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EXAMINER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MITSUHIRO OKUDA,
KAZUAKI NISHIO, and ICHIRO YAMASHITA

Appeal 2009-015032
Application 11/508,261
Technology Center 1600

Decided: May 27, 2010

Before ERIC GRIMES, DEMETRA J. MILLS, and LORA M. GREEN,
Administrative Patent Judges.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of making a zinc oxide-ferritin complex, which the Examiner has rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

STATEMENT OF THE CASE

Claims 1-9 are on appeal. Claim 1 is the only independent claim and reads as follows:

1. A process for producing a zinc-oxide protein complex comprising:
the step a) of preparing a buffer containing a protein having a cavity inside thereof, zinc ion, and ammonia, wherein the protein having a cavity inside thereof is ferritin; and
a step b) of adding hydrogen peroxide to the buffer so that the concentration of said hydrogen peroxide is 60 mM or greater and 150 mM or less.

Issue

The Examiner has rejected claims 1-9 under 35 U.S.C. § 103(a) as unpatentable over Yamashita '386¹ (Ans. 3) or the combination of Yamashita '047² and Yamashita '386 (*id* at 6).

The Examiner finds that Yamashita '386 teaches "that zinc and oxides thereof can be introduced into apoferritin. Further, it is taught (column 6, lines 9-10) that H₂O₂ (hydrogen peroxide) is added to the solution to introduce metal oxide complexes into apoferritin." (Ans. 4.) The Examiner acknowledges that Yamashita '386 does not teach the H₂O₂ concentration range recited in the claims, but concludes that "it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions, because such conditions are art-recognized result-effective variables" (*id.* at 5).

¹ Yamashita, U.S. Patent 6,838,386 B2, Jan. 4, 2005.

² Yamashita, US 2004/0158047 A1, Aug. 12, 2004. The Examiner actually relies on Yamashita '047 or Yamashita (EP 1433743 A1, June 30, 2004) in the alternative. Since the disclosures of these references appear to be identical, we will discuss only Yamashita '047.

The Examiner finds that Yamashita '047 discloses a method of making cobalt-ferritin complexes using metal ions, apoferritin, HEPES buffer, and an H_2O_2 concentration in the range of 1 mM to 5 M (Ans. 6). The Examiner finds that Yamashita '386 discloses that “not only zinc but zinc oxide can be incorporated into apoferritin via the addition of hydrogen peroxide. Thus one would be motivated to substitute[] zinc oxide for zinc [sic, cobalt?].” (*Id.*). With regard to the H_2O_2 concentration range recited in the claims, the Examiner again concludes that “it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions, because such conditions are art-recognized result-effective variables” (*id.* at 7).

Appellants contend that Yamashita '047 would have led those skilled in the art to expect that apoferritin would be denatured by a H_2O_2 concentration in the range recited in the claims, and that the evidence of record showing efficient production of a zinc oxide-ferritin complex at the recited H_2O_2 concentrations is an unexpectedly superior result that rebuts the evidence relied on by the Examiner (Appeal Br. 4-5). Appellants also contend that the range of 1 mM to 5 M in Yamashita '047 is a mistake and should read “1 mM to 5 mM” (*id.* at 6). Appellants have submitted declaratory evidence to show that Yamashita '047 was translated incorrectly, resulting in the mM-to-M error (Appendixes III to VI attached to the Appeal Brief).

The issue with respect to both rejections is: Have Appellants shown that the H_2O_2 concentration range recited in claim 1 provides results that are superior to what would have been expected based on the prior art?

Findings of Fact

1. Yamashita '386 discloses a method of introducing iron into apoferritin by mixing HEPES buffer, apoferritin, and iron ammonium sulfate (Yamashita '386, col. 5, ll. 13-17).

2. Yamashita '386 discloses that “the concentration of iron ammonium sulfate . . . is preferably in the range of 5 to 10 mmol/L” (*id.* at col. 5, ll. 21-23).

