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Note

Mayo, Myriad, and a Muddled Analysis: Do Recent Changes to the Patentable Subject Matter Doctrine Threaten Patent Protections for Epigenetics-Based Inventions?

Mike Sikora*

When an entire industry builds itself around a legal right, any change to that right can irrevocably alter the industry. The pharmaceutical and biotechnology industries rely on patent protection perhaps more than any other industry, leaving them highly susceptible to legal changes. Unfortunately for them, patent protections have begun to erode in recent years, starting with the America Invents Act, which created new Patent Office procedures for invalidating patents.¹ But the changes did not end there. In deciding three cases from 2012 to 2014, the Supreme Court reformed the patentable subject matter doctrine, which interprets 35 U.S.C. § 101.² Together, the doctrine and § 101 serve as a preliminary patenting requirement that identifies what types of subject matter is eligible to be patented. This Note argues that by changing the inquiry for this fundamental

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1. See Donika P. Pentcheva et al., *Invalidating Patents after the America Invents Act*, AM. BAR ASS'N (Apr. 16, 2014), <http://apps.americanbar.org/litigation/committees/youngadvocate/articles/spring2014-0414-invalidating-patents-after-america-invents-act.html> (discussing invalidation procedures including Post-Grant Review and *Inter Partes* Review).

2. 35 U.S.C. § 101 (2012). Though § 101 formally refers to “*patentable*” inventions, this Note intentionally uses a different phrasing, patent *eligibility*, to avoid conflating a § 101 inquiry with the full patentability determination made by the Patent Office. This difference acknowledges that a given invention may satisfy § 101, yet remain unpatentable because it fails to satisfy another requirement.

patentability requirement, the Supreme Court has opened Pandora's Box; it has categorically undercut patent protections for biotechnology in a manner that could irrevocably and undesirably alter the industry.

Traditionally, the patentable subject matter doctrine has considered anything man-made to be patent eligible, but excludes three categories of subject matter as patent ineligible: (1) abstract ideas; (2) laws of nature; and (3) natural phenomena.³ These categories effectively preclude patenting anything that a person did not actually invent. In perhaps the most high-profile § 101 case this century, *Association for Molecular Pathology v. Myriad Genetics, Inc.*,⁴ the Supreme Court unanimously invalidated patents on human genes commonly associated with breast cancer because they covered ineligible natural phenomena. Many lauded *Myriad*, the second of the Court's three recent rulings on patentable subject matter, because it removed "a major barrier to innovation in the areas of biotechnology, drug development and medical diagnostics,"⁵ despite the negative consequences for biotech investments.⁶ As this Note discusses, however, *Myriad's* more important contribution lies with how it and the other two cases transformed the patentable subject matter doctrine.

The Court's three-year reevaluation culminated in *Alice Corp. v. CLS Bank International*,⁷ where it articulated a new two-part test for determining when subject matter is patent eligible (the "*Mayo* test"). This doctrinal shift, which altered how courts determine when a patent impermissibly claims an ab-

3. See *Bilski v. Kappos*, 561 U.S. 593, 601–02 (2010). This Note focuses on the natural phenomena and natural law categories, which interact closely with epigenetics-based technology.

4. 133 S. Ct. 2107, 2111 (2013).

5. Eleonore Pauwels, Op-Ed, *Our Genes, Their Secrets*, N.Y. TIMES (June 18, 2013), <http://www.nytimes.com/2013/06/19/opinion/our-genes-their-secrets.html>; see also Editorial, *Are Human Genes Patentable?*, N.Y. TIMES (Apr. 14, 2013), <http://www.nytimes.com/2013/04/15/opinion/are-human-genes-patentable.html> (reiterating Judge William Bryson's statement in dissent that patents "like those of Myriad are 'a significant obstacle to the next generation of innovation in genetic medicine'").

6. See Adam Liptak, *Justices, 9–0, Bar Patenting Human Genes*, N.Y. TIMES (June 13, 2013), <http://www.nytimes.com/2013/06/14/us/supreme-court-rules-human-genes-may-not-be-patented.html> (noting that the decision would likely "reduce the cost of genetic testing" but "discourage investment in some forms of genetic research").

7. 134 S. Ct. 2347 (2014).

stract idea, law of nature, or natural phenomena, led to a whirlwind of patent invalidations. Litigants challenged patents based on this new standard, and in the first two years courts invalidated seventy percent of them.⁸ The extent to which this phenomenon, labeled by one commentator as “#Alicestorm,”⁹ will continue to affect proceedings, both in federal courts and at the U.S. Patent and Trademark Office (USPTO), remains unknown. In the wake of *Alice*, however, biotechnology patents appear especially susceptible to § 101 invalidations, alongside software, business methods, and communications patents.¹⁰

Biotechnology’s apparent susceptibility to § 101 invalidation stems from the close relationship between biotech inventions and the natural phenomena and laws of nature that they rely on. Natural phenomena refers to anything, or any characteristic of a thing, that could be discovered in nature.¹¹ Similarly, natural laws include correlations, causes, and other laws governing how the natural world works.¹² Under the *Mayo* test, patent eligibility arises when the claimed subject matter amounts to “significantly more than a patent upon the natural [phenomenon or] law itself.”¹³ The term biotechnology calls to mind images of medical devices, but more broadly encompasses engineered biomolecules and cells, synthetic organisms, molecular diagnostics, and pharmaceuticals. The *Mayo* test thus proves problematic for biotech scientists who invent by manipulating natural biological structures into nonnatural arrangements, as this approach makes it

8. Robert R. Sachs, *Two Years After Alice: A Survey of the Impact of a “Minor Case,”* BILSKI BLOG (June 16, 2016), <http://www.bilskiblog.com/blog/2016/06/two-years-after-alice-a-survey-of-the-impact-of-a-minor-case.html> (noting higher invalidation rates at the Federal Circuit, which ruled against the patentee thirty-eight out of forty times on § 101 motions).

9. Robert R. Sachs, *A Survey of Patent Invalidations Since Alice*, LAW360 (Jan. 13, 2015), <https://www.law360.com/articles/604235/a-survey-of-patent-invalidations-since-alice>.

10. See Sachs, *supra* note 8 (demonstrating in Figure 2 that outcomes for Federal Court § 101 invalidity challenges differ based on the type of patent at issue).

11. See *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116–17 (2013) (contrasting the discovery of natural phenomena with invention).

12. See *Mayo Collab. Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 66 (2012) (deciding that the relation between certain blood metabolites and the likelihood a thiopurine compound would “prove ineffective or cause harm” was “a consequence of the ways in which thiopurine compounds are metabolized by the body” and therefore an ineligible natural law).

13. *Id.* at 72–73.

difficult for nonexperts to distinguish the invention from the underlying biological structures. With such a nebulous standard (“significantly more”), and judges that lack the scientific training to draw informed distinctions, one would expect inconsistent decisions on biotechnology’s patent eligibility.

Long-term, inconsistent decisions on § 101 invalidations impose a significant burden on the biotechnology industry. Biotech-related ventures require large investments of time and money to attain profitability, and have historically relied on guaranteed patent monopolies to justify the expense.¹⁴ As changes to the patentable subject matter doctrine have decreased the certainty of biotech patent rights, the risk associated with investing in nascent biotech industries has greatly increased. In the absence of clearly enforceable patent rights, biotech firms may begin choosing to protect their inventions through trade-secret laws.¹⁵ This alternative proves suboptimal for both biotech firms and the scientific field, as the firm lacks its assured monopoly and the secrecy hinders rapid scientific advancement. Relatively unestablished fields of biotechnology will suffer the most from inconsistent patent rights, as they will lack the attractiveness to investors and public technology disclosures that other fields enjoyed in their infancy.¹⁶

Epigenetics, which many consider integral to the future of personalized medicine, is perhaps the most prominent biotech field currently at this crossroads.¹⁷ Though academics have extensively researched epigenetics, widespread epigenetics-based medical applications have yet to be developed. As start-ups begin

14. See Byron V. Olsen, *The Biotechnology Balancing Act: Patents for Gene Fragments, and Licensing the “Useful Arts,”* 7 ALB. L.J. SCI. & TECH. 295, 321 (1997); see also Oren Ginsberg, *Unwinding the DNA Double-Helix: An Alternate Resolution to the Federal Circuit’s Decision in Association for Molecular Pathology for Simplifying §101 Patent Eligibility Determinations*, 22 FED. CIR. B.J. 563, 563 (2013) (stating that the USPTO’s issuance of “patents covering isolated human DNA molecules” sparked advancements in genetic engineering and the medical sciences).

15. See Pauwels, *supra* note 5 (suggesting that the *Myriad* decision will prompt biotech firms to rely on trade secret protection more heavily).

16. See Stuart J.H. Graham & Ted Sichelman, *Why Do Start-Ups Patent?*, 23 BERKELEY TECH. L.J. 1063, 1078 (2008) (“[I]ncreased patenting by venture-backed companies in . . . biotech industries is significantly correlated with total investment, total number of financing rounds, and firm longevity . . .”).

17. See Mahmood Rasool et al., *The Role of Epigenetics in Personalized Medicine: Challenges and Opportunities*, 8 BMC MED. GENOMICS (SUPPLEMENT 1) S5, at 3 (2015) (noting that epigenetic biomarkers “are imperative to achieve personalized . . . therapies”).

developing marketable applications and face a gauntlet of federal regulations, most will seek investment and/or acquisition. Without a clearly enforceable patent, however, investors or acquiring companies will lack incentives to involve themselves early, which will result in cures and treatments reaching markets much more slowly.

This Note seeks to address the new patent eligibility inquiry's impact on biotechnology by demonstrating how convoluted the analysis becomes when applied to epigenetics. Part I details the change in the Supreme Court's treatment of § 101 and provides background information on biotechnology and epigenetics. Part II demonstrates how the close relation between epigenetics-based inventions and their underlying subject matter complicates the analysis, creating difficult questions that judges are ill-equipped to resolve, and resulting in uncertain patent rights. Part III argues that uncertain patent rights for epigenetic-based technology is unacceptable because it leaves patent holders in a quickly advancing industry without efficient means to bring their inventions to market. It concludes that Congress should address these uncertain intellectual property rights by exempting epigenetics-based technology from § 101 and relying on either the 35 U.S.C. § 103 nonobviousness requirement or the European inventive-step concept to prevent overly broad patents from stagnating scientific progress.

I. THE *MAYO* TEST FOR PATENT ELIGIBILITY UNDER § 101 AND THE BASICS OF BIOTECHNOLOGY

This Part begins by discussing how recent Supreme Court rulings have changed the core patent eligibility inquiry and how the *Myriad* ruling may have complicated its application to biotechnology. It then briefly reviews other patentability requirements, including novelty and nonobviousness requirements in the United States and the inventive-step concept used by the European Patent Office (EPO). Lastly, Part I prepares readers for its later application of the *Mayo* test by describing the unique features of biotechnology and explaining epigenetics and its potential role in personalized medicine.

A. UNDERSTANDING THE ANALYSIS FOR DETERMINING
35 U.S.C. § 101 PATENT ELIGIBLE SUBJECT MATTER: THE *MAYO*
TEST AND *MYRIAD*

Though the Constitution permits granting “[i]nventors the exclusive [r]ight to their . . . [d]iscoveries,” Congress more narrowly defines what can be patented in 35 U.S.C. § 101.¹⁸ Patent eligible subject matter includes “any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.”¹⁹ Historically, the Supreme Court construed § 101 broadly, stating that “anything under the sun . . . made by man” could be patented.²⁰ The Court constrained its broad construction only by noting that “laws of nature, physical phenomena, and abstract ideas [are] . . . not patentable.”²¹ These three categorical exceptions are rooted in the common law and lack a statutory basis.²²

In 2010, the Court began to revisit § 101, rejecting the notion that it “ha[d] endorsed the machine-or-transformation test as the exclusive test” for patent eligibility, despite the Federal Circuit’s longstanding use of it.²³ This ruling merely confused courts engaging in § 101 inquiries, since it provided no replacement test. Two years later, the Supreme Court began to clarify its position on § 101 in *Mayo Collaborative Services. v. Prometheus Labs., Inc.*, where it first used—but did not formally articulate—the current two-part test for determining patent eligibility.²⁴ It eventually described the two-step *Mayo* test in *Alice* as follows: “We must *first determine whether the claims at issue are*

18. U.S. CONST. art. I, § 8, cl. 8 (emphasis added); 35 U.S.C. § 101 (2012).

19. 35 U.S.C. § 101. The Patent Act of 1952 introduced this language as part of Congress’s patent law reform. See Pub. L. No. 82-593, § 101, 66 Stat. 792, 797 (1952).

20. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952)). *Chakrabarty* holds particular relevance to the patent eligibility of biotechnology because the Court ruled that organisms, if man-made, are patent eligible. *Id.* at 310.

21. *Chakrabarty*, 447 U.S. at 303.

22. See *Bilski v. Kappos*, 561 U.S. 593, 601–02 (2010) (“While these exceptions are not required by the statutory text, they are consistent with the notion that a patentable process must be ‘new and useful.’”).

23. *Id.* at 604. The Court also held that business methods were not categorically excluded from patentability, but that the method in dispute was an ineligible abstract idea. *Id.* at 606–612. The machine-or-transformation test provides patent eligibility when a process is: (1) tied to a machine; and (2) transforms an article into a different state or thing. See *id.* at 600 (citing *In re Bilski*, 545 F.3d 943, 954 (Fed. Cir. 2008) (en banc)).

24. *Mayo Collab. Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 77–80 (2012) (engaging in a two-step inquiry the Court eventually named the *Mayo* test).

*directed to a patent-ineligible concept. . . . [If so,] we must [then] examine the elements of the claim to determine whether it contains an ‘inventive concept’ sufficient to ‘transform’ the claimed abstract idea into a patent eligible application.”*²⁵

By providing this new test, the Court significantly streamlined the analysis for § 101 into a straightforward inquiry, representing a large improvement over the variety of nonexclusive tests used prior to *Alice*. But despite finally articulating the test for patent eligible subject matter, the Supreme Court created a new problem by declining to discuss how much a law of nature, abstract idea, or physical phenomenon must minimally be transformed to become patent eligible.²⁶

For biotechnology, this problem is exacerbated by *Myriad*, the Court’s 2013 case decided after *Mayo* (2012), but before the two-part test’s articulation in *Alice* (2014). Despite the *Alice* Court’s assertion that it had already “set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent eligible applications of those concepts,”²⁷ in *Myriad* it failed to use the two-part *Mayo* test for either of its holdings. Nowhere did it examine whether the patent claims (1) were directed to an ineligible concept; and, if so, (2) whether they nevertheless contained an inventive concept. Instead, the Court based its first holding on the difference between discovery and invention, noting that “*Myriad* found the location of the BRCA1 and BRCA2 genes, but that discovery, by itself, does not render the BRCA genes . . . patent eligible.”²⁸ For its second holding, the *Myriad* Court ruled cDNA, a gene copy from which humans have removed noncoding DNA, patent eligible simply because “it is *distinct* from the DNA from which it was derived” and therefore “not a ‘product of nature.’”²⁹

25. *Alice Corp. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2355–57 (2014) (quoting *Mayo*, 566 U.S. at 72) (emphasis added).

26. *See id.* at 2357–59.

27. *Id.* at 2355.

28. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2117 (2013). Even if decided post-*Alice*, this first holding would not require a *Mayo* analysis, as *Myriad Genetics* had expressly claimed a natural phenomenon, violating decades of judicial rulings describing natural phenomena as ineligible subject matter.

29. *Id.* at 2119 (emphasis added). Genes naturally contain alternating coding and noncoding regions of DNA, with the important information for protein synthesis located in the coding regions. BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* 317 (6th ed., 2015). In effect, cDNA is a copy of the gene which excludes the “filler” portions. *See id.* at 315–18, 469–70.

The confusion regarding how to conduct a § 101 inquiry for biotechnology stems from the lack of *Mayo* analysis in *Myriad*'s second holding. Under the *Mayo* test, being *distinct* from a natural product does not necessarily make cDNA patent eligible. *Mayo* requires asking (1) whether the claims were *directed* to (not distinct from) an abstract idea, natural phenomena or law of nature; and if so (2) whether they incorporated an “inventive concept sufficient to transform” the ineligible subject matter.³⁰ By not applying the test, the Court left a significant question regarding *Mayo*'s application to biotechnology: can a claim be *directed* to natural phenomena without expressly *claiming* a product of nature?³¹ In other words, is something that closely resembles or is designed for a natural phenomenon, yet is not naturally occurring, directed to the underlying natural phenomenon? If so, most biotechnology would be categorically directed to natural phenomena because of the close relation between biotechnology and the natural phenomena it repurposes.³² Accordingly, almost all forms of biotechnology would satisfy § 101 only by sufficiently transforming the natural phenomena.

B. NOVELTY, NONOBVIOUSNESS, AND INVENTIVE STEP IN PATENTABILITY DETERMINATIONS

This Section provides a brief overview of additional patentability requirements in the United States and European Union.

30. *Alice*, 134 S. Ct. at 2357 (quoting *Mayo Collab. Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 72 (2012)). Dan L. Burk attempts to overlay this two-step analysis onto the *Myriad* opinion, concluding that the *Myriad* cDNAs must have “passe[d] the first prong of the test and never reache[d] the second.” Dan L. Burk, *Dolly and Alice*, 2 J.L. & BIOSCIENCES 606, 610–611 (2016). “It seems implausible that cDNA could pass the second prong of the test; there is no palpable ‘inventive concept.’” *Id.* at 610.

31. This question remains unanswered, in part because none of the Supreme Court's other rulings on patentable subject matter concerned a natural phenomenon. Burk, *supra* note 30, at 610. Though unaddressed by the Supreme Court, but the Federal Circuit did provide an example of patent claims directed to a natural phenomenon, despite not expressly claiming the phenomenon, in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1376 (Fed. Cir. 2015) (holding that a method for detecting cell-free fetal DNA was directed to its natural occurrence). Thus, for the time being, the answer is yes: a claim can be directed to natural phenomena without expressly claiming a product of nature.

32. See generally Philip Merksamer, *Ariosa Diagnostics v. Sequenom: Metastasis of Mayo and Myriad and the Evisceration of Patent Eligibility for Molecular Diagnostics*, 31 BERKELEY TECH. L.J. 495, 531 (2016) (arguing that the Supreme Court expanded the judicial exceptions to patentable subject matter in *Mayo* and *Myriad* enough to “endanger patentability for molecular diagnostics”).

Subsection 1 describes the American novelty and nonobviousness requirements. Subsection 2 then compares those requirements to the European Union's novelty and inventive-step requirements. Because these doctrines are distinct from a § 101 analysis, they offer an alternative means for Congress to limit broad grants of biotechnology patents, as discussed in Part III.B.

1. Novelty and Nonobviousness in U.S. Patentability Determinations

After satisfying 35 U.S.C. § 101 by claiming patent eligible subject matter, any U.S. patent application must also satisfy novelty³³ and nonobviousness³⁴ requirements to be patented. The novelty inquiry examines whether a single prior art reference contains each and every element of a claim in the same arrangement.³⁵ If subject matter of a claim was previously “patented, described in a printed publication, or in public use, on sale, or otherwise available to the public,” it cannot be patented.³⁶ In effect, novelty ensures that only new and uncopied inventions can be patented.

Nonobviousness examines prior art as well, but its inquiry focuses more on potential modifications to or combinations of prior art references.³⁷ To be patentable, an invention cannot be “obvious . . . to a person having ordinary skill in the art to which the claimed invention pertains.”³⁸ Unlike novelty, which prevents patenting old inventions, nonobviousness prevents patenting *obvious variations* of old inventions. Together, the novelty and nonobviousness requirements ensure that patentees deserve the exclusive rights a patent grants them over their inventions.

33. 35 U.S.C. § 102 (2012).

34. *Id.* § 103.

35. *Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987) (“[E]ach and every element . . . is found . . . in a single prior art reference.”). Prior art can be defined as “a reference of some type . . . or some type of knowledge or event . . . that demonstrates that the invention in question is not new.” Gene Quinn, *What Is Prior Art?*, IPWATCHDOG (Oct. 2, 2010), <http://www.ipwatchdog.com/2010/10/02/what-is-prior-art/id=12677>.

36. 35 U.S.C. § 102.

37. *See* Application of Winslow, 365 F.2d 1017, 1019–20 (describing the nonobviousness analysis).

38. 35 U.S.C. § 103.

