AIPLA QUARTERLY JOURNAL

Volume 53, Number 2 Page 247 Spring 2025

ALPHAFOLD 3, AI, ANTIBODY PATENTS, THE FUTURE OF BROAD PHARMACEUTICAL PATENT CLAIMS, AND DRUG DEVELOPMENT

*Brendan Bargmann and Robert A. Bohrer**

LIST OF FIGURES

* © 2025 Brendan Bargmann is a member of the California Bar and an associate at Fennell Law, APLC. Robert A. Bohrer is Professor of Law Emeritus at California Western School of Law. The authors are grateful for the helpful comments and suggestions made by Mark Lemley, Arti Rai, Jake Sherkow, Brenda Simon and Andrew Torrance. We also benefitted from the comments and suggestions of the participants at Biolawlapalooza 6.0 and the 2024 ASLME Health Law Professors Conference.

I. INTRODUCTION

Artificial intelligence (AI) will have an enormous impact both on pharmaceutical development and patent protection, particularly for antibody therapeutics.[1] In *Amgen Inc. v. Sanofi*, the U.S. Supreme Court limited the scope of Amgen's therapeutic antibody patent to only those antibodies that were specifically described in Amgen's patent application and that had been shown to bind to a particular region of the target antigen, blocking the activity of the antigen that caused disease.[2] The reason for this limitation was the patent requirement of enablement: that potentially millions of antibodies could be generated to the target antigen but that not all would bind in a way that produced the therapeutic effect.[3] The Court concluded that Amgen's patent had not enabled other scientists to produce antibodies with the desired activity without "undue" experimentation, concluding a decades-long shift in their caselaw limiting the permissible scope of monoclonal antibody patents.[4] Our primary conclusion is that artificial intelligence has the power to overcome the problem of enablement that currently limits the scope of antibody patents. We also conclude that the rapid pace of improvement in AI is likely to bring about significant changes in pharmaceutical patents generally, with the potential to transform the future of drug development and the pharmaceutical industry.

In Part I of this Article, we provide a brief explanation of the science of antibodies in simple terms. In Part II, we discuss pharmaceutical patents in general, monoclonal antibody patents, and the Supreme Court's decision in *Amgen Inc. v. Sanofi.* In Part III of this Article, we provide introduction to AI as it is developing in the field of protein and antibody structure and function and its likely future impact on the field of antibody therapeutics. In Part IV, we briefly discuss how the development of AI in this field will overcome the limitations on patenting antibody therapeutics that were the basis of the Court's decision in *Amgen* while raising new issues for pharmaceutical patents. Lastly, in Part V, we

---

1 *See, e.g.*, Tânia Cova et al., *Artificial Intelligence and Quantum Computing as the Next Pharma Disruptors*, 2390 METHODS MOL. BIOL. 321, 321–47 (2022); Andrew Hill et al., *Transforming Drug Development with Synthetic Biology and AI*, 42 TRENDS IN BIOTECHNOL. 1072, 1072 (2024); Tim W. Dornis, *Artificial Intelligence and Innovation: The End of Patent Law as We Know It*, 23 YALE J.L. & TECH. 97, 97 (2020); Matthew Chun, *Artificial Intelligence for Drug Discovery: A New Frontier for Patent Law*, 104 J. PAT. & TRADEMARK OFF. SOC'Y 5, 5 (2024).

2 Amgen Inc. v. Sanofi, 598 U.S. 594, 642 (2023).

3 *Id.* at 613.

4 *See id.*

conclude with a discussion of the broader implications of the future developments in pharmaceutical AI on antibody patents, drug development, and possibly the pharmaceutical industry as a whole.

II. THE SCIENCE OF ANTIBODIES

While scientists had long been immunizing mice with various substances to study and use their B-cells and the antibodies those B-cells produced, in 1975, two British scientists, César Milstein and Georges Köhler, developed the ability to create "immortal" antibody-producing cell lines (hybridomas) that could be maintained indefinitely in cell culture.[5] Each of these immortal cell lines produces identical clones of the original antibodies and the antibodies they produce are known as monoclonal antibodies."[6] These monoclonal antibodies, which can be mass produced, are the basis of the modern application of antibody science to medicine and are seen as "magic bullets" that can be specifically targeted to hone in on disease agents or diseased cells without unwanted effects on normal tissue or organs.[7] Since the first monoclonal antibody was approved by the United States Food and Drug Administration (FDA) in 1986, therapeutic antibodies have become a major class of new drugs developed in recent years, and have been described as the "workhorses" and "backbone" of modern biotechnology.[8] Their growing financial impact on the pharmaceutical industry is hard to overstate. In 2020, the global monoclonal antibody therapy market was worth $157.33 billion, a tremendous sum, but one which is projected to grow at a 14.1% annual rate to a total of $451.89 billion by 2028.[9] Needless to say, the exclusive rights to the intellectual property for those therapies is of vital importance to the companies

---

5 Olive Leavy, *The Birth of Monoclonal Antibodies*, 17 NATURE IMMUNOLOGY S13, S13 (2016).

6 *Id.*

7 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, 8 (2003).

8 Ruei-Min Lu et al., *Development of Therapeutic Antibodies for the Treatment of Diseases*, 27 J. BIOMEDICAL SCI. 1, 1 (2020).

9 *Monoclonal Antibody Therapy Market Size to Surpass USD 451.89 Billion by 2028*, FORTUNE BUS. INSIGHTS (Aug. 3, 2023), https://www.globenewswire.com/news-release/2023/08/30/2734142/0/en/Monoclonal-Antibody-Therapy-Market-Size-to-Surpass-USD-451-89-Billion-by-2028-exhibiting-a-CAGR-of-14-1.html [https://perma.cc/JHB8-G5J8].

and universities which create and hold it and of significant concern to the overall healthcare industry.

The science of antibodies is a subfield of the science of proteins. Antibodies are proteins made by the B-cells of the immune system that can achieve a therapeutic effect by binding to a target "antigen" and preventing the target antigen from performing its function in a disease pathway.[10] The construction of any protein begins with a DNA sequence that contains the instructions for an amino acid sequence.[11] Amino acids are the building blocks of proteins and proteins are simply long chains of amino acids that are strung together and then folded into a complex three dimensional shape.[12] On a simplified structural level, an antibody is a large, Y-shaped protein, as shown in Figure 1.[13] The more complex, three-dimensional structure of an antibody is shown in Figure 2.[14]

---

[10] Mayo Clinic Staff, *Monoclonal Antibody Drugs for Cancer: How They Work*, MAYO CLINIC, https://www.mayoclinic.org/diseases-conditions/cancer/in-depth/monoclonal-antibody/art-20047808 [https://perma.cc/VB2F-2JUV].

[11] Kimberly Smith, *Science Snippet: The Power of Proteins*, NAT'L INST. GEN. MED. SCI.: BIOMEDICAL BEAT BLOG (May 3, 2023), https://biobeat.nigms.nih.gov/2023/05/science-snippet-the-power-of-proteins/ [https://perma.cc/AQZ2-3JVS].

[12] *Id.*

[13] *Antibody*, NIH: NAT'L HUMAN GENOME RESEARCH INST. (May 16, 2025), https://www.genome.gov/genetics-glossary/Antibody [https://perma.cc/C9DQ-E9K6].