3. Yamashita '386 discloses that “the technology of introducing chromium, manganese, cobalt, nickel, aluminum, tungsten, zinc, and oxides thereof into apoferritin has already been reported” (*id.* at col. 6, ll. 2-5).

4. Yamashita '386 discloses that “in the case of cobalt, inorganic atoms can be introduced into apoferritin by merely adding apoferritin to an ammonium solution of cobalt sulfate, adjusting the pH value to around 8.0, and then adding a small amount of H₂O₂ solution” (*id.* at col. 6, ll. 6-10).

5. Yamashita '047 discloses a “method for producing a cobalt-protein complex” (Yamashita '047 at 2, ¶ 17); the protein may be apoferritin (*id.* at 2, ¶ 21).

6. Yamashita '047 discloses that “a reaction solution is prepared by mixing a HEPES buffer solution, an apoferritin solution and Co²⁺ ion solution” (*id.* at 3, ¶ 42). “Next, . . . an oxidizing agent (e.g., H₂O₂) is added to the reaction solution” (*id.* at 3, ¶ 43).

7. Yamashita '047 discloses that the “concentration of apoferritin in the reaction solution is adjusted to be in a range from 0.1 to 1 mg/ml (about 0.2-2 µM). More specifically, it is preferably about 0.5 mg/ml (1 µM).” (*Id.* at 3, ¶ 48).

8. Yamashita '047 discloses that the " Co^{2+} ion concentration may be about 1000 to 5000 times more than . . . preferably 2000 to 3000 more than that of the apoferritin concentration. . . . For example, when the apoferritin concentration is 0.5 mg/ml (about 1 μM), Co^{2+} ions are added at a concentration of 2-3 mM." (*Id.* at 3, ¶¶ 49-50.)

9. Yamashita '047 discloses that, in the oxidizing step, "hydrogen peroxide . . . in an equal quantity or a $\frac{1}{2}$ quantity of that of cobalt ion is added to the reaction solution. For example, when the concentration of Co^{2+} ion is 2 mM, H_2O_2 is added to the reaction solution so that the final concentration of H_2O_2 is in a range from 1 mM to 2 mM." (*Id.* at 4, ¶ 52.)

10. Yamashita '047 discloses that "there may be cases in which apoferritin is denatured by addition of a hydrogen peroxide solution. Therefore, adding a salt is effective to stabilize apoferritin." (*Id.* at 4, ¶ 53.)

11. Yamashita '047 discloses that apoferritin and H_2O_2 are used at a ratio between 1:1000 and 1:5000 (*id.* at 4, Table 2). Yamashita '047 states that this corresponds to a H_2O_2 concentration of 1 mM to 5M for an apoferritin concentration of 1 μM (*id.*).

12. The Specification states that "in case of formation of the cobalt-protein complex, hydrogen peroxide is essential, although it cannot be introduced at a high concentration. The concentration is presumed to be 5 mM." (Spec. 11.)

13. The Specification provides evidence that zinc oxide-ferritin complexes form at H_2O_2 concentrations between 60 mM and 150 mM but not at a H_2O_2 concentration of 40 mM or 200 mM (*id.* at 14).

14. Appellants have provided declaratory evidence showing the results of combining different concentrations of H₂O₂ with apoferritin, zinc acetate, and ammonium (Declaration under 37 C.F.R. § 1.132, filed Feb. 8, 2008). The declaration states that at 40 mM H₂O₂, “[m]ost of the ferritin remained as apoferritin” (*id.* at ¶ 8), that at 60 mM or 150 mM H₂O₂, the zinc oxide-ferritin yield was approximately 20% (*id.* at ¶¶ 9, 11); that at 100 mM H₂O₂, the yield of zinc oxide-ferritin was 80% or higher (*id.* at ¶ 10); and that at 200 mM H₂O₂, the apoferritin was denatured and no zinc oxide-ferritin was formed (*id.* at ¶ 12).

