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Patents 101: A Path to DNA Primer Eligibility

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In *Roche Molecular Systems, Inc. v. Cepheid*,[1] the Federal Circuit affirmed the grant of summary judgment holding claims of U.S. Patent No. 5,643,723 ("the '723 patent") invalid under 35 U.S.C. § 101 as patent-ineligible subject matter.

When determining patent-eligibility of the '723 patent claims, the Federal Circuit considered whether a natural phenomenon underlay the claims at issue. In its analysis, the court turned to the patent specification, giving weight to the inventors' description of their invention over the prior art. With this approach, the Federal Circuit appears to use anticipation or obviousness analysis in order to answer patent-eligibility under § 101. The analysis begs the question if an inventor's disclosure could be tailored to drive a more favorable determination on § 101 subject matter enquiries.

The '723 patent, "Detection of a Genetic Locus Encoding Resistance to Rifampin in Mycobacterial Cultures and in Clinical Specimens," provides a method of detecting the bacteria *Mycobacterium tuberculosis* ("MTB") from biological samples by amplifying the bacterial DNA.[2] The inventors found eleven position-specific signature nucleotides in the *rpoB* gene of MTB that are not present in related bacterial species.[3] Mutations in the *rpoB* gene were previously found to confer resistance to rifampin, a first-line antibiotic to treat MTB infections.[4] The invention of the '723 patent utilizes these signature nucleotides, allowing detection of MTB as well as prediction of rifampin resistance, offering advantages over the common method of MTB detection.[5] The '723 patent claims 1) primers (short pieces of DNA) that bind to the MTB *rpoB* gene,[6] and 2) methods of detecting MTB by amplifying a portion of the *rpoB* gene using a primer that binds to a position-specific signature nucleotide.[7]

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[1] Roche Molecular Sys., Inc. v. Cepheid, No. 2017-1690, 2018 WL 4868033 (Fed. Cir. Oct. 9, 2018).

[2] *Roche*, 2018 WL 4868033, at *1–2; '723 patent at Abstract.

[3] *Roche*, 2018 WL 4868033, at *1–2; '723 patent at 2:60–3:2.

[4] *Roche*, 2018 WL 4868033, at *1; '723 patent at 1:31–60. The opinion erroneously states that the *rpoB* gene is the target of the antibiotic rifampin. Rifampin targets the product of the *rpoB* gene (the beta subunit of the bacterial RNA polymerase enzyme), not the gene itself. '723 patent at 1:35–42.

[5] *Roche*, 2018 WL 4868033, at *2; '723 patent at 2:60–3:2, 3:16–29.

[6] *Roche*, 2018 WL 4868033, at *2–3; '723 patent, claims 1–13 at 25:57–27:51.

[7] *Roche*, 2018 WL 4868033, at *3; '723 patent, claims 17–20 at 28:14–46.

On January 17, 2017, the District Court for the North District of California ruled in summary judgment that the '723 patent was invalid under 35 U.S.C. § 101.[8] Roche brought the patent infringement suit on July 16, 2014, fifteen days after the '723 patent expired,[9] alleging that Cepheid's Xpert® MTB/RIF Assay infringed primer and method claims.[10] The district court held the primer claims invalid because the primer sequences were "identical to those found in nature" and thus "indistinguishable from those held to be directed to nonpatentable subject matter."[11] The district court held the method claims invalid because they were "directed to 'nonpatentable laws of nature or natural phenomena'" and that the combination of nonpatentable DNA primers and a routine DNA amplification protocol did not transform the methods into patent-eligible subject matter.[12] Roche appealed the grant of summary judgment of invalidity to the Court of Appeals for the Federal Circuit.

Writing for the majority, Judge Reyna affirmed the district court's decision. The analysis followed the two-step framework established by the Supreme Court in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*[13] and *Alice Corp. v. CLS Bank International*,[14] examining if the patent claimed ineligible subject matter: laws of nature, natural phenomena, or abstract ideas.[15] The Federal Circuit concluded that its decision in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litiga-*

[8] Roche Molecular Sys., Inc. v. Cepheid, No. 14-CV-03228-EDL, 2017 WL 6311568, at *1 (N.D. Cal. Jan. 17, 2017). The district court also concluded that assignor estoppel did not bar Cepheid's arguments related to unpatentability because the legal landscape of DNA patent eligibility changed significantly after an inventor assigned his rights to the Mayo Clinic and because Roche knew of this change before acquiring the Mayo Clinic's rights in the '723 patent. *Id.* at 6–9. Issues related to assignor estoppel were not presented on appeal.

[9] *Roche*, 2017 WL 6311568 at *1. Roche sought compensatory damages for past infringement only. Roche Molecular Sys., Inc. v. Cepheid, No. C-14-3228-EDL, 2015 WL 124523, at *2 (N.D. Cal. Jan. 7, 2015).

[10] *Roche*, 2018 WL 4868033, at *3; *Roche*, 2017 WL 6311568, at *1. It also worth noting the significant impact of the Xpert system on tuberculosis diagnostics. *See, e.g.*, Lekha Puri et al., Xpert MTB/RIF for tuberculosis testing: access and price in highly privatised health markets, 4 Lancet Glob Health e94, e94 (2016) ("Xpert MTB/RIF . . . is the biggest recent advance in tuberculosis diagnosis, and since 2010 more than 15 million cartridges have been procured through concessional pricing.").