[14] *IgG2a Monoclonal Antibody*, ADOBE STOCK, https://stock.adobe.com/images/igg2a-monoclonal-antibody-immunoglobulin-many-biotech-drugs-are-antibodies-atoms-are-represented-as-color-coded-spheres-per-chain-coloring/532836585?asset_id=532836585&content_id=532836585 [https://perma.cc/6H2Q-6ST7].

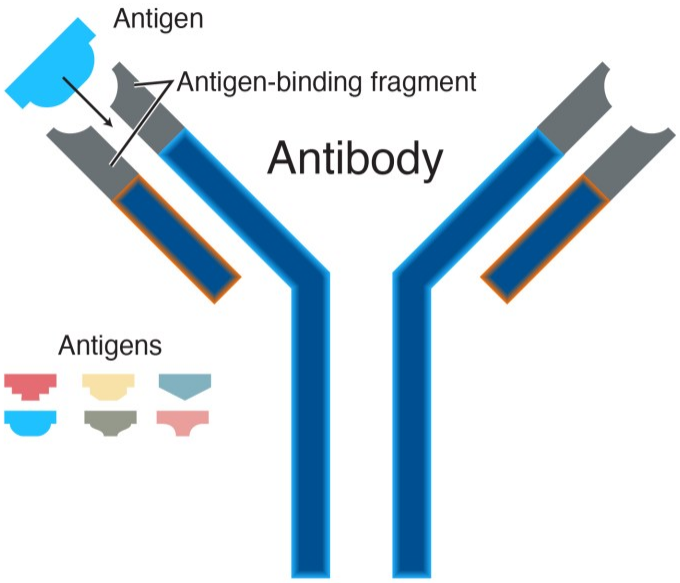


Figure 1. [15] **Structure of an Antibody and Antigen**

[15] *Antibody*, *supra* note 13.

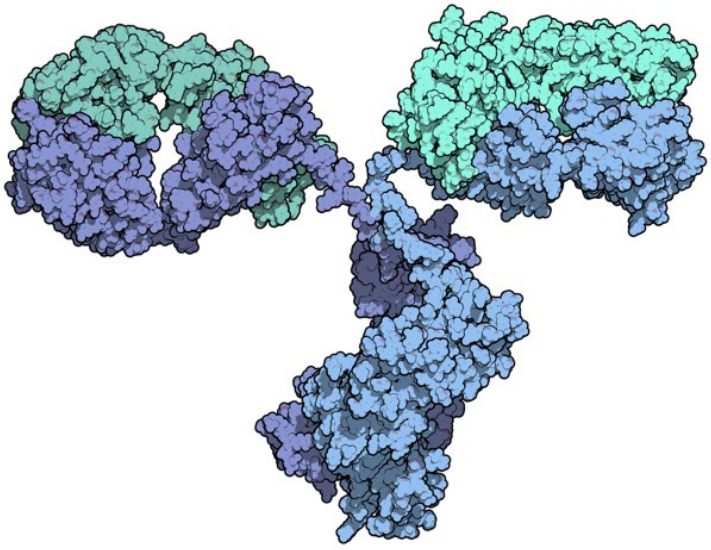


Figure 2. IgG2a Monoclonal Antibody.[16]

Each tip of the "Y" of an antibody contains a metaphorical "lock" or "antigen-binding fragment" that is specific for one particular "key" or "epitope" on an antigen, allowing these two structures to bind together with precision.[17] Using this binding mechanism, an antibody can tag a microbe or an infected cell for attack by other parts of the immune system, or it can neutralize it directly (for example, by blocking a part of a virus that is essential for its invasion).[18] In one recent application, monoclonal antibodies that bound to the spike protein on SARS-CoV-2 could prevent the virus from docking with and entering human

[16] *IgG2a Monoclonal Antibody*, *supra* note 14.

[17] There are actually two ways of defining the epitope—the first is by the linear sequence of the amino acids in the region of the antigen to which the antibody binds, the second is by the three-dimensional conformation of the region of the antigen to which the antibody binds. *See* Ning Lin et al., *Epitope Binning for Multiple Antibodies Simultaneously Using Mammalian Cell Display and DNA Sequencing*, 7 COMMUN. BIOL. 652, 652 (2024). For the purposes of this Article, the term epitope will be used to include either method for describing the region of the antigen to which the antibody binds.

[18] Smith, *supra* note 11.

cells.[19] It is the three-dimensional shape of an antibody and the antigen to which it binds that determines its functionality and reactivity; as in all biochemistry, structure determines function.[20] A hammer is a hammer because of its shape, just as a wrench does what it does because of its shape. An antibody binds to a particular region (epitope) of a specific antigen because the shape of the complementarity-determining region ("CDR") of that antibody enables it to bind to that epitope.[21]

The immune system produces antibodies in response to the challenge of a foreign ("non-self") substance in the body, which could be any virus, bacteria, toxin, foreign protein, cell, etc. An essential characteristic of the immune system is that it is capable of producing a staggering number of different antibodies in response to any foreign substance.[22] Therefore, the selection of antibodies with the desired characteristics is, inherently, a process of trial-and-error experimentation, albeit a well-defined and increasingly routine process.[23] Again, whether or not an antibody has the desired characteristics, in terms of its affinity for and manner of binding to the antigen, is determined by the three-dimensional shape formed as a result of that antibody's genetic sequence.[24] In *Amgen*, the Court's decision rested, at least in part, on the inability of scientists to predict which amino acid sequences would produce three-dimensional shapes with the desired characteristics.[25]

---

19 Erin Bryan, *Potent Neutralizing Antibodies Target New Regions of Coronavirus Spike*, NAT'L INST. HEALTH: RSCH. MATTERS (Aug. 4, 2020), https://www.nih.gov/news-events/nih-research-matters/potent-neutralizing-antibodies-target-new-regions-coronavirus-spike [https://perma.cc/2XYT-FDUQ].

20 *SAR | Structure Activity Relationships*, COLLABORATIVE DRUG DISCOVERY: VAULT (Oct. 8, 2024), https://info.collaborativedrug.com/tofu-content-what-is-sar [https://perma.cc/E2NT-R3HH]; *see also* Smith, *supra* note 11.

21 Amgen Inc. v. Sanofi, 598 U.S. 594, 600 (2023).

22 MorphoSys AG v. Janssen Biotech, Inc., 358 F. Supp. 3d 354, 369 (D. Del. 2019).

23 *See, e.g.*, Baxalta Inc. v. Genentech Inc. 597 F. Supp. 3d 595, 618 (D. Del. 2022). As we discuss in Part III, the courts have shifted their focus from whether or not the description enables the POSITA following the procedures outlined to make a working embodiment of the claimed invention to the question of how many working embodiments are within the scope of the claimed invention. *See infra* Part III.

24 *Amgen*, 598 U.S. at 600.

