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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte OTTO O. YANG, YUNFENG LU, CHENG JI, MING YAN, and YANG LIU

Appeal 2018-006733
Application 14/131,159
Technology Center 1600

BEFORE ULRIKE W. JENKS, JENNIFER MEYER CHAGNON, and ELIZABETH A. LAVIER, *Administrative Patent Judges*.

LAVIER, *Administrative Patent Judge.*

DECISION ON APPEAL

STATEMENT OF THE CASE

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 1–8 and 21–30. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

[1] We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies the real party in interest as Regents of the University of California. Appeal Br. 2.

CLAIMED SUBJECT MATTER

The claims are directed to methods for decreasing an individual's ethanol concentration. Claim 1, reproduced below, is illustrative:

> 1. A method of decreasing the concentration of ethanol in an individual comprising the steps of:
>
> (a) administering a multiple-enzyme nanocomplex system to the individual, wherein the multiple-enzyme nanocomplex system comprises:
>
> an alcohol oxidase enzyme that generates hydrogen peroxide in a first enzymatic reaction with ethanol;
>
> a catalase enzyme that converts the hydrogen peroxide into water in a second enzymatic reaction; and
>
> a polymeric network configured to form a shell that encapsulates the alcohol oxidase and the catalase, wherein:
>
> the shell is formed *in situ* on a complex comprising the alcohol oxidase enzyme coupled to the catalase enzyme so as to encapsulate the alcohol oxidase enzyme together with the catalase enzyme;
>
> the polymeric network encapsulates the alcohol oxidase and the catalase in a manner that inhibits degradation of the alcohol oxidase and the catalase when the multiple-enzyme nanocomplex is disposed in an *in vivo* environment;
>
> the polymeric network exhibits a permeability sufficient to allow the ethanol to diffuse from an external environment outside of the shell to the alcohol oxidase so that the hydrogen peroxide is generated;
>
> the polymeric network exhibits a permeability sufficient to allow the hydrogen peroxide to diffuse away from the alcohol oxidase and to the catalase so that the water is generated; and
>
> the alcohol oxidase is coupled to the catalase; or

the polymeric network is coupled to the alcohol oxidase or the catalase; and

(b) allowing the alcohol oxidase and the catalase in the multiple-enzyme nanocomplex system to react with ethanol in the individual and generate hydrogen peroxide and water;

so that the concentration of ethanol in the individual is decreased.

Appeal Br. 10 (Claims Appendix).

REFERENCES

The Examiner relies on the following references:

Name	Reference	Date
Hopkins	US 4,450,153	May 22, 1984
Somberg et al.	US 2009/0060894 A1	Mar. 5, 2009
Lu et al. ("Lu '873")	App. No. 14/130,873, published as US 2014/0134700 A1	May 15, 2014
Hnaien et al., *A rapid and sensitive alcohol oxidase/catalase conductometric biosensor for alcohol determination*, 81 TALANTA 222−27 (2009)		
Bäumler et al., C*oupled Enzyme Reactions in Multicompartment Microparticles*, BIOMACROMOLECULES, Vol. 11, No. 6, 1480−87 (2010)		
Niemeyer et al., *DNA-Directed Assembly of Bioenzymic Complexes from In Vivo Biotinylated NAD(P)H:FMN Oxidoreductase and Luciferase*, 02-03 CHEMBIOCHEM 242−45 (2002)		
Wang et al. *Semi-permeable nanocapsules of konjac glucomannan-chitosan for enzyme immobilization*, 364 INT'L J. PHARMACEUTICS 102−07 (2008)		

REJECTIONS

1. Claims 1, 3–6, and 30 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hopkins, Hnaien, and Bäumler. Final Action 3.
2. Claims 2 and 7 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hopkins, Hnaien, Bäumler, and Somberg. Final Action 7.

