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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/557,372	07/25/2012	Ian Harding	AGAM.P-073	9310

57381 7590 01/28/2020

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ART UNIT	PAPER NUMBER
1795	

MAIL DATE	DELIVERY MODE
01/28/2020	PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte IAN HARDING, MARY Y. LEE, and SANDIE TAN

Appeal 2018-005558
Application 13/557,372
Technology Center 1700

Before CATHERINE Q. TIMM, JEFFREY R. SNAY, and MICHAEL G. McMANUS, *Administrative Patent Judges.*

TIMM, *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, 5, 6, 8–11, 15–18, 22–24, 27–32, and 37.[2] We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Agamatrix, Inc. Appeal Br. 1.

[2] Claims 12, 13, 19, 20, 38, and 39 have been allowed. Ans. 12.

CLAIMED SUBJECT MATTER

The rejected claims are directed to a dry reagent composition (*see, e.g.*, claim 1), a test strip using the dry reagent composition (*see*, *e.g.*, claim 27), a method for testing for an analyte in a liquid sample using the test strip (*see, e.g.*, claim 30), and a method for forming a dry shelf-stable electrochemical test reagent for use in detection of an analyte (*see, e.g.*, claim 32). All of the claims require the formation or use of a dry reagent composition including an active redox enzyme and tris-tetramethylammonium ferricyanide. Claim 1, reproduced below, is illustrative of dry reagent composition of the claims:

> 1. A dry reagent composition comprising:
>
> (a) an active redox enzyme that oxidizes an analyte as a specific substrate to produce an inactive reduced form of the enzyme; and
>
> (b) tris-tetramethylammonium ferricyanide.

Appeal Br. 15 (Claims Appendix).

REFERENCES

The prior art relied upon by the Examiner is:

Name	Reference	Date
Yaginuma	US 5,008,078	Apr. 16, 1991
Harding '035[3]	US 2005/0258035 A1	Nov. 24, 2005
Lau	US 2006/0096859 A1	May 11, 2006
Harding	US 2007/0295616 A1	Dec. 27, 2007
Martin	US 2009/0295616 A1	Dec. 3, 2009

[3] The Examiner discusses Harding'035 when rejecting claims 28 and 29 (Final Act. 8; Ans. 9), but does not include Harding'035 in the statement of the rejection and, thus, the Examiner did not properly inform Appellant of the reliance on this reference. This was error, but harmless given that we are reversing on other grounds.

Bertin[4]	US 2010/0003710 A1	Jan. 7, 2010
Pei	US 2010/0270175 A1	Oct. 28, 2010
Carrington	US 2013/0092536 A1	Apr. 18, 2013
Cheng	Determination of stepwise stability constants for aqueous hexacyanoferrate-tetramethylammonium ions pairs by cyclic voltammetry, Analytic Chimica Acta, 251 (1991) 35–38	1991

REJECTIONS

Due to the entry of the After-Final Amendment of May 25, 2017 (Advisory Action of July, 3, 2017), the status of the claims has changed and is reflected in the Answer, which indicates the following rejections are maintained:

A. The rejection of claims 1, 5, 6, 8–10, 27–32, and 37 under 35 U.S.C. § 103(a) as obvious over Harding, Lau, and Cheng;[5]

B. The rejection of claims 11 and 18 under 35 U.S.C. § 103(a) as obvious over Harding, Lau, Cheng, and further in view of Carrington and Yaginuma; and

[4] The Examiner cites Bertin for the first time in the Answer to support the determination that Appellant's unexpected result showing is not commensurate in scope with the claims. Ans. 15. Appellant recognizes the Examiner's new reliance on Bertin. Reply Br. 2. Given Appellant recognized the Examiner was relying on Bertin and we reverse on other grounds, any error was harmless.

[5] In the Answer, the Examiner added Lau to the statement of rejection of claim 32. *Compare* Ans. 4, *with* Final Act. 3. Lau had previously been mentioned only in the body of the rejection. Final Act. 3.

C. The rejection of claims 15–17 and 22–24 under 35 U.S.C. § 103(a) as obvious over Harding, Lau,[6] Cheng, and further in view of Pei and Martin.[7]

OPINION

After reviewing the evidence of record, we determine a preponderance of the evidence supports Appellant's contention that the Examiner reversibly erred in weighing the evidence of unexpected results.

As a first matter, we consider the evidence of what was known in the prior art as that evidence is important in our weighing of the evidence of unexpected results.

Harding and Lau both provide evidence of what was known in the art of reagents used for detecting analytes such as glucose. Harding ¶ 2; Lau ¶¶ 1–2. As evidenced by Harding and Lau, it was known in the art to pair an active redox enzyme and a mediator such that a redox reaction occurs that produces a measurable current representative of the concentration of an analyte such as glucose. Harding ¶ 3; Lau ¶¶ 2–13. The redox enzyme maybe, e.g., glucose oxidase, which oxidizes glucose, to produce an inactive reduced form of the enzyme in a redox reaction. Harding ¶ 2; Lau ¶ 2.

Various mediators were known in the art including ferricyanide anion-based $[(Fe(CN)_6]^{3-}$ mediators. Harding ¶ 4; Lau ¶¶ 20, 29. Harding does not

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[6] Although the Examiner omits Lau, we treat the rejection as including Lau given the statement in the rejection "as applied to claim 11 and 18 above." The rejection of claims 11 and 18 included Lau. Given the disposition of the issues on appeal, the error was harmless.
[7] The Examiner refers to US 2009/0295616 to Martin as "Marfurt."

discuss pairing the ferricyanide anion with any cation, much less Appellant's tetramethylammonium cations.

Harding discloses that there are several factors considered when selecting the mediator. Harding ¶ 4. For example, to detect glucose, one selects a mediator with a redox potential that will quickly oxidize the enzyme to regenerate it from its reduced state, i.e., a mediator that has fast kinetics. *Id.* The problem is that, frequently, mediators with the desired redox potential and fast kinetics are poorly soluble in aqueous solutions, such as blood. *Id.* Poor solubility limits the maximum concentration of mediator and, as a result, limits the maximum amount of signal that can be generated. *Id.*

Harding discloses that the mediator is an electron transfer agent. Harding ¶ 5. Harding tackles the solubility problem by adding another electron transfer agent, which Harding calls a shuttle. *Id.* The shuttle interacts with the electrodes and, optionally, the mediator, and serves as a major source of current. *Id.* As acknowledged by Appellant, in some embodiments of Harding, the ferricyanide anion performs the role of the shuttle because of its solubility, but it can also function as a mediator as in the prior art of Figure 1 when a more effective mediator is not present. Appeal Br. 4; Harding ¶¶ 4, 51, 77.

As pointed out by Appellant, Harding is silent on the stability of reagents in a dry test strip. Appeal Br. 4. Lau, however, discloses that mediators can be unstable and tend to undergo autoxidation. Lau ¶ 14. Lau solves the stability problem by a different method than Appellant. Lau uses a ferricyanide mediator selective for hydrogen peroxide. Lau ¶ 16. Lau's general formula of ferricyanides ($X_3Fe(CN)_6$) encompasses Appellant's tris-tetramethylammonium ferricyanide, however, Lau specifically requires the ferricyanide mediator have more carbon atoms so the compound is insoluble, which Lau discloses is an advantage. Lau ¶¶ 20–25. Lau specifically limits the genus to species where at least one of the quaternary ammonium ions contains at least four carbon atoms. Lau ¶ 24. Thus, Lau does not include the more soluble tris-tetramethylammonium ferricyanide of Appellant's claims.

To summarize, Harding indicates that, generally, ferricyanides were known for use as mediators and shuttles and Lau indicates that quaternary ammonium ferricyanides with higher numbers of carbons than Appellant's tris-tetramethylammonium ferricyanide were known mediators in dry reagent compositions selective for hydrogen peroxide.

The Examiner, recognizing that Harding does not explicitly teach that the shuttle compound is tris-tetramethylammonium ferricyanide, turns to Cheng. Ans. 6–7.

Cheng is a research paper that studies ion pairing between aqueous hexacyanoferrate (ferricyanide/ferrocyanide) and tetramethylammonium ions (TMA^+). Cheng, Abs. Cheng creates aqueous solutions including 10 mM potassium hexacyanoferrate(II) in two solutions, one containing 0.146 M tetramethylammonium chloride (TMACl) and one containing 3.494 M TMACl. Cheng, Experimental. Cheng measures a redox shift that Cheng attributes to the association of tetramethylammonium (TMA^+) ions with ferricyanide ions $[(Fe(CN)_6]^{3-}$. Cheng, Results and Discussion. Based on the experiments, Cheng determines that $(TMA)_3Fe(CN)_6$ (tris-tetramethylammonium ferricyanide) predominates at high tetramethylammonium ion activity. Cheng, Abs. and Results and Discussion last paragraph.

Cheng's research paper was published in 1990. Cheng indicates that, at that time, tetraalkylammonium (TAA) hexacyanoferrate salts were "commonly employed as oxidizing agents in a variety of synthetic schemes that include the oxidation of phenols and proteins." Cheng, first paragraph. Cheng further conveys that, at that time, very little systematic work had been done on the role of TAA ionic activity on hexacyanoferrate redox potentials. *Id.* Cheng suggests that bioelectrochemical sensors based on enzymes are a likely application of $(TMA)_3Fe(CN)_6$, i.e., tris-tetramethylammonium ferricyanide, and that the kinetics of electron transfer from glucose oxidase to $Fe(CN)_6^{3-}$, i.e., ferricyanide, "is currently being examined." Cheng, Applications.

Although Cheng does not state that tris-tetramethylammonium ferricyanide was, in 1990, used in enzyme-based sensors, Lau discloses the use of other tetraalkylammonium ferricyanides in enzyme-based sensors that detect hydrogen peroxide, and Harding discloses using ferricyanides as mediators and shuttles in sensors that operate without hydrogen peroxide detection. Appellant's Specification indicates that it was known to use potassium, sodium, lithium, magnesium, etc. as the cation paired with the ferricyanide anion. Spec. 2. Potassium ferricyanide has been used in various commercial test strips. Spec. 30. Together the prior art provides a suggestion of using tris-tetramethylammonium ferricyanide as a mediator or shuttle with a reasonable expectation that it would have the necessary redox potential required by Harding.

That being said, based on the evidence discussed above, there is little reason to suspect that the tris-tetramethylammonium cation would provide results significantly different than other cations. However, Appellant's results indicate the results are, in fact, significantly different. According to Appellant, the use of tris-tetramethylammonium ferricyanide ($(TMA)_3Fe(CN)_6$) in place of potassium ferricyanide ($K_3Fe(CN)_6$) or other salts of ferricyanide results in a substantial and unpredictable increase in the shelf-stability of test strips. Appeal Br. 7. Appellant points to Figures 4–6 as showing this unexpected stability. Appeal Br. 8–10. We agree with Appellant that Figure 6 shows a substantial improvement in the stability of the baseline current. Appeal Br. 8. Figure 6 shows that the baseline current of ferricyanide paired with tris-tetramethylammonium cation (TMA) changes much less than the baseline of ferricyanides paired with other cations (Cs, Na, K, Rb) when aged at 50°C for 14 days. A comparison of Figures 4 (containing potassium) and 5 (containing TMA) shows that baseline current stability translates to stability of the current in test strips containing glucose oxidase enzyme and buffers.

The Examiner finds that the results are not commensurate in scope with the claims because Appellant reports results for only test strips containing glucose oxidase, but the claims encompass test strips containing any active redox enzyme. Ans. 15.

Appellant contends that it is the change in cation that causes the stability increase and not the composition of the enzyme, thus, comparison with test strips including other enzymes is not necessary. Appeal Br. 11; Reply Br. 2.

The Specification supports Appellant's contention. Figure 6 shows that the difference arises from the change in cation. Figures 4 and 5 show how that change effects the current stability. The Specification explains the stability increase in terms of the cation difference. Spec. 31.

In response to Appellant's argument, the Examiner points out that the claimed genus encompasses oxidoreductase enzymes other than glucose oxidase (Ans. 15), which is true, but does not address Appellant's contention that the identity of the enzyme is not important to the showing because it is the cation that provides the unexpected result. The Examiner offers no persuasive technical reasoning or evidence countering the evidence supporting Appellant's argument.

The Examiner also suggests that Lau is the closest prior art and Appellant should compare their TMA ferricyanide-based test strip to Lau's quaternary alkylammonium ion-based ferricyanide salts. Ans. 16–17. However, we agree with Appellant that, although there is a superficial structural similarity between the longer chain alkylammonium cations of Lau and Appellant's methylammonium cations, Lau's teaching of using insoluble cations make Lau's cations less closely related than the soluble cations of Appellant's tests. Reply Br. 3–4.

After weighing the evidence relied on by the Examiner and Appellant in this appeal, we determine that Appellant has identified a reversible error in the Examiner's evaluation of the showing of unexpected results, which affected all the rejections. Thus, we do not sustain the rejections.

CONCLUSION

The Examiner's rejections are reversed.

More specifically,

A. we do not sustain the rejection of claims 1, 5, 6, 8–10, 27–32, and 37 under 35 U.S.C. § 103(a) as obvious over Harding, Lau, and Cheng;

B. we do not sustain the rejection of claims 11 and 18 under 35 U.S.C. § 103(a) as obvious over Harding, Lau, Cheng, and further in view of Carrington and Yaginuma; and

C. we do not sustain the rejection of claims 15–17 and 22–24 under 35 U.S.C. § 103(a) as obvious over Harding, Lau, Cheng, and further in view of Pei and Martin.

DECISION SUMMARY

Claims Rejected	**35 U.S.C. §**	**Reference(s)/Basis**	**Affirmed**	**Reversed**
1, 5, 6, 8–10, 27–32, 37	103(a)	Harding, Lau, Cheng		1, 5, 6, 8–10, 27–32, 37
11, 18	103(a)	Harding, Lau, Cheng, Carrington, Yaginuma		11, 18
15–17, 22–24	103(a)	Harding, Lau, Cheng, Pei, Martin		15–17, 22–24
Overall Outcome				1, 5, 6, 8–11, 15–18, 22–24, 27–32, 37

REVERSED