among Healthcare Workers, Israel*, 27 *EMERGING INFECTIOUS DISEASES* 1220, 1220 (2021) (“Large-scale vaccination of risk groups and later the general population is the single most effective public health measure for mitigation of the coronavirus disease (COVID-19) pandemic.”).
 2. See Borrebaeck, *supra* note 1, at 379; Nicholas A.P.S. Buss, Simon J. Henderson, Mary McFarlane, Jacintha M. Shenton & Lolke de Haan, *Monoclonal Antibody Therapeutics: History and Future*, 12 *CURRENT OPINION PHARMACOLOGY* 615, 615 (2012).
 3. See Asher Mullard, *FDA Approves 100th Monoclonal Antibody Product*, 20 *NATURE REVIEWS DRUG DISCOVERY* 491, 495 tbl.3 (2021) (noting the popularity of TNF- α as a target); Patrick Frater, *Global Box Office Hit \$21.4 Billion in 2021, Says Analyst*, *VARIETY* (Jan. 6, 2022, 9:34 PM PT), <https://variety.com/2022/film/box-office/global-box-office-2021-1235148732> [<https://perma.cc/65TU-T7YR>]; *Global Music Report*, *INT’L FED’N OF THE PHONOGRAPHIC INDUS.* 12 (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*, 858 F.2d 731 (Fed. Cir. 1988).

almost all other antibodies that bound to it.⁵ In part, this claim practice was one of necessity. Unlike typical “small-molecule” drugs, scientists had long identified antibodies not by their precise molecular structure but by what they *did*.⁶ Indeed, characterizing antibodies atom by atom was both impractical and pointless – akin to describing a fighter jet by listing every nut and bolt.⁷ “Functional claiming,” the ownership of “*any device* 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 at the U.S. Court of Appeals for the Federal Circuit, no antibody patent in over a decade has survived a challenge based on overbreadth and inadequate disclosure,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 ordinary skill in the art” (a PHOSITA, or a

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5. See *Centocor Ortho Biotech, Inc. v. Abbott Lab’s*, 636 F.3d 1341, 1352 & n.5 (Fed. Cir. 2011) (describing the “newly characterized antigens” test); see also Mullard, *supra* note 3, at 492 (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 40 and Polyoma Virus*, 41 J. VIROLOGY 709, 709 (1982) (establishing nomenclature system for antibodies based on antigen).
 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 WIS. L. REV. 905, 923; see Colin G. Sandercock & Ulrich Storz, *Antibody Specification Beyond the Target: Claiming a Later-Generation Therapeutic Antibody by Its Target Epitope*, 30 NATURE BIOTECH. 615, 617 (2012).
 9. See Lena Meyer, Tomás López, Rafaela Espinosa, Carlos F. Arias, Christopher Vollmers & Rebecca M. DuBois, *A Simplified Workflow for Monoclonal Antibody Sequencing*, 14 PLOS ONE art. no. e0218717, at 10 (2019).
 10. See *infra* Section 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 any person skilled in the art to which it pertains . . . to make and use” the invention. 35 U.S.C. § 112(a) (2018). 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. See, 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, 1332 (Fed. Cir. 2021) (\$1.2 billion); *Centocor Ortho Biotech, Inc. v. Abbott Lab’s*, 636 F.3d 1341, 1344 (Fed. Cir. 2011) (\$1.67 billion); see also *Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1080–81 (Fed. Cir. 2021) (jury verdict overturned before damages assessment).

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 the related doctrinal ground of 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 With antibodies, however, a paradox has emerged. In the early days of the industry, when scientists often knew little about the precise molecular and genetic structures of antibodies 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 of 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 enablement or written description doctrines.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

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12. See Timothy R. Holbrook, *Possession in Patent Law*, 59 SMU L. REV. 123, 127 (2006).
 13. See Dmitry Karshedt, Mark A. Lemley & Sean B. Seymore, *The Death of the Genus Claim*, 35 HARV. J.L. & TECH. 1, 61-62 (2021).
 14. See *Amgen*, 987 F.3d at 1087-88.
 15. See, e.g., *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.”); *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 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. See, e.g., *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1330 (Fed. Cir. 2021); *Amgen*, 987 F.3d at 1080; *Centocor Ortho Biotech, Inc. v. Abbott Lab’s*, 636 F.3d 1341, 1342 (Fed. Cir. 2011).
 18. See Joel Finney, Chen-Hao Yeh, Garnett Kelsoe & Masayuki Kuraoka, *Germinal Center Responses to Complex Antigens*, 284 IMMUNOLOGICAL REV. 42, 46-47 (2018) (measuring high genetic diversity of antibodies specific to a given antigen).

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 development 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 patent 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 the single, convoluted sentence that is a patent claim.²² Or perhaps it is simply the result of a circumstance in which the more we learn, the more we learn what we don't know.²³ We explore all of these possibilities.²⁴

Regardless of the explanation, the antibody patent 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.²⁵ If we get those questions wrong, we could end up with a second 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, but the likely effects on innovation are complicated. We suggest some possible middle ground that might 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

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. Karshedt et al., *supra* note 13, at 4.

21. See Lemley, *supra* note 8, at 907-08.

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.").

23. Cf. Jacob S. Sherkow, *The Natural Complexity of Patent Eligibility*, 99 IOWA L. REV. 1137, 1142-43 (2014) (suggesting courts redefine the doctrine of patentable subject matter based on the complexity of articulating "natural" laws).

24. See *infra* Part III.

25. See Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1592-95 (2003) (describing such concerns as policy levers in patent law).

the current period of hostility to antibody patents. Part III considers several possible explanations for this shift, none of which are completely satisfactory. In Part IV, we explain how the antibody patent 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.²⁶ The key to this adaptive immune system is the body's ability to quickly and precisely flag such threats as potentially harmful even though the immune system hasn't encountered them before.²⁷ Once a threat is identified, the immune system also needs the tools to neutralize and dispose of it without harming healthy tissue or commandeering too many of the body's resources.²⁸ An overaggressive immune response risks harming the body by attacking foreign but benign material,²⁹ while an apathetic immune response risks yielding the body to systemic infections.³⁰ Functional adaptive immune systems must therefore be precise without sacrificing flexibility.³¹

This marriage of precision and flexibility is largely mediated by a class of complex proteins known as immune receptors, specifically antibodies and T-cell

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26. See Enkelejda Miho, Alexander Yermanos, Cédric R. Weber, Christoph T. Berger, Sai T. Reddy & Victor Greiff, Review, *Computational Strategies for Dissecting the High-Dimensional Complexity of Adaptive Immune Repertoires*, 9 FRONTIERS IMMUNOLOGY art. no. 224, at 1-2 (2018).
27. See William H. Robinson, *Sequencing the Functional Antibody Repertoire – Diagnostic and Therapeutic Discovery*, 11 NATURE REVIEWS RHEUMATOLOGY 171, 171 (2015); Doreen E. Szollosi, Clinton B. Mathias & Jeremy P. McAleer, *Modulation of the Adaptive Immune System*, in PHARMACOLOGY OF IMMUNOTHERAPEUTIC DRUGS 67, 68 (Clinton B. Mathias, Jeremy P. McAleer & Doreen E. Szollosi eds., 2020).
28. See David H. Raulet & Russell E. Vance, *Self-Tolerance of Natural Killer Cells*, 6 NATURE REVIEWS IMMUNOLOGY 520, 520 (2006).
29. See, e.g., Hannah J. Gould, Brian J. Sutton, Andrew J. Bevil, Rebecca L. Bevil, Natalie McCloskey, Heather A. Coker, David Fear & Lyn Smurthwaite, *The Biology of IgE and the Basis of Allergic Disease*, 21 ANN. REV. IMMUNOLOGY 579, 579-80 (2003).
30. See Sudhir Gupta & Ankmalika Gupta Louis, *Tolerance and Autoimmunity in Primary Immunodeficiency Disease: A Comprehensive Review*, 45 CLINICAL REVIEWS ALLERGY & IMMUNOLOGY 162, 162 (2013).
31. See Szollosi et al., *supra* note 27, at 67-68.

receptors.³² These immune receptors are produced by two types of immune-system cells – B cells and T cells for antibodies and T-cell receptors, respectively – that circulate throughout the blood and the lymphatic system.³³ 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.³⁴ If recognized as a foreign substance, this contact 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 bind to the offending material.³⁵ 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.³⁶ 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 incredibly diverse, with a given individual likely having tens of billions of different variations of immune receptors circulating in their blood at any given time.³⁷ 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?³⁸ The answer lies in how immune receptors are made.³⁹ 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.⁴⁰ The tips of this Y-shaped structure, known as the complementarity-determining region (CDR), are the portion of the antibody that interact with the antigen.⁴¹ Both of these chains are produced, incredibly, by only three genes – *V*, *D*, and *J* – each of which contains multiple

32. See Felix Breden et al., *Reproducibility and Reuse of Adaptive Immune Receptor Repertoire Data*, 8 FRONTIERS IMMUNOLOGY art. no. 1418, at 1-2 (2017).

33. See Miho et al., *supra* note 26, at 1.

34. Clinton B. Mathias, *Overview of the Immune System and Its Pharmacological Targets*, in PHARMACOLOGY OF IMMUNOTHERAPEUTIC DRUGS, *supra* note 27, at 1, 17-19.

35. *Id.* at 21-23.

36. *Id.* at 23.

37. Anthony R. Rees, Review, *Understanding the Human Antibody Repertoire*, 12 MABS art. no. 1, at 1 (2020).

38. See Miho et al., *supra* note 26, at 2.

39. See generally Martin F. Flajnik & Louis Du Pasquier, *Evolution of the Immune System*, in FUNDAMENTAL IMMUNOLOGY 67, 90-123 (William E. Paul ed., 7th ed. 2012) (providing a complete overview of immune-receptor development).

40. See Szollosi et al., *supra* note 27, at 70-71.

41. See Robinson, *supra* note 27, at 171.

smaller “cassettes” – for example, V_1 , V_2 , V_3 , and so on.⁴² Naive B cells, 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.⁴³ T cells create their receptors through a similar mechanism.⁴⁴ 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.⁴⁵

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.⁴⁶ The specific place on an antigen to which an antibody binds is known as the “epitope.”⁴⁷ Even multiple antibodies specific to a single epitope may bind more or less strongly to it, an antibody’s “affinity” in immunological parlance.⁴⁸ 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.”⁴⁹ Because antibodies are produced through the $V(D)J$ recombination mechanism, however, all have different genetic sequences – which is to say that, at a molecular level, all antibodies are different.⁵⁰

Immune receptors are of immense biologic value, the “central feature” of the adaptive immune system as a whole.⁵¹ This is because the CDRs of antibodies have the potential to bind to almost any other large molecule, extant or yet to be

42. Fumihiko Matsuda, Kazuo Ishii, Patrice Bourvagnet, Kei-ichi Kuma, Hidenori Hayashida, Takashi Miyata & Tasuku Honjo, *The Complete Nucleotide Sequence of the Human Immunoglobulin Heavy Chain Variable Region Locus*, 188 J. EXPERIMENTAL MED. 2151, 2151 (1998).

43. See Breden et al., *supra* note 32, at 2.

44. See Miho et al., *supra* note 26, at 1-2.

45. See *id.* at 1.

46. See, e.g., Lihong Liu et al., *Potent Neutralizing Antibodies Against Multiple Epitopes on SARS-CoV-2 Spike*, 584 NATURE 450, 450 (2020) (“[N]ineteen antibodies . . . potently neutralized authentic SARS-CoV-2 in vitro . . . [T]his collection of nineteen antibodies was about equally divided between those directed against the receptor-binding domain (RBD) and those directed against the N-terminal domain (NTD), indicating that both of these regions at the top of the viral spike are immunogenic.”).

47. Mathias, *supra* note 34, at 17-18.

48. *Id.* at 21-23.

49. *Id.* at 22-23.

50. See Max D. Cooper & Matthew N. Alder, *The Evolution of Adaptive Immune Systems*, 124 CELL 815, 815-16 (2006).

51. *Id.* at 815.

conceived.⁵² But the interaction of any *particular* CDR is incredibly specific; generally speaking, each antibody binds to only a single epitope.⁵³ 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.⁵⁴ Today, researchers appreciate that there is some “fuzziness” to this lock-and-key model, more accurately describing CDR binding as an “induced fit.”⁵⁵ But even with molecularly large antigens, antibodies can recognize atomic—and, in extreme cases, subatomic—differences in epitopes.⁵⁶ As noted above, this pairing is not unique: a given antibody can bind to only a single antigen, but a single antigen can—and frequently does—bind with multiple, slightly different antibodies.⁵⁷ 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 a few other biologic molecules that have similar properties.⁵⁸

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.”⁵⁹ Antibodies can be used, for example, to assess whether a specific antigen exists in a large mixture of proteins,

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52. See Richard A. Norman, Francesco Ambrosetti, Alexandre M.J.J. Bonvin, Lucy J. Colwell, Sebastian Kelm, Sandeep Kumar & Konrad Krawczyk, *Computational Approaches to Therapeutic Antibody Design: Established Methods and Emerging Trends*, 21 BRIEFINGS BIOINFORMATICS 1549, 1558-1559 (2020).
 53. 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. SCIS. E8707, E8708 (2018) (calling “one-antibody-one-epitope” a “dogma”).
 54. See Abner Louis Notkins, Opinion, *Polyreactivity of Antibody Molecules*, 25 TRENDS IMMUNOLOGY 174, 174 (2004) (challenging this view, but nonetheless noting it “has long dominated immunological thinking”).
 55. Ping Zhang et al., *Capturing Transient Antibody Conformations with DNA Origami Epitopes*, 11 NATURE COMM’NS art. no. 3114, at 2 (2020).
 56. See *id.*
 57. See, e.g., Liu et al., *supra* note 46, at 450 (describing this phenomenon in the COVID-19 context).
 58. See Cooper & Alder, *supra* note 50, at 815.
 59. Mathias Uhlen et al., *A Proposal for Validation of Antibodies*, 13 NATURE METHODS 823, 823 (2016).

like a powerful magnet to find a needle in a haystack.⁶⁰ This also allows researchers to isolate a specific protein from an undifferentiated mass for further study.⁶¹ Researchers can further modify this technique to assess whether one protein interacts with another or whether a given protein interacts with another molecule of interest.⁶² This includes research into how certain proteins, or other large molecules, bind to DNA – instrumental in investigating how genes function.⁶³ 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.⁶⁴ The use of antibodies as research tools is a large market unto itself, clocking in at \$3.4 billion per year in 2020.⁶⁵

Relatedly, antibodies can also be used as diagnostics for diseases or other health conditions.⁶⁶ A diagnostic technique known as immunochromatography, for example, pairs antibodies with fluorescent or other color-providing molecules so that they “glow” when they come into contact with a particular antigen.⁶⁷ 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.⁶⁸ A variation on the technique tags the antibody not with a fluorescent molecule but with an enzyme that detectably

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60. See, e.g., *id.* at 824-25 (describing Western blots).
61. See, e.g., Yiling Gao, Xinxin Huang, Yongbo Zhu & Zhiyuan Lv, *A Brief Review of Monoclonal Antibody Technology and its Representative Applications in Immunoassays*, 39 J. IMMUNOASSAY & IMMUNOCHEMISTRY 351, 358-59 (2018) (describing immunoprecipitation).
62. See Shane C. Masters, *Co-Immunoprecipitation from Transfected Cells*, in 261 PROTEIN-PROTEIN INTERACTIONS: METHODS AND APPLICATIONS 337, 337 (Haian Fu ed., 2004) (describing co-immunoprecipitation as “[o]ne of the most commonly used methods for determining whether two proteins can interact”).
63. See Philippe Collas, *The Current State of Chromatin Immunoprecipitation*, 45 MOLECULAR BIOTECH. 87, 87 (2010) (describing chromatin immunoprecipitation as “a technique whereby a protein of interest is selectively immunoprecipitated from a chromatin preparation to determine the DNA sequences associated with it”).
64. See Gao et al., *supra* note 61, at 356-58.
65. See Jan L.A. Voskuil et al., Perspective, *The Antibody Society’s Antibody Validation Webinar Series*, 12 MABS art. no. e1794421, at 2 (2020).
66. See 21 C.F.R. § 809.3 (2022) (defining “in vitro diagnostic products” as “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions”).
67. See Gao et al., *supra* note 61, at 359-61.
68. See Valentin Parvu, Devin S. Gary, Joseph Mann, Yu-Chih Lin, Dorsey Mills, Lauren Cooper, Jeffrey C. Andrews, Yukari C. Manabe, Andrew Pekosz & Charles K. Cooper, *Factors that Influence the Reported Sensitivity of Rapid Antigen Testing for SARS-CoV-2*, 12 FRONTIERS MICROBIOLOGY art. no. 714242, at 1-2 (2021); Garrett A. Perchetti, Meei-Li Huang, Margaret G. Mills, Keith R. Jerome & Alexander L. Greninger, *Analytical Sensitivity of the Abbott BinaxNOW COVID-19 Ag Card*, 59 J. CLINICAL MICROBIOLOGY art. no. e02880-20, at 3 (2021).

reacts when the antibody is bound to it, a technique known as an enzyme-linked immunoassay or ELISA.⁶⁹ This is the primary technique used to detect a number of diseases, including influenza and rotavirus.⁷⁰ Other diagnostics test for the presence of antibodies themselves in the blood to determine whether a patient has been exposed to a particular infection.⁷¹ 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 immunohistochemistry.⁷² Like research tools, antibody-based diagnostics are big business, yielding their manufacturers roughly \$23 billion per year.⁷³

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.⁷⁴ Antibodies that bind to TNF- α (i.e., anti-TNF- α antibodies), in turn, disrupt this pathway and are immensely useful in regulating an overstimulated inflammatory response.⁷⁵ This is the mechanism of three of the top-selling antibody therapies in the world: Humira, Enbrel, and Remicade.⁷⁶ Antibodies can similarly be

69. See Gao et al., *supra* note 61, at 355-56.

70. See Karen Leirs et al., *Bioassay Development for Ultrasensitive Detection of Influenza A Nucleoprotein Using Digital ELISA*, 88 ANALYTICAL CHEMISTRY 8450, 8450 (2016); T. Anand, T.A. Narasa Raju, C. Vishnu, L. Venkateswar Rao & G. Sharma, *Development of Dot-ELISA for the Detection of Human Rotavirus Antigen and Comparison with RNA-PAGE*, 32 LETTERS APPLIED MICROBIOLOGY 176, 176 (2001); Ana S. Cerda-Kipper, Bernardo E. Montiel & Samira Hosseini, *Immunoassays | Radioimmunoassays and Enzyme-Linked Immunosorbent Assay*, in 5 ENCYCLOPEDIA OF ANALYTICAL SCIENCE 55, 55, 70-73 (Paul Worsfold, Colin Poole, Alan Townshend & Manuel Miró eds., 3d ed. 2019).

71. See, e.g., Eleftherios Mylonakis, Maria Paliou, Michelle Lally, Timothy P. Flanigan & Josiah D. Rich, *Laboratory Testing for Infection with the Human Immunodeficiency Virus: Established and Novel Approaches*, 109 AM. J. MED. 568, 568-70 (2000) (describing such a technique to test for HIV infections).

72. See Atsuko Kitamura, Waki Hosoda, Eiichi Sasaki, Tetsuya Mitsudomi & Yasushi Yatabe, *Immunohistochemical Detection of EGFR Mutation Using Mutation-Specific Antibodies in Lung Cancer*, 16 CLINICAL CANCER RSCH. 3349, 3349 (2010).

73. *Diagnostic Specialty Antibodies Market Insights, New Innovations, Research and Growth Factor till 2027*, BIOSPACE (Nov. 30, 2021) [hereinafter *Antibodies Market Insights*], <https://www.biospace.com/article/diagnostic-specialty-antibodies-market-insights-new-innovations-research-and-growth-factor-till-2027> [https://perma.cc/YX8R-R5PC].

74. See Michael A. Palladino, Frances Rena Bahjat, Emmanuel A. Theodorakis & Lyle L. Moldawer, *Anti-TNF- α Therapies: The Next Generation*, 2 NATURE REV. DRUG DISCOVERY 736, 736 (2003).

75. See *id.* at 737.

76. See *id.* at 738-39.

used as therapies to signal biologic targets to other systems in the body, including other components of the immune system. Modified antibodies that precisely target vascular endothelial growth factor A (VEGF-A), a protein known to be overexpressed in certain cancers,⁷⁷ can 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.⁷⁸ Lastly, antibodies can be used to precisely 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” – or “constant region” – is attached to a therapeutic drug.⁷⁹ 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.⁸⁰

C. *The History and Development of Antibody Research*

Antibodies’ present-day power belies a long and difficult development history. While researchers have 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.⁸² In 1975, Georges Köhler and César Milstein first published a paper on producing monoclonal antibodies—antibodies derived from a single B-cell

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77. See S. Lien & H.B. Lowman, *Therapeutic Anti-VEGF Antibodies*, in *THERAPEUTIC ANTIBODIES* 131, 132-33 (Yuti Chernajovsky & Ahuva Nissim eds., 2008).
78. *Id.* at 131.
79. See generally Alexis Q. Dean, Shen Luo, Julianne D. Twomey & Baolin Zhang, *Targeting Cancer with Antibody-Drug Conjugates: Promises and Challenges*, 13 *MABS* art. no. e1951427 (2021) (discussing the mechanics and design of antibody-drug conjugates as well as the status of this biotherapeutic both on the market and in clinical trials).
80. See *id.* at 3-7.
81. See Alison Farrell, *Serum Power*, *NATURE* (Sept. 28, 2020), <https://www.nature.com/articles/d42859-020-00009-4.pdf> [<https://perma.cc/JL5Y-3JF8>] (describing early antibody discoveries by Emil von Behring in 1890); Gerald M. Edelman, *Dissociation of γ -Globulin*, 81 *J. AM. CHEM. SOC.* 3155, 3155 (1959); R. R. Porter, *The Hydrolysis of Rabbit γ -Globulin and Antibodies with Crystalline Papain*, 73 *BIOCHEM. J.* 119, 119 (1959). Emil von Behring, Gerald M. Edelman, and R. R. Porter all won Nobel Prizes for their work. *Nobel Prizes and the Immune System: 1901-2010*, *NOBEL PRIZE* (Sept. 6, 2010) [hereinafter *Nobel Prizes*], <https://www.nobelprize.org/prizes/themes/nobel-prizes-and-the-immune-system> [<https://perma.cc/72VM-TMEU>].
82. See G. Köhler & C. Milstein, *Continuous Cultures of Fused Cells Secreting Antibody of Predefined Specificity*, 256 *NATURE* 495, 495 (1975).

“clone”—at something approaching a large-enough scale for research purposes.⁸³ Their method of 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 Köhler and Milstein’s efforts, as well as those of numerous other researchers on the path to discovering antibodies, yielded Nobel Prizes.⁸⁵

Despite Köhler and Milstein’s success, generating antibodies remained a laborious and error-prone process for decades.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 target protein and wait several weeks for the animal to develop antibodies against the target. Afterwards, researchers would 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 to see if they 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 as high as 97%.⁹⁰

This process provided a crude method for manufacturing antibodies that targeted a specific antigen. But it posed several problems. Back then, it was almost impossible to determine whether two antibodies were from the same line of B cells (“monoclonal”) or different ones (“polyclonal”).⁹¹ It was also difficult to determine 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

83. *Id.* at 497.

84. *Id.*

85. *Nobel Prizes*, *supra* note 81.

86. See Harold F. Stills, *Polyclonal Antibody Production*, in *THE LABORATORY RABBIT, GUINEA PIG, HAMSTER, AND OTHER RODENTS* 259, 259-60 (Mark A. Suckow, Karla A. Stevens & Ronald P. Wilson eds., 2012).

87. Gerald Corbitt & Christopher C. Storey, *Monoclonal Antibodies—Current Techniques and Applications*, 11 *BIOCHEM. EDUC.* 125, 125-26 (1983).

88. See *id.* at 126-29.

89. *Id.* at 126.

90. Köhler & Milstein, *supra* note 82, at 497.

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

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

93. See *id.* at 613 (describing the sources of “large variations in the yield”).

change over time.⁹⁴ And, given the random nature of antibody production (the *V(D)J* recombination process discussed earlier),⁹⁵ this procedure was not replicable from animal to animal or laboratory to laboratory.⁹⁶ Even today, “validating” antibodies to ensure that they are similar enough to be considered the “same” remains a persistent and significant challenge in the field.⁹⁷

For these reasons, early researchers 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.⁹⁸ Consequently, even after Köhler and Milstein, researchers thought of and named antibodies not by their molecular features but solely by which antigen they bound to.⁹⁹ Thus, a variety of antibodies specific to the protein CD3 were called “anti CD3 antibodies.”¹⁰⁰ 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.¹⁰¹ 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.¹⁰² But there was still no way to assess precisely what the molecular differences were.¹⁰³

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94. See Sandra J. Kromenaker & Friedrich Sreenc, *Stability of Producer Hybridoma Cell Lines After Cell Sorting: A Case Study*, 10 BIOTECH. PROGRESS 299, 306-07 (1994) (noting that this was a rare, albeit measurable, event).
95. See *supra* note 50 and accompanying text.
96. See Corbitt & Storey, *supra* note 87, at 125.
97. Uhlen et al., *supra* note 59, at 823.
98. Corbitt & Storey, *supra* note 87, at 125-26.
99. See, e.g., Crawford & Harlow, *supra* note 6, at 709 & nn.1-6.
100. W. Holter, O. Majdic, H. Stockinger & W. Knapp, *Analysis of T Cell Activation with a Non-Mitogenic Anti CD3 Antibody and the Phorbol Ester TPA*, 62 CLINICAL & EXPERIMENTAL IMMUNOLOGY 600, 600 (1985).
101. See, e.g., Xin-Lin Zhang, Qing-Qing Zhu, Li Zhu, Jian-Zhou Chen, Qin-Hua Chen, Guan-Nan Li, Jun Xie, Li-Na Kang & Biao Xu, *Safety and Efficacy of Anti-PCSK9 Antibodies: A Meta-Analysis of 25 Randomized, Controlled Trials*, 13 BMC MED. art. no. 123, at 3 (2015) (referring to a variety of antibodies as “anti-PCSK9” antibodies because they bind to PCSK9).
102. See, e.g., Crawford & Harlow, *supra* note 6, at 709.
103. See P. M. Alzari, M.-B. Lascombe & R. J. Poljak, *Three-Dimensional Structure of Antibodies*, 6 ANN. REV. IMMUNOLOGY 555, 555 (1988) (“[U]nderstanding of the structural bases of specificity physicochemical characterization of antibody action at the molecular level [is] only beginning.”).

Today, molecular biology is significantly more advanced, and obtaining the precise genetic sequence of an antibody from a single B-cell clone is routine.¹⁰⁴ Antibodies can also be reengineered in a variety of ways to fit their epitopes better.¹⁰⁵ There are even efforts to design immune receptors from scratch and to predict what an immune receptor binds to without validation experiments.¹⁰⁶ But the old norm of characterizing antibodies by their function – what they bind to and how well – still prevails.¹⁰⁷

D. Patents and the Antibody Market Today

Because antibodies are so specific to their targets, they are increasingly preferred, in many therapeutic contexts, over older, “small molecule” drugs that might have unwanted side effects on other body systems.¹⁰⁸ Today, six of the top-ten selling therapies in the United States are antibodies or fragments of antibodies, generating a total of roughly \$75 billion of revenue per year.¹⁰⁹ Not only is that just the top six – that is just antibodies used for *therapies*. As noted earlier, antibodies used for research tools or diagnostics command similarly impressive markets: \$3.4 billion and \$23 billion per year, respectively.¹¹⁰ Totaling just these figures – leaving out *all* antibody drugs that fall below the top six and ancillary uses of antibodies in things like manufacturing applications – yields more than \$100 billion in annual revenue. The total antibody market is estimated at about

104. See Cristina Parola, Daniel Neumeier & Sai T. Reddy, *Integrating High-Throughput Screening and Sequencing for Monoclonal Antibody Discovery and Engineering*, 153 IMMUNOLOGY 31, 31 (2017) (“[I]t has now become more routine to perform high-throughput sequencing on antibody repertoires to also directly discover antibodies.”).

105. See *id.* at 33.

106. See William D. Chronister et al., *TCRMatch: Predicting T-Cell Receptor Specificity Based on Sequence Similarity to Previously Characterized Receptors*, 12 FRONTIERS IMMUNOLOGY art. no. 640725, at 1, 2 (2021).

