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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JOHN A. McINTYRE[1]

Appeal 2017-000477
Application 12/554,497[2]
Technology Center 1600

Before DEMETRA J. MILLS, ERIC B. GRIMES, and JEFFREY N. FREDMAN, *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 for obviousness, obviousness-type double patenting, and as directed to patent ineligible subject matter. We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Real Party in interest is REDOX-REACTIVE REAGENTS, LLC.

[2] The present application claims priority to Provisional Application 61/094167, filed September 4, 2008.

We reverse the obviousness and obviousness-type double patenting rejections. We affirm the rejection of the claims as directed to patent ineligible subject matter.

NATURE OF THE INVENTION

Appellant's Specification is directed to methods of screening, diagnosing, monitoring, or staging Alzheimer's disease (AD) by determining if the levels of redox-reactive antiphospholipid autoantibodies (aPL) that have been exposed to an oxidative agent in the laboratory are elevated. (See Spec. abstract and 10–11.)

The following claim is selected as representative claim.

1. A method for diagnosing, monitoring and/or staging Alzheimer's disease which comprises:

providing a blood sample from a human subject;

oxidizing the blood sample from a human subject; and

conducting a blood test for determining a level of at least one redox-reactive autoantibody in the blood sample;

comparing the level of the at least one redox-reactive autoantibody to a predetermined value; and

diagnosing, monitoring and/or staging Alzheimer's disease based on the comparison between the level of the at least one redox-reactive autoantibody and the predetermined value.

Cited References

McIntyre '681	US 2005/0260681 A1	Nov. 24, 2005
McIntyre '541	US 2006/0141541 A1	June 29, 2006
McIntyre '751	US 7,892,751 B2	Feb. 22, 2011[3]

Irizarry, "*Biomarkers of Alzheimer Disease in Plasma*," NeuroRx: J. Am. Soc. Exper. Neurotherapeutics, Vol. 1, p 226-234 (2004).

Grounds of Rejection

1. Claims 1–7 and 20–22 stand rejected under 35 U.S.C. § 101 because the claimed invention is directed to a judicial exception to patent eligible subject matter (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more.
2. Claims 1–7 and 20–22 stand rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over McIntyre '541and McIntyre '681.
3. Claims 1–7 and 20–22 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1–9 of McIntyre '541 (which is the same disclosure as U.S. Patent No. 7,892,751), in view of Mcintyre '681.

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Final Action at pages 2–15.

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[3] Filed February 23, 2006.

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).

With respect to the patent ineligible subject matter rejection, in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015), the claimed invention was a method for detecting cell-free fetal DNA (cffDNA) in maternal blood and diagnosing a pre-natal condition based on such DNA. *Ariosa*, 788 F.3d at 1373–74. The inventors developed tests for detecting paternally inherited cffDNA in maternal blood to diagnose certain genetic defects thereby avoiding the risks of other more invasive techniques. *Id.* at 1373. The Federal Circuit determined that the claimed methods were patent ineligible because they begin and end with a natural phenomenon, cffDNA, and each of the steps was well-understood, routine, and conventional. *Id.* at 1376–78.

Lack of Patentable Subject Matter

The Examiner contends that

> Claims 1-7 and 20-22 are directed to the natural correlation between natural redox-reactive autoantibodies and a disease state. The claims do not include additional elements that are sufficient to amount to significantly more than the judicial exception because there are no features in addition to the exception that are more than purely conventional or routine in the art.

Ans. 2. The Examiner further argues that the steps and "factors for determining patent subject eligibility in light of recent court decisions including *Association for Molecular Pathology v. Myriad Genetics, Inc., Mayo Collaborative Services v. Prometheus Laboratories, Inc.,* and *Alice Corporation Pty. Ltd. v. CLS Bank International, et al.*)"[4] are

> determining if the claim is directed to one of the four statutory categories (process, machine, manufacture, or composition of matter). In this case, the claims are directed to a method, which is considered a process. In step 2A, one is determining if the claims recite or involve judicial exception(s), such as laws of nature, natural phenomena, or natural products. In this case, the claims involve the natural correlation between natural redox-reactive autoantibodies and a disease state. In Step 2B, it must be determined if the claim as a whole amounts to something significantly more than the judicial exception(s).
>
> The claims encompass[] diagnosing, monitoring and/or staging Alzheimer's disease (AD) using a blood sample to detect levels of redox reactive autoantibodies. This is the judicial exception itself, i.e., There is/are no steps additional to the judicial exception, as the comparing and diagnosing steps can be mental processes and are simply drawn to the observance of nature. There is no indication of particular levels to detect and the steps do no more than describe the correlation with the instructions to "apply it". There are no elements that include a particular machine or transformation as no specific machine is required and the information obtained is not transformed into anything useful for a different purpose, i.e., the claim amounts to data gathering. There are no features in addition to the exception that are more than purely conventional or routine in the art. On the other hand, there is a high level of generality (any level of antibody

