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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte SUBHA V. RAMAN, ORLANDO P. SIMONETTI, and JAY L. ZWEIER[1]

Appeal 2017-001873
Application 12/811,292
Technology Center 1600

Before MICHAEL J. FITZPATRICK, RICHARD J. SMITH, and TAWEN CHANG, *Administrative Patent Judges*.

SMITH, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for in vivo characterization of atherosclerotic plaque. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm the rejection under Section 103 for obviousness and reverse the rejection under Section 101 for non-statutory subject matter.

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[1] According to Appellants, the real party in interest is Ohio State Innovation Foundation. (Appeal Br. 3.)

STATEMENT OF THE CASE

Claims on Appeal[2]

Claims 1, 2, 4, and 19 are on appeal. (Claims Appendix, Br. 10–11.)

Claims 1 is illustrative and reads as follows:

> 1. A method for *in vivo* atherosclerotic plaque characterization in a subject in need thereof, comprising:
>
> identifying an atherosclerotic plaque in a subject;
>
> conducting a magnetic resonance imaging (MRI) of the atherosclerotic plaque *in vivo* in the subject using a MRI device;
>
> incorporating a double inversion blood suppression pre-imaging pulse into T2* magnetic resonance imaging (MRI) mapping using the MRI device;
>
> incorporating a chemical shift selective fat suppression pre-imaging pulse into T2* MRI mapping using the MRI device;
>
> detecting a level of endogenous iron Fe(III) complexes in the atherosclerotic plaque in the subject by measuring T2*, wherein no iron-containing contrast agent is used;
>
> characterizing the atherosclerotic plaque for intraplaque iron content of Fe(III); and
>
> distinguishing symptom-producing atherosclerotic plaque from non-symptom producing atherosclerotic plaque in the subject when Fe(III) levels are higher in non-symptom-producing atherosclerotic plaque than in symptom producing plaque.

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[2] The Examiner identifies Appellants' elected subject matter as "directed to a method for characterizing an atherosclerotic plaque comprising *i)* detecting the level of endogenous iron (III) complexes in the atherosclerotic plaque by T2* magnetic resonance imaging (MRI) with a non-iron contrast agent using double inversion blood suppression and fat suppression, *ii)* comparing the detected value to a reference value, and *iii)* drawing conclusions about the vulnerability of the plaque." (Final Office Action mailed Jan. 12, 2015, ("Final Act") 4; *see also* Response to Restriction Requirement dated July 23, 2012.) We limit discussion and consideration to the elected species. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987).

Examiner's Rejections

1. Claims 1, 2, 4, and 19 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Yuan,[3] Anderson,[4] and Stadler.[5] (Final Act. 4–6.)

2. Claims 1, 2, 4, and 19 stand rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter (a natural principle). (*Id.* at 2–3.)

DISCUSSION

We adopt the Examiner's findings, analysis, and conclusions regarding the obviousness rejection, including with regard to the scope and content of, and motivation to combine, the prior art, as set forth in the Final Action and Answer. We discern no error in the rejection of the claims as obvious.

Rejection No. 1

Issue

Whether a preponderance of evidence of record supports the Examiner's rejection under 35 U.S.C. § 103(a).

Principles of Law

The test for obviousness is "what the combined teachings of the references would have suggested to those of ordinary skill in the art" and not

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[3] C. Yuan et al., *MRI of Atherosclerosis*, J. Magnetic Resonance Imaging 19, 710–19 (2004) ("Yuan").

[4] L.J. Anderson et al., *Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload*, European Heart J., The European Soc'y of Cardiology 22, 2171–79 (2001) ("Anderson").

[5] N. Stadler et al., *Direct Detection and Quantification of Transition Metal Ions in Human Atherosclerotic Plaques: Evidence of the Presence of Elevated Levels of Iron and Copper*, Arteriosclerosis, Thrombosis, and Vascular Biology, J. Am. Heart Ass'n 24, 949–54 (2004) ("Stadler").

