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Table with 5 columns: APPLICATION NO., FILING DATE, FIRST NAMED INVENTOR, ATTORNEY DOCKET NO., CONFIRMATION NO. Includes application details for Thomas Haas and examiner information for RAGHU, GANAPATHIRAM.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte THOMAS HAAS, OLIVER THUM,
JAN CHRISTOPH PFEFFER, PHILIP ENGEL,
CHRISTIAN GEHRING, and MARKUS POETTER

Appeal 2018-003341
Application 14/367,610
Technology Center 1600

Before DONALD E. ADAMS, ULRIKE W. JENKS, and JOHN G. NEW,
Administrative Patent Judges.

JENKS, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant¹ appeals from Examiner's decision to reject claims as obvious. 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 Evonik Degussa GmbH. Appeal Br. 2.

STATEMENT OF THE CASE

Claims 1, 5–10, 12–16, 19–22, and 25–28 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claim 1, reproduced below, is illustrative of the claimed subject matter²:

Claim 1: A prokaryotic microorganism expressing a recombinant alkane oxidase, wherein:

the expressed recombinant alkane oxidase is AlkB from *Pseudomonas putida* GPo1 comprising the sequence of SEQ ID NO: 1 or a variant thereof having at least 90% identity to SEQ ID NO: 1;

the prokaryotic microorganism has a reduced fatty acid degradation capacity compared to its wild type, and the fatty acid degradation capacity is reduced by deletion, inhibition or inactivation of a gene encoding an enzyme involved in a β -oxidation pathway; the enzyme involved in the β -oxidation pathway is selected from the group consisting of:

a fatty acid importer comprising the sequence of SEQ ID NO: 2 or a variant thereof having at least 90% identity to SEQ ID NO: 2,

a fatty acid-CoA ligase comprising the sequence of SEQ ID NO: 3 or a variant thereof having at least 90% identity to SEQ ID NO: 3,

an acyl-CoA dehydrogenase comprising the sequence of SEQ ID NO: 4 or a variant thereof having at least 90% identity to SEQ ID NO: 4,

an enoyl-CoA hydratase comprising the sequence of SEQ ID NO: 5 or a variant thereof having at least 90% identity to SEQ ID NO: 5, and

a 3-ketoacyl-CoA thiolase comprising the sequence of SEQ ID NO: 6 or a variant thereof having at least 90% identity to SEQ ID NO: 6; and

² Examiner identifies SEQ ID NOs: 2, 3, 5–13, and 16–19 as being directed to a non-elected invention. Final Act. 2–3.

the prokaryotic microorganism is suitable for oxidizing an alkyl.

Appeal Br. 23–24 (Claims Appendix).

REFERENCES

The prior art relied upon by Examiner is:

Name	Reference	Date
Sieber et al. (“Sieber”)	US 8,841,096 B2	Sept. 23, 2014
Karau et al. (“Karau”)	US 9,012,227 B2	April 21, 2015
Jessen et al., (“Jessen”)	US 9,090,918 B2	July 28, 2015
Gaertner	US 2011/0162259 A1	July 7, 2011
Campbell and Cronan Jr., <i>The Enigmatic Escherichia coli fadE Gene Is yafH</i> , 184 J. BACTERIOLOGY 3759–64 (2002) (“Campbell”)		
Handke et al., <i>Application and engineering of fatty acid biosynthesis in Escherichia coli for advanced fuels and chemicals</i> , 13 METABOLIC ENGINEERING 28–37 (2011) (“Handke”)		
Lennen et al., <i>A Process for Microbial Hydrocarbon Synthesis: Overproduction of Fatty Acids in Escherichia coli and Catalytic Conversion to Alkanes</i> , 106 BIOTECHNOLOGY AND BIOENGINEERING 193–202 (2010) (“Lennen”)		
van Beilen and Funhoff, <i>Expanding the alkane oxygenase toolbox: new enzymes and applications</i> , 16 CURRENT OPINION IN BIOTECHNOLOGY 308–14 (2005) (“van Beilen”)		

REJECTION

Appellant requests review of the rejection of claims 1, 5–10, 12–16, 19–22, and 25–28 under pre-AIA 35 U.S.C. § 103(a) as unpatentable over Karau, in view of Gaertner, Lennen, Handke, Campbell, Sieber, Jessen, and van Beilen.

ANALYSIS

Appellant contends that Examiner made a new ground of rejection adding Gaertner to the previous combination, but never adequately addresses Appellant’s rebuttal evidence of unexpected results. Appeal Br. 9.

Appellant [contends that their] rebuttal arguments were sufficient to overcome the previous rejection over the combination of Karau, Lennen, Handke, Campbell, Sieber, Jessen and van Bielen, then these rebuttal arguments also were sufficient to overcome the rejection when Gaertner was added as a new secondary reference. This is because when considering rebuttal arguments based on unexpected results, the proper comparison is to the closest prior art (Karau). . . . Instead, the showing of unexpected results compared to Karau rebuts any case of prima facie obviousness using Karau as a primary reference.

Id. at 11. Appellant identifies Karau is the closest prior art. *Id.* at 9.

We are not persuaded by Appellant's contention that Examiner's withdrawal of the prior rejection relying on all but the Gaertner reference (*see* Non-Final Act. 3–4) supports the position that Examiner was persuaded by Appellant's prior unexpected results argument. Examiner indicated that the prior rejection "is being withdrawn upon further review and reconsideration." Non-Final Act. 4. Although Examiner did not articulate the underlying reasons for reformulating the rejection, there is no reason to conclude that Examiner was persuaded by Appellant's argument of unexpected result.

We turn to Examiner's prima facie case. We have reviewed the record and agree with Examiner's factual findings and conclusion, as set out in the Non-Final Action and Answer which we adopt and incorporate herein by reference. To summarize, Examiner finds that Karau teaches a recombinant *E. coli* comprising an alkane oxidase/alkane monooxygenase having the same sequence as listed in claim 1. Non-Final Act. 7. Examiner finds that Karau teaches increased production of carboxylic acid esters when the alkaline oxidase is overexpressed in conjunction with an alcohol dehydrogenase, an amino acid dehydrogenase, a transaminase, and an

alanine dehydrogenase. *Id.* Karau supports increasing the production of precursors of fatty acids leading to increased fatty acid production.

Examiner acknowledges that Karau does not disclose using a modified *E. coli* that has reduced fatty acid degradation capacity. *Id.*

Examiner finds that Gaertner teaches a recombinant *E. coli* with reduced fatty acid degradation capacity. Non-Final Act. 8. Gaertner (as well as some of the other cited references) supports the position that the disruption of fatty acid metabolism allows for fatty acid accumulation.

Examiner concludes that it is obvious to combine:

[A] host cell involving enhancing the activities of enzymes that are involved in the synthesis of precursors/intermediate products and the enhanced production of final product carboxylic acid esters [taught in Karau] and disrupting the activities of enzymes in said host cell that divert the precursors/intermediate products (fatty acid derivatives) towards formation other unwanted by-products/i.e., break down of intermediate fatty acid derivatives [taught in Gaertner (as well as others)],

Id. at 14. Put another way, Examiner finds it obvious to combine Karau's recombinant *E. coli* mechanism that increases the production of carboxylic acid esters, precursors in the fatty acid production, with Gaertner's *E. coli* mechanism that reduces the ability of the cells to degrade fatty acids in order to produce a third organism that incorporates both mechanisms in order to improve fatty acid accumulation. According to Examiner, "[m]otivation to generate such a modified microorganism derives from the fact that fatty acid derivatives and carboxylic acid esters of said fatty acid derivatives are commercial products of importance and useful in the preparation of fine chemicals, oil, biofuels and in plastic industry." *Id.* We find no error with

Examiner's rationale and agree with Examiner's conclusion that the claims are obvious.

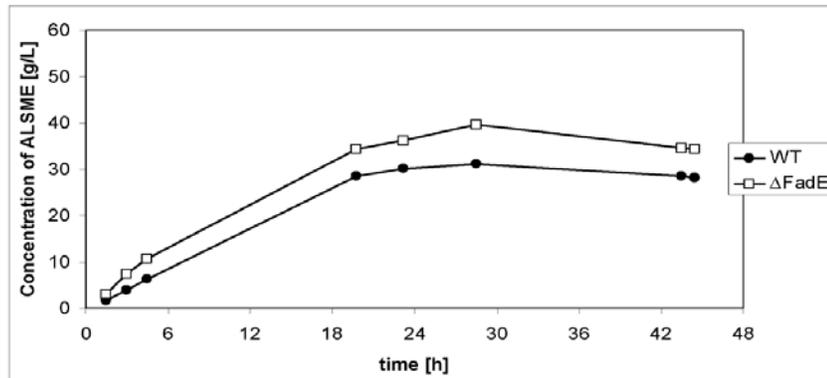
Because Examiner presents a prima facie case of obviousness, we consider whether Appellant submits sufficient evidence or argument in rebuttal. *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993); *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986) (“If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed”). Evidence rebutting a prima facie case of obviousness may include “[e]vidence of unexpected results.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007). “[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). The unexpected results must be “different in kind and not merely in degree from the results of the prior art.” *In re Applied Materials, Inc.*, 692 F.3d 1289, 1297 (Fed. Cir. 2012).

Appellant directs us to the Declaration of Dr. Thum³ and the originally filed Specification. Appeal Br. 8. Appellant contends that the unexpected results in the Specification show improved phase separation and lower oxygen consumption. *Id.* at 14.

The Specification describes “[t]he conversion of lauric acid methyl ester to ω -amino lauric acid (ALS) methyl ester, via ω -hydroxy lauric acid, . . . from DASGIP, using strains W3110 Δ FadE [alkB-alaD-TA] and W3110

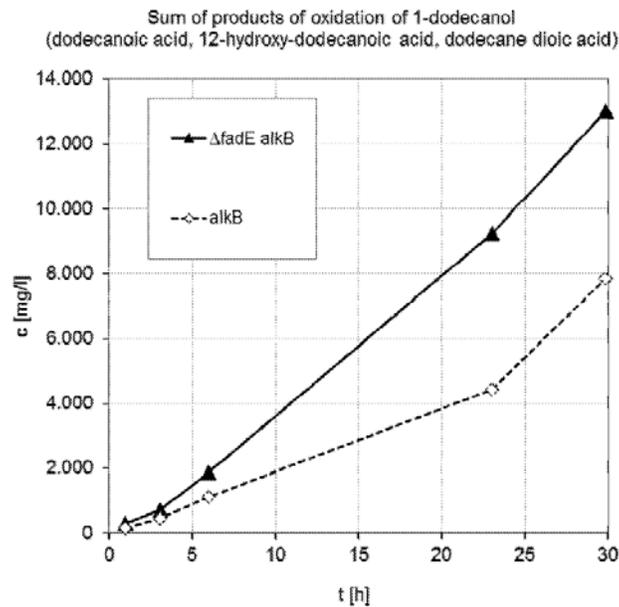
³ Declaration under 37 C.F.R. § 1.132 by Dr. Oliver Thum signed August 25, 2016 (“Thum Declaration”).

[alkB-alaD-TA].” Spec. 19:5–7. The Specification describes *E. coli* strain W3110 [alkB-alaD-TA] as the wild type (WT). *Id.* at 18:31–32. Figure 4 of the Specification compares the production of ω -amino lauric acid methyl ester over time.



The figure shows the amount ω -amino lauric acid methyl ester product produced by the two different *E. coli* strains tested. According to the Specification, “[t]he amount of product formed by both strains is comparable (Fig. 4), in fact the yield is slightly better in case the mutant is used.” Spec. 21: 26–27.

The Thum Declaration shows a figure of an *E. coli* (strain W3110 Δ FadE [alkB]) “with knocked-out fatty acid dehydrogenase (Δ fadE) accumulated over 50 % more of 1-dodecanol oxidation products” when compared *E. coli* (strain W3110 [alkB]) comprising increased oxidoreductase AlkB. Thum Dec. ¶¶ 5, 6, 16. The figure, reproduced below, shows sum of oxidation products of 1-dodecanol.



Id. ¶ 16.

Providing evidence of allegedly unexpected results, however, does not necessarily mean that the evidence presented is persuasive. Here, Examiner's position is that the results shown in the Thum Declaration, specifically, the figure reproduced above are expected based on the cited references. Ans. 29– 32. Examiner explains that

the sum products of oxidation of 1-dodecanol is around ~1.63 fold increase ($13/8 = \sim 1.63$ fold) between *E.coli* comprising alKB and Δ fadE (deletion) yields -13.0 mg/l and *E.coli* comprising alKB alone yields ~8.0 mg/l. This result of the instant invention i.e. yield of fatty acid derivative a ~1.63 fold increase in yield is very much expected and predictable based on the combined teachings [of the references].

Id. at 29 (emphasis removed). Examiner finds that Karau suggests product yields of 10–10,000 times more than for wild type cells can be expected. *Id.* (citing Karau 2:56–65). Examiner finds that Gaertner also teaches increased production of fatty acid derivatives (in the range of 0.5–50 g/ 100 g glucose). *Id.* at 30–31. Contrary to Appellant's contention, Examiner has not ignored

Appellant's unexpected result rebuttal but instead has found that is the results are not persuasive based on the teachings in the art. *See* Ans. 29–32.

We have reviewed Appellant's contentions in light of Examiner's rebuttals as set out in the Answer and Non-Final Action and find no error with Examiner's position. We further note that the data provided in the Specification as well as Thum Declaration does not provide a comparison to *E. coli* host cells without additions or deletions. For example, both the Specification and the Thum Declaration use the following modified strains W3110 Δ FadE [alkB-alaD-TA] and W3110 [alkB-alaD-TA] in their experiments. Contrary to Appellant's assertion (*see* Appeal Br. 14), the Specification does not recognize that the yield between the two strains is unexpected. *See* Spec. 21: 26–27 (“[t]he amount of product formed by both strains is comparable (Fig. 4), in fact the yield is slightly better in case the mutant is used.”). Describing something as being “slightly better” does not persuade us that the results are unexpected, especially when balanced against the teachings in the prior art. What is missing from the results presented in the Specification and the Thum Declaration are comparisons to an *E. coli* strain that has no modification and a strain that only contains a deletion in Δ FadE. Without such comparison, it is difficult to assess that the combination of modifications produced anything unexpected rather than showing the additive effect of incremental improvements by interfering with fatty acid processing. For these reason, we are not persuaded by Appellant's unexpected result argument. Although the record may establish evidence of secondary considerations which are indicia of nonobviousness, the record may also establish such a strong case of obviousness that the objective evidence of nonobviousness is not sufficient to outweigh the evidence of

obviousness. *Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 769 (Fed. Cir. 1988), *cert. denied*, 493 U.S. 814 (1989). Accordingly, we affirm the rejection of claim 1 as obvious over the cited references.

With respect to claims 5–10, 12–16, 19–22, and 26–28, Appellant relies on the same argument relied upon with respect to claim 1. Appeal Br. 15–21. For the reasons discussed above, we find that Examiner has established a prima facie showing of obviousness with respect to claim 1, which Appellant has failed to rebut. Accordingly, we affirm the rejection of claims 5–10, 12–16, 19–22, and 26–28 for the same reasons.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	References/Basis	Affirmed	Reversed
1, 5–10, 12–16, 19– 22, 25–28	103	Karau, Gaertner, Lennen, Handke, Campbell, Sieber, Jessen, van Bielen	1, 5–10, 12–16, 19– 22, 25–28	

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