25 *Id.* However, while the desired amino acid sequence was too complex to be reliably predicted at the time Amgen Inc. filed its patent and even when the

Throughout the entire period of antibodies' use as therapeutic tools to the present day, the only method by which one could determine if a particular antibody would bind appropriately to a particular antigen was to observe whether or not it in fact did so.[26]

III. PATENTS

Patent law is one of the most significant areas of law and policy that impact the drug development decisions of pharmaceutical companies. A patent is a government grant providing the owner of the patent to exclude others, for a limited time, from making, using, or selling the patented invention.[27] Simply, pharmaceutical companies are very unlikely to undertake the lengthy and costly effort to develop a drug if drug patent claims cannot protect their drug against direct competition by copycat competitors.[28] The breadth of that protection obviously matters: the broader the protection, the greater the incentive and potential reward. The "optimal" breadth of protection is a difficult question because the value of follow-on competitor drugs that enter the marketplace after an innovator drug with a new mechanism of action is hotly debated.[29] However, despite the ongoing debate, the breadth of allowable patent claims for

Supreme Court rendered its decision, the technology to make such predictions is rapidly changing because of developments in artificial intelligence, as discussed in Part V of this article. *See infra* Part V.

[26] *Amgen*, 598 U.S. at 614.

[27] DONALD S. CHISUM, CHISUM ON PATENTS § 1.01 (2025).

[28] Sanofi–Synthelabo v. Apotex, Inc., 470 F.3d 1368, 1383 (Fed. Cir. 2006).

[29] *Compare* Joshua J. Gagne & Niteesh K. Choudhry, *How Many "Me-Too" Drugs Is Too Many?*, 305 J. AM. MED. ASSOC. 711, 711 (2011) (discussing that the benefits of follow-on drugs may be outweighed by the downsides) *with* Anupam B. Jena et al., *'Me-Too' Innovation in Pharmaceutical Markets*, 12 FORUM HEALTH ECON. & POLICY 5, 10–11 (2009) (finding that follow-on drugs may provide distinct benefits).

pharmaceuticals generally and monoclonal antibodies in particular has been continually narrowed over the past thirty years.[30]

A. THE IMPORTANCE OF PATENTS

The protection of an invention, as described in the claims of a patent, is referred to as the ".patent bargain"[31]: a quid pro quo in which an inventor receives a limited term of exclusivity and freedom from competition by copiers of the invention in exchange for teaching how to make and use the invention after the expiration of the patent.[32] The requirement that the inventor teach others how to make and use the invention is the requirement of enablement and is codified in 35 U.S.C. § 112(a), which states that an application for a patent must contain:

> a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.[33]

In other words, the application must describe the invention and teach (enable) others (commonly referred to as the "PHOSITA" or "Person Having Ordinary Skill In The Art") to make it and use it. The scope of a patent claim and the breadth of the exclusive rights that come with it are determined by the scope of that enablement: "the more a party claims, the broader the monopoly it demands, the more it must enable."[34] While this seems straightforward on its face, its interpretation has increasingly tightened the requirement of enablement and narrowed the scope of allowable claims to monoclonal antibodies.

---

30 *See* Sean Tu & Christopher M. Holman, *Antibody Patents: Use of the Written Description and Enablement Requirements at The Patent & Trademark Office*, 38 BERKELY TECH. L.J. 1, 40 (2023).

31 *Amgen*, 598 U.S. at 604.

32 Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 150 (1989).

33 35 U.S.C. § 112(a).

34 *Amgen*, 598 U.S. at 613.

B. PATENT CLAIMS

The boundaries of the ownership of real property are usually defined by a legal description on a deed and can be shown by lines on a survey.[35] The boundaries of the ownership of an invention are defined by their description in the claims of a patent.[36] In the life sciences, patent claims are generally divided into so-called "species claims" and "genus claims." Species claims in chemistry and biology are patent claims to a single embodiment of the invention or "thing": a single described molecule or compound or organism that the patentee actually built or conceived. Genus claims are much broader, covering a group of molecules or compounds that share some but not all features of a single species.[37] The claim shown in Figure 3 is a an abridged version of a typical genus claim that provides a core structure (the pentagonal shape in the diagram) with multiple positions labeled as "R" (R1-R4 in Figure 3), and then provides a number of different chemical combinations that can be used at each R position ("substitutions" e.g., where "R^1 is phenyl substituted …with …halo, C_2-C_{10}-alkyl, and sulfanyl").[38]

---

35 Hansford v. Silver Lake Heights, LLC, 280 P.3d 756, 760 (Kan. 2012).

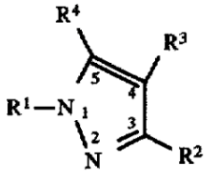
36 Dmitry Karshtedt et al., *The Death of the Genus Claim*, 35 HARV. J.L. & TECH. 1, 3 (2021).

37 Mark A. Lemley & Jacob S. Sherkow, *The Antibody Patent Paradox*, 132 YALE L.J. 994, 1000 (2023).

38 U.S. Patent No. 5,760,068 (filed June 2, 1998).

What is claimed is:

1. A method of treating inflammation or an inflammation-associated disorder in a subject, said method comprising administering to the subject having or susceptible to such inflammation or inflammation-associated disorder, a therapeutically-effective amount of a compound of Formula I



(I)

wherein R^1 is phenyl substituted at a substitutable position with one or more radicals selected from halo, C_1–C_{10}-alkyl, and sulfamyl

wherein R^2 is selected from hydrido, C_1–C_6-haloalkyl, cyano, carboxy, C_1–C_6-alkoxycarbonyl, C_1–C_6-carboxyalkyl, C_1–C_6-alkoxy, C_1–C_6-alkylthio,

Figure 3. A portion of Claim 1 of US Patent No. 5,760,068.[39]

[39] *Id.*

Genus claims are an important way to allow an inventor to capture the benefit of the invention and prevent others from competing by making relatively minor changes to any single species of the invention. The U.S. Patent and Trademark Office (USPTO) has long "grant[ed] broad genus claims as a matter of course in the chemical industries"[40] where they are "ubiquitous."[41] Genus claims protect against competitors who might otherwise make minor changes to an invention covered by a species claim.[42] However, the trend in recent years has been to increasingly restrict genus claims for pharmaceutical patents, just as the courts have increasingly restricted genus claims to antibody therapeutics.[43]

In the antibody context, a genus claim for an antibody treatment would be a claim to a whole class of antibodies defined by their characteristic binding to a particular protein and some specific effect on that protein. For example, a claim to "'the entire genus' of antibodies that (1) bind to specific amino acid residues on PCSK9 [a protein that degrades LDL cholesterol receptors], and (2) block PCSK9 from binding to [LDL receptors]" (brackets in original).[44] In contrast, a species claim for that same treatment would be for one particular antibody that bound to specified sites within PCSK9 and prevented PCSK9 binding to the LDL receptor. Because the human immune system can produce many different antibodies upon being challenged by a particular antigen, the value of the genus claim to the antibody is straightforward: a patentee can block competition from other drug developers who would seek to sell any of the "vast number" of other antibodies that bind to the same antigen and perform the same function; for example, binding to the specified sites within PCSK9 and blocking PCSK9 from binding to LDLR.[45]

C. ANTIBODY PATENTS: THE EVOLVING INTERPRETATION OF ENABLEMENT AND UNDUE EXPERIMENTATION.

In the 1980s, when monoclonal antibodies were first developed into commercial products, patentees who desired to patent a genus of antibodies did so by depositing a cell-line that produced the antibody and providing a functional,

---

40 Karshtedt et al., *supra* note 36, at 3.

41 *Id.*

42 *Id.*

43 *Id.* at 4; *see also* Lemley & Sherkow, *supra* note 37, at 1000.

44 Amgen Inc. v. Sanofi, 598 U.S. 594, 594 (2023).

45 *See Amgen*, 598 U.S. at 597 ("The record reflects that this class of antibodies does not include just the 26 that Amgen Inc. has described by their amino acid sequences, but a 'vast' number of additional antibodies that it has not.").

rather than structural, description of the antibody.[46] This was before the technology was developed to provide the DNA or amino acid sequences of newly discovered but commercially valuable antibodies.[47] Without that relatively broad patent protection it would have been relatively easy for competitors to develop other antibodies that performed essentially the same function.[48] Applicants for patents on monoclonal antibodies provided descriptions of the functional relationship between an antibody (or a class of antibodies) and their targets with increasing precision as the scientific tools to do so developed.[49] In 1999, the USPTO Guidelines provided that patentees could claim an antibody genus by providing a description of the antigen (in terms as specific as the state of technology then allowed) by "disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention . . . [including] functional characteristics [such as] . . . binding affinity, binding specificity, molecular weight, and length."[50]

While a detailed discussion of patent law is beyond the scope of this article, four sections of the United States Code provide the basic requirements for a claimed invention to be patentable:

35 U.S.C. § 101-patentable subject matter and utility;
35 U.S.C. § 102-novelty;
35 U.S.C. § 103-non-obviousness;
35 U.S.C. § 112-adequate written description and enablement.

The most frequently contested issue of patentability for non-antibody pharmaceutical patents is whether or not the claimed invention is anticipated by prior art (§ 102 and § 103), but the most common issue for antibody patents has shifted to § 112.[51] Although the term "undue experimentation" is not found in

---

46 *In re* Wands, 858 F.2d 731, 733 (Fed. Cir. 1988); *see also* Lemley & Sherkow, *supra* note 37, at 1014.

47 Lemley & Sherkow, *supra* note 37, at 1015 ("[D]efining 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.").

48 *Id.*

49 *Id.* at 1013.

50 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).

51 *See* Tu & Holman, *supra* note 30, at 1.

§ 112, it has long been understood to be a key to determining whether or not the patent application meets the requirement of enablement:

> The term "undue experimentation" does not appear in the statute, but it is well established that enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.[52]

Wands, which also was a case involving a monoclonal antibody patent, set out an eight factor test, known as the "*Wands* factors" or the "*Wands* analysis," that continues to be used to assess whether or not a disclosure was enabling.[53] Those factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and, (8) the breadth of the claims.[54]

The *Wands* factors continue to "provide the factual considerations that a court may consider when determining whether the amount of that experimentation is either 'undue' or sufficiently routine such that an ordinarily skilled artisan would reasonably be expected to carry it out."[55] However, even though the skill in the art of making antibodies has steadily increased (and with it the relative certainty that the PHOSITA would be able to produce an effective antibody that meets the description of the claim), the courts have increasingly found broad, functional claims to antibodies to novel antigens to require undue experimentation and limited the scope of claims to antibody inventions. This "inverse relationship" between the skill in the art and the sufficiency of a disclosure to support a claim is what Mark Lemley and Jacob Sherkow have termed the "antibody paradox."[56]

---

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

53 *See, e.g.*, Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc., 714 F. Supp. 3d 652, 729 (N.D. W.Va. 2024).

54 *In re Wands*, 858 F.2d at 737.

55 Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1085 (Fed. Cir. 2021).

56 Lemley & Sherkow, *supra* note 37, at 1000.

A comparison of the language of the claim upheld in *Wands* and the claim rejected in *Amgen v. Sanofi* exemplifies this paradox because the two claims are very much alike. Both patents claim monoclonal antibodies by describing their binding to the target antigen, HBsAG (Hepatitis B surface antigen) in *Wands* and PCSK9 in *Amgen*.[57] The claim upheld in *Wands* was to an immunoassay for diagnosing Hepatitis B using "a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9M-1."[58] One of the core claims rejected in *Amgen* was to a therapeutic monoclonal antibody that "when bound to PCSK9, the monoclonal antibody binds to at least one of the following residues: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, or S381 of SEQ ID NO:3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR."[59]

The two claims do describe the claimed antibodies binding in different ways, in *Wands* by the affinity or strength of binding to HBsAG and in *Amgen* by the binding sites on the antigen and the result of preventing PCSK9 from binding to LDLR.[60] However, whether the antibody is described by functional characteristics such as the strength of its binding to the target, or by specifying the individual amino acids which bind to the target, that difference in describing the antibodies binding and therefore limiting the scope of the claim can hardly explain the differing conclusions that the claim in *Wands* was enabled and that the claim in *Amgen* was not. After all, there were significant advances in the available laboratory equipment and experimental sophistication that occurred between 1989 when the *Wands* patent was filed and 2014 when the first of the two Amgen patents was filed.[61] Perhaps the most telling line in the *Amgen* opinion is this: "Amgen offers persons skilled in the art little more than advice to engage in 'trial and error.'"[62] Of course, the invention in *Wands* also required trial and error to select antibodies that met or exceeded the affinity of 10^9M-1.[63] Since, the science of

---

57 *In re Wands*, 858 F.2d at 733; *Amgen*, 987 F.3d at 1083.

58 *In re Wands*, 858 F.2d at 734.

59 *Amgen*, 987 F.3d at 1083.

60 *In re Wands*, 858 F.2d at 734; *Amgen*, 987 F.3d at 1083.

61 *See* Justin K.H. Liu, *The History of Monoclonal Antibody Development–Progress, Remaining Challenges and Future Innovations*, 3 ANNALS OF MEDICINE AND SURGERY 113, 113–16 (2014); Aaron L. Nelson et al., *Development Trends for Human Monoclonal Antibody Therapeutics*, 9 NATURE REVIEWS DRUG DISCOVERY 767, 767–74 (2010).

62 Amgen Inc. v. Sanofi, 598 U.S. 594, 615 (2023).

63 *In re Wands*, 858 F.2d at 737–38.

making and screening antibodies had significantly advanced as had the technology used in the lab,[64] how did the trial and effort involved in screening and selecting antibodies become an unduly burdensome effort or undue experimentation? A brief quote from each of the two opinions reveals the answer. In *Wands*, the Federal Circuit responded to the issue of undue experimentation with this:

> Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. No evidence was presented by either party on how many hybridomas would be viewed by those in the art as requiring undue experimentation to screen. However, it seems unlikely that undue experimentation would be defined in terms of the number of hybridomas that were never screened.[65]

However, while to Judge Smith in Wands it would have seemed "unlikely" to define undue experimentation in terms of the number of hybridomas that were never screened, that is precisely what Judge Lourie did in ruling against Amgen:

> What emerges from our case law is that the enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim.[66]

In other words, how many hybridomas were within the scope of the claim but not adequately described? The "breadth of the claims" is the eighth of the eight *Wands* factors. The *Wands* court and the USPTO throughout the 1990s through at least 2006 did not find functional and binding characteristic claims to antibodies

---

[64] For an excellent exploration of the tools and equipment available that allowed orders of magnitude more "experiments" to be done in parallel and at high speed even by 2005, see Hennie R. Hoogenboom, *Selecting and Screening Recombinant Antibody Libraries*, 23 NATURE BIOTECHNOLOGY, 1105, 1105–16 (2005).