"that the claimed invention must be expressly suggested in any one or all of the references." *In re Keller*, 642 F.2d 413, 425 (CCPA 1981) (citing cases).

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Analysis

Claims 1 and 19 are the only independent claims on appeal and recite similar limitations. We limit our consideration to claim 1 because the claims were not argued separately.

Examiner's Position

The Examiner finds that Yuan discloses a method for characterizing atherosclerotic carotid plaque using MRI techniques, with or without gadolinium (a non-iron contrast agent), and further using double inversion blood suppression and fat suppression, to detect plaque constituents and composition, comparing MRI data to standard references, and identifying vulnerable plaque. (Final Act. 4.) The Examiner also finds that Anderson discloses the use of T2*-MRI to detect endogenous tissue iron levels, and that Stadler discloses the detection of elevated endogenous carotid plaque iron (III) complexes, that positively correlate with plaque cholesterol levels and disease progression, and that elevated iron (III) levels may affect plaque stability and propensity to rupture. (Final Act. 5.)

Based on those findings, the Examiner concludes that the claims would have been prima facie obvious, and that

> one of ordinary skill in the art would be motivated to characterize an atherosclerotic carotid plaque by employing T2*-MRI techniques with or without a gadolinium (i.e. non-iron) contrast agent using double inversion blood suppression and fat suppression to detect endogenous iron (III) within the plaque, and comparing MRI data to standard references, with the reasonable expectation that the resulting technique will successfully correlate with disease progression and identify vulnerable plaque.

(Final Act. 5–6.)

We find that the Examiner has established a prima facie case of obviousness based on the combined teachings of Yuan, Anderson, and Stadler. (*Id.* at 4–6.)

Appellants' Arguments

Appellants argue that Anderson does not remedy the deficiencies of Yuan because Anderson only teaches using the T2*-MRI on heart tissue, and that there is no teaching or suggestion in Anderson that a non-tissue material, such as plaque, can be examined in vivo within a tissue such as a carotid artery. (Br. 7.) Appellants also argue that there is no correlation suggested in Anderson "between heart iron levels [in] thalassemia major patients and the intraplaque Fe(III) levels in atherosclerotic patients" or between cardiomyopathy and symptom-producing atherosclerosis. (*Id.*)

We are not persuaded. We note that the rejection is based on the combined teachings of Yuan, Anderson, and Stadler, and not just on Yuan and Anderson. *See Keller*, 642 F.2d at 425. Yuan teaches the use of MRI to examine plaque in vivo, and Anderson is cited for the use of T2*-MRI to detect endogenous tissue iron levels. (Final Act. 5; *see also* Anderson 2171 ("We have developed a new magnetic resonance T2-star (T2*) technique for

the measurement of tissue iron."). The Examiner also relies on Stadler (not Anderson) for the correlation of "intraplaque Fe(III) levels in atherosclerotic patients." (*See* Br. 7; *see also* Final Act. 5.)

Although the working example in Anderson may be directed to myocardial tissue and cardiomyopathy, Anderson may still be cited because a prior art reference is not limited to its working examples, *In re Mills*, 470 F.2d 649, 651 (CCPA 1972), and "'[a] reference must be considered not only for what it expressly teaches, but also for what it fairly suggests'" *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (quoting *In re Burckel*, 592 F.2d 1175, 1179 (CCPA 1979)). Here, Anderson fairly suggests the use of T2*-MRI in the *in vivo* detection of iron levels in body tissue. (*See* Ans. 10–11.) We are also unpersuaded by Appellants' distinction between tissue and plaque, based at least on Yuan's numerous references to "plaque tissue."[6] (*See, e.g.,* Yuan 710–12 and 717.)

