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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Ex parte FRANÇOIS MALLET,
NATHALIE MUGNIER, and PHILIPPE PEROT

_____

Appeal 2021-003081
Application 14/367,635
Technology Center 1600

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Before JEFFREY N. FREDMAN, JOHN G. NEW, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134(a) involving claims to a method for detecting at least two RNA transcripts. The Examiner rejected the claims as failing to comply with the written description requirement, as indefinite, and as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the Real Party in Interest as BIOMÉRIEUX and HOSPICES CIVILS DE LYON (*see* Appeal Br. 2). We have considered the Specification filed June 20, 2014 ("Spec."); Non-Final Rejection of June 4, 2020 ("Non-Final Act."); Appeal Brief filed Nov. 4, 2020 ("Appeal Br."); Examiner's Answer filed Feb. 8, 2021 ("Ans."); and Reply Brief filed Apr. 8, 2021 ("Reply Br.").

Statement of the Case

Background

"Endogenous retroviruses constitute the progeny of infectious retroviruses which have integrated, in their proviral form, into germ line cells," such as human egg or sperm cells (*see* Spec. 1:3–5). "The abundance of endogenous retroviral elements (ERVs) currently present in the human genome is the result of about 100 endogenizations which have successfully taken place during the course of the evolution" (*id*. at 1:13–16). "The abundance and the structural complexity of ERVs makes analyses of their expression very complicated and often difficult to interpret" (*id.* at 2:8–10).

The Specification teaches the "present inventors have now discovered and demonstrated that nucleic acid sequences corresponding to precisely identified loci of endogenous retroviral elements are associated with prostate cancer and that these sequences are molecular markers of the pathological condition." (Spec. 2:14–18).

The Claims

Claims 1, 5–8, 22, and 28–34 are on appeal. Claim 1 is an independent claim, is representative and reads as follows:

> 1. A method for detecting at least two RNA transcripts, comprising:
>
> obtaining a biological sample that is collected from a human patient suspected of having prostate cancer; and
>
> detecting, in the biological sample, the presence or absence of at least two RNA transcripts comprising a first RNA transcript expressed by a first nucleic acid sequence having at least 99% identity with SEQ ID NO: 1, and a second RNA transcript expressed by a second nucleic acid sequence having at least 99% identity with SEQ ID NO: 3.

The Rejections

A. The Examiner rejected claims 1, 5–8, 22, and 28–34 under 35 U.S.C. § 112(a) as failing to comply with the written description requirement (Ans. 3–4).

B. The Examiner rejected claims 1, 5–8, 22, and 28–34 under 35 U.S.C. § 112(b) as indefinite (Ans. 5–6).

C. The Examiner rejected claims 1, 5–8, 22, and 28–34 under 35 U.S.C. § 103(a) as obvious over Wang-Johanning[2] and Stauffer[3] (Ans. 7–10).

D. The Examiner rejected claims 1, 5–8, 22, and 28–33 under 35 U.S.C. § 103(a) as obvious over Wang-Johanning, Stauffer, GenBank Accession AC087436.5,[4] Giminez,[5] Yi (2004),[6] Ishida,[7] Pačes,[8] Yi (2007),[9] and

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[2] Wang-Johanning et al., *Detecting the Expression of Human Endogenous Retrovirus E Envelope Transcripts in Human Prostate Adenocarcinoma*, 98 Cancer 187–97 (2003).
[3] Stauffer et al., *Digital expression profiles of human endogenous retroviral families in normal and cancerous tissues*, 4 Cancer Immunity 1–18 (2004).
[4] GenBank Accession AC087436.5 (2002).
[5] Giminez et al., *Custom human endogenous retroviruses dedicated microarray identifies self-induced HERV-W family elements reactivated in testicular cancer upon methylation control*, 38 Nucleic Acids Res. 2229–46 (2010).
[6] Yi et al., *Expression of the human endogenous retrovirus HERV-W family in various human tissues and cancer cells*, 85 J. Gen. Vir. 1203–10 (2004).
[7] Ishida et al., *Identification of the HERV-K gag antigen in prostate cancer by SEREX using autologous patient serum and its immunogenicity*, 8 Cancer Immunity 1–10 (2008).
[8] Pačes et al., *HERVd: the Human Endogenous Retroviruses Database: update*, 32 Nucleic Acids Res. 1 (2004).
[9] Yi et al., *Molecular Phylogenetic Analysis of the Human Endogenous Retrovirus E (HERV-E) Family in Human Tissues and Human Cancers*, 82 Genes Genet. Syst. 89–98 (2007).