[65] *In re Wands*, 858 F.2d at 740.

[66] Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1086 (Fed. Cir. 2021).

to be overly broad or to require unduly burdensome experimentation.[67] There were no cases before the Federal Circuit Court of Appeals during that time which focused on the breadth of those claims. Yet in *Amgen Inc. v. Sanofi* the breadth of the claim was not just one of the factors, it was clearly the deciding factor.[68] Although Justice Gorsuch stated that the Court:

> [A]gree[d] with Amgen that enablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim, we are not so sure the Federal Circuit thought otherwise. That court went out of its way to say that it "do[es] not hold that the effort required to exhaust a genus is dispositive." 987 F. 3d, at 1088 (emphasis deleted). Instead, the [Federal Circuit] court stressed, the problem it saw is the same problem we see: Amgen offers persons skilled in the art little more than advice to engage in "trial and error." [69]

However, in asserting that Amgen "has failed to enable all that it has claimed, even allowing for a reasonable degree of experimentation" Justice Gorsuch is clearly adopting the Federal Circuit Cour's evolution of the meaning of undue experimentation from the amount of experimentation required to find *an* antibody within the scope of the claim to the amount of experimentation required to find some indeterminate (but implicitly large) number of antibodies (even if not *all* as Justice Gorsuch noted).[70] Nowhere does either Judge Lourie, writing for the Federal Circuit, or Justice Gorsuch writing for the Supreme Court, discuss how much "trial and error" would be required to produce just one successful antibody, in light of all the other *Wands* factors. Justice Gorsuch, writing for the Court, echoed the focus of the Federal Circuit on the breadth of the claims: "For if our cases teach anything, it is that the more a party claims, the broader the monopoly it demands, the more it must enable."[71] The shift in the test of enablement for pharmaceutical patents from the eight *Wands* factors to just the eighth *Wands* factor is now complete.

Sean Tu and Christopher Holman demonstrated that this change over time in antibody patent claims from broad functional descriptions to narrow

---

[67] Tu & Holman, *supra* note 30, at 25.

[68] Amgen Inc. v. Sanofi, 598 U.S. 594, 615 (2023).

[69] *Id.* (emphasis deleted in original text).

[70] *See id.*

[71] *Id.* at 613.

structural claims correlated with the changes in antibody inventions from primarily being developed as diagnostic tools to primarily being developed as therapeutics.[72] Tu and Holman note that the risk and uncertainty is greater in developing a therapeutic antibody compared with the risk and uncertainty in developing a diagnostic antibody that is used in vitro to simply detect the target pathogen or disease marker.[73] It could be argued that the greater risk should provide a greater reward: successfully identifying an antigen that is a good target for an antibody therapy and developing an effective antibody to that antigen in order to treat or cure disease arguably deserves the greater reward that exclusivity based on a functional claim would bring.[74] Modern drug development begins with the identification of a target for the drug and remains a high-risk proposition.[75] A very recent illustration of the difficulty of validating an antigen target and the high cost of developing an antibody drug for a relatively poor antigen target are the beta-amyloid targeting antibodies, a number of which failed in clinical trials[76] and the most recent of which have shown only limited effectiveness.[77]

The risky and expensive effort required to validate a new antigen target for antibody development would seem to be an argument for providing the inventor who has done so with reasonably effective protection from competition

---

72 Tu & Holman, *supra* note 30, at 5.

73 S. Sean Tu & Christopher M. Holman, *Antibody Claims and the Evolution of the Written Description/Enablement Requirement*, 63 IDEA 84, 125–26 (2022).

74 *See infra* Part VI. We argue that relative risk and reward have been the central justification for the patent system since its beginning.

75 Chris Finan et al., *The Druggable Genome And Support For Target Identification And Validation In Drug* Development, 9 SCI. TRANSLATIONAL MED. 383, 383 (2017) ("Only 4% of drug development programs yield licensed drugs."); *see also* Mark E. Bunnage, *Getting Pharmaceutical R&D Back on Target*, 7 NATURE CHEMICAL BIOLOGY 335, 335 (2011).

76 Stephen Salloway et al., *Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease*, 370 NEW ENG. J. OF MED. 322, 322 (2014); Reisa A. Sperling et al., *Trial of Solanezumab in Preclinical Alzheimer's Disease*, 389 NEW ENG. J. MED. 1096, 1096 (2023); Suzanne Ostrowitzki et al., *Evaluating the Safety and Efficacy of Crenezumab vs Placebo in Adults with Early Alzheimer Disease: Two Phase 3 Randomized Placebo-Controlled Trials*, 79 J. AM. MED. ASSOC. NEUROL. 1113, 1113 (2022).

77 Asher Mullard, *FDA Approves Third Anti-Amyloid Antibody for Alzheimer Disease*, 23 NATURE REVIEWS DRUG DISCOVERY 570, 571 (2024) ("Neurologists are divided over whether the benefits provided by these antibodies are clinically meaningful.").

by subsequent developers of antibodies to that same target. Lemley and Sherkow suggest several possible reasons that might explain the antibody paradox of increasing skill in the art being accompanied by an increasingly difficult enablement standard as antibody research shifted from diagnostic applications to therapeutic applications. One suggestion 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."[78] Of course, that approach to patent scope brings us back to the question of the optimal scope of patent protection for pharmaceuticals.

Broader patent protection for the first drug to work through a new target, known as first-in-class drugs, might lead to fewer "me-too" drugs that merely iterate prior advancements and more innovation.[79] However, the other side of that coin is the argument that narrower patent protection provides competition that might lead to lower prices and that "me-too" drugs may well have advantages in terms of adverse effects or efficacy in different subpopulations.[80] While the optimal scope of pharmaceutical patents continues to be debated, the rapid development of AI and its application to the life sciences is about to transform the problem of patenting therapeutic monoclonal antibodies in particular and pharmaceutical inventions in general, with consequences for patents and the pharmaceutical industry that are difficult to predict.

IV. THE POWER OF AI TO DETERMINE THE STRUCTURE OF PROTEINS: A REVOLUTION IN BIOLOGY AND THE DEVELOPMENT OF MONOCLONAL ANTIBODY THERAPEUTICS

The relationship between three-dimensional structure and function, which is a fundamental characteristic of proteins generally and is discussed in more detail in Part I,[81] is the key to the way in which AI is beginning to

---

78 Lemley and Sherkow, *supra* note 37, at 1037.

79 *See* Robert A. Bohrer, *Reach-Through Claims for Drug Target Patents: Rx for Pharmaceutical Policy*, 26 NAT. BIOTECHNOL. 55, 55 (2008); *cf.* Joseph A. DiMasi & Laura B. Faden, *Competitiveness in Follow-On Drug R&D: A Race or Imitation?*, 10 NATURE REVIEWS DRUG DISCOVERY 23, 23 (2011).

