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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JAMES C.D. HENGST and GREGORY R. CHIKLIS

Appeal 2019-000695
Application 15/394,085
Technology Center 1600

Before ERIC B. GRIMES, DEBORAH KATZ, and
RACHEL H. TOWNSEND, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Appellant[1] seeks our review,[2] under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 1–6. We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

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[1] We use the word "Appellant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party-in-interest as Zeptometrix Corporation. (Appeal Br. 2.)

[2] We consider the Final Office Action issued November 14, 2017 ("Final Act."), the Appeal Brief filed May 14, 2018 ("Appeal Br."), the Examiner's Answer issued on September 5, 2018 ("Ans."), the Reply Brief filed November 5, 2018 ("Reply Br.").

Appellant's Specification is directed to control material for use in nucleic acid amplification assays to detect viruses in biological samples. (Spec. 1:16–18.)

The Examiner rejected claims 1–4 and 6 under 35 U.S.C. § 103(a) over James,[3] Cory,[4] Hulskotte,[5] Feldman,[6] and Natarajan.[7] (*See* Final Act. 3–10.) The Examiner rejected claim 5 under 35 U.S.C. § 103 over these references and also Johnson.[8] (*See* Ans. 3–10.)

Appellant's claim 1 recites:

> A method for making a full process positive control material for detection of virus in biological samples comprising:
>
> a) purifying an intact virus from a source;
>
> b) exposing the purified intact virus to an aldehyde at a temperature and for a time such that one or more surface proteins are irreversibly modified while leaving the nuclear components substantially intact thereby rendering the purified intact virus non-pathogenic and wherein nucleic acids of the purified intact virus are amenable to amplification; and
>
> c) identifying that the purified intact virus can be used as a full process positive control by confirming absence of active

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[3] U.S. Patent 6,072,086, issued June 6, 2000.
[4] Cory et al., "Effects of Cellular Fixatives on Human Immunodeficiency Virus Production," Cytometry 11:647–51 (1990).
[5] Hulskotte et al., "Chemical inactivation of recombinant vaccinia viruses and the effects on antigenicity and immunogenicity of recombinant simian immunodeficiency virus envelope glycoproteins," Vaccine, 15:1839–45 (1997).
[6] Feldman, "Reactions of Nucleic Acids and Nucleoproteins with Formaldehyde," Prog. Nucleic Acid Res. Mol. Biol. 13:1–49 (1973).
[7] Natarajan, et al., "An Internally Controlled Virion PCR for the Measurement of HIV-1 RNA in Plasma," Genome Res. 3: 346–50 (1994).
[8] Johnson, "Transport of Viral Specimens," Clinical Microbiological Reviews, 3:120–31 (1990).

> virus and an ability of viral nucleic acids in the purified intact virus to be amplified.

(Appeal Br. 15.)

Findings of Fact and Analysis

As the Examiner finds, James teaches fixing biological samples by contacting a tissue with formaldehyde solutions, including paraformaldehyde. (*See* James 17:6–8, 15–18; *see* Ans. 4, 7.) James teaches that fixation is a first important step in preparing samples for a wide range of analytical tests, including PCR. (*See* James 1:20–25; *see* Ans. 5.) The biological samples that James teaches for formaldehyde fixation include single cells, tissues, and viruses. (*See* James 17:23–24 and 25:24–32 (claims 48 and 50); *see* Ans. 5.)

The Examiner determines, and we agree, that because James teaches using a virus as a sample and teaches contacting a sample with a formaldehyde as the fixative, Appellant's claimed step of purifying the virus from a source prior to treating it with the fixative would have been obvious to one of ordinary skill in the art. (*See* Ans. 4.) The Examiner finds, and we agree, that James' teaching of contacting the sample with a formaldehyde fixative, such as paraformaldehyde, meets the claim step of exposing the purified virus to an aldehyde. (*See* Ans. 5, 7.)