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[4] See, *Interim Guidance on Patent Subject Matter Eligibility*, Fed. Reg., Vol. 79, No. 241, p. 74618, et. seq. (2014); http://www.gpo.gov/fdsys/pkg/FR-2014-12-16/pdf/2014-29414.pdf.

> detected), which also supports the conclusion that in order to use the judicial exception (the correlation) others are required to somehow detect these antibodies in Alzheimer's disease and draw a conclusion about their correlation. The element of oxidizing the sample is well-understood in the art and is simply mirroring that which occurs naturally (see for example [McIntyre '751 and McIntyre '681] . . . , which note these redox-reactive autoantibodies are known to be found in Alzheimer's disease).

Ans. 3–4.

Appellant contends that

> the Examiner has deviated from the analysis set out in *Mayo* and applied a test explicitly forbidden by the Supreme Court. The Examiner has not demonstrated that oxidizing a blood sample from a human subject prior to conducting a blood test for determining a level of at least one unmasked redox-reactive autoantibody in the blood sample is so well-known as to have become standard, routine and conventional. The Examiner, instead, has simply demonstrated such was known, i.e. not novel. In so doing, the Examiner is relying only on the inventor's recent patent publications. Based upon only this lack of novelty, the Examiner has concluded claims 1-7 and 20-22 lack a sufficient inventive concept as to be patent eligible under § 101. Basing the rejection under § 101 only upon a lack of novelty, the Examiner has transformed the second part of the *Mayo* test into a § 102 analysis that disregards the novelty of the law of nature in determining patentability. As such a test has been explicitly forbidden by the Supreme Court in *Mayo,* the rejection of claims 1-7 and 20-22 is based upon a misapplication of the test.

App. Br. 11–12.

Appellant further argues that

> Oxidizing the blood sample, as detailed in the second full paragraph on page 10 of the Application as filed, enables the detection of redox-reactive autoantibodies which are previously "masked" and undetectable. Thus, oxidizing the blood sample

> "unmasks" redox-reactive autoantibodies present in the blood sample so that their levels can be determined. As noted in first full paragraph on page 13 and the last paragraph on page 18 of the Application as filed, the progression of Alzheimer's disease is marked by a continual decline in the amount of redox-reactive autoantibodies detectable after unmasking via oxidation, such that individuals with Alzheimer's show a deficit compared with healthy individuals. Thus, it is the amount of the masked antibodies present in blood that is being assessed to diagnose, monitor and/or stage Alzheimer's disease. Accordingly, the law of nature being exploited in the methods detailed in claims 1-7 and 20-22 is the relationship between the amount of masked antibodies within blood and Alzheimer's disease.

Reply Br. 7–8.

ANALYSIS

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. Supreme Court precedents, however, provide three specific exceptions to the broad categories of patentable subject matter under § 101: laws of nature, natural phenomena, and abstract ideas. *Bilski v. Kappos*, 561 U.S. 593, 601 (2010). "The 'abstract ideas' category embodies the longstanding rule that '[a]n idea of itself is not patentable.'" *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (citing *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)).

In *Alice*, the Supreme Court referred to the two-step analysis set forth in *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012), as providing "a 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*, 134 S. Ct. at 2355 (citing *Mayo*, 132 S. Ct. at 1289). Under *Mayo*, "[w]e must first determine whether the claims at issue are directed to a patent-ineligible concept." *Id.* Next, "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.* (citing *Mayo*, 132 S. Ct. at 1297–98).

Under *Mayo*, to be patentable, a claim must do more than simply state the law of nature or abstract idea and add the words "'apply it.'" *Mayo*, 132 S. Ct. at 1294; *Benson*, 409 U.S. at 67. For example, "the mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into a patent-eligible invention." *Alice*, 134 S. Ct. at 2358.

A challenged patent claim, properly construed, must incorporate enough meaningful limitations to ensure that it claims more than just an abstract idea and not just a mere "drafting effort designed to monopolize the [abstract idea]." *Alice*, 134 S. Ct. at 2357 (quoting *Mayo*, 132 S. Ct. at 1297). "Simply appending conventional steps, specified at a high level of generality," is not "*enough*" for patent eligibility. *Id.* (quoting *Mayo*, 132 S. Ct. at 1300).

