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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MICHAEL RUVOLO and EMILY MARINE LEPROUST[1]

Appeal 2021-001708
Application 14/772,063
Technology Center 1600

Before ERIC B.GRIMES, TINA E. HULSE, and
RACHEL H. TOWNSEND, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to an oligonucleotide-containing composition and a related kit, which have been rejected as ineligible for patenting and anticipated. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] Appellant identifies the real party in interest as Agilent Technologies, Inc. Appeal Br. 2. "Appellant" refers to "applicant" as defined in 37 C.F.R. § 1.42.

STATEMENT OF THE CASE

"Chromosomal rearrangements, deletions, and other aberrations have long been associated with genetic diseases." Spec. 1:5–6. "There is an ongoing need to develop efficient ways to make probes for use in genomics, particular in the detection and analysis of chromosomal abnormalities." *Id*. at 1:11–12.

The Specification discloses "a method of making a pool of probes by primer extension," using two populations of oligonucleotides having the formulas V_1-B-3' and V_2'-B'-3' (where V_1, V_2', B, and B' are defined in claim 12, below) that hybridize to each other and can be "extended to produce a population of double stranded products comprising a top strand sequence having the following formula V_1-B-V_2, where V_2 is complementary to V_2'." *Id*. at 1:15–28.

The Specification discloses that the V_1-B-V_2 oligonucleotides can be used in an assay for chromosomal abnormalities:

> In certain cases, the test genome may have a chromosomal rearrangement relative to the reference genome that effectively moves a V_1-complemenary [sic] sequence to a site that is both proximal to and on the same strand as V_2-complemenary [sic] sequence. In these cases, if a first oligonucleotide contains V_1 and V_2 sequences that are complementary to the sequences moved into proximity by the rearrangement, [a] complex . . . that comprises a single genomic fragment that is hybridized to both ends of a first oligonucleotide is produced.

Id. at 19:14–20. Following steps of ligation and amplification, a product indicating chromosomal rearrangement can be detected. *See id.* at 19:28 to 20:17.

Claims 12–20 are on appeal.[2] Claim 12, reproduced below, is illustrative:

> 12. A composition of matter comprising:
>
> a first population of oligonucleotides comprising a top strand sequence having the following formula:
>
> V_1-B-3'; and
>
> a second population of oligonucleotides comprising a bottom strand sequence having the following formula:
>
> V_2'-B'-3';
>
> wherein:
>
> the nucleotide sequences of B and B' are complementary and are at least 15 nucleotides in length;
>
> the nucleotide sequence of B is the same for each oligonucleotide of said first population;
>
> the nucleotide sequence of B' is the same for each oligonucleotide of said second population;
>
> the nucleotide sequence of V_1 is variable between the oligonucleotides of the first population;
>
> the nucleotide sequence of V_2' is variable between the oligonucleotides of the second population;
>
> the first and second population of oligonucleotides are capable of hybridizing to each other to produce a population of duplexes, and
>
> V_1 and V_2' hybridize to different sites in a reference genome.

Appeal Br. 15 (Claims App.).

Claim 16 is the other independent claim and is directed to a kit comprising the oligonucleotides defined by claim 12.

[2] The Examiner has indicated that claims 1–11 are allowable. Office Action mailed Apr. 8, 2020, page 14.

The claims stand rejected as follows:

Claims 12–20 under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter (Non-Final Action[3] 7) and

Claims 12–20 under 35 U.S.C. § 102(a)(2) as anticipated by Koroulis[4] (Non-Final Action 11).

OPINION

Eligibility

The Examiner has rejected claims 12–20 on the basis that "the claimed invention is directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more." Non-Final Action 7. The Examiner finds that "the claims are to oligonucleotides, the nucleotide sequence of which can occur in nature," and therefore "are directed to a natural phenomenon." *Id*.

The Examiner also finds that the claims do not recite additional elements that integrate the judicial exception into a practical application, because "the claims simply define the types of sequences that can be present." *Id*. at 8. Finally, the Examiner finds that the claims "do not include additional elements that are sufficient to amount to significantly more than the judicial exception because the oligonucleotides can be that which occurs in nature." *Id*.

Appellant argues that, in *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013),

> claims to an isolated DNA having the same sequence as naturally occurring genes were found to be ineligible products

[3] Office Action mailed Apr. 8, 2020.
[4] Koroulis et al., US 2002/0187476 A1, published Dec. 12, 2002.