80 DiMasi, *supra* note 79, at 23.

81 RICHARD A. HARVEY & DENISE R. FERRIER, LIPPINCOTT'S ILLUSTRATED REVIEWS: BIOCHEMISTRY S1 (Richard A. Harvey ed., 5th ed. 2011).

revolutionize pharmaceutical development.[82] Rational drug design, the dominant approach to drug discovery, relies on protein structures determined by x-ray crystallography.[83] However, X-ray crystallography and other laboratory-based approaches to determining the three-dimensional structure of proteins face numerous technical challenges and, as a result, by 2021 only 17% of human proteins had been partially or fully structurally described.[84] Google's first-generation application of "AI" to protein structure determination was a widely celebrated advance in computational approaches to protein structure.[85] A little more than a year later an "entirely redesigned version"— "AlphaFold2"— demonstrated even greater power:

> Here we provide the first computational method that can regularly predict protein structures with atomic accuracy even in cases in which no similar structure is known. We validated an entirely redesigned version of our neural network-based model, AlphaFold [AlphaFold2], in the challenging 14th Critical Assessment of protein Structure Prediction (CASP14), demonstrating accuracy competitive with experimental structures in a majority of cases and greatly outperforming other methods.[86]

AlphaFold 2 was able to provide highly accurate three-dimensional structures for proteins from the proteins' linear amino acid sequences and essentially solved the

---

82 Xinru Qiu et al., *Advances in AI for Protein Structure Prediction: Implications for Cancer Drug Discovery and Development*, 14 BIOMOLECULES 339, 339 (2024).

83 *See, e.g.*, Cody Aplin, et al., *Evolving Experimental Techniques for Structure-Based Drug Design*, 126 J. PHYSICAL CHEMISTRY & BIOPHYSICS 6599, 6607 (2022); *see also* Wim G. J. Hol, *Protein Crystallography and Computer Graphics—Toward Rational Drug Design*, 25 ANGEWANDTE CHEMIE INT'L ED. ENG. 767, 778 (1986).

84 Kathryn Tunyasuvunakool et al., *Highly Accurate Protein Structure Prediction for the Human Proteome*, 596 NATURE 590, 590 (2021); Cade Metz, *London A.I. Lab Claims Breakthrough That Could Accelerate Drug Discovery*, N. Y. TIMES (Nov. 1, 2020), https://www.nytimes.com/2020/11/30/technology/deepmind-ai-protein-folding.html [https://perma.cc/S2S3-NPMA].

85 Andrew W. Senior et al., *Improved Protein Structure Prediction Using Potentials from Deep Learning*, 577 NATURE 706, 706 (2020). For a representative reaction to the Nature article see e.g. Metz, *supr*a note 84.

86 John Jumper et al., *Highly Accurate Protein Structure Prediction with AlphaFold*, 596 NATURE 583, 583 (2021).

protein folding problem.[87] The power of this breakthrough in the application of AI to protein structure was immediately recognized as bringing with it a corresponding increase in the utility of AI in drug discovery.[88]

The most recent evolution of Google's AlphaFold neural network, AlphaFold 3.0 ("AlphaFold 3"), announced in Nature on May 8, 2024,[89] made the leap from predicting the structure of individual proteins to enabling high-confidence modeling of the interaction of two biomolecules, including antibodies binding to antigens.[90] One of the applications of AlphaFold 3, highlighted in the Abramson and Adler paper announcing its development, was the ability to produce "substantially higher antibody–antigen prediction accuracy compared with AlphaFold-Multimer v.2.3."[91] One of the antibody-antigen examples provided in the paper is illustrated in Figure 3c of Abramson and Adler, showing "mesothelin c-terminal peptide" bound to the monoclonal antibody 15B6 (mAb 15B6).[92] The antigen mesothelin c-terminal peptide is believed to be a good target for cancer therapeutics and the 15B6 antibody to mesothelin c-terminal peptide had already been shown to have anticancer activity and potentially serve as a

---

87 Andrei N. Lupas et al., *The Breakthrough in Protein Structure Prediction*, 479 BIOCHEMICAL J. 1885, 1885 (2021)

> We were part of the assessment team for the most recent CASP experiment, CASP14, where we witnessed an astonishing breakthrough by DeepMind, the leading artificial intelligence laboratory of Alphabet Inc. The models filed by DeepMind's structure prediction team using the program AlphaFold2 were often essentially indistinguishable from experimental structures, leading to a consensus in the community that the structure prediction problem for single protein chains has been solved.

88 Jose Jiménez-Luna et al., *Artificial Intelligence in Drug Discovery: Recent Advances and Future Perspectives*, 16 EXPERT OPINION ON DRUG DISCOVERY 949, 949 (2021).

89 Josh Abramson et al., *Accurate Structure Prediction of Biomolecular Interactions with AlphaFold 3*, 630 NATURE 493, 493 (2024).

90 *Id.*

91 *Id.* (internal citations omitted).

92 *Id.* at 496.

springboard for developing anticancer therapeutics.[93] This made mAb 15B6's interaction with its target antigen an important demonstration of the power of AlphaFold 3 to model the interaction of antibody and antigen in a disease-relevant context.

V. AI & THE ENABLEMENT OF ANTIBODY GENUS CLAIMS

The significance of the AlphaFold 3 modeling of the antibody-antigen interaction taken together with the experimental results of the NCI scientists is this: Once an antibody to a particular antigen has been shown to have a potential therapeutic benefit in laboratory studies, AlphaFold 3 can model the interaction of the antibody and the antigen. AlphaFold 3 should also be able to model the interaction between that antigen and antibodies with variations in the antibody's binding region (CDR). Ironically, Justice Gorsuch's opinion in *Amgen* included this quote from Amgen's own expert: "`[T]he way in which you get from sequence to that three-dimensional structure isn't fully understood today. It is going to get a Nobel Prize for somebody at some point, but translating that sequence into a known three-dimensional structure is still not possible.'"[94] Yet not quite one year after that opinion was released, AlphaFold 3 did more or less exactly that, going from the sequence of two proteins to both three-dimensional structures and the interaction of the two.[95] On the day that this manuscript was being completed, the Nobel Prize Committee announced awarded Nobel Prize in Chemistry to David Baker, of the University of Washington "for protein structure design' and Demis Hassabis and John Jumper of Google DeepMind "for protein structure prediction."[96]

The work recognized by the Nobel Prize is recognition that pharmaceutical scientists are now or soon will be in the position of being able to determine which amino acid sequences would produce antibody structures with the desired structure and antigen-binding characteristics for a target antigen.[97]

---

93 X.F. Liu, et al., *Tumor Resistance to Anti-Mesothelin CAR-T Cells Caused by Binding to Shed Mesothelin is Overcome by Targeting a Juxtamembrane Epitope*, 121 PROC. NAT'L ACAD. SCIS. 1, 1 (2024).

94 Amgen Inc. v. Sanofi, 598 U.S. 594, 600 (2023).

95 Senior et al., *supra* note 85, at 713.

96 *The Nobel Prize in Chemistry 2024*, ROYAL SWEDISH ACAD. OF SCIS., (Oct. 9, 2024), https://www.nobelprize.org/uploads/2024/10/press-chemistryprize2024-3.pdf [https://perma.cc/9U84-6DKZ].

97 Tanja Kortemme, *De Novo Protein Design—From New Structures to Programmable Functions*, 187 CELL 526, 526 (Feb. 1, 2024).

This power to go from the amino acid sequence of an antibody CDR and the amino acid sequence of a protein antigen essentially eliminates the "undue experimentation" issue that barred Amgen's broad claims to its therapeutic antibody, paving the way for a renaissance of "genus" claims.

