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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KALLE GÜNTHER, RALF WYRICH, and UWE OELMÜLLER

Appeal 2019-006621
Application 14/423,062
Technology Center 1600

Before DONALD E. ADAMS, ULRIKE W. JENKS, and ELIZABETH A. LAVIER, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from Examiner's decision to reject claims 1–22 (*see* Final Act.[2] 3). We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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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 "Qiagen GmbH" (Appellant's April 30, 2019 Appeal Brief (Appeal Br.) 4).

[2] Examiner's April 16, 2018 Final Office Action.

STATEMENT OF THE CASE

Appellant's disclosure relates "to the isolation of nucleic acids from samples that were stabili[z]ed using a formaldehyde releaser" (Spec. 1).

Appellant's claims 1, 11, 14, 15, 19, and 21 are reproduced below:

> 1. A method for isolating nucleic acids from a stabilized sample or portion or fraction of the stabilized sample, wherein the sample stabilization involved the use of at least one formaldehyde releaser, comprising:
>
> step (a) lysing the stabilized sample or portion or fraction of the stabilized sample *in the presence of at least one cationic detergent* to provide a lysed sample, and
>
> step (b) isolating nucleic acids from the lysed sample.

(Appeal Br. 33 (emphasis added).)

> 11. The method according to claim 1, wherein the sample was stabilized using a stabilization composition comprising:
>
> a) a formaldehyde releaser agent selected from a chemical fixative that contains urea; and
>
> b) at least one, two or all of the following components:
>
> (i) an enzyme inhibitor;
>
> (ii) a metabolic inhibitor; and
>
> (iii) a metal ion chelator.

(*Id.* at 38.)

> 14. The method according to claim 1, wherein
>
> - the sample is blood,
>
> - the blood stabilization involves the use of at least one formaldehyde releaser and at least one anticoagulant,
>
> - step (a) comprises:
>
> step (a)(l) obtaining the stabilized blood sample or a portion or fraction of the stabilized sample wherein the portion or fraction of the stabilised blood sample is selected from blood cells; and

step (a)(2) contacting the stabilized blood sample or the portion or fraction of the stabilized sample with at least one cationic detergent to provide a lysed sample;

and

- the nucleic acids isolated in step (b) comprise or consist of RNA.

(*Id.* at 39.)

15. The method according to claim 14, wherein

the formaldehyde releaser is selected from a heterocyclic urea, diazolidinyl urea and imidazolidinyl urea, and

in step (a)(2), the cationic detergent is selected from the group consisting of:

a) a cationic compound of the general formula (1):

$Y^+R_1R_2R_3R_4X$"(1)

wherein,

Y represents nitrogen or phosphorus,

$R_1R_2R_3$ and R_4 independently represent a branched or unbranched C_1-C_{20}-alkyl group, a C_6-C_{20}-aryl group or a C_6-C_{26} aralkyl group;

X" represents an anion of an inorganic monobasic acid, an inorganic polybasic acid, an organic monobasic acid, or an organic polybasic acid;

b) a detergent comprising, under the used lysis conditions, a charged quaternary ammonium cation as a polar head group;

c) a cationic detergent obtained in a composition comprising

(i) an amino surfactant having the following formula (2):

R1R2R3N(O)x (2)

wherein,

R1 and R2 each independently is H, C_1-C_{20} alkyl residue, C_6-C_{26} aryl residue or C_6-C_{26} aralkyl residue,

R3 is C_1-C_{20} alkyl group, C_6-C_{26} aryl residue or C_6-C_{26} aralkyl residue,

