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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STEEN H. MATTHIESEN

Appeal 2018-006689
Application 13/513,164
Technology Center 1600

Before JEFFREY N. FREDMAN, ULRIKE W. JENKS, and RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims to a method of hybridizing nucleic acid (or "n.a.") sequences (or "n.a.s"). Appellant appeals the Examiner's rejection of claims 1, 2, 4–29, 35–39, 41–47, 50–58, and 62 under 35 U.S.C. § 103(a) and for obviousness-type double patenting.[1] We have jurisdiction under 35 U.S.C. § 6(b).

We affirm; however, we designate new grounds of rejection under 35 U.S.C. §§ 102(e) and 103(a), and for obviousness-type double patenting, pursuant to our authority under 37 C.F.R. § 41.50(b).

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[1] "Appellant" herein refers to the "applicant" as defined by 37 C.F.R. § 1.42. Appellant identifies "Agilent Technologies, Inc.," as the real party-in-interest. Appeal Br. 1.

STATEMENT OF THE CASE

The application includes two independent claims, 1 and 2. Independent claim 1, reproduced below, is representative:

> 1. A method of hybridizing nucleic acid sequences using a denaturation step performed at or below 82°C or, without a denaturation step comprising:
>
> providing a first nucleic acid sequence within a cell in a sample having a preserved cell morphology,
>
> providing a second nucleic acid sequence,
>
> providing a hybridization composition comprising an effective amount of at least one polar aprotic solvent to enable hybridization, and
>
> combining the first nucleic acid sequence, the second nucleic acid sequence, and the hybridization composition for at least a time period sufficient to hybridize the first and second nucleic acid sequences within the cell such that the first and second nucleic acid sequences hybridize within the cell and the sample morphology is preserved,
>
> wherein the polar aprotic solvent is not dimethyl sulfoxide;
>
> with the proviso that the hybridization composition does not contain formamide.

Appeal Br. 24 (Claims Appendix). Independent claim 2 is similar to claim 1, but requires the recited second n.a. sequence to be a part of the hybridization composition applied to the first n.a. sequence, rather than merely provided in the method, generally. *Id.* at 25.

The Specification states that:

> The present invention also relates to compositions and methods for eliminating the denaturation step from hybridization applications. In one embodiment, the present invention can be used for the *in vivo*, *in vitro*, and *in situ* molecular examination of DNA and RNA. In particular, the invention can be used for

> the molecular examination of DNA and RNA in the fields of cytology, histology, and molecular biology. In other embodiments, the present invention can be sued [*sic*] for *in situ* hybridization (ISH) applications.

Spec. 1:7–13. The Specification explains that "*in situ* hybridization (ISH), includes hybridization to a target in a specimen wherein the specimen may be *in vivo*, *in situ*, or for example, fixed or adhered to a glass slide." *Id.* at 1:23–25. The Specification further explains that in such a process, complementary strands of n.a.s must be separated in a step "termed 'denaturation,'" which "typically requires aggressive conditions." *Id.* at 2:4–5. The Specification states that traditionally in ISH assays, formamide solutions are used to denature the n.a., but that formamide is a toxic, hazardous material. *Id.* at 2:10–28. Denaturation, the Specification explains, is followed by the "hybridization" step, which includes binding primers or probes (n.a.s) to the target nucleic acid in the sample. *Id.* at 2:6–9.

The Specification states that the invention overcomes, *inter alia*, the drawbacks of traditional denaturation steps by reducing denaturation temperature, eliminating or reducing the use of formamide, or eliminating the denaturation step entirely. *Id.* at 3:11–13, 4:27–28. The key to this objective is explained to be the use of at least one polar aprotic solvent in an amount effective to denture double-stranded nucleotide sequences and enable hybridization. *Id.* at 5:3–8. The Specification identifies as suitable polar aprotic solvents γ-butyrolactone (GBL), sulfolane (SL), acetonitrile (AN), glycol sulfite/ethylene sulfite (GS), ethylene carbonate (EC), propylene carbonate (PC), ethylene thiocarbonate (ETC), ε-caprolactone,

and N-methyl pyrrolidinone. *Id.* at 7:10–15, 16:21–17:13; *see also id.* at 18–20 (Tables 2 and 3).

The Specification states that the polar aprotic solvent is a part of a "[h]ybridization composition," which it defines as "an aqueous solution of the invention for performing a hybridization procedure, for example, to bind a probe to a nucleic acid sequence," and states the composition "may comprise, *e.g.*, at least one polar aprotic solvent, at least one nucleic acid sequence, and a hybridization solution." *Id.* at 12:18–23. The Specification states that "'[h]ybridization solution' refers to an aqueous solution for use in a hybridization composition of the invention . . . and may comprise, *e.g.*, buffering agents, accelerating agents, chelating agents, salts, detergents, and blocking agents." *Id.* at 12:24–27.

The following rejections by the Examiner are on appeal:

A. Claims 1, 2, 5, 8–13, 15–23, 25–29, 35–38, 42–47, 55–58, and 62 stand rejected under 35 U.S.C. § 103(a) over Kim,[2] Bischoff,[3] Shimizu,[4] and Matthiesen.[5] Answer 3.

B. Claims 4–8, 24, 50, and 51 stand rejected under 35 U.S.C. § 103(a) over Kim, Bischoff, and Gray.[6] Answer 18.

C. Claim 14 stands rejected under 35 U.S.C. § 103(a) over Kim, Bischoff, and Kalra.[7] Answer 20.

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[2] US 5,750,340 (issued May 12, 1998) ("Kim").
[3] US 6,656,734 B1 (issued Dec. 2, 2003) ("Bischoff").
[4] US 2007/0166641 A1 (published July 19, 2007) ("Shimizu").
[5] US 2011/0281263 A1 (published Nov. 17, 2011) ("Matthiesen").
[6] US 6,475,720 B1 (issued Nov. 5, 2002) ("Gray").
[7] US 2003/0175852 A1 (published Sept. 18, 2003) ("Kalra").

D. Claims 29, 35–39, 41–43, 56–58, and 62 stand rejected under 35 U.S.C. § 103(a) over Kim, Bischoff, Bekki,[8] and Matthiesen. Answer 21.

E. Claims 35–38 and 52–54 stand rejected under 35 U.S.C. § 103(a) over Kim, Bischoff, Bresser,[9] and Matthiesen. Answer 23.

F. Claims 29, 37, 38, and 62 stand rejected under 35 U.S.C. § 103(a) over Kim, Bischoff, and Garcia.[10] Answer 26.

G. Claims 52–54 stand rejected under 35 U.S.C. § 103(a) over Kim, Bischoff, and Amorese.[11] Answer 28.

H. Claim 62 stands rejected under 35 U.S.C. § 103(a) over Kim, Bischoff, and Virtanen.[12] Answer 30.

I. Claims 1, 2, 5, 8–13, 15–23, 25–29, 35–38, 42–47, 55–58, and 62 stand rejected on the ground of obviousness-type double patenting over claims 49–52 of U.S. Patent No. 9,297,035 ("the '035 patent") and Bischoff and Kim. Answer 33.

J. Claims 4–8, 24, 50, and 51 stand rejected on the ground of obviousness-type double patenting over claims 49–52 of the '035 patent and Bischoff, Kim, and Gray. Answer 33.

K. Claim 14 stands rejected on the ground of obviousness-type double patenting over claims 49–52 of the '035 patent and Bischoff, Kim, and Kalra. Answer 35.

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[8] WO 2007/037341 A1 (published Apr. 5, 2007), and English language translated U.S. counterpart US 2009/0294305 A1 (published Dec. 3, 2009) (the latter of which is cited to herein as "Bekki").
[9] US 5,521,061 (issued May 28, 1996) ("Bresser").
[10] US 2006/0030541 A1 (published Feb. 9, 2006) ("Garcia").
[11] US 2004/0241666 A1 (published Dec. 2, 2004) ("Amorese").
[12] US 5,718,915 (issued Feb. 17, 1998) ("Virtanen").

L. Claims 29, 35–39, 41–43, 56–58, and 62 stand rejected on the ground of obviousness-type double patenting over claims 49–52 of the '035 patent and Bischoff, Kim, Bekki, and Matthiesen. Answer 37.

M. Claims 35–38 and 52–54 stand rejected on the ground of obviousness-type double patenting over claims 49–52 of the '035 patent and Bischoff, Kim, Bresser, and Matthiesen. Answer 38.

N. Claims 29, 37, 38, and 62 stand rejected on the ground of obviousness-type double patenting over claims 49–52 of the '035 patent and Bischoff, Kim, and Garcia. Answer 41.

O. Claims 52–54 stand rejected on the ground of obviousness-type double patenting over claims 49–52 of the '035 patent and Bischoff, Kim, and Amorese. Answer 42.

P. Claim 62 stands rejected on the ground of obviousness-type double patenting over claims 49–52 of the '035 patent and Bischoff, Kim, and Virtanen. Answer 44.

Q. Claims 1, 2, 4–29, 35–39, 41–47, 50–58, and 62 stand rejected on the ground of obviousness-type double patenting over claims 1–58 of U.S. Patent No. 9,309,562 ("the '562 patent"). Answer 45.

FINDINGS OF FACT

We generally agree with the Examiner's findings of fact and rationale for obviousness as set forth in the Final Action and Answer, as well as in the Final Action. *See* Final Action 2–43; Answer 3–57. However, although the Examiner cited Matthiesen in the prior art combination in the obviousness rejection of independent claims 1 and 2 (*see* Answer 3), the Examiner did

not discuss the reference substantively.[13] *Cf. id.* at 16. Furthermore, apparently at least partially for this reason, Appellant presents no substantive arguments over Matthiesen, arguing only that the Office Action does not explain how or why Matthiesen's teachings would be combined with the other cited prior art. Appeal Br. 18. Upon our review of the record, the Examiner's citation to, but failure to discuss Matthiesen in any depth is puzzling, particularly in view of the complexity of rejections presented in such absence of analysis. Thus, the following findings of fact (FF) highlight certain evidence of record:

FF1. Matthiesen was published on November 17, 2011, from an application filed May 27, 2009. Matthiesen, codes (43), (22). Therefore, it is prior art to the Appellant's claims, which have an earliest possible priority date of December 2, 2009.

FF2. Matthiesen discloses that its

> invention provides compositions and methods for the detection of nucleic acid sequences associated with chromosomal aberrations. The invention may, for example, eliminate the use of or reduce the dependence on formamide in hybridization. Compositions for use in the invention include an aqueous composition comprising at least one nucleic acid sequence and at least one polar aprotic solvent in an amount effective to denature double-stranded nucleotide sequences.

Matthiesen, Abstract.

FF3. Matthiesen discloses its

> invention relates generally to compositions and methods for detecting chromosomal aberrations in vivo, in vitro, and in situ. The present invention further relates to compositions comprising

[13] Each of the Examiner's § 103 rejections (and several of the obviousness-type double patenting rejections) rely in some way on Matthiesen, either directly or indirectly by claim dependency.

> molecular probes [n.a.s] for the detection of particular nucleotide sequences (including normal sequences and those associated with chromosomal aberrations and/or infectious disease) and aqueous compositions comprising at least one polar aprotic solvent in an amount sufficient to denature double-stranded nucleotide sequence for use in hybridization, particularly for use in in situ hybridization (ISH).

Matthiesen ¶ 1.

FF4. Matthiesen discloses its hybridization composition and procedure is non-toxic. Matthiesen ¶ 15.

FF5. Matthiesen expressly discloses:

> In one embodiment, the invention provides a method of determining whether a chromosomal aberration is present in a nucleic acid sequence, the method comprising:
>
> providing a molecular probe that detects the chromosomal aberration,
>
> providing the nucleic acid sequence,
>
> providing an aqueous composition comprising 1% (v/v) to 95% (v/v) of at least one polar aprotic solvent,
>
> combining the molecular probe and the nucleic acid sequence and the aqueous composition for at least a time period sufficient to hybridize the molecular probe and the nucleic acid sequence, and
>
> determining whether the molecular probe has hybridized to the nucleic acid sequence,
>
> thereby determining whether the chromosomal aberration is present in the nucleic acid sequence.

Matthiesen ¶¶ 168–174.

FF6. Further to the preceding finding of fact, Matthiesen also discloses "an aqueous composition of the invention comprising at least one polar aprotic solvent and a molecular probe that detects the chromosomal aberration," which is applied "to said nucleic acid

sequence for at least a time period sufficient to hybridize the molecular probe and nucleic acid sequence." Matthiesen ¶ 182.

FF7. Matthiesen further discloses, "[i]n one embodiment, the present invention relates to molecular probes for use in, e.g., the fields of cytology." Matthiesen ¶ 2. Matthiesen discloses that "[c]ytology involves the examination of individual cells," "fixed on [a] microscope slide," and "[c]ytological examination of a sample begins with obtaining a specimen of cells" where a biological sample can be "cell preparations . . . and isolated or enriched cell component preparations," treated "to preserve the tissue for later sample analysis." *Id.* ¶¶ 192–196. Matthiesen teaches that in this process, nucleic acids of the specimen are denatured at 82°C. *Id.* ¶ 197. Matthiesen teaches that hybridization in such a cytological process occurs *in situ*, in the sample cells. *Id.* ¶¶ 201–203.

FF8. Matthiesen discloses "[t]he hybridization compositions and methods of the invention may, for example, eliminate the use of, or reduce the dependence on, formamide." Matthiesen ¶ 43.

FF9. Matthiesen discloses using effective amounts of polar aprotic solvents at 1% to about 95% in hybridization compositions for denaturation of n.a.s. Matthiesen ¶¶ 43–45, 145.

FF10. Matthiesen discloses that its polar aprotic solvent can include γ-butyrolactone (GBL), sulfolane (SL), acetonitrile (AN), glycol sulfite/ethylene sulfite (GS), ethylene carbonate (EC), propylene carbonate (PC), ethylene thiocarbonate (ETC), s-caprolactone, and N-methylpyrrolidone, among many others. Matthiesen ¶¶ 58, 124–126, Tables 2 and 3; *see also id.* ¶¶ 48–58, 68,

114–127 (describing the properties and chemical structures of suitable polar aprotic solvents).

FF11. Matthiesen teaches the polar aprotic solvent in its hybridization composition can have a dispersion solubility parameter between 17.7–22.0 $MPa^{1/2}$, a polar solubility parameter between 13–23 $MPa^{1/2}$, and a hydrogen bonding solubility parameter between 3–13 $MPa^{1/2}$. Matthiesen ¶¶ 120–122.

FF12. Matthiesen teaches that "[t]he polar aprotic solvents specified in the present invention speed up this [denaturation and the reannealing of the probe to target] process considerably and reduce the harshness and toxicity of the hybridization conditions compared to formamide." Matthiesen ¶ 210.

FF13. Matthiesen teaches "the denaturation temperature is from 60 to 70° C., 70 to 80° C., 80 to 90° C. or 90 to 100° C., and . . . [i]n other embodiments, the compositions of the invention will produce strong signals when the denaturation temperature is 72, 82, or 92° C," and that the invention may allow for hybridization at room temperature. Matthiesen ¶¶ 43, 213.

FF14. Matthiesen teaches its hybridization process takes less than 8 hours, under 30 minutes, and even under 5 minutes. Matthiesen ¶ 215.

FF15. Matthiesen teaches that its composition can exclude DMSO. Matthiesen ¶ 127.

FF16. Matthiesen teaches that its composition can include components such as buffering agents (e.g., 0–1200 mM NaCl and/or 0–200 mM phosphate buffer, 1–50 mM citric acid–pH of 5.0–8.0),

accelerating agents (e.g., dextran sulfate at 1–80%), chelating agents, salts, detergents, and blocking agents (e.g., denatured salmon sperm DNA at 0.05–100 mg/mL). Matthiesen ¶¶ 130, 132, 135, 137, 140, 142.

FF17. Matthiesen teaches that its polar aprotic solvent may cause the compositions of its invention to exist as one phase, to separate into multi-phase systems under certain conditions, that some polar aprotic solvents may exist in two phases at room temperature, and that phases may be mixed. Matthiesen ¶¶ 150–151, 156.

FF18. Matthiesen is explicit that "[t]he compositions of the invention can be varied in order to optimize results for a particular application. For example, the concentration of polar aprotic solvent, salt, accelerating agent, blocking agent, and hydrogen ions (i.e. pH) may be varied in order to improve results for a particular application." Matthiesen ¶ 158.

FF19. Matthiesen teaches that, after its hybridization process, sample tissues are intact and maintain good cell morphology. Matthiesen ¶¶ 248, 260.

FF20. Matthiesen discloses that its sample nucleic acid can be DNA or RNA, i.e., double or single stranded nucleic acid sequences. Matthiesen ¶ 67.

FF21. Matthiesen discloses that its probe nucleic acid can be DNA or RNA, i.e., double or single stranded nucleic acid sequences. Matthiesen ¶ 81.

FF22. Matthiesen teaches that a heating (energy addition) step in its hybridization process uses microwaves, hot baths, hot plates, heat

wire, peltier element, induction heating, or heat lamps. Matthiesen ¶ 483.

FF23. Matthiesen discloses "the step of hybridizing includes the steps of heating and cooling the hybridization composition, molecular probe, and nucleic acid sequence." Matthiesen ¶ 486.

DISCUSSION

I. LEGAL STANDARDS

Arguments made by Appellant in the Appeal Brief and properly presented in the Reply Brief have been considered; arguments not so-presented are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2017); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

"To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996).

"The combination of familiar elements [or steps] according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). The test for obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991). "What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *KSR*, 550 U.S. at 419.

"[T]he law of obviousness-type double patenting looks to the law of obviousness generally. As . . . explained in *Amgen*, '[t]his part of the obviousness-type double patenting analysis is analogous to an obviousness analysis under 35 U.S.C. § 103.'" *AbbVie Inc. v. The Mathilda & Terrence Kennedy Inst. of Rheumatology Trust*, 764 F.3d 1366, 1378 (Fed. Cir. 2014) (second alteration in original) (citing *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1661 (Fed. Cir. 2009); *see also In re Braithwaite*, 379 F.2d 594, 600 n.4 (CCPA 1967) (A nonstatutory double patenting rejection is "analogous to the non-obviousness requirement of 35 U.S.C. 103," except that only the claims of, not the disclosure of, the reference patent underlying the double patenting rejection is considered prior art.).

With these standards in mind and in view of the Findings of Facts set forth above, we address the Examiner's rejections and Appellant's arguments there-over.

II. ANTICIPATION AND/OR OBVIOUSNESS OF CLAIMS 1, 2, 4–29, 35–39, 41–47, 50–58, AND 62 OVER MATTHIESEN

The Examiner developed an unnecessarily complicated series of obviousness rejections (*see supra* Statement of the Case) rejecting the claims primarily over Kim, Bischoff, Shimizu, and Matthiesen, adding Gray for the certain claims, Kalra for another claim, Bekki for other claims, Bresser for still other claims, Garcia for others, Amorese for still other claims, and, finally, adding Virtanen for the final claim, totaling eight separate obviousness rejections. *See generally* Answer. Such prior art combinations may indeed support an obviousness rejection, but make for a prosecution history that lacks clarity. As noted above, although citing and including it, generally, in the prior art combinations, the Examiner wholly overlooked the significance of Matthiesen. In the interest of clarifying the record, we will

not overlook Matthiesen's significance in view of the appealed claims. For this reason, we set forth a new ground of rejection of claims 1, 2, 4–29, 35–39, 41–47, 50–58, and 62 under (pre-AIA) 35 U.S.C. § 102(e) for anticipation and/or § 103(a) for obviousness over Matthiesen. *See* FF1.