By finding the first antibody with the desired characteristics and its gene sequence and corresponding amino acid sequence, AlphaFold 3 or its successor, the as-yet-to-be released "AlphaFold 4," should indeed be able to predict essentially all of the variations on the original antibody's sequence that would also bind to the target antigen with the desired characteristics. The Federal Circuit in *Amgen* stated that "the scope of the claims encompasses millions of candidates claimed with respect to multiple specific functions, and that it would be necessary to first generate and then screen each candidate antibody to determine whether it meets the double-function claim limitations."[98] That will no longer be the case. Even if not every amino acid sequence that is AI-generated is experimentally confirmed to work as well as the original claimed sequence, if a significant percentage of those sequences are successful, it would certainly be the case that the inventor of the first antibody has taught the PHOSITA how to practice the full scope of the claim through the use of AI. Amgen, through trial and error, found 26 antibodies to the same region of PCSK9. Sanofi, through trial and error, found at least one more. Whether there was more value added for consumers through Sanofi's research and entry into the marketplace or whether consumers would have been better served by research into other targets is not an issue that can be resolved here.

As a matter of legal doctrine, however, the argument made here is that in the near future, once that first antibody is made, the written description of that antibody would immediately enable all other antibodies that bind in a similar way to the same region of the same antigen for the PHOSITA using an AI similar to AlphaFold3 or its successors. Claims such as Amgen's (where the first claim describes a specific monoclonal antibody, the amino acid sequence of its CDR, and its manner of binding to a specific epitope of the described antigen) would support a second claim to *all* the similar antibodies predicted by an AlphaFold 3-like AI to function in the same way, as long as the original antibody sequence was not obvious.[99]

---

[98] Amgen Inc. v. Sanofi, Aventisub LLC, 987 F.3d 1080, 1088 (Fed. Cir. 2021).

[99] *See infra* Part VI.

VI. AI & THE FUTURE OF THE PHARMACEUTICAL INDUSTRY: RISK, REWARD, & NONOBVIOUSNESS

Even though AI should eliminate the undue experimentation limitation on monoclonal antibody patent genus claims, and the paradox of increasing skill in the art being met with more scope of allowable claims, the issues it raises of inventorship and obviousness are best understood as questions of risk, reward, and the fundamental purpose of patent law.[100] In the United States, the function and purpose of patent law are expressed in Article I, Section 8, Clause 8 of the U.S. Constitution, which states that "The Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."[101] Congress' first exercise of that power was the Patent Act of 1790.[102] In *Graham v. Deere*, the Supreme Court was asked to interpret the issue of nonobviousness for the first time since the enactment of § 103 of the Patent Act of 1952 had added that statutory requirement, which had long been understood by the courts to be a requirement for patentability.[103] In the course of interpreting the significance and meaning of § 103, Justice Clark looked to Thomas Jefferson who had authored the Patent Act of 1790:

> [Jefferson] rejected a natural-rights theory in intellectual property rights and clearly recognized the social and economic rationale of the patent system. The patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge. The grant of an exclusive right to an invention was the creation of society—at odds with the inherent free nature of disclosed ideas—and was not to be freely given. Only inventions and discoveries which furthered human knowledge, and were new and useful, justified the special inducement of a limited private monopoly. . ..

---

100 *See supra* Section III.B. One of us (Bohrer) has previously argued for an approach to monoclonal antibody patents that rewards the taking of the greatest risk reduction steps in antibody development.

101 U.S. CONST. art. I, § 8, cl. 8.

102 *See generally* Patent Act of 1790, ch. 7, 1 Stat. 109 (1790).

103 *See generally* Graham v. Deere, 383 U.S. 1 (1965).

> His writings evidence his insistence upon a high level of patentability.[104]

The inducement to undertake research and the reward of a patent were, to both Jefferson and Clark, a recognition that every such undertaking involves the risk of failure, and the loss of whatever expenditures were made in pursuit of that project.[105] A patent, in their view, is the reward for undertaking the hard work of invention and the risk of failure.[106] To the extent that AI would be reasonably certain to provide a successful solution to a problem and the means of applying AI to the problem are well known, then finding a solution to the problem entails little risk.

At least one example of where we now are in the application of AI to the process of drug discovery and development is an illustration of where we are heading in this process of reducing the risk (and the effort involved) in drug development. An article reviewing the application of AlphFold2 to biology and medicine[107] provided an interesting partial answer with this summary of research published by Feng Ren et al.:

> Ren et al. applied AF2 in their end-to-end AI-powered drug discovery engines, which include a biocomputational platform named PandaOmics and a generative chemistry platform named Chemistry. PandaOmics provides the targets of interest and Chemistry42 is responsible for generating molecules based on the AF2 predicted structures, and the selected molecules are then synthesized and tested in biological assays. Through this approach, they discovered a small molecule hit compound for CDK20 (Cyclin-dependent Kinase 20) …. within 30 days from target selection and after only synthesizing 7 compounds. This compound was the first small molecule targeting CDK20 at that

---

104 *Graham*, 383 U.S. at 3 ("We have concluded that the 1952 Act was intended to codify judicial precedents embracing the principle long ago announced by this Court in Hotchkiss v. Greenwood, 11 How. 248, 13 L.Ed. 683 (1851), and that, while the clear language of § 103 places emphasis on an inquiry into obviousness, the general level of innovation necessary to sustain patentability remains the same.").

105 *See id.*

106 *See id.*

107 Zhenyu Yang et al., *Alphafold2 and Its Applications in the Fields of Biology And Medicine*, 8 SIGNAL TRANSDUCTION & TARGETED THERAPY 115, 115 (2023).

> time, and this work is the first demonstration of AF2's successful application in the early drug discovery process.[108]

CDK20, also referred to as CCRK, is a protein that is of significant interest as a target for cancer therapeutics.[109] So, even before the more powerful AlphaFold 3 was released, a research group was able to go from identifying a target to synthesizing a small molecule lead compound in 30 days while testing only seven compounds (hardly undue experimentation).[110] The human contribution was in combining three different AI platforms, structuring the queries to each, and testing the seven molecules that were generated by Chemistry42.[111] If we assume that the human contribution in this illustrative example is significant, the question is where will we be in a decade or so, when the human contribution might be a simple query such as this: "Based on the known mutations most common in cancer 'X', provide the structure of a small molecule drug that would be a highly selective inhibitor of the most common mutation that drives the growth of cancer 'X' that would have minimal toxic effect on other tissues or organs." It certainly would be reasonable to conclude that the question is obvious, and that the human contribution is not so substantial as to warrant granting the status of "inventor" to the person who generated the query.

---

[108] *Id.* at 121 (internal citations omitted); *see generally* Feng Ren et al., *AlphaFold Accelerates Artificial Intelligence Powered Drug Discovery: Efficient Discovery Of A Novel CDK20 Small Molecule Inhibitor*, 14 CHEM. SCI. 1443 (2023).

[109] Myth T. Mok, et al., *CCRK Is a Novel Signalling Hub Exploitable in Cancer Immunotherapy*, 186 PHARMACOLOGY & THERAPEUTICS 138, 138 (2018).

[110] *See* Yang et al., *supra* note 107, at 121.