Under step 1 of *Mayo*, in the present case we find that the Examiner has shown that the pending claims are directed to a law of nature, natural phenomenon, or patent ineligible concept. In particular, the present inventor discovered that the redox-reactive autoantibody (R-RAA) in the blood of AD patients show a departure from the normal antiphospholipid autoantibodies (aPL) levels. Spec. 11. "Comparisons between the AD and normal populations for antiphosphatidylethanolamine (aPE) activities

revealed highly significant differences." Spec. 12. This realization amounts to identification of a natural phenomenon, the correlation between the presence of R-RAA in the blood and AD. Thus, pending claim 1 is directed to a law of nature or natural phenomenon.

We further agree with the Examiner that there are no claimed features in addition to the claimed natural phenomenon (a correlation between the presence of R-RAA in the blood and AD) than those that are purely conventional or routine in the art.

Claim 1 recites a high level of generality, such as the detection of any level of redox-reactive autoantibody. This level of claim generality supports the conclusion that in order to use the natural phenomenon (the correlation), others are required to detect these redox-reactive autoantibodies and draw a conclusion about their correlation to the presence of AD.

"Whether something is well-understood, routine, and conventional to a skilled artisan at the time of the patent is a factual determination." *Berkheimer v. HP Inc.*, 881 F.3d 1360, 1369 (Fed. Cir. 2018). The additional claim element of oxidizing the sample is well-understood in the art and is simply mirroring that which occurs naturally. This is evidenced by McIntyre '541, which discloses that blood and other bodily fluids have previously been reported to "contain a significant number of antibodies, that, when treated with an oxidizing agent, become capable of binding self antigens." McIntyre '541 ¶ 7. McIntyre '541 cites references published in 2004, 2005, and 2006 disclosing such antibodies, and states that over a dozen types of such antibodies have been detected in the blood of normal individuals, including antiphospholipid antibodies. *Id.* at ¶¶ 8–10, 13.

> Appellant contends that
>
> the Examiner has deviated from the analysis set out in *Mayo* and applied a test explicitly forbidden by the Supreme Court. The Examiner has not demonstrated that oxidizing a blood sample from a human subject prior to conducting a blood test for determining a level of at least one unmasked redox-reactive autoantibody in the blood sample is so well-known as to have become standard, routine and conventional.

App. Br. 11.

We are not persuaded by Appellant's argument. The Examiner cited McIntyre '541 (published June 29, 2006, over two years before the effective filing date of the present application), for evidence that "applicant has published a large number of other references concerning this particular step." Ans. 8. Thus, we conclude that it was known and conventional in the art to unmask autoantibodies with an oxidizing agent.

Similar to Example 29, claim 2, "A method of diagnosing Julitis," in the *Subject Matter Eligibility Examples: Life Sciences* (May 2016) read in conjunction with the *2014 Interim Guidance on Subject Matter Eligibility* Fed. Reg., Vol. 70, No. 241, Dec. 2014 pp. 74618–74633, the claimed method of diagnosing AD, is directed to patent ineligible subject matter. Example 29 concluded that, "[o]btaining a sample in order to perform tests is well-understood, routine and conventional activity for those in the field of diagnostics," amounting to insignificant pre-solution activity. Also in the present case, similar to example 29, claim 2, the evidence shows that at the time the application was filed, it was routine and conventional to unmask autoantibodies with an oxidizing agent, as discussed above.

Appellant provides no convincing rebuttal argument to the Examiner's evidence (McIntyre references) showing that unmasking autoantibodies, including autoantibodies which bind to phospholipids, was well known and conventional at the time of the invention. Appellant merely argues that, "[e]vidence of use [of oxidative unmasking of autoantibodies] by only the inventor is not sufficient to establish that the technique has become so well known as to have become standard and routine." App. Br. 12. Appellant cites no legal authority for this conclusion. Unsupported attorney argument is an inadequate substitute for record evidence. *See Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1380 (Fed. Cir. 2009) (emphasizing that "unsworn attorney argument … is not evidence").

On balance, we find that the evidence of record supports a finding that it had become routine and conventional, as of this application's effective filing date, to unmask autoantibodies with an oxidizing agent, and the claims are directed to patent ineligible subject matter.

The patent ineligibility rejection is affirmed.