Independent claim 1 is set forth above and independent claim 2 is discussed therewith. Matthiesen anticipates independent claims 1 and 2 in that it discloses a hybridization method, performed with a denaturation step at or below 82°C, including providing a first nucleic acid sequence in a cell sample, the cell morphology being preserved, and hybridizing a second nucleic acid sequence with the first using a hybridization composition including an effective amount of a polar aprotic solvent (these components can both be a part of a hybridization composition) within the cell (in an *in situ* cytology process) where, again, cell morphology is preserved; no DMSO is included in the process and no formamide is used in the process. FF2–FF10, FF13, FF15, FF19.

Regarding the dependent claims, the subject matter of each is either expressly disclosed by Matthiesen or would have been obvious in view of Matthiesen's express disclosure. These dependent claims are discussed below.

Claim 4 requires the first nucleic acid sequence to be in a cytology sample, which is disclosed by Matthiesen. FF7.

Claims 5–8 require various combinations of single and double stranded n.a. sequences for the claimed first and second n.a. sequences. This is taught by Matthiesen. FF20, FF21.

Claims 9–14 require providing enough energy, e.g., heating, during the process to denature and hybridize the claimed nucleic acid sequences, in

one or more steps, including by using, for example, a microwave. This is taught by Matthiesen. FF7, FF13, FF22, FF23. The specific temperatures or temperature ranges recited by claims 15–17 are also taught by Matthiesen. FF13. Likewise, the claimed heating and cooling of claim 18 is also taught by Matthiesen. FF23.

Claims 19–23 require certain time periods for the hybridizing to occur, e.g., as few as 5 minutes. This is disclosed by Matthiesen. FF14.

Claim 24 requires adding a blocking step to the process of claim 1. Matthiesen teaches this. FF16.

Claims 25–28 require certain amounts of the polar aprotic solvent in the hybridization composition, e.g., as much as 95% and as little as 1%. This is disclosed by Matthiesen. FF9.

Claim 29 requires that the polar aprotic solvent be non-toxic. Matthiesen teaches this. FF4, FF10, FF12.

Claim 35 recites specific solubility and bonding characteristics of the claimed polar aprotic solvent. These characteristics are disclosed by Matthiesen. FF11.

Claims 36–39 and 41–43 require specific classes or types of polar aprotic solvents. These claimed polar aprotic solvents are disclosed by Matthiesen. FF10.

Claims 44–47 and 50–54 require additional components for the hybridization composition, for example, buffering agents salts, accelerating agents, chelating agents, detergents, and blocking agents, as well as specific types thereof in certain concentrations or amounts. All of this is disclosed, or at the least taught or suggested by Matthiesen. FF16, FF18 (any specific amounts not disclosed by Matthiesen are taught thereby to be optimized).

Claims 55–58 require the hybridization composition to be in single, two, or mixed phases at room temperature. Matthiesen discloses this. FF17.

Finally, claim 62 mixes several of the limitations/steps discussed above, for example, combining n.a.s in a cell, preserving cell morphology, hybridizing (by combining the composition and n.a.s for sufficient time), and heating and cooling the mixture. As discussed above, this is taught or suggested by Matthiesen. *See, e.g.*, FF5–FF7, FF13, FF14, FF19, FF23.

As set forth above, Matthiesen discloses within its four corners each and every limitation and step of each claim on appeal, in the same fashion as claimed. Thus, Matthiesen anticipates each claim. If, for any reason, it should be considered that Matthiesen fails to explicitly disclose, or that the skilled artisan would fail to at once envisage based on Matthiesen's disclosure, any limitation or step as set forth in the appealed claims, it is apparent that such would be a mere obvious modification of Matthiesen's teachings, for example, by optimizing any parameters taught by Matthiesen, which Matthiesen explicitly suggests. Therefore, we set forth a new ground of rejection of claims 1, 2, 4–29, 35–39, 41–47, 50–58, and 62 under (pre-AIA) 35 U.S.C. § 102(e) and/or § 103(a) for anticipation and/or obviousness over Matthiesen.

As for the rejections appealed here, we address Appellant's arguments, as they are set forth in Appellant's briefing, below.

Appellant argues that Kim and Bischoff would not have been combined because Bischoff is non-analogous art as directed to cell transfection using a polar aprotic solvent, which is very different from hybridizing nucleic acids with such a solvent. Appeal Br. 8–11.

In response, the Examiner argues that the claimed methods hybridize nucleic acids inside cells (Examiner points to claim 62, however, this also applies to claims 1 and 2, which recite that the nucleic acids "hybridize within the cell") and, therefore, Bischoff's transfection is reasonably pertinent to the claims, making the reference analogous to the claimed invention. Answer 48. Examiner also argues that Bischoff's transfection with polar aprotic solvent is useful for allowing nucleic acids into cells, which is required by Kim, making the two references analogous to one another. *Id.* at 46–47.

