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EXAMINER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BRAIN K. AGAN, ERIC H. HANSON, MICHAEL J. JENKINS,
BAOCHUAN LIN, CHRIS C. OLSEN, ROBB K. ROWLEY,
DAVID A. STENGER, DZUNG C. THACH, CLARK J. TIBBETTS,
ELIZABETH A. WALTER, and JINNY LIN LIU

Appeal 2015-001596
Application 12/713,554¹
Technology Center 1600

Before DONALD E. ADAMS, RICHARD M. LEBOVITZ, and
JOHN E. SCHNEIDER, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims directed to methods for identifying gene expression markers for distinguishing between healthy, febrile, or convalescence subjects exposed to a pathogen. The Examiner rejected the claims under 35 U.S.C. § 101, under 35 U.S.C. § 112, first paragraph, and under 35 U.S.C. § 103(a). We have jurisdiction under 35 U.S.C. § 134. The Examiner’s decision is affirmed.

¹ “The ’554 Application.” The real party in interest listed in the Appeal Brief is “the Government of the United States of America.” Appeal Br. 2.

STATEMENT OF THE CASE

Claims 1–9 stand rejected by the Examiner as follows:

1. Claim 2 under 35 U.S.C. § 101 as directed to non-statutory subject matter. Ans. 3.

2. Claim 2 under 35 U.S.C. § 112, first paragraph (pre-AIA), as failing to comply with the written description requirement. Ans. 6.

3. Claims 1–4 under 35 U.S.C. § 103(a) (pre-AIA) as obvious in view of Eremeeva (*Ann. N.Y. Acad. Sci.* 2003, vol. 990, pages 468-473) and Lockhart (WO 97/10365, published March 20, 1997). Ans. 12.

4. Claims 5 and 6 under 35 U.S.C. § 103(a) (pre-AIA) as obvious in view of Eremeeva, Lockhart, Scherf (US 2005/0170375 A1, published August 4, 2005; filed Sept. 24, 2004), and GLOBINclear™ Kit manual (“GLOBINclear”). Ans. 16.

5. Claim 7 under 35 U.S.C. § 103(a) (pre-AIA) as obvious in view of Eremeeva, Lockhart, Scherf, GLOBINclear, and Conner (U.S. Patent No. 6,506,565 B1, patented January 14, 2003). Ans. 20.

6. Claim 8 under 35 U.S.C. § 103(a) (pre-AIA) as obvious in view of Eremeeva, Lockhart, Scherf, GLOBINclear, and Christians (US 2005/0003369 A1, published January 6, 2005, filed October 10, 2003). Ans. 21.

7. Claim 9 under 35 U.S.C. § 103(a) (pre-AIA) as obvious in view of Eremeeva, Lockhart, and Ideker (*Journal of Computational Biology* 2000, vol. 7, no. 6, pages 805-817). Ans. 23.

Claim 1, the only independent claim on appeal, reads as follows:

1. A method for identifying gene expression markers for distinguishing between healthy, febrile, or convalescence in reference to one or more infectious pathogens comprising:

acquiring a gene expression profile for a subject that has been exposed to one or more infectious pathogens and having a fever of 100.4°F or above;

acquiring a gene expression profile for a subject that has recovered from exposure to the one or more infectious pathogens;

acquiring a gene expression profile for a healthy subject that has not been exposed to the one or more infectious pathogens;

comparing the gene expression profiles for the exposed subject, the recovered subject and the healthy subject by a pairwise comparison;

determining the identity of the nested to minimal set(s) of genes that classify the subject's phenotypes as healthy, febrile, or convalescent by class prediction algorithm based on the pairwise comparison; and

assigning the classification of healthy, febrile, or convalescence based on gene expression profile of the minimal set of genes;

wherein the gene expression profile are acquired by:

collecting biological sample from the subject;

isolating RNA from the sample;

removing DNA contaminants from the sample;

spiking into the sample a normalization control;

synthesizing cDNA from the RNA contained in the sample;

in vitro transcribing cRNA from the cDNA and labeling the cRNA;

hybridizing the cRNA to a gene chip followed by washing, staining, and scanning; and

acquiring the gene expression profile from the gene chip and analyzing the gene expression profile represented by the RNA in the sample.

1. § 101 REJECTION

Claim 2, depends from claim 1, and further requires “classifying the patient as healthy, febrile, or convalescence” based on the patient’s gene expression profile. *Citing Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012), the Examiner rejected the claim under 35 U.S.C. § 101 as directed to non-statutory subject matter. Office Action 3.

