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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ROBERT TERBRUEGGEN[1]

Appeal 2016-005406
Application 12/798,108
Technology Center 1600

Before DEMETRA J. MILLS, DONALD E. ADAMS, and
RYAN H. FLAX, Administrative Patent Judges.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims as directed to non-patent eligible subject matter. Claims 1–31 were cancelled. 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 Dx Terity Diagnostics Incorporated. (App. Br. 2).

STATEMENT OF CASE

According to the Specification, page 4, when using DNA microarrays

> [t]he requirement of many upstream processing steps prior to contacting the DNA array with the sample can significantly increase the time and cost of detecting a nucleic acid target(s) by these methods. It can also have significant implications on the quality of the data obtained. For instance, some amplification procedures are very sensitive to target degradation and perform poorly if the input nucleic acid material is not well preserved . . . . Technologies that can eliminate or reduce the number and/or complexity of the upstream processing steps could significantly reduce the cost and improve the quality of results obtained from a DNA array test. One method for reducing upstream processing steps involves using ligation reactions to increase signal strength and improve specificity.
>
> . . . There remains a need for methods and compositions for efficient and specific nucleic acid detection. Accordingly, the present invention provides methods and compositions for nonenzymatic chemical ligation reactions which provides very rapid target detection and greatly simplified processes of detecting and measuring nucleic acid targets.

The following claims are representative.

32. A method for detecting in a sample, comprising a plurality of sample nucleic acids of different nucleic acid sequences, the presence of at least one specific target nucleic acid sequence comprising a first and a second target domain, the domains located adjacent to one another, comprising the steps of:

(a) contacting the sample nucleic acids with a plurality of different probes sets, each probe set comprising:

(i) a first ligation probe comprising:

(1) a first probe domain complementary to said first target domain;

(2) a first non-complementary region being non-complementary to the said target nucleic acid sequence; and

(3) a 5'-ligation moiety comprising *a DABSYL moiety*; and

(ii) second ligation probe comprising:

(1) a second probe domain complementary to said second target domain;

(2) a second non-complementary region, being non-complementary to the said target nucleic acid sequence;

(3) a 3' ligation moiety comprising a phosphorothioate moiety;

(b) ligating said first and second ligation probes in the absence of a ligase enzyme to form a ligation product; wherein at least one of said ligation probes comprises a variable spacer nucleic acid sequence such that each ligation product is a different length;

(c) amplifying said ligation product to form ligation amplicons under conditions whereby a fluorescent label is incorporated into said amplicons; and

(d) detecting the presence of said ligation amplicons by detecting the presence of said fluorescent label. (Emphasis added.)

36. A method for detecting in a sample, comprising a plurality of sample nucleic acids of different nucleic acid sequences, the presence of at least one specific target nucleic acid sequence comprising a first and a second target domain, the domains located adjacent to one another, comprising the steps of:

(a) contacting the sample nucleic acids with a plurality of different probes sets, each probe set comprising:

(i) a first ligation probe comprising:

(1) a first probe domain complementary to said first target domain;

(2) a first non-complementary region being non-complementary to the said target nucleic acid sequence; and

(3) a 5'-ligation moiety comprising *a halogen leaving group*; and

(ii) second ligation probe comprising:

(1) a second probe domain complementary to said second target domain;

(2) a second non-complementary region, being non-complementary to the said target nucleic acid sequence;

(3) a 3' ligation moiety comprising a phosphorothioate moiety;

(b) ligating said first and second ligation probes in the absence of a ligase enzyme to form a ligation product; wherein at least one of said ligation probes comprises a variable spacer nucleic acid sequence such that each ligation product is a different length;

(c) amplifying said ligation product to form ligation amplicons under conditions whereby a fluorescent label is incorporated into said amplicons; and

(d) detecting the presence of said ligation amplicons by detecting the presence of said fluorescent label. (Emphasis added.)

Cited References

Barany et al.	US 2006/0024731 A1	Feb. 2, 2006
Kool et al.	US 2006/0199192 A1	Sept. 7, 2006
Thomas	US 2007/0218477 A1	Sept. 20, 2007

Grounds of Rejection

Claims 32–43 are rejected under 35 U.S.C. § 101, because the claimed invention is not directed to patent eligible subject matter.

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Final Action 6–10, Examiner's Answer 3–11.

