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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PAUL HOWLEY, SONJA LEYRER, MARY JANE CARDOSA, and MAGDELINE SIA HENRY SUM

Appeal 2011-004534
Application 12/038,141
Technology Center 1600

Before ERIC GRIMES, FRANCISCO C. PRATS, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a recombinant viral vector, which have been rejected for obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

Dengue virus, which causes Dengue fever (Spec. 1: 25-26), occurs in four serotypes (*id*. at 2: 28). One of the proteins encoded by the Dengue virus genome is nonstructural glycoprotein NS1 (*see id*. at 1: 28 to 2: 10).

The Specification discloses that "the NS1 protein derived from a Dengue virus of one serotype expressed *de novo* after vaccination can evoke an antibody response that will cross react with NS1 proteins of Dengue virus serotype 1, 2, 3 and 4" (*id*. at 6: 15-18). The Specification also discloses that a modified vaccinia virus Ankara (MVA) vector (*id*. at 12: 10) can be used to express a recombinant protein (*id*. at 12: 1-5) to provide a vaccine (*id*. at 12: 18-21).

Claims 23-37 are on appeal. Claim 23 is representative and reads as follows:

> 23. An MVA virus vector that expresses an entire Flavivirus NS1 protein of a Dengue virus or a part thereof;
>
> wherein the MVA is an MVA capable of reproductive replication in chicken embryo fibroblasts (CEF) and the Baby Hamster kidney cell line BHK, but is not capable of reproductive replication *in vitro* in the human keratinocyte cell line HaCaT or the human cervix adenocarcinoma cell line HeLa; and
>
> wherein the MVA virus vector induces an immune response against the NS1 proteins of at least two Dengue virus serotypes, when the MVA virus vector is administered to an animal.

I.

Issue

The Examiner has rejected all of the claims on appeal under 35 U.S.C. § 103(a) based on Cardosa[1] and Chaplin[2] (Answer 4). The Examiner finds that Cardosa discloses an MVA vector that expresses a Dengue virus NS1 protein (*id*.) but not an MVA vector having the replication properties recited

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[1] Cardosa et al., WO 98/13500, Feb. 4, 1998
[2] Chaplin et al., US 6,761,893 B2, July 13, 2004

in claim 23 (*id*. at 5). The Examiner finds that Chaplin discloses vector MVA-BN, which has the required properties (*id*.), and concludes that it would have been obvious "to substitute Chaplin's MVA-BN strain for Cardosa's MVA . . . because Chaplin discloses that the MVA-BN strain, or derivatives thereof having the same properties, have enhanced safety for the development of vaccines" (*id*. at 6).

The Examiner also concludes that the construct made obvious by the prior art would have induced an immune response against different Dengue virus serotypes upon administration to an animal "because the same construct [ ] is administered: MVA-BN . . . expressing NS1 protein from Dengue serotype 2" (*id*.).

Appellants contend that the Examiner has combined the references based on hindsight (Appeal Br. 12-13). Appellants also argue that the references do not disclose achieving a cross-reacting immune response (*id*. at 11) and do not provide a basis for reasonably expecting such a response (*id*. at 14).

The issue presented is: Does the evidence support the Examiner's conclusion that the cited references would have made obvious a viral vector having the properties recited in claim 23?

Findings of Fact

1. Cardosa discloses "recombinant vaccinia viruses derived from the modified vaccinia virus Ankara (MVA) encoding and capable of expressing dengue virus antigens, and the use of such recombinant MVA viruses encoding dengue virus antigens in vaccines" (Cardosa 1).

2. Cardosa discloses that a "cDNA fragment of dengue virus serotype 2, New Guinea C (NGC) strain comprising a signal sequence of 24 amino acids preceding NS1 and all NS1 residues was isolated by PCR from Dengue virus type 2 cDNA" (*id*. at 15).

3. Cardosa discloses that the "fragment carrying the NS1 fragment under transcriptional control of the vaccinia virus early/late promoter P7.5 was inserted into deletion II within the MVA using homologous recombination" (*id*.).

4. Chaplin discloses "vaccinia virus strains that are not capable of reproductive replication in any of the following human cell lines: human cervix adenocarcinoma cell line HeLa . . . and the HaCat cell line" (Chaplin, col. 2, ll. 23-30).

5. Chaplin discloses that "MVA-BN, which is a representative strain of the invention, does not reproductively replicate in any of the human cell lines tested" (*id*. at col. 3, ll. 15-17).