Since *Mayo*, a two-step for patent eligibility under Section 101 has emerged. As set forth in *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S.Ct. 2347, 2355 (2014):

First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts [e.g., a law of nature, natural phenomenon, or abstract idea]. If so, we then ask, what else is there in the claims before us? . . . We have described step two of this analysis as a search for an inventive concept—i.e., an element or combination of elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the ineligible concept itself.

Id. (alterations, citations, and quotation marks omitted).

With respect to the first step, in *Mayo*, the Supreme Court considered method claims that required analysis of a metabolite in the blood of a patient being treated with a thiopurine drug to determine the likelihood that the patient could suffer toxic side effects from particular doses of the drug. *Mayo*, 132 S.Ct. at 1296–9. The Court concluded that “the claims were necessarily directed to an underlying law of nature or natural phenomenon, even if implementation of the method involves substantial human labor and ingenuity.” *Genetic Technologies Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1375 (Fed. Cir. 2016). The Court stated:

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.

Mayo, 132 S.Ct. at 1297.

In this case, it is undisputed that a gene expression profile is a “natural phenomenon” because it is a snapshot of the naturally-occurring genes expressed by an organism at a given time. The inventors have not done anything to the profile other than detect it in a biological sample obtained from the subject. The subsequent “classifying” step is a correlation step between the gene expression profile and the disease status of the subject. We conclude that the classifying step is a manifestation of the naturally occurring gene expression observed in a subject who happens to be healthy, febrile, or convalescent with respect to an infectious pathogen. While the discovered gene expression profile might be new, the claim simply characterizes a “discovered fact about . . . biology” and therefore is a natural law. *Genetic Technologies*, 818 F.3d at 1376. As a consequence, we conclude claim 2 is directed to unpatentable subject matter in accordance with the first step of the *Mayo/Alice* test.

The second part of the test asks whether the claims contains an “inventive concept” sufficient to transform the claimed law of nature into patent-eligible subject matter. *Id.*

“The question ... is whether the claims do significantly more than simply describe [a] natural relation[].”, 132 S.Ct. at 1297. The inventive concept necessary at step two *Mayo* of the *Mayo/Alice* analysis cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself.

That is, under *the Mayo/Alice* framework, a claim directed to a newly discovered law of nature (or natural phenomenon or abstract idea) cannot rely on the novelty of that discovery for the inventive concept necessary for patent eligibility; instead, the application must provide something inventive, beyond mere “well-understood, routine, conventional activity.” *Mayo*, 132 S.Ct. at 1294; see also *Myriad*, 133 S.Ct. at 2117; *Ariosa*, 788 F.3d at 1379. “[S]imply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable.” *Mayo*, 132 S.Ct. at 1300. Claims directed to laws of nature are ineligible for patent protection when, “(apart from the natural laws themselves) [they] involve well-understood, routine, conventional activity previously engaged in by researchers in the field.” *Mayo*, 132 S.Ct. at 1294.

Id.

In this case, we have not been directed to evidence that the steps of claim 2 in determining the gene expression profile adds anything more to the routine technology conventionally used to characterize gene expression in an organism. Appellants contend that the claim is “more limiting than simply ‘applying the law.’” Appeal Br. 3. However, Appellants only pointed to conventional gene detection steps. *Id.* As held in *Mayo*, the claim as a whole sets forth “laws of nature” because the relationship between the gene expression levels and the disease state “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.” *Mayo* at 1297. Accordingly, we conclude that the additional elements of claim 2 are insufficient to provide the inventive concept necessary to render the claim patent-eligible.

2. WRITTEN DESCRIPTION REJECTION

The Examiner found that the inventors were not in possession of a representative number of gene expression profiles to justify a genus claim Office Action 7–8 (hereinafter, “Office Act.”, mailed Nov. 1, 2013). The Examiner found that the inventors described gene expression analysis of subjects infected with adenovirus, but not “for a reasonable number of species of pathogens so as to justify the genus embraced by the instant claims.” *Id.* at 9. The Examiner stated that “the sets of genes which Applicants were in possession of were based on a single type of pathogen, Ad4.” *Id.* at 10. The Examiner concluded that the ’554 Application lacks a written description of the genus of pathogens encompassed by the claims, and rejected the claims under 35 U.S.C § 112. *Id.* at 11–12.