PRINCIPLES OF LAW

In making our determination, we apply the preponderance of the evidence standard. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

§ 101- Patent Eligible Subject Matter

The Examiner finds that, based upon an analysis with respect to the claim as a whole, claims 32–43 are directed to a law of nature/natural principle, which the Examiner finds to be a judicial exception to patentable subject matter eligibility. Final Act. 6. The Examiner then analyses whether the claim as a whole recites something significantly more than the judicial exception(s). Final Act. 7–8.

The Examiner determines, after reviewing whether the claims as a whole recites something significantly different than the judicial exceptions, that factors weight against patent eligibility and the claims do not recite subject matter significantly different than the judicially excepted subject matter. Final Act. 8. For example, the Examiner finds that the claims recite, in addition to the judicial exception, merely steps that are well-understood, purely conventional or routine in the relevant field. In support of this position, the Examiner directs attention to US 2006/0199192 Al (Kool et al.). Kool et al., paragraph [0137], which teaches synthesis of oligonucleotides that comprise DABSYL on the 5' terminus (applicant's first probe domain). And in paragraph [0138], Kool et al., teach DABSYL-mediated autoligation wherein the oligo with the DABSYL 5'-ligation moiety autoligates with a second ligation probe that comprises a 3' ligation

moiety comprising a phosphorothioate moiety wherein the first and second ligation probes are annealed to a complementary nucleic acid. *Id.*

The Examiner analyzes the additional method steps and determines that the additional steps constitute insignificant extra-solution activity, e.g., are merely appended to the judicial exception and recite elements/steps in addition to the judicial exception(s) that amount to nothing more than a mere field of use. *Id.* at 9–10. Thus, the Examiner concludes that claims 32–43 are directed to patent ineligible subject matter. *Id* at 10.

Appellant contends that the

> Examiner uses the incorrect standard in analyzing whether the claims are drawn to patent eligible subject matter. In particular, the Examiner fails to analyze the claims a whole. Moreover, Appellant submits that the claims, when analyzed under the proper standard, are not wholly directed to a judicial exception and, therefore, qualify as patent eligible subject matter under 35 U.S.C. §101.

App. Br. 10.

Appellant argues that, "even assuming, *arguendo,* that the claims include a 'natural phenomenon,' the claims in no way preempt the use of such natural phenomenon and thus represent patent eligible subject matter." *Id.* at 12. Appellant further argues that, "[t]he claims do include nucleic acids, but they are not, in fact, naturally occurring, as they have been chemically modified with synthetic moieties; the claims actually relate to the detection of target nucleic acid sequences using specific non-naturally occurring ligation probes." *Id.* at 17. Appellant argues that the claims include, "two ligation probes [that] are transformed into a single ligation product with a number of different, synthetic components, which are further transformed using amplification to form an additional synthetic component

(amplicons with fluorescent labels)." *Id.* at 20. Appellant argues that the claims "include additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the alleged laws of nature." *Id.* at 23.

ANALYSIS

We do not find that, on balance, the Examiner has provided sufficient evidence to support a prima facie case of lack of patentable eligible subject matter. It has been established that

> "while a claim drawn to a fundamental principle"—i.e., a law of nature, natural phenomenon, or abstract idea—"is unpatentable, 'an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection.'" *Bilski*, 545 F.3d at 953 (quoting *Diehr*, 450 U.S. at 187). The key issue for patentability, then, at least on the present facts, is whether a claim is drawn to a fundamental principle or an application of a fundamental principle.

Prometheus Laboratories Inc. v. Mayo Collaborative Services, 581 F.3d 1336, 1242 (Fed. Cir. 2009). The Supreme Court has also made clear that the patent eligibility of a claim as a whole should not be based on whether selected limitations constitute patent-eligible subject matter. *See Bilski v. Kappos,* 130 S.Ct. 3218, 3230 (2010), (citing *Diamond v. Diehr*, 450 U.S. 175, 185 (1981); *Parker v. Flook*, 437 U.S. 584, 594 (1978)).

In analyzing patent eligibility questions under 35 U.S.C. § 101, the Supreme Court instructs us to "first determine whether the claims at issue are directed to a patent-ineligible concept." *Alice Corp. Pty Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014). If this threshold is met, we move to a second step of the inquiry and "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 Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1297 (2012) (italicized emphasis added)); *see also* "*Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products*," (Guidance) issued by the U.S. Patent and Trademark Office, March 2014.

Step One

Taking up the first step of the patent-eligibility analysis, we do not find that claim 1 is has been established to be directed to a law of nature or natural phenomenon. "At some level, 'all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas,'" and whether one takes a macroscopic or microscopic view of a claim may be determinative on the issue. *Alice*, 134 S. Ct. at 2354 (quoting *Mayo*, 132 S. Ct. at 1293); and *see Amdocs (Israel) Ltd. v. Openet Telecom, Inc.*, 841 F.3d 1288, 1299 (Fed. Cir. 2016).