107. See, e.g., Zhang et al., *supra* note 101, at 2.

108. See, e.g., Kohzoh Imai & Akinori Takaoka, *Comparing Antibody and Small-Molecule Therapies for Cancer*, 6 NATURE REVIEWS CANCER 714, 722-23 (2006) (comparing adverse events in small-molecule drugs versus monoclonal-antibody therapies).

109. Mullard, *supra* note 3, at 495.

110. Voskuil et al., *supra* note 65, at 2; *Antibodies Market Insights*, *supra* note 73.

\$146 billion per year and is expected to grow about 11% each year before inflation.¹¹¹ By 2027, the global market is expected to occupy a staggering \$248.9 billion.¹¹²

It is easy in a gilded age to lose perspective of the size of these numbers, but they are absolutely massive. The antibody market's current value of \$145 billion is more than triple the entire global music and movie markets combined.¹¹³ It is comparable to the entirety of domestic revenue for Apple, the world's largest company, or all of its global sales of its bestselling product, the iPhone.¹¹⁴ It is more than the total gross domestic product (GDP) of 135 countries and more than the bottom-ranked 51 countries' GDP combined.¹¹⁵ And if the antibody market indeed grows as expected, it's not far-fetched to say it could be larger than the output of *half* the world's nations before 2030.¹¹⁶

For this reason, patents covering antibodies have been tremendously valuable—arguably the most valuable patents ever. Humira, the world's best-selling antibody therapy, nets its developer, AbbVie, about \$20 billion per year.¹¹⁷ Humira is covered, in some form, by more than one hundred U.S. patents.¹¹⁸

111. *Global Antibodies Market Size, Share Trends, COVID-19 Impact & Growth Analysis Report—Segmented by Product Type, Indication, End User, Application and Region—Industry Forecast (2022 to 2027)*, MARKET DATA FORECAST (Jan. 2022) [hereinafter *Market Size Report*], <https://www.marketdataforecast.com/market-reports/antibodies-market> [https://perma.cc/VK6J-3QAX].

112. *Id.*

113. See Frater, *supra* note 3 (noting that the film industry's box-office revenue was around \$21 billion in 2021); *Global Music Report*, *supra* note 3, at 12 (reporting around \$21.6 billion in total music-industry revenue in 2020).

114. See Apple Inc., Annual Report (Form 10-K) 21, 22 (Oct. 28, 2021), <https://www.sec.gov/Archives/edgar/data/320193/000032019321000105/aapl-20210925.htm> [https://perma.cc/P3YZ-QPE5].

115. See *GDP (Current US\$)*, WORLD BANK (2021), <https://data.worldbank.org/indicator/NY.GDP.MKTP.CD> [https://perma.cc/DNV7-XRGG].

116. Compare *id.* (displaying the GDP of the world's nations), with *Monoclonal Antibody Therapy Market Size, Analysis, Development, Revenue, Future Growth, Business Prospects and Forecast to 2027*, MARKETWATCH (Jan. 3, 2022, 1:38 AM ET), <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] (projecting the monoclonal-antibody market to grow roughly 250% between 2021 and 2028).

117. Kevin Dunleavy, *Humira Rings Up \$20.7B in 2021, but AbbVie Still Mum on Post-Biosimilar Expectations*, FIERCE PHARMA (Feb. 2, 2022, 11:33 AM), <https://www.fiercepharma.com/pharma/humira-rings-up-20-7-billion-sales-but-abbvie-still-mum-a-projection-for-2023-when-it-faces> [https://perma.cc/5ZNU-FN8A].

118. Cynthia Koons, *This Shield of Patents Protects the World's Best-Selling Drug*, BLOOMBERG (Sept. 7, 2017, 6:00 AM EDT), <https://www.bloomberg.com/news/articles/2017-09-07/this-shield-of-patents-protects-the-world-s-best-selling-drug> [https://perma.cc/FE3S-TKUA].

The value of that portfolio of patents, the bulk of which expire in 2023, is worth about \$9 billion in revenue per year, or about \$90 million per patent, per year.¹¹⁹ That dwarfs other patent portfolios, such as the set of more than 17,000 patents that Google acquired from Motorola Mobility for a mere \$5.5 billion — a relatively paltry \$323,000 per-patent average.¹²⁰ In addition to the value of the market exclusivity they provide, antibody patents often generate significant licensing revenue. Antibody-patent licensing is among the most valuable for universities, with antibody licensing often commanding a substantial portion of a university's technology transfer revenue.¹²¹ And biopharma acquisitions for early-stage companies with antibody patents tend to be large.¹²²

Because antibody patents are so valuable, invalidating even one can cost a company billions of dollars and changing the law of antibody patents can send shock waves through the industry. Patents are widely viewed as a necessary incentive lever to bring forms of the technology from bench to market.¹²³ For universities and biotechnology companies, they are, in the words of one report from *Nature*, among the “most valuable assets.”¹²⁴

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119. See, e.g., Logan Frick, *AbbVie: Diversified Strength Tempers the Humira Patent Cliff Ahead*, SEEKING ALPHA (Aug. 8, 2021, 9:39 PM ET), <https://seekingalpha.com/article/4447020-abbvie-diversified-strength-tempers-the-humira-patent-cliff-ahead> [https://perma.cc/PKK2-D4EH].
120. See Phil Goldstein, *Google: Motorola's Patents Worth \$5.5B*, FIERCE WIRELESS (July 25, 2012, 10:30 AM), <https://www.fiercewireless.com/wireless/google-motorola-s-patents-worth-5-5b> [https://perma.cc/P9E4-PRLB].
121. See Maureen Farrell, *Universities that Turn Research into Revenue*, FORBES (Sept. 12, 2008, 6:00 PM EDT), https://www.forbes.com/2008/09/12/google-general-electric-ent-tech-cx_mf_0912universitypatent [https://perma.cc/PU3S-UNKV] (describing how the antibody drug Remicade has accounted for “the bulk of NYU’s licensing revenue in the last decade”); *Technology Commercialization Report*, UNIV. OF CAL. 5 (2020), https://www.ucop.edu/knowledge-transfer-office/_files/ott/genresources/documents/fy2020-tech-comm-rpt.pdf [https://perma.cc/S86E-7J5Q] (noting substantial license revenues for antibody-related technologies such as peptide libraries, macromolecules for drug discovery, and chromosome painting).
122. See, e.g., Conor Hale, *Otsuka to Acquire Antibody Developer Visterra in \$430M Deal*, FIERCE BIOTECH (July 11, 2018, 10:47 AM), <https://www.fiercebiotech.com/medtech/otsuka-to-acquire-antibody-developer-visterra-430m-deal> [https://perma.cc/P9F7-WR6C].
123. See Mark A. Lemley, *Ex Ante Versus Ex Post Justifications for Intellectual Property*, 71 U. CHI. L. REV. 129, 129 (2004).
124. Heidi Ledford, *Rush to Protect Billion-Dollar Antibody Patents*, 557 NATURE 623, 623 (2018).

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 F-16 fighter jet by its every nut and bolt, an exercise of equal utility as Jorge Luis Borges’s map of an empire drawn on a globe at a 1:1 scale.¹²⁵ For this reason, among others, patent law has long allowed inventors of complex biologic materials to deposit those materials in a public depository in order, at a minimum, to demonstrate possession of the invention.¹²⁶ At the same time, the mere act of depositing isn’t dispositive; courts must still engage in a case-by-case factual determination of whether the deposit was “sufficient” to demonstrate possession “representative of the scope of those claims.”¹²⁷

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 the 2004 Federal Circuit case *Noelle v. Lederman*.¹²⁸ But such claims are extremely expansive. Claims specific to nothing more than a single antigen would encompass *every* antibody that happened to bind to it—potentially thousands, if not millions, of molecules.¹²⁹ They are also almost purely functional and therefore possibly invalid on several grounds.¹³⁰ Moreover, claims directed solely to an antibody’s antigen made no distinction among different antibody clones, which means that the existence of even a single prior antibody would invalidate the patent.¹³¹

125. Price & Rai, *supra* note 7, at 1026; JORGE LUIS BORGES, *On Exactitude in Science*, in COLLECTED FICTIONS 325, 325-36 (Andrew Hurley trans., Penguin Books 1998) (1946).

126. See Donald Levy & Lucile Burd Wendt, *Microbiology and a Standard Format for Infra-Red Absorption Spectra in Antibiotic Patent Applications*, 37 J. PAT. OFF. SOC’Y 855, 857-59 (1955) (first describing the practice).

127. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 967 (Fed. Cir. 2002).

128. 355 F.3d 1343, 1349 (Fed. Cir. 2004).

129. See *Centocor Ortho Biotech, Inc. v. Abbott Lab’y*, 636 F.3d 1341, 1352 (Fed. Cir. 2011) (describing the relationship as “a [key] ring with a million keys on it”).

130. See *Noelle*, 355 F.3d at 1348-49 (discussing the deficiencies in functional claiming for antibodies).

131. See *Nichols Inst. Diagnostics, Inc. v. Scantibodies Clinical Lab’y, Inc.*, 195 F. App’x 947, 951-952 (Fed. Cir. 2006) (concluding that claims directed to antibody derived from well-known antiserum containing other antibodies were anticipated).

In addition to merely describing the antigen to which it binds, one could also claim an antibody by how it bound to its particular epitope.¹³² Although this claiming strategy significantly circumscribes the universe of antibodies encompassed by the claims, the technique still claims the antibody by its function, albeit a more specific one.¹³³ Nonetheless, the Patent Office routinely granted patents to epitope-specific antibody claims.¹³⁴

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.¹³⁵ While these were even more specific, to the point of likely narrowing down a gargantuan class of antibodies to only hundreds or fewer,¹³⁶ 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.”¹³⁷ 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.”¹³⁸ For antibodies, these functional characteristics included “binding affinity, binding specificity, molecular weight, and

132. 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.”).

133. See *Centocor*, 636 F.3d at 1352 (“Claiming antibodies with specific properties, e.g., an antibody that binds to human TNF- α with A2 specificity, can result in a claim that does not meet written description even if the human TNF- α protein is disclosed because antibodies with those properties have not been adequately described.”).

134. See, e.g., U.S. Patent No. 5,703,213 (filed Feb. 7, 1994) (claiming an anti-AF-20 antibody with a specific epitope profile); U.S. Patent No. 5,700,649 (filed June 5, 1995) (claiming a method of using an anti-Urinary Tumor Associated Antigen antibody with particular epitope locations); U.S. Patent No. 5,688,918 (filed June 14, 1994) (claiming an anti-p53as antibody with an epitope “within the final 50 carboxyl terminal amino acids of p53as”).

135. See *In re Wands*, 858 F.2d 731, 738 n.26 (Fed. Cir. 1988) (explaining this practice).

136. See, e.g., Rhys M. Adams, Thierry Mora, Aleksandra M. Walczak & Justin B. Kinney, *Measuring the Sequence-Affinity Landscape of Antibodies with Massively Parallel Titration Curves*, 5 ELIFE art. no. e23156, at 10 (2016) (screening eighteen antibody clones using tight affinity controls).

137. Revised Interim § 112 Guidelines, *supra* note 19, at 71435.

138. *Id.*

length.”¹³⁹ 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.¹⁴⁰

All of these strategies served as substitutes for disclosing antibodies by their structure. They were workarounds 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 atom-by-atom approach of smaller chemical compounds.¹⁴¹ 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.¹⁴²

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.¹⁴³ Moreover, disclosing this 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.¹⁴⁴

Applicants had, in the past, attempted to write patents to cover these trivial changes by claiming “homology percentages” – for example, antibodies with an 80% similarity to the claimed sequence – but the Patent Office’s guidance made

139. *Id.* at 71439 n.39.

140. *See id.* at 71432. This practice was consecrated by *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 965 (Fed. Cir. 2002).

141. *Cf. Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997) (requiring, for written description purposes, claims to genes to include “structure, formula, chemical name, or physical properties,” such as DNA sequences).

142. *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*, 27 J. BIOMED. SCI. art. no. 1, at 7 (2020) (discussing the history of phage display technology).

143. *See, e.g., Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1094 (Fed. Cir. 2013) (affirming the district court’s noninfringement ruling because the competitor’s antibody had a slightly different sequence and affinity profile).

144. *See Water Techs. Corp. v. Calco, Ltd.*, 850 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 the trade secret protection on “self-disclosing” products is meaningless).

clear that any such claims would still need to satisfy the written description requirement.¹⁴⁵ In other words, claims to a group of sequences that share homology would need to disclose the variations of the sequences in the patent application's specification.¹⁴⁶ The problem is that slight changes in antibodies' sequences were likely to yield nonfunctional embodiments—antibodies that didn't bind to the particular antigen disclosed—thus risking Patent Office rejections on other doctrines.¹⁴⁷ For all of these reasons, as antibody technology progressed, applicants tended to avoid claims directed primarily to antibodies' 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.¹⁴⁸

B. Functional Claiming of Antibodies: 1986-2002

For years, the Federal Circuit 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.¹⁴⁹ 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.¹⁵⁰ 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

145. See 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 COMPUT. & HIGH TECH. L.J. 55, 71-72 (2004).

146. See *id.* at 64-66; *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212-14 (Fed. Cir. 1991).

147. See, e.g., *Novozymes A/S v. DuPont Nutrition Bioscis. APS*, 723 F.3d 1336, 1338 (Fed. Cir. 2013) (affirming rejection of a patent for including such nonfunctional embodiments in the claims).

148. See Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, “Written Description” Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 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.”).

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

150. See Laura R. Ford, *Alchemy and Patentability: Technology, “Useful Arts,” and the Chimerical Mind-Machine*, 42 CAL. W. 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”).

certain starting materials even though they may not know exactly how to describe the resulting product.¹⁵¹ So long as the inventor could teach others how to replicate the process (which requires making and using the product from the disclosed process), whether or not the inventor could describe the structure of the resulting product was irrelevant.¹⁵²

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.¹⁵³ 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 infrared light.¹⁵⁴ These supplanted more structural claims, including for oxy-tetracycline and chlortetracycline, “the structures of [which] were determined years after the patents on these compounds issued.”¹⁵⁵ 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, make, and use similar antibodies.¹⁵⁶ Concerns related to written description aside, so long as the PHOSITA could replicate the process without “undue experimentation”—that is, so long as the claims satisfied patent law’s enablement requirement—the Federal Circuit largely held that the patent had disclosed

151. See 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 Karshedt, *Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology’s Compliance with the Enablement Requirement*, 3 HASTINGS SCI. & TECH. L.J. 109, 120-27 (2011).