2. Patentability at the European Patent Office

Where the USPTO uses eligible subject matter, novelty, and nonobviousness requirements to determine patentability, the EPO instead uses invention, novelty, and an inventive step.³⁹ The invention requirement serves the same purpose as the eligible subject matter requirement, but operates without a specific test.⁴⁰ Rather than undergo a *Mayo*-type analysis, the EPO simply rejects any application claiming an invention that falls into a category prohibited by the European Patent Convention.⁴¹ The novelty requirements match almost exactly, except for minor differences in how each jurisdiction defines which prior art references apply.⁴² Even the nonobviousness and inventive-step concepts share similarity, as the inventive-step inquiry asks whether the invention is “obvious to [a] skilled person in the light of the state of the art.”⁴³ Inventive step differs greatly from nonobviousness, however, in that it “is usually evaluated on the basis of the ‘problem-solution’ approach,” which places more emphasis on whether the solution to the problem would have been obvious.⁴⁴

C. THE UNIQUE DISPOSITION OF BIOTECHNOLOGY AND EPIGENETICS

This Section introduces the close relation between biotechnology and underlying natural phenomena, which Part II argues is problematic for the *Mayo* test. Subsection 1 focuses on broader characteristics of biotechnology, including a description of how and why scientists repurpose natural components. It describes synthetic biology and systems biology, explaining how innovation in each field involves repurposing natural components in very distinct ways. In doing so, Subsection 1 provides a broader

39. EUROPEAN PATENT OFFICE, HOW TO GET A EUROPEAN PATENT 15 (2016) [hereinafter EPO GUIDE], [http://documents.epo.org/projects/babylon/eponet.nsf/0/8266ED0366190630C12575E10051F40E/\\$File/how_to_get_a_european_patent_20160422_en.pdf](http://documents.epo.org/projects/babylon/eponet.nsf/0/8266ED0366190630C12575E10051F40E/$File/how_to_get_a_european_patent_20160422_en.pdf).

40. See *id.* at 15–16 (broadly discussing the invention concept).

41. *Id.* The European Patent Convention specifically excludes programs for computers, methods of treatment or diagnosis of the human or animal body, and plant and animal varieties. *Id.* Notably, the list of unpatentable categories is considered nonexhaustive. *Id.* at 15.

42. *Id.* at 16–17 (“An invention is considered to be new if it does not form part of the state of the art.”).

43. *Id.* at 17.

44. *Id.*

view of how biotechnology inherently causes problems for § 101 inquiries.

Subsection 2 provides a much more detailed tutorial on epigenetics, a specific field of systems biology, which will later serve as the basis for Part II's argument that the *Mayo* test leads to inconsistent results and Part III.A's argument that the inconsistency could strangle a promising field of biotechnology. In a § 101 inquiry, judges must understand both the technology and how it relates to its field to reach a proper decision. With this in mind, Subsection 2 explains the core epigenetic features and the field's future importance to personalized medicine.

1. Biotechnology Generally

All biotechnology repurposes or manipulates a biological process or molecule to either perform a nonnatural function or perform its natural function differently.⁴⁵ To understand just how powerful biological systems are, one must understand that biological systems consist of countless intricate interactions, all optimized by evolution over billions of iterations to *help the system function better*.⁴⁶ Because natural selection favors overall system functionality, evolution usually only optimizes interactions between biomolecules to the extent that doing so benefits the entire system.⁴⁷ In other words, biological systems contain countless biomolecules that perform varied functions at different levels of optimization.

In light of their diverse functionality and moderate optimization, biomolecules frequently provide an excellent starting point for industrial applications. The enzyme Lipase is used industrially in its natural form for stain removal, cheese flavoring, dough stability in baking, contaminant control in paper manu-

45. See *What is Biotechnology?*, BIOTECH. INNOVATION ORG., <https://www.bio.org/what-biotechnology> (last visited Apr. 19, 2018) (defining biotechnology broadly as “technology based on biology”).

46. See Michael Lynch et al., *Evolutionary Cell Biology: Two Origins, One Objective*, 111 PNAS 16990, 16990 (2014) (“[A]ll evolutionary change ultimately requires modifications at the cellular level . . .”). The term biological system used here refers to a self-sufficient biological unit, usually self-enclosed units like cells. The terminology is meant to provide a comparison to mechanical systems, which generally speaking do not self-optimize.

47. See ALBERTS ET AL., *supra* note 29, at 15 (“[G]enetic specifications change, giving [organisms] new ways to exploit the environment more effectively, to survive in competition with others, and to reproduce successfully.”).

facturing, and as a catalyst in the synthesis of organic chemicals.⁴⁸ But unlike Lipase, many biomolecules must be optimized beyond their natural function to fulfill an industrial need.⁴⁹ This process of engineering biomolecules for use in an engineered system is commonly referred to as “synthetic biology.”⁵⁰ Synthetic biology and its industrial applications may eventually offer more efficient means to “produce enzymes, chemicals, polymers, or even everyday products such as vitamins and fuel.”⁵¹

Though components of biological systems can readily be modified and used outside the system, biological systems can only incorporate nonnatural components in rare circumstances. This is because nearly “all [bio]molecules are produced from a small set of about 50 monomers” (which are small molecules that serve as subunits).⁵² Cells create a wealth of complex biomolecules from standardized, “nearly universal” monomers by combining them in various lengths and patterns into polymers, just as songwriters create intricate melodies with a few well-chosen notes.⁵³ DNA, RNA, and proteins exemplify this principle.⁵⁴ All natural DNA strands consist of only four types of deoxy-ribonucleotide monomers;⁵⁵ all natural RNA strands consist of only four types of ribonucleotide monomers;⁵⁶ and the vast majority of proteins consist of only twenty different types of amino acid

48. Ole Kirk et al., *Industrial Enzyme Applications*, 13 CURRENT OPINION BIOTECH. 345, 346 tbl. 1 (2002).

49. See Inge J. Minten, et al., *Post-Production Modification of Industrial Enzymes*, 98 APPLIED MICROBIOLOGY & BIOTECH. 6215, 6215 (2014) (“The demands of these industries with regard to enzyme performance, substrate specificity, stability, solubility, pharmacokinetic and pharmacodynamics properties are diverse and tuning of enzymes to fit the needs of a specific process is often desired.”). To make patent eligibility determination, courts must first decide how much a natural molecule must minimally be transformed for patent eligibility to arise. See *infra* Part II.B (identifying the types of biological questions which may arise in deciding a line of minimum transformation).

50. *Synthetic Biology Explained*, BIOTECH. INNOVATION ORG., <https://www.bio.org/articles/synthetic-biology-explained> (last visited Apr. 19, 2018).

51. *Id.*

52. See Regina Bailey, *Biological Polymers - Biomolecules*, THOUGHTCO., <https://www.thoughtco.com/biological-polymers-373562> (last updated Oct. 17, 2017).

53. *Id.*

54. Though this Note specifically mentions the types of monomers that compose DNA, RNA and protein (deoxy-ribonucleotides, ribo-nucleotides, and amino acids), it does so only to illustrate that different types of biomolecules utilize different monomers. The functional differences between them are not important for the purposes of this Section.

55. ALBERTS ET AL., *supra* note 29, at 3.

56. *Id.* at 4.

monomers.⁵⁷ Your various genes, RNA strands, and proteins are created by combining these base components in countless ways.

Evolution has both created this system of standardized components and optimized molecular interactions between the components, meaning biological systems are largely inflexible and only function with very specific sets of interactions. Continuing with the DNA-RNA-protein example, the “central dogma” of biology states that genetic information is encoded in DNA, transcribed into RNA, and then translated into functional proteins.⁵⁸ This core relationship between DNA, RNA, and proteins defines almost all biological systems and cannot be replaced or significantly altered.⁵⁹ In part, the relationship relies on how standardized the subunits (or monomers) of DNA, RNA, and protein are. This standardization allows cell machinery to recognize and convert a sequence of DNA monomers into a corresponding sequence of RNA monomers during transcription, and then recognize and convert that RNA sequence into a sequence of amino acid monomers during translation.⁶⁰ Replacing these essential building blocks with synthetic nucleotides or amino acids is both rare and extraordinarily difficult to achieve because the cell machinery must also be changed to recognize the synthetic components.⁶¹ This same idea holds true for biomolecules generally, as

57. *Id.* at 6. Many proteins undergo posttranslational chemical modifications that alter certain amino acids, leading to significant diversity among protein structures. *Id.* at 165–66.

58. *Id.* at 299. DNA consists of four types of monomers (nucleotides) and stores genetic information by arranging them in a meaningful sequence. *Id.* at 175. Transcription is the process of unwinding DNA strands and copying the genetic information by creating a single-stranded RNA molecule that mirrors the gene’s nucleotide sequence. *Id.* at 301–04. Translation is the process of reading this RNA copy’s nucleotide sequence and converting it into an amino acid sequence. *Id.* at 333–36. After posttranslational modifications and folding, the amino acid sequence becomes a functional protein. *Id.* at 353.

59. *See id.* at 299 (noting that all cells express genetic information “from DNA to RNA to protein,” making the principle “fundamental” to molecular biology).

60. *See id.* at 3–6 (describing generally how genetic information becomes functional proteins).

61. *See generally* Alexis J. Rovner et al., *Recoded Organisms Engineered to Depend on Synthetic Amino Acids*, 518 NATURE 89 (2015) (discussing their breakthrough in engineering cells to rely on synthetic amino acids); William Herkewitz, *X & Y: Two New Letters for the DNA Alphabet*, POPULAR MECHANICS (May 7, 2014), <http://www.popularmechanics.com/science/health/a10512/x-y-scientists-create-two-new-letters-for-dna-16769967> (“Many in the broader community thought that [integrating synthetic nucleotides into a living organism] would be impossible to achieve.”).

cell machinery is only optimized to recognize natural components.

For this reason, innovations in systems biology usually come from rearranging the naturally occurring base components of DNA, RNA, proteins, or other cellular features in a nonnatural conformation.⁶² Rather than modify biomolecules as in synthetic biology, systems biology seeks to uncover natural cellular interactions and construct a larger picture of natural biological systems.⁶³ The larger picture consists not only of DNA, RNA, and proteins, but also cell signaling, gene expression, and epigenetic modifications, all of which also rely on specific, evolutionarily optimized interactions for functionality.⁶⁴ This reliance on natural interactions limits how much one can transform a system component before it ceases to function within the system.⁶⁵ Though this limitation on transformation proves problematic for industrial applications, it actually makes systems biology particularly useful for biomedical applications. Synthetic components can rarely function in a patient's natural biological system, whereas a biomolecule subtly modified through a systems biology approach would likely function properly.

2. Epigenetics Basics

Epigenetics involves “the study of phenomena and mechanisms that cause chromosome-bound, heritable changes to gene expression that are not dependent on changes to DNA sequence.”⁶⁶ Importantly, epigenetics studies changes in gene *expression*, not substantive changes to actual genes.⁶⁷ Changes to

62. See *Synthetic Biology Explained*, *supra* note 50 (noting that systems biology focuses on natural biological systems while synthetic biology focuses on engineered biological systems).

63. Christopher Wanjek, *Systems Biology as Defined by NIH: An Intellectual Resource for Integrative Biology*, 19 NIH CATALYST 1, 1 (Nov.–Dec. 2011), <https://irp.nih.gov/catalyst/v19i6/systems-biology-as-defined-by-nih> (last visited Apr. 19, 2018). Systems biology also seeks to understand biology at the organism and tissue level, but this Note will focus only on the concept as applied to the cellular system.

64. *Id.*

65. The close reliance of epigenetics-based inventions on cellular features and interactions obscures the *Mayo* analysis, as discussed in Part II.B.

66. Carrie Deans & Keith A. Maggert, *What Do You Mean, “Epigenetic”?*, 199 GENETICS 887, 892 (2015). Some confusion exists regarding how to properly define epigenetics, but Deans and Maggert suggest limiting the definition to heritable, chromosome-bound changes to avoid unnecessary overlap between epigenetics and extracellular gene regulation. See *id.*

67. WHAT IS EPIGENETICS, *Epigenetics: Fundamentals*, <https://www.whatisepigenetics.com/fundamentals> (last visited Apr. 19, 2018); see ALBERTS

gene expression alter how often a cell reads the gene, while substantive changes alter the gene itself, and therefore the protein for which the gene codes.⁶⁸ Differential gene expression has allowed scientists to explain how all cells contain the same genes, yet carry out drastically different functions; they express genes differently.⁶⁹ By limiting itself to chromosome-bound changes, epigenetics only examines heritable changes to gene expression (changes that can be passed to one's children) that originate on or near the gene itself.⁷⁰

Though many such changes originate near genes, this Subsection will limit its discussion to two major epigenetic mechanisms that are considered in Part II's application of the *Mayo* test: chromatin structure and DNA methylation. Like many other interactions identified through systems biology, the interactions that control chromatin structure and DNA methylation are evolutionarily-optimized and not receptive to transformation. The complexity and intricacy of these epigenetic mechanisms rely on the standardization of histone modifications, just as the DNA-RNA-protein relationship relies on the standardization of nucleotides and amino acids. Together, these mechanisms form an evolutionarily optimized *system* of interactions (the histone code) that controls heritable changes in gene expression—a system that cannot easily be altered.

The structure of chromatin, the DNA-protein complex present in the nucleus of eukaryotic cells, determines how loosely or compactly DNA is condensed.⁷¹ This complex exists for the primary purpose of condensing DNA down to a storable size by

ET AL., *supra* note 29, at 6–7. Because regulatory genes moderate the expression of other genes, substantive changes to regulatory genes often interest epigeneticists studying the expression of the regulated genes. See Deans & Maggert, *supra* note 66, at 890–91 (discussing the impact of sequence changes in regulatory genes).

68. See ALBERTS ET AL., *supra* note 29 at 6–7. Substantively changing a gene involves substituting, adding, or deleting nucleotides from the DNA sequence, which may or may not alter the amino acid sequence of the protein the gene codes for, depending on the substantive change made. See *id.* at 6–7 (“[T]here are many cases in which several codons correspond to the same amino acid.”). Gene expression describes how often the cell transcribes the gene. See *id.*

69. See *id.* at 1171. Higher transcription of a gene creates many RNA copies, which in turn cause the cell to create many copies of the protein the gene codes for. See *id.* at 372 (“[A] cell can control the proteins it makes by . . . controlling when and how often a given gene is transcribed . . .”).

70. See ALBERTS ET AL., *supra* note 29, at 194 (“DNA is packaged into nucleosomes to create a chromatin fiber . . .”).

71. *Id.* at 187.

“coil[ing] and fold[ing] the DNA into higher and higher levels of organization.”⁷² If all DNA from a human cell were stretched end-to-end, it would measure two meters in length, but chromatin condensing allows it to fit inside a microscopic nucleus.⁷³ Epigeneticists show interest in chromatin structure for multiple reasons: (1) high levels of gene expression accompany areas of low DNA condensation (loose chromatin or “euchromatin”);⁷⁴ (2) DNA condensation differs across locations on a chromosome and over the course of the cell cycle;⁷⁵ and (3) chromatin patterns are often inherited.⁷⁶ So, how does chromatin work?

Chromatin consists of DNA, histones, and other proteins, but the primary determinant of DNA condensation is histones.⁷⁷ Histones are a family of proteins, each shaped like a ball with a tail, that serve as monomers.⁷⁸ Eight histones combine to form a nucleosome (an eight-subunit complex or “octamer”) around DNA roughly every two hundred nucleotides, creating the appearance of “beads on a string.”⁷⁹ Chemical modifications to the nucleosomes, both on histone cores and protruding tails, determine how they interact with DNA and neighboring nucleosomes.⁸⁰ Certain modifications promote loose chromatin and high gene expression, while others promote condensed chromatin and low gene expression.⁸¹ Often, other proteins control the addition or removal of chemical modifications, making most modifications reversible.⁸² Histones also contribute to chromatin regulation through the different effects each different histone monomer has on DNA condensation.⁸³ Together, the chemical

72. *Id.*

73. *See id.* at 179.

74. *Id.* at 194–95 (discussing the silencing effect of heterochromatin).

75. *See id.* at 187, 194, 196–97.

76. *Id.* at 194.

77. *Id.* at 187.

78. *Id.* at 187–89.

79. *Id.* at 187–88.

80. *Id.* at 196–97. Common covalent modifications include “the acetylation of lysines, the mono-, di-, and trimethylation of lysines, and the phosphorylation of serines.” *Id.* at 196.

81. *Id.* at 196–98. The acetylation of lysines removes positive charges, which reduces nucleosome affinity for each other, causing them to spread out, loosen the chromatin, and allow transcription in those DNA regions. *See id.* at 197. Trimethylation of a lysine on the histone H3 tail recruits HP1, which condenses DNA further and reduces transcription. *See id.*

82. *Id.* at 196.

83. *See id.* at 198–99.

modifications and histone variants create meaningful combinations that epigeneticists have termed the “histone code.”⁸⁴ These very specific combinations instruct cell machinery to repair chromatin, increase gene expression, or decrease gene expression.⁸⁵ But other combinations, such as nonnatural ones a researcher may wish to introduce, would not be recognized without significantly altering the cell machinery.

Apart from chromatin structure, the other main epigenetic mechanism is DNA methylation.⁸⁶ This chemical modification, the addition of a methyl group, is made directly on DNA strands to prevent cell machinery from recognizing the gene.⁸⁷ In most scenarios, this blocking effect reduces gene expression by preventing transcription factor proteins from binding and starting transcription.⁸⁸ Occasionally the blocking effect actually increases gene expression by preventing repressor proteins from binding to the gene.⁸⁹ DNA methylation also impacts gene expression by recruiting histone-modifying proteins that promote DNA condensation, which also hinders transcription.⁹⁰ As with chemical modifications to histones, a series of proteins exist to add and remove the methyl group from target genes, making this epigenetic mechanism reversible and therefore a potential tool that researchers may wish to manipulate into epigenetics-based treatments.⁹¹

Epigenetic features interest scientists because their susceptibility to environmental impact and heritability make them likely to play an essential role in personalized medicine. Environmental factors such as heat or diet can impact DNA methylation patterns and histone modifications at any stage of life, both during gestation and after birth.⁹² Because DNA methylation and histone modifications can be inherited, these environmental

84. *Id.* at 198.

85. *See id.*

86. *See* Joseph Loscalzo & Diane E. Handy, *Epigenetic Modifications: Basic Mechanisms and Role in Cardiovascular Disease*, 123 *CIRCULATION* 2145, 2145–46 (2011) (discussing DNA methylation as an epigenetic tag).

87. *Id.* at 2145.

88. *Id.*

89. *Id.*

90. *Id.* at 2146.

91. *Id.*

92. *See generally* Robert Feil & Mario F. Fraga, *Epigenetics and the Environment: Emerging Patterns and Implications*, 13 *NATURE REV. GENETICS* 97 (2012) (describing how environmental factors impact epigenetic features in both plants and animals at various stages of development).

effects could last generations.⁹³ Each person's epigenetic features differ based on their own inheritance and environment, making future epigenetic applications distinctly personal in nature. Epigenetic diseases have already been identified, and the development of reliable diagnostics might allow for personalized "behavioral or nutritional advice."⁹⁴ Epigenetics may also allow options for "drug targeting and discovery," or even the creation of an anticancer drug that "reactivat[es] tumor-suppressor genes with the use of demethylating agents."⁹⁵

It is important, however, to note a key limitation of epigenetics; it exemplifies a field of biotechnology that cannot readily utilize synthetic components. Just as DNA, RNA, and protein rely on standardized components to ensure accurate transcription and translation, the histone code and DNA methylation rely on a very specific set of interactions to correctly manage gene expression. The mammalian histone code relies on at least fifteen specific *sets* of histone modifications, not simply fifteen modifications, to manage expression.⁹⁶ Additionally, histone proteins themselves "are among the most highly conserved eukaryotic proteins."⁹⁷ In other words, their function is so fundamental that histones in all eukaryotes, from single-celled organisms to humans, share a highly similar structure despite hundreds of millions of years of evolution. Like most components of biological systems, epigenetic mechanisms are not easily replaceable with synthetic components.

II. APPLYING THE *MAYO* TEST TO EPIGENETICS: THE DIFFERENT CHALLENGES IMPOSED BY STEPS ONE AND TWO

This Part examines how applying the *Mayo* test to epigenetics-based inventions results in inconsistent patent eligibility determinations. It begins by arguing that recent rulings make epigenetics-based technology categorically directed to either

93. See ALBERTS ET AL., *supra* note 29, at 413 (noting that "inherited forms of DNA methylation and . . . chromatin condensation [are] additional mechanisms for generating cell memory of gene expression patterns"). Cells actually assemble new, identical nucleosomes in a similarly semiconservative manner as DNA replication occurs. See *id.* at 261–62 (detailing the process of nucleosome assembly behind the replication fork).

94. Ruth Chadwick & Alan O'Connor, *Epigenetics and Personalized Medicine: Prospects and Ethical Issues*, 10 PERSONALIZED MED. 463, 464 (2013).

95. *Id.*

96. ALBERTS ET AL., *supra* note 29, at 198.

97. *Id.* at 190.

natural phenomena or laws, conditioning patent eligibility on the outcome of step two. It then identifies the type of questions judges must answer when deciding whether each epigenetics-based invention sufficiently transforms underlying natural phenomena or laws. Part II concludes that the judiciary's lack of technical expertise and the inapplicability of prior art leave judges without the context necessary to make consistent § 101 rulings on epigenetics-based technology.