As the Examiner also finds, Cory teaches safe handling of samples for flow cytometric analysis to avoid the risk of accidental exposure to HIV-1. (*See* Cory 647; *see* Ans. 6.) Cory teaches that "[v]arious treatments have been shown to inactivate free HIV-1 virions. . . , while post-labeling fixation with 0.5% or greater paraformaldehyde . . . decreases concerns regarding residual infectious HIV-1 in cells destined for flow cytometric analysis."

(*See* Cory 647 (internal citations omitted); *see* Ans. 5.) Cory further teaches that "[w]hen cell samples must be labeled live or are treated for cell labeling with a fixative that has not been shown to fully inactivate HIV-1, samples may be treated with an HIV-1 inactivating agent after labeling and prior to flow cytometric analysis. For this purpose, we routinely use PBS containing 2% paraformaldehyde." (Cory 650.)

The Examiner cites Hulskotte for its teaching that formaldehyde was known to inactivate viruses used in vaccines. (*See* Hulskotte 1839; *see* Ans. 6.) Hulskotte teaches that because formaldehyde causes cross-linking of the peptide bonds in a protein, the three-dimensional architecture is preserved. (*See* Hulskotte 1839; *see* Ans. 6.) As the Examiner finds, Feldman provides a similar teaching of the use of formaldehyde to inactivate viruses for vaccine production without disturbing the polypeptide or polynucleotide backbone chains of proteins or nucleic acids, respectively. (*See* Feldman 37; *see* Ans. 6–7.)

We also agree with the Examiner's finding that Natarajan teaches the use of infectious viruses as an internal control for PCR measurements to eliminate errors and enhance accuracy. (*See* Natarajan 346; *see* Ans. 7.)

The Examiner determines that Appellant's claimed method would have been obvious because James teaches fixing samples, including virus samples, in paraformaldehyde, Cory, Hulskotte, and Feldman teach that viruses, including HIV-1 viruses, can be fixed with an aldehyde and inactivated with that same aldehyde by modifying surface proteins, and Natarajan provides a reason to use viruses as positive controls in assays such

as PCR. (*See* Ans. 7–9.) We agree with the Examiner's reasoning and conclusion.

Appellant argues that the Examiner fails to present a *prima face* case for obviousness for several reasons. First, Appellant argues that the Examiner "concedes" that the combination of cited references fails to teach or suggest rendering an intact virus non-pathogenic as required in claim 1. (*See* Appeal Br. 4–6; *see also* Reply Br. 2–3.) Appellant cites to the Examiner's statements that combination of references result in a virus that retains some viability as a sample for use in analytical testing. (*See* Appeal Br. 5.) For example, the Examiner states:

> Since James et al. already teaches or suggests performing analytical tests such as nucleic acid amplification using such samples, one of ordinary skill in the art would have been motivated in view of Cory et al. as evidenced by Hulskotte et al. and Feldman to use the paraformaldehyde fixative and concentration as taught in order to inactivate virion for improved safety *yet still retain some viability* in sample for use in analytical testing.

(Final Act. 7–8 (emphasis added).) Similarly, the Examiner states:

> James et al. in view of Cory et al. as evidenced by Hulskotte et al. and Feldman teaches such a virus (inactivated, *retaining some viability*) for use in analytical tests, including nucleic acid amplification methods, and Natarajan et al. teaches wherein the use of an internal control virion in PCR methods eliminates errors and enhances accuracy of assay.

(Final Act. 8 (emphasis added).)

Appellant argues that the term "non-pathogenic" is defined in the Specification to mean that "as a result of the modification of the surface proteins according to the methods of the invention, the microorganism is not able to infect cells, replicate or cause disease despite having its nuclear

contents substantially intact." (Spec. 7:27–8:2.) Appellant argues that the Examiner's statements regarding the retention of viability or allegedly similar statements about "reduction in infectivity" demonstrate that the prior art does not teach a "non-pathogenic" virus as claimed. (*See* Appeal Br. 5; *see* Reply Br. 2.)

We are not persuaded that the Examiner's statements mean what Appellant asserts. The Examiner's statements are not a concession that the prior art failed to teach creating non-pathogenic viruses by treatment with an aldehyde. Although perhaps somewhat confusing, we understand the Examiner's statements about "viability" to refer to their usefulness in assays, even after inactivation with aldehyde. As the Examiner explains (*see* Ans. 13–14), Cory teaches:

> When cell samples must be labeled live or are treated for cell labeling with a fixative that has not been shown to fully inactivate HIV-1, samples may be treated with an HIV-1 inactivating agent after labeling and prior to flow cytometric analysis. For this purpose, we routinely use PBS containing 2% paraformaldehyde.

(Cory 650.) Although Appellant argues that this passage includes a first part of treatment that only partially inactivates virus (*see* Appeal Br. 7; *see* Reply Br. 4), the passage nevertheless states that more complete inactivation can be achieved with 2% paraformaldehyde. (*See* Ans. 18.) Accordingly, we are persuaded that at least Cory demonstrates it was known to render virus non-pathogenic by treating with an aldehyde as claimed.

We note further that even if it were forbidden in an obviousness rejection, we do not agree with Appellant that the Examiner is "picking and choosing" from Cory because the passage cited clearly states that 2%

paraformaldehyde is used to fully inactivate HIV-1 – thus rendering it non-pathogenic. (*See* Appeal Br. 7.) *See In re Arkley*, 455 F.2d 586, 587–88 (CCPA 1972) ("Such picking and choosing may be entirely proper in the making of a 103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art . . . ."). We are not persuaded by Appellant's argument that the Examiner failed to make a *prima facie* case for obviousness because none of the prior art teaches using an aldehyde to obtain a non-pathogenic virus.

Appellant also argues that the cited prior art fails to teach or suggest "purifying an intact virus from a source," as recited in claim 1. (*See* Appeal Br. 6; *see* Reply Br. 3–4.) According to Appellant, the Examiner's reading of James as suggesting the use of a purified virus for paraformaldehyde inactivation is "expansive." (*See* Appeal Br. 6.)

We are not persuaded by this argument because, as the Examiner notes, Appellant does not define "purifying" in the Specification with any particular steps or degree of isolation. (*See* Ans. 16.) Instead, the Specification refers to "using techniques known to those of ordinary skill in the art" and provides a "typical method" wherein cells and cells debris are initially removed. (*See* Spec. 7:4–6.) James teaches that the biological sample subject to fixation with formaldehyde can be single cells, tissues, organisms, or viruses. (*See* James 17:14–23; 28:24–32.) We agree with the Examiner that the teaching in James to use a single cell or viruses as a biological sample suggests, if not teaches, fixation of a virus that has been at

least initially isolated from a larger biological sample and then treated with formaldehyde. (*See* Ans. 16.)

Appellant argues that the cited prior art fails to teach or suggest inactivation of viruses that retain intact nuclear components capable of nucleic acid amplification as recited in claim 1. (*See* Appeal Br. 6–9.) Appellant's arguments regarding the teachings of Cory, Hulskotte, and Feldman are unpersuasive because James teaches treating viruses with formaldehyde and subsequent use in PCR assays. (*See* James 17:15–34; *see* Ans. 17–18.)

Appellant also argues that there is insufficient reason to combine the teachings of Natarajan with other references. (*See* Appeal Br. 9–10; *see* Reply Br. 5.) Appellant argues further that combining the teachings would frustrate the purpose of Natarajan. (*See* Appeal Br. 10–11.) We are not persuaded by either argument.

According to Appellant, one of ordinary skill in the art would not have had a reason to use the viruses of James or Cory as a positive control, such as taught in Natarajan. (*See* Appeal Br. 9.) The Examiner's rejection is based on the teachings of James, Cory, and Hulskotte to inactivate viruses with aldehydes, while leaving the nuclear components intact and amenable to amplification, as recited in claim 1. Natarajan was cited only for its teaching that isolated viruses can be positive controls in PCR amplification assays. (*See* Ans. 22.) We agree that with this knowledge, one of ordinary skill in the art would have considered it obvious to combine the teachings and use aldehyde-inactivated virus as a positive control in PCR amplification assays.