Appellants argue that Stadler "only describes the use of electron paramagnetic resonance (EPR) spectroscopy and inductive coupled plasma mass spectroscopy (ICPMS) to quantify ex vivo carotid lesions," and that "[t]hus, there is no teaching or suggestion in Stadler[] for the conducting of an *in vivo* MRI on the subject itself," or "that **any tissue** could be examined *in vivo*." (Br. 7–8.) We are not persuaded. The combination of Yuan and Anderson teaches the use of T2*-MRI for conducting *in vivo* analysis of tissue such as plaque.

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[6] *See also* definition of plaque: "A thickened area consisting of fibrous *tissue* and lipid, often with calcification, in the intima of an atherosclerotic artery." (emphasis added). Oxford English Dictionary, http://www.oed.com/view/Entry/145203?redirectedFrom=plaque#eid, last visited Oct. 30, 2018.

Appellants also argue that "Stadler[] does not distinguish[] 'symptom-producing atherosclerotic plaque' as compared to 'non-symptom producing atherosclerotic plaque.' Nor does Stadler[] teach or suggest that Fe(III) is lower in symptom-producing atherosclerotic plaque than in non-symptom producing plaque." (Br. 8.) According to Appellants, Stadler teaches the "exact opposite" of the correlation recited by Appellants, citing Stadler's statement that "[t]he g≈4 Fe(III) species was quantified, and although the levels varied (Figure IB), the **mean value for all the plaques** examined is **significantly elevated** over that detected in health[y] intima samples." (*Id.*, quoting Stadler 951 (emphasis added).) Appellants further argue that the Examiner is applying a Section 101 analysis to the "distinguishing" step because the correlation between endogenous plaque iron (III) levels and "symptoms" is a natural phenomenon that is not patentable subject matter. (Br. 8.) According to Appellants, a Section 101 analysis has no bearing in a Section 103 analysis of "determining whether a claim defines over the prior art." (*Id.*)

We are not persuaded. Stadler is cited for teaching a correlation between iron (III) levels in plaque and disease progression (Final Act 5), and Stadler concludes that "[t]hese data support the hypothesis that iron accumulates in human lesions and may contribute to disease progression." (Stadler Abstract.) Appellants' Specification also states that "the term 'harmful or symptom-producing plaque' can generally include the presence of plaque that produces one or more atherosclerotic symptoms in a subject" (Spec. ¶ 10), which can reasonably be interpreted to mean plaque that "may contribute to disease progression" (Stadler Abstract). We are thus not persuaded by the argument that Stadler does not distinguish "symptom-

producing atherosclerotic plaque from non-symptom producing atherosclerotic plaque" as recited in claim 1.

Appellants also argue that Stadler teaches a correlation between plaque iron levels and disease progression that is opposite to that claimed by Appellants. (Br. 8.) However, as Appellants point out, Stadler's example is not *in vivo* and does not use T2*-MRI. (*Id.* at 7.) Appellants' Specification also distinguishes inductively coupled plasma mass spectroscopy and electron paramagnetic resonance (that Appellants argue is used by Stadler) from T2*-MRI. (Spec. ¶¶ 7–8.) Stadler's and Appellants' respective correlations are thus not directly comparable, but a direct comparison is not required for obviousness. (*See also* Spec. ¶ 6 ("[S]tudies relating to iron and atherosclerosis have provided conflicting results.").) Moreover, Stadler's conclusion regarding "the *hypothesis* that iron accumulates in" plaques and that iron accumulation "*may* contribute to disease progression" (emphasis added) is a suggestion to correlate iron levels to distinguish symptom producing plaque versus non-symptom producing plaque (as taught by Stadler and relied on by the Examiner), but is not a definitive statement of what that correlation may be. Stadler is thus an appropriate reference to combine with Yuan and Stadler to render claim 1 prima facie obvious.