6. Chaplin discloses that "the virus of the present invention may be recombinant, i.e., may express heterologous genes as, e.g., antigens or epitopes heterologous to the virus, and may thus be useful as a vaccine. . . . Examples of such epitopes . . . include e.g., epitopes from proteins derived from other viruses, such as the Dengue virus." (*Id*. at col. 7, ll. 17-20, 55-57.)

7. Chaplin discloses that "[s]ince the virus of the invention is highly growth restricted in human and monkey cells and thus, highly attenuated, it is ideal to treat a wide range of mammals, including humans" (*id*. at col. 9, ll. 22-24).

8. Chaplin discloses that "all viruses amplified well in CEF cells as expected, since this is a permissive cell line for all MVAs. Additionally, it was demonstrated that all viruses amplified well in BHK (Hamster kidney cell line)" (*id*. at col. 17, ll. 59-62).

9. The Specification states that "the object to provide a vaccine that is derived from one Dengue virus serotype and that protects an individual at least against an infection with at least two, preferably at least three, more preferably all Dengue virus serotypes . . . has been solved by using the NS1 protein or a part thereof of a Dengue virus, in particular of Dengue virus serotype 2" (Spec. 6: 6-13).

10. The Specification states that "the NS1 protein derived from a Dengue virus of one serotype expressed *de novo* after vaccination can evoke an antibody response that will cross react with NS1 proteins of Dengue virus serotype 1, 2, 3 and 4" (*id*. at 6: 15-18).

11. The Specification states that the "NS1 protein can preferably be of any Dengue virus serotype. More preferably the NS1 protein coding sequence is derived from a Dengue virus serotype 2 such as the Dengue virus New Guinea strain ('NGC strain' . . .)." (*Id*. at 10: 22-24.)

12. The Specification states that "[t]ypical virus vectors that may be used according to the present invention are adenoviral vectors, retroviral vectors or vectors on the basis of the adeno associated virus 2 (AAV2). . . . Most preferred is MVA-BN or a derivative thereof." (*Id*. at 12: 6-13.)

13. The Specification states that, because the NS1 protein is produced as part of a polyprotein precursor, it is not preceded by an ATG codon, and "[t]herefore, a cDNA sequence coding for the NS1 protein must require the

addition of a 'ATG' start codon" (*id*. at 29: 17-18). "This is then followed by the addition of a signal sequence so that the newly synthesized NS1 protein becomes glycosylated in the endoplasmic reticulum. Finally, the protein-coding cassette needs a stop codon." (*Id*. at 29: 18-21.)

14. The Specification provides a working example in which the NS1-encoding cDNA from Dengue virus serotype 2 NGC strain (*id*. at 29: 12-13) was preceded by "the 'ATG+signal sequence' element . . . derived from the hydrophobic C-terminal end of the E protein (the last 28 amino acids, which for NGC strains starts with the amino acid M (ATG))" (*id*. at 29: 23-25).

15. Appellants have provided a declaration under 37 C.F.R. § 1.132 of Mary Jane Cardosa (Cardosa Declaration, dated June 10, 2008; Appeal Br. Evidence Appendix).

16. Dr. Cardosa declares that the Cardosa reference did not assay for NS1 protein expression (Cardosa Declaration, ¶¶ 62, 63)

17. Dr. Cardosa declares that, since no protein was assessed in the Cardosa reference, there is no evidence that the NS1 protein in the reference and the NS1 protein in the instant Specification would have the same function (*id*. at ¶ 64).

18. Dr. Cardosa declares that the Cardosa reference does not disclose whether the NS1 protein that might be produced from its construct would induce a cross-reactive immune response (*id*. at ¶ 65).

Principles of Law

> Where . . . the claimed and prior art products are identical or substantially identical . . . the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the

> rejection is based on "inherency" under 35 U.S.C. § 102, on "prima facie obviousness" under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products.

In re Best, 562 F.2d 1252, 1255 (CCPA 1977) (citations and footnote omitted).

Analysis

We agree with the Examiner that it would have been obvious, based on the disclosures of Cardosa and Chaplin, to combine the Dengue virus NS1-encoding cDNA disclosed by Cardosa with the MVA-BN vector disclosed by Chaplin. Cardosa discloses that recombinant MVA vectors encoding Dengue virus antigens are useful in vaccines (FF 1), and Chaplin discloses that MVA-BN can be used to express viral antigens for use in vaccines (FF 6) and that its replication properties make it "ideal to treat a wide range of mammals, including humans" (FF 7). The cited references thus provide ample reason to combine their disclosures. Appellants' argument that the rejection is based on hindsight (Appeal Br. 12-13) is therefore unpersuasive.