[11] *Roche*, 2018 WL 4868033, at *3 (quoting *Roche*, 2017 WL 6311568, at *14).

[12] *Id.*

[13] 566 U.S. 66 (2012).

[14] 134 S. Ct. 2347 (2014).

[15] *Roche*, 2018 WL 4868033, at *1, *4.

tion ("*BRCA1*")[16] foreclosed Roche's arguments that the claimed primers were structurally different from naturally occurring DNA.[17] Roche unsuccessfully argued that having a 3' end with a hydroxyl group made the claimed linear primers structurally different from natural MTB DNA, which is in a circular chromosome. Following its reasoning in *BRCA1*, the court instead focused on the primers' nucleic acid sequences and not structural elements of the DNA backbone.[18] The court also determined that a primer did not gain subject matter eligibility if it "can selectively hybridize to a certain position of naturally occurring DNA" because hybridization of complementary sequences is a natural phenomenon.[19]

As for the method claims, the court concluded that they were "*directed to* a relationship between the eleven naturally occurring position-specific signature nucleotides and the presence of MTB in a sample" and thus directed to a natural phenomenon.[20] To support its conclusion, the court used the inventors' explanation of their discovery as presented in the specification. This approach was used previously by the Federal Circuit in *Ariosa Diagnostics, Inc. v. Sequenom, Inc*.[21] At step two of the *Alice/Mayo* framework, the court determined that the site-specific nucleotides were not transformed into patent-eligible subject matter because the claimed DNA amplification did not include improvements to the technique and detection was "a mental determination."[22]

Judge O'Malley concurred, stating that the decision in *BRCA1* "compel[led] the conclusion" that the asserted claims of the '723 patent were ineligible for patent protection.[23] However, she wrote separately to suggest that the court revisit the holding of *BRCA1* "at least with respect

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[16] 774 F.3d 755 (Fed. Cir. 2014).

[17] *Roche*, 2018 WL 4868033, at *4–5.

[18] *Id.* at *5 ("As this court determined in BRCA1, the subject matter eligibility inquiry of primer claims hinges on comparing a claimed primer to its corresponding DNA segment on the chromosome—not the whole chromosome.").

[19] *Id.* at *6.

[20] *Id.* at *7.

[21] 788 F.3d 1371 (Fed. Cir. 2015).

[22] *Roche*, 2018 WL 4868033, at *7.

[23] *Id.* at *9 (O'Malley, J., concurring). Judge O'Malley's concurrence here is reminiscent of Judge Linn's concurrence in *Ariosa*. There, Judge Linn criticized the breadth of the Supreme Court's *Mayo* holding, which bound him to find a patent invalid under § 101, "excluding a meritorious invention from the patent protection it deserves and should have been entitled to retain." Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1380 (Fed. Cir. 2015) (Linn, J., concurring).

to the primer claims."[24] She gave two reasons: 1) the question presented in *BRCA1* was narrower than its holding, and 2) the present case provided additional facts not available when *BRCA1* was considered.[25] In *BRCA1*, the question was whether the district court abused its discretion in finding that the accused infringer raised a substantial question regarding invalidity, rather than inquiring into invalidity itself, which places a different burden on a different party. In addition, a decision at the preliminary injunction stage is made without all of the evidence that may be shown at trial.[26] O'Malley further questioned the holding in *BRCA1* because it was "not clear'—given the lack of record evidence in *BRCA1*—why the court reached the conclusion that primers were "structurally identical" to the ends of DNA found in nature.[27]

Another in a line of decisions related to DNA patentability, *Roche* leaves us wondering if changes in the specification would have saved the '723 patent from being found invalid under § 101. The opinion in *Roche* opened by stating that the '723 patent was "directed to methods for detecting the pathogenic bacterium [MTB]."[28] At first glance, this could have pointed toward patent-eligibility for the patent's method claims.[29] However, under its analysis of whether the claims were "directed to" patent-ineligible subject matter under *Alice/Mayo*, the court concluded that the method claims were "*directed to* a relationship between the eleven naturally occurring position-specific signature nucleotides and the presence of MTB in a sample."[30] This conclusion may not be too surprising, given the similar fate medical diagnostic claims have met under § 101 analyses.[31] But the approach of digging into what the method claims are *really* "directed to" could be leading to activity

[24] *Roche*, 2018 WL 4868033, at *10.

[25] *Id.* at *10.

[26] *Id.* at *10.

[27] *Id.* at *12.

[28] *Id.* at *1.

[29] Assoc. for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 595 (2013) (noting that method claims were not implicated in the holding that a naturally occurring DNA segment was not patent-eligible); Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1376 (Fed. Cir. 2015) ("Methods are generally eligible subject matter.").

[30] *Roche*, 2018 WL 4868033, at *7.

