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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MIKHAIL KHARISOVICH ZIYATDINOV,
VIKTOR VASILIEVICH SAMSONOV, and
MIKHAIL MARKOVICH GUSYATINER

Appeal 2018-004761
Application 13/432,519
Technology Center 1600

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

SMITH, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 12–14 and 18–24. 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. Appellant identifies the real party in interest as Ajinomoto Co., Inc. Appeal Br. 3.

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 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 12–14 and 18–24 are on appeal. Appeal Br. 13–14 (Appendix A). Claim 12, the only independent claim on appeal, 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 the *cysDNC* genes.

Id. at 13.

Dependent claim 18 reads as follows:

> 18. The method according to claim 12, wherein the bacterium has additionally been modified to have enhanced expression of *cysQ* gene.

Id.

Examiner's Rejection

Claims 12–14 and 18–24 stand finally rejected under 35 U.S.C. § 103(a) as unpatentable over Siebelt,[2] Sheremet'eva,[3] Neuwald,[4] and Sekowska.[5] Final Act. 2;[6] Ans. 3.

FINDINGS OF FACT

The following findings are included for emphasis and reference purposes.

FF 1. Siebelt teaches a method for producing L-amino acids comprising cultivating a bacterium of the *Enterobacteriaceae* family in a culture medium containing sulfate, which produces the desired amino acid, and in which the bacterium has been modified so that the *cysDNC* genes are enhanced (over-expressed), the method further including collection of the desired L-amino acid. Siebelt 44, ll. 1–19 (claim 1); 6, ll. 15–22; 18, ll. 23–34; 31, l. 11–34, l. 2 (Example 5); Ans. 4.

FF 2. The term L-amino acids, as used in Siebelt, includes L-cysteine. *Id.* at 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

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[2] Siebelt et al., WO 03/006666 A2, published Jan. 23, 2003 ("Siebelt").
[3] Sheremet'eva et al., US 2006/0286643 A1, published Dec. 21, 2006 ("Sheremet'eva").
[4] A.F. Neuwald et al., *cysQ, a Gene Needed for Cysteine Synthesis in Escherichia coli K-12 Only during Aerobic Growth*, JOURNAL OF BACTERIOLOGY 174(2), 415–25 (1992) ("Neuwald").
[5] A. Sekowska et al., *Sulfur Metabolism in Escherichia coli and Related Bacteria: Facts and Fiction*, J. MOL. MICROBIOL. BIOTECHNOL. 2(2), 145–77 (2000) ("Sekowska").
[6] Office Action dated May 30, 2017.

particular over-expression, of at least one or more of the genes of the cysteine biosynthesis pathway chosen from the group consisting of . . . cysD, cysN, cysC." *Id*. at 6, ll. 15–21; claim 1.

FF 4. Neuwald teaches that the cysQ gene is needed for cysteine synthesis, and that because "[p]revious work had suggested that 3'-phosphoadenoside 5'-phosphosulfate is toxic if allowed to accumulate, [] we propose that CysQ helps control the pool of 3'-phosphoadenoside 5'-phosphosulfate, or its use in sulfite synthesis." Neuwald 415 (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

Appellant argues claims 12–14 and 19–24 as a group, and separately argues claim 18. We select claim 12 as representative of the group, and separately address claim 12 and claim 18.

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. 3–5; FF 1–4. We address Appellant's arguments below.

As an initial matter, we find that claim 12 would have been obvious in view of Siebelt alone for the reasons set forth in the Answer. Ans. 4, 6–8; FF 1–3. Moreover, we do not find that Sheremet'eva, Neuwald, or Sekowska are necessary to support the obviousness rejection of claim 12. *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

Appellant argues that although "Siebelt discloses methods of overexpressing one or two of the genes of the *cysDNC* cluster for producing various L-amino acids, and provide[s] one example of overexpressing all three specifically to produce L-threonine, it fails to disclose or suggest the claimed method of producing cysteine or its derivatives." Appeal Br. 6; *see also* Reply Br. 4–5.

