

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte
MISAKO MATSUMOTO and TSUKASA SEYA

Appeal 2008-3534
Application 10/512,873
Technology Center 1600

Decided: October 29, 2008

Before DONALD E. ADAMS, DEMETRA J. MILLS, and ERIC GRIMES,
Administrative Patent Judges.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an isolated antibody. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

“[A]n immunocompetent cell of the innate immunity system such as [a] macrophage and a dendritic cell detects foreign substances entered via a receptor, induces release of cytokine and activates lymph cells by expression of sub-stimulating molecules” (Specification 3). “A Toll-like receptor which recognizes various microbial components and transmits a danger signal into a host is one of the foregoing microbial receptors” (*id.*). The Specification discloses that “it is known that type I interferon … plays an important role in defending against viral infection,” (*id.* at 4) but that it “was not known that signaling pathways … in the production of the type I interferon exist … downstream of the human Toll-like receptor 3” (*id.* at 4-5).

The Specification discloses “an antibody against a Toll-like receptor having a function for inhibiting production of type I interferon which is induced by a viral double-stranded RNA” (*id.* at 5).

DISCUSSION

1. CLAIMS

Claim 1 is on appeal. Claims 2-8 are also pending but have been withdrawn from consideration by the Examiner. Claim 1 reads as follows:

Claim 1: An isolated antibody which specifically binds to human Toll-like receptor 3 and inhibits production of type I interferon.

2. OBVIOUSNESS

Claim 1 stands rejected under 35 U.S.C. § 103(a) as obvious in view of Hardiman¹ and Alexopoulou.²

¹ Hardiman et al., WO 98/50547, Nov. 12, 1998.

² Alexopoulou et al., 413 NATURE 732-738 (2001).

The Examiner relies on Hardiman as disclosing “an antibody to the human Toll-like receptor (TLR) 3 . . . [that] blocks physiological responses to the receptor ligands which may be a result of the inhibition of binding of the ligand to the receptor” (Answer 3).

The Examiner relies on Alexopoulou as disclosing “that mammalian TLR3 recognizes dsRNA, and that the activation of the receptor induces the activation of NF- κ B and the production of type I interferons” (*id.*).

The Examiner concludes that “[o]ne of ordinary skill in the art would have been motivated to combine Alexopoulou et al. and Hardiman et al. because both are directed to antibodies of TLR-3 and the therapeutic uses thereof” (*id.*) and that Alexopoulou provides “a mechanism of action for the application of the antibody and explanation for the link between the antibody and some of its functional elements” (*id.* at 3-4).

We conclude that the Examiner has set forth a *prima facie* case that claim 1 would have been obvious to the ordinary artisan. Hardiman discloses nucleic acids encoding several human Toll-like receptors, designated DTLR2-10 (Hardiman, abstract). The amino acid sequence of human TLR-3 is shown in Hardiman’s SEQ ID NO: 6 (*id.* at 14-15, 108-111). Hardiman also discloses that the disclosed protein sequence “can be used as an immunogen for the production of antisera or antibodies specific . . . for the DTLR or various fragments thereof,” and specifically “contemplates antibodies having binding affinity to or being raised against the amino acid sequences shown in SEQ ID NOS: 4, 6, [etc.]” (*id.* at 36).

Finally, Hardiman discloses that such antibodies “can have significant diagnostic or therapeutic value. They can be potent antagonists that bind to

the receptor and inhibit binding to ligand or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate” (*id.* at 46).

Alexopoulou discloses that “mammalian TLR3 recognizes dsRNA, and that activation of the receptor induces the activation of NF-κB and the production of type I interferons (IFNs)” (Alexopoulou 732).

We agree with the Examiner that it would have been *prima facie* obvious to one of skill in the art to combine the teachings of Hardiman and Alexopoulou and thereby arrive at the invention of claim 1. Hardiman discloses the complete amino acid sequence of TLR-3, and discloses that antibodies to TLR-3 have diagnostic and therapeutic value, and can inhibit its ability to elicit a biological response. Alexopoulou discloses that a response elicited by the TLR-3 receptor in response to ligand stimulation is the production of type I interferons. Thus, the references would have suggested to one of skill in the art an isolated antibody that specifically binds to human Toll-like receptor 3 and inhibits production of type I interferon, as recited in claim 1.

Appellants argue that the references fail to provide a reasonable expectation that a neutralizing antibody could be obtained (Appeal Br. 3). Appellants cite three reasons as support for their position: (1) low levels of expression of TLR-3 compared to other Toll-like receptors (Appeal Br. 3-4); (2) the fact that peptide fragments do not show tertiary structure (Reply Br. 6); and (3) the Japanese Patent Office Examination Guidelines indicate that the probability of obtaining neutralizing antibodies is low (Appeal Br. 3; Reply Br. 8).

First, Appellants cite Matsumoto³ as evidence that TLR3 is expressed at lower levels on human cells than TLR2 or TLR4 (Appeal Br. 3). Appellants argue that “the number of antibody-secreting cells in an immunized animal prior to fusion/production of hybridoma … will vary in direct proportion with abundance of antigen” and therefore “when immunization is performed with human TLR3 expressing cells, the probability of producing hybridoma expressing anti-TLR3 antibody is low” (Appeal Br. 3-4).

We are not persuaded by this argument. Matsumoto states that, in immature dendritic cells (iDC), “TLR2 and TLR4 were marginally detected by cell surface staining, while TLR3 was detected only by intracellular staining” (Matsumoto 3156, left-hand column). However, Appellants have cited no evidence to show that a person of ordinary skill in the art would have been led by Hardiman to use immature dendritic cells expressing TLR3 in order to raise antibodies. Nor have Appellants cited evidence in the record to show that TLR3 is expressed at a low level in all cells, or that the level of expression of TLR3 is so low that using recombinant cells expressing TLR3 to raise antibodies would have required undue experimentation.

Second, Appellants argue that if “peptide fragments or purified TLR are used as antigens …, it is impossible to present human TLR3 in its native state to the immune system” and thus using peptides “only allows antibodies to be obtained that do not recognize active sites of human TLR3 in its native state,” such that “it would be difficult to obtain antibodies capable of

³ Matsumoto et al., 171 JOURNAL OF IMMUNOLOGY 3154-3162 (2003).

inhibiting the function of human TLR3” (Reply Br. 5). Appellants further argue that, “with the method of using purified TLR as an antigen, TLR gets denatured at the time of purification, and accordingly it is impossible to present TLR3 in its native state to the immune system” (*id.* at 7).

Appellants also argue that the method described in Hardiman’s prophetic example VIII does not support a reasonable expectation of success because the specific cells described in that example would result in a large amount of antibodies to the cells themselves rather than to the cell-expressed TLR3 and “[t]his would make it difficult to screen for antibodies that specifically bind to human TLR3” (Reply Br. 4).⁴

We are not persuaded by these arguments. Hardiman states that a purified TLR protein can be used as an immunogen to raise antibodies specific to the TLR protein (Hardiman 36, 45). Hardiman also teaches that the antibodies can be potent antagonists that inhibit the receptor’s ability to elicit a biological response (*id.* at 46). Finally, Hardiman describes in detail methods of making, screening, and using anti-TLR antibodies (*id.* at 46-51) and provides a prophetic example of one specific method of making an antibody to TLR4 (*id.* at 85-86).

“Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.” *In re O’Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). We agree with the Examiner that Hardiman’s disclosure is sufficient to provide a

⁴ Appellants actually refer to Example VIII in Hardiman’s published U.S. patent application (US 2003/0032090), but the Hardiman European patent application contains the same example (pages 85-86).

reasonable expectation of success, and therefore to support a *prima facie* case of obviousness.

“After a *prima facie* case of obviousness has been established, the burden of going forward shifts to the applicant. Rebuttal is merely ‘a showing of facts supporting the opposite conclusion,’ and may relate to any of the *Graham* factors including the so-called secondary considerations.” *In re Piasecki*, 745 F.2d 1468, 1472 (Fed. Cir. 1984) (citations omitted). Appellants have not cited evidence in the record that supports their position that Hardiman’s disclosure of raising anti-TLR3 antibodies using TLR3-expressing cells, purified TLR3, or fragments of TLR3 would not have provided a skilled artisan with a reasonable expectation of success. Attorney argument does not take the place of evidence. *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974).

Finally, Appellants argue that a document headed “Examination Guideline for Patent and Utility Model,” which Appellants state is part of the Examination Guidelines of the Japanese Patent Office, provides evidence that that there is a low probability that an antibody raised in an animal administered a protein will recognize a neutralizing epitope (Reply Br. 8).⁵

We are not persuaded by this argument. The document relied on by Appellants reads, in its entirety,

⁵ Appellants state that the Examination Guidelines were “published by a public institution (JPO) on October 15, 2001 (prior to the filing of the present application) based on general technical standards at that time” (Reply Br. 8).

...an antibody for inhibiting an activity of a material, that is, a neutralizing antibody needs to recognize a neutralizing epitope that rarely exists in the material in general. The probability of raising such an antibody is very low. Thus, there is very low probability that an antibody raises [sic] in an animal administer[ed] with a protein A, the antibody recognizing a ‘neutralizing epitope’ that is unknown to be present or not in the protein A.

(Examination Guideline for Patent and Utility Model 1.)

This document does not rebut the Examiner’s prima facie case.

Appellants’ Examination Guidelines document does not provide or cite to any evidence to support the per se rule that it states. Nor have Appellants presented any other evidence that the Examination Guidelines show the level of ordinary skill in the art (i.e., evidence to rebut the Examiner’s reasoned finding), and attorney argument does not take the place of evidence, as discussed above. *Pearson*, 494 F.2d at 1405.

SUMMARY

The Examiner’s rejection is supported by the preponderance of the evidence of record. We therefore affirm the rejection of claim 1 under 35 U.S.C. § 103(a).

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

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