152. See Meurer & Nard, *supra* note 151, at 1975. That approach is no longer available to patentees after the Federal Circuit changed the law in *Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282 (Fed. Cir. 2009) (en banc).

153. Levy & Wendt, *supra* note 126, at 861-62; see *id.* at 859-62.

154. See *id.* at 859-62.

155. *Id.* at 859.

156. See, e.g., *Scripps Clinic & Rsch. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1583-84 (Fed. Cir. 1991); *In re Wands*, 858 F.2d 731, 736-40 (Fed. Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

enough.¹⁵⁷ This was, in fact, the basis for the Federal Circuit's first decision on monoclonal-antibody technology in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*¹⁵⁸

In that case, Hybritech's patent claimed the use of a novel monoclonal-antibody assay to detect an antigen of a hepatitis virus.¹⁵⁹ Because structurally characterizing antibodies was at that time virtually impossible, Hybritech's patent disclosed the method of producing the antibody using hybridoma technology, along with certain binding characteristics, including affinity.¹⁶⁰ Monoclonal Antibodies defended on various grounds, including a lack of enablement—an argument that prevailed at trial.¹⁶¹ But the Federal Circuit reversed, calling the district court's decision an “utterly baseless determination.”¹⁶² 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.”¹⁶³ This was true even if “those calculations [pertaining to affinity] are not precise.”¹⁶⁴ 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.”¹⁶⁵

The Federal Circuit extended this reasoning 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 surface-antigen antibody defined by binding affinity.¹⁶⁶ In *Wands*, the applicants had deposited the relevant hybridomas with a depository (American Type Culture Collection) and taught, in their specification, how to use affinity-based screening for the relevant antibodies from their deposit.¹⁶⁷ This screening, the Federal Circuit concluded, was not “undue experimentation” in violation of patent law's enablement requirement.¹⁶⁸ No additional description was required.¹⁶⁹ Indeed, the Federal Circuit understood that “[w]here an

157. *Wands*, 858 F.2d at 736-40.

158. 802 F.2d 1367.

159. *Id.* at 1377.

160. *Id.* at 1369-70.

161. *See id.* at 1368.

162. *Id.* at 1384.

163. *Id.*

164. *Id.* at 1385.

165. *Id.*

166. 858 F.2d 731 (Fed. Cir. 1988).

167. *Id.* at 734.

168. *Id.* at 740.

169. *See id.* In a separate opinion, however, Judge Newman presciently noted:

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.”¹⁷⁰ But that impossibility would not prevent the court from upholding a patent.

The first cracks in this analysis began to appear in 2002 in *Enzo Biochem, Inc. v. Gen-Probe Inc.*¹⁷¹ *Enzo*, a case about not antibodies but short snippets of DNA that matched other pieces of DNA called genetic probes, was decided against a backdrop of a new invigoration of the written description doctrine.¹⁷² In *Enzo*, the Federal Circuit clarified that § 112 of the patent statute “requir[ed] a ‘written description’ of an invention separate from enablement.”¹⁷³ 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.”¹⁷⁴ But, relying on the Patent Office’s 2001 Guidelines, it carved out an exception for antibodies.¹⁷⁵ 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 developed and mature.¹⁷⁶

At the time, this “antibody exception” seemed to cut against prevailing winds in favor of a more robust written description requirement, including several cases

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).

^{170.} *Id.* at 735.

^{171.} 323 F.3d 956 (Fed. Cir. 2002).

^{172.} See, e.g., *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-69 (Fed. Cir. 1997); *Fiers v. Revel*, 984 F.2d 1164, 1170-71 (Fed. Cir. 1993); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

^{173.} *Enzo*, 323 F.3d at 963.

^{174.} *Id.* at 963-64.

^{175.} *Id.* at 964.

^{176.} *Id.*

in which functional descriptions of DNA-based claims were being struck down.¹⁷⁷ But it reinforced the idea that antibodies were special.¹⁷⁸

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

That relief proved short-lived. Starting in 2004 and continuing to the modern day with *Amgen Inc. v. Sanofi*¹⁷⁹ and *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*,¹⁸⁰ the Federal Circuit has renounced antibody exceptionalism. In addition, after a long history of carefully trying to separate the two doctrines, the Federal Circuit’s antibody jurisprudence has started to conflate enablement with written description. Historically, the object of enablement was the hypothetical person having ordinary skill in the art, and the question was whether that person could “make or use” the claimed invention based on what they knew and what was recited in the specification. Written description, by contrast, was pegged to the patent document itself; it asked whether the scope of the claims aligned with the scope of what was disclosed in the patent document. But *Amgen* and *Juno Therapeutics* have effectively linked the two approaches, smuggling a “full scope of the claims” requirement into enablement in *Amgen* and a “functional adequacy according to a PHOSITA” requirement into written description in *Juno Therapeutics*.

Today, 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. In the following Sections, we document this departure from the Federal Circuit’s earlier antibody-patent jurisprudence and this turn away from earlier claiming practices.

1. *Enablement*

The Federal Circuit took the first step toward invalidating antibody claims in *Chiron Corp. v. Genentech, Inc.*¹⁸¹ There, the court affirmed the invalidation of

177. See, e.g., *Regents of Univ. of Cal.*, 119 F.3d at 1568; *Fiers*, 984 F.2d at 1170–71; *Amgen*, 927 F.2d at 1213.

178. 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).

179. 872 F.3d 1367 (Fed. Cir. 2017); *Amgen Inc. v. Sanofi*, 987 F.3d 1080 (Fed. Cir. 2021), *cert. granted*, 143 S. Ct. 399 (2022).

180. 10 F.4th 1330 (Fed. Cir. 2021).

181. 363 F.3d 1247 (Fed. Cir. 2004). Full disclosure: one of us (Lemley) represented Genentech in this case.

Chiron's antibody patent, claiming "[a] monoclonal antibody that binds to human c-erbB-2 antigen";¹⁸² erbB-2, now known as HER2, is a cellular marker of many breast cancers.¹⁸³

To be fair, the claims in *Chiron* were dubious. The asserted patent's prosecution history was complex but ultimately was based on a series of continuations-in-part over a fifteen-year period, the earliest of which disclosed murine (i.e., mouse-derived) antibodies that bound to erbB-2, but not human or chimeric (i.e., hybrid mouse-human) ones.¹⁸⁴ To satisfy § 112, the patentee also deposited a hybridoma line that produced the mouse antibodies at the American Type Culture Collection (ATCC).¹⁸⁵ Beaten to the finish line by Genentech in producing an antibody cancer therapy that targeted HER2, Chiron then sued Genentech for infringement by Herceptin (trastuzumab), Genentech's humanized antibody product.¹⁸⁶

The primary issue at trial was whether Chiron's broad claims, read as covering *any* monoclonal antibody that bound to HER2, satisfied the enablement and written description requirements.¹⁸⁷ A jury found that they did not and found the patent invalid for failing to comply with § 112.¹⁸⁸ On appeal, the Federal Circuit, relying on its "full-scope" jurisprudence for enablement, stated that the boundaries of any claims must be commensurate with the specification's disclosure.¹⁸⁹ 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."¹⁹⁰ 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.¹⁹¹ 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

182. *Id.* at 1250.

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

184. *Chiron*, 363 F.3d at 1251-52.

185. *Id.* at 1250 n.1.

186. *Id.* at 1252.

187. *Id.*

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

189. *Id.* at 1253.

190. *Id.* at 1254 (quoting *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1368 (Fed. Cir. 1997)).

191. *Id.* at 1256.

did not “provid[e] a ‘specific and useful teaching’ of all antibodies within the scope of the claim.”¹⁹²

The court also 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.¹⁹³ Furthermore, the specification included an additional disclaimer that the term “monoclonal” meant all antibodies produced from the same source, even if they possessed functional variations.¹⁹⁴ 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.¹⁹⁵

Chiron might 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.¹⁹⁶ But it sought to apply those patents to cover humanized antibody technology that didn’t exist at the time it made its mouse-derived antibodies.¹⁹⁷ For these reasons, it very well may be the case that the *Chiron* court got things correct as a 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 & Co.*¹⁹⁸ 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 describe sufficiently.

192. *Id.* (quoting *Novo Nordisk*, 108 F.3d. at 1368 (citation omitted)).

193. *Id.* at 1257.

194. *Id.* at 1257-58.

195. *Id.*

196. *Id.* at 1257.

197. *See id.* at 1257-58.

198. *See* 598 F.3d 1336, 1340 (Fed. Cir. 2010) (en banc).

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 yet invented at the time).¹⁹⁹

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.²⁰⁰ Like Chiron, Noelle had only disclosed the murine sequence but claimed the later-developed, far more valuable chimeric, humanized, and fully human sequences.²⁰¹ The Federal Circuit concluded that “a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated.”²⁰² As a consequence, Noelle lost some claims on written description grounds.²⁰³

As a general matter, the Federal Circuit’s description of genus claims is consistent with its other life-science cases.²⁰⁴ But the *Noelle* court was the first to apply this understanding directly to antibodies and in the written description

199. See Jorge L. Contreras, *Patent Reality Checks: Eliminating Patents on Fake, Impossible and Other Inoperative Inventions*, 102 J. PAT. & TRADEMARK OFF. SOC’Y 2, 7 (2021) (describing the role that “gun jumping” plays in mistaken patent claims); Holbrook, *supra* note 12, at 161-62 (referring to the prevention of late claiming as a “priority policing” function); Karshedt et al., *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) (describing “gun jumping” as “rushing to the PTO before spelling out what the invention actually is”); Lemley, *supra* note 8, at 940 (discussing the problems of “late claiming” for functional claims); Mark A. Lemley, Michael Risch, Ted Sichelman & R. Polk Wagner, *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 1357-58 (finding a patent claim invalid where it claimed a method to create molecules with a particular effect, but the patent disclosed “no completed syntheses of any of the molecules prophesized to [have the effect]”).

200. 355 F.3d 1343, 1350 (Fed. Cir. 2004); see Robert D. Stout & Jill Suttles, *The Many Roles of CD40 in Cell-Mediated Inflammatory Responses*, 17 IMMUNOLOGY TODAY 487, 487 (1996) (detailing CD40’s role in the inflammatory response).

201. *Noelle*, 355 F.3d at 1345-48.

202. *Id.* at 1350.

203. *Id.* at 1353.

204. See Karshedt et al., *supra* note 13, at 14-17 (reviewing other cases supporting this assertion).

context.²⁰⁵ Noelle unsuccessfully argued that “because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described [the claimed antibody] by stating that it binds to [the] human CD40CR antigen.”²⁰⁶ 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.”²⁰⁷ The court distinguished Noelle’s circumstance from that in *Enzo*—the case that established the “fully characterized antigen” test—because Noelle had not “fully characterized” *human* CD40CR.²⁰⁸ Without disclosing the structure of the claimed antibody *or* its antigen, the court held that the contested claims had not satisfied the written description requirement.²⁰⁹ Notably, however, the antigen was well known at the time as described in various pieces of prior art; Noelle simply hadn’t described its *structure* in his specification.²¹⁰ The Federal Circuit, by changing *Enzo*’s focus from “structure, formula, chemical name, or physical properties” and “specification to a deposit [of the protein] in a public depository,”²¹¹ to structure alone, limited the universe of cases in which the patentee could rely on characterization of the antigen to provide a written description for the antibody.

This universe was further circumscribed in 2011 in *Centocor Ortho Biotech, Inc. v. Abbott Laboratories*,²¹² a case that also involved an instance of likely 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: it nixed the Patent Office’s previous reliance on satisfying written description for antibody claims even if the antigen was “well-characterized.”²¹³ *Centocor* consequently marked a

205. The Federal Circuit addressed this issue in *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342, 1357, 1361-62 (Fed. Cir. 1998), in the context of claim construction, but ultimately declined to directly address the written description aspects because that issue was not raised at the district-court level.

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

207. *Id.* (emphasis added).

208. *Id.*

209. *Id.* at 1349-50.

210. *Id.* at 1349.

211. *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 964, 965 (Fed. Cir. 2002).

212. 636 F.3d 1341, 1346-47 (Fed. Cir. 2011).

213. *Id.* at 1351-52 n.4.

bright-line shift toward 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.²¹⁴

The claims in *Centocor* involved antibodies to TNF- α , the overproduction of which can lead to inflammatory conditions like arthritis.²¹⁵ Originally, Centocor and Abbott separately embarked on different research programs to develop antibodies for use in human patients.²¹⁶ 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).²¹⁷ Centocor filed a patent application disclosing murine and chimeric antibodies in 1991 and filed various continuations-in-part until 1994.²¹⁸

Abbott pursued a different research strategy, however, and filed a patent application in 1996 for an antibody that was “fully-human,” with both a human constant region and a human CDR; the patent was issued in 2000.²¹⁹ Abbott’s fully humanized antibodies were far more successful than chimeric ones; Abbott used the technology to create Humira (adalimumab), now the world’s highest-selling therapeutic drug.²²⁰ After Abbott obtained regulatory approval on Humira, Centocor filed additional claims to fully human antibodies.²²¹ 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.²²² Centocor then sued Abbott on this late patent and won a \$1.67 billion jury verdict.²²³

The Federal Circuit invalidated Centocor’s claims under an invigorated approach to written description.²²⁴ The court reiterated that written description required an applicant to “convey with reasonable clarity to those skilled in the

214. Karshstedt et al., *supra* note 13, at 62-63.

215. *Centocor*, 636 F.3d at 1344-45.

216. *Id.* at 1344.

217. *Id.* at 1344-45.

218. *Id.* at 1345-46.

219. *Id.* at 1346.

220. See Mullard, *supra* note 3, at 495.

221. *Centocor*, 636 F.3d at 1346.

222. *Id.* at 1346-47.

223. *Id.* at 1343-44.

224. See *id.* at 1350-51.

art that, as of the filing date sought, he or she was in possession of the invention.”²²⁵ Yet, in the Federal Circuit’s view, Centocor’s 1994 application did not adequately disclose a fully human antibody to TNF- α ; the application disclosed, instead, only a chimeric one.²²⁶ And although human antibodies and human TNF- α were mentioned in the specification, it only provided amino-acid sequences for a single mouse CDR.²²⁷ 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 asserted claims.”²²⁸

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.²²⁹ The court explained that while, in some simple situations, possessing a protein makes it trivially easy to secure a complementary antibody,²³⁰ this was not so for TNF- α .²³¹ Indeed, anti-TNF- α antibodies were already in the prior art.²³² The challenge instead was finding an efficient and therapeutically tolerable antibody that bound to TNF- α in the desired way. But finding one essentially required a canvassing of all possible CDR sequences that met such requirements.²³³ In the court’s view, Centocor’s patent was therefore not like claiming a lock openable by a single known key, but rather claiming a lock with “a ring with *a million* keys on it.”²³⁴ Centocor’s claims were consequently found invalid for lacking sufficient written description.²³⁵

The door to claiming antibodies from their antigens closed further in *AbbVie Deutschland GmbH v. Janssen Biotech, Inc.*²³⁶ Unlike prior cases, the patentee in *AbbVie* wasn’t seeking to stretch its claims to cover a different form of technology it hadn’t invented.

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

226. *Id.* at 1349.

227. *Id.*

228. *Id.* at 1351.

229. *Id.* at 1351-52.

230. *Id.* at 1352.

231. *See id.* at 1352-53.

232. *Id.* at 1352.

233. *Id.*

234. *Id.* (quoting Abbott’s expert, Dr. Jochen Salfeld).

235. *Id.* at 1353.

236. 759 F.3d 1285 (Fed. Cir. 2014).

In *AbbVie*, the patents at issue were directed toward human antibodies that bind to the human protein interleukin 12 (IL-12).²³⁷ AbbVie’s specification described amino-acid sequences of about 300 antibodies with a range of binding affinities.²³⁸ Importantly, though, the patent described only one type of heavy and light chains, which shared “90% or more amino acid sequence similarity in [the CDR].”²³⁹ While the accused product had different heavy and light chains with only 50% sequence similarity to AbbVie’s disclosed sequences, it was nonetheless covered by AbbVie’s claims.²⁴⁰ This is because AbbVie’s claims were predicated on one aspect of the antibodies’ *functionality*—how *strong* the antibodies bound to IL-12 by a measure of its disassociation rate from the antigen.²⁴¹ And, in that respect, the defendant’s antibodies were essentially indistinguishable from the plaintiff’s.²⁴²

This mix of some disclosed structure and functional claims—typical of antibody patents at the time—still failed the written description requirement.²⁴³ 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.”²⁴⁴ 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 other types of antibodies such as [the accused product].”²⁴⁵

237. *Id.* at 1291.

238. *See id.*

239. *Id.*

240. *See id.* at 1292–94.

241. *See id.* at 1292 (quoting U.S. Patent No. 6,914,128 col. 386 ll. 55–59 (filed Mar. 24, 2000)).

242. *See id.* at 1293.

243. *See id.* at 1297–1302.

244. *Id.* at 1299 (quoting *Ariad Pharms. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010)).

245. *Id.* at 1301. 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.

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 all, antibodies with a range of affinities and not antibodies with a range of structures.²⁴⁶ The court called this an “inapposite attempt[.]” that “merely” recited “a desired result, rather than the actual means for achieving that result.”²⁴⁷ 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.”²⁴⁸

AbbVie represented a fundamental shift away from the functional characterization of antibodies. It was 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.²⁴⁹ 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.”²⁵⁰ Since *AbbVie*, this has no longer been enough: the Federal Circuit

....

... 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 V_{H3}/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 V_{H3} 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.

Id. at 1298-1300.

246. *See id.* at 1298.

247. *Id.* at 1301.

248. *Id.*

249. *See id.* at 1291.

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

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, Inc. v. Kite Pharmaceuticals, Inc.*²⁵¹ 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, anti-PCSK9 antibodies, without undue experimentation.²⁵² 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.²⁵³

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 enzymes (PCSK9), enzymes important in the processing of cholesterol.²⁵⁴ 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.²⁵⁵ 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.²⁵⁶

At the first trial, the jury and the district court found the patents not invalid and the court ordered a permanent injunction.²⁵⁷ But on an emergency appeal from the injunction order, the Federal Circuit reversed the underlying validity determination.²⁵⁸ 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.²⁵⁹ The Federal Circuit

251. *Amgen Inc. v. Sanofi*, 987 F.3d 1080 (Fed. Cir. 2021), cert. granted, 143 S. Ct. 399 (2022); *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330 (Fed. Cir. 2021).

252. See *Amgen*, 987 F.3d at 1088.

253. *Juno*, 10 F.4th at 1342.

254. See *Amgen*, 987 F.3d at 1082-83.

255. See *id.* at 1083 (citing U.S. Patent Nos. 8,859,741 & 8,829,165).

256. *Id.*

257. *Id.* at 1084.

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

259. See *id.* at 1376-78.

pointedly took issue with the district court's jury instructions on § 112.²⁶⁰ Consistent with prior law, the district court had instructed the jury:

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.²⁶¹

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).”²⁶² 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.”²⁶³

In the Federal Circuit's view, this instruction “ran afoul” of the written description requirement²⁶⁴:

We cannot say that this particular context, involving a “newly characterized antigen” and a functional genus claim to corresponding antibodies, is one in which 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.²⁶⁵

On remand, a second jury once again found that Sanofi had not proven the patents invalid.²⁶⁶ But the district court ultimately granted Sanofi's motion for judgment as a matter of law for lack of enablement.²⁶⁷ On a second appeal, the

^{260.} *See id.* at 1378.

^{261.} *Id.* at 1376.

^{262.} *Id.* at 1377 (second alteration in original) (internal quotation marks omitted).

^{263.} *Id.* at 1377-78 (alteration in original).

^{264.} *Id.* at 1378.

^{265.} *Id.*

^{266.} *Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1084 (Fed. Cir. 2021), *cert. granted*, 143 S. Ct. 399 (2022).

^{267.} *Id.*

Federal Circuit upheld the district court's invalidity ruling.²⁶⁸ At the Federal Circuit, Amgen argued that a person of ordinary skill in the art could "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."²⁶⁹ Indeed, under the *Wands* factors, Amgen argued, its claimed invention required only routine experimentation²⁷⁰—experimentation made all the more routine by the development of antibody science in the intervening thirty-three years since *Wands* was decided.

The court disagreed. It took less issue with Amgen's factual assertions than with prior Federal Circuit law.²⁷¹ "[A]lthough *Wands* gave birth to its eponymous factors," the court wrote, "*Wands* did not proclaim that all broad claims to antibodies are necessarily enabled."²⁷² The functional claim limitations here "did not enable preparation of the full scope of these double-function claims without undue experimentation."²⁷³ 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."²⁷⁴ A person of ordinary skill in the art, it concluded, could only discover the claimed embodiments through massive trial-and-error or accidental discovery.²⁷⁵ The court saw broad functional claims coupled with narrow guidance, and concluded that no reasonable jury could find "anything but 'substantial time and effort' would be required to reach the full scope of claimed embodiments."²⁷⁶

This seeming repudiation of *Wands*—and, by extension, of genus claims in the life-sciences and chemical fields—reflects a fundamental reorientation of § 112 jurisprudence. It imposes a new requirement that a patentee teach the PHOSITA how to identify every working claim in the genus rather than just teach people how to find working examples in the genus. This novel requirement

268. *Id.* at 1088.

269. *Id.* at 1085.

270. *Id.*

271. *See id.* at 1086–88.

272. *Id.* at 1086.

273. *Id.* at 1087.

274. *Id.*

275. *Id.* at 1088.

276. *Id.*

is at odds with the rule in other countries,²⁷⁷ and it has been subject to academic criticism, including from one of us who has argued that it represents “the death of the genus claim.”²⁷⁸ 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. In his concurrence, Judge Lourie asserted that, despite arguments to the contrary, there was no change in the law; patentees could still obtain genus claims provided that they show enough working examples.²⁷⁹

Notably, however, there were 26 working examples in *Amgen* and 300 working examples in *AbbVie*.²⁸⁰ In *Amgen*, that still was not sufficient written description for the Federal Circuit despite a jury finding to the contrary.²⁸¹ Nor did the jury’s factual findings that PHOSITAs could identify other working antibodies move the court in either case.²⁸² 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. With-

277. 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 34-35* (Jan. 2022) (L.L.M. dissertation, Waseda University) (on file with authors).

278. Karshtedt et al., *supra* note 13, at 1; see also Jeffrey A. Lefstin, *The Formal Structure of Patent Law and the Limits of Enablement*, 23 BERKELEY 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 (suggesting 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, 286-87 (2008) (discussing the requirement in the context of *Liebel-Flarsheim Co. v. Medrad, Inc.*, 481 F.3d 1371 (Fed. Cir. 2007), among other cases); Guang Ming Whitley, Comment, *A Patent Doctrine Without Bounds: The “Extended” Written Description Requirement*, 71 U. CHI. L. REV. 617, 628-30 (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*, BERKELEY TECH. L.J. (forthcoming) (manuscript at 15-22), <https://ssrn.com/abstract=4025167> [<https://perma.cc/CXU7-ZFYW>] (measuring prosecution changes in response to this shift in doctrine).

279. *Amgen Inc. v. Sanofi*, 850 F. App’x 794, 795-96 (Fed. Cir. 2021) (Lourie, J., concurring in denial of reh’g en banc).

280. *Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1083 (Fed. Cir. 2021); *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1291 (Fed. Cir. 2014).

281. *Amgen*, 987 F.3d at 1084, 1088.

282. *Id.* at 1088; *AbbVie*, 759 F.3d at 1305.

out 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's impossible 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.

Juno Therapeutics, Inc. v. Kite Pharma, Inc. cements the court's structural turn.²⁸³ *Juno* concerned a remarkable application of immune receptors: re-engineering patients' T cells to produce chimeric antibodies that specifically target their unique blood cancers.²⁸⁴ The technology—chimeric antigen receptor T-cell therapy, or "CAR-T"—is arguably the first true gene therapy approved by the Food and Drug Administration (FDA).²⁸⁵

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 innovations 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.²⁸⁶ Juno subsequently sued Kite Pharma for infringing its patents with Kite's Yescarta (axicabtagene ciloleucel) product.²⁸⁷ A jury found that the claims were adequately described.²⁸⁸

On appeal, however, the Federal Circuit reversed, finding that Juno's patent for nucleic acids encoding chimeric T-cell receptors was invalid as a matter of law for lack of written description.²⁸⁹ 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.²⁹⁰ 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."²⁹¹ This was so even though the '190 patent disclosed

283. 10 F.4th 1330 (Fed. Cir. 2021).

284. *Id.* at 1333-34.

285. See Jacob S. Sherkow, Patricia J. Zettler & Henry T. Greely, *Is It 'Gene Therapy'?*, 5 J.L. & BI-OSCIS. 786, 786-87, 790-92 (2018).

286. *Juno*, 10 F.4th at 1333-34.

287. *Id.* at 1334.

288. *Id.*

289. *Id.* at 1332.

290. *Id.* at 1333-34 (discussing claims 3 and 9 of U.S. Patent No. 7,446,190).

291. *Id.* at 1342.

two working examples of scFvs, albeit without disclosing the amino-acid sequence of either.²⁹² 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.”²⁹³ But that seemed unlikely, given that the court’s definition of the functional genus – anything scFvs bound to their targets – claimed potentially quadrillions of candidates.²⁹⁴

Remarkably, the scFv fragments were not even the inventive part of the patent. The point of novelty was the double-inclusion of the zeta (ζ) chain and the costimulatory region.²⁹⁵ 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.²⁹⁶

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.²⁹⁷ 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.²⁹⁸ 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

292. *Id.* at 1333.

293. *Id.* at 1337.

294. *Id.* at 1336.

295. *Id.* at 1334.

296. *See id.* at 1337-38.

297. *See Centocor Ortho Biotech, Inc. v. Abbott Lab’s*, 636 F.3d 1341, 1352 (Fed. Cir. 2011) (suggesting the number could be “million[s]”). We note, however, that the precise number of undisclosed antibodies is potentially calculable for each given case and, depending on the affinity constraints of the patent, could be as few as a dozen-and-a-half undisclosed examples. *See Adams et al.*, *supra* note 136, at 10 (finding only eighteen antibodies from a universe of thousands that met the experimental binding-affinity constraints).

298. *See In re Wands*, 858 F.2d 731, 736-40 (Fed. Cir. 1988).

beyond the examples and guidance provided.”²⁹⁹ Given what we now know about antibody science, no robust specification could possibly encompass all possible examples of functionally claimed antibodies. Although in other fields, enablement has long been satisfied by linking the scope of claims to instructions for their use, for antibodies post-*Amgen*, “one cannot claim everything that works.”³⁰⁰

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.”³⁰¹ But, again, the science of antibodies has made the legal standard impossible; similar *functions* for antibodies do not mean similar *structures*.³⁰² Antibodies are made, naturally at least, through semirandom rearrangement of the *V(D)J* cassettes.³⁰³ They can be further selected for based on their function (that is, by the antigens to which they bind), but their utility and inventiveness is based on these functions, not on their underlying structure. Put less abstractly, researchers have little interest in the particular DNA sequence that gives rise to a particular antibody; they are instead interested in what the antibody does and how it does it. So, although *function* can make an antibody representative of a class, by establishing a group of molecules according to what they bind to and how, this class might have no “common structural features.”³⁰⁴ This representative-structure standard is, if not scientifically impossible, textually impractical. Demanding it is 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.*³⁰⁵ In *Baxalta*, Judge Dyk, a Federal Circuit judge sitting by designation in the District of Delaware, determined that Baxalta’s claims to bispecific antibodies, in which one arm of a CDR’s Y-shape binds to one antigen

299. *Amgen Inc. v. Sanofi*, 850 F. App’x 794, 796 (Fed. Cir. 2021) (Lourie, J., concurring in denial of reh’g en banc).

300. *Id.* at 797.

301. *Juno*, 10 F.4th at 1342.

302. See *supra* notes 46–50 and accompanying text; see also Adams et al., *supra* note 136, 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.”).

303. See *supra* notes 40–43 and accompanying text.

304. *Juno*, 10 F.4th at 1336.