X is an integer of 0 and 1 and

(ii) an acid or acid salt;

d) a cationic detergent obtained from an amino surfactant selected from the group consisting of the protonated forms of dodecylamine, N- methyldodecylamine, N, N-dimethyldodecylamine, N, N- dimethyldodecylamine N oxide and 4-tetradecylaniline;

e) a cationic detergent comprising a permanently charged quaternary ammonium cation as polar head group; or

f) a cationic detergent selected from the group consisting of cetyl trimethyl ammomum bromide, tetra decyl trimethyl ammomum bromide,[]dodecyl trimethyl ammonium bromide, cetyl trimethyl ammonium chloride, tetra decyl trimethyl ammonium chloride, and dodecyl trimethyl ammonium chloride; or

step (a)(l) uses a lysis composition comprising:

(i) a cationic compound of the general formula (1):

$$Y^{+}R_1R_2R_3R_4X^{-} \quad (1)$$

wherein Y represents nitrogen or phosphor, $R_1R_2R_3$ and R_4 independently represent a branched or unbranched C_1-C_{20}-alkyl group, a C_6-C_{20}-aryl group or a C_6-C_{26} aralkyl group;

X^{-} represents an anion of an inorganic monobasic acid, an inorganic polybasic acid, an organic monobasic acid, or an organic polybasic acid; and

(ii) at least one proton donor;

or

(i) an amino surfactant having the following formula (2):

$$RIR2R3N(O)x \quad (2)$$

wherein,

R1 and R2 each independently is H, C_1-C_6 alkyl residue, C_6-C_{12} aryl residue or C_6-C_{12} aralkyl residue,

R3 is C_1-C_{20} alkyl group, C_6-C_{26} aryl residue or C_6-C_{26} aralkyl residue,

X is an integer of 0 and 1 and

(ii) an acid or acid salt;

- step (a) further comprises incubating the composition comprising the stabilized sample or the portion or fraction of the stabilized sample, the at least one cationic detergent and

optionally one or more further lysis agents to provide the lysed sample; and

- step (b) comprises the following steps:

step (i) contacting the lysed sample or a nucleic acid containing portion obtained from the lysed sample with one or more additional lysing agents thereby providing a lysis mixture;

- optionally removing DNA from the lysis mixture;

step (ii) adding alcohol to the lysis mixture to adjust the binding conditions and binding RNA to a nucleic acid binding solid phase;

step (iii) separating the solid phase with the bound RNA from the remaining sample; and

step (iv) optionally washing the RNA; and

step (v) optionally eluting RNA from the solid phase.

(*Id.* at 40–42.)

19. The method according to claim 11, wherein the metabolic inhibitor is glyceraldehyde, sodium fluoride, or both glyceraldehyde and sodium fluoride.

(*Id.* at 42.)

21. The method of claim 1, wherein the cationic detergent is obtained in a composition comprising (i) an amino surfactant having the following formula (2):

R1R2R3N(O)x (2)

wherein,

R1 and R2 each independently is H, C_1-C_6 alkyl residue, C_6-C_{12} aryl residue or C_6-C_{12} aralkyl residue,

R3 is C_1-C_{20} alkyl group, C_6-C_{26} aryl residue or C_6-C_{26} aralkyl residue,

X is an integer of 0 and 1 and

(ii) an acid or acid salt.

(*Id.* at 42–43.)

Grounds of rejection before this Panel for review:

Claims 1–18 and 20 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan[3] and Weisburg.[4]

Claim 19 stands rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan, Weisburg, and Fernando.[5]

Claims 21 and 22 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan, Weisburg, and Kappel.[6]

Claims 1–14, 16–18, 21, and 22 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan and Kappel.

Claims 15 and 20 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan, Kappel, and Weisburg.

Claim 19 stands rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan, Kappel, and Fernando.

ISSUE

Does the preponderance of evidence relied upon by Examiner support a conclusion of obviousness?

FACTUAL FINDINGS (FF)

FF 1. Ryan discloses:

> A method for isolating nucleic acids is disclosed, wherein a sample having nucleic acid containing starting material is fixed, lysed, and treated to remove unwanted contaminants. The initial fixing of the sample aids in maintaining the structure and

[3] Ryan et al., US 2009/0081678 A1, published Mar. 26, 2009.
[4] Weisburg et al., US 2009/0048439 A1, published Feb. 19, 2009.
[5] Fernando, US 2010/0209930 A1, published Aug. 19, 2010.
[6] Kappel et al., US 2004/0259162 A1, published Dec. 23, 2004.