Garcia[10] (Ans. 11–16).

A. 35 U.S.C. § 112(a), written description

The Examiner finds

> teachings of the specification for "suspected of suffering" does not support a full range of possibilities of suspected of having prostate cancer. The specification only provides blaze marks to subjects requiring a biopsy or diagnosed with prostate cancer with metastasis. The examples of the specification are limited to samples from subjects with prostate cancer or healthy prostate tissue samples. The specification provides no specific guidance in the specification outside the examples to identify the metes and bounds of suspected of having prostate cancer. The limitation as written encompasses any condition or symptom which is identified as suspected of having prostate cancer. Further the specification provides no guidance as to if a subject diagnosed with prostate cancer is encompassed by suspected of having prostate cancer. Thus suspected of having prostate cancer expands the scope of the claim such that the artisan is apprised of where suspected of having prostate cancer begins or ends

(Ans. 4).

Appellant contends "the specification provides literal support for obtaining a biological sample from a patient 'suspected of suffering from prostate cancer'" (Appeal Br. 7). Appellant contends

> the concept of a human patient suspected of having prostate cancer was known in the art at the time of invention, and thus, a detailed description of such a patient is preferably omitted from the specification. . . . Such symptoms were well known in the art and thus there is no requirement that the specification provide a detailed description of all possible circumstances that

[10] Garcia et al., US 7,776,523, issued Aug. 17, 2010.

> might give rise to a patient being suspected of having prostate cancer.

(*id.* at 8). Appellant contends: "It is plainly evident that the diagnostic methods described in the specification would be performed on biological samples from human patients suspected, but not confirmed to have (i.e., not diagnosed with) prostate cancer" (*id.* at 9).

We appreciate the Examiner's concerns because one purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification." *Reiffin v. Microsoft Corp*., 214 F.3d 1342, 1345–46 (Fed. Cir. 2000). However, "written description is about whether the skilled reader of the patent disclosure can recognize that what was claimed corresponds to what was described; it is not about whether the patentee has proven to the skilled reader that the invention works, or how to make it work, which is an enablement issue." *Alcon Research Ltd. v. Barr Labs., Inc*., 745 F.3d 1180, 1191 (Fed. Cir. 2014).

That is, the "'written description' requirement must be applied in the context of the particular invention and the state of the knowledge." *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005). The phrase "suspected of having prostate cancer" in claim 1 would therefore be understood in the context of physicians concerned with diagnosing a patient.[11]

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[11] We appreciate that claim 1, which Appellant describes as a diagnostic method, appears to implicate a patentability concern under *Mayo Collaborative Servs. v. Prometheus Labs., Inc*., 566 U.S. 66, 75–77 (2012), in that the presence of the transcripts are being assessed to diagnose prostate cancer (Spec. 2), but the Examiner likely followed USPTO guidance like that in Example 29 of the Subject Matter Eligibility Examples: Life

The Specification teaches a sample "may be derived from a biopsy of the prostate" (Spec. 15:18) from a patient "suspected of suffering from prostate cancer" (Spec. 15:19). But the ordinary physician would have been aware of a number of tests and symptoms leading to a suspicion of prostate cancer. Garcia teaches the "prostate grows and pushes against the urethra and bladder, blocking the normal flow of urine" (Garcia 1:26–28). Garcia also teaches the "level of PSA [prostate specific antigen] in blood may rise in men who have prostate cancer, BPH [benign prostatic hyperplasia]" (Garcia 1:39–40). Garcia teaches other tests "to help determine whether conditions of the prostate are benign or malignant . . . such as transrectal ultrasonography, intravenous pyelogram, and cystoscopy" (Garcia 1:47–49).

We therefore agree with Appellant that, consistent with *Capon*, an ordinary artisan or physician would have understood before the time of filing of the instant claims that a patient "suspected of having prostate cancer" would have symptoms like reduced urine flow, enlarged prostates, increased PSA blood levels, or sonographic imaging (*see* Garcia, generally) that would indicate, but not confirm, a concern that the patient might suffer from prostate cancer. "It 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." *Capon*, 418 F.3d. at 1359. We reverse the written description rejection.

Sciences, https://www.uspto.gov/sites/default/files/documents/101_examples_1to36.pdf.

B. 35 U.S.C. § 112(b), indefiniteness

The Examiner finds "it is unclear clear if suspected of having prostate cancer encompasses all subjects undergoing prostate cancer screening, only subjects that are symptomatic, if it encompasses subjects with benign prostate hyperplasia, etc.[] Thus suspected of having [prostate] cancer is unclear to what is encompassed by the claim" (Ans. 6).

Appellant responds

> "suspected of having prostate cancer" is a plain English phrase that is clear on its face and readily understood by persons skilled in the art. For example, a patient suspected of having prostate cancer can be understood as a patient for whom there is some reason to suspect prostate cancer, such as a patient undergoing diagnostic testing for prostate cancer.

(Appeal Br. 11).

We agree with Appellant that the phrase "suspected of having prostate cancer" is readily understood as a person who some person thinks may have prostate cancer. We are not persuaded by the Examiner's finding that the breadth of claim 1 is unclear. That claim 1 broadly encompasses any person where there is a concern of a prostate cancer diagnosis but not a definite diagnosis does not render the claim indefinite, only broad. Even "undue breadth is not indefiniteness." *In re Johnson*, 558 F.2d 1008, 1016 n. 17 (CCPA 1977). We reverse the indefiniteness rejection.

C. 35 U.S.C. § 103(a) over Wang-Johanning and Stauffer

The Examiner finds

> the language of "detecting, in the biological sample, the presence or absence of at least two RNA transcripts [c]omprising a first RNA transcript expressed-by a first nucleic acid sequence having at least 99% identity with SEQ ID NO: 1, and a second RNA transcript expressed by a second nucleic

> acid sequence having at least 99% identity with SEQ ID NO: 3" allows for the broadest reasonable interpretation of the detection of fragments of the recited SEQ ID NO. The specification on pages 12-13 teaches methods of detecting nucleic acids using probes/and or at least one primer, consistent with this interpretation.

(Ans. 7). The Examiner finds Wang-Johanning teaches "HERV-E, was expressed in some prostate carcinoma tissues (38.8% positive; n 49 specimens) but not in normal prostate tissues" (*id.* at 7–8). The Examiner finds "Wang-Johanning teaches the use of HERV genes for diagnosis and thus clearly teaches use of HERV sequences for detection of prostate cancer or subjects suspected of having prostate cancer" (*id.* at 8).

The Examiner acknowledges that "Wang-Johanning does not specifically teach detection of SEQ ID NO 1 or fragment of SEQ ID NO 1 and SEQ ID NO 3" (Ans. 9). The Examiner finds Stauffer teaches "samples which include AB047240 and M10976. M10976.1 provides nucleotides 1 to 8812 of SEQ ID NO 3 with 99% identity (nt2-8806). Further AB047240 teaches nucleotides 873-909 of SEQ ID NO 1 with 100% identity (10467-10500)" (*id.*). The Examiner finds "Stauffer teaches numerous of the HERV sequences analyzed were detected in multiple normal tissues and cancerous tissues, including normal prostate and prostate tumors" (*id.*).

The Examiner finds it obvious to detect "expression of HERV sequences . . . in subjects being assayed for prostate cancer. The artisan would be motivated to examine additional HERV sequences to provide a great understanding of the molecular biology and identify potential targets of immunotherapy" (*id.* at 9–10).

The issue with respect to this rejections is: Does a preponderance of the evidence of record support the Examiner's conclusion that the combination of Wang-Johanning and Stauffer render the rejected claims obvious?

Findings of Fact

1. Wang-Johanning teaches "RNA was isolated from various prostate tissues and was tested for the expression of various HERV envelope (env) genes by reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, RNA in situ hybridization (ISH), and Northern blot analysis" (Wang-Johanning, abstract).

2. Wang-Johanning teaches obtaining "human tissues, including prostate adenocarcinoma (n = 49 samples), prostate intraepithelial neoplasia (PIN; n = 12 samples), benign prostate hyperplasia (BPH; n = 51 samples), tissues from patients with other prostate disorders (n = 24 samples), and normal prostate tissues (n = 18 samples)" (Wang-Johanning 188, col. 2).