A. EPIGENETICS-BASED TECHNOLOGY MAY BE CATEGORICALLY DIRECTED TO NATURAL PHENOMENA OR NATURAL LAWS

As set forth in Part I, the non application of the *Mayo* test in *Myriad* left an open question: can a claim be directed to a natural phenomenon when not expressly claiming a natural product?⁹⁸ The Federal Circuit answered this question affirmatively in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, ruling that a method for detecting cell-free fetal DNA (cffDNA) was directed to naturally occurring cffDNA.⁹⁹ This ruling significantly broadens the natural phenomena exception to patent eligible subject matter, threatening patent rights for all biotechnology.¹⁰⁰ The *Mayo* decision similarly expanded the natural-law exception.¹⁰¹ There, the Court found a method of treating gastrointestinal disorders directed to a natural law because the claim utilized the natural “relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm.”¹⁰²

These expansions of the natural-phenomena and natural-law exceptions almost certainly make epigenetics-based inventions categorically directed to ineligible subject matter, because virtually all epigenetics-based technology utilizes natural phenomena and/or natural associations or correlations that courts

98. See *supra* note 31 and accompanying text.

99. 788 F.3d 1371 (Fed. Cir. 2015). Cell-free fetal DNA is a type of fetal DNA that can be detected in the pregnant mother's bloodstream by the diagnostic test being considered by the Federal Circuit. *Id.* at 1373. For the purposes of this Note, readers need only understand that cffDNA is a natural phenomenon.

100. Cf. *Merksamer*, *supra* note 32, at 521–25 (arguing that the ruling jeopardizes the patent eligibility of DNA diagnostic tests).

101. *Id.* at 509.

102. *Mayo Collab. Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66, 77 (2012).

would now consider natural laws.¹⁰³ Epigenetics-based technology works by understanding the relevance of gene locations, the histone code, chemical modifications to DNA, chromatin condensation and the relationships between gene expression levels and other cellular features. This reliance of epigenetics-based technology on naturally occurring features makes the directed-to standard from step one of the *Mayo* test especially problematic.¹⁰⁴ After *Mayo*, methods that diagnose epigenetic diseases based on that understanding would be directed towards the natural correlations between epigenetic features, gene expression and disease. After *Ariosa*, methods of detecting or altering epigenetic features would be directed towards those features, just as the method of detecting cffDNA in *Ariosa* was directed to cffDNA. These rulings also suggest that a claimed biological apparatus or large biomolecule that utilizes epigenetic features, such as a vector for gene insertion that targets only noncondensed DNA regions, would be directed to the features its function depends on.¹⁰⁵ Thus virtually all epigenetics-based technology is directed to ineligible subject matter and must undergo *Mayo* step two.

103. Software faces an almost identical problem, where courts consider most software patents directed to abstract ideas. In *Enfish* and *D.D.R. Holdings*, the first Federal Circuit cases to distinguish *Alice*, the court found that the patent claims were directed to a specific improvement or problem, despite using an abstract idea. *Enfish, LLC v. Microsoft, Inc.*, 822 F.3d 1327 (Fed. Cir. 2016) (holding that the claims were directed towards making a specific improvement to database functionality); *D.D.R. Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245 (Fed. Cir. 2014) (holding that the claims were directed to solving a specific problem unique to the digital world). Unfortunately for those seeking to patent epigenetics-based inventions, these rulings do not appear easily analogous. The *Enfish* ruling for a specific improvement seemingly holds potential, but the practical constraints on altering epigenetic features while preserving natural functionality will limit its applicability. The *D.D.R. Holdings* ruling concerning a problem unique to the digital world appears inapplicable to biotechnology because the biological world is natural, not man-made like the digital world. Thus, directing an invention to a specific, naturally occurring biological problem would still direct it towards a natural phenomenon.

104. *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014).

105. In molecular biology, vector refers to “[a] vehicle . . . used to transfer . . . genetic material such as DNA sequences from the donor organism to the target cell of the recipient organism.” *Vector*, BIOLOGY ONLINE, <http://www.biology-online.org/dictionary/Vector> (last updated June 16, 2010).

B. IDENTIFYING A SUFFICIENT TRANSFORMATION UNDER *MAYO*
STEP TWO INVOLVES ASKING NUANCED QUESTIONS ABOUT
MOLECULAR BIOLOGY

Given the strong likelihood that courts will consider epigenetics-based technology categorically directed to ineligible subject matter, patent eligibility will depend on the second step of the analysis: whether the invention contains an inventive concept sufficient to transform it into a patentable invention.¹⁰⁶ Unfortunately, the close relation between epigenetics-based technology and underlying natural phenomena or laws obscures this analysis. Though “all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas,”¹⁰⁷ epigenetics relies on natural features, interactions, and correlations to an exceptional degree, even among fields of biotechnology.¹⁰⁸ It cannot readily utilize synthetic biology tools that clearly distinguish inventions from their underlying subject matter.¹⁰⁹ Accordingly, resolving *Mayo* step two for epigenetics-based inventions requires examining subtle distinctions between the invention and its underlying subject matter, making the analysis akin to separating shades of gray. To highlight the subtlety of the distinctions that must be drawn, one must consider what types of modifications, and what extent of modification, would be necessary to transform an epigenetically relevant, naturally occurring protein into a patent eligible invention.¹¹⁰ Three types of alterations to consider include: (1) use in a nonnatural context; (2) chemical modification after translation; and (3) change to the protein’s amino acid sequence.¹¹¹

An epigenetically relevant protein could be used outside its natural context in many ways. Molecular biologists often use natural proteins in cells where the proteins are not naturally

106. *Mayo*, 566 U.S. at 72–73.

107. *Id.* at 71.

108. *See supra* notes 96–97 and accompanying text.

109. *Id.*

110. A similar question regarding type and extent of modification could be asked for most inventions in the field of molecular biology. For the purposes of this Note, the discussion will limit itself to epigenetics. Nevertheless, it is important to note that courts may similarly struggle to define minimum transformation when examining biotechnology beyond epigenetics.

111. A nonnatural context would not alter the protein in any way, whereas chemical modification or amino acid changes would alter its structure. Any impact on the protein’s function would depend on the extent of contextual change, chemical modification, or amino acid sequence changes.

present.¹¹² Given the stark differences between bacteria and human cells, using a bacterial protein in a human cell would likely be transformative.¹¹³ While a good starting point, it does not define the line of minimum transformation that will give rise to patent eligibility. Does the use of the protein stop being transformative when the natural protein comes from a eukaryotic microorganism, a mammal, a primate, or a human? If the protein is a histone, how does the fact that eukaryotic histones share highly similar structures affect the analysis? Could it be sufficiently transformative to use a human nonhistone protein naturally expressed only in one cell type in another cell type? Also, consider uses of natural proteins in an in-vitro setting: Does using a natural histone in a diagnostic for epigenetic disease give rise to patentability, despite the diagnostic's dependence on recognition of the histone code? What if the diagnostic utilizes multiple natural nonhistone proteins that respond to the histone code in different ways?

Chemical and amino acid changes also invoke questions about what constitutes a minimum transformation. Is it transformative to change a protein's structure, but not its function? Do changes sufficiently transform the protein if they change how well the protein functions, but not how it carries out that function? What if the changes add a new function, but leave the natural function unaffected? As an example, consider chemical and amino acid modifications to histone-modifying proteins. Does a sufficient transformation occur if the protein structure changes, even though it still modifies histones the same way? What if the changes reduce the rate of histone modification by fifty percent? What if the protein no longer modifies histones, but still recognizes and binds to them?

Imagine an inventor wanted to identify condensed chromatin by creating a protein that binds to areas of high DNA methylation and is visible under a fluorescent microscope.¹¹⁴ This inventor would begin with a protein that recognized DNA

112. See ALBERTS ET AL., *supra* note 29, at 495–98 (describing how microbiologists create genetically engineered, or “transgenic,” organisms by deleting or replacing genes).

113. Bacteria are prokaryotic, making them extremely dissimilar to humans, which have eukaryotic cells. See *id.* at 12–13 (listing differences between prokaryotic and eukaryotic cells).

114. Fluorescent tagging proteins are highly common and easy to construct. See *id.* at 539. Such a hybrid protein likely would fail the obviousness test, but that is irrelevant to whether the subject matter would itself be patent eligible.

methylation and modify it, using other naturally occurring proteins as blueprints. At what point would this protein become patent eligible? If the inventor combined natural protein with a synthetic sequence that resulted in fluorescence, it would likely be considered transformed. But what if she combined natural protein with another natural protein that fluoresced? What if the second natural protein came from a different species, and the combination would never occur naturally?

This Section poses many questions, but intentionally offers few answers in the belief that no definite answers exist. It is important to pose these questions regardless, as judges must answer the same or analogous questions when engaging in a § 101 inquiry for a modified biomolecule. Even epigenetics experts could reasonably disagree as to whether a given type or extent of modification sufficiently transforms subject matter into a patentable invention. But judges, not experts, make the patent eligibility determination, and they do so lacking an understanding of both the subject matter and the scientific field.

C. WITHOUT TECHNICAL EXPERTISE OR GUIDANCE FROM PRIOR ART, JUDGES LACK THE ABILITY TO MAKE CONSISTENT § 101 RULINGS ON EPIGENETICS-BASED TECHNOLOGY

The questions set forth above demonstrate the judicial need for scientific context when deciding whether an epigenetics-based invention sufficiently transforms the underlying subject matter. “[T]he judge has to understand [the scientific] background just to get to the factual basis of the problem and then deal with legal aspects.”¹¹⁵ Few judges possess that understanding, with only five percent having studied any type of science.¹¹⁶ Justice Scalia recognized this deficiency regarding molecular biology, concurring with the majority in *Myriad* solely to note that he “join[ed] the judgment of the Court, and all of its opinion except . . . some portions of the rest of the opinion going into fine details of molecular biology. *I am unable to affirm those details*

115. Peter Lee, *Patent Law and the Two Cultures*, 120 YALE L.J. 2, 4 (2010) (quoting Hon. James F. Holderman speaking about patent litigation generally).