> integrity of the isolated DNA and reduces the incidence of end product contaminants and DNA shearing.

(Ryan, Abstract; *see id.* ¶ 2 (Ryan "relates to DNA isolation from a biological sample and more particularly to the isolation of DNA from whole blood having been fixed and preserved"); *id.* ¶ 19 (Ryan's "samples from which the nucleic acids may be isolated include any biological sample including whole blood"); *see* Ans. 4 and 13.)

FF 2. Ryan's method comprises suspending a sample in a fixative agent, such as the formaldehyde releaser, diazolidinyl urea, contacting the sample with a nucleus lysis buffer comprising a buffer, a chelating agent, such as EDTA, and an anionic surfactant, contacting the sample with proteinase K and contacting the sample with ethanol (*see* Ryan ¶¶ 9–11; *see also* Ans.[7] 4, 13, and 19; Spec. 10: 21–22 (Appellant discloses diazolidinyl urea as a preferred formaldehyde releaser)).

[7] Examiner's July 12, 2019 Answer.

FF 3. Ryan's Figure 2 is reproduced below:

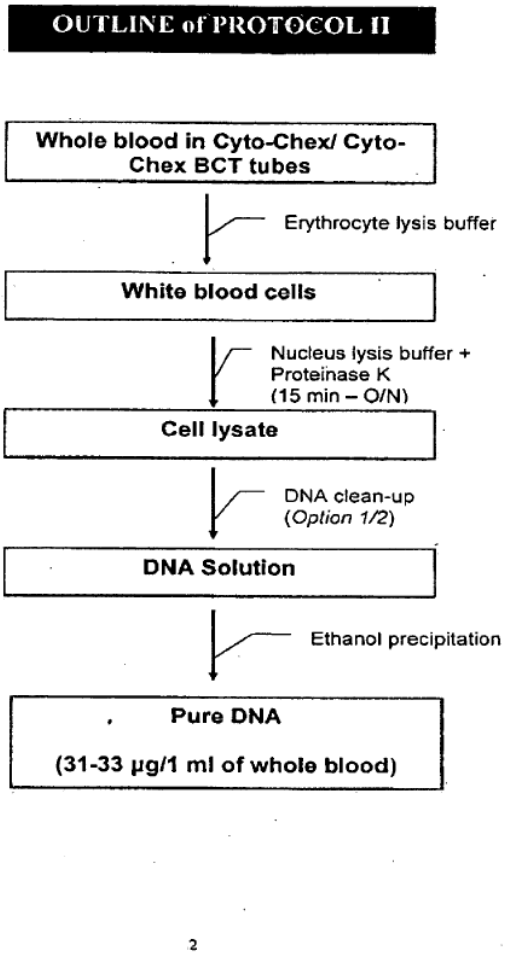

FIGURE 2

"FIG. **2** is a flow diagram illustrating an example protocol for [Ryan's] DNA isolation method" (Ryan ¶ 17; *see generally* Ans. 4–5).

FF 4. Ryan discloses that its "nucleus lysis buffer includes ingredients selected from the group consisting of a chelating agent, a buffer, an anionic surfactant, a polysorbate surfactant, a non-ionic surfactant, and a chaotrope (Ryan ¶ 15; *see* Ans. 5, 13, and 19).

FF 5. Ryan discloses that its "erythrocyte lysis buffer includes ammonium chloride, ammonium bicarbonate, and a chelating agent, the chelating agent is EDTA" (Ryan ¶ 15; *see also id.* ¶ 29 (Ryan discloses that its "erythrocyte

lysis buffer . . . may contain NH_4Cl, NH_3HCO_3, EDTA, sodium dodecyl sulfate, NaOH, sodium citrate, sodium acetate, citric acid, HCl, cacodylic acid sodium salt, sodium dihydrogen phosphate, disodium hydrogen phosphate, imidazole, triethenolamine hydrochloride, tris-HCl, or combinations thereof"); *see* Ans. 5 (Examiner finds that Ryan discloses "the use of cationic (i.e., ammonium) salts during [a] lysis" step); *id.* at 19).

FF 6. Examiner finds that Ryan does not disclose that the "cationic ammonium salt is a detergent" (Ans. 5; *see also id.* at 13 (Examiner finds that Ryan does not disclose Appellant's "claimed cationic amine oxide and salt of species c) of [Appellant's] claim 2")).

FF 7. Weisburg discloses "[s]olid supports and methods for isolating nucleic acid molecules" (Weisburg ¶ 4; *see* Ans. 5 and 20 (citing Weisburg ¶¶ 5, 20, 122, and 125–132) (Examiner finds that Weisburg discloses "a method wherein a lysis mixture has alcohol added thereto so as to bind to a solid phase . . . that the solid phase is separated, optionally washed, and the nucleic acids are then eluted . . . and that the isolated nucleic acids comprise RNA")).

FF 8. Weisburg discloses that a "sample can be a solution containing eukaryotic or prokaryotic cells or cellular material, or virus or viral material, or bacteria or bacterial material or microorganisms or pathogens" (Weisburg ¶ 41; *see also id.* ¶ 113 (Weisburg discloses that "[n]ucleic acid molecules can be isolated from any sample containing them"); *id.* ¶ 122 (Weisburg exemplifies blood as a sample starting material); *see* Ans. 5).

FF 9. Weisburg discloses that "a chaotropic buffer . . . can function as a lysis buffer, whereby lysis of any cells, viruses, or associated matrices or packaging, is initiated to release all of the nucleic acid present in the starting

material" and that "[o]ther denaturants, or detergents, also can be included in the buffer to aid extraction and subsequent precipitation of nucleic acids from such starting material," wherein "[t]he detergent can act to solubilize the sample" (Weisburg ¶ 120; *see* Ans. 5).

FF 10. Weisburg discloses that the detergent may be ionic or nonionic and exemplifies the cationic detergent "cetyltrimethylammoniumbromide (CTAB)" (Weisburg ¶ 120; *see* Ans. 5).

FF 11. Examiner finds that the combination of Ryan and Weisburg fails to suggest a stabilization composition comprising sodium fluoride (Ans. 11).

FF 12. Fernando "relates to the identification and isolation of cell-free nucleic acids in blood samples and more particularly to the preservation of cell-free RNA within a blood sample" (Fernando ¶ 2).

FF 13. Fernando discloses a method comprising contacting a blood sample with a protective agent, wherein "[t]he protective agent may include one or more preservative agents, [such as the formaldehyde releaser, diazolidinyl urea,] one or more enzyme inhibitors, [such as glyceraldehydes,] one or more metabolic inhibitors, [such as sodium fluoride,] or any combination thereof" (Fernando ¶¶ 9–10).

FF 14. Examiner finds that the combination of Ryan and Weisburg fails to disclose detergents within the scope of Appellant's claims 21 and 22 (Ans. 12).

FF 15. Examiner finds that Kappel discloses "the lysis of cells using combinations of detergents, including N,N-dimethyldodecylamine oxide, which [Examiner finds] meets the claimed formula, and docusate sodium salt, which [Examiner finds] is an acid salt" and detergents, including

CTAB, "useful for lysing animal and bacterial cells" to obtain DNA (*see* Ans. 12 (citing Kappel ¶¶ 110 and 118); *see also* Ans. 15).

FF 16. Examiner finds that Kappel discloses:

> combinations of detergents, including N,N-dimethyldodecylamine oxide, which meets the claimed formula, and docusate sodium salt, which is an acid salt (paragraph 0110); thus, R1 and R2 are C1 (i.e., methyl), R3 is dodecyl (i.e., unbranched C12), and X is 1, docusate sodium salt, which is the acid salt. The lysis buffer further comprises a chaotropic agent (paragraph 0116) and a protease and salt (paragraph 0117). Kappel et al also teach the proton donor TrisHCl (paragraph 0117), and that the isolated nucleic acids comprise RNA (paragraph 0033), as well as binding to a solid phase and washing (paragraph 0091).

(Ans. 19.)

FF 17. Examiner finds that "[n]either Kappel . . . nor Ryan . . . explicitly teach adding alcohol and binding RNA" (Ans. 19).

FF 18. Examiner finds that the combination of Ryan and Kappel fails to suggest a stabilization composition comprising sodium fluoride (Ans. 21).

ANALYSIS

The rejection over the combination of Ryan and Weisburg:

Based on the combination of Ryan and Weisburg, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to solubilize Ryan's sample using Weisburg's lysis buffer that comprises the cationic detergent CTAB (*see* Ans. 5; *see also* FF 1–10). As Examiner explains, a person of ordinary skill in the art would have found it prima facie obvious to utilize known techniques as disclosed by the combination of Ryan and Weisburg to achieve the predictable result of prepping and lysing a sample for nucleic acid isolation (*see id.* at 4–5).

Appellant and Examiner agree that Ryan does not disclose a cationic surfactant (*see* Appeal Br. 16; *see also* Reply Br. 3 (Ryan "does not teach or suggest the inclusion of any cationic surfactants" (emphasis omitted)); FF 6). Appellant recognizes, however, that Weisburg discloses a number of different detergents that "may be used to solubilize a sample," including the cationic detergent, CTAB (Appeal Br. 16; *see also* Reply Br. 3). Thus, the combination of Ryan and Weisburg discloses that a sample may be lysed using a variety of different reagents, including a lysis buffer comprising CTAB. Therefore, we are not persuaded by Appellant's contention that "it is not apparent why a person of ordinary skill in the art would have been motivated by Weisburg . . . to use cationic detergents in the method of Ryan" (Appeal Br. 17; *see id.* (Appellant recognizes that "the disclosure of Weisburg . . . shows that a skilled artisan could have replaced various surfactants of Ryan . . . with a cationic detergent of Weisburg").

We are not persuaded by Appellant's contention that Weisburg does not exemplify the use of CTAB (*see* Appeal Br. 16–17). A reference disclosure is not limited only to its preferred embodiments, but is available for all that it discloses and suggests to one of ordinary skill in the art. *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976); *see also In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971) (explaining that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments).

As Examiner explained, a person of ordinary skill in the art would have found it prima facie obvious to utilize known techniques as disclosed by the combination of Ryan and Weisburg to achieve the predictable result of prepping and lysing a sample for nucleic acid isolation (*see* Ans. 4–5; *see*

also Appeal Br. 17 (Appellant recognizing that "the disclosure of Weisburg . . . shows that a skilled artisan could have replaced various surfactants of Ryan . . . with a cationic detergent of Weisburg"). *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). Therefore, we are not persuaded by Appellant's contention that Examiner "failed to articulate why the combination of Ryan . . . and Weisburg . . . would have provided a skilled artisan with a reasonable expectation of success" (Appeal Br. 17).

We are not persuaded by Appellant's reliance on the "Cell Lysis Handbook"[8] and "Guide to the Disruption of Biological Samples—2012"[9] to support a contention that "different classes of detergents were known to have different functionalities and . . . not all surfactants are chemically equal, as some are capable of completely solubilizing membranes and denaturing proteins, while others, like mild surfactants, will disassociate loosely bound proteins" (*see* Appeal Br. 17–18). On this record, the combination of prior art relied upon by Examiner discloses that a cationic detergent such as CTAB can be used in "a lysis buffer, whereby lysis of any cells, viruses, or associated matrices or packaging, is initiated to release all of the nucleic acid present in the starting material" (*see* FF 9–10).

In addition, we direct attention to Example 3 of Appellant's disclosure (Spec. 43–44), wherein Appellant discloses that control samples of blood

[8] THERMO SCIENTIFIC PIERCE CELL LYSIS TECHNICAL HANDBOOK, Featuring Cell Lysis Reagents and Detergents, Version 2, 1–50 (Part of Thermo Fisher Scientific 2009).
[9] David W. Burden, Ph.D., *Guide to the Disruption of Biological Samples – 2012, Version 1.1*, 12 RANDOM PRIMERS, 1–25 (2012).

were "directly drawn into PreAnalytiX PAXgene Blood RNA Tubes" and "processed with the PAXgene Blood RNA Kit according to the instructions of the handbook (Version 2, April 2008)" (Spec. 43: 21–24). As Appellant explains, "[t]hese samples served as control samples, because said stabili[z]ation tubes are specifically designed to ensure the preservation of RNA and allow the preparation of RNA from the respectively stabilized sample with excellent results with respect to RNA quantity and quality" (*id.* at ll. 23–26; *see* Reply Br. 7–8).

The PAXgene® Blood RNA Kit Handbook (Version 2, June 2015) directs attention to Holländer '953[10] and Holländer[11] '790 (*see* PAXgene® Blood RNA Kit 2).[12] Holländer '953 discloses that "it has long been known from the prior art to use cationic compounds . . . [such as those described in, *inter alia*, Macfarlane[13]] to isolate nucleic acids from biological samples" (Holländer '953 5: 63–67). Holländer '953 discloses that "nucleic acids can be stabili[z]ed over a long time if the nucleic acids of a biological sample are brought into contact with a cationic compound such as those disclosed inter alia in . . . [Macfarlane] and combined according to . . . [Holländer '953's] invention" (Holländer '953 6: 60–65). Macfarlane discloses a method "for purifying DNA and RNA from a variety of sources, including cells, cell lysates, viruses, tissues, blood and other body fluids employing a cationic

[10] Holländer et al., US 7,270,953 B2, issued Sept. 18, 2007.
[11] Holländer et al., US 7,682,790 B2, issued Mar. 23, 2010.
[12] We note that the April 2008 version of the PAXgene® Blood RNA Kit Handbook could not be located. Nonetheless, we find that the June 2015 version of this handbook identifies the state of the art prior to Appellant's filing date, by reference to Holländer '953, Holländer '790, and the prior art cited therein.
[13] Macfarlane, US 5,010,183, issued Apr. 23, 1991.

detergent to complex with the nucleic acids" (Macfarlane, Abstract). Macfarlane further discloses that "[a] number of cationic detergents have been shown to be able to precipitate DNA and RNA from aqueous phases," including "cetyltrimethylammonium bromide" (CTAB) (Macfarlane 2: 48–54).

Thus, notwithstanding Appellant's contentions to the contrary, cationic detergents where long recognized by those of ordinary skill in this art as useful in isolating nucleic acid from biological samples, including blood. One skilled in the art must be presumed to know something about the art apart from what the references disclose. *In re Jacoby*, 309 F.2d 513, 516 (CCPA 1962). Skill in the art is presumed. *In re Sovish*, 769 F.2d 738, 743 (Fed. Cir. 1985). *See also KSR*, 550 U.S. at 418 (An analysis under 35 U.S.C. § 103 "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.").

Therefore, unlike the facts in *Stepan* wherein our reviewing court found that the Board failed to "articulate why a person of ordinary skill in the art would have had a reasonable expectation of success to formulate the claimed surfactant system with a cloud point above at least 70°C," *In re Stepan*, 868 F.3d 1342, 1347 (Fed. Cir. 2017), the evidence on this record supports a conclusion that those of ordinary skill in this art would have used a cationic detergent, such as CTAB, as part of a lysis buffer to lyse cells in a sample with a reasonable expectation of success (*see, e.g.*, FF 9–10; *see also* Appeal Br. 17; *see id.* (Appellant recognizes that "the disclosure of Weisburg . . . shows that a skilled artisan could have replaced various

surfactants of Ryan . . . with a cationic detergent of Weisburg"). Therefore, we are not persuaded by Appellant's contentions regarding *Stepan*, 868 F.3d at 1347, or contention that the use of CTAB, as disclosed by Weisburg, would lead to an unpredictable result in Ryan's method (*see* Appeal Br. 18–19; *see generally* Reply Br. 3–5).

For the foregoing reasons, we are not persuaded by Appellant's contention that Examiner relied upon improper hindsight reasoning (Appeal Br. 19).

Appellant contends that its Specification "shows that combining a formaldehyde releaser with a cationic detergent according to the claims not only (i) allows stabilization of a sample prior to nucleic acid isolation, but also (ii) results in high RNA yield and purity" compared to "standard, commercial nucleic acid isolation protocols" (Appeal Br. 20 (citing Spec. 41:23–48:29 (Examples 1–5) and Figures 3A–7B)). We are not persuaded. Appellant failed to explain how the evidence provided in its Specification compares against the closest prior art relied upon by Examiner, specifically Ryan. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). As Examiner explains, "[n]either the Brief nor the [S]pecification state what is in the STRECK tubes" (Ans. 29). Thus, we are not persuaded by Appellant's asserted unexpected results (*see* Appeal Br. 20–23; *see also* Reply Br. 6–7).

In addition, as discussed above with respect to Holländer '953 and Macfarlane, the prior art recognized the benefit of isolating nucleic acid from cells using a lysis solution comprising a cationic detergent, such as

CTAB, thus, we are not persuaded that a person of ordinary skill in this art would have considered Appellant's results unexpected.

The rejection over the combination of Ryan, Weisburg, and Fernando:

Based on the combination of Ryan, Weisburg, and Fernando, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to have used Fernando's stabilization solution in the method suggested by the combination of Ryan and Weisburg, with the reasonable expectation of isolating nucleic acid using techniques known to those of ordinary skill in this art (Ans. 11; *see* FF 1–13).

Having found no deficiency in the combination of Ryan and Weisburg, we are not persuaded by Appellant's contention that Fernando "fails to remedy the deficiencies of Ryan . . . and Weisburg" (Appeal Br. 24).

The rejection over the combination of Ryan, Weisburg, and Kappel:

Based on the combination of Ryan, Weisburg, and Kappel, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to use Kappel's detergents in the method suggested by Ryan and Weisburg to lyse cells (Ans. 12–13; *see* FF 1–10 and 14).

Having found no deficiency in the combination of Ryan and Weisburg, we are not persuaded by Appellant's contention that Kappel "fails to remedy the deficiencies of Ryan . . . and Weisburg" (Appeal Br. 25). In addition, as discussed above, those of ordinary skill in this art recognized the utility of cationic detergents in methods of isolating nucleic acid from biological samples, including blood. Therefore, we are not persuaded by

Appellant's contention that those of ordinary skill in this art would not have understood what detergent to use in a method suggested by the combination of Ryan, Weisburg, and Kappel (*see id.*). For the reasons set forth above, we are also not persuaded by Appellant's contention their asserted unexpected results rebuts Examiner's prima facie case of obviousness on this record (*id.* at 25–26).

The rejection over the combination of Ryan and Kappel:

Based on the combination of Ryan and Kappel, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to use Kappel's cationic detergent in Ryan's method of isolating nucleic acid (Ans. 14; *see* FF 1–6, 15, and 16).