305. 579 F. Supp. 3d 595 (D. Del. 2022).

and the other arm to another antigen, were invalid for lack of enablement.³⁰⁶ Baxalta's claims were indeed broad, including, for example, "[a]n isolated antibody or antibody fragment thereof that binds Factor IX or Factor IXa and increases the procoagulant activity of Factor IXa."³⁰⁷ 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.³⁰⁸ Nonetheless, this combination of functional claims and structural disclosure was 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.³⁰⁹ The issue instead was that "potential candidates number in the millions."³¹⁰ 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."³¹¹ This failed to satisfy the enablement standard.³¹² 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 after *Juno* to imagine 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."³¹³ Such an assurance would be technically impossible — an empty promise for almost all functional antibody claims.

In November 2022, as this Article was going to press, the Supreme Court granted certiorari in *Amgen* on the enablement issue while denying certiorari in

306. *Id.* at 625.

307. *Id.* at 601 (quoting U.S. Patent No. 7,033,590).

308. *Id.* at 606.

309. *Id.* at 599.

310. *Id.* at 614.

311. *Id.* at 599-600.

312. *Id.* at 600.

313. *Id.* at 622.

Juno on the written description issue. The *Amgen* case, which represents the Court's first foray into the law of enablement in over a century, offers it the chance to fix the problem the Federal Circuit has created with its full-scope enablement doctrine. The fact that the Court denied certiorari in *Juno*, however, means that the same full-scope problems may arise in the written description context regardless of how the Court rules on enablement.³¹⁴

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, but none of the four, by itself, is perfectly satisfying.

The first is to take at face value the court's assertion that, when it comes to molecules, structure is king. Perhaps, independent of the technical nuances of biology, patent law prefers claims covering "atoms" — that is, 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.

314. The *Juno* petition asked the Court to eliminate the written description doctrine altogether, an extreme position that may explain why the Court didn't take the case or even hold it pending the resolution of *Amgen*. See Petition for Writ of Certiorari at 4, 29, *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 143 S. Ct. 402 (2022) (No. 21-1566).

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.³¹⁵ Pithily: antibodies are molecules, and so they are chemistry, albeit chemistry on a scale large enough that atomic identity is impractical.³¹⁶ 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 do not, you cannot 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 claims it's doing. It is also 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.³¹⁷ 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

315. See Elizabeth Bailey, *Products of Human Ingenuity: The Isolation and Purification of Genes Under the Natural Product Doctrine*, 32 TEMP. J. SCI. TECH. & ENV'T 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 could result in a whole new, and patentable, invention.”); Dan L. Burk, Lecture, *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 25, at 1684-86 (discussing the relationship between molecular structure and inventiveness).

316. See *supra* notes 98-103 and accompanying text.

317. See, e.g., Dan L. Burk, *Biotechnology in the Federal Circuit: A Clockwork Lemon*, 46 ARIZ. L. REV. 441, 442-44 (2004) (arguing that the Federal Circuit “requires a very detailed disclosure, preferably a structural disclosure”); Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155, 1174-75 (2002) (“According to the court’s reasoning, disclosing a method for obtaining the molecule was not the same as disclosing the molecule itself.”).

know what even small structural changes will do.³¹⁸ 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.³¹⁹

But a structural story cannot 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 preventing gun jumping and late claiming, but it has been applied more broadly in the life sciences as a sort of "super-enablement" requirement.³²⁰

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

318. See Dan L. Burk & Mark A. Lemley, *Biotechnology's Uncertainty Principle*, 54 CASE W. RES. L. REV. 691, 735 (2004) (noting "[t]he Federal Circuit's insistence that the results of biotechnology research are unforeseeable or unpredictable"). For criticism that the Federal Circuit takes an excessively formalist view in its jurisprudence, and should move from bright lines to more flexible standards, see, for example, BURK & LEMLEY, *supra* note 178, at 79-94 ("[P]atents work differently in different industries, and we should not expect our analysis of patents in one industry to apply easily to another industry with radically different characteristics."); Timothy R. Holbrook, *The Supreme Court's Complicity in Federal Circuit Formalism*, 20 SANTA CLARA COMPUT. & HIGH TECH. L.J. 1, 1-2 (2003) (critiquing the Supreme Court's role in encouraging the Federal Circuit's formalistic approach); Lucas S. Osborn, *Instrumentalism at the Federal Circuit*, 56 ST. LOUIS U. L.J. 419, 425-26 (2012) (claiming that the Federal Circuit's "forced" decisional formalism leads to opinions lacking full legitimacy and, if continued, could harm judicial legitimacy"); Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1102-22 (2003) (stating that "formalism is a poor fit" for statutory interpretation of patent statutes intended to evolve over time); and John R. Thomas, *Formalism at the Federal Circuit*, 52 AM. U. L. REV. 771, 775, 796-808 (2003) (casting "a wary glance at the prevailing trend towards adjudicative rule formalism in the patent law"). 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) (explaining how formalism "helps reduce information costs associated with lay engagement with technology").

319. See, e.g., Chronister et al., *supra* note 106, at 1 (partially predicting antibody function based on sequence).

320. Burk & Lemley, *supra* note 25, at 1653; see also 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) ("Lilly has been perceived by many as transforming written description into a 'super-enablement' requirement specifically targeting biotechnology and substantially restricting the patentability of biotechnology-related inventions."); Karshedt et al., *supra* note 13, at 39 ("[S]ome commentators have explicitly called Lilly written description 'super-enablement' or 'enablement plus,' suggesting that it creates an extra hurdle for biotechnological inventions." (first citing Burk & Lemley, *supra* note 25, at 1653; and then citing Holman, *supra*, at 4)); Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 BERKELEY TECH. L.J. 615, 633 (1998) (coining the term "super-enablement").

years.³²¹ 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.³²² This has permitted 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.³²³ Simply put, if antibody claims written in functional form are, in some senses, the ultimate genus claims, a Federal Circuit intent on demise of such claims 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.

It would be particularly ironic if this were the explanation though, 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.³²⁴ 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 biological 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.³²⁵ The resulting functional software patents (many of which are outrageously overbroad) overlap and create patent thickets that have been widely identified as a significant problem in the software and information-technology

321. Karshedt et al., *supra* note 13, at 4.

322. *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. 58, 59 (2022). Holman does not deny the cases that we identify, but points to other genus patents that survived. But most of those cases were ones in which enablement and written description were not raised.

323. See *supra* notes 283-296 and accompanying text.

324. See Adams et al., *supra* note 136, at 10 (listing antibody clones with the same function but different structure); *supra* notes 40-45 and accompanying text (describing the *V(D)J* arrangement process).

325. See Lemley, *supra* note 8, at 923.

fields.³²⁶ The Federal Circuit might view antibody patents in this same vein today.

Patent law has faced functional claims before. They were quite common in the early twentieth century.³²⁷ The Wright brothers, for instance, notoriously claimed the idea of creating a warped-wing “aeroplane,” however implemented.³²⁸ The Supreme Court ultimately rejected such broad functional claiming in the 1940s as inconsistent with the purposes of the patent statute.³²⁹ 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 cover not 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.³³⁰

326. See *id.* at 920–23. Portions of this paragraph and the next are adapted from Lemley, *supra* note 8.

327. Among the early cases permitting functional claiming was *Morley Sewing Machine 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 919–22 (collecting software cases from 1996 to 2013).

328. *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 thus entitled to broad scope). The Wrights successfully enforced their patent to defeat all alternative aircrafts, including many that surpassed the technical achievement of the Wrights. See *Glenn Curtiss and the Wright Patent Battles*, U.S. CENTENNIAL 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, 725–26 (2012).

329. *Haliburton Oil Well Cementing Co. v. Walker*, 329 U.S. 1, 13 (1946); see also *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 368 (1938) (rejecting a claim to lighting filament claimed in functional terms to be “made up mainly of a number of 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 [that] are 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. See *Wyeth v. Stone*, 30 F. Cas. 723 (C.C.D. Mass. 1840) (opinion of Story, J.).

330. Patent Act of 1952, ch. 950, § 112, 66 Stat. 792, 798–99 (codified at 35 U.S.C. § 112(f)):

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.

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 flavor.³³¹ 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- κ B.³³² The Federal Circuit rejected this attempt as "a vague functional description and an invitation for further research [that] does not constitute written disclosure of a specific inhibitor."³³³ One could, perhaps, look at antibody claims and say something similar.³³⁴

But if this 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 software patent trolls who, claiming the idea of solving a problem without ever having made a product, sue those who actually do solve the problem.³³⁵ To date, at least, most antibody cases don't present similar worries, both because antibody patentees have almost invariably discovered and made new antibodies and because function can still be defined at a much lower level of abstraction.³³⁶ Even if claims directed to binding to a particular antigen are like "ring[s] with a million keys on [them],"³³⁷ that is still a significantly

331. 598 F.3d 1336 (Fed. Cir. 2010) (en banc).

332. *Id.* at 1340-41.

333. *Id.* at 1356.

334. 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 that solved it. Indeed, it took *Ariad*, which was founded in 1991, *twenty-one years* to get its first drug approved by the Food and Drug Administration (FDA) – decades after it filed its first patents on the technology at issue. See Julie M. Donnelly, *Ariad Wins Its First FDA Approval – Leukemia Drug Iclusig*, BOS. BUS. J. (Dec. 14, 2012, 1:46 PM EST), <https://www.bizjournals.com/boston/news/2012/12/14/ariad-wins-first-fda-approval-for.html> [<https://perma.cc/CYC4-EVES>]. That is much 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.

335. See Lemley, *supra* note 8, at 908.

336. To be clear, some of the early cases occasioning this shift do involve overclaiming. See, e.g., *Centocor Ortho Biotech, Inc. v. Abbott Lab'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.

337. *Centocor*, 636 F.3d at 1352 (emphasis omitted).

smaller subset than functional software claims, some of which are akin to claiming the very concept of “unlocking” – unlocking *anything*.³³⁸ Despite this, the Federal Circuit has done relatively little to rein in functional claiming in software, where it is generally overbroad, causing significant social harm,³³⁹ and employed by patentees who add little social value.³⁴⁰ Indeed, two Federal Circuit decisions that came down in 2022 essentially endorse pure functional claiming in software, undermining en banc circuit precedent established in *Williamson v. Citrix Online, LLC*.³⁴¹ But the court has been hypervigilant in preventing functional claiming for antibodies, extending this vigilance even past the point of novelty in *Juno*.

One of us has argued with Dan Burk that patent law is technology-specific, allowing the law to adapt to different technologies and market conditions.³⁴² The Federal Circuit periodically denies any such differences, even in the doctrines that most exhibit those differences – for example, antibodies and software.³⁴³ But by 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.”³⁴⁴

338. 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. See Kevin Emerson Collins, *Patent Law’s Functionality Malfunction and the Problem of Overbroad, Functional Software Patents*, 90 WASH. U. L. REV. 1399, 1402 n.5 (2013) (noting that software is “functional all the way down”). *But cf.* Lemley, *supra* note 8, at 961 (arguing that courts can nonetheless usefully limit claims to own the result, however it is achieved, rather than the problem).

339. See Lemley, *supra* note 8, at 906, 928-36.

340. See *id.* at 934-35. To some extent the doctrine of patentable subject matter has stepped in to police functional software claims by treating them as unpatentable abstract ideas, as one of us (Lemley) warned might happen. *Id.* at 937-38; see, e.g., *Alice Corp. Pty. Ltd. v. CLS Bank Int’l*, 573 U.S. 208, 216-27 (2014). But the cases are all over the map, and many cases allow functional software claims under § 101. See T. Vann Pearce, Jr. & Christopher Higgins, *The Effect of Alice and Its Progeny in 2020 on Software and 3D Printing Patents*, ORRICK, HERRINGTON & SUTCLIFFE LLP, <https://www.orrick.com/Articles/The-Effect-of-the-Alice-Decision-on-Software-and-3D-Printing-Patents> [<https://perma.cc/42BK-A9MG>] (reviewing cases).

341. 792 F.3d 1339, 1349 (Fed. Cir. 2015). The two cases that contravene *Williamson* are *Dyfan LLC v. Target Corp.*, 28 F.4th 1360, 1369 (Fed. Cir. 2022), which held that the mere use of the term “code” satisfied the requirement to show particular structure to implement a computer program; and *VDPP LLC v. VIZIO, Inc.*, No. 2021-2040, 2022 WL 885771, at *4 (Fed. Cir. Mar. 25, 2022), which held the same for the term “a storage.”

342. BURK & LEMLEY, *supra* note 178, at 49-65; Burk & Lemley, *supra* note 25, at 1589-95.

343. See, e.g., *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc).

344. Burk & Lemley, *supra* note 318, at 692.

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 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, and 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.”³⁴⁵ The Federal Circuit allowed those claims, not because it intended to give ownership over a vast, poorly defined genus of molecules, but for pragmatic reasons. *Function* was the only practical touchstone researchers could use to describe a particular antibody that the patentee had in fact identified.³⁴⁶ As the science advanced, however, it became easier to identify the attributes of a given antibody in more 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 inventor had identified. But now that researchers can routinely identify the underlying DNA sequence of a particular antibody, under this account patent claims 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, perhaps, analogous to how courts have historically treated product-by-process claims. They allowed claims that covered a chemical product to be written in the form of “the product produced by process X” when all that was known about the product is how it was 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.³⁴⁷ 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

345. See Revised Interim § 112 Guidelines, *supra* note 19, at 71439 (“[I]dentifying characteristics [of an antigen] . . . may be sufficient to show possession of the claimed invention to one of skill in the art.”).

346. See *supra* notes 149-152 and accompanying text (discussing the early state of the science).

347. See, e.g., *Abbott Lab’s v. Sandoz, Inc.*, 566 F.3d 1282, 1293 (Fed. Cir. 2009) (en banc); *Meurer & Nard*, *supra* note 151, at 1975. For a history of this development, see *Karshtedt*, *supra* note 151, at 109.

they knew about the product at the time, 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 is no indication that this is what the Federal Circuit thinks it is doing. To the contrary, all of the court's statements suggest that it is concerned (and has always been concerned) with identifying molecular structure. At least according to Judge Lourie, nothing has changed: "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."³⁴⁸

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. That is this Article's titular paradox, and the opposite of how both the enablement and written description doctrines normally work.