> of nature. However, claims to cDNA prepared from RNA transcribed from those same genes was eligible for patenting, since the sequence only contained exons of the gene. Because the recited sequence had "markedly different characteristics" than naturally occurring sequences, it was not "directed to" a product of nature.

Appeal Br. 7.

Appellant argues that the Examiner "did not identify any **naturally occurring counterpart for comparison** to the claimed composition, and . . . did not consider whether it had markedly different characteristics." *Id*. "The Office Action does not make any attempt to identify a naturally occurring counterpart which has first and second populations of oligonucleotides," as recited in claim 12. *Id*. at 8. Appellant argues that, contrary to the Examiner's conclusion, "[t]he claimed composition is not directed to a product of nature or any other natural phenomenon, but is man-made and not found in nature." *Id*. at 9.

Principles of Law

Section 101

Patent-eligible subject matter is defined in 35 U.S.C. § 101. An invention is patent-eligible if it claims a "new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. § 101. The Supreme Court, however, has carved out exceptions to what would otherwise appear to be within the literal scope of § 101, e.g., "[l]aws of nature [and] natural phenomena" such as products of nature that are considered "building blocks of human ingenuity." *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014) (citing *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013) and *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*,

566 U.S. 66 (2012)). "[T]he 'manifestations of laws of nature' are 'part of the storehouse of knowledge,' 'free to all men and reserved exclusively to none.'" Manual of Patent Examiner Procedure ("MPEP") § 2106.04(b)(I) (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). "When a law of nature or natural phenomenon is claimed as a physical product, the courts have often referred to the exception as a 'product of nature.'" MPEP § 2106.04(b)(II).

The Supreme Court has established a two-step framework for "distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice*, 573 U.S. at 217. "First, we determine whether the claims at issue are directed to . . . [a] patent-ineligible concept[]." *Id*. "If so, . . . we consider the elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id*. (quoting *Mayo*, 566 U.S. at 78–79).

The United States Patent and Trademark Office ("PTO") issued the 2019 Revised Patent Subject Matter Eligibility Guidance ("Revised Guidance"), indicating how the PTO would analyze patent eligibility under the Supreme Court's two-step framework. 84 Fed. Reg. 50 (January 7, 2019). In response to received public comments, the Office issued further guidance on October 17, 2019, clarifying the 2019 Revised Guidance. USPTO, *October 2019 Update: Subject Matter Eligibility* (the "October 2019 Update") (available at https://www.uspto.gov/sites/default/files/documents/peg_oct_2019_update.pdf).

Under the Revised Guidance, in determining what concept the claim is "directed to," we first look to whether the claim recites any judicial exceptions, including laws of nature, natural phenomena, and/or abstract ideas. 84 Fed. Reg. at 53–54 ("Step 2A, Prong One"). If it does, then we look to whether the claim recites additional elements that integrate the recited judicial exception into a practical application. *Id*. at 54–55 (citing MPEP § 2106.05(a)–(c), (e)–(h)) ("Step 2A, Prong Two").

Only if a claim (1) recites a judicial exception and (2) does not integrate that exception into a practical application, i.e., it is found to be "directed to" a judicial exception, do we then look to whether the claim contains an "'inventive concept' sufficient to 'transform'" the claimed judicial exception into a patent-eligible application of the judicial exception. 84 Fed. Reg. at 56; *see also Alice*, 573 U.S. at 221 (quoting *Mayo*, 566 U.S. at 82).

Claims alleged to be patent-ineligible because they recite products of nature are properly analyzed under the framework of the Revised Guidance. *See* 84 Fed. Reg. at 54 n.20 ("This notice does not change the type of claim limitations that are considered to recite a law of nature or natural phenomenon. For more information about laws of nature and natural phenomena, including products of nature, see MPEP 2106.04(b) and (c).").

Revised Guidance Step 2(A), Prong 1

Following the Revised Guidance, we first consider whether the claims recite a judicial exception; i.e., whether they set forth or describe a product

of nature in accordance with the guidance in MPEP § 2106.04(b) and (c). Revised Guidance, 84 Fed. Reg. at 54; October 2019 Update, at 1.

Each of independent claims 12 and 16 recites a first population of oligonucleotides V_1-B-3' having a common B sequence and a variable V_1 sequence, and a second population of oligonucleotides V_2'-B'-3' having a common B' sequence and a variable V_2' sequence, where B and B' are complementary and at least 15 nucleotides long, and where V_1 and V_2' hybridize to different sites in a reference genome.