Appellants' blanket contention that a Section 101 analysis has no bearing in a Section 103 analysis is incorrect. *See Praxair Distribution, Inc. v. Malllinckrodt Hosp. Prods. IP Ltd.*, 890 F.3d 1024, 1032–34 (Fed. Cir. 2018) (citing cases). Although *Praxair* addressed printed matter limitations in the context of an obviousness analysis, it also applied the same analysis to mentally-processed information. *Id.* at 1033–34. Here, the step of distinguishing plaque based on Fe(III) levels is taught by the prior art

(Stadler). The correlation of iron levels in symptom-producing plaque as compared to non-symptom producing plaque is a natural phenomenon, and is not accorded any patentable weight, at least because that natural phenomenon is analyzed using "information [(i.e., the correlation)] together with a purely mental step [(i.e., comparing Fe(III) levels)]." *See Praxair*, 890 F.3d at 1033–34. Moreover, "[s]cientific confirmation of what was already believed to be true may be a valuable contribution, but it does not give rise to a patentable invention." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1347, 1363–64 (Fed. Cir. 2007) (reversing nonobviousness of claims that were based on the discovery that human umbilical cord blood could be used as a source of transplantable hematopoietic stem cells); *see* Spec. ¶¶ 4–7.

We are also unpersuaded by Appellants' "impermissible hindsight" argument. (Br. 6, 8.) It is well-established that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, "but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971). Appellants adduce no evidence that the Examiner's findings were beyond the level of ordinary skill in the art at the time of invention, nor do they point to any of the Examiner's findings that could have been taken only from Appellants' Specification.

Accordingly, for the reasons of record and as set forth above, we affirm the rejection of claim 1 for obviousness. Claims 2, 4, and 19 were not argued separately and fall with claim 1.

Rejection No. 2

Issue

Whether a preponderance of evidence of record supports the Examiner's rejection under 35 U.S.C. § 101.

Analysis

The Examiner's statement of rejection reads as follows:

> The above identified claims are in fact directed to a natural principle since they are based merely on detecting the level of *endogenous* iron (III) complexes in plaque using an established, conventional technique (i.e. MRI imaging), comparing the detected value to a reference value, and drawing conclusions. The claimed subject matter thus amounts to diagnosing or "characterizing" a condition based on a naturally occurring relationship or correlation between the presence or level of an endogenous substance when a condition/disease is present, and do not include additional elements or steps that amount to significantly more than the natural principle itself. Applicant is detecting the endogenous iron (III) by a generic "T2*-MRI imaging" method, which method is well known in the art for detecting tissue iron levels. Thus, the manner in which the endogenous iron (III) is being detected is commonplace, and comparing numbers and drawing conclusions are nothing more than abstract mental processes (i.e. "thinking").

(Final Act. 2–3.)

Appellants refer to the 2014 *Interim Guidance on Patent Subject Matter Eligibility*[7] to argue that "applying Step 2B, the Appellant[s] note[] that the claims recite 'significantly more' [than] the judicial exception when the claims are analyzed as a whole." (Br. 5–6.) Appellants proceed to identify the steps that follow the step of identifying an atherosclerotic plaque

[7] https://www.federalregister.gov/documents/2014/12/16/2014-29414/2014-interim-guidance-on-patent-subject-matter-eligibility.

in a subject, and conclude that the Examiner erred in concluding that the claims "fail to meet at least Step 2B of the *Alice/Mayo* two-part test." (Br. 6.) The Examiner responds to Appellants' contention by stating that the claimed steps were "well known" based on the respective references of Yuan, Anderson, and Stadler. (Ans. 7–8.)

"[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). We find in this case that the Examiner has failed to meet that burden.

Since the docketing of this appeal in December 2016, the Federal Circuit issued its decision in *Berkheimer v. HP Inc.*, 881 F.3d 1360 (Fed. Cir. 2018), after which the USPTO published an examination procedure entitled "Changes in Examination Procedure Pertaining to Subject Matter Eligibility, Recent Subject Matter Eligibility Decision (*Berkheimer v. HP, Inc.*)" (hereinafter "PTO Memorandum").[8] The PTO Memorandum clarifies that a conclusion that an element (or combination of elements) represents well-understood, routine, conventional activity must be based on a factual determination as set forth in Section III of the PTO Memorandum. Section III.A.3. is pertinent here, and reads as follows (emphases and formatting added):

> 3. A citation to a publication that demonstrates the well-understood, routine, conventional nature of the additional element(s). An appropriate publication could include a book, manual, review article, or other source *that describes the state of the art and discusses what is well-known and in common use in the relevant industry.* It does not include all items that might

[8] https://www.uspto.gov/sites/default/files/documents/memo-berkheimer-20180419.PDF.