3. Wang Johanning teaches a northern blot analysis example where "[l]abeled probe was hybridized overnight at 62 °C with the membrane using a high-efficiency hybridization buffer . . . . Membranes were washed 3 times at room temperature with prehybridization/wash solution . . . followed by 3 washes at 65 °C in the same solution, and exposure to autoradiography film" (Wang-Johanning 189, col. 2).

4. Stauffer teaches "HERV-H was the only family expressed in cancers of the intestine, bone marrow, bladder and cervix, and was more

highly expressed than the other families in cancers of the stomach, colon and prostate" (Stauffer, abstract).

5. Stauffer teaches because "HERV expression has been reported in multiple cancer tissues and that HERV-K endogenous retroviral proteins have been identified using the SEREX methodology suggests that these proteins could be useful antigens for diagnostic purposes or cancer immunotherapy" (Stauffer 1).

6. Table 1 of Stauffer is reproduced in part below:

Table 1. Mapping of HERV proviral sequences to the human genome.

Provirus	EST[a]	Chr.	Accession[b]	Start	Stop	S[c]	Length	Chr. Start[d]	Chr. Stop	S[c]	Prov. Ac.[e]	Comment
HERV-K												
C3_NT005863.11	32	3	AC084198	94740	103862	+	9123	102691966	102701086	+	AB047240	
. . .												
HERV-E	35	19	AC010329	96143	104955	-	8813	20705675	20714487	-	M10976	

Table 1 shows the accession numbers for several HERV or human endogenous retroviral sequences (*see* Stauffer 4).

7. The Examiner finds Table 1 of Stauffer teaches "AB047240 and M10976. M10976.1 provides nucleotides 1 to 8812 of SEQ ID NO 1 with 99% identity (nt2-8806). Further AB047240 teaches nucleotides 873-909 of SEQ ID NO 1 with 100% identity (10467-10500).

Principles of Law

Although we apply the broadest reasonable interpretation during examination, "[a]bove all, the broadest reasonable interpretation must be reasonable in light of the claims and specification." *PPC Broadband, Inc. v.*

Corning Optical Commc'ns RF, LLC, 815 F.3d 747, 755 (Fed. Cir. 2016).

Analysis

We begin with claim construction because before a claim is properly interpreted, its scope cannot be compared to the prior art. During prosecution, we interpret terms in a claim using the broadest reasonable interpretation in light of the Specification. *In re Morris*, 127 F.3d 1048, 1056 (Fed. Cir. 1997).

In this case, we interpret the phrase in claim 1 requiring

> detecting, in the biological sample, the presence or absence of at least two RNA transcripts comprising a first RNA transcript expressed by a first nucleic acid sequence having at least 99% identity with SEQ ID NO: 1, and a second RNA transcript expressed by a second nucleic acid sequence having at least 99% identity with SEQ ID NO: 3.

(Claim 1).

The Examiner contends that this phrase encompasses "detection of fragments of the recited SEQ ID NO" (Ans. 7). Appellant contends

> the specification does not support the Examiner's assertion that the claims encompass detection of RNA transcripts expressed by any sequence that happens to have least 99% identity with a fragment of SEQ ID NOs: 1 and 3. Nor would a person skilled in the art interpret the experimental data in the specification as showing differential expression of RNA transcripts expressed by fragments of SEQ ID NOs: 1 and 3 in prostate cancer.

(Appeal Br. 22).

We agree with Appellant that the broadest reasonable interpretation of claim 1 requires identifying transcripts with 99% sequence identity to the entirety of the recited SEQ ID NO:s, and not simply a portion of those SEQ ID NO:s. While the Examiner is correct that there are embodiments in the

Specification that appear to contemplate detection of fragments or smaller portions of the SEQ ID NO:s (*see, e.g.*, Spec. 8:10 "hybridization on a chip"), the Specification also contemplates "at least one probe . . . designed so as to hybridize to the mRNA transcripts" (Spec. 8:4–5).