As Appellant pointed out (Appeal Br. 7), the Examiner has not identified any naturally occurring populations of oligonucleotides that meet the structural requirements recited in Appellant's claims. The fact that *some* oligonucleotides are naturally occurring is not sufficient to show that the combination of *specific* oligonucleotides of Appellant's claims are naturally occurring.

In *Myriad*, for example, the Supreme Court distinguished between naturally occurring and non-naturally occurring DNAs. Myriad "assert[ed] a patent on '[a]n isolated DNA coding for a BRCA1 polypeptide,' which has 'the amino acid sequence set forth in SEQ ID NO:2.'" 569 U.S. at 584. The Court held that the DNA recited in this claim was not eligible for patenting because "Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention." *Id*. at 591.

The *Myriad* Court also held, however, that "cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments" because a cDNA is "an exons-only molecule that is not naturally occurring." *Id*. at 594. The Court reasoned that "the lab technician

unquestionably creates something new when cDNA is made. cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived." *Id*. at 595.

The same reasoning applies here: the V_1 and V_2' segments recited in Appellant's claims might have the same sequence of nucleotides as found in a naturally occurring genome (since they hybridize to a reference genome) but the Examiner has not shown that a population of such segments—having variable sequences—are naturally found next to a common B or B' sequence in their natural state. Thus, on this record, the Examiner has not shown that either the first or second population of oligonucleotides V_1-B-3' or V_2'-B'-3', having a common B or B' sequence and a variable V_1 or V_2' sequence, is a product of nature, much less the combination of those oligonucleotides, as recited in Appellant's claim 12.

"If the claim does not recite a judicial exception, it is not directed to a judicial exception . . . and is eligible. This concludes the eligibility analysis." Revised Guidance, 84 Fed. Reg. at 54. We reverse the rejection of claims 12–20 under 35 U.S.C. § 101.

Anticipation

The Examiner has rejected claims 12–20 as anticipated by Koroulis. The Examiner finds that Koroulis discloses arrays containing oligonucleotides, and also states that its "array can contain all possible oligonucleotides of a given length n." Non-Final Action 11–12. The Examiner reasons that, "[g]iven that the composition/array of Koroulis et al., encompasses all possible oligonucleotides of a length n, such must encompass the very oligonucleotides present in the claimed composition and

kit, including that represented by the formulae of V_1-B-3' and V_2'-B'-3'." *Id*. at 12.

Appellant argues that the Examiner "relies on Koroulis' single, generic sentence that 'an array can contain all possible oligonucleotides of a given length n.' However, . . . [t]he Office Action makes no attempt to identify where Koroulis discloses the particular claim elements recited by the rejected claims." Appeal Br. 12. Appellant argues that, in fact, "Koroulis does not disclose a composition of matter or a kit having a first and second population of oligonucleotides" having the structural characteristics recited in Appellant's claims 12 and 16. *Id*. at 12–13.

We agree with Appellant that the Examiner has not persuasively shown that Koroulis discloses the composition or kit of Appellant's claims. "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

> [U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102.

Net MoneyIN, Inc. v. VeriSign, Inc., 545 F.3d 1359, 1371 (Fed. Cir. 2008).

In this case, the Examiner relies solely on the following disclosure:

> An array can contain a chosen collection of oligonucleotides, e.g., probes specific for all known clinically important pathogens or specific for all known clinically important pathogens or specific for all known sequence markers of genetic diseases. Such an array can satisfy the needs of a diagnostic laboratory. Alternatively, an array can contain all possible oligonucleotides of a given length n.

Koroulis ¶ 6. The Examiner reasons that "[g]iven that the composition/array of Koroulis et al., encompasses all possible oligonucleotides of a length n, such must encompass the very oligonucleotides present in the claimed composition and kit." Non-Final Action 12.

We do not agree with the Examiner's reasoning. The bare statement that an array can include all possible nucleotides having an undefined length is not a disclosure of the two populations of oligonucleotides—having segments meeting specified structural requirements, arranged in a specified way—that are recited in Appellant's claims. Thus, the cited disclosure "cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Net MoneyIN*, 454 F.3d at 1371.

We conclude that the Examiner has not met the initial burden of showing that Koroulis discloses "all of the limitations arranged or combined in the same way as recited in the claim[s]," *id*., and has not made out a prima facie case of anticipation. The rejection of claims 12–20 under 35 U.S.C. § 102(a)(2) is reversed.

DECISION SUMMARY

In summary:

Claim(s) Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
12–20	101	Eligibility		12–20
12–20	102(a)(2)	Koroulis		12–20
Overall Outcome				12–20

REVERSED