This might 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 simply a first step; it is not the invention of a genus. Instead, 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 million times over*.³⁴⁹ Pathbreaking innovation dec-

348. *Amgen Inc. v. Sanofi*, 850 F. App'x 794, 795 (2021) (Lourie, J., concurring in denial of reh'g en banc). By contrast, the Solicitor General, in opposing certiorari in *Amgen*, acknowledged that the Federal Circuit's law had adopted the full-scope enablement approach, but took the position that that change was a good thing. Brief for the United States as Amicus Curiae at 16-17, *Amgen Inc. v. Sanofi*, 143 S. Ct. 399 (2022) (No. 21-757).

349. See Iakes Ezkurdia, David Juan, Jose Manuel Rodriguez, Adam Frankish, Mark Diekhans, Jennifer Harrow, Jesus Vazquez, Alfonso Valencia & Michael L. Tress, *Multiple Evidence Strands Suggest that There May Be as Few as 19,000 Human Protein-Coding Genes*, 23 *HUM. MOLECULAR GENETICS* 5866, 5866 (2014).

ades ago, like Köhler and Milstein's Nobel Prize-winning work, allowed researchers simply to identify and produce antibodies *generally*.³⁵⁰ Pathbreaking biologics innovation today concerns sequencing and optimizing a single antibody.³⁵¹ 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 that 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 might suggest that the Federal Circuit's doctrinal turn regarding antibody patents is in response to public ire over pharmaceutical patents and drug pricing.³⁵² Antibody therapies are, of course, enormously expensive. Humira, the world's best-selling antibody therapy, stickers for \$77,586 per patient, every year – about two Teslas' worth.³⁵³ Globally, antibody therapies netted their manufacturers about \$157.33 billion in 2020.³⁵⁴ And while the relationship between patents and prices for biologics is

350. See Köhler & Milstein, *supra* note 82, at 495.

351. See, e.g., Stefan Schreiber, Katsuhiko Yamamoto, Rafael Muniz & Takafumi Iwura, *Physico-chemical Analysis and Biological Characterization of FKB327 as a Biosimilar to Adalimumab*, 8 PHARMACOLOGY RSCH. & PERSPS. art. no. e00604, at 1 (2020) (comparing the sequence of Humira to a biosimilar of Humira in a prospective therapeutic assessment).

352. The reports on the public's wrath over patents and drug prices are leviathan. See, for example, BUKO Pharma-Kampagne, medico international, Outras Palavras, People's Health Movement & Society for International Development, PATENTS KILL, <https://www.patents-kill.org> [<https://perma.cc/4XX6-RGJU>]; and *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.*, 7 F.4th 1320, 1342 (Fed. Cir. 2021) (Prost, J., dissenting) (criticizing the majority opinion for not encouraging generic access to carvedilol, a beta blocker).

353. Compare STAFF OF H.R. COMM. ON OVERSIGHT & REFORM, 117TH CONG., DRUG PRICING INVESTIGATION: ABBVIE – HUMIRA AND IMBRUVICA 1 (Comm. Print 2021), <https://oversight.house.gov/sites/democrats.oversight.house.gov/files/Committee%20on%20Oversight%20and%20Reform%20-%20AbbVie%20Staff%20Report.pdf> [<https://perma.cc/3TWP-T9P7>], with *\$35,000 Tesla Model 3 Available Now*, TESLA (Feb. 28, 2019), <https://www.tesla.com/blog/35000-tesla-model-3-available-now> [<https://perma.cc/BD3E-NEY3>].

354. *Monoclonal Antibody Therapy Market Size, Analysis, Development, Revenue, Future Growth, Business Prospects and Forecast to 2027*, *supra* note 116.

complex, especially given the fractured U.S. healthcare system,³⁵⁵ patents are certainly a significant component in that equation.³⁵⁶ The public has digested this information and turned its bile on drug manufacturers who are routinely vilified in the press and, increasingly, on Capitol Hill.³⁵⁷ 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.

But there is no compelling reason to think politics are driving the court's decisions. The political story doesn't explain why the appellate court upholds some biologics patents and not others.³⁵⁸ 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, Inc. v. Sanofi*, Repatha (evolocumab) and Praluent (alirocumab), are rather inexpensive, all things considered.³⁵⁹ But the Federal Circuit invalidated Amgen's claims regardless.³⁶⁰ Humira, by contrast, is wildly expensive, getting more expensive still, and yet its patents have largely been upheld.³⁶¹ Lastly, such a political explanation doesn't address why, of all provisions in the patent statute, the

355. See Robin Feldman, *Perverse Incentives: Why Everyone Prefers High Drug Prices—Except for Those Who Pay the Bills*, 57 HARV. J. ON LEGIS. 303, 306-08 (2020).

356. Evidence from small-molecule drugs suggests that prices decline by 80% to 85% once several generics enter. See Robin Feldman, *May Your Drug Price Be Evergreen*, 5 J.L. & BIOSCIS. 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. See Victor L. Van de Wiele, Reed F. Beall, Aaron S. Kesselheim & Ameet Sarpatwari, *The Characteristics of Patents Impacting Availability of Biosimilars*, 40 NATURE BIOTECH. 22, 22 (2022).

357. See STAFF OF H.R. COMM. ON OVERSIGHT & REFORM, *supra* note 353.

358. Compare, e.g., *Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1088 (Fed. Cir. 2021) (invalidating Amgen's anti-PCSK9 antibody patent), *cert. granted*, 143 S. Ct. 399 (2022), with *Eli Lilly & Co. v. Teva Pharm. Int'l GmbH*, 8 F.4th 1331, 1349 (Fed. Cir. 2021) (upholding Teva's anti-CGRP antibody patents).

359. See Gregg C. Fonarow, Ben van Hout, Guillermo Villa, Jorge Allerano & Peter Lindgren, *Updated Cost-Effectiveness Analysis of Evolocumab in Patients with Very High-Risk Atherosclerotic Cardiovascular Disease*, 4 JAMA CARDIOLOGY 691, 694 (2019) ("At 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 . . .").

360. See *Amgen*, 987 F.3d at 1088.

361. See *In re Humira Antitrust Litig.*, 465 F. Supp. 3d 811, 819 (N.D. Ill. 2020) (noting that most Humira patents have survived challenges); STAFF OF H.R. COMM. ON OVERSIGHT & REFORM, *supra* note 353, at 1 (describing Humira's recent price increases). *But see* STAFF OF H.R. COMM. ON OVERSIGHT & REFORM, *supra* note 353, at 25 ("In 2017, the U.S. Patent Trial and Appeal Board . . . invalidated three additional Humira patents that covered dosing for the treatment of rheumatoid arthritis because the dosing was 'obvious' and therefore unpatentable."). Notably, the Humira patents are generally not genus claims and have not been challenged on § 112 grounds.

Federal Circuit chose to make its stand on § 112, the source of the written description and enablement requirements. Other validity doctrines, like obviousness under § 103, are widely available in antibody cases.³⁶² A court interested in burying outcome-focused decisions has much better and subtler ways of doing so.

Moreover, such political explanations are a bit too thin. They are 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. Quite the contrary, it has from time to time gone out of its way to deny political motivations.³⁶³ If anything, the court has a political reputation for *protecting* the patent system.³⁶⁴ It would seem odd, therefore, that a political explanation for this doctrinal shift ends up destroying some of the patent system's most valuable assets.

* * *

In short, while there are several possible explanations for the antibody patent paradox, none of them is completely satisfying, either as a descriptive matter or as a justification for the change in the law.

362. See, e.g., John R. Allison, Mark A. Lemley & David L. Schwartz, *Understanding the Realities of Modern Patent Litigation*, 92 TEX. L. REV. 1769, 1785 tbl.2 (2014) (finding that more than a third of all reported decisions involved obviousness, more than twice as many as enablement or written description decisions).

363. See, e.g., *Ass'n for Molecular Pathology v. U.S. Pat. & Trademark Off.*, 689 F.3d 1303, 1324-25 (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. But disapproving of patents on medical methods and novel biological molecules are policy questions best left to Congress . . .”). More broadly, one early study found no connection between the political affiliations of Federal Circuit judges and how they vote on patent cases. See John R. Allison & Mark A. Lemley, *How Federal Circuit Judges Vote in Patent Cases*, 27 FLA. ST. U. L. REV. 745, 765-66 (2000).

364. See, e.g., JORGE L. CONTRERAS, *THE GENOME DEFENSE: INSIDE THE EPIC LEGAL BATTLE TO DETERMINE WHO OWNS YOUR DNA* 215 (2021) (noting the Federal Circuit's long-standing “pro-patent” reputation).

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 than claims to genera of antibodies with similar functions. The patent office still issues functional genus claims, but those claims are unlikely to survive in court. Recent work by S. Sean Tu and Christopher M. Holman suggests that patentees are taking this lesson to heart, as an increasing number of patents directed to antibodies are directed to individual species.³⁶⁵ Some are definitely narrow, limited to particular CDR sequences of particular antibodies.³⁶⁶ Others attempt to create narrow genus claims out of a specified group of CDR sequences.³⁶⁷

It is unclear whether that is truly a problem. 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 constrain them.³⁶⁸ The law used to speak of such patents as “pioneering” and therefore entitled to broad scope, especially in the old days of central

365. See Tu & Holman, *supra* note 278 (manuscript at 24-27).

366. See *id.* (manuscript at 25).

367. See *id.* (manuscript at 22-24).

368. See, e.g., Jacob S. Sherkow, *Law, History and Lessons in the CRISPR Patent Conflict*, 33 NATURE BIOTECH. 256, 256-57 (2015) (describing this for several biotechnological inventions); SAMANTHA ZYONTZ & CASSIDY POMEROY-CARTER, STAN. L. SCH., STUDY ON THE GERMAN INNOVATION SYSTEM: MAPPING OF THE RESEARCH, INNOVATION AND DIFFUSION ACTIVITY OF CRISPR ACROSS COUNTRIES, No. 12-2021, at 12-16 (Comm’n of Experts for Rsch. & Innovation 2021), https://www.e-fi.de/fileadmin/Assets/Studien/2021/StuDIS_12_2021.pdf [<https://perma.cc/289Z-JR8B>] (describing this in the context of genome editing technologies).

rather than peripheral claiming.³⁶⁹ 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.³⁷⁰ 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,³⁷¹ 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

369. For discussion of the pioneer patents doctrine, see, for example, *Miller v. Eagle Manufacturing 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 Electric Corp.*, 822 F.2d 1528, 1532 (Fed. Cir. 1987) (“A pioneer invention is entitled to a broad range of equivalents”); Meurer & Nard, *supra* note 151, 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); and 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, 429-35 (2012) (arguing that most “pioneering” inventions are in fact merely one of many similar independent and simultaneous breakthroughs by different innovators). The Court of Claims, the predecessor to the Federal Circuit, applied the pioneer patent doctrine. *See* *Autogiro Co. of Am. 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. *See* Burk & Lemley, *supra* note 22, at 1745; Lemley, *supra* note 8, at 910.

370. *See, e.g.*, STRUCTURAL GENOMICS CONSORTIUM, <https://www.thesgc.org> [<https://perma.cc/A4GG-BPZA>].

371. *See* Price & Rai, *supra* note 7, at 1026.

the same antigen and compete in the same market for lowering persistently high cholesterol. That competition can lower prices, which is a good thing.³⁷²

But we're skeptical of the more general argument 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.”³⁷³ To the contrary, what we've learned is that different structures can produce similar effects and vice versa. We know more about the antibodies we make, but that doesn't mean that making them has become routine. Generating effective, high-affinity, high-specificity, therapeutically tolerable, scalable, soluble, nonimmunogenic antibodies remains a challenge.³⁷⁴ 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.³⁷⁵ There is still good reason to encourage investment, and some form of patenting, in the task of identifying new antibodies.

We think this is true despite the existence of other forms of incentives, such as trade secrets or regulatory protections associated with developing new biologics. Trade secrecy can, of course, encourage investment in costly, difficult, or uncertain technologies.³⁷⁶ But for antibodies, trade secrets seem too blunt an instrument to best mediate the trade-off between innovation and follow-on competition. Secrets related to the antibody itself will often have to be disclosed if the antibody is administered to patients. Secrets related to the making of the

372. See, e.g., 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>].

373. Richard A. Norman, Francesco Ambrosetti, Alexandre M.J.J. Bonvin, Lucy J. Colwell, Sebastian Kelm, Sandeep Kumar & Konrad Krawczyk, *Computational Approaches to Therapeutic Antibody Design: Established Methods and Emerging Trends*, 21 BRIEFINGS BIOINFORMATICS 1549, 1549 (2020).

374. See *id.*

375. And perhaps rightfully so. See Adam Feuerstein & 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/EW8A-K5H4>].

376. See, e.g., Jacob S. Sherkow & Christopher Thomas Scott, *The Pick-and-Shovel Play: Bioethics for Gene-Editing Vector Patents*, 97 N.C. L. REV. 1497, 1500-01 (2019) (describing this in the context of gene-editing vector technology).

antibody, by contrast, may create IP protection that is too effective. This is because trade secrets often render a significant portion of the antibody-manufacturing process opaque, making it difficult if not downright impossible for competitors to develop their own antibodies through similar means, even if those antibodies have different functional characteristics.³⁷⁷ At least here, patent protection seems to be an improvement to the alternative.

Regulatory incentives might limit the development of biosimilars that copy the antibody exactly. But many antibody cases, like *Amgen v. Sanofi* and the development of anti-PCSK9 antibodies, involve not generic substitutes but competing brand owners developing and testing their own antibodies. That is, even with regulatory exclusivities for a given biologic product, well-heelled competitors can develop their own antibodies to the same antigen, armed with the knowledge of the progenitor's success. Some might conclude that we should permit competitors to develop their own antibodies. But effective patent protection might require preventing that competition for a limited period, just as it does in other industries.

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.³⁷⁸ This suggests that 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 in, say, 1984 (when Chiron first applied for patents covering its antibody), that doesn't mean that getting such a therapy across FDA's finish line has gotten substantially easier.³⁷⁹ Instead, broader patents covering multiple embodiments likely give larger pharmaceutical developers some solace that they will have the time (and exclusivity) to optimize antibody candidates.³⁸⁰ Narrowing claiming strategies to only a few embodiments of an early-

377. See Price & Rai, *supra* note 7, at 1046.

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

379. See, e.g., *id.*

380. 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.”).

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.³⁸¹ 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. Species patents that turn out to be easy for competitors to evade may not sufficiently encourage the sort of investment we need.

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.³⁸² 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.³⁸³ Claims that are too broad, even if they provide an 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."³⁸⁴ 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.

