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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DAVID C. DIAMOND and ADRIAN ION BOT

Appeal 2011-002613
Application 11/323,520
Technology Center 1600

Before DONALD E. ADAMS, DEMETRA J. MILLS, and
LORA M. GREEN, *Administrative Patent Judges*.

Opinion for the Board filed by *Administrative Patent Judge* Green.

Opinion Concurring filed by *Administrative Patent Judge* Mills.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's rejection of claims 1-3, 6-10, 13-17, 19-42, 44, and 45.¹ We have jurisdiction under 35 U.S.C. § 6(b).

¹ Claims 4, 5, 11, 12, 18, and 43 are also pending, but stand withdrawn from consideration (App. Br. 4).

STATEMENT OF THE CASE

Claim 1 is representative of the claims on appeal, and reads as follows:

1. A method of immunization, the method comprising the steps of:
 - delivering directly to a lymphatic system of a mammal a composition comprising an immunogen, the immunogen comprising a class I MHC-restricted epitope or a B cell epitope, wherein the composition does not comprise an effective class II MHC-restricted epitope; and
 - administering an immunopotentiator to the mammal such that an epitope-specific immune response is induced without substantial activation or expansion of CD4+ T cells.

The Examiner required an election of species in an office action dated April 9, 2008. In response to the species election requirement, Applicants elect (i) HIV as the viral disease, (ii) a nucleic acid molecule expressing SEQ ID NO: I as the first immunogen, (iii) CpG as the immunopotentiator, and (iv) the epitopic peptide of SEQ ID NO: 1 as the second immunogen. (Response to Restriction Requirement dated April 28, 2008.)

When the Examiner has required the Applicant to elect a chemical species for examination, the issue on appeal is the patentability of the elected species. We thus limit discussion to that single issue and take no position respecting the patentability of the broader generic claims, including the remaining, non-elected species. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987).

The following grounds of rejection are before us for review:

- I. Claims 1-3, 6-10, 13-17, 19-42, 44 and 45 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Giri,² Kan-Mitchell,³ Maloy⁴ and Krieg⁵ (Ans. 4).
- II. Claims 1-3, 6-10, 13-17, 19-42, 44, and 45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7, 15-19, 26, 27, 30, 33, 34, 43, 45, 85, and 86 of copending Application No.10/871,707 (Ans. 7).

We reverse Rejection I, but affirm Rejection II.

ISSUE (Obviousness)

Does the preponderance of evidence of record support the Examiner's conclusion that the claimed method of immunization is rendered obvious by the combination of Giri, Kan-Mitchell, Maloy and Krieg?

² Giri et al., *DNA Vaccines against Human Immunodeficiency Virus Type 1 in the Past Decade*, 17 CLINICAL MICROBIOLOGY REVIEWS 370-389 (2004).

³ Kan-Mitchell, *The HIV-1 HLA-A2-SLYNTVATL Is a Help-Independent CTL Epitope*, 172 J. IMMUNOLOGY 5249-5261 (2004).

⁴ Maloy et al., *Intralymphatic immunization enhances DNA vaccination*, 98 PNAS 3299-3203 (2001).

⁵ Krieg et al., *The role in CpG dinucleotides in DNA vaccines*, 6 TRENDS IN MICROBIOLOGY 23-27 (1998).

FINDINGS OF FACT

- FF1. The Examiner relies on Giri for teaching advantages of DNA vaccines, as well as teaching the CpG immunomodulator (Ans. 4-5).
- FF2. The Examiner notes that Giri “fails to disclose the delivery of a class I MHC-restricted epitope to a lymphatic system” (*id.* at 5).
- FF3. The Examiner relies on Kan-Mitchell for teaching the “HIV-1 Gag epitope HLA-A2 SLYNTVATL [“SL9”] (or SEQ ID NO: 1, the elected immunogen)” (*id.*).
- FF4. The Examiner finds that Kan-Mitchell teaches that the epitope “has a role in restricting viral replication (page 5249)” (*id.*).
- FF5. The Examiner also finds that Kan Mitchell teaches “‘... the ability to produce autocrine mediators to sustain proliferation may explain the predominance of SL9-CTLs in the circulation as well as in gut-associated lymphoid tissues during chronic HIV-infection, when CD4 helper activity is diminished’ (see p. 5259)” (*id.*).
- FF6. Kan-Mitchell teaches that the SL9 is the most studied of the five HLA-A2-restricted Gag epitopes (Kan-Mitchell, p. 5249, second col.). According to Kan-Mitchell, “[u]sing SL9-tetramers, a strong negative association was shown between levels of SL9-CTLs [cytotoxic T-lymphocytes] and viral load in A*0201-positive adults with chronic infection, which suggests a role in restricting viral replication” (*id.* (reference omitted)).
- FF7. Kan-Mitchell teaches further that the “failure of SL9-CTLs to control initial viremia has led to the suggestion that this epitope, at least the native consensus sequence, is a poor choice for vaccine design” (*id.*).