We are also not persuaded that because Natarajan teaches genetically modified, infectious virus as a positive control, combining the teachings of the other cited references to use an aldehyde-inactivated virus instead would frustrate the purpose of Natarajan, as Appellant argues. (*See* Appeal Br. 10–11.)

> The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.

In re Keller, 642 F.2d 413, 425 (CCPA 1981). Because, as explained above, we are persuaded that there would have been a reason to combine the teachings of the cited references and the combination would have suggested Appellant's claimed method, we are persuaded that the method would have been obvious.

Appellant argues that the Examiner improperly ignored the declaration under 37 C.F.R. § 1.132 by inventor Gregory Chiklis ("Chiklis Decl.") regarding the commercial success of the claimed method. (*See* Appeal Br. 11–13.) At the outset, we disagree that the Examiner ignored the declaration because it was addressed on page 17 of the Final Office Action. The Examiner determined that the declaration was not persuasive of nonobviousness because it refers to a product, "NATTROL," sold commercially, without a comparison to the claimed method. (*See* Final Act. 17.)

We agree with the Examiner. Dr. Chiklis states that "[t]he process of making the positive control material sold under the name NATTROL

includes all the limitations of current claim 1 of the '085 application." (Chiklis Decl. ¶ 11.) But Dr. Chiklis does not testify that NATTROL is a virus, testifying instead that it is "a purified, whole *microorganism* . . . ." (Chiklis Decl. ¶ 12 (emphasis added).) Dr. Chiklis states further that "NATTROL products allow the viral nucleic acid to remain intact for testing" (Chiklis Decl. ¶ 13), but it is unclear if all "NATTROL products" are viruses. Thus, it is not clear from the Chiklis Declaration whether the sales figures reported by Dr. Chiklis are all due to viral positive controls as recited in claim 1, or to other purified, whole microorganisms. (*See* Chiklis Decl. ¶¶ 14–17.) Appellant does not direct us to any other evidence that the "NATTROL products" discussed by Dr. Chiklis are viruses only. (*See* Reply Br. 5–6.) Accordingly, we agree with the Examiner that the evidence of commercial success is not commensurate in scope with the claimed method. Appellant has not shown that the success is due to the claimed features, for example a method of producing a *viral* positive control. (*See* Ans. 24.)

We agree with the Examiner, further, that recitation of gross sales figures in the Chiklis Declaration is insufficient to show nonobviousness due to commercial success without evidence of the market share these figures represent. (*See* Ans. 26.) Information solely on numbers of units sold is insufficient to establish commercial success without supporting evidence, such as market share. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991); *see also Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1151 (Fed. Cir. 1983).

Appellant has not persuaded us that the Examiner erred in rejecting claim 1 as being obvious over the cited prior art. Appellant does not raise a

separate argument against the rejection of claims 2–4 or 6, which depend on claim 1. Thus, we are not persuaded that the Examiner erred in the rejection of these claims either.

The Examiner rejects claim 5 separately, citing James, Cory, Hulskotte, Feldman, and Natarajan, as well as Johnson as rendering the recited method obvious under 35 U.S.C. § 103. (*See* Ans. 10–11; *see* Reply Br. 6.) Claim 5 recites the method of claim 1, "further comprising storing the purified intact virus at a refrigeration temperature." (Appeal Br. 15.) Johnson teaches that is was commonly recommended that specimens for virus isolation be immediately placed in a refrigerator. (Johnson 120; *see* Ans. 11.)

Appellant argues only that "Johnson does not cure the deficiencies of the references cited in the rejection of claim 1." (Appeal Br. 14.) Because, as explained above, we determine that there are no deficiencies in the Examiner's rejection of claim 1, we are not persuaded that the rejection of claim 5 was an error.

Conclusion

Upon consideration of the record and for the reasons given, we affirm the Examiner's rejection.

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1–4, 6	103	James, Cory, Hulskotte, Feldman, Natarajan	1–4, 6	

5	103	James, Cory, Hulskotte, Feldman, Natarajan, Johnson	5	
Overall Outcome			1–6	

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

AFFIRMED