Looking to the Specification to enlighten us as to the claimed invention, as did the Federal Circuit in *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327 (Fed. Cir. 2016), we find that the Specification explains the invention to be directed to "methods for detecting one or more nucleic acid targets present in a sample . . . ." Spec. ¶ 1. The Examiner finds that the claims focus on the natural phenomenon of autoligation of adjacent termini of nucleic acids that are annealed to a complementary sequence. Final Act 6. The claims also are arguably focused on the natural phenomenon of

nucleic acids occurring as DNA and/or RNA, that they can be "amplified" and also be separated and detected via capillary electrophoresis. *Id.*

While the method claims may, tangentially, broadly read on detection of nucleic acids, we find that the method steps within the scope of the claims, when read as a whole, ordered combination, are directed to patent eligible subject matter. In particular, the objective of the claim 32 method of detecting a target nucleic acid, using a non-naturally occurring ligation probe having a 5'-ligation moiety comprising a DABSYL[2] moiety, is to reduce "upstream processing steps . . . using ligation reactions to increase signal strength and improve specificity." Spec. 4. We are persuaded by Appellants that the method of "the claims include[s], 'two ligation probes [that] are transformed into a single ligation product with a number of different, synthetic components, which are further transformed using amplification to form an additional synthetic component (amplicons with fluorescent labels).'" App. Br. 20.

The Examiner contends that the claimed process steps include the natural phenomenon of "autoligation" without the use of ligase enzymes. Ans. 4. Appellant responds, arguing that

> Naturally occurring nucleic acids do not "autoligate;" it is only in the presence of the synthetic ligation moieties that are spatially

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[2] 4-(4-Dimethylaminophenylazo)benzenesulfonyl chloride (DABYSL). DABYSL provides a synthetic or non-natural 5' leaving group to the upstream probe. Spec. 16. Thus, the first ligation probe has a 5'synthetic or non-natural leaving group attached through a flexible linker and a downstream oligonucleotide which has a 3' thiophosphoryl group. This configuration leads to a significant increase in the rate of reaction and results in multiple copies of ligated product being produced for every target. Spec. 15.

> adjacent does such ligation occur. Essentially, by providing particular specific chemical moieties, a chemical reaction will occur when the moieties are spatially adjacent.

App. Br. 17.

Thus, the issue is whether the claimed method for detecting nucleic acids in a sample involves something other than conventional physical implementation of a natural phenomenon. *See Genetic Technologies v. Merial LLC*, 818 F.3d 1369, 1380 (Fed. Cir. 2016). We answer this question in the affirmative. As argued by Appellants, we find that the ordered combination of the limitations in the method for detection of claim 32 provides the requisite inventive concept. *BASCOM Glob. Internet Servs., Inc. AT&T Mobility LLC*, 827 F3d. 1341, 1349-52; *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1298 (2012)(("[A] new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made," *citing Diehr,* 450 U. S. at 188). The claimed method provides a "technology based solution" that improves performance of the nucleic acid detection method by increasing signal strength and improve reaction specificity. In other words, claim 32 is drawn to an application of a method of detection of nucleic acids deserving of patent protection.

Even if we were to agree that claim 32 is directed to an ineligible natural phenomenon under *Alice's* step one, the claim is eligible under *Alice's* step two because it contains a sufficient "inventive concept." *Alice*, 134 S. Ct. at 2355. In other words, the claimed method provides "a technological solution" to a technological problem in the DNA detection

method technology, providing a detection method with improved signal strength and specificity. This provides the requisite something more than the performance of "'well-understood, routine, [and] conventional activities previously known to the industry.'" *See Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat'l Ass'n*, 776 F.3d 1343, 1347–48 (quoting *Alice*, 134 S.Ct. at 2359) (alteration original).

The claims here are not simply directed to the ability of DNA and RNA to be detected or the natural phenomenon of autoligation, instead the claims are directed to a new and useful method of detection, which provides improved performance of the detection method by increasing signal strength and improve reaction specificity, using synthetic intermediates. *Compare*, *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048 (2016) ("The end result of the '929 patent claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims are directed to a new and useful method of preserving hepatocyte cells.").