Appellant's arguments are not persuasive. Although we agree with the Examiner's position, Appellant's argument is mooted by the new ground of rejection set forth above.

Appellant also argues that Kim teaches away from the claimed invention, which requires denaturation at or below 82°C (if it occurs), but Kim discloses that upon testing the non-formamide solution (glycerol solution) in denaturation at temperatures ranging from 80°C–115°C, Kim reported that the range of 95°C–105°C was "most effective" and temperatures lower than 85°C showed the fluorescence signals to be "considerably diminished." Appeal. Br. 12–14 (citing Kim 2:56–63, 9:61–10:12). Based on this disclosure, Appellant contends:

> No person of ordinary skill in the art would read Kim's study of denaturation temperature and believe that denaturing at or below 82°C without formamide was achievable. Nor would any person believe that denaturing with Kim's solutions could be optimized by lowering the temperature since Kim established an optimal temperature of 100°C (at least with respect to Kim's solutions).

Id. at 14. Appellant further argues that such statements in Kim establish that the skilled artisan would have no reasonable expectation of success in

hybridizing n.a. sequences using a denaturation step at or below 82°C. *Id.* at 15.

In response, the Examiner points to Kim's Example 2 as teaching a denaturation step performed at 75°C. Answer 52 (citing Kim 6:10–15 (Example 2)). Appellant counter-argues that even in reading such disclosure in Kim, the skilled artisan "would not believe that this was true, in light of Kim's many other passages stating that a denaturation temperature of 100°C±5°C should be used, and Kim's experimental data showing that a denaturation temperature below 85°C was ineffective." Appeal Br. 15 (citing Kim 7:55–57, 11:31, 16:11–12).

Appellant's arguments are not persuasive. Although we agree with the Examiner's position, Appellant's argument is mooted by the new ground of rejection set forth above.

Appellant argues Bekki does not teach using its polar aprotic solvent in hybridizing n.a. sequences, but as a part of detecting analytes using photocurrent (photoexciting sensitizing dye) and, further, Bekki's methods may result in destruction of cells rather than preserving sample morphology, as claimed (Appellant states "Bekki is ambivalent" on this). Appeal Br. 17–18. Appellant argues that this potential cell destroying method would lead a skilled artisan to not substitute Bekki's polar solvents in Kim's hybridization method and would foreclose a reasonable expectation of success in preserving sample morphology if Bekki's solvents were used. *Id.* at 18.

The Examiner responds that Bekki specifically teaches an n.a. hybridization solution including cyclic ethylene carbonate and propylene carbonate. Answer 54 (citing Bekki ¶ 72). Regarding Bekki's disclosure of destroying cells (at ¶ 80), the Examiner identifies that this disclosure of the

reference is not related to hybridization or use of the polar aprotic solvent as a hybridization solution, but to extracting n.a. from cells to provide an analyte. *Id.*

Appellant's arguments are not persuasive. Although we agree with the Examiner's position, Appellant's argument is mooted by the new ground of rejection set forth above.

Appellant argues that the claims require a hybridization composition that does not contain formamide, but Bresser's hybridization composition includes 30% formamide. Appeal Br. 19 (citing Bresser 8:65–9:5). Thus, Appellant argues, the skilled artisan would not arrive at the claimed composition in view of Bresser's taught solvents. *Id.*

In response, the Examiner argues the cited portions of Bresser discuss using the claimed solvent as a permeation enhancer and as an additive, thus, it would have been obvious to combine it with the compositions of Kim and Bischoff for the same purpose. Answer 54–55 (citing Bresser Abstract, Example 5).

Appellant's arguments are not persuasive. Although we agree with the Examiner's position, Appellant's argument is mooted by the new ground of rejection set forth above.

Appellant argues that Garcia does not teach hybridizing an n.a. to another in a cell, but rather introducing an n.a. into a cell using a synthetic vector and a polar aprotic compound so that the n.a. is expressed. Appeal Br. 19–20. Appellant appears to argue that this is, in essence, a teaching away from the claimed hybridization.

The Examiner responds that Garcia is cited for teaching "the functionally equivalent solvent or acetonitrile," which provides the

advantage of providing a high level of transfection. Answer 55 (citing Garcia ¶ 93). The Examiner argues that, because of this functional equivalence, it would be obvious to modify the other prior art to use the solvent acetonitrile. *Id.*

Appellant's arguments are not persuasive. Although we agree with the Examiner's position, Appellant's argument is mooted by the new ground of rejection set forth above.

Appellant argues Amorese requires the use of formamide, thus, the skilled artisan would not arrive at the claimed invention using Amorese's solvents. Appeal Br. 20.

The Examiner responds that Amorese is cited for teaching alternative pH and use of phosphate as a buffering agent, but, even were Amorese's teachings not relied upon, the claimed pH range would have been obvious based on its close similarity to that taught by the other cited prior art or upon routine optimization of the ranges taught by the other cited prior art. Answer 55–56.

Appellant's arguments are not persuasive. Although we agree with the Examiner's position, Appellant's argument is mooted by the new ground of rejection set forth above.

Appellant argues that Kim and Gray teach hybridization compositions including formamide, while Virtanen teaches polar aprotic solvents, such as acetonitrile to hybridize n.a.s outside a cell to generate supramolecules. Appeal Br. 20. Appellant argues that, because Virtanen hybridizes outside a cell, it would not be relied upon to arrive at the claimed invention or modify the teachings of Bischoff and Kim. *Id.* at 20–21.

The Examiner points out that Gray is not a part of the prior art combination for the argued rejection (it was in the prior art combination under Rejection B, discussed above). Answer 56. The Examiner further responds that Kim has been identified as teaching solvents free of formamide and Virtanen is relied upon for teaching the functionally equivalent solvent acetonitrile. *Id.*

Appellant's arguments are not persuasive. Although we agree with the Examiner's position, Appellant's argument is mooted by the new ground of rejection set forth above.

Although we discern no error in the Examiner's determinations, which we conclude presented a prima facie case for the claims' obviousness over the cited prior art combinations, we nonetheless find the Examiner's rejections overly complicated and confusing. However, as discussed above, we have considered Appellant's arguments over the rejections in their entirety, but find them unpersuasive on the record on appeal.

III. OBVIOUSNESS-TYPE DOUBLE PATENTING

Under the doctrine of obviousness-type double patenting, the Examiner set forth another eight rejections of Appellant's claims over the claims of the '035 patent, in view of the teachings, again, of Kim, Bischoff, Matthiesen, Gray, Kalra, Bekki, Bresser, Garcia, Amorese, and Virtanen, and another rejection over claims of the '562 patent individually.

Appellant does not expressly argue the eight double patenting rejections over the '035 patent on their merits, but only refers to the arguments made over the obviousness rejections regarding the common, cited prior art, stating that the office action is not specific in identifying

which limitations are found in the claims of the ’035 patent and which are in the other cited prior art. Appeal Br. 21.

As discussed above, the subject matter for which the various prior art was cited can be found in Matthiesen, which, again, the Examiner generally overlooked in his analysis. Although Matthiesen was cited in the obviousness-type double patenting rejection as combined with the ’035 patent’s claims, for the same reasons set forth above, we herein substitute Matthiesen’s teachings for the teachings of each of Kim, Bischoff, Gray, Kalra, Bekki, Bresser, Garcia, Amorese, and Virtanen, and, therefore, designate the affirmance of the obviousness rejection over the ’035 patent’s claims as a new ground.

Similarly, regarding the rejection over the ’562 patent, Appellant argues the office action is not specific as to how the claim limitations are found in the ’562 patent’s claims or in the other cited prior art and does not explain how the ’562 patent’s claims disclose or suggest the pending claims’ elements. Appeal Br. 22.

THE REJECTION OVER THE ’562 PATENT

We begin with a discussion of the rejection over the ’562 patent. Claim 1 of the ’562 patent is reproduced below:

> 1. A method of hybridizing nucleic acid sequences comprising:
>
> providing a first nucleic acid sequence within a sample having a preserved cell morphology, with a first composition comprising at least one polar aprotic solvent in an amount effective to denature a double-stranded nucleotide sequence while preserving cell morphology, and at least 10% dextran sulfate,
>
> providing a second nucleic acid composition comprising a second nucleic acid sequence and a second aqueous composition

> comprising at least one denaturing agent in an amount effective to denature double-stranded nucleotide sequences, and
>
> combining the first and the second nucleic acid sequence compositions for at least a time period sufficient to hybridize the first and second nucleic acid sequences such that the cell morphology is preserved,
>
> wherein the polar aprotic solvent is not dimethyl sulfoxide (DMSO).

The '562 patent 58:48–67. Claim 14 of the '562 patent indirectly depends from claim 1 and adds the requirement that the denaturing takes place between 70–80°C. *Id.* at 60:5–7. Claim 34 of the '562 patent also depends from claim 1 and requires that the claimed composition does not contain formamide. *Id.* at 60:57–58.

Based on this subject matter claimed in the '562 patent as compared to the steps of Appellant's claims 1 and 2, we conclude the Examiner established that the appealed claims would have been obvious over the claims of the '562 patent. As noted, the Appellant does not provide any substantive argument over this rejection; we affirm the rejection.

THE REJECTION OVER THE '035 PATENT

Turning next to the rejection over the '035 patent, we find it similarly cumbersome compared with the Examiner's obviousness rejections discussed above because it relies on various combinations of ten different prior art references with the claims of the '035 patent when Matthiesen alone would have sufficed. Rather than simply affirming the Examiner's eight rejections over the '035 patent in view of the various cited prior art combinations, we set forth a new ground under the doctrine of obviousness-type double patenting over the claims of the '035 patent in view of Matthiesen.