116. Jules Epstein, *When Must Lawyers Learn Science?*, NAT'L JUDICIAL COLL.: THE JUDICIAL EDGE (Jan. 21, 2016) <http://www.judges.org/when-must-lawyers-learn-science>.

on my own knowledge or even my own belief.”¹¹⁷ Some would argue that it is the job of attorneys to educate judges on the technology at issue and that their tutorials adequately prepare judges to grapple with difficult subject matter.¹¹⁸ This reasoning assumes that judges freely embrace science-heavy tutorials, which seems unlikely given “[t]he discomfort of the legal profession, including the judiciary, with science and technology.”¹¹⁹ Even Congress, by allowing the USPTO to use a different standard of proof, seems to imply that fact-intensive patent issues are better handled by those familiar with the technical subject matter. District court judges may only invalidate patents based on clear and convincing evidence, but the USPTO may invalidate based on a mere preponderance of the evidence.¹²⁰

The judiciary’s lack of scientific knowledge proves especially troublesome in § 101 challenges because judges decide patent eligibility as a question of law, with the inquiry focused exclusively on the patent’s claims.¹²¹ Courts “consider the elements of each

117. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 596 (2013) (Scalia, J., concurring) (emphasis added).

118. Erin Coe, *Program for Patent Judges Could Cut Case Delays*, LAW360 (Apr. 3, 2009), <https://www.law360.com/articles/95376/program-for-patent-judges-could-cut-case-delays>.

119. *Jackson v. Pollion*, 733 F.3d 786, 788 (7th Cir. 2013); *see also Id.* at 787–88 (discussing the “widespread, and increasingly troublesome, discomfort among lawyers and judges confronted by a scientific or other technological issue”); Lee, *supra* note 115, at 20–25 (arguing that the judiciary takes cognitive shortcuts consistent with the “cognitive miser” model when attempting to understand science, as illustrated by their “use of metaphors to understand new technologies”). Concerns over the judiciary’s inadequacies regarding patent cases has motivated Congress to pass a pilot program which experiments with specialized patent courts. *See Coe, supra* note 118 (“A pilot program allowing for some federal judges to sharpen their expertise in patent law could help whittle down pending cases and speed up patent litigation[—]a process that practitioners say has become painfully slow.”); *see also* MARGARET S. WILLIAMS, REBECCA EYRE, & JOE CECIL, FED. JUDICIAL CTR., PATENT PILOT PROGRAM: FIVE-YEAR REPORT 1 (2016) (describing the structure of the Patent Pilot Program), [https://www.fjc.gov/sites/default/files/2016/Patent%20Pilot%20Program%20Five-Year%20Report%20\(2016\).pdf](https://www.fjc.gov/sites/default/files/2016/Patent%20Pilot%20Program%20Five-Year%20Report%20(2016).pdf).

120. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144 (2016). *Inter partes* reviews, which allow challenging a patent on novelty or obviousness grounds, are conducted before USPTO examiners who have some level of expertise in the subject matter. *Inter Partes Review*, USPTO, <https://www.uspto.gov/patents-application-process/appealing-patent-decisions/trials/inter-partes-review> (last modified May 9, 2017). While Article III judges decide patent issues using a clear and convincing evidence standard, the examiners need only decide them by a mere preponderance of the evidence. *Cuozzo*, 136 S. Ct. at 2144.

121. *See Alice Corp. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2355 (2014).

claim both individually and ‘as an ordered combination’ to determine whether the additional elements ‘transform the nature of the claim.’”¹²² This narrow focus on claim language causes problems by excluding prior art from the analysis, which eliminates another source of scientific knowledge from consideration.¹²³ In the novelty and obviousness doctrines, judges compare the patent-in-suit to closely related patents and publications (the “prior art”) to determine whether its invention is new¹²⁴ and non-obvious.¹²⁵ Though judges make § 101 determinations without a comparison, prior art references could inform judges about closely related inventions in the field, helping them develop an understanding of both the subject matter and what inventive contribution the patent-in-suit might be making.

Because epigenetics-based technology often blurs the line between invention and underlying natural phenomena and laws, judges already face a difficult task when making § 101 determinations.¹²⁶ Absent background knowledge of molecular biology or context from prior art, how can the judiciary hope to understand, much less consistently answer, any of the questions posed in Part II.B?¹²⁷ With difficult subject matter, varying levels of background knowledge, and minimal context for the invention, one should expect judges to make inconsistent decisions regarding the patent eligibility of epigenetics-based inventions. Absent an understanding of epigenetics-based technology, we should expect courts to differ with regards to where they set the line of minimum transformation. The inconsistency arises not because the judiciary is incapable, but because the *Mayo* test requires

122. *Id.*

123. Another problem with focusing the § 101 inquiry exclusively on claim language is the judiciary’s poor performance when attempting to interpret the scope of patent claims. The Federal Circuit reverses claim construction rulings in roughly one-third of cases. Coe, *supra* note 118. Comparatively, “[c]laim construction rulings by U.K. courts were overturned [only] 15 percent of the time.” *Id.* Some practitioners even report instances in which courts improperly approached patent claims like contract terms. *Id.* This poor performance contributed to Congress’s decision to begin the Patent Pilot Program, which tracks courts’ performance in deciding claim construction. See WILLIAMS, EYRE & CECIL, *supra* note 119, at 23–25 (detailing the results of *Markman* hearings for claim construction over the first five years of the pilot program).

124. 35 U.S.C. § 102(a) (2012).

125. *Id.* § 103.

126. Judges must simultaneously combat the interpretive problems of trying to read *Myriad*, *Alice*, and *Mayo* together. See Burk, *supra* note 30, at 609–11 (demonstrating the difficulty of combining the different frameworks used by the Supreme Court); *supra* Part II.A.

127. See *supra* notes 112–14 and accompanying text.

judges to define a “sufficient transformation” for complex subject matter in a vacuum, with no reference to prior art—a difficult task that none of the other patent doctrines require.

III. THE INADEQUACY OF INCONSISTENT PATENT RIGHTS AND ALTERNATIVES TO APPLYING MAYO TO BIOTECHNOLOGY

This Part builds upon the inconsistent patent rights for epigenetics-based technology likely to result from the *Mayo* test, arguing that the uncertainty of validity threatens to freeze investment and prevent acquisition of epigenetics start-ups, which would impede the process of bringing epigenetics-based technology to markets. It then argues that categorically exempting epigenetics-based technology from § 101 would solve the uncertainty problem without leading to patents “‘improperly tying up the’ . . . building blocks of human ingenuity.”¹²⁸

A. ALLOWING INCONSISTENT INVALIDATIONS UNDER § 101 HARMS BIOTECHNOLOGY FIRMS AND HINDERS EPIGENETICS FROM ENTERING MEDICAL MARKETS QUICKLY

Historically, biotechnology companies have relied on patents to protect their investments in research and development, perhaps more than any other industry.¹²⁹ Pharmaceutical companies helped drive this trend through their own patenting practices and their targeted acquisition of biotech start-ups. Epigenetics start-ups appear to be following the same strategy, likely because it develops strong intellectual property assets that can later be leveraged during an acquisition or when attracting investors.¹³⁰ This Section discusses the dominant biotech patenting strategy, how it pays off for both the start-up and acquiring company in an acquisition, and why inconsistent § 101 invalidations undermine it.

128. *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1301 (2012)).

129. Esteban Burrone, *Patents at the Core: The Biotech Business*, WIPO (2006), http://www.wipo.int/sme/en/documents/patents_biotech_fulltext.html.

130. *See id.* (describing the importance of strong intellectual property assets to investors in biotech companies).

The biotech strategy of patenting early and frequently arises from the capital-intensive process of bringing a product to market, which can best be demonstrated with pharmaceuticals.¹³¹ Recent estimates place the total capitalized cost of bringing a drug to market at \$2.558 billion.¹³² Capital covers not only the cost of creating the drug, but also the cost of conducting clinical trials, seeking FDA approval, and educating consumers and healthcare providers through marketing.¹³³ Biotech firms incur these extreme costs only because patent monopolies ensure a return on their investment.¹³⁴ Their aggressive pursuit of patents, sometimes more than six years prior to *any* drug in the class being approved,¹³⁵ demonstrates just how essential they consider patents to their business model.

For those developing epigenetics-based technology—often start-ups—the incentives to patent differ from those motivating large pharmaceutical companies. Epigenetics start-ups face many of the same capital requirements as pharmaceutical companies, but lack the resources to ensure they can bring the product to market. Accordingly, start-ups focus on shorter-term goals when patenting, each of which contributes to the start-up’s long-term viability. Acquiring a patent serves as a deterrent to others who would otherwise assert their intellectual property against the start-up, the threat of countersuit serving as a form of mutually assured destruction or an incentive to cross-license.¹³⁶ Additionally, patenting attracts investment and acquisition, which provides the resources to get technology to market.¹³⁷ Only with acquisition or investment can the patented technology reach the

131. Pharmaceutical companies have escalated how early and frequently they patent in recent years. From 1998 to 2004, pharmaceutical companies only patented eighty percent of later-in-class drugs prior to the first-in-class drug’s approval, but between 2005 to 2011 that number increased to 100%. Joseph A. DiMasi & R. Chakravarthy, *Competitive Development in Pharmacologic Classes: Market Entry and the Timing of Development*, 100 *CLINICAL PHARMACOLOGY & THERAPEUTICS* 754, 757 (2016).

132. Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 *J. HEALTH ECON.* 20, 26 (2016). DiMasi et al.’s estimate that the capitalized cost of bringing a drug to market has increased 145% since 2003. *Id.* at 31. Almost half of this increase can be attributed to increasing drug failure rates. *Id.* at 28.

133. Emily Michiko Morris, *The Myth of Generic Pharmaceutical Competition Under the Hatch-Waxman Act*, 22 *FORDHAM INTELL. PROP. MEDIA & ENT. L.J.* 245, 255–57 (2012).

134. *Id.* at 257.

135. DiMasi & Chakravarthy, *supra* note 131, at 758.

136. See Graham & Sichelman, *supra* note 16 at 1065–66.

137. *Id.* at 1067.

market and serve its ultimate purpose: recouping the start-up's research and development costs.

Though initial public offering (IPO) markets have been promising for biotechnology,¹³⁸ most start-ups follow the acquisition track to obtain resources and regulatory expertise from large pharmaceutical companies.¹³⁹ Epigenetics start-ups, such as Epizyme, have already begun to seek out buyers.¹⁴⁰ Leveraging a larger company's resources and regulatory expertise lessens the burden of a grueling FDA approval process, allowing technology to reach markets more quickly.¹⁴¹ At the same time, large pharmaceutical companies have moved away from research and development and towards acquisition because they can "acquire potential [sic] commercially viable products that can shave years off of R&D effort."¹⁴² This trend might also be linked to the steady increase in research and development costs over recent years, resulting from decreases in drug success rates.¹⁴³ In other words, acquiring a biotech start-up may be a more certain and cost-effective investment than performing one's own research and development.