The Examiner finds that individual method steps of the claim 32 method are known in the art and that the claimed method employs known, conventional and routine assay steps. Ans. 5. However, we agree with Appellant that the Examiner has not reviewed the claimed method as an ordered combination or as a whole, consistent with *2014 Interim Guidance On Patent Subject Matter Eligibility*, 70 Federal Register 74618 (December 16, 2014), at 74622. App. Br. 13. In fact, while not determinative under the rejection at issue, it is also significant that the Examiner has presented no prior art rejection of the detection methods of claims 32, 36 or 40, as an

ordered combination, or for the remaining pending claims.[3] In particular, the Examiner presents no element by element claim analysis, or reasoned analysis for anticipation and/or obviousness with respect to patentability of the pending claims in view of Kool or other cited prior art.

Appellant contends that Claim 36 is directed to a similar method, although the "5' ligation moiety is a halogen leaving group rather than DABSYL. As is well known in the art, naturally occurring nucleic acids do not comprise halogen leaving groups. Similarly, Claim 40 uses leaving groups and nucleophilic groups as ligation moieties." App. Br. 16. Again, while the Examiner may have provided evidence that individual process steps were conventional or known in the art, the Examiner has not provided a reasoned analysis as to why the claims as a whole, or ordered combination do not recite patent eligible subject matter.

Step Two

For the sake of completeness, turning to the second step under *Alice*, we have determined that the claims recite the "something more" or significantly different than the judicial exception, as required by the Supreme Court to transform a law of nature or natural phenomenon into a

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[3] Under the principles of compact prosecution, regardless of whether a rejection under 35 U.S.C. § 101 is made based on lack of subject matter eligibility, a complete examination should be made for every claim under each of the other patentability requirements: 35 U.S.C. §§ 102, 103, 112, and 101 (utility, inventorship and double patenting) and non-statutory double patenting. Thus, Office personnel should state all non-cumulative reasons and bases for rejecting claims in the first Office action. MPEP § 2106 (III).

patent-eligible invention. *See Alice*, 134 S. Ct. at 2355 (citing *Mayo*, 132 S. Ct. at 1303).

The Examiner finds that the

> Use of these target sequences, probes, primers, fluorescent labels, and polymerases, as well as any of the requisite 5' and 3 ligation moieties, and "uncharacterized" means (e.g., "leaving group" of claim 40) for performing ligation without use of a ligase enzyme, amplification, and detection- all of which are discovered by others in the future, yet encompassed by, and when used to practice the claimed invention, would constitute both certain practices of well known, conventional and routine assaying steps and the lack of substantive and significant claimed embodiments that reflect a patent-eligible practical application of the judicial exception.
>
> In contrast to appellant's assertions, the reasons set forth above clearly do teach that the claimed method would preempt many aspects of the biotech industry.

Ans. 5. Thus, the Examiner concludes that the claims recite elements/steps in addition to the judicial exception(s) that are well-understood, purely conventional or routine in the relevant field. Final Act. 9 (factor j weighing against eligibility). In sum, the Examiner finds that the claims are impacted by guidance factors h–l[4] weighing against patent eligibility. *Id.* at 8.

> Appellant disagrees with the Examiner's assertion that the claims encompass "natural and spontaneous chemical ligation reactions of naturally present target nucleic acid domains." For example, the ligating step of independent claim 32 occurs between a 5' ligation moiety that includes a DABSYL moiety and a 3'-ligation moiety that includes a phosphorothioate moiety. The ligating step of independent claim 36 occurs between a 5'-ligation moiety that includes a halogen leaving group moiety and a 3' -ligation moiety that

[4] Guidance 4–5.

> includes a phosphorothioate moiety. Appellant submits that such DABSYL, halogen leaving groups and phosphorothioate moieties are not "naturally present" in target nucleic acid. Such moieties are attached to non-naturally occurring nucleic acid. As such, the autoligation that occurs between such non-naturally occurring molecules is not a natural phenomenon.

Reply Br. 11–12.

For the reasons discussed herein, we do not find that the Examiner has established that the claims, when read in view of the Specification, encompass merely naturally occurring autoligation reactions falling within the judicial exception as directed to a natural phenomenon and are, thus, not patent eligible. The Specification reasonably supports that the ligation steps of the claims require non-naturally occurring ligation moieties. Spec. 13-18. Furthermore, we find that the Examiner has not fully considerd 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 of a law of nature or natural phenomenon. *Compare*, *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1298 (2012).

In view of our findings above, the claim rejection for lack of patent eligible subject matter under 35 U.S.C. § 101 is reversed.

CONCLUSION OF LAW

The rejection of the claims for lack of patent eligible subject matter under 35 U.S.C. § 101 is reversed.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

REVERSED