3. Claim 8 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Hopkins, Hnaien, Bäumler, and Niemeyer. Final Action 9.
4. Claims 21–27 and 29 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hopkins, Hnaien, Bäumler, and Wang. Final Action 10.
5. Claim 28 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Hopkins, Hnaien, Bäumler, Wang, and Niemeyer. Final Action 11.
6. Claims 1–8 and 21–30 stand provisionally rejected on the ground of nonstatutory double patenting over the claims of Lu '873, in view of Hopkins, Hnaien, Bäumler, Wang, and/or Somberg. Final Action 16.

OPINION

Obviousness

Appellant addresses the independent claims (i.e., claims 1, 21, and 30) together (*see* Appeal Br. 4–8), and does not present additional arguments regarding the dependent claims (*see id.* at 8–9). Accordingly, we treat claim 1 as representative. *See* 37 C.F.R. § 41.37(c)(1)(iv).

In rejecting claim 1, the Examiner begins with Hopkins, which teaches administering alcohol oxidase to decrease the alcohol content of human blood. Final Action 3 (citing Hopkins claim 1). Although Hopkins provides for a microencapsulating the alcohol oxidase in a semipermeable membrane (*see* Hopkins 7:11–16, claim 13; *see also* Ans. 4–5), Hopkins does not teach also using a catalase. For the coupling of alcohol oxidase and catalase, as well as the claimed permeability characteristics, the Examiner turns to Hnaien. *See* Final Action 4–5. Hnaien describes a bi-enzymatic

biosensor for quantitating alcohol in a sample, by immobilizing alcohol oxidase and catalase in a polymeric coating on an electrode. *See* Hnaien 222–23. Hnaien describes the utility of co-immobilizing alcohol oxide and catalase:

> Catalase . . . catalyzes both the decomposition of hydrogen peroxide into water and oxygen and the degradation of ethanol in the presence of H_2O_2 . . . . The first advantage of the bi-enzymatic system proposed is that ethanol acts as a substrate for both enzymes. In addition, hydrogen peroxide, produced by the alcohol oxidation at the outer membrane of the biosensor (alcohol oxidase membrane), is used as a co-substrate in the inner membrane containing catalase and regenerates oxygen, required for [the oxidization of alcohol by alcohol oxidase]. In addition, H_2O_2 consumption by catalase can help to improve [alcohol oxidase] stability.

Hnaien 223. Also with respect to claim 1, the Examiner cites Bäumler, as teaching coupling together enzymatic reactions to form a chain reaction. *See* Final Action 5 (discussing Bäumler Abstract, 1481).

Appellant offers two arguments: (1) modifying the multicompartment microparticles taught in Bäumler would render them unsatisfactory for their intended purpose, and (2) Hnaien teaches away from encapsulating the enzymes. *See* Appeal Br. 5, 7; *see also* Reply Br. 5–7. We are not persuaded by either argument.

First, Appellant is correct that in Bäumler's microparticles, the enzymes are separated into different compartments, and that this separation (and resultant spacing) controls the reaction kinetics. *See* Appeal Br. 5–6 (discussing Bäumler 1485). But "[t]he test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference . . . . Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill

in the art." *In re Keller*, 642 F.2d 413, 425 (CCPA 1981). In rejecting claim 1, the Examiner does not cite Bäumler for the *internal* structure of its microparticles, or the identity of its enzymes. Rather, the Examiner relies on Bäumler for its teaching of coupling enzymes inside a complete polymeric shell. *See* Ans. 5. Furthermore, as the above-quoted passage from Hnaien makes clear, co-immobilizing alcohol oxidase and catalase is advantageous insofar as alcohol is a substrate for both enzymes, and also because the hydrogen peroxide produced in the alcohol oxidase reaction serves as a substrate for the catalase reaction (the consumption of which, in turn, improves alcohol oxidase stability). *See* Hnaien 223. As the Examiner explains:

> The Examiner notes that the structural configuration of the Hnaien biosensor does not in any way separate into individual compartments the oxidase and catalase that are immobilized inside the polymeric covering, yet Hnaien discloses that the bi-enzymatic system described therein nevertheless successfully acts in concert to degrade ethanol. Therefore, the skilled artisan reading Hnaien would have recognized that while the enzymes could indeed be separated into different compartments as taught by Baumler, no such separation is necessary in order to couple the oxidase and catalase together; otherwise, the Hnaien configuration could not function as a biosensor that quantitates ethanol levels.

Ans. 4. In contrast, Bäumler uses different enzymes (with different reaction kinetics), for which it is helpful to separate those enzymes into different compartments. Accordingly, Appellant's argument regarding Bäumler is not persuasive.

Appellant's second argument, regarding Hnaien, is also unpersuasive because it focuses on aspects of Hnaien not relied on the by Examiner in formulating the rejection. Here, Appellant asserts that "Hnaien teaches

away from the encapsulation of enzymes because **the bienzymatic biosensor of Hnaien requires contact between the enzymes and the electroactive surface of the electrodes** in the biosensor (contact that cannot occur if the alcohol oxidase and catalase were encapsulated by a polymeric shell)." Appeal Br. 7. Such incomplete encapsulation may well be necessary for *electrodes*, but not for formulating a composition (i.e., a "multiple-enzyme nanocomplex system" as recited in claim 1) for administration. As the Examiner explains:

> this argument is not persuasive because the rejection does not propose to modify the Hnaien biosensor by encapsulating the glucose oxidase and catalase together within a polymer shell. Hnaien is merely a secondary reference used to modify the method of the primary reference Hopkins (which does not involve the use of an electrode) by providing a motivation to couple the oxidase with a catalase inside a polymeric membrane as taught by Hnaien. Consequently, the method of the prior art as combined in the rejection does not even comprise an electrode that would be rendered useless if the enzymes were fully encapsulated as argued by Appellant.

Ans. 6. We agree. Accordingly, we are not persuaded that Hnaien teaches away from claim 1.

Having considered Appellant's two arguments, we are not convinced of any reversible error by the Examiner in rejecting claim 1. Accordingly, we affirm the rejection of claim 1. Claims 3–6 and 30 fall with claim 1. The rejections of the remaining claims (i.e., the rejections of claims 2, 7, 8, and 21–29) rely on the same combination of Hopkins, Hnaien, and Bäumler, in addition to other references. *See generally* Final Action 7–14. Appellant offers no separate arguments regarding these other rejections and claims. *See* Appeal Br. 8–9. For the same reasons that we affirm the rejection of claim 1, we likewise affirm the rejections of claims 2, 7, 8, and 21–29.

Nonstatutory Double Patenting

Appellant does not argue the provisional nonstatutory double patenting rejection. *See* Appeal Br. 4. Accordingly, we summarily affirm this rejection. *See* 37 C.F.R. § 41.37(c)(1)(iv); *Hyatt v. Dudas*, 551 F.3d 1307, 1314 (Fed. Cir. 2008); MPEP § 1205.02 ("If a ground of rejection stated by the examiner is not addressed in the appellant's brief, appellant has waived any challenge to that ground of rejection and the Board may summarily sustain it.").

CONCLUSION

The Examiner's rejections are affirmed.

DECISION SUMMARY

Claims Rejected	**35 U.S.C. §**	**Reference(s)/Basis**	**Affirmed**	**Reversed**
1, 3–6, 30	103	Hopkins, Hnaien, Bäumler	1, 3–6, 30	
2, 7	103	Hopkins, Hnaien, Bäumler, Somberg	2, 7	
8	103	Hopkins, Hnaien, Bäumler, Niemeyer	8	
21–27, 29	103	Hopkins, Hnaien, Bäumler, Wang	21–27, 29	
28	103	Hopkins, Hnaien, Bäumler, Wang, Niemeyer	28	
1–8, 21–30		nonstatutory double patenting	1–8, 21–30	
Overall Outcome			1–8, 21–30	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED