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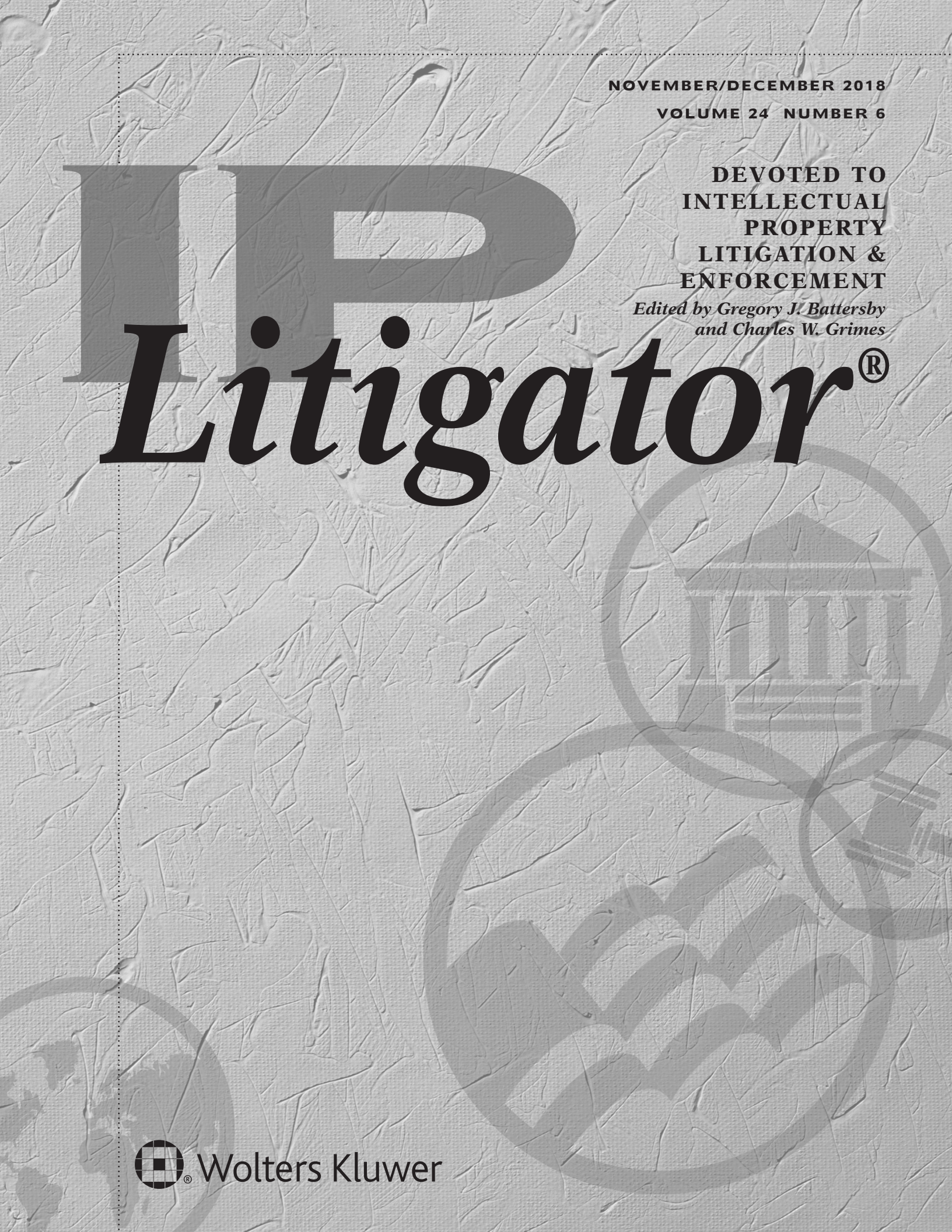

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Federal Circuit Reiterates That Nucleotide Sequences Are Not Patent Eligible under 35 U.S.C. § 101

On October 9, 2018, in *Roche Molecular Systems, Inc.* v. *Cepheid*, No. 17-1690 (Fed. Cir. 2018), the Federal Circuit upheld a district court decision that claims reciting nucleotide primers in U.S. Patent No. 5,643,723 (the '723 patent) were invalid under 35 U.S.C. § 101.

The '723 patent (assigned to Roche) relates to methods for detecting the pathogenic bacterium *M. tuberculosis*, a major cause of tuberculosis. Prior to the '723 patent, standard treatment for *M. tuberculosis* infection included antibiotics, specifically rifampin. Certain strains of *M. tuberculosis*, however, were resistant to rifampin, requiring an alternative therapy. It was difficult to rapidly detect rifampin-resistant strains of *M. tuberculosis*, and a faster diagnostic test was desired.

The methods of the '723 patent allow for the rapid detection of *M. tuberculosis*, including rifampin-resistant strains. Rifampin acts on the *rpoB* gene, which encodes the β subunit of bacterial RNA polymerase. The inventors of the '723 patent discovered that the *rpoB* gene in *M. tuberculosis* contained eleven "position-specific 'signature nucleotides'" that are present in *M. tuberculosis* but not in other bacteria.

Based on these eleven *M. tuberculosis*-specific signature nucleotides, the inventors of the '723 patent developed a diagnostic test (i) to identify whether a biological sample contains *M. tuberculosis*, and (ii) to predict whether the *M. tuberculosis*, if present, is resistant to rifampin. The diagnostic test involved subjecting DNA from the biological sample to amplification by polymerase chain reaction (PCR), using nucleotide primers that could hybridize to at least one of the eleven position-specific signature locations in the *M. tuberculosis rpoB* gene.

