UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/982,248	10/23/2013	James H. Doudna Cate	B11-097-3US	2850

23379 7590 01/31/2019

RICHARD ARON OSMAN
530 Lawrence Expy # 332
Sunnyvale, CA 94085

EXAMINER	
EKSTROM, RICHARD C	

ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
01/31/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

richard@sci-tech.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JAMES H. DOUDNA CATE, YONG-SU JIN, JONATHAN M. GALAZKA, and SUK-JIN HA[1]

Appeal 2017-011527
Application 13/982,248
Technology Center 1600

Before TAWEN CHANG, RYAN H. FLAX, and DAVID COTTA, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims directed to a fungal host cell comprising a recombinant Major Facilitator Superfamily (MFS) cellodextrin transporter and a recombinant cellodextrin phosphorylase. Claims 286–301 and 304–314 are on appeal as rejected under 35 U.S.C. § 103(a). We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

---

[1] Appellants identify the Real Parties in Interest as "The Regents of the University of California, and The Board of Trustees of the University of Illinois." Appeal Br. 1.

STATEMENT OF THE CASE

The Specification states:

> The engineering of microorganisms to perform the conversion of lignocellulosic biomass to ethanol efficiently remains a major goal of the biofuels field. Much research has been focused on genetically manipulating microorganisms that naturally ferment simple sugars to alcohol to express cellulases and other enzymes that would allow them to degrade lignocellulosic biomass polymers and generate ethanol within one cell, a process known as consolidated bioprocessing (CBP).

Spec. ¶ 4. The Specification further states that "*Saccharomyces cerevisiae*, also known as baker's yeast, has been used for bioconversion of simple hexose sugars into ethanol for thousands of years," "[i]t has a well-studied genetic and physiological background," but "does not naturally degrade and ferment the more complex biomass polymers, such as cellulose." *Id.* ¶¶ 5–6. The Specification describes a yeast cell host having genes whose expression transports cellodextrin past the cell membrane for metabolizing. *Id.* ¶ 71.

Claim 286 is representative and is reproduced below:

> 286. A fungal host cell comprising a recombinant Major Facilitator Superfamily (MFS) cellodextrin transporter, and a recombinant cellodextrin phosphorylase.

Appeal Br. 22.

The following rejections are appealed (numbering added to correspond to Appellants' briefing):[2]

1. Claims 286–298, 300, 307, 313, and 314 stand rejected under 35 U.S.C. § 103(a) over Blanchard,[3] Thompson,[4] and GenBank XP.[5] Final Action 4–5.

2. Claims 286–298, 300, 307, 309, 310, 313, and 314 stand rejected under 35 U.S.C. § 103(a) over Blanchard, Thompson, GenBank XP, Strobel,[6] and GenBank AAA91282.1.[7] *Id.* at 6–7.

3. Claims 286–298, 300, 307, and 311–314 stand rejected under 35 U.S.C. § 103(a) over Blanchard, Thompson, GenBank XP, Strobel, and GenBank AAA34698.1.[8] *Id.* at 8.

---

[2] Rejections under 35 U.S.C. § 112 for lack of written description and indefiniteness were withdrawn by the Examiner. Answer 9.
[3] US 2010/0028966 A1 (published Feb. 4, 2010) ("Blanchard").
[4] US 2011/0081683 A1 (published Apr. 7, 2011) ("Thompson").
[5] NCBI Reference Sequence: XP_963801.1, *hypothetical protein NCU00801 [Neurospora crassa OR74A]* (2008), accessed at https://www.ncbi.nlm.nih.gov/protein/85111152?sat=21 &satkey=3077027, visited Nov. 13, 2016 ("GenBank XP").
[6] H.J. Strobel et al., *Carbohydrate Transport by the Anaerobic Thermophile Clostridium thermocellum LQRI*, 61(11) APPL. AND ENVIRON. MICROBIO. 4012–15 (1995) ("Strobel").
[7] NCBI Reference Sequence: GenBank: AAA91282.1, *phosphoglucomutase [Saccharomyces cerevisiae]* (1996), accessed at http://www.ncbi.nlm.nih.gov/protein/AAA91282.1, visited June 25, 2015 ("GenBank AAA91281.1").
[8] NCBI Reference Sequence: GenBankAAA34698.1, *hexokinase (HXK1) [Saccharomyces cerevisiae]* (1993), accessed at http://www.ncbi.nhn.nih.gov/protein/AAA34698.l, visited June 25, 2015 ("GenBank AAA34698.1").

4. Claims 286–298, 300, 307, 308, 313, and 314 stand rejected under 35 U.S.C. § 103(a) over Blanchard, Thompson, GenBank XP, and Brat.[9] *Id.* at 9.

5. Claims 286–302, 305, 307, 313, and 314 stand rejected under 35 U.S.C. § 103(a) over Blanchard, Thompson, GenBank XP, and GenBank BAB.[10] *Id.* at 10.

6. Claims 286–298, 300, 301, 303, 304, 306, 307, 313, and 314 stand rejected under 35 U.S.C. § 103(a) over Blanchard, Thompson, GenBank XP, and GenBank ABD.[11] *Id.* at 11.

