

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 41

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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

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Ex parte HARUO YOSHII,  
MITSURU NAIKI, and  
YURIKO FUKATA

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Appeal No. 2001-1907  
Application No. 08/694,315

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ON BRIEF

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Before WINTER, ADAMS, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

An oral hearing in this case was scheduled for November 21, 2002. Upon reviewing the case, however, we have determined that an oral hearing will not be necessary and we render the following decision based on the record. See 37 CFR § 1.194(c).

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 2, 5-16, 18-23 and 25-27. Claims 1, 15 and 23 are representative of the subject matter on appeal, and read as follows:



Wood et al. (Wood), "Proteins in Solution and Enzyme Mechanisms," Biochemistry A Problems Approach, 2<sup>nd</sup> edition, pp. 126-172 (1981)

Takashi et al. (Takashi), "Basic studies on nebulizer therapy with histaglobin, Systemic effects and histological findings of nasal and tracheal mucosa in guinea pigs exposed to histamine-added guinea pig gamma-globulin," Chemical Abstracts, Vol. 112, p. 50, Abstracts No. 112:111828b (1990)

Fahey et al. (Fahey), "Immune-based therapies in HIV infection," Clin. Exp. Immunol., Vol. 89, pp. 3-5 (1992)

Buckley, "Primary Immunodeficiency Diseases," Fundamental Immunology, 3<sup>rd</sup> Edition, Chp. 38, pp. 1354-1368 (1993)

Yoshii, (Yosshii II), "Arerugi," Japanese Journal of Allergology, Vol. 44, Issue 5, pp. 567-570 (1995)

Naiki et al. (Naiki), "Rat  $\gamma$ -Globulin/Histamine inhibits Experimental Allergic Encephomyelitis (EAE) in Lewis Rats," Cong. Immun., 9<sup>th</sup> Inter., Abstract 1084 (1995)

Claims 23, 26 and 27 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Claims 1-2, 5-16, 18-23 and 25-27 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by the combination of Yoshii I, Yoshii II, Naiki, Getlik, Takashi, McMichael and Wood. In addition, claims 23, 26 and 27 stand rejected under the judicially created doctrine of obviousness-type double patenting over the combination of claims 1-11 of U.S. Patent No. 5,780,026, McMichael and Wood. After careful review of the record and consideration of the issues before us, we reverse all of the rejections of record.

## DISCUSSION

1. Rejection under 35 U.S.C. § 112, first paragraph

Claims 23, 26 and 27 stand rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

According to the examiner, the specification is only enabling for the use of the activated immunoglobulin for i) inhibiting eosinophilia in mice intraperitoneally injected with ragweed pollen; ii) increasing anti-TNP antibody titers in mice immunized with SRBC; iii) decreasing DTH response in mice immunized with SRBC; and iv) inhibiting the clinical symptoms of EAE in rats. The rejection notes while the claims are drawn to a number of diseases, that “[t]here are no data of any kind regarding the use of histamine activated immunoglobulin in humans for any disease,” and that Appellants have “not established a nexus between the administration to humans of histamine activated immunoglobulin and treatment of disease commensurate in scope with [the] claim language.” Examiner’s Answer, page 4.

The rejection then lists reasons why therapeutic methods using antibodies are unpredictable. The examiner also addresses specific disease conditions, such as HIV infection, and others that “do not involve an autoimmune component in which eosinophilia is implicated in the pathology of the immunodeficiency.” Id. at page 5. The rejection concludes that “[i]n view of the previous cited teachings and in absence of data to the contrary, one with skill in the art would doubt that

histamine activated immunoglobulin has a therapeutic effect in he numerous diseases and conditions encompassed by the claims.” Id. at page 5.

The burden is on the examiner to set forth a prima facie case of unpatentability. See In re Alton, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1581 (Fed. Cir. 1996). “[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original). “[It] is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.” Id. at 224, 169 USPQ at 370. Here, the examiner has not provided “acceptable evidence or reasoning which is inconsistent” with the specification, and therefore has not met the initial burden of showing nonenablement.

In this case, one issue that the rejection focuses on is the alleged unpredictability of the therapeutic use of antibodies. That discussion, however, is very generic, and does not specifically address the claims at issue. Moreover, it ignores the data presented in the specification. In addition, merely because the

specification does not present data acquired from humans, without specific reasons and evidence why the mouse models are not reasonably predictive of performance of the method in humans, does not support the conclusion that the method claims at issue are not enabled throughout their scope. See In re Brana,

With respect to the examiner's concerns that the specification does not enable the use of the method to treat diseases that do not involve an autoimmune component in which eosinophilia is implicated in the pathology of the immunodeficiency, the specification teaches that the histamine activated immunoglobulin demonstrates therapeutic efficacy against diseases which have an autoimmune basis, as well as for eosinophilia. See Specification, page 19. Thus, based on the teachings of the specification, the skilled artisan would understand that the claimed method excludes those diseases that do not involve an autoimmune component, or those diseases in which eosinophilia is not implicated.

Because, as discussed above, the rejection fails to set forth a prima facie case that the specification fails to enable the method claims at issue throughout their scope, it is reversed.

2. Rejections over the prior art

Claims 1-2, 5-16 and 25-27 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Yoshii I, Yoshii II, Naiki, Getlik, Takashi, McMichael and Wood. Moreover, as the issues and arguments are the same for the rejection of claims 23, 26 and 27 under the judicially created doctrine of obviousness-type double patenting over the combination of claims 1-11 of U.S.

Patent No. 5,780,026, McMichael and Wood, that rejection is also included in the discussion below.

Initially, the panel would like to note that our review was hampered by the lack of claim-by-claim analysis. For example Yoshii II was cited for teaching that histamine activated immunoglobulin has eosinophilia-suppressive action, immunomodulating action, etc., as well as for disclosing methods of treating eosinophilia, inflammation and allergic diseases through the use of administering histamine activated immunoglobulin. The claims drawn to the histamine activated immunoglobulin per se, however, do not include these limitations. Moreover, the examiner cited several abstracts in the rejection. While the abstracts appeared to be cumulative to the Yoshii I reference, the panel strongly urges the examiner to obtain the full text articles in order to allow for meaningful review of prior art that serves the basis for the rejection.

Yoshii I is cited by the rejection for teaching histamine activated immunoglobulin and pharmaceutical compositions thereof. In addition, the reference teaches the activity of the activated immunoglobulin, i.e., that the activated immunoglobulin has eosinophilia-suppressive action, immunomodulating action, etc., as well as disclosing methods of treating eosinophilia, inflammation and allergic disease by administering histamine activated immunoglobulin. Yoshii II is cited as explained above. Naiki is cited for teaching that histamine activated immunoglobulin is useful for treating allergic disease, Getlik is cited for teaching the treatment of asthma with histamine

activated immunoglobulin, and Takashi is cited for teaching histamine activated immunoglobulin.

According to the rejection, McMichael teaches that histamine activated immunoglobulin is useful in the treatment of rheumatoid arthritis. In addition, McMichael is cited for teaching that:

the positive therapeutic results occur when the histamine and immunoglobulin are administered together but not when administered individually and that this result indicates a type of synergistic, joint activity or formation of a histamine/immunoglobulin complex which acts as a regulatory molecule (see column 5, lines 18-27 and column 7, lines 48-57, in particular). McMichael further teaches that essentially minute quantities within the range of  $8.8 \times 10^{-6}$  to about  $45.5 \times 10^{-3}$  mg of histamine is an effective dose of histamine . . . .

Examiner's Answer, page 7.

The examiner acknowledges that "[t]he claimed invention differs from the prior art teachings only by the removal of histamine from the . . . histamine-immunoglobulin mixture by dialysis or gel filtration." Id. Wood is then cited for teaching the separation of proteins by dialysis or gel filtration based on their size.

The rejection concludes:

Therefore a routiner [sic] in the art at the time of the invention would have been motivated to remove the histamine from the histamine-immunoglobulin mixture taught by [Yoshii I], [Yoshii II], [Naiki], [Getlik], [Takashi] and [McMichael] using the methods of separating small molecular weight molecules from larger molecules taught by [Wood] with the expectation that the histamine activated immunoglobulin would retain activity for the reasons disclosed by McMichael and that the histamine activated immunoglobulin with histamine removed would have fewer undesirable side effects.

Id.

Appellants argue that “[n]one of the references disclose any . . . activity of histamine-activated immunoglobulin that is virtually histamine free, nor could it have been expected from the disclosure of any of the references, alone or in combination. We agree.

The burden is on the examiner to make a prima facie case of obviousness, and the examiner may meet this burden by demonstrating that the prior art would lead the ordinary artisan to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). The findings of fact underlying the obviousness rejection, as well as the conclusions of law, must be made in accordance with the Administrative Procedure Act, 5 U.S.C. 706 (A), (E) (1994). See Zurko v. Dickinson, 527 U.S. 150, 158, 119 S.Ct. 1816, 1821, 50 USPQ2d 1930, 1934 (1999). Findings of fact underlying the obviousness rejection, upon review by the Court of Appeals for the Federal Circuit, must be supported by substantial evidence within the record. See In re Gartside, 203 F.3d 1305, 1315, 53 USPQ2d 1769, 1775 (Fed. Cir. 2000). In addition, in order for meaningful appellate review to occur, the examiner must present a full and reasoned explanation of the rejection. See, e.g., In re Lee, 277 F.3d 1338, 1342, 61 USPQ2d 1430, 1432 (Fed. Cir. 2002). The obviousness rejection and the obviousness-type double-patenting rejection of record do not meet the above criteria.

The claims are drawn to activated immunoglobulin in which the histamine is removed from the mixture, wherein the amount of histamine after its removal is

less than 0.2 nm. As taught by the specification, 0.2nm is the sensitivity of a radioimmunoassay method used to determine the amount of histamine remaining after its removal by dialysis. See Specification, page 10.

As acknowledged by the rejection, Yoshii I, Yoshii II, Naiki, Getlik, Takashi, while teaching histamine added immunoglobulin, do not teach the removal of the histamine after activation of the immunoglobulin. The examiner relies upon McMichael for providing motivation for removing the histamine from the histamine/immunoglobulin mixture. That reliance, however, is misplaced.

McMichael is drawn to compositions comprising histamine and one or more immunogenic substances “specifically immunologically associated with the disease state,” wherein “[t]he compositions are administered in small, ‘neutralizing doses.” McMichael, column 4, lines 27-33. Immunoglobulin, which McMichael teaches is associated with rheumatoid arthritis, is just one example of an immunogen that may be used according to the method taught by the patent. See id. at column 6, Table. While admittedly McMichael teaches that only minute doses of histamine are required, see id. at column 7, lines 22-27, the rejection neglected to read that portion in light of the teaching that the total volume of a total dose is also small, i.e., from 0.05 cc to 0.5 cc, see id. at column 7, lines 4-12. Thus the reference does not support the conclusion that one would have been motivated to remove the histamine because of the small amount of histamine administered, as the volume of the unit dosage is also small.

The examiner's finding that McMichael teaches that positive therapeutic results occur when the histamine and the immunoglobulin are administered together but not when administered individually actually teaches away from the combination, as the ordinary artisan would read that to mean that the immunogen, in order to obtain a positive therapeutic effect, should be administered with the histamine, and not as teaching that the histamine could be disposed of altogether. Finally, the examiner's assertion that one of ordinary skill would have been motivated to remove histamine because the histamine activated immunoglobulin with histamine removed would have fewer undesirable side effects is not supported by the prior art of record, but appears to be a conclusory statement, and such statements do not provide sufficient motivation to support the combination. See In re Lee, 277 F.3d 1338, 1343-44, 61 USPQ2d 1430,1433-34 (Fed. Cir. 2002) (in reviewing an obviousness rejection, the court noted that "conclusory statements" as to teaching, suggestion or motivation to arrive at the claimed invention "do not adequately address the issue.").

As neither the rejection under 35 U.S.C. § 103(a) over the combination of Yoshii I, Yoshii II, Naiki, Getlik, Takashi, McMichael and Wood, nor the obviousness-type double patenting rejection over the combination of claims 1-11 of U.S. Patent No. 5,780,026, McMichael and Wood set forth an adequate teachings, suggestions or motivations to combine the references, both rejections are reversed.

CONCLUSION

For the reasons stated above, all of the rejections of record are reversed.

REVERSED

SHERMAN D. WINTERS	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
DONALD E. ADAMS	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
LORA M. GREEN	)	
Administrative Patent Judge	)	

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