Principles of Law

When determining obviousness, “the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill.” *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986).

“[T]he meaning of a prior art reference requires analysis of the understanding of an artisan of ordinary skill.” *Finisar Corp. v. DirecTV Group, Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008).

“One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of ‘unexpected results,’ i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.” *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

Analysis

Yamashita '386 discloses a method of making a cobalt-ferritin complex by mixing apoferritin with an ammonium solution of cobalt sulfate and adding a "small amount" of a hydrogen peroxide solution (FF 4). Yamashita '386 also discloses that "the technology of introducing . . . cobalt, . . . zinc, and oxides thereof into apoferritin has already been reported" (FF 3), although it does not expressly state that methods using zinc are similar to those using cobalt.

Yamashita '047 discloses a method of making cobalt-ferritin complexes by mixing HEPES buffer, apoferritin, and Co^{2+} ions, and then adding H_2O_2 (FF 6). Yamashita '047 discloses that the concentration of Co^{2+} ions is preferably 2000-3000 times that of the apoferritin (FF 8) and the concentration of H_2O_2 should be equal to or half that of the Co^{2+} ions (FF 9). Yamashita '047 states that the concentration of apoferritin is preferably 1 μM , in which case the concentration of Co^{2+} ions would be 2-3 mM, and that for a Co^{2+} ion concentration of 2 mM, the H_2O_2 concentration would be 1-2 mM (FFs 7-9).

Yamashita '047 also discloses that the concentration of H_2O_2 is 1000-5000 times that of the apoferritin (FF 11). The same table states that when apoferritin is used at 1 μM , H_2O_2 is used at a concentration of 1 mM to 5M (*id.*). Based on the totality of Yamashita '047, however, those of skill in the art would recognize that the "5M" in Table 2 of Yamashita '047 is a typographical error, and that "5 mM" was intended, because (a) 1 μM is equivalent to 10^{-6} M, and $5000 \times 10^{-6} \text{ M} = 5 \times 10^{-3} \text{ M}$, or 5 mM, and (b) a concentration of 5 M is over a thousand-fold higher than the other

concentrations discussed by Yamashita '047, which are consistently in the millimolar range or below.³

Thus, Yamashita '047 provides evidence that a skilled worker would have interpreted Yamashita '386's disclosure of "adding a small amount of H₂O₂ solution" (FF 4) to mean an amount of H₂O₂ on the order of 1-5 mM, rather than the 60-150 mM required by the claims on appeal.

Yamashita '047 also states that "there may be cases in which apoferritin is denatured by addition of a hydrogen peroxide solution" and that adding a salt will stabilize the apoferritin (FF 10). A skilled worker would recognize that the disclosure of this potential problem, and its solution, applies to the reaction described in Yamashita '047; i.e., a reaction using 1-5 mM H₂O₂. The instant Specification and Appellants' declaration, however, present evidence that H₂O₂ concentrations of 60-150 mM not only do not denature apoferritin but effectively form ferritin-zinc oxide complexes (FFs 13, 14). We agree with Appellants that the results presented in the Specification and declaration are unexpectedly superior to what would have been expected based on the cited prior art.

³ Appellants have presented evidence to show that the "5M" in Yamashita '047 was the result of a translating error, and that "5 mM" was intended (see Appeal Br. 6). Whether a prior art reference says what was intended by its author is not the issue, however: it says what is written, regardless of what its author intended. On the other hand, if the reference contains a typographical error that would be readily apparent to a skilled worker, then the skilled worker would understand the reference to mean something other than what it actually says. Such is the case here.

Conclusion of Law

Appellants have shown that the H₂O₂ concentration range recited in claim 1 provides results that are superior to what would have been expected based on the prior art.

SUMMARY

We reverse the rejection of claims 1-9 based on Yamashita '386 and the rejection of claims 1-9 based on Yamashita '047 combined with Yamashita '386.

REVERSED

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