We are not persuaded by this argument. Siebelt "'must be considered not only for what it expressly teaches, but also for what it fairly suggests.'" *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994) (quoting *In re Burckel*, 592 F.2d 1175, 1179 (CCPA 1979)). Here, Siebelt clearly teaches and suggests all of the limitations of claim 12, specifically disclosing a "bacterium" which "has been modified to have enhanced expression of the *cysDNC* genes." FF 1–3. Moreover, the fact that Example 5 of Siebelt is directed to producing L-threonine by enhancing the *cysDNC* genes does not diminish Siebelt's teachings and suggestions as a whole regarding the production of L-amino acids generally, including the production of the claimed L-cysteine (FF 2). *See In re Mills*, 470 F.2d 649, 651 (CCPA 1972) ("a reference is not limited to the disclosure of specific working examples"); *see also In re Applied Materials*, 692 F.3d 1289, 1298 (Fed. Cir. 2012) ("A reference must be considered for everything that it teaches, not simply the described invention or a preferred embodiment.").

In response to the Examiner's statement that Sekowska teaches that "reactions performed by cysDN and cysC consume ATP and are clearly rate-limiting," thus providing a motivation to overexpress those genes (Non-Final

Act 5),[7] Appellant argues that Sekowska indicates that, "the CysDN reaction can be rate-limiting. However, Sekowska does not disclose or suggest that a phosphosulfate, or PAPS,[8] is not sufficiently produced due to insufficient CysDN activity." Appeal Br. 7. Appellant thus argues that, "the rate-limiting effect is not due to the conversion speed but to the equilibrium constant, and hence, 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)." *Id.*

The Examiner disagrees with Appellant's analysis of Sekowska, but also states that the methods taught by Siebelt alone are sufficient to establish obviousness, including a reason to practice Siebelt's methods and a reasonable expectation of success in practicing those methods to meet the limitations of claim 12, even without the teachings of Sekowska. Ans. 5–8. The Examiner specifically states that Siebelt's teaching "of overexpressing *cysDNC* genes of the cysteine biosynthesis pathway which in turn [] improves the production of L-amino acids . . . provides strong motivation for one of skill in the art to practice such methods." *Id.* at 8. We further note that claim 12 does not recite or require *improved* production of L-cysteine, L-cystine, derivatives thereof, or precursors thereof. Appeal Br. 13.

Appellant argues that the claimed method includes several steps, including the step of collecting L-cysteine, and that "[c]learly, none of the cited references disclose or suggest this step, which represents a distinct

[7] Office Action dated Nov. 22, 2016.
[8] Sekowska uses the acronym PAPS for 3' phosphoadenosine phosphosulfate. *See* Sekowska 146, right col.

difference between the claimed method and the method of Siebelt, which is a method for producing L-threonine." Appeal Br. 8.

We are not persuaded by this argument. As the Examiner explains, Siebelt teaches that the desired L-amino acid can be isolated or collected. Ans. 8–9 (quoting claim 1 of Siebelt); FF 1. The Examiner further states that given Siebelt's teaching that the "bacterium of *Enterobacteriaceae* family is modified to have enhanced expression of all three cysDNC genes in the cysteine biosynthesis pathway for increased production [of a desired L-amino acid including L-cysteine]," one of ordinary skill in the art would have been "motivated to collect any or all L-cysteine overproduced by said modified bacterium." *Id.* at 9.

Claim 18

The rejection of claim 18 relies on the combined teachings of Siebelt and Neuwald. *See* Ans. 4; FF 1–4; *see Bush*, 296 F.2d at 496.

Appellant argues that "[t]he *cysQ* gene is not disclosed or suggested in S[ie]belt."[9] Appeal Br. 9, 11. Appellant further argues that "Neuwald actually discloses that CysQ is necessary for L-cysteine ***synthesis***, not production so that the amino acid can be collected from the culture medium." Appeal Br. 9. Appellant argues further that, "the actual function of CysQ is not identified or disclosed." *Id.* Thus, according to Appellant, "the person of ordinary skill in the art would not have expected that L-

[9] Our decision does not rely on whether Siebelt teaches enhanced expression of the *cysQ* gene (e.g., by referring to cysH and/or cysI), but Siebelt does teach enhanced expression of genes of the cysteine biosynthesis pathway. *See* FF 1, 4.

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.* at 9–10.