FF8. The Examiner finds that Maloy teaches “intralymphatic immunization enhancement of DNA vaccination” (Ans. 5).

FF9. The Examiner finds that Maloy teaches that “direct administration of naked DNA to lymphoid organs is 100- to 1000-fold more efficient than immunization via conventional routes and this route may be a means for optimizing the immunogenicity of DNA vaccines (see 3299)” (*id.*).

FF10. The Examiner finds that Krieg teaches “the effects of using CpG dinucleotides within DNA vaccines” (*id.* at 6).

FF11. The Examiner concludes:

[I]t would have been obvious to one of ordinary skill in the art to combine the teachings above and perform the claimed method. One would have been motivated to do so given that the DNA prime-boost strategy is well-characterized and widely used as disclosed by Giri et al, Maloy describes that lymphatic immunization is 100- to 1000-fold more efficient than other conventional routes, and Kan-Mitchell provides that SEQ 1D NO: 1 has a role in restricting viral replication. Additionally, the sequence set forth by SEQ 1D NO: 1 and CpG-containing sequences have been extensively studied and are well-characterized both structurally and functionally in potential vaccine compositions (see Kan-Mitchell).

(*Id.*)

ANALYSIS

Appellants argue that the Examiner has “ignore[d] and/or mischaracterized key teachings within the cited references, in order to find an alleged motivation to cobble together a combination of elements that would correspond to the claims” (App. Br. 10). Appellants assert that the ordinary artisan, upon reading Kan-Mitchell, would not envision using the

“disclosed epitope to immunize a mammal by direct delivery to the lymphatic system” (*id.* at 12), asserting that deficiency is not remedied by Maloy (*id.* at 15).

We agree with Appellants that the Examiner has failed to set forth a prima facie case of obviousness. As the Supreme Court pointed out in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” Rather, the Court stated:

[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added); *see also id.* at 418 (requiring a determination of “whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue”) (emphasis added).

The Examiner relies on Kan-Mitchell for its characterization of SL9 epitope (FFs3 and 4), and for teaching that the epitope has a role in restricting viral replication, and that SL9-CTLs are predominant in the gut-associated lymphoid tissues as well as circulation during chronic HIV-infection (FF5). The Examiner then relies on Maloy for teaching that intralymphatic immunization enhances DNA vaccination (FF8).

The Examiner, however, has not provided a reason as to why the ordinary artisan would use the SL9 peptide epitope of Kan-Mitchell, which Kan-Mitchell teaches is a poor choice for vaccine design (FF7), in a naked DNA vaccine for intralymphatic immunization of as taught by Maloy.

The Examiner states that one would use the SL9 epitope as a vaccine because of its role in restricting viral replication (FF4). The Examiner presents no evidence or scientific reasoning, however, as to why that property would suggest to the ordinary artisan that a DNA encoding the SL9 peptide epitope of Kan-Mitchell would be a good candidate for the intralymphatic DNA vaccination method of Maloy.

Giri and Krieg fail to make up for the foregoing deficiencies in the combination of Kan-Mitchell and Maloy.

CONCLUSION OF LAW

We conclude that the preponderance of evidence of record does not support the Examiner's conclusion is rendered obvious by the combination of Giri, Kan-Mitchell, Maloy and Krieg.

ANALYSIS (Obviousness-type double patenting)

As Appellants have failed to address the merits of the obviousness-type double patenting rejection (*see* App. Br. 16), the rejection is summarily affirmed.

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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

cdc

MILLS, *Administrative Patent Judge*, concurring.

“Embodiments of the present invention generally relate to a general manner of eliciting the induction, expansion and/or differentiation of the CD8⁺ T cell population while eliciting only a modest or no CD4⁺ T helper response (in a fashion independent of CD4⁺ T helper response).” (Spec. ¶ [0014].)