> otherwise qualify as a "printed publication" as used in 35 U.S.C. § 102.[]
>
> Whether something is disclosed in a document that is considered a "printed publication" under 35 U.S.C. § 102 is a distinct inquiry from whether something is well-known, routine, conventional activity. A document may be a printed publication but still fail to establish that something it describes is well-understood, routine, conventional activity. *See Exergen Corp.*, 2018 WL 1193529, at *4 (the single copy of a thesis written in German and located in a German university library considered to be a "printed publication" in *Hall* "would not suffice to establish that something is 'well-understood, routine, and conventional activity previously engaged in by scientists who work in the field"').
>
> The nature of the publication and the description of the additional elements in the publication would need to demonstrate that the additional elements *are widely prevalent or in common use in the relevant field*, comparable to the types of activity or elements that are so well-known that they do not need to be described in detail in a patent application to satisfy 35 U.S.C. § 112(a). *For example*, while U.S. patents and published applications are publications, *merely finding the additional element in a single patent or published application would not be sufficient* to demonstrate that the additional element is well-understood, routine, conventional, *unless the patent or published application demonstrates that the additional element are widely prevalent or in common use in the relevant field.*

(PTO Memorandum III.A.3 (internal citations omitted).)

On the record before us, we have the Examiner's conclusory statement of rejection that the claims "do not include additional elements or steps that amount to significantly more than the natural principle itself," based on the unsupported statement that the '"T2*-MRI imaging' method . . . is well known in the art for detecting tissue iron levels." (Final Act. 3.) The Examiner elaborates on that finding in the Answer by citing to

Anderson as support for the statement that "[e]mploying T2* MRI to detect iron (III) levels in the body is well known." (Ans. 8.)

Simply stated, we cannot reconcile the requirements of the PTO Memorandum with the unsupported statement in the Final Action regarding T2*-MRI imaging, and the insufficient statement regarding T2*-MRI imaging in the Answer. Rather than describing that T2*-MRI imaging is well known and in common use in the relevant industry, Anderson states that "[w]e have developed a *new* magnetic resonance T2-star (T2*) technique for the measurement of tissue iron." (Anderson 2171 (emphasis added).) Although that teaching may be used in an obviousness analysis, we do not find on this record that it satisfies the required showing that the use of T2*-MRI imaging for detecting tissue iron levels was "widely prevalent or in common use in the relevant field" at the time of the invention.[9] (PTO Memorandum III.A.3.)

We find that the Examiner has failed to establish a prima facie case of non-statutory subject matter. Accordingly, we reverse the rejection of claims 1, 2, 4, and 19 under 35 U.S.C. § 101.

Conclusions of Law

A preponderance of evidence of record supports the Examiner's rejection of claims 1, 2, 4, and 19 under 35 U.S.C. § 103(a).

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[9] "[A] showing that additional elements are obvious under 35 U.S.C. § 103 . . . is not by itself sufficient to establish that the additional elements are well-understood, routine, conventional activities or elements to those in the relevant field." (PTO Memorandum II, at 3 (citing MPEP § 2106.05 and *Berkheimer*, 881 F.3d at 1369).)

A preponderance of evidence of record fails to support the Examiner's rejection of claims 1, 2, 4, and 19 under 35 U.S.C. § 101.

SUMMARY

We affirm the obviousness rejection and reverse the non-statutory subject matter rejection.

TIME PERIOD FOR RESPONSE

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

AFFIRMED