B. Practical Alternatives to Functional Antibody Claims

Perhaps there is a middle ground in patent law, some 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.³⁸⁵ One solution, sequence "homology" or "structure-

381. Cf. 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).

382. Palladino et al., *supra* note 74, at 738.

383. See Tu & Holman, *supra* note 278 (manuscript at 43).

384. Karshtedt et al., *supra* note 13, at 3.

385. 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.

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.³⁸⁶ 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.³⁸⁷ Tu and Holman provide some evidence of this occurring: claims directed to a combination of function and *some* sequence to the claimed antibodies’ CDRs.³⁸⁸ The problem, however, is that there is no direct relationship between structure and functional binding characteristics, so such a strategy wouldn’t create a genuinely broad genus claim; it would create only a loose subset of particular antibody species that 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.³⁸⁹

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.³⁹⁰ 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.³⁹¹ Homology claims for antibodies might be easy to evade and, in any event, it’s not clear that sequence-homology claims would avoid condemnation

386. See Holman, *supra* note 145, at 65-68 (noting problems with this approach historically); Tu & Holman, *supra* note 278 (manuscript at 33-34) (noting problems with this approach today).

387. See Tu & Holman, *supra* note 278 (manuscript at 24-26).

388. See *id.*

389. This is also why product-by-process claims to the same would fail; many of the resulting products would not function in the way required for them to work. See *supra* notes 151-155 and accompanying text.

390. Holman, *supra* note 145, at 65-68.

391. See *supra* notes 37-50 and accompanying text.

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 describe and enable the “full scope” of the claimed genus.³⁹² 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.³⁹³ A variation on this, a functional claim to an antibody coupled with a method of treatment limitation, is likely to face the same fate.³⁹⁴ 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, and replace them with pure structure limitations, for example, 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, might lie in how Congress treated functional claiming when it passed the Patent Act of 1952. Patent owners a century ago often wrote claims in purely functional terms.³⁹⁵ 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.³⁹⁶ In *Halliburton Oil Well Cementing Co. v. Walker*, the Supreme Court invalidated a patent claiming a resonator added to gas tubing that doubled

392. Karshedt et al., *supra* note 13, at 4.

393. *See id.*

394. *See* Tu & Holman, *supra* note 278 (manuscript at 43-44).

395. *See supra* notes 327-330 and accompanying text.

396. *Halliburton Oil Well Cementing Co. v. Walker*, 329 U.S. 1, 8 (1946). The Court held that the patent claim was indefinite because it did not specify how the patent performed the function or limit the invention to the particular means that 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. *Id.* at 12-14.

as a “tuned acoustical means which performs the functions of a sound filter” – a functional effect.³⁹⁷

Congress reversed *Halliburton* in the 1952 Patent Act by explicitly allowing means-plus-function claims – claims that used functional language when coupled with a means of achieving the result.³⁹⁸ This was so even if the means was the only novel part of the invention.³⁹⁹ 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.⁴⁰⁰

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.⁴⁰¹ 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 is 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 is not 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)) represents a significant narrowing of claim scope. While the 1952 Act rejected *Halliburton* and permitted functional claiming, the sort of functional claiming that 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

397. *Id.* at 7.

398. See Patent Act of 1952, ch. 950, § 112, 66 Stat. 792, 798-99 (codified at 35 U.S.C. § 112(f)).

399. See *In re Swinehart*, 439 F.2d 210, 212 (C.C.P.A. 1971) (“[T]here is nothing intrinsically wrong with . . . [defin[ing] something . . . by what it *does* rather than by what it *is*] . . . in drafting patent claims.”); see also *In re Schreiber*, 128 F.3d 1473, 1478 (Fed. Cir. 1997) (relying on the *Swinehart* holding).

400. § 112, 66 Stat. at 798-99.

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

claim construction, limiting the scope of these claims to only those disclosed in the patent's specification and equivalents thereof.⁴⁰² To take an example, suppose that a patent claim includes, as an element, a “means for processing data.”⁴⁰³ 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.”⁴⁰⁴

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.⁴⁰⁵ This means that such a claim would satisfy written description requirements because it would not “cover an enormous number (millions of billions) of . . . candidates”—only those disclosed in the specification.⁴⁰⁶ 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 would extend to equivalents.⁴⁰⁷ Some

402. See *In re Hyatt*, 708 F.2d 712, 714-15 (Fed. Cir. 1983).

403. 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 715. If there is more than one element, however, each of the elements can itself be a means-plus-function claim.

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

405. The use of the phrase “means for doing *X*” is standard but not required to invoke § 112(f). Rather, the question is whether the claim element discloses the function without disclosing the 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) (en banc).

406. *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1336 (Fed. Cir. 2021). At the same time, it should allow the legitimate bases for written description—preventing gun jumping and late claiming—to operate. A means-plus-function claim still has to disclose some structure, so patentees won't be able to file claims before identifying any antibodies at all. The fact that means-plus-function claims are tested as of the time the patent issues raises a risk of abuse of late claiming. As one of us has argued elsewhere, it makes more sense to test the scope of claims as of the filing date rather than later. Mark A. Lemley, *The Changing Meaning of Patent Claim Terms*, 104 MICH. L. REV. 101, 115-21 (2005).

407. See 35 U.S.C. § 112(a) (2018) (requiring a patentee to enable a PHOSITA to “make and use” the invention).

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. We think patentees like Amgen and Juno, who disclosed multiple working examples, could easily take advantage of our approach.

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.”⁴⁰⁸ 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 obtain the same result.”⁴⁰⁹ Some courts even speak of “known interchangeability” between the products.⁴¹⁰ The traditional doctrine of equivalents expressly encompasses later-developed equivalents, which is likely

One complication is that at least some Federal Circuit cases suggest that anything in the scope of the equivalents of a means-plus-function term must be enabled. *Auto. Techs. Int’l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1285 (Fed. Cir. 2007) (holding that a specification that taught only mechanical sensors did not support a means-plus-function claim that was construed to include undisclosed electronic sensors). Too broad a reading of this case, coupled with the modern “full scope” doctrine, would undermine the means-plus-function approach by demanding that the patent teach things that by definition it didn’t teach.

A limitation on *Automotive Technologies* is that enablement is tested only at the time of invention, so it doesn’t prevent the application of equivalents to antibodies discovered after the date of invention. See *In re Hogan*, 559 F.2d 595, 606 (C.C.P.A. 1977) (noting that it would be unfair to require a patentee to enable technologies that had not yet been invented); Lemley, *supra* note 406, at 106–08 (noting the different timing of the tests for enablement and means-plus-function claiming).

408. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39–40 (1997).

409. *Id.* at 38 (quoting *Mach. Co. v. Murphy*, 97 U.S. 120, 125 (1878)). Strictly speaking, after *Warner-Jenkinson*, equivalence is tested not by reference to the patent claim 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 multielement format.

410. *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 Indus., Inc.*, 145 F.3d 1303, 1307–08 (Fed. Cir. 1998); see also Lemley, *supra* note 406, at 109 (noting the cases setting the time at which equivalents is judged under means-plus-function claiming).

to include most cases of structurally different antibodies with identical functions.⁴¹¹ Even with massive structural differences between 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.⁴¹² 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*.⁴¹³

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.⁴¹⁴ Notably, it appears absent from the most recent empirical assessments of

411. *E.g.*, *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731-32 (2002). Means-plus-function equivalence *also* encompasses those later-developed technologies by applying the traditional 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 1307-08; *see also* John N. Kandara, Note, *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) (noting the intended balance between protecting patent holders and providing public notice of a patent's scope). Yes, we know that's needlessly confusing and makes no sense. We didn't write the law.

412. 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 Pharms. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1371-72 (Fed. Cir. 2015); and ensnarement (banning expansion of claims to cover things in the prior art), *see Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 683 (Fed. Cir. 1990).

413. Tu and Holman suggest using the reverse doctrine of equivalents to achieve balance in antibody genus claims. Tu & Holman, *supra* note 278 (manuscript at 34). 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. *See id.* at 35.

414. 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

antibody claiming practices.⁴¹⁵ Patentees would also need to decide how to describe the function: is the invention a “means for binding”? A “means for targeting” a particular antigen? A “means for interacting with” a particular molecule? We don’t deny that there would be difficulties in drafting means-plus-function claims for antibodies – and we don’t venture a guess as to which of these terms, or others, is optimal. But one of the virtues of means-plus-function claiming is that it is flexible enough to incorporate a variety of approaches. And it allows antibody patentees to avoid tethering either the “means” or the “function” part of their claims to the vagaries of antibody structure. We strongly suggest that patentees interested in avoiding this structure trap begin to think about means-plus-function claims when filing new antibody patents.

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

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% in January 2013. Dennis Crouch, *Means Plus Function Claiming*, PATENTLY-O (Jan. 14, 2013), <http://www.patentlyo.com/patent/2013/01/means-plus-function-claiming.html> [<https://perma.cc/M7TF-ES3N>]. 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, 176-81 (2011). Litigators, too, viewed them as narrower than other alternatives. See, e.g., Steven W. Lundberg, Gregory M. Stark & Ann M. McCrackin, *Crafting the Claims*, in ELECTRONIC AND SOFTWARE PATENTS: LAW AND PRACTICE 6-1, 6-20 (Steven W. Lundberg, Stephen C. Durant & Ann M. McCrackin eds., 4th ed. 2016) (“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].”); Ryan Sharp, Suneel Aurora & Greg Stark, *Can Beauregard Claims Show You the Money?*, 2 CYBARIS: INTEL. PROP. L. REV. 25, 34 (2011) (“[I]t is well known that means-plus-function claims are narrowly construed . . .”); 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.”); James Yang, *Drafting Tip: Avoid Means Plus Function Claims*, OC PAT. LAW. (Nov. 23, 2015), <https://opatentlawyer.com/claim-drafting-tip-avoid-means-plus-function-claims> [<https://perma.cc/XAS9-3K9K>]; see also 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 (Prac. L. Inst. ed., 2011) (warning against the efficacy of such claims in the software context). For a dissenting view, see Gregory J. Maier & Bradley D. Lytle, *The Strategic Use of Means-Plus-Function Claims*, 80 J. PAT. & TRADEMARK OFF. SOC’Y 241, 243 (1998). See also Zimmeck, *supra*, 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.

415. See Tu & Holman, *supra* note 278 (manuscript at 23-26) (explaining how patent-application strategies have evolved, and failing to find examples of means-plus-function applications).

the structure as well as the function of the antibody. As Tu and Holman 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.⁴¹⁶ While that claim will not be literally infringed by a different antibody, it might be infringed under the traditional equitable doctrine of equivalents. That doctrine applies the same basic tripartite “function-way-result” test that courts use to assess means-plus-function claims, with some differences that broaden its reach and some that narrow it.⁴¹⁷ 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.⁴¹⁸

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 (to mean the structure of the antibody rather than the antigen).

3. Policy Implications

Arguably the intermediate scope that 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 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 might 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

416. *Id.* at 24-26.

417. See Mark A. Lemley, *The Economics of Improvement in Intellectual Property Law*, 75 TEX. L. REV. 989, 1005-07 (1997). Some of this assessment may turn on factual questions about the economic value of given improvements, if any. See *id.*

418. See *supra* notes 46-50 and accompanying text.

likely to require substantial investment and actual reductions to practice. And it certainly 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.⁴¹⁹

This intermediate level of protection is crucial, in our estimation, for non-therapeutic antibody technologies, which are 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.⁴²⁰ So some might argue that we don't need strong patents at all for those therapeutics.

Unlike their therapeutic brethren, nontherapeutic 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.⁴²¹ Without such protections, copying, as evinced by allegations in a small but increasing spate of patent infringement cases, appears to be an ongoing concern.⁴²² But the patents in some of these suits are clearly overbroad and subject to invalidation.⁴²³ Means-plus-function claiming seems to strike the 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.

419. See Lemley, *supra* note 417, at 996–97 (explaining this balancing act).

420. A substantial literature considers whether and to what extent we need patents in the life-sciences industry at all, given the robust nonpatent exclusivities the law provides, including twelve years of data exclusivity for biologics. See, e.g., Thomas, *supra* note 380, at 39–53; Rebecca S. Eisenberg, *Patents and Regulatory Exclusivity*, in *THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY* 167 (Patricia M. Danzon & Sean Nicholson eds., 2012); Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 *TEX. L. REV.* 303 (2013); Mark A. Lemley, Lisa Larrimore Ouellette & Rachel E. Sachs, *The Medicare Innovation Subsidy*, 95 *N.Y.U. L. REV.* 75 (2020). We don't delve further into that debate.

421. Yaniv Heled, *Regulatory Competitive Shelters in the Area of Personalized Medicine*, 21 *B.U. J. SCI. & TECH. L.* 287, 288–93 (2015).

422. 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 Med. 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 Found. v. True Health Diagnostics*, No. 17-cv-198, 2017 WL 3381976 (E.D. Va. Aug. 4, 2017), *aff'd*, 760 F. App'x 1013 (Fed. Cir. 2019) (alleging copying of anti-JUL-1 antibody diagnostic).

423. E.g., *Athena*, 915 F.3d at 746.

But even where regulatory exclusivities are concerned, as they are with therapeutic antibodies under the Biologics Price, Competition, and Innovation Act (BPCIA), we think that 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 bio-similar. And oftentimes, as with anti-PCSK9 patent infringement, accused infringers are *not* accused of directly copying a patent holder’s technology.⁴²⁴ Means-plus-function claiming would allow 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 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.⁴²⁵ And even nonfunctional genus claims in the more traditional pharmaceutical industry are at risk under the full-scope-enablement and written description approaches.⁴²⁶ Means-plus-function claiming might 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 \$146 billion annual market – an amount projected to almost double by 2027.⁴²⁷ 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

424. See generally Complaint for Patent Infringement and Declaratory Judgment of Patent Infringement, *Amgen Inc. v. Sanofi*, No. 14-cv-01317 (D. Del. Oct. 17, 2014) (not accusing Sanofi of directly copying Amgen’s PCSK9 technology).

425. The Humira and Opdivo patent portfolios are examples.

426. Karshtedt et al., *supra* note 13, at 38-39.

427. *Market Size Report*, *supra* note 111.

with the science underlying the molecules themselves. Immune receptor production, a semirandom and expansive process, produces antibodies that are startlingly 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 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 industry. Perhaps the Federal Circuit is wary of a similar result in biotechnology.

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