Although Appellant recognizes that Kappel discloses "the use of lytic reagents, which may comprise a detergent, a lytic enzyme, a chaotropic reagent, or combinations thereof, for inducing a cell to release a target cellular component[, such as nucleic acid,] from a host cell," Appellant contends that Kappel "does not provide any guidance for what types of detergents should be used to extract different types of cells or cellular components" (Appeal Br. 27; *see also* Reply Br. 9). We are not persuaded. We are also not persuaded by Appellant's contentions regarding the properties of different detergents or that "[i]t is known in the art that the use of detergents is application specific and may be unpredictable" (Appeal Br. 27–28). As discussed above, notwithstanding Appellant's contention to the contrary, those of ordinary skill in this art recognized that cationic detergents, including those within the scope of Appellant's claimed invention, are useful for isolating nucleic acid from cells. *In re Jacoby*, 309

F.2d 513, 516 (CCPA 1962) ("Those skilled in the [] art must be presumed to know something about [the art] apart from what the references disclose.").

In addition, for the reasons discussed above, we are not persuaded by Appellant's asserted unexpected results. Thus, for the foregoing reasons, we are not persuaded by Appellant's contention that Kappel "does not provide motivation for one skilled in the art to modify Ryan . . . to arrive at the claimed method, provide a reasonable expectation of success for such a combination, or predict the superior properties of the claimed method of . . . [Appellant's] application" (Appeal Br. 28; *see generally* Reply Br. 9).

The rejection over the combination of Ryan, Kappel, and Weisburg:

Based on the combination of Ryan, Kappel, and Weisburg, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to combine Weisburg's solid phase technology to the method of isolating nucleic acid suggested by the combination of Ryan and Kappel (*see* Ans. 20; *see also* FF 1–10 and 15–17).

For the reasons discussed above, we are not persuaded by Appellant's contention that "one of ordinary skill in the art would not have been motivated to substitute . . . [Ryan's detergent] with the cationic detergent of Kappel . . . or Weisburg . . . and would not have had [a] reasonable expectation of success" (Appeal Br. 30). In addition, for the reasons discussed above, we are not persuaded by Appellant's contention regarding its asserted unexpected results (*see id.*).

The rejection over the combination of Ryan, Kappel, and Fernando:

Based on the combination of Ryan, Kappel, and Fernando, Examiner concludes that, at the time Appellant's invention was made, it would have been prima facie obvious to have used Fernando's stabilization solution in the method suggested by the combination of Ryan and Kappel, with the reasonable expectation of isolating nucleic acid using techniques known to those of ordinary skill in this art (Ans. 21; *see* FF 1–5, 12, 13, 15, 16, and 18).

For the reasons discussed above, we are not persuaded by Appellant's contention that because Fernando "does not have any disclosure relating to cationic detergents," Fernando "does not provide motivation for one skilled in the art to modify Ryan . . . in view of Weisburg . . . to arrive at the claimed method, provide a reasonable expectation of success for such a combination, or predict the superior properties of the claimed method of the present application" (Appeal Br. 31).

CONCLUSION

The preponderance of evidence relied upon by Examiner supports a conclusion of obviousness.

The rejection of claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan and Weisburg is affirmed. Claims 2–18 and 20 are not separately argued and fall with claim 1.

The rejection of claim 19 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan, Weisburg, and Fernando is affirmed.

The rejection of claims 21 and 22 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan, Weisburg, and Kappel is affirmed.

The rejection of claim 1 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan and Kappel is affirmed. Claims 2–14, 16–18, 21, and 22 are not separately argued and fall with claim 1.

The rejection of claims 15 and 20 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan, Kappel, and Weisburg is affirmed.

The rejection of claim 19 under 35 U.S.C. § 103(a) as unpatentable over the combination of Ryan, Kappel, and Fernando is affirmed.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–18, 20	103	Ryan, Weisburg	1–18, 20	
19	103	Ryan, Weisburg, Fernando	19	
21, 22	103	Ryan, Weisburg, Kappel	21, 22	
1–14, 16–18, 21, 22	103	Ryan, Kappel	1–14, 16–18, 21, 22	
15, 20	103	Ryan, Kappel, Weisburg	15, 20	
19	103	Ryan, Kappel, Fernando	19	
Overall Outcome			1–22	

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