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11491 SUNSET HILLS ROAD
SUITE 340
RESTON, VA 20190

EXAMINER
MARTINEZ, TARA L

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JEAN-CLAUDE SIRARD and JOSE A. CHABALGOITY

Appeal 2017-007361
Application 14/185,077[1]
Technology Center 1600

Before DEBORAH KATZ, RACHEL H. TOWNSEND, and DAVID COTTA *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of treating an acute respiratory tract infection, which have been rejected as obvious and on the ground of obviousness-type double patenting. Oral argument was heard on January 17, 2019. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

STATEMENT OF THE CASE

"Current therapies for respiratory tract infections involve the administration of antiviral agents, anti-bacterial, and antifungal agents for

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[1] Appellants identify the real party in interest as Institut National de la Sante et de la Recherche Medicale. (Appeal Br. 3.)

the treatment, prevention, or amelioration of viral, bacterial, and fungal respiratory tract infections, respectively." (Spec. 1.) An example of a bacterium that causes upper and lower respiratory tract infections is *Streptococcus pneumoniae*." (*Id.*)

"Unfortunately, in regard to certain infections, there are no therapies available, infections have been proven to be refractory to therapies, or the occurrence of side effects outweighs the benefits of the administration of a therapy to a subject." (*Id.*) "Therefore, new therapies for the treatment, prevention, management, and/or amelioration of respiratory tract infections and symptoms thereof are needed." (*Id.* at 2.)

"Activation of innate defen[s]es is essential to control pneumococcal infection." (*Id.*) "Modulating immunity by the activity of innate receptors is an emerging concept to elicit protective responses against infections." (*Id.*) "The effectiveness of TLR [(toll-like receptor)] agonists for therapeutic treatment of infectious diseases has been demonstrated in several animal models, including models of respiratory tract infections." (*Id.*) "Various cells of the pulmonary tract including the epithelial cells express TLR5 but the modulation of the TLR5 signalling pathway has not yet been investigated for the treatment of respiratory tract infections." (*Id.*) "[T]he present invention relates to a TLR5 agonist for use in a method for treating a respiratory tract infection." (*Id.* at 3.)

Claims 24, 27, 28–35, and 41–46 are on appeal. Claim 24 is representative and reads as follows:

> 24. A method of treating an acute respiratory tract infection comprising administering to a subject that has an acute respiratory tract infection caused by *Streptococcus pneumonia* a therapeutically effective amount of a TLR5 agonist, wherein the

> TLR5 agonist consists of a flagellin polypeptide, and wherein said TLR5 agonist is administered topically by intranasal administration or pulmonary administration.

(Appeal Br. 27.)

The following grounds of rejection by the Examiner are before us on review:

Claims 24 and 27 under 35 U.S.C. § 103(a) as unpatentable over Aderem[2] and CDC.[3]

Claims 28–32 under 35 U.S.C. § 103(a) as unpatentable over Aderem and Sirard '415.

Claims 33, 35, 41–44, and 46 under 35 U.S.C. § 103(a) as unpatentable over Aderem, Sirard '415,[4] and Nempont.[5]

Claims 28–34 and 41–45 under 35 U.S.C. § 103(a) as unpatentable over Aderem and Sirard '962.[6]

Claims 24 and 26–46, provisionally, for nonstatutory double patenting as being unpatentable over claims 1, 8–11, 13, and 20 of copending Application No. 13/000167 in view of Aderem.

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[2] Aderem et al., US 2009/0297552 A1, published Dec. 3, 2009.
[3] Centers for Disease Control and Prevention, Pneumococcal Disease, In Hamborsky J, Kroger A, Wolfe S, (Eds.), *Epidemiology and Prevention of Vaccine-Preventable Diseases*, 13th Ed. (2015), retrieved from https://www.cdc.gov/vaccines/pubs/pinkbook/pneumo.html.
[4] Sirard et al., US 2006/0257415 A1, published Nov. 16, 2006.
[5] Nempont et al., *Deletion of Flagellin's Hypervariable Region Abrogates Antibody-Mediated Neutralization and Systemic Activation of TLR5-Dependent Immunity*, 181 J. Immunol., 2036–2043 (2008).
[6] Sirard, US 2011/0110962 A1, published May 12, 2011.

DISCUSSION

Obviousness

The Examiner finds that Aderem teaches that flagellin polypeptides stimulate an innate immune response and that endogenously expressed flagellin polypeptides stimulate TLR5. (Final Action 3.) The Examiner further finds that Aderem teaches a method of treating or reducing the risk of pathogenic infection such as viral, bacterial, and parasitic infections, that includes administration of flagellin. (*Id.*) The Examiner finds that Aderem "clearly states [in paragraph 4] that the flagellin **can be used alone or** in conjunction with antigens." (Ans. 14; Final Action 4.)

The Examiner notes that while Appellants' claim requires that the "TLR5 agonist **consists** of a flagellin polypeptide" and therefore cannot include any other elements other than being a flagellin polypeptide, the composition that is "administered for treatment . . . is open and does not exclude additional, unrecited elements" because the claim recites "[a] method of treating acute respiratory tract infection **comprising** administering. . . ." (Ans. 14.)

The Examiner further finds that Aderem discloses intranasal administration of flagellin polypeptide and provides an example of such intranasal administration. (Final Action 4.)