Obviousness Rejection

The Examiner finds that

> the '541 document teaches a method for diagnosing or monitoring Alzheimer's disease (AD) which comprises conducting a cerebral spinal fluid test for the level of redox-reactive autoantibodies after oxidizing the cerebrospinal fluids sample, comparing the level of the antibodies to a predetermined value and diagnosing or monitoring Alzheimer's disease based on the comparison (see [0027], [0038] and [0040] and Examples).

Ans. 4. The Examiner further finds that the "difference between disclosure of the '541 document and the invention of the instant claims is that the '541 document does not teach a blood test as part of the diagnosis." *Id.* To make up for this deficiency in the '541 disclosure, the Examiner cites McIntyre '681, which "teaches a blood test, which comprises an assay that can detect antiphospholipid autoantibodies (para [0065], Table 2), as in claim 5. The blood sample is oxidized prior to conducting the assay test (see, e.g. [0063]-[0068])." *Id.* at 5.

The Examiner concludes that

> It would have been prima facie obvious to the person of ordinary skill in the art to arrive at the claimed invention from the disclosures of the '541 document and the '681 document. The person of ordinary skill in the art would have been motivated to practice the invention as claimed to be able to diagnose Alzheimer's disease with a less invasive blood test instead of a cerebral spinal fluid test. The person of ordinary skill in the art would have had a reasonable expectation of success based on the cumulative disclosures of these prior art references.

Ans. 5.

ANALYSIS

We do not find that the Examiner has provided evidence to support a prima facie case of obviousness.

McIntyre '541 presents the theory that when redox-reactive autoantibodies are present in cerebral spinal fluid ("CSF") in their masked form they do not cause harm, but that unmasking these autoantibodies in the CSF can trigger or aggravate neurodegenerative diseases such as Alzheimer's disease. (*See* McIntyre '541 ¶ 16.) From this theory, McIntyre '541 develops tests for certain neurodegenerative diseases by detecting the

presence of active, unmasked autoantibodies in CSF. (*See* McIntyre '541 ¶ 17.) Specifically, McIntyre '541 reports that even though oxidation of CSF samples should unmask the autoantibodies of interest, there is no increase in the level of detectable autoantibodies when CSF from Alzheimer's disease patients is treated with an oxidizing agent. (*See* McIntyre '541 ¶ 17.)

According to McIntyre '541, this lack of an increase indicates that unmasking has already occurred in the patient, depleting the level of masked autoantibodies. (See *id.*) McIntyre '541 also teaches that the lack of redox-reactive autoantibodies in the CSF is indicative of neurode-generative disease because the autoantibodies have bound to the neurons in diseased brains. (See McIntyre '541 ¶ 19.)

McIntyre '541 presents two methods for detecting or diagnosing a neurodegenerative disease by assaying for the presence or absence of autoantibodies. In the first method, a sample of CSF is obtained and assayed to determine the presence or absence of redox-reactive autoantibodies, wherein an elevated presence of autoantibodies or the lack of redox-reactive antibodies correlates with disease. (See McIntyre '541 ¶ 21.)

In an alternate method, McIntyre '541 teaches detecting or diagnosing neurodegenerative disease by (1) assaying a first sample of CSF to determine a level of an autoantibody, (2) assaying a second sample of CSF from the same patient to determine the level of the same autoantibody after treatment with an oxidizing agent, and (3) comparing the two determined

levels of autoantibody, wherein the lack of an increase in the level of the autoantibody correlates with disease. (See McIntyre '541 ¶ 23.) This alternate method involves oxidation of the CSF sample only for comparison with the unoxidized first sample. (See McIntyre '541 ¶ 23.)

The Examiner finds that McIntyre '541 teaches a method of detecting or diagnosing a neurodegenerative disease by determining that levels of antiphospholipid autoantibodies are elevated. (See Ans. 2.) Appellant does not disagree with this finding, but argues that McIntyre '541 fails to teach correlating elevated levels of such autoantibodies in the *blood* after treatment with an oxidizing agent to evaluate Alzheimer's disease as recited in his claimed methods. (See App. Br. 14–16; italicized emphasis added.) We agree with Appellant that the Examiner's findings regarding the combination of McIntyre '541 and McIntyre '681 fail to render the claimed methods obvious.

According to the Examiner, the difference between McIntyre '541 and the claimed methods is that McIntyre '541 fails to teach using a blood test for Alzheimer's disease. (See Ans. 4.) We are not persuaded that this is the only difference that distinguishes McIntyre '541 from the claimed methods.