Appellants also argue that the references do not disclose that the NS1 protein cloned by Cardosa will induce an immune response to at least two serotypes of Dengue virus (Appeal Br. 11-12), and that "[n]othing in either of the cited references provides any expectation that Appellant's claimed vector would induce an immune response against the NS1 proteins of at least two Dengue virus serotypes, when the MVA virus vector is administered to an animal" (*id*. at 14).

Appellants argue that the Examiner's position – that the recited properties would have been inherent in the product made obvious by the prior art (Answer 6) – "is legally in error. The question is not whether the prior art construct would have had the same characteristics as Appellant's claimed vector, but whether these characteristics would have been obvious at the time the application was filed" (Appeal Br. 15).

Appellants also argue that the "coding sequence described in the specification for Appellant's NS1 protein appears to differ from the NS1 protein coding sequences described in Cardosa" (*id*. at 17). Appellants argue that their "NS1 protein contained an 'ATG + signal sequence' element derived from the last 28 amino acids of the E protein. . . . Also, the cassette encoding Appellant's NS1 protein contained a 'TAG' stop codon after the NS1 coding sequence. . . . Cardosa does not indicate the precise amino acid sequence of the NS1 protein encoded by the MVA construct." (*Id*. at 18.)

These arguments are not persuasive. It is true that the references do not disclose that combining Cardosa's NS1-encoding cDNA and Chaplin's vector would produce a vector that would express an NS1 protein that would induce an immune response to multiple Dengue virus serotypes. However, "the discovery that a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a *prima facie* case." *In re Dillon*, 919 F.2d 688, 693 (Fed. Cir. 1990). The *Dillon* court expressly held that "the statement that a *prima facie* obviousness rejection is not supported if no reference shows or suggests the newly-discovered properties and results of a claimed structure is not the law." *Id*.

The evidence of record here provides a reasonable basis for concluding that Cardosa's NS1 protein and the Specification's NS1 protein would induce the same kind of immune response, even though Cardosa's NS1 sequence differs slightly from that of the Specification's working example. The vectors exemplified in both Cardosa and Appellants' Specification include the full coding sequence of NS1 from Dengue virus serotype 2, NGC strain (FFs 2, 14). The mature NS1 protein encoded by both vectors would therefore be expected to be identical, and Appellants have not provided evidence showing that they differ.

In addition, both Cardosa's vector and the vector exemplified in Appellants' Specification include a signal sequence, "so that the newly synthesized NS1 protein becomes glycosylated in the endoplasmic reticulum," as stated in the Specification (FF 13). Both NS1 proteins therefore would be expected to be glycosylated when expressed in cells.

It is true, as Appellants point out (Appeal Br. 17-18), that Cardosa's construct differs from Appellants' exemplified construct in the length of the signal sequence: 24 amino acids in Cardosa, compared to 28 amino acids in the Specification (FFs 2, 14). However, Appellants have not pointed to evidence showing that the difference in the signal sequence would result in a structural difference in the final, processed proteins that would produce different immune responses when administered to an animal – specifically, no immune response, or one limited to a single serotype, when the signal sequence is 24 amino acids long (Cardosa) but an immune response against two or more serotypes when the signal sequence is 28 amino acids long (Specification).

The Specification itself provides evidence that the property of inducing the immune response recited in claim 23 is not limited to the NS1 protein encoded by Appellants' exemplified vector. The Specification states that a protective immune response to multiple serotypes can be induced "using the NS1 protein or a part thereof of a Dengue virus, in particular of Dengue virus serotype 2" (FF 9), and that "the NS1 protein coding sequence . . . derived from a Dengue virus serotype 2 such as the Dengue virus New Guinea strain ('NGC strain' . . .)" is more preferred (FF 11). The Specification provides no indication that a difference of four amino acids in the length of the signal sequence preceding the NS1 coding sequence of Dengue virus serotype 2, NGC strain, will prevent it from inducing an immune response to multiple serotypes.

In summary, the prior art would have made obvious a vector comprising cDNA encoding full-length NS1 protein from Dengue virus serotype 2, NGC strain, plus a 24-amino acid signal sequence, in an MVA-BN vector. Appellants' Specification states that an MVA vector, preferably MVA-BN, encoding a Dengue virus NS1 protein, preferably from serotype 2, NGC strain, induces an immune response that will cross react with different Dengue virus serotypes, and does not indicate that the particular construct in the working examples is required for such a response. Based on the evidence of record, it is reasonable to shift the burden of proof to Appellants to show that the vector made obvious by the prior art does not meet the limitations of claim 23. *See In re Best*, 562 F.2d at 1255 ("Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie

obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same.").

Appellants argue that "[t]here is no evidence of record that Cardosa's vector would produce an NS1 in the correct form to produce this type of immune response" (Appeal Br. 16). We disagree; the evidence is discussed in detail above.

Appellants also point to the Cardosa declaration as "objective evidence that Cardosa et al. does not report expression of NS1 from MVA" and that "Cardosa et al. does not disclose whether the NS1 protein that might be produced from such a construct would induce an immune response to Dengue" (*id*. at 17). The statements for which the Cardosa Declaration are asserted are true – the Cardosa reference does not disclose assaying for expression of NS1 from its exemplified vector, or disclose testing the immune response produced by the vector.

However, claim 23 is directed to a product, and a product is unpatentable if the same product would have been obvious based on the prior art. "[T]he discovery that a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a *prima facie* case." *In re Dillon*, 919 F.2d at 693. The *Dillon* court made clear the same standard applies to compounds, as well as compositions. *See id*. at 693 n.3 For the reasons discussed in detail above, we agree with the Examiner that it is reasonable to conclude that the product made obvious by Cardosa and Chaplin would have had the structure and properties recited in claim 23. The fact that Cardosa did not measure, and therefore does not

disclose, all of the relevant properties does not mean that Cardosa's product did not possess those properties.

In the Reply Brief, Appellants point to the Cardosa Declaration as evidence that NS1 is synthesized as a monomer that undergoes dimerization; that the immune responses induced by the monomeric and dimeric forms were expected to be different; and that inducing an immune response to NS1 depends on appropriate delivery (Reply Br. 4). Appellants conclude that "the mere expression of NS1 would not have been expected to necessarily produce a protein with Appellant's claimed properties" (*id*. at 4-5).

This argument is also unpersuasive. Dr. Cardosa does state that she "would expect that the antibody responses induced by monomeric and dimeric forms of NS1 would be quite different" (Cardosa Declaration, ¶ 45). However, Appellants have not pointed to evidence showing that expression of NS1 using the vector made obvious by the prior art would have been expected to result in the monomeric form of the protein.

The evidence, in fact, suggests the opposite. The Cardosa Declaration cites prior art as showing that the native form of NS1 is a dimer (*id*. at ¶ 35), and that the monomeric form is generated by acidic conditions (*id*. at ¶ 36) such as acid elution (*id*. at ¶ 38). Appellants' Specification does not disclose that any special treatment is required to express NS1 in the dimeric form, but rather that "crude protein extracts" of mammalian cells expressing NS1 from a recombinant vector contained NS1 in the dimeric form (Spec. 34: 13-28). The evidence therefore does not show that the product made obvious by the prior art would have been expected to lack the properties recited in claim 23.

Finally, Appellants argue that a showing of unpatentability requires more than showing that "the prior art construct would have had the same characteristics as Appellant's claimed vector, but [that] these characteristics would have been obvious at the time the application was filed" (Appeal Br. 15).

We disagree with Appellants' view of the legal standard. As noted above, a product is the same product regardless of whether all of its properties are known. Thus, a claimed product is not distinguished from the prior art simply because the claim recites a property that is not disclosed in the prior art. *See In re Dillon*, 919 F.2d at 693 ("[T]he discovery that a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a *prima facie* case."). As discussed above, the evidence in this case provides sufficient basis for shifting the burden to Appellants to show that what would have been obvious based on Cardosa and Chaplin is different from what is defined by claim 23.

Conclusion of Law

The evidence supports the Examiner's conclusion that the cited references would have made obvious a viral vector having the properties recited in claim 23. Claims 24-37 were not argued separately and therefore fall with claim 23. 37 C.F.R. § 41.37(c)(1)(vii).

II.

The Examiner has rejected claims 23-37 under the doctrine of obviousness-type double patenting based on the claims of each of five issued patents (U.S. Patents 7,097,842 B2; 6,761,893 B2; 7,335,364 B2; 6,913,752

B2; and 7,459,270 B2), each combined with Cardosa (Answer 7-10). The Examiner concludes that the claims on appeal are not patentably distinct from the claims in the commonly assigned, issued patents (*see id*.).

Appellants argue that, as with the rejections for obviousness, the double patenting rejections should be reversed because neither the patented claims nor Cardosa teach or provide an expectation that the claimed vector would induce an immune response against at least two Dengue virus serotypes (Appeal Br. 20).

This argument is not persuasive for the reasons discussed above in the context of the obviousness rejection. Because Appellants have not provided any other basis for concluding that the pending claims are patentably distinct from the previously patented claims, we affirm the rejections for obviousness-type double patenting.

SUMMARY

We affirm the rejection of claims 23-37 under 35 U.S.C. § 103(a) based on Cardosa and Chaplin. We also affirm the rejections of claims 23-37 for obviousness-type double patenting.

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

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