35 U.S.C. § 112 requires a patentee to provide a written description of the claimed subject matter that allows a person of skill in the art to recognize that the patentee invented what is claimed. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

In this case, Appellants have described a generic invention using gene expression technology to characterize the gene expression profile of subjects exposed to a pathogen and classify the subjects as healthy, febrile, or convalescent based on the profiles. It is not disputed that disease pathogens are known in the art. The inventor have not asserted to have invented a pathogen or gene expression profile, but instead assert to have invented a method of detecting changes in genes expression characteristic of a pathogen or infection. ’554 Application 10: 12–16.

“[W]hat is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the

particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.” *Capon v. Eshhar*, 418 F.3d 1349, 1359 (Fed. Cir. 2005). “[I]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976).” *Capon*, 418 F.3d at 1359. The inventors are not asserting to have invented a specific expression profile or pathogen. It is evident from the ’554 Application, and reflected in the claim, that the invention is a method to determine and classify disease status upon exposure to a pathogen. Thus, to meet the written description requirement, it is not necessary for the inventors to have described additional gene expression profiles associated with different pathogens. The illustrative gene expression profiles based on adenovirus infection demonstrate how the claimed method is performed and establish that the inventors had possession of a generic invention.

The rejection is reversed.

3–7. OBVIOUSNESS REJECTIONS

The Examiner found that Eremeeva describes a method of identifying gene expression markers for distinguishing between healthy, febrile, or convalescent pine voles in reference to one or more infectious pathogens. Office Act. 14. The Examiner identified where each step in the claimed method could be found in Eremeeva. *Id.* The Examiner stated that Eremeeva does not teach that the identified gene expression markers are used to classify subjects as required by the claims. *Id.* However, the

Examiner found that Lockhart described such a step. *Id.* at 15–16. The Examiner determined it would have been obvious to apply Lockhart’s techniques to Eremeeva for the advantages described by Lockhart. *Id.* at 16.

Appellants contend that neither Eremeeva nor Lockhart describe the recited step of “determining the identity of the nested to minimal set(s) of genes that classify the subjects’ phenotypes as healthy, febrile, or convalescent.” Appeal Br. 5. Appellants contend that the Examiner did not provide a rationale to have arrived at this limitation. *Id.* at 6.

We do not agree. The Examiner found that, while the skilled worker would begin by assaying for a plurality of genes expressed during the various disease and non-disease states, the skilled worker would have been motivated to identify a minimal set of genes in order to arrive at a gene signature which is indicative of a particular phenotype. Office Act. 19. Thus, the Examiner provided a clear reason as to why a minimal set of genes would be selected by one of ordinary skill in the art at the time of the invention.

The Examiner further explained:

A typical gene expression study involves sampling a patient/subject population with a particular phenotype (e.g., disease) and identifying a set of genes which are similarly expressed in the population. Once such genes are identified, a test subject's sample is analyzed for the same set of genes to see if there is a similar expression pattern between the two for diagnosis.

Therefore, based on the teachings of Eremeeva et al. who demonstrated the difference in gene expression levels from subjects undergoing various stages of infections (e.g., healthy, infection, and convalescent), one of ordinary skill in the art would have been motivated to arrive at a set of genes which are

able to classify a subject's health status and then classify a test subject's health status by comparison.

Ans. 32.

The Examiner's logic is that there would be motivation to identify the recited set of minimal genes to classify a subject's health status because such set would enable the skilled worker to distinguish between the various stages of infection. *Id.* Appellants did not persuasively identify an error in the Examiner's reasoning. Rather, Appellants argue that Eremeeva does not identify a minimal gene set, but instead looks at the same enzyme genes. Reply Br. 2. However, this statement ignores the fact that rejection is based on the obviousness of applying Lockhart's method of conducting gene expression assays for distinguishing between healthy patients and patients with disease as the motivation to pick minimal sets of differentially expressed genes. Office Act. 18–20.

In addition to this, Appellants have not provided a definition of "minimal set of genes" as recited in claim 1 which would distinguish the set of enzyme genes utilized in the Eremeeva publication to characterize the infectious state of the pine voles.

For the foregoing reasons, the obviousness rejection of claim 1 is affirmed. Appellants did not argue the dependent claims separately, or Rejections 3–7. Consequently, the rejections of claims 2–9 are affirmed for the reasons set forth by the Examiner. *See* 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

1. The § 101 of claim 2 is affirmed.
2. The § 112, first paragraph rejection of claim 2 is reversed.
3. Obviousness rejections 3–7 of claims 1–9 are affirmed.

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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)(1)(iv).

AFFIRMED