Independent claim 1 of the '035 patent is reproduced below:

> 1. A composition comprising:
>
> (a) a first molecular probe that detects a nucleotide sequence associated with a chromosomal aberration,
>
> (b) at least one polar aprotic solvent in an amount effective to denature double-stranded nucleotide sequences within a sample having a preserved cell morphology, and
>
> (c) a hybridization solution,
>
> wherein the nucleotide sequence is a marker for a chromosomal aberration,
>
> wherein the polar aprotic solvent has lactone, sulfone, sulfite, nitrile, and/or carbonate functionality, and
>
> wherein the polar aprotic solvent has a cyclic base structure.

The '035 patent, 55:56–56:4. Further, the '035 patent's claim 29 requires that the polar aprotic solvent be non-toxic; claim 30 requires that the composition not contain formamide; and claim 33 requires the polar aprotic solvent be selected from a list overlapping the solvents of appealed claims 38 and 43. *Id.* at 58:24–27, 58:63–59:8. This subject matter would have rendered obvious the subject matter of appealed independent claims 1 and 2, particularly in view of Matthiesen, as discussed above. *See* FF1–FF23. Furthermore, the subject matter of each appealed dependent claim is taught or suggested by Matthiesen, as discussed above. *Id.*; *see also supra* Discussion, Section II. For these reasons, the appealed claims would have been obvious over the claims of the '035 patent in view of Matthiesen.

We appreciate that Matthiesen is the published version of the application that issued as the '035 patent and, therefore, shares the same specification, and we acknowledge the general rule that an earlier patent's

specification is not available as prior art to show obviousness-type double patenting. *See Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1385 (Fed. Cir. 2003). However, here, Matthiesen is also prior art under 35 U.S.C. § 102(e), therefore, its specification can be consulted like any other prior art reference in combination with the claims of the '035 patent. *See* FF1.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s) /Basis	Affirmed	Reversed	New Ground
1, 2, 5, 8–13, 15–23, 25–29, 35–38, 42–47, 55–58, 62	103(a)	Kim, Bischoff, Shimizu, Matthiesen	1, 2, 5, 8–13, 15–23, 25–29, 35–38, 42–47, 55–58, 62		
4–8, 24, 50, 51	103(a)	Kim, Bischoff, Gray	4–8, 24, 50, 51		
14	103(a)	Kim, Bischoff, Kalra	14		
29, 35–39, 41–43, 56–58, 62	103(a)	Kim, Bischoff, Bekki, Matthiesen	29, 35–39, 41–43, 56–58, 62		
35–38, 52–54	103(a)	Kim, Bischoff, Bresser, Matthiesen	35–38, 52–54		
29, 37, 38, 62	103(a)	Kim, Bischoff, Garcia	29, 37, 38, 62		
52–54	103(a)	Kim, Bischoff, Amorese	52–54		

Claims Rejected	35 U.S.C. §	Reference(s) /Basis	Affirmed	Reversed	New Ground
62	103(a)	Kim, Bischoff, Virtanen	62		
1, 2, 5, 8–13, 15–23, 25–29, 35–38, 42–47, 55–58, 62		Nonstatutory Double Patenting	1, 2, 5, 8–13, 15–23, 25–29, 35–38, 42–47, 55–58, 62		
4–8, 24, 50, 51		Nonstatutory Double Patenting	4–8, 24, 50, 51		
14		Nonstatutory Double Patenting	14		
29, 35–39, 41–43, 56–58, 62		Nonstatutory Double Patenting	29, 35–39, 41–43, 56–58, 62		
35–38, 52–54		Nonstatutory Double Patenting	35–38, 52–54		
29, 37, 38, 62		Nonstatutory Double Patenting	29, 37, 38, 62		
52–54		Nonstatutory Double Patenting	52–54		
62		Nonstatutory Double Patenting	62		
1, 2, 4–29, 35–39, 41–47, 50–58, 62		Nonstatutory Double Patenting	1, 2, 4–29, 35–39, 41–47, 50–58, 62		
1, 2, 4–29, 35–39, 41–47, 50–58, 62	102(e)	Matthiesen			1, 2, 4–29, 35–39, 41–47, 50–58, 62

Claims Rejected	35 U.S.C. §	Reference(s) /Basis	Affirmed	Reversed	New Ground
1, 2, 4–29, 35–39, 41–47, 50–58, 62	103(a)	Matthiesen			1, 2, 4–29, 35–39, 41–47, 50–58, 62
1, 2, 4–29, 35–39, 41–47, 50–58, 62		Nonstatutory Double Patenting			1, 2, 4–29, 35–39, 41–47, 50–58, 62
Overall Outcome			1, 2, 4–29, 35–39, 41–47, 50–58, 62		1, 2, 4–29, 35–39, 41–47, 50–58, 62

TIME PERIOD FOR RESPONSE

This Decision contains new grounds of rejection pursuant to 37 C.F.R. § 41.50(b), which provides, "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review." 37 C.F.R. § 41.50(b) also provides:

> When the Board enters such a non-final decision, the appellant, within two months from the date of the decision, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:
>
> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.

> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in MPEP § 1214.01.

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; 37 C.F.R. § 41.50(b)