[111] *See id.*

The issues of inventorship and nonobviousness in the context of patent applications for inventions made with the assistance of AI have already been the subject of attention by the USPTO and legal scholars.[112] The USPTO has largely focused on explaining its view of how AI fits into the existing patent law practice and procedures. For example, with respect to inventorship, the USPTO has ruled out the possibility that an AI engine such as AlphaFold 3 could be listed as an inventor on a patent application and stressed that "the inventorship analysis should focus on human contributions… Patent protection may be sought for inventions for which a natural person provided a significant contribution . . ."[113] Of course that raises the issue of what is a "significant contribution"? While the PTO *Inventorship Guidance for AI-Assisted Inventions* lists five considerations, perhaps the most useful in the context of both monoclonal antibody development and pharmaceutical research generally is the second consideration:

> Merely recognizing a problem or having a general goal or research plan to pursue does not rise to the level of conception [citation omitted]. A natural person who only presents a problem to an AI system may not be a proper inventor or joint inventor of an invention identified from the output of the AI system. *However, a significant contribution could be shown by the way the person constructs the prompt in view of a specific problem to elicit a particular solution* from the AI system.[114]

---

112 *See, e.g.*, *AI-Related Resources*, USPTO, https://www.uspto.gov/initiatives/artificial-intelligence/artificial-intelligence-resources [https://perma.cc/47ZS-47TE]; Christopher M. Holman, *The U.S. Patent and Trademark Office's Response to Recent Developments in Artificial Intelligence*, 43 BIOTECHNOLOGY L. REP. 116, 116 (2024); Tim W. Dornis, *Artificial Intelligence and the End of Patent Law as We Know It*, 23 YALE J. L. & TECH. 97, 97 (2020); Matthew Chun, *Artificial Intelligence for Drug Discovery: A New Frontier for Patent Law*, 104 J. PAT. & TRADEMARK OFF. SOC'Y 5, 5 (2024); Kenny Truong, *Expanding Nonobviousness to Account for AI-Based Tools*, 104 J. PAT. & TRADEMARK OFF. SOC'Y 51, 51 (2024); Daniele Fabris, *From the PHOSITA to the MOSITA: Will ''Secondary Considerations'' Save Pharmaceutical Patents from Artificial Intelligence?*, 51 IIC–INT'L REV. INTELL. PROP. & COMPETITION L. 685, 685 (2020).

113 Inventorship Guidance for AI-Assisted Inventions, 89 Fed. Reg. 10043, 10044 (Feb. 13, 2024).

114 *Id.* at 10048 (emphasis added).

Before the advent of AI, the issues of inventorship and nonobviousness were distinct and separate inquiries. The question of inventorship turned on who contributed to the "conception" of the invention, which was not always a simple question to resolve.[115] However, since all of the conceptualization was in human minds, the question was always "who?" and not "who or what?" Similarly, determining who contributed to the conception of an invention did not necessarily implicate the question of whether or not the conceived invention would have been obvious to the PHOSITA.

In focusing the issue of inventorship on the question of whether or not a human has made a "significant contribution" to the invention, rather than attributing the invention to AI, the issue of inventorship and the issue of obviousness are entwined. When AI is used in the process of invention the issue of non-obviousness depends on the skill and ingenuity required to make use of AI in that particular context. For a "natural person" to make a "significant contribution" to an invention made with the assistance of AI, the questions ("prompts") used to generate the AI result must be nonobvious. It must not be too easy to see both the usefulness of the AI for that problem and the means of obtaining the solution from AI. It is clear that the question of inventorship is inseparable from the question of obviousness of the end solution itself. If the existence of the tool and the ease of generating the solution would make that solution obvious, then it certainly would be reasonable to conclude that the human contribution is not so substantial as to warrant granting the status of inventor to the person who generated the query.

While the USPTO's *AI Related Resources*[116] attempts to simply acknowledge the growing use of AI and how it fits into existing practice, commentators have been more focused on the threat that AI poses to current patent practice and the potential difficulty AI will create for obtaining patents on new products. For example, Ryan Abbott argued that the increasing power of inventive machines will mean "the end of patents, at least as they are now."[117] Other commentators have attempted to deal with the obviousness question by positing grounds that would still grant a patent for the drugs that were designed

---

115 *See, e.g.*, Dana-Farber Cancer Inst., Inc. v. Ono Pharm. Co., 964 F.3d 1365, 1367–1371 (Fed. Cir. 2020); Ono Pharm. Co. v. Dana-Farber Cancer Inst., Inc., 141 S. Ct. 2691, 2691 (2021); Toshiko Takenaka, *Unravelling Inventorship*, 21 CHI.-KENT J. INTELL. PROP. 71, 71 (2022).

116 USPTO, *supra* note 112.

117 Ryan Abbott, *Everything is Obvious*, 66 UCLA L. REV. 2, 2 (2019).

in this way.[118] For example, Daniele Fabris has suggested that the doctrine of secondary considerations of nonobviousness be used to grant patents where the human contribution is largely limited to straightforward interaction with a computer that generates a new and useful product.[119] This doctrine grew out of *Graham v. Deere*, in which Justice Clark stated that the fact that there had been "long felt but unsolved needs" as well as the failure of others to come up with a solution and the immediate commercial success of the claimed invention, among other factors, were objective evidence of the nonobviousness of the claimed invention.[120] However, the weakness in using these secondary considerations to judge nonobviousness is the fact that once the PHOSITA is in possession of a tool that is very likely to produce a solution to the problem, awarding a patent simply rewards the winner of a race in which the risk is not in the failure of the invention but in failing to get to the PTO and the market first. The need may well have been long felt and the first to market may well be commercially successful, but clearly this is not what Thomas Jefferson or Justice Clark believed was the purpose of the inducement or reward of the limited-time monopoly of a patent.[121] Mark Lemley has suggested that "simultaneous invention can defeat long-felt need where some exogenous shock (like AI here) means that everyone could easily achieve what they had long been unable to do."[122]

Similar criticisms can be made of other proposals to preserve the current standards for patentability of, for example, small molecules that inhibit a known enzyme. The simple truth is that AI will greatly reduce the risk of developing new products in fields such as drug development where the risk has traditionally been high. That may well transform the industries, such as the pharmaceutical industry, that have historically relied on patents to bring high prices as rewards for costly, high-risk research programs. One need not opine on the virtues of capitalism to understand such upheavals and transformation as what economists have long referred to as creative destruction.[123] The day when in silico biology and AI have

---

118 *See, e.g.*, Dornis, *supra* note 1, at 97; Chun, *supra* note 1, at 1; Truong, *supra* note 112, at 51.

119 Fabris, *supra* note 112, at 685.

120 Graham v. Deere, 383 U.S. 1, 17–18 (1965).

121 *Id.*

122 E-mail from Mark Lemley, William H. Neukom Professor of L., Stan. L. Sch., to Robert A. Bohrer, Emeritus Professor of L., Cal. W. Sch. of L. (Aug. 30, 2024, 4:34 PDT) (on file with author).

123 Ricardo J. Caballero, *Creative Destruction, in* ECONOMIC GROWTH 24, 24 (Steven N. Durlauf & Lawrence E. Blume eds., 2010).

progressed to the point where a safe and effective drug for a serious disease can be developed simply by asking a next-generation AI to provide one may be a decade or more in the future, but it cannot come too soon. If along the way, to paraphrase Shakespeare, the first thing we'll do is fire all the pharmaceutical company CEOs, then all we can do is hope that there still will be a need for law professors and lawyers.