We are not persuaded by these arguments. Appellant's argument regarding Neuwald's disclosure of "L-cysteine ***synthesis***, not production," is based on the contention that Neuwald does not teach "production so that the amino acid can be collected from the culture medium." *Id.* at 9. That is, according to Appellant, Neuwald teaches how L-cysteine is made, but not its production and subsequent collection. *Id.*

Even if we viewed Neuwald's teachings as so limited, it would not change our decision because, as discussed above, Siebelt teaches production and isolation (collection) of the desired amino acid from the culture medium. Siebelt 44, ll. 1–19; FF 1. As the Examiner explains, Neuwald teaches that *cysQ* is required for cysteine biosynthesis, and therefore "one would have been motivated to enhance expression of cysQ in addition to cysDNC because the cell culture medium taught by Siebelt [] is enriched with sulfate and also because cysQ plays a crucial role in sulfate assimilation during cysteine biosynthesis by controlling the pool of 3'-phosphoadensoside 5'-phosphosulfate." Ans. 9–10 (citing Neuwald 415, Abstract, left col.); *see also* FF 4. Neuwald thus provides a reason to enhance expression of the *cysQ* gene, which need not be for the same reason that Appellant enhances expression of the *cysQ* gene. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007) ("[i]n determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls").

Appellant argues that Neuwald teaches away from the present invention and, accordingly, "there would not have been any motivation to enhance the expression of the *cysQ* gene with any reasonable expectation of success." Appeal Br. 10. This argument is premised on the contentions that (1) "the person of ordinary skill in the art would have likely concluded from [Neuwald] that if excess PAPS[10] is wasted when L-cysteine is overproduced, L-cysteine production would decrease," and (2) "[t]hat is, the person of ordinary skill in the art would [not] have expected that L-cysteine production is improved by enhancing the expression of *cysQ* gene." *Id.*

We are not persuaded by these arguments. Appellant's arguments fail to show how 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).

Appellant's first premise is a single sentence (without citation) that does not provide adequate factual basis, evidence, or explanation for the contention that "if excess PAPS is wasted when L-cysteine is *overproduced*, L-cysteine *production would decrease*." Appeal Br. 10 (emphasis added). That sentence does not persuasively explain how overproduction of L-cysteine causes L-cysteine production to decrease, based on the teachings of Neuwald. An argument made by counsel in a brief does not substitute for evidence lacking in the record. *Estee Lauder, Inc. v. L'Oréal, S.A.*, 129 F.3d 588, 595 (Fed. Cir. 1997).

[10] Neuwald refers to 3'-phosphoadenosine 5'-phosphosulfate as "PAPS." Neuwald 415, right col.

Appellant's second premise incorrectly assumes that the reason for enhancing expression of the *cysQ* gene must be to improve L-cysteine production. But, as the Examiner explains, a motivation (based on Neuwald) is to control the pool of 3'-phosphoadensoside 5'-phosphosulfate (which may be toxic if allowed to accumulate) in the sulfate enriched culture medium of Siebelt. Ans. 9–10; FF 4; *see also KSR*, 550 U.S. at 419. Appellant fails to specifically address the Examiner's indicated motivation with factual evidence.

Prior Decision

Appellant refers to a previous decision in this application dated September 23, 2016.[11] Appeal Br. 11. According to Appellant, "the only reason [in the Prior Decision] for upholding the rejection of claim 12" was that prior claim 12 did not require enhanced expression of "the combination of all three genes of cysDNC." *Id.* (citing Prior Decision 5). Thus, according to Appellant, "prima facie obviousness has been clearly rebutted." *Id.*

Claim 12 in the Prior Decision was different in several ways from current claim 12. *Compare* Prior Decision 2 *with* Appeal Br. 13. In response to Appellant's argument in the Prior Decision that "Siebelt 'does not disclose or suggest increased expression of the combination of all the three genes of *cysDNC* cluster,'" we found that "claim 12 does not require enhanced expression of 'the combination of all the three genes of *cysDNC*' as Appellants contend." Prior Decision 5. That finding was not a statement

[11] *Ex parte Ziyatdinov*, Appeal No. 2014-003823 (PTAB Sept. 23, 2016) ("Prior Decision").

that a claim reciting the combination of all three genes of *cysDNC* would be patentable over Siebelt. Moreover, Finding of Fact 1 in the Prior Decision expressly states that Siebelt taught enhanced expression of "one or more" genes, including cysD, cysN, and cysC. *Id.* at 3 (FF 1). Siebelt thus expressly teaches "the combination of all the three genes of *cysDNC*." *See* FF 1, *supra*.

CONCLUSION

A preponderance of evidence of record supports the Examiner's conclusion that claims 12 and 18 would have been obvious under 35 U.S.C. § 103(a). Claims 13, 14, and 19–24 were not argued separately and fall with claim 12.

SUMMARY

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
12–14, 18–24	§ 103(a)	Siebelt, Sheremet'eva, Neuwald, Sekowska	12–14, 18–24	

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