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PROMETHEUS UNBOUND

THE UNTETHERING OF LAWS OF NATURE AND
PATENT ELIGIBILITY FROM SCIENTIFIC REALITY

In March 2012 the Supreme Court ruled, in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. ____ (2012), that a patent claim on a method of determining whether a given dose of a particular type of medication was safe and effective was a “law of nature” and thus invalid. The Court’s characterization does not withstand critical analysis.

Prometheus Labs is the exclusive licensee of U.S. patents 6,355,623 and 6,680,302. The patents deal with a protocol to determine the safe and effective dosage for thiopurines, which are medications that treat autoimmune diseases such as Crohn’s disease and ulcerative colitis. These medications metabolize in the patient’s body to 6-thioguanine (6-TG). The different rates at which the medications metabolize make it difficult for physicians to determine whether a given dose is too high (and thus toxic) or too low (and thus ineffective). The Prometheus patents’ claims identify the range for safe and effective dosages as those that result in a concentration of 6-TG between about 230 pmol and 400 pmol per 8×10^8 red blood cells (RBC). The patents claim no underlying biological process that accounts for the differences in metabolism.

The Supreme Court ruled that Prometheus’ claims were not eligible for patent protection, holding that Prometheus did nothing more than identify a law of nature. However, the Court’s analysis is based on a superficial understanding of the scientific status of laws of nature.

What Is a Law of Nature?

To understand what counts as a law of nature, we must distinguish three types of statements:

Accidental generalization: All robin eggs observed to date are greenish-blue.

Universal truth: Every robin egg, both those observed in the past and those to be observed in the future, is greenish-blue.

Law-like statement: It is a law that robin eggs are greenish-blue.

An *accidental generalization* summarizes past experience—every robin egg found to date has been greenish-blue—and leaves open the possibility that some robin egg found in the future will not be

greenish-blue. An accidental generalization heeds the principle that *correlation does not imply causation*. An assertion that something is a law of nature simply because every observation of relevance has certain properties (e.g., all the robin eggs observed are greenish-blue) is never sufficient.

A *universal truth* is stronger. Not only has every observed robin egg been greenish-blue—but a universal truth also *predicts* that every egg in the future will be the same color. This assertion has more force, but it provides no *reason that necessitates* this result. Intuitively, a robin egg could be, for example, pale white, due to a genetic mutation. Merely stating the relationship in conditional form—“If x is a robin egg, then x is greenish-blue”—does not make it a law of nature.

A *law-like statement* means something more than just the accidental generalization or the predictions of a universal truth. For a law-like statement to be *necessary*, it *must* be true for some reason or property.

Without distinguishing among accidental generalizations, universal truths, and law-like statements, one cannot explain what makes a law of nature. “What is a law of nature?” thus becomes

“What properties are required of a law-like statement to make it a *law of nature*?” The philosophical literature discusses a number of such conditions:

1. *Universality*: the statement is true under any and all conditions and thus is independent of contingent facts. Continuing the above example, there would have to be no examples of robin eggs that are not greenish-blue for the statement to be a law of nature; otherwise the statement is merely an accidental generalization.
2. *Necessity*: the statement expresses something that *must* be true and not just true by definition (e.g., “all humans are mammals”) or by mathematics (e.g., “there is no largest prime number”). This requirement is called *physical, natural, or nomological* necessity. Loosely speaking, is there something that makes it necessary that all robin eggs are blue? Necessity is what distinguishes a law-like statement from a (mere) universal truth.
3. *Explanation*: the statement explains the phenomena and all instances. A law of nature about the particular color of robin eggs would provide an explanation as to why and how this occurs.
4. *Prediction*: the statement makes predictions about future instances and which predictions can be confirmed (or disconfirmed). Will all robin eggs that are found in the future be greenish-blue?
5. *Inference*: the statement supports inferences from sets of facts to further sets of facts that can be confirmed. Given the color of robin eggs, can we infer any other useful facts?
6. *Counterfactuals*: a statement like “It is law that robin eggs are greenish-blue” must be true in *counterfactual* examples where

there are no robin eggs at all.