Such primers are recited in claim 17 of the '723 patent, as follows:

> Claim 17: A primer having 14-50 nucleotides that hybridizes under hybridizing conditions to an *M. tuberculosis rpoB* gene at a site comprising at least one position-specific *M. tuberculosis* signature nucleotide selected, with reference to FIG. 3 (SEQ ID NO: 1), from the group consisting of:
>
> a G at nucleotide position 2312,
> a T at nucleotide position 2313,
> an A at nucleotide position 2373,
> a G at nucleotide position 2374,
> an A at nucleotide position 2378,
> a G at nucleotide position 2408,
> a T at nucleotide position 2409,
> an A at nucleotide position 2426,
> a G at nucleotide position 2441,
> an A at nucleotide position 2456, and
> a T at nucleotide position 2465.

Roche brought a patent infringement case against Cepheid, alleging that Cepheid's commercial assay for detecting *M. tuberculosis* infringed the '723 patent. Cepheid filed a motion for summary judgment, arguing that the asserted claims were invalid under 35 U.S.C. § 101 as directed to patent-ineligible subject matter. The district court granted Cepheid's motion.

In particular, the district court found that the primer claims of the '723 patent, "which have genetic sequences identical to those found in nature, are indistinguishable from those held to be directed to nonpatentable subject matter," and thus were invalid.

The Federal Circuit panel reviewed the question of whether the claims were invalid under 35 U.S.C. § 101 *de novo*.

The panel relied heavily on precedent from *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755 (Fed. Cir. 2014) (*BRCA1*) and *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013) (*Myriad*). In particular, the panel held that "*BRCA1* forecloses Roche's arguments" that the claimed primers differed from naturally occurring bacterial DNA by virtue of the 3-prime hydroxyl group on the primers. *Slip op*. at 10. The panel noted the holding from *BRCA1* that the primers in that case were "not distinguishable from the isolated DNA found patent-ineligible in *Myriad*" and thus were not patent-eligible. *Id.* (citing *BRCA1* at 760). The panel further noted that in *BRCA1*, the court found that "[p]rimers necessarily contain the identical sequence of the [nucleotide]

sequence directly opposite to the [DNA] strand to which they are designed to bind. They are structurally identical to the ends of DNA strands found in nature." *Id.* at 10-11 (citing *BRCA1* at 760).

Based on this, the panel affirmed the district court decision that the primer claims of the '723 patent were invalid under 35 U.S.C. § 101.

The panel acknowledged that "Roche's discovery of these signature nucleotides on the [*M. tuberculosis*] *rpoB* gene and the designing of corresponding primers are valuable contributions to science and medicine, allowing for faster detection of [*M. tuberculosis*] in a biological sample and testing for rifampin resistance." *Slip op.* at 13-14. The panel, however, stated that "[t]he primers are not patent-eligible because they can be found in nature, not because they are not valuable scientific discoveries." *Slip op.* at 14.

Judge O'Malley filed a concurring opinion. In it, she agreed that *BRCA1* "compels the conclusion that the primer…claims of [the '723 patent] are not eligible for patent protection." *Slip op.* at 1. She expressed concern, however, about the *BRCA1* holding.

In particular, Judge O'Malley acknowledged the finding of *BRCA1* that primers have identical sequences to the natural DNA strands directly opposite the strands to which they bind. She noted, however, that "a finding that the two have identical *sequences* does not entirely resolve the question of whether they are *structurally* identical because structure is not defined solely by nucleotide sequence." *Slip op.* at 7.

Judge O'Malley discussed the evidence provided by Roche concerning structural differences between the claimed primers and naturally occurring DNA. For example, she discussed Roche's explanation of a structural difference relating to the 3-prime hydroxyl group on the primers, which is absent in the naturally occurring bacterial DNA. *See slip op.* at 7-8. She concluded that "although it is undisputed that all the claimed primers here have nucleotide *sequences* that are identical to segments of the naturally occurring *rpoB* gene found in [*M. tuberculosis*], a genuine factual dispute exists as to whether they have a *materially different structure* than any DNA molecules typically found in nature." *Slip op.* at 9. Because of this, Judge O'Malley appears to believe that, at the very least, Cepheid's motion for summary judgment should not have been granted.

The decision in *Roche* reiterates the previous holdings from *BRCA1* and *Myriad* that naturally occurring nucleotide sequences are not patent eligible under 35 U.S.C. § 101. As seen in *Roche*, emphasizing the structural differences between synthetic nucleotide primers and naturally occurring DNA may not be sufficient to establish patent eligibility, especially when the nucleotide sequences are identical.

Instead, to overcome the eligibility hurdle of § 101, it appears that other structural differences are required for nucleotide sequences. Footnote 5 of the panel opinion acknowledges that this is an open question ("We do not address the subject matter eligibility of primers that have been altered - e.g., investigator-induced mutation(s) such that their nucleotide sequences are not found in nature, or primers which are chemically modified or labeled by investigators such that they cannot be isolated directly from naturally occurring DNA." *Slip op.* at 13). It seems unlikely, however, that such altered nucleotide sequences reasonably could be considered to be 'products of nature' under § 101—especially with a chemical modification, such as an added fluorophore for a fluorescence *in situ* hybridization probe.

In view of this, to overcome the eligibility hurdle of § 101, practitioners should emphasize structural differences between claimed nucleotide sequences and naturally occurring sequences whenever possible—especially when those differences are not merely the presence of a 3-prime hydroxyl group in the synthetic nucleotide sequence. Absent such differences, it remains an uphill battle to establish patent eligibility for nucleotide sequences.

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