Prior to the instant invention, vaccine strategies commonly relied upon interaction with CD4⁺ cells, or resulted in their expansion. This can have detrimental consequences in instances in which the activation or expansion of CD4⁺ cells is associated with a pathological process. For example, in HIV infection, otherwise common vaccination strategies can detrimentally provide the virus with more target cells to infect.

(App. Br. 9.)

Grounds of Rejection

Claims 1-3, 6-10, 13-17, 19-42, 44 and 45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Giri, Kan-Mitchell, Maloy and Krieg.

Claims 1-3, 6-10, 13-17, 19-42, 44, and 45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7, 15-19, 26, 27, 30, 33, 34, 43, 45, 85, and 86 of copending Application No.10/871,707 (PGPUB 20050079152).

Discussion

Claims 1-3, 6-10, 13-17, 19-42 and 44-45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Giri, Kan-Mitchell, Maloy and Krieg.

ISSUE

The Examiner concludes that

it would have been obvious to one of ordinary skill in the art to combine the teachings above and perform the claimed method. One would have been motivated to do so given that the DNA prime-boost strategy is well-characterized and widely used as disclosed by Giri et al, Maloy describes that lymphatic immunization is 100- to 1000-fold more efficient than other conventional routes, and Kan-Mitchell provides that SEQ ID NO: 1 has a role in restricting viral replication. Additionally, the sequence set forth by SEQ ID NO: 1 and CpG-containing sequences have been extensively studied and are well-characterized both structurally and functionally in potential vaccine compositions (see Kan-Mitchell). ... There would have been a reasonable expectation of success given the successes taught by the above art in DNA inoculation, SEQ ID NO:1 responses and CpG-mediated responses.

(Ans. 6.)

Appellants summarize their arguments as follows:

a person of ordinary skill in the art, familiar with the teachings of these references but unfamiliar with Appellants' disclosure and claims, would not make the combination that is relied upon by the Examiner for at least the following reasons:

(a) The study of Kan-Mitchell, using an epitope in an *in vitro* system in which CD4⁺ T cells and/or IL-2 were absent, is not directly analogous to doing *in vivo* immunizations with an aim of avoiding activation or expansion of CD4⁺ cells.

(b) Kan-Mitchell itself teaches that, for *in vivo* treatments, using a helper T cell-independent epitope “may actually be deleterious to the development of a protective antiviral immunity.”

(c) Giri teaches that the generation of CD4⁺ helper cells provides an advantageous effect for generating an immune

response, confirming Kan-Mitchell's teaching to seek-not avoid-involvement of CD4⁺ helper cells for *in vivo* treatments.

Accordingly, the Examiner's obviousness argument fails because no real motivation exists for combining the references, and no reasonable expectation of success in making the combination for *in vivo* immunization.

(App. Br. 15.)

Appellants assert that the ordinary artisan, upon reading Kan-Mitchell, would not envision using the “disclosed epitope to immunize a mammal by direct delivery to the lymphatic system” (*id.* at 12), asserting that deficiency is not remedied by Maloy (*id.* at 15).

The issue is: Does the cited prior art support the Examiner’s conclusion that the claimed invention is obvious? Does the prior art teach away from the Examiner’s proposed combination of references?

ANALYSIS

I concur with the majority Decision to reverse the obviousness rejection, but on a different basis. I am persuaded by Appellants’ arguments and do not find that the Examiner has set forth a prima facie case of obviousness on the cited evidence.

Kan-Mitchell et al. indicates that, “The failure of SL9-CTLs to control initial viremia has led to the suggestion that this epitope, at least the native consensus sequence, is a poor choice for vaccine design.” (Page 5249, col. 2.) Although Kan-Mitchell et al. observed in *in vitro* studies that “SL9-CTLs were capable of recognizing naturally processed viral peptides” (page 5251, col. 2), Kan-Mitchell ultimately concluded from their research that,

Our studies demonstrate that SL9 produces a poor CTL response, one that appears to be overstimulated and sensitive to destruction by apoptosis. Moreover, SL9-CTLs may lack the ability to differentiate into memory cells: help-independent CTL responses have been shown to be defective in secondary encounters with Ags (86, 87). Because an immunodominant epitope can inhibit T cell expansion against other epitopes during an immune response (88), the anti-SL9 response may actually be deleterious to the development of a protective antiviral CTL immunity.