7. *Objectivity*: whether a statement is a law of nature does not depend on any human knowledge, belief, interest, need, or other subjective or pragmatic consideration. Thus, if it is a law that robin eggs are greenish-blue, it does not depend on any of our beliefs about robins, our perception of what is greenish-blue, or whether it is useful to humans that robin eggs have this color.
8. *Scientific*: a statement should be discoverable by scientists; it is what scientists would consider a law.

None of these properties are entirely undisputed. But in general the more of them that are met by a given statement, the stronger the case for properly identifying it as a law of nature. See B. van Fraassen, *Laws and Symmetry* (1989), for a detailed analysis of these criteria and a critique of the leading theories of laws of nature.

The question of whether there are laws in biology is one of the oldest questions in the philosophy of biology. Biology is distinct from physics because biological systems are the result of evolutionary processes. Different biological outcomes are inherent in the operation of evolution and have several sources: (1) random mutation, which is necessary for any adaptation; (2) variances in the environment that present selection pressure; and (3) the existence of multiple different functionally equivalent adaptations. Stephen Jay Gould, in *Wonderful Life: The Burgess Shale and the Nature of History* (1989), puts it vividly: “Evolution is like a videotape that, if replayed over and over, would have a different ending every time.”

Ernst Mayr contributed to the Modern Synthesis of evolutionary theory. In his masterwork *The Growth of Biological Thought: Diversity, Evolution, and Inheritance* (1989), Mayr wrote:

The question has been raised in recent years whether or not laws are as important in biology as

they seem to be in the physical sciences. . . . Biologists have paid virtually no attention to the argument, implying that this question is of little relevance to the working biologist. . . . If one looks at a modern textbook of almost any branch of biology, one may not encounter the term “law” even a single time.

This view, by one of the foremost biologists of our time, is a devastating rebuttal to the Supreme Court’s assertion that “laws of nature” are “the basic tools of scientific and technological work.” If working biologists do not think that “laws” have much to do with their work, from what authority, other than perhaps degenerate Cartesian rationalism, does the Supreme Court derive this proposition?

Does Prometheus’ Claim Recite a Law of Nature?

We can consider whether Prometheus’ claim recites a law of nature under the variously described criteria. Here is claim 1 of the ‘623 patent:

1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
 - (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
 - (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 RBC indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 RBC indicates a need to decrease the amount of said drug subsequently administered to said subject.

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The Supreme Court's analysis of this claim in its entirety is:

Prometheus' patents set forth laws of nature—namely, 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. Claim 1, for example, states that if the levels of 6-TG in the blood (of a patient who has taken a dose of a thiopurine drug) exceed about 400 pmol per 8×10^8 RBC, then the administered dose is likely to produce toxic side effects. While it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action. The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes. And so a patent that simply describes that relation sets forth a natural law.

The Supreme Court assumes that there are laws of nature and concludes that the specific dosage-toxicity relationship claimed is such a law. The structure of the Court's reasoning is that:

- 1) there is a *natural relationship* between the concentration of the metabolite and its effective/toxic dosages;
- 2) expressing this relationship in *if . . . then* form is important because it operates as a prediction of what will happen; and
- 3) the relationship exists apart from human action.

The Court holds that to be eligible for a patent, something more than merely *applying* a natural law must be claimed. The Court found that Prometheus claimed nothing more than the law itself.

First, let us find the *natural relationship* between 6-TG and effective and

GROUP	N	MEDIAN 6-TG	6-TG > 225	MEDIAN 6-MMP
Responders	58	295	45/58 (78%)	3094
Non-responders	31	184*	8/31 (26%)	2048
Hepatic toxicity	7	258	5/7	9211**
Pancreatic toxicity	6	211	2/6	2342
Hematologic toxicity	6	414+	5/5	7042
p Values		* < 0.001 + < 0.03	‡ < 0.001	** < 0.001

toxic doses, which formed the basis for the alleged law of nature. As stated in the '623 patent, this relationship is based on two studies of patients who received daily administrations of 6-mercaptopurine (6-MP) or AZA. One study had 89 patients; the other had 93. Hepatic, pancreatic, and hematological tests for toxicity were obtained every three months. The results of the first study are shown above in Table 1 (from the '623 patent).

In the first study, 58 patients showed specific clinical improvement. Of these, 78% (45) had 6-TG levels > 225 pmol per 8×10^8 RBC. In the second study (not shown here), 78% of patients above a median 6-TG of 230 pmol per 8×10^8 RBC responded to treatment. From these findings comes the claim limitation that a 6-TG level *less than about 230* "indicates a need" to increase the dosage.

Now consider the toxicity level. Table 1 shows that just *six* people out of 89 (6.74%) experienced hematologic toxicity; for them, the median 6-TG level was 414 pmol per 8×10^8 RBC. There is no direct statistical evidence that the toxic concentration is *greater than about 400*; that number was most certainly selected by the patent attorney to give some leeway in the patent claim. These six patients are very impressive, because they (no doubt unknowingly) form the smallest sample of data upon which a "law of nature" has ever rested.

The inventors of the '623 patent, Drs. Siedman and Theoret, never suggested that they discovered any law of nature—instead, it was the Supreme Court that gave this imprimatur to the claim.

One would think that, if the inventors believed they had discovered something

as fundamental as a law of nature, they would have said so.

Applying some of the above criteria shows what Drs. Siedman and Theoret "discovered"—if they discovered anything at all—was an *accidental generalization*. First, as Table 1 shows, neither the effective nor the toxic dosages approach anywhere near *universality*. Although the effective dose need not result in a 6-TG level of about 230 pmol per 8×10^8 RBC in, say, 99% of patients, being effective for less than 80% seems a rather weak condition, especially when 26% of the *non-responders* had a 6-TG level greater than 225 pmol per 8×10^8 RBC. Indeed, it is easy to see that the claimed level could have been shifted one way or the other by 5 or 10 pmol per 8×10^8 RBC with little impact. Real laws of nature are not so malleable. Similarly, it can be argued that the claimed minimum dosage level could have been set lower, perhaps to 220 pmol per 8×10^8 RBC. That would have provided superficial support for an assertion that the level was "universal." Finally, that the confidence level for this finding was $p < 0.001$ simply means there is less than 1 chance in 1,000 that this is a random outcome. Thus, there may be a strong correlation, but that does not tell us there is a *necessary* one.

The toxic dosage is even more suspect, as just *six* people experienced toxicity in the first study, and the toxic level of *about 400* pmol per 8×10^8 RBC was not the average but the median level. With a sample that small, the median can be an unreliable measure of central tendency. Thus, for another group in another study, the results not merely could have,

but very likely would have, been different to a noticeable degree. Indeed, this is acknowledged in the *Prometheus* decision itself: Mayo's own research led them to pick 450 pmol per 8×10^8 RBC as the toxic level. Are there then *two* laws of nature of 6-TG toxicity, Prometheus' Law and Mayo's?

Nor does the *natural relationship* have any sort of *necessity*. In line with the laws of biology, the particular ability of humans to metabolize 6-MP or AZA into 6-TG at all is a historical accident of evolution. Given that 26% of the patients in the first study metabolized these drugs too poorly to have any therapeutic effect, it is not beyond reason to think we could have evolved to be entirely unable to metabolize 6-MP or AZA. But we do not even need this strong an outcome; we need consider only that humans certainly could have evolved so that the effective or toxic dosages were different from that which was claimed, say both higher by 25%. This implies another possible *counterfactual* analysis, in which there is a world like ours in all respects except that this alleged law of nature would not apply.

The claimed natural law does not *explain* anything either. There is no causal explanation why the dosages are effective or toxic; there is only a statement of what they are. Once the causal mechanism is discovered, the particular levels may fall away as unnecessary.

Predictive power also marks a law of nature. Here, Prometheus' claim does provide a prediction. From the data in Table 1 and Bayes' Theorem, we can determine the probability that a patient will demonstrate a clinical response to 6-TG, given a concentration above 225 pmol per 8×10^8 RBC, is approximately 85%. That means about 15% of the time patients treated in accordance with the patent claim will not show any clinical response at 225 pmol 8×10^8 RBC. In that case, what is a doctor to do? As Table 1 shows, there were seven patients who did not respond and who developed hepatic toxicity; of these, five (71%) had 6-TG levels greater than 225 pmol per 8×10^8 RBC. Thus, if the doctor increases their dosage, there is

significant probability that the patients will have a *toxic reaction* to 6-TG at a level *well below* the claimed "about 400." Thus, on its face, claim 1 does not present a certain path for a successful treatment.

The next criterion above is *objectivity*, that the claimed law does not depend on human knowledge, beliefs, needs or other pragmatic concerns—in short that, like $E = mc^2$ or $F = ma$, it is true regardless of any facts about the human condition. Here the Supreme Court's assertion of lawhood fails miserably: the claimed law is based on a human need to modify a dosage of drugs for a specific disease—drugs that were invented by humans in the first place. No other generally accepted law of nature in physics, chemistry, or any other science has any such intimate connection to an unmistakably subjective human need. Even the Supreme Court in *Funk Bros.* did not fasten upon such a human-centric law of nature.

Finally, we come to the "scientific" requirement, what scientists would consider a law of nature. As we've seen above, Mayr tells us that biologists have little use for calling statements laws of nature—they get on with their work quite nicely without such a label.

We have sketched out a number of reasons that Prometheus' claim is not a law of nature any more than (and indeed quite possibly less than) it is a law of nature that robin eggs are greenish-blue. Natural relationships surround us, but being *natural* does not make them *laws* of nature. Einstein famously said that "God does not play dice with the world," but it can be equally said that God did not jot down every possible correlation in human biology and make it a law.

The Supreme Court's recent decision in *Association for Molecular Pathology, et al. v. Myriad Genetics, Inc., et al.* 569 U.S. ___ (2013) demonstrates that the Court continues to engage in a superficial analysis of patent claims without regard to the unintended consequences of its logic. The Court ruled that isolated *naturally occurring* DNA was not patent-eligible, while isolated complementary

DNA (cDNA) was patent-eligible. The Court held that isolated DNA was still a *product of nature*, in part because the informational content of the isolated DNA was the same as DNA in the body. On the other hand, the Court held that cDNA was "man made," because by removing non-coding regions the "lab technician unquestionably creates something new."

The problem here is that the two explanations are at odds with each other. If isolated DNA is not patent-eligible because the informational content is the same as naturally occurring DNA, then cDNA also should not be patent-eligible because its information content is the same as naturally occurring messenger RNA. Contrariwise, if cDNA is patent-eligible because it is created in the laboratory by human-imposed processes, then so should the human-imposed processes used to create isolated DNA afford it patent eligibility. Further, the Court overlooked the fact that in many cases the steps taken to create cDNA are common and routine, the very type of activity that the Court condemned in *Prometheus*.

Finally, the Court stated that there may be *applications* of isolated DNA or cDNA that may be patent-eligible. But they did not consider that *Prometheus* foreclosed an important type of application: genetic testing based on correlations between given DNA sequences and particular diseases; under *Prometheus* such correlations are simply laws of nature. Thus we can expect future litigation to assert that cDNA is unpatentable as well.

The Court's analysis in *Prometheus* is both unwise and unfortunate. Unfortunate, because the analysis of what is a law of nature sweeps far too broadly and thus potentially can invalidate patents in a variety of scientific and technological disciplines simply because they make use of specific scientific facts or "natural relations." Unwise, because the Court's superficial treatment sets a standard that other courts, as well as the U.S. Patent and Trademark Office, will mimic in implementing the Court's ruling for future cases and patent applications. ♦