DISCUSSION

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Arguments made by Appellants in the Appeal Brief and properly presented in the Reply Brief have been considered; arguments not so presented in the Briefs are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for

---

[9] US 8,986,948 B2 (issued Mar. 24, 2015) ("Brat").
[10] NCBI Reference Sequence: GenBank: BAB71818.1, *cellodextrin phosphorylase [Ruminiclostridium thermocellum]* (2001), accessed at https://www.ncbi.nlm.nih.gov/protein/16797805?report=genbank&log$=protalign&blast . . . , visited Nov. 13, 2016 ("GenBank BAB").
[11] NCBI Reference Sequence: Genbank: ABD80580.1, *cellobiose phosphorylase [Saccharophagus degradans 2-40]*, accessed at https://www.ncbi.nlm.nih.gov/protein/89950565?sat= 14&satkey=5430048, visited Nov. 13, 2016 ("GenBank ABD").

asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "[W]hen a patent claims a structure [or method] already known in the prior art that is altered by the mere substitution of one element [or step] for another known in the field, the combination must do more than yield a predictable result." *Id.* (citing *United States v. Adams*, 383 U.S. 39, 50–51 (1966)). "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *Id.* at 419. "[T]he question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the *most desirable* combination available." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (citation omitted).

"[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. "[F]amiliar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 420.

"[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.,* 480 F.3d 1348, 1364 (Fed. Cir. 2007) (citing *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985)). "[A] presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003).

Findings of Fact

We adopt the Examiner's findings of fact and rationale on obviousness as set forth in the Final Action and Answer. Final Action 4–13 and Answer 2–22 (collectively citing Blanchard Abstract, ¶¶ 105, 134, Table 18, ¶ 252 (Example 7); Thompson Abstract, ¶¶ 13, 17, 31; GenBank XP generally; Strobel Figure 5; GenBank AAA91282.1 generally; GenBank AAA34698.1 generally; Brat Abstract, 6:45–62; GenBank BAB generally; and GenBank ABD generally). The following findings of fact highlight certain evidence:

FF1. Blanchard discloses methods and compositions for improving the production of fuel products such as ethanol by microorganisms utilizing genes identified in bacteria, for example *Clostridium phytofermentans*, those genes (of interest) encoding for combinations of hydrolases, ATP-binding cassette (ABC) transporters, and transcriptional regulators. Blanchard Abstract, ¶¶ 4, 6–9, 11, 74, 76.

FF2. Further to the preceding finding of fact, Blanchard discloses transforming a microorganism host cell with a nucleic acid

including some combination of the genes of interest. Blanchard ¶¶ 32, 76, 110.

FF3. Blanchard discloses the "[a]dvantages to utilizing nucleic acids encoding ABC-transporters include ***increasing the capacity of transformed organisms to transport compounds into the organism*** and utilize such compounds in the biochemical pathways to produce fuel, and ***thus improve fuel production***." Blanchard ¶ 101–102 (emphasis added). Thus, Blanchard teaches and suggests it is advantageous to genetically enhance the transport of compounds, e.g., sugars and amino acids, important to fermentation production of ethanol.

FF4. Blanchard discloses that "[c]ertain embodiments include predicted ABC-transporters that ***transport cellobiose***, for example, predicted ABC-transporters encoded by Cphy2464, Cphy2465, and Cphy2466," i.e., transport systems with permease and periplasmic components encoded by genes from *C. phytofermentans*. Blanchard ¶¶ 103–105 (Table 7), 118 (Table 9) (emphasis added).

FF5. Blanchard suggests that transporters for the disaccharides lactose and cellobiose are the same or similar. *Id.* ¶ 104.

FF6. Further to the preceding findings of fact, Blanchard discloses:

Cellobiose Utilization

> Some embodiments described herein relate to polynucleotides, polynucleotide cassettes, expression cassettes, expression vectors, and microorganisms comprising nucleic acids identified in *C. phytofermentans* encoding enzymes/ protein domains involved in cellobiose utilization. Other

> embodiments relate to methods for producing fuel utilizing the polynucleotides, polynucleotide cassettes, expression cassettes, expression vectors, and microorganisms including nucleic acids identified in *C. phytofermentans* encoding enzymes/protein domains involved in cellobiose utilization. Cellobiose is a disaccharide derived from the condensation of two glucose molecules linked in a β(1→4) bond. Examples of genes identified as upregulated during growth on cellobiose include Cphy0430, Cphy2464, Cphy2465, Cphy2466, and Cphy2467 (see FIG. **17**).

Blanchard ¶ 134; *see also id.* ¶ 221, Table 18 (listing genes for, *inter alia*, extracellular solute-binding protein and cellobiosidase).

FF7. Further to the preceding findings of fact, Blanchard discloses:

> Some embodiments relate to microorganisms containing any of the polynucleotides, polynucleotide cassettes, expression cassettes, or expression vectors described herein. Host cells can include, but are not limited to, eukaryotic cells, such as animal cells, insect cells, ***fungal cells, and yeasts***, and prokaryotic cells, such as ***bacteria***. In some embodiments, the host is *C. phytofermentans*. In some embodiments, a potential host organism can comprise a recombinant organism.

Blanchard ¶ 176–178 (emphasis added). Specifically, Blanchard discloses a variety of examples of yeasts for host organisms, including *Saccