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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/432,519	03/28/2012	Mikhail Kharisovich Ziyatdinov	US-413	1432

38108 7590 09/23/2016

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ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
09/23/2016	ELECTRONIC

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MIKHAIL KHARISOVICH, VIKTOR VASILIEVICH, and MIKHAIL MARKOVICH[1]

Appeal 2014-003823
Application 13/432,519
Technology Center 1600

Before DEMETRA J. MILLS, LORA M. GREEN, and RICHARD J. SMITH, *Administrative Patent Judges*.

SMITH, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for producing a compound that have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

Background

"The present invention relates to the microbiological industry, and specifically to a method for producing an L-cysteine, L-cystine, a derivative

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[1] According to Appellants, the real party in interest is Ajinomoto Co., Inc. (Appeal Br. 3.)

or precursor thereof or a mixture thereof using a bacterium of *Enterobacteriaceae* family which has been modified to have enhanced expression of the genes involved in the process of sulphur assimilation." (Spec. ¶ 2.)

Claims on Appeal

Claims 12–15 and 18–24 are on appeal. (Appendix A, Appeal Br. 12–13.) Independent claim 12 is illustrative and reads as follows:

> 12. A method for producing a compound selected from the group consisting of L-cysteine, L-cystine, derivatives thereof, and precursors thereof, which comprises cultivating an L-cysteine-producing bacterium of *Enterobacteriaceae* family in a culture medium containing sulphate, and collecting the compound from the culture medium,
>
> wherein the bacterium has been modified to have enhanced expression of one or more genes involved in the process of sulphur assimilation, and
>
> wherein said one or more genes involved in the process of sulphur assimilation comprise the *cysQ* gene or the *cysDNC* genes.

Examiner's Rejection

Claims 12–15 and 18–24 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Siebelt,[2] Neuwald,[3] and Sheremet'eva.[4] (Ans. 2.)

Claims 13–15 and 19–24 were not argued separately, and therefore, as to those claims, we limit our discussion to claim 12, the only independent claim.

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[2] Siebelt et al., WO 03/006666 A2, published Jan. 23, 2003 ("Siebelt").
[3] Neuwald et al., *cysQ, a Gene Needed for Cysteine Synthesis in Escherichia coli K-12 Only during Aerobic Growth*, 174 JOURNAL OF BACTERIOLOGY 2, 415–25 (1992) ("Neuwald").
[4] Sheremet'eva et al., US 2006/0286643 A1, published Dec. 21, 2006 ("Sheremet'eva").

FINDINGS OF FACT

We adopt as our own the Examiner's findings and analysis concerning the scope and content of the prior art. The following findings are included for emphasis and reference convenience.

FF 1. Siebelt teaches a method for the preparation of L-amino acids comprising fermentation of microorganisms of the *Enterobacteriaceae* family which produce the desired amino acid, and in which at least one or more of the genes of the cysteine biosynthesis pathway, including cysD, cysN, cysC, and cysH, are enhanced (over-expressed), the method further including isolation of the desired L-amino acid. (Siebelt 44, ll. 1–19 (claim 1).)

FF 2. The term L-amino acids, as used in Siebelt, includes L-cysteine. (*Id.* 3, ll. 14–18.)

FF 3. Siebelt teaches that "microorganisms of the Enterobacteriaceae family produce L-amino acids . . . in an improved manner after enhancement, in particular over-expression, of at least one or more of . . . cysD, cysN, cysC . . . [and] cysH." (*Id.* 6, ll. 15–22.)

FF 4. The Specification states that "[t]here are many genes involved in the process of sulphur assimilation including the genes involved in sulphate activation *(cysD, cysN, cysC)* and adenosine 3'-phosphate 5'-phosphosulphate (PAPS) degradation (cysQ)." (Spec. ¶ 5.)

FF 5. The Examiner finds that "[a]lthough Siebelt [] do[es] not mention that *cysD, CysN or CysC* genes are involved in the process of sulphur assimilation, i.e., sulphate activation, it is an inherent property of *cysD, cysN or cysC* genes to be involved in such process." (Ans. 3; *see* FF 4.)

FF 6. The Examiner finds that the art is inconsistent in the nomenclature of the genes involved in the cysteine biosynthesis pathway, and provides the following Table for clarification:

	Siebelt	Neuwald	Appellants
A gene encoding Phosphoadenosine phosphosulfate reductase (PAPS)	CysH (see p. 10., ll. 23-35)	CysH (see p. 415, 2nd col.)	CysQ (see p. 2, paragraph 0005)
Additional disclosure	CysI/CysQ is a NADPH sulfite reductase (see p. 10., ll. 13-22)	CysQ controls the levels of CysH (PAPS) (see p 416, 1st col., 1st paragraph)	

(Ans. 5.)

FF 7. Siebelt teaches that cysH (i.e. Appellants' cysQ) is a gene of the cysteine biosynthesis pathway. (Siebelt 10, l. 23–35; FF 6.)

FF 8. Neuwald teaches that the cysQ gene is needed for cysteine synthesis and that CysQ helps control the pool of PAPS, or its use in sulfite synthesis. (Neuwald Abstract.)

ISSUE

Whether a preponderance of the evidence of record supports the Examiner's conclusion of obviousness under 35 U.S.C. § 103(a).

ANALYSIS

We agree with the Examiner's conclusion that claims 12 and 18 would have been obvious to a person of ordinary skill in the art at the time of the invention based on the cited prior art. (Ans. 2–5; FF 1–8.) We address Appellants' arguments below.

As an initial matter, we find that claims 12 and 18 are obvious in view of Siebelt for the reasons set forth in the Answer. (FF 1–7.) Moreover, we do not find that Neuwald (or Sheremet'eva) are necessary to support the

obviousness rejection of claims 12 and 18. *See In re Bush*, 296 F.2d 491, 496 (CCPA 1961) (holding that the Board may rely on fewer references than relied upon by the Examiner without designating it as a new ground of rejection).

Claim 12

Siebelt

Appellants argue that Siebelt "does not disclose or suggest increased expression of the combination of all the three genes of *cysDNC* cluster or the *cysQ* gene **in a method for producing L-cysteine**." (Appeal Br. 6, 8.)

We are not persuaded by Appellants' arguments. Claim 12 recites "one or more genes" which comprise "the *cysQ* gene or the *cysDNC* genes." (Appeal Br. 12.) Thus, claim 12 does not require enhanced expression of "the combination of all the three genes of *cysDNC*" as Appellants contend. (Ans. 7.) Consistent with the doctrine of claim differentiation, this construction is further borne out by claim 18, which is indirectly dependent on claim 12 and recites "one or more genes of the *cysDNC* cluster." (*Id.*) Claim 18 would be incongruent if claim 12 was limited to the combination of all three *cysDNC* genes.

Although claim 12 does not require increased expression of the *cysQ* gene, provided one or more genes of *cysDNC* are expressed, Siebelt also discloses increased expression of the *cysQ* gene in its process for the preparation of L-amino acids. As the Examiner explains, Siebelt teaches that "*over-expression of one or more genes of the cysteine biosynthesis pathway including cysH (Appellants' cysQ) . . . improve[s] the production of L-amino acids*." (Ans. 10; *see also* FF 3, 6, and 7.) Siebelt also makes clear

that its reference to L-amino acids, and specifically improved production thereof, includes L-cysteine. (FF 2.)

Motivation to Enhance Expression

Appellants make several arguments, generally based on Neuwald and the L-cysteine biosynthesis pathway,[5] for example, that a person of ordinary skill in the art would not have been motivated to increase expression of the *cysQ* gene or the *cysDNC* genes. (Appeal Br. 8–9.)

In particular, as to the increased expression of the *cysQ* gene, Appellants argue that

> L-cysteine is synthesized via a series of sequential steps using a plurality of enzymes, and hence, the necessary steps for improving L-cysteine production will differ depending on a variety of factors, such as, for example, which step is the rate-limiting step. Therefore, the disclosure in Neuwald that CysQ is beneficial for L-cysteine synthesis does not necessarily mean, nor would this fact suggest to the skilled art worker, that L-cysteine production can be improved by enhancing the expression of *cysQ* gene. . . . Neuwald refers to the possibility that CysQ is involved in sulfite generation or that CysQ sequesters or consumes excess PAPS or the like . . . the person or ordinary skill in the art could not have expected that L-cysteine production can be improved by enhancing the expression of *cysQ* gene based only on the knowledge that CysQ may be involved in one step among many sequential and complicated steps in L-cysteine biosynthesis.

(*Id.*)

Appellants make a similar argument regarding the increased expression of the *cysDNC* genes; namely, that

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[5] Figure 1 of Neuwald illustrates the pathway of cysteine biosynthesis. (Neuwald 416, FIG. 1.)

> the person of ordinary skill in the art would not have been motivated to choose to increase the expression of the CysDNC genes for the purpose of increasing production of L-cysteine. This is because the rate-limiting feature is simply due to the fact that the equilibrium of the CysDN reaction is strongly guided in the reverse direction, that is, towards ATP synthesis. Therefore, the rate-limiting aspect is not caused by insufficient amounts of CysDN, and so even by increasing CysDN, the equilibrium of the reaction will not be shifted in the forward direction, that is, towards APS generation.

(*Id.*)

Appellants also point to Sekowska[6] to argue that "the rate-limiting effect [of the CysDN reaction] is not due to the conversion speed but to the equilibrium constant" and, therefore, "the person of ordinary skill in the art would not have expected that L-cysteine production can be improved by enhancing the expression of *cysDNC* gene(s)." (Appeal Br. 9–10, citing Sekowska 146, par. bridging left and right cols.)

We are unpersuaded by Appellants' arguments. We note that Siebelt teaches and suggests improved production of L-amino acids, including L-cysteine, by increased expression of the cysH (i.e. cysQ) and cysDNC genes. (FF 2, 3.) That teaching alone suggests the subject matter of claim 12. Moreover, Appellants cannot establish nonobviousness by arguing Neuwald separately from Siebelt. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (citing *In re Keller*, 642 F.2d 413, 425 (CCPA 1981)) (nonobviousness cannot be established by attacking references individually where the Examiner bases the rejection on a combination of references). In

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[6] Sekowska et al., *Sulfur Metabolism in Escherichia coli and Related Bacteria: Facts and Fiction*, J. MOL. MICROBIOL. BIOTECHNOL 2(2), 145–77 (2000) ("Sekowska").

addition, we are unpersuaded by Appellants' arguments regarding Neuwald and the pathway for L-cysteine synthesis for the reasons set forth in the Examiner's Answer. (Ans. 6–10.)

Teaching Away

Appellants argue that Neuwald teaches away from the present invention based on its reference to the possibility "that CysQ is involved in sulfite generation or that CysQ sequesters or consumes excess PAPS or the like." (Appeal Br. 9, citing Neuwald 423–24; *see also* Reply Br. 4.) In particular, Appellants argue that a person of ordinary skill in the art would therefore not have been motivated to enhance expression of the cysQ gene because they "would have likely concluded from [Neuwald] that if excess PAPS is wasted when L-cysteine is overproduced, L-cysteine production would decrease." (Appeal Br. 9.)

We are not persuaded. Siebelt discloses the subject matter of the claimed invention. Appellants have failed to show how the combination of Siebelt and Neuwald criticizes, discredits, or otherwise discourages one of ordinary skill in the art from the subject matter of the claimed invention. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Moreover, Appellants' teaching away argument is contradicted by the express teaching of Siebelt that production of L-amino acids, including L-cysteine, is improved by enhancement (over-expression) of cysH (cysQ). (FF 3.) Furthermore, claim 12 does not require enhanced expression of the cysQ gene. (Appeal Br. 12.)

Claim 18

Claim 18 recites "[t]he method according to claim 15,[7] wherein the bacterium has been modified to have enhanced expression of *cysQ* gene and one or more genes of *cysDNC* cluster." (Appeal Br. 12.) Appellants argue that "claim 18 limits the claims to a combined use of the *cysQ* gene and the *cysDNC* gene(s)," and that the Examiner has failed to explain how the prior art discloses this combination. (*Id.* 10.) We are not persuaded. Claim 18 clearly recites the combination of the cysQ gene and "one or more" of the genes of the cysDNC cluster. Moreover, given that cysH corresponds to Appellants' cysQ (Ans. 10, FF 6), and Siebelt teaches the combination of cysH with cysD, cysN, and cysC (FF 3), claim 18 would have been obvious to a person of ordinary skill based on the disclosure of Siebelt.

CONCLUSION

A preponderance of evidence of record supports the Examiner's conclusion that claims 12 and 18 are obvious under 35 U.S.C. § 103(a).

Claims 13–15 and 19–24 were not argued separately and fall with claim 12.

SUMMARY

We affirm the rejection of all claims on appeal.

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).

AFFIRMED

[7] Claim 15 depends on claim 12. (Appeal Br. 12.)