Patent eligibility invalidations and the resulting uncertainty in patent rights undercut this trend in multiple ways. First, the uncertainty of successfully asserting the patent

138. See Percy H. Carter et al., *Investigating Investment in Biopharmaceutical R&D*, 15 NATURE REVIEWS DRUG DISCOVERY 673, 674 (2016) ("The optimism stems from the clear indication that investors are still willing to back projects and companies that have advanced to the preclinical stage.").

139. Mary Ann Rafferty, *Managing Change in Biotech: Mergers and Acquisitions*, 25 NATURE BIOTECHNOLOGY 689, 689 (2007). Assuming DiMasi et al.'s estimates on the increasing costs of drug development are correct, see DiMasi et al., *supra* note 132, pharmaceutical companies' growing interest in acquisition likely stems from the relative certainty, and therefore cost-effectiveness, of an acquired product vis-à-vis internal development.

140. Luke Timmerman, *Celgene Emerges as Biotech's Shrewdest, Nimblest Dealmaker*, EXOME: BIOBEAT (Aug. 5, 2013), <http://www.xconomy.com/national/2013/08/05/celgene-emerges-as-biotechs-savviest-nimblest-dealmaker>.

141. Rafferty, *supra* note 139 ("[B]iotechs are often eager to gain regulatory and marketing expertise—both of which are big pharma's strengths.").

142. *Id.*; see also Timmerman, *supra* note 140 ("Celgene has gotten its hooks into some of the . . . leaders in epigenetic-based drug development, cancer metabolism, antibody drugs, gene therapy, immunotherapy, and regenerative medicine. If even one-fourth or one-fifth of these companies do what they say they are aspiring to do, Celgene will win big.").

143. See generally DiMasi et al., *supra* note 132 (discussing new costs estimates of drug research and development). Accounting for inflation, the capitalized cost per approved drug grew 8.5% per year from 2005 to 2013. *Id.* at 26.

greatly reduces its deterrence value,¹⁴⁴ reducing incentives for competing start-ups to cross-license and making lawsuits more likely.¹⁴⁵ Uncertain patent rights also reduce the appeal of investment and acquisition of biotech start-ups, as investors lack certainty that they can recoup their investment or acquisition costs when the technology eventually reaches the market. With many investments or acquisitions occurring before any clinical testing begins,¹⁴⁶ the larger company must still spend hundreds of millions of dollars before the product reaches markets. It makes little sense to incur both acquisition and development costs if the patent cannot exclude competitors. Research already indicates underinvestment in IPOs for large-molecule biologics, a category that includes certain forms of epigenetics-based technology.¹⁴⁷ Though it remains unclear whether uncertain patent rights contribute to this underinvestment,¹⁴⁸ pharmaceutical companies' need for "a healthy, big pipeline to fuel [them]," made up of "the highest science [and] novelty" should ensure that the market for acquiring biotech start-ups does not disappear, even if the lack of consistently enforceable patent rights does make it less robust.¹⁴⁹

Unfortunately, a less robust market for biotech investment and acquisition may still irreparably harm newer fields of biotechnology, like epigenetics. A limited market for investment discourages epigenetics-based start-ups from forming, which in turn limits the innovation in the field. Large pharmaceutical companies "pick up . . . groundbreaking treatments" from start-ups, specifically looking for ones that can be disruptive to the

144. Graham & Sichelman, *supra* note 16, at 1080 ("[W]hen it is very likely the defendant would be able to show . . . that the asserted patents are invalid or unenforceable—the patent system may not function optimally because of the high costs and uncertainty of patent litigation.").

145. *See id.* at 1076–77, 79–80 (discussing the leverage a strong patent portfolio provides in licensing scenarios and as a deterrence to litigation).

146. *See* Timmerman, *supra* note 140 (explaining that most of Celgene's acquisitions occurred when the smaller company "had technology still in preclinical testing").

147. *See* Carter et al., *supra* note 138, at 674. Investors prefer small molecules over biologics at the pre-clinical phase, despite biologics having a net present value "2.5-fold higher" than small molecules. *Id.*

148. Researchers suggest that the underinvestment may occur either because "investors may not be sophisticated enough to form an efficient public market for a space as complex as biopharmaceuticals," or because investors "are focused on their 'exit' and not on the ultimate marketing of the compound." *Id.*

149. Timmerman, *supra* note 140 (quoting George Golumbeski, Celgene's senior vice president of business development, regarding Celgene's approach to acquisitions and investment).

field.¹⁵⁰ With fewer epigenetics start-ups, one can expect fewer novel treatments for serious epigenetic diseases that currently lack a cure, such as Prader-Willi Syndrome, Angelman's Syndrome, and ATR-X Syndrome.¹⁵¹ Those epigenetics start-ups that do move forward may encounter pharmaceutical companies no longer willing to invest or acquire technology in preclinical stages. Investing or acquiring at a later stage somewhat offsets the risk of patent invalidity,¹⁵² as clinical-phase technology is usually more proven than preclinical technology. Entrance at a later stage also lessens the investor's financial burden in bringing the technology to market, further offsetting the risk of patent invalidity. While delaying acquisition or investment decreases risk for investors, it also places a heavy burden on epigenetics start-ups, who must begin the FDA approval process without financial backing or regulatory expertise. Accordingly, any treatments or technology developed by epigenetics start-ups will be delayed in reaching markets.

Whether the inconsistency of patent rights manifests itself in a lack of innovative epigenetics technology or a delay in bringing that technology to market, it inflicts an unacceptable harm on a growing field of technology. Epigenetic technology not only combats epigenetic diseases, but also holds the potential to expand personalized medicine, provide individualized cancer treatments, and assist with drug targeting.¹⁵³ In an age where funding and regulatory compliance serve as major hurdles to

150. *Id.*

151. Symptoms of Prader-Willi Syndrome, which results from deletions on chromosome 15, include life-threatening obesity, delays in intellectual development, and difficulty controlling emotions. *Prader-Willi Syndrome (PWS): Condition Information*, NAT'L INST. HEALTH, <https://www.nichd.nih.gov/health/topics/prader-willi/conditioninfo/default> (last updated Dec. 1, 2016). Angelman Syndrome causes "developmental delay and neurological problems" as early as six months into a child's life, and later causes seizures. *Angelman Syndrome Information Page*, NAT'L INST. NEUROLOGICAL DISORDERS & STROKE, <https://www.ninds.nih.gov/Disorders/All-Disorders/Angelman-Syndrome-Information-Page> (last visited Apr. 19, 2017). Alpha Thalassemia X-Linked Intellectual Disability Syndrome (ATR-X) not only impairs development and intellectual abilities, but also causes a blood disorder, skeletal anomalies, and genital abnormalities. *Alpha Thalassemia X-Linked Intellectual Disability Syndrome*, GENETICS HOME REFERENCE (Apr. 7, 2017), <https://ghr.nlm.nih.gov/condition/alpha-thalassemia-x-linked-intellectual-disability-syndrome>.

152. See Carter et al. *supra* note 138, at 673 (demonstrating that net present valuations increase dramatically when conducted at later stages of development).

153. See *supra* notes 92–95 and accompanying text.

bringing these advancements to market, biotech start-ups' ability to provide patients with new treatments depends on their attractiveness to investors. Patent law should help start-ups attract investors and acquiring companies, not act as an impediment.

B. CATEGORICALLY EXEMPTING EPIGENETICS FROM § 101 AND RELYING ON OBVIOUSNESS UNDER § 103 OR THE EUROPEAN PATENT OFFICE'S INVENTIVE-STEP STANDARD TO CLEAR PATENT THICKETS WOULD LEAD TO MORE CONSISTENT PATENT RIGHTS

This Section presents an easily implemented solution to the inconsistent patent rights resulting from the *Mayo* test: categorically exempting epigenetics from § 101. It argues that the Supreme Court's concern in adopting the *Mayo* test, that patents would “improperly t[ie] up the' . . . building blocks of human ingenuity,”¹⁵⁴ can be adequately addressed for epigenetics-based technology through the obviousness doctrine. It also addresses a potential problem arising from the TRIPS Agreement—which sets global intellectual property standards for World Trade Organization (WTO) members—by offering a variant of this solution in which a European inventive-step analysis replaces the *Mayo* test for epigenetics.¹⁵⁵

1. Categorically Exempting Epigenetics-Based Technology from § 101 Resolves the Inconsistency Problem and Falls Well Within Congressional Authority

Considering the various problems with applying the *Mayo* test to epigenetics-based technology identified in Part II, countless adjustments could be made to the doctrine. This Note argues that the simplest solution is the best: categorically exempting epigenetics-based technology from § 101. Unlike other potential solutions, such as the introduction of prior art to the analysis or requiring a court-appointed technical expert for each § 101 determination, categorical exemption ensures both that the solution does not convolute patent eligibility doctrine further and that patent rights for epigenetics-based technology become consistently enforceable. In other words, categorical exemption

154. *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1301 (2012)).

155. Agreement on Trade-Related Aspects of Intellectual Property Rights Preamble, Apr. 15, 1994, 33 I.L.M. 1197 [hereinafter TRIPS Agreement] (expressing a desire to reduce intellectual property-related trade disputes).

serves as a cure to the inconsistent patent rights problem, not a band-aid that merely mitigates it.

This solution also has the advantage of being practical. The constitutional authority to define patentable subject matter, including declaring certain subject matter patent eligible, resides with Congress.¹⁵⁶ Based on recent events, there may even be congressional support for a categorical exemption of epigenetics-based technology from § 101. Justice Frankfurter noted in 1943 that it was already “an old observation that the training of Anglo-American judges ill fits them to discharge the duties cast upon them by patent legislation.”¹⁵⁷ Yet only recently did Congress seek to remedy the problem, “steering cases to judges who have an interest in them” through a patent pilot program.¹⁵⁸ Established in early 2011, the program experiments with specialized patent courts by examining outcomes from thirteen pilot districts over a ten-year period.¹⁵⁹ This legislation constitutes congressional acknowledgement of what Justice Frankfurter noted over seventy years ago: that judges are ill-equipped to handle certain patent matters.

Recent events around Capitol Hill also indicate congressional interest in strengthening bio-pharma patents specifically. Powerful lobbying organizations representing bio-pharma have advocated for a similar categorical exemption that would exclude certain bio-pharma patents from postgrant proceedings at the USPTO.¹⁶⁰ Responding to these requests, Congresswoman Mimi Walters, a member of the House Judiciary Committee, introduced an amendment that would exempt certain pharmaceutical

156. See generally U.S. CONST. art. I, § 8, cl. 8 (granting power to congress to “promote the Progress of Science and useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their . . . Discoveries”).

157. *Marconi Wireless Tel. Co. of Am. v. United States*, 320 U.S. 1, 60–61 (1943) (Frankfurter, J., dissenting).

158. Coe, *supra* note 118.

159. WILLIAMS, EYRE & CECIL, *supra* note 119, at 1.

160. The Biotechnology Industry Organization and PhRMA sent a joint letter to the Senate and House Judiciary Committees arguing that allowing bio-pharma patents to be challenged in *inter partes* reviews, a common post-grant proceeding, “threatens to disrupt the careful balance that Congress achieved over 30 years ago” when it passed legislation outlining how biopharmaceutical patent litigation should proceed. Letter from James C. Greenwood, President & CEO, Biotechnology Indus. Org., & John J. Castellani, President & CEO, Pharm. Research Mfrs. Am., to Chuck Grassley, Chairman, Senate Judiciary Comm., & Robert Goodlatte, Chairman, House Judiciary Comm. (July 15, 2015), http://www.ptabwatch.com/wp-content/uploads/sites/630/2015/09/Final_Joint_Phrma_Bio_Letter_on_IPR_071515.pdf.

patents from Patent Trial and Appeal Board (PTAB) proceedings.¹⁶¹ Rep. Walters eventually withdrew the amendment after opposition from committee chairmen Rep. Robert Goodlatte. However, Chairmen Goodlatte later remarked that he thought everyone agreed with Rep. Walters, but that the amendment “was too complex to resolve in the markup session.”¹⁶²

2. In the Absence of a § 101 Requirement, Obviousness or European Inventive-Step Doctrines Adequately Address the Supreme Court’s Concerns and Provide a Means to Avoid Violating the TRIPS Agreement

Though categorically exempting epigenetics-based technology from § 101 provides a straightforward solution that recent events indicate may be Congressionally popular, two important questions remain. First, how does this solution address the Supreme Court’s “repeatedly emphasized . . . concern that patent law not inhibit further discovery by improperly tying up the future use of” these building blocks of human ingenuity?¹⁶³ Second, would the categorical exemption constitute “discrimination as to . . . the field of technology,” which the TRIPS Agreement forbids?¹⁶⁴ Both questions can be resolved with either the obviousness doctrine or its European equivalent, the inventive step.

The Supreme Court’s main concern in redefining the patentable subject matter doctrine was preventing patents from claiming the “building blocks of human ingenuity” and thereby excluding others from utilizing them.¹⁶⁵ Obviousness determinations under § 103 should adequately address this concern by eliminating unnecessary and overbroad patents. Under obviousness, inventions are patentable if nonobvious to a person having ordinary skill in the art.¹⁶⁶ The hypothetical person of skill knows all pertinent prior art references, which would include underlying natural phenomena and laws already known to man.¹⁶⁷ Because

161. See Tony Dutra, *House Judiciary Committee Moves Patent Bill Forward, Battle over Fee Shifting Looms*, BLOOMBERG BNA (June 18, 2015), <https://www.bna.com/house-judiciary-committee-n17179927818>.

162. *Id.*

163. *Alice Corp. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2354 (2014) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1301 (2012)).

164. TRIPS Agreement, *supra* note 155, art. 27, ¶ 1.

165. *Alice Corp.*, 134 S. Ct. at 2354.

166. 35 U.S.C. § 103 (2012).

167. See *In re Winslow*, 365 F.2d 1017, 1020 (C.C.P.A. 1966) (“We think the proper way to apply the 103 obviousness test to a case like this is to first picture

epigenetics-based technology so closely utilizes underlying natural phenomena and laws, many patents that insufficiently transform their underlying subject matter should also be obvious to a person skilled in molecular biology.

This likely obviousness can be illustrated using *Myriad's* ruling on cDNA. Scientists create cDNA by removing noncoding regions of nucleotides from a natural RNA molecule and then converting it into a DNA-equivalent.¹⁶⁸ Under a § 101 analysis, the Court considered cDNA patent eligible because it “is distinct from the DNA from which it was derived.”¹⁶⁹ Under an obviousness analysis, however, the cDNA likely would not be patentable. The process of generating cDNA, reverse transcription, is well known to those skilled in the art of molecular biology, making the invention obvious.¹⁷⁰ As this example shows, obviousness sometimes poses a larger hurdle to patentability than § 101 does. Accordingly, the Supreme Court’s concerns about overbroad patents chilling scientific advancement can still be met even if Congress categorically exempts epigenetics-based technology from § 101.

The TRIPS Agreement poses another interesting hurdle for the solution posed by this Note. Article 27.1 states that “patents shall be available and patent rights enjoyable without discrimination as to . . . the field of technology.”¹⁷¹ Neither TRIPS nor subsequent WTO decisions provide much clarification regarding the scope of this discrimination provision.¹⁷² The only WTO panel to consider Article 27.1 defined discrimination as “the unjustified imposition of differentially disadvantageous treatment”

the inventor as working in his shop with the prior art references—which he is presumed to know—hanging on the walls around him.”)

168. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2119 (2013).

169. *Id.*

170. Generating cDNA has become such a routine practice for molecular biologists that commercial suppliers sell kits that allow even high-school-age students to generate it. *See, e.g., Cells-to-cDNA™ II Kit*, THERMOFISHER SCIENTIFIC, <https://thermofisher.com/order/catalog/product/AM1722> (last visited Apr. 19, 2018).

171. *See* TRIPS Agreement, *supra* note 155, art. 27, ¶ 1.

172. Apart from article 27, ¶ 1 itself, the only guidance on how to interpret TRIPS’s prohibition on discrimination comes from WTO panel decision DS114 concerning Canadian pharmaceutical patents. A HANDBOOK ON THE WTO TRIPS AGREEMENT 107–08 (Antony Taubman et al. eds., 2012).

and noted that discrimination “may arise from explicitly different treatment, sometimes called ‘de jure discrimination.’”¹⁷³ A categorical exemption from § 101 explicitly treats epigenetics-based technology differently, and, in that sense, could be construed as discrimination favoring epigenetics.¹⁷⁴ Considering biotechnology’s susceptibility to § 101 invalidation,¹⁷⁵ however, the categorical exemption would remedy a disadvantage rather than provide an advantage. The United States already has taken the position “that not all differential treatment is ‘discrimination,’”¹⁷⁶ and could defend a categorical exemption by arguing that biotechnology’s susceptibility justifies the differential treatment, and results in no disadvantage for other fields of technology. Based on the WTO panel’s own definition,¹⁷⁷ such treatment would not be discrimination. It would not impact the availability of patents or patentees’ ability to enjoy patent rights for other technology, and merely ensures that the same holds true for epigenetics.

If the solution does violate the TRIPS Agreement, however, then a minor modification should bring it into compliance. Instead of categorically exempting epigenetics-based inventions from § 101, Congress could replace the *Mayo* analysis with the EPO’s inventive-step standard. This solution removes epigenetics-based technology from the *Mayo* analysis, leaving it with different, but not necessarily lesser, patentability requirements than other types of technology. Accordingly, epigenetics would not gain an unjustified advantage over other fields of technology. While adopting a foreign standard seems complicated, the similarities between obviousness and inventive step should make it

173. Panel Report, *Canada—Patent Protection of Pharmaceutical Products*, ¶ 7.94, WTO Doc. WT/DS114/R (adopted Mar. 17, 2000) [hereinafter Panel Report]. Unfortunately, the panel provided no clarification on when discrimination does not “arise from explicitly different treatment,” as it decided the Canadian law did not *de jure* discriminate. See *id.* at ¶ 7.94–99.

174. Exempting epigenetics from § 101 does not conflict with TRIPS’s three mandatory patentability requirements: novelty, nonobviousness, and “capable of industrial application.” See TRIPS Agreement, *supra* note 155, art. 27, ¶ 1. Even absent § 101, U.S. patent law still imposes these three patentability requirements. See 35 U.S.C. § 102 (2012) (novelty); *id.* § 103 (nonobviousness); *id.* § 112 (best mode and enablement).

175. See Sachs, *supra* note 8, fig.2 (showing that § 101 challenges invalidate certain fields, including biotechnology, at a disproportionately high rate).

176. Panel Report, *supra* note 173, ¶ 7.100. Australia and the United States, both third parties, took this position based on legal rulings on the General Agreement on Tariffs and Trade (GATT) and WTO. *Id.*

177. *Id.* ¶ 7.94 (defining discrimination as “the unjustified imposition of differentially disadvantageous treatment”).

relatively easy to implement. Judges engage in the same basic analysis, but use a problem-solution approach to decide whether a person of skill in the art would consider the invention obvious.¹⁷⁸ As discussed above for obviousness,¹⁷⁹ inventive-step analysis should adequately address the Supreme Court's concerns about patents "'improperly tying up the' . . . building blocks of human ingenuity."¹⁸⁰ In fact, inventive step appears even better suited for this purpose than obviousness, given its resemblance to *Mayo* step two's inventive concept requirement.¹⁸¹ Replacing § 101 analysis with inventive-step analysis should also avoid any doctrinal changes which could convolute the *Mayo* test further.

CONCLUSION

Mayo, *Myriad*, and *Alice* streamlined the patentable subject matter doctrine into a two-part test that proves difficult to apply to epigenetics-based inventions. The close relation between epigenetics-based inventions and their underlying natural phenomena and laws complicates patent eligibility determinations, resulting in inconsistent invalidation decisions and uncertain patent rights. This uncertainty creates problems in growing biotech fields, where start-ups need clearly enforceable patent rights to attract investment or acquisition. Without investment or acquisition, epigenetics start-ups lack the capital and regulatory expertise to efficiently bring new cures to market. Instead of leaving epigenetics mired in uncertain intellectual property rights, Congress should address this issue by categorically exempting epigenetics-based inventions from § 101, with the understanding that the obviousness requirement from § 103 adequately addresses the Supreme Court's concerns about overly broad patents stagnating progress.

178. EPO GUIDE, *supra* note 39, at 17.

179. See *supra* notes 166–70 and accompanying text.

180. *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014) (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1301 (2012)).

181. *Id.* at 2357. The problem-solution approach of an inventive-step analysis also comports with a recent Federal Circuit ruling on § 101 in which it found claims "directed to a specific implementation of a solution to a problem in the software arts." *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1339 (Fed. Cir. 2016). In effect, an inventive-step analysis may be roughly equivalent to a *Mayo* analysis that utilizes prior art.