Regarding the requirement that the treatment be for an acute respiratory tract infection, the Examiner points out that Aderem teaches "treatment of *Streptococcus pneumonia*" and that "[t]he CDC-Pneumococcal diseases reference teaches that *Streptococcus pneumonia* causes an acute bacterial infection." (*Id.*)

We disagree with the Examiner's factual finding that Aderem teaches administration of flagellin polypeptide alone and the Examiner's conclusion of obviousness based thereon. Paragraph 4 of Aderem, which the Examiner relies on as the disclosure in Aderem supporting the use of flagellin polypeptides alone states in its entirety:

> The invention relates to vaccines that provide flagellin polypeptides for stimulation of an innate immune response. The flagellin polypeptides may be used alone or in conjunction with antigens for eliciting adaptive immune responses.

As Appellants point out, the vaccine to which this paragraph of Aderem refers is discussed more fully under the section entitled "Disclosure of the Invention," which beings at paragraph 15. There it is noted that the vaccine employs flagellin polypeptides that are able to elicit both extracellular and intracellular based innate immune responses. (Aderem ¶ 15.) It is further explained that toll like receptor 5 (TLR5) and Ipaf mediate aspects of the innate immune response and that Ipaf is an intracellular pathway, while TLR5 molecules are on the cell surface. (*Id.* ¶¶ 25, 34.) It is noted that (1) the innate immune responses due both to the response to TLR5 and Ipaf are "independent of specific antigens, but can act as an adjuvant to an adaptive immune response that is antigen specific," and (2) the antigen for the adaptive immune response "may be supplied externally in the form of a vaccine or infection, or may be indigenous, for example, as is the case for tumor-associated antigens." (*Id.* ¶ 10.)

The specification of Aderem goes on to explain that direct administration of isolated flagellin polypeptides does not stimulate an Ipaf-mediated response because it does not enter the cytoplasm of a targeted immune cell in intact form that is capable of stimulating Ipaf. (*Id.* ¶ 34.)

The invention is thus to "vaccine compositions [that] include nucleic acids that encode an immunomodulatory flagellin polypeptide and direct[s] its expression, thereby stimulating certain aspects of the innate immune response." (Aderem ¶ 33.) The Aderem specification explains that such expression can result in flagellin being released into the extracellular environment by cell lysis or secretion where the flagellin can interact with and/or stimulate TLR5. (*Id.*) Aderem further explains that where the flagellin remains in the cytosol of a mammalian cell that has been infected with a flagellin-expressing transgenic virus or bacterium (or by use of a fusion protein consisting essentially of an immunomodulatory flagellin polypeptide fused to an antigen and/or an amino acid sequence that facilitates cell penetration in the cells), the cytosolic flagellin may "interact with and/or stimulate an Ipaf-mediated signaling pathway within the cell." (*Id.*; *see also* Aderem claim 1.)

Example 1 of Aderem describes creation of recombinant viruses expressing flagellin, and Example 2 indicates that the flagellin expressed thereby once in the extracellular space is capable of activating TLR5. Example 3 indicates that when the flagellin is expressed as a free protein in the cytosol of a macrophage infected with the recombinant virus expressing flagellin, Ipaf signaling is activated. (Aderem ¶¶ 102–105.)

In light of the foregoing, we understand the second sentence of paragraph 4 of Aderem to indicate that, in the context of the vaccine that provides flagellin for stimulation of the innate immune response, the flagellin polypeptide produced from the flagellin-expressing transgenic virus or bacterium flagellin polypeptide is used by the cell alone to produce the adaptive immune response or in conjunction with antigens to produce the

adaptive immune response. We do not understand Aderem to teach or suggest administering flagellin polypeptide to treat an infection, as the Examiner asserted.

While it is true, as the Examiner asserted in the Answer (Ans. 14), that Appellants' claim allows for additional, unrecited elements in the treatment, it does require administration of a flagellin polypeptide. Aderem teaches administration of a recombinant vaccine where the vaccine produces flagellin. We do not find that such an administration of the vaccine is administration of flagellin.

"A rejection based on section 103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art". *In re Warner*, 379 F.2d 1011, 1017 (CCPA 1967). For the reasons discussed above, we determine that the Examiner has not set forth a factual basis that is sufficient to support a conclusion of obviousness of the Appellants' claimed invention. Accordingly, we reverse the Examiner's rejection of claims 24 and 27 under 35 U.S.C. § 103(a) as unpatentable over Aderem and CDC.

The Examiner's rejections of the remaining claims as obvious rest on the position that Aderem teaches administration of flagellin to treat infection (Final Action 5, 8, and 11), which we rejected above. Accordingly, we reverse the remaining obviousness rejections for the reasons provided above.

Nonstatutory Double Patenting

The Examiner's nonstatutory double patenting rejection also rests on the position that Aderem teaches administration of flagellin to treat infection

(Final Action 19), which we rejected above. Accordingly, we reverse this rejection of the claims as well.

SUMMARY

We reverse the rejection of claims 24 and 27 under 35 U.S.C. § 103(a) as unpatentable over Aderem and CDC.

We reverse the rejection of claims 28–32 under 35 U.S.C. § 103(a) as unpatentable over Aderem and Sirard '415.

We reverse the rejection of claims 33, 35, 41–44, and 46 under 35 U.S.C. § 103(a) as unpatentable over Aderem, Sirard '415, and Nempont.

We reverse the rejection of claims 28–34 and 41–45 under 35 U.S.C. § 103(a) as unpatentable over Aderem and Sirard '962.

We reverse the rejection of claims 24 and 26–46, provisionally, for nonstatutory double patenting as being unpatentable over claims 1, 8–11, 13, and 20 of copending Application No. 13/000167 in view of Aderem.

REVERSED