Native viral proteins may not be optimal vaccines (89), although most currently available HIV vaccines are based on the natural form of the pathogen, leading groups to explore purposeful alterations to increase potency (89-91). Proof-of-principle studies have validated that epitope enhancement can improve immunogenicity and the quality of an antiviral immune response (88-92). Modifications of the antigenic peptides can result in significant changes in T cell activation (92) and AICD (44). In contrast to previous assumptions (93), we propose that less immunogenic but *help-dependent peptide variants of SL9* will be better in vivo immunogens, because they will provoke memory responses. SL9 variants might be incorporated into multiepitopic vaccines or rationally modified for vaccines containing HIV Gag. The availability of consistently generated, highly homogeneous SL9-specific CTL cultures would significantly facilitate this effort.

(Page 5259, bridging paragraph, cols. 1-2.) These observations by Kan-Mitchell would suggest that one of ordinary skill in the art explore the possibility that, “*that less immunogenic but help-dependent peptide variants of SL9 will be better in vivo immunogens,*” and be dissuaded from pursuing unmodified SL9 as a vaccine because “*the anti-SL9 response may actually be deleterious to the development of a protective antiviral CTL immunity.*” (*Id.*)(Emphasis added.)

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

I therefore agree with Appellants that Kan-Mitchell teaches away from the cited combination of references and that a person of ordinary skill, upon reading the Kan-Mitchell reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The Examiner has not provided a reason as to why the ordinary artisan would use the SL9 peptide epitope of Kan-Mitchell, which Kan-Mitchell teaches "is a poor choice for vaccine design" (Kan-Mitchell, p. 5249, second col.). Kan-Mitchell's teaching that "*that less immunogenic but help-dependent peptide variants of SL9 will be better in vivo immunogens,*" would have dissuaded one of ordinary skill in the art from pursuing unmodified SL9 as a vaccine because "*the anti-SL9 response may actually be deleterious to the development of a protective antiviral CTL immunity.*" The Examiner has not explained how such negative teachings in Kan-Mitchell would have provided motivation to use the Kan-Mitchell peptide in a vaccine to be administered directly to the lymphatic system with an expectation of success.

The obviousness rejection should be reversed as Kan-Mitchell teaches away from the proposed combination of references.

Obviousness-type double patenting

Claims 1-3, 6-10, 13-17, 19-42 and 44-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 7, 15-19, 26, 27, 30, 33-34, 43, 45 and 85-86 of copending Application No. 10/871,707 (PGPUB 20050079152).

“Appellants submit that they have acknowledged the provisional double-patenting rejection, the Examiner has noted this acknowledgement, and that Appellants are not required to address the merits of the provisional double-patenting rejections until such time as the copending application issues and the rejection [is] made non-provisional.” (App. Br. 16.) Appellants cite no specific authority for not reaching the merits of the obviousness-type double patenting rejection.

However, MPEP 804(B)(1) states:

If “provisional” ODP rejections in two applications are the only rejections remaining in those applications, the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer. A terminal disclaimer must be required in the later-filed application before the ODP rejection can be withdrawn and the application permitted to issue. If both applications are filed on the same day, the examiner should determine which application claims the base invention and which application claims the improvement (added limitations). The ODP rejection in the base application can be withdrawn without a terminal disclaimer, while the ODP rejection in the improvement application cannot be withdrawn without a terminal disclaimer.

Thus, Appellants' argument that they are not required to address the merits of the provisional double-patenting rejections until such time as the copending application issues and the rejection is made non-provisional, is not applicable in the present case.

Copending Application No. 10/871,707 was originally filed on June 17, 2004, and is the earlier filed application. The present application was filed on December 29, 2005 claiming priority to a provisional application filed December 29, 2004. Thus, the pending application is not the earlier application and the examiner cannot withdraw the ODP rejection in the present application to permit it to issue without need of a terminal disclaimer.

Moreover, recent activity in the copending application includes the filing of an RCE application on Sept. 26, 2011, and a Rule 1.132 Affidavit on the same date. Therefore, the provisional obviousness-type double patenting rejections are not the only remaining rejections in each application, and the present application is the later filed application, so Appellants are required to file a terminal disclaimer in the present application or address the merits of the obviousness-type double patenting rejection. MPEP 804(B)(1). As Appellants have failed to address the merits of the obviousness-type double patenting rejection and there is no terminal disclaimer of record in the application, the rejection is summarily affirmed.

Even though the obviousness rejection is reversed, all claims remain subject to the affirmed obviousness-type double patenting rejection, and therefore, the rejection of the claims is affirmed.