[31] *See, e.g.*, *Ariosa*, 788 F.3d 1371; BRCA1, 774 F.3d 755 (Fed. Cir. 2014); Genetic Techs. Ltd. v. Merial L.L.C., 818 F.3d 1369 (Fed. Cir. 2016), *cert. denied*, 137 S. Ct. 242 (2016); *see also* Colleen Chien, *The Impact of 101 on Patent Prosecution*, PATENTLYO (Oct. 21, 2018), https://patentlyo.com/patent/2018/10/impact-patent-prosecution.html (indicating that recent calls for clarification in § 101 subject matter

the Supreme Court cautioned against—finding patent-ineligibility by hunting for a claim's connection to an ineligible concept.[32] The Federal Circuit similarly warned that "describing the claims at such a high level of abstraction and untethered from the *language of the claims* all but ensures that the exceptions to § 101 swallow the rule."[33]

Following the approach described in *Enfish, LLC v. Microsoft Corp.*[34] and *Ariosa*, the court here turned to disclosures in the '723 patent specification to apply the "stage-one filter" in determining what the method claims were "directed to."[35] In *Roche*, the court looked to language in the specification describing the "heretofore undiscovered presence" of the signature nucleotides, focusing on what the inventors said were advances over the prior art.[36] The analysis suggests that if the specification had instead stated the novelty of the invention was the use of DNA amplification to detect rifampin-resistant MTB, the Federal Circuit may have concluded differently what the claims were "directed to." Perhaps if the specification described prior art that taught away from DNA amplification in GC-rich bacteria like MTB, for example, the claims would have stood. The answer to this may also turn on whether § 101 analysis includes underlying issues of fact, a question currently disputed in the Federal Circuit.[37]

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eligibility is partially due to concern that the Alice/Mayo two-step test "has stripped protection from meritorious inventions, particularly in medical diagnostics").

[32] Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347, 2354 (2014) ("[W]e tread carefully in construing this exclusionary principle lest it swallow all of patent law. At some level, 'all inventions ... embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'") (citing Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 71 (2012)).

[33] Enfish, L.L.C. v. Microsoft Corp., 822 F.3d 1327, 1337 (Fed. Cir. 2016) (emphasis added).

[34] 822 F.3d 1327 (Fed. Cir. 2016).

[35] *Roche*, 2018 WL 4868033, at *4 ("[T]he 'directed to' inquiry applies a stage-one filter to claims, considered in light of the specification, based on whether 'their character as a whole is directed to excluded subject matter.'") (quoting *Enfish*, 822 F.3d at 1335); *Ariosa*, 788 F.3d at 1376 ("The written description supports the conclusion that the claims of the '540 patent are directed to a naturally occurring thing or natural phenomenon.").

[36] *Roche*, 2018 WL 4868033, at *7 (citing the '723 patent at 2:60–65) ("The language makes clear what the inventors' discovery entails: the revelation of a previously undiscovered natural phenomenon." *Roche*, 2018 WL 4868033, at *7).

[37] Berkheimer v. HP Inc., 890 F.3d 1369, 1370 (Fed. Cir. 2018) (Moore, J., concurring in the denial of rehearing en banc) ("While the ultimate question of patent eligibility is one of law, it is not surprising that it may contain underlying issues of fact."); *Id.* at 1380 (Reyna, J., dissenting in the denial of rehearing en banc) (arguing

The court distinguished the method claims in *Roche* from those in *Vanda Pharmaceuticals*.[38] In *Vanda Pharmaceuticals*, the court held that methods of treatment were eligible because they claimed a new way of using existing drug that was safer for patients.[39] In contrast, the method claims of the '723 patent do not recite a method of treatment, but a method of detection. The court concluded that the '723 patent "did not claim method of treatment based on an underlying natural phenomenon, but natural phenomenon itself."[40] The court described practicing the method claimed in the '723 patent as an investigator "simply rediscovering" the natural phenomenon of position-specific nucleotides in MTB.[41] The distinction made between the method claims in *Vanda* and in *Roche* suggest that the claims of the '723 patent could have been eligible if they recited a method of treatment comprising first testing a sample using DNA amplification and then treating a patient with antibiotics. Further, the court indicated that it was not expressing an opinion as to eligibility of method claims that "exploit" DNA in for "drug-like new applications."[42] How the court would distinguish methods of *diagnosis* that rely on complementarity of nucleic acids from methods of *treatment* that rely on complementarity of nucleic acids (e.g., using CRISPR-Cas9 genome editing) remains to be seen.

In her concurrence, Judge O'Malley laid out a way for the court to revisit the patent-eligibility of DNA primers, based on structural differences from natural chromosomal DNA. It's not clear if a revisit of primer claims would also affect the patent-eligibility of method claims involving primers. Given the Federal Circuit's approach to hunt for underlying mechanisms behind methods, the patent-eligibility of primers themselves may not save method claims under § 101 inquiry. ■

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that after recent Federal Circuit decisions, he sees "no principled reason that would restrain extending a factual inquiry to step one of Alice").

[38] 887 F.3d 1117 (Fed. Cir. 2018).

[39] *Roche*, 2018 WL 4868033, at *8 n.7.

[40] *Id.* at *8 n.7.

[41] *Id.*

[42] *Id.* at *8 n.6.