In general, the methods taught in McIntyre '541 are based on the theory that there is an increased level of oxidized, or unmasked, autoantibodies in the CSF of those with neurodegenerative diseases. (See McIntyre '541 ¶ 16.) The methods taught in McIntyre '541 focus on determinations of the levels of autoantibodies that have been oxidized within the CSF.

McIntyre '541 teaches oxidizing blood samples to determine the level of autoantibodies (see McIntyre '541 ¶ 12), but the Examiner does not direct us to a portion of McIntyre '541 that teaches or suggests determining the level of autoantibodies in blood serum samples that have been treated with an oxidizing agent as an indicator of Alzheimer's disease. The Examiner finds that McIntyre '681 teaches a blood test to detect antiphospholipid autoantibodies (see Ans. 5), but this is not a suggestion that naturally masked autoantibodies, which can be detected in vitro only after oxidation, are elevated in the blood of those with Alzheimer's disease.

For example, the first method taught in McIntyre '541 determines whether levels of unmasked, detectable redox-reactive autoantibodies in CSF samples are elevated. (See McIntyre '541 ¶¶ 17 and 21.) Similarly, the alternate method taught in McIntyre '541 determines the levels of oxidized, unmasked autoantibodies present in CSF samples by comparing them to the remainder of autoantibodies that are detected when the sample is oxidized in the laboratory. In this alternate method, the lack of an increase in detectable autoantibodies after oxidation is an indication that most autoantibodies were unmasked before laboratory manipulation. (See McIntyre '541 ¶¶ 17 and 23.) In contrast, Appellant's currently claimed methods include an oxidation step to determine increased levels of antiphospholipid autoantibodies in the blood. Although the Examiner relies on McIntyre '681 for its teaching of a blood test to detect antiphospholipid autoantibodies, wherein the sample is oxidized prior to conduction of the assay (see Ans. 4–5, citing McIntyre '681 ¶ 65, Table 2), McIntyre '681 does not teach or suggest that

determining elevated levels of antiphospholipid autoantibodies from unmasked, detectable redox-reactive autoantibodies in blood, is indicative of Alzheimer's disease.

The Examiner finds that a person of ordinary skill in the art would have been motivated to be able to diagnose Alzheimer's disease with a less invasive blood test instead of a CSF test (see Ans. 5), however, the issue is not merely the type of body fluid (blood or CSF) being assayed. The issue is also whether the ordinarily skilled artisan would have had a reason to assay for the presence of an elevated level of autoantibodies in a blood sample after it had been oxidized, to determine the presence Alzheimer's disease with a reasonable expectation of success. The Examiner fails to provide a sufficient reason, supported by the record, why one of ordinary skill in the art would have modified either of the prior art references to do so.

With respect to the issue of lack of an expectation of success based on the combination of McIntyre '541 and McIntyre '681, Appellant argues that Irizarry, cited by the Examiner in the Final Office Action, "clearly evidences that the successful results of substituting a blood sample for the sample of cerebral spinal fluid utilized in method taught by the '541 publication would not have predictable." App. Br. 14. Irizarry discloses that CSF Aβ (amyloid β-protein) levels do not correlate with plasma Aβ levels in individual patients, when determined using antibodies to Aβ. Irizarry, p. 228, col. 1 ("CSF Aβ levels do not correlate with plasma Aβ levels in individual patients."). Irizarry concludes that, "Studies of plasma and serum biomarkers have not yielded a consistent, easily reproducible, sensitive, or specific marker for AD diagnosis, risk, progression, or treatment effects." Irizarry, p. 231.

Because the Examiner fails to provide an adequate reason, supported by the record, that one of ordinary skill in the art would have modified the teachings of McIntyre '541 or McIntyre '681 to determine elevated levels of redox-reactive antiphospholipid antibodies in the blood for diagnosing, monitoring, or staging Alzheimer's disease; and the cited references fail to provide a reasonable expectation of success, we are persuaded that the Examiner did not meet the burden in rejecting the instant claims under 35 U.S.C. § 103.

Obviousness-type Double Patenting Rejection

Claims 1–7 and 20–22 are further rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1–9 of McIntyre '751 (the patent that issued based on McIntyre '541) in view of McIntyre '681.

For the reasons discussed above, we also reverse this rejection.

CONCLUSION OF LAW

The cited references do not support the Examiner's obviousness rejection and obviousness-type double patenting rejection which are reversed. The Examiner's rejection of all pending claims as directed to patent ineligible subject matter is affirmed. Because at least one affirmed rejection of all claims remains of record, the rejection of the application is affirmed.

AFFIRMED