In order for probes or primers to ensure, for example, that the entire 7,464 nucleotides of the transcript of SEQ ID NO: 1 or the entire 8,812 nucleotides of SEQ ID NO: 3 are present, and result in 99% sequence identity as required by claim 1, the detection process must be sufficiently robust to ensure that the hybridized target comprises the entirety of SEQ ID NOs: 1 and 3 and not simply a subsection of those targets.

Thus, we interpret claim 1 as requiring detection of the entire transcripts of SEQ ID NO: 1 and SEQ ID NO: 3 and does not encompass the detection of only portions of those sequences.

Applying this interpretation to the prior art, we note that the M10976.1 sequence disclosed by Stauffer in Table 1 shares 99% identity with the entire 8,812 nucleotide sequence of SEQ ID NO: 1. However, we note that, as the Examiner acknowledges, the AB047240 sequence disclosed by Stauffer in Table 1 shares only about a 38 nucleotide portion of the 7,464 nucleotide sequence of SEQ ID NO: 1 (*see* Ans. 9 "AB047240 teaches nucleotides 873–909 of SEQ ID NO 1 with 100% identity (10467–10500)").

Thus, Stauffer does not teach detection of "a first RNA transcript expressed by a first nucleic acid sequence having at least 99% identity with SEQ ID NO: 1" as required by claim 1.

In addition, reviewing the Examiner's search results, we note that Result 23 of the Genbank search (.rge) loaded on September 30, 2015 showed detection of a sequence from Chromosome 4 with at least one region

of 48 nucleotides in common with SEQ ID NO: 1 and Result 19 showed detection of a sequence from Chromosome 18 with 35 nucleotides in common with SEQ ID NO: 1. However, the transcript expressed by SEQ ID NO: 1 is stated by the Specification to be present on chromosome 8 (*see* Spec. 3, Table).

"An inherent characteristic of a formulation can be part of the prior art in an obviousness analysis . . . . But, inherency 'may not be established by probabilities or possibilities.'" *Endo Pharm. Solutions, Inc. v. Custopharm Inc*., 894 F.3d 1374, 1381 (Fed. Cir. 2018) (*citing Par Pharmaceuticals, Inc. v. TWI Pharmaceutical, Inc*., 773 F.3d 1186, 1194–95 (Fed. Cir. 2014).

The evidence of record shows that use of a single probe that hybridizes to a small region of nucleotide sequences that are found in SEQ ID NO:1 do not necessarily permit the artisan to obtain unique transcripts that compose the entirety of SEQ ID NO: 1 as required by claim 1. The Examiner has therefore not persuasively satisfied the obviousness burden to show that sequences detected using fragments of SEQ ID NO: 1, and particularly the fragments in AB047240, necessarily, inherently, or obviously result in detecting a transcript that is 99% identical to the 7,464 nucleotides recited in SEQ ID NO: 1.

Conclusions of Law

A preponderance of the evidence of record does not support the Examiner's conclusion that the combination of Wang-Johanning and Stauffer render the rejected claims obvious.

D. 35 U.S.C. § 103(a) over Wang-Johanning, Stauffer, GenBank Accession AC087436.5, Giminez, Yi (2004), Ishida, Pačes, Yi (2007), and Garcia

Appellants separately argue this obviousness rejection and rely upon the same arguments to overcome these further combinations (*see* Appeal Br. 23). Having reversed the obviousness rejection of claim 1 over Wang-Johanning and Stauffer for the reasons given above, we find that the further cited references do not render the rejected claims obvious for the same reasons because the Examiner does not establish that any of these references would function to detect SEQ ID NO:s 1 and 3 as required by claim 1 (*see* Ans. 15–16). We therefore reverse this rejection.

DECISION SUMMARY

In summary: In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 5–8, 22, 28–34	112(a)	Written Description		1, 5–8, 22, 28–34
1, 5–8, 22, 28–34	112(b)	Indefiniteness		1, 5–8, 22, 28–34
1, 5–8, 22, 28–34	103	Wang-Johanning, Stauffer		1, 5–8, 22, 28–34
1, 5–8, 22, 28–34	103	Wang-Johanning, Stauffer, GenBank Accession AC087436.5, Giminez, Yi (2004), Ishida, Pačes, Yi (2007), Garcia		1, 5–8, 22, 28–34

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
Overall Outcome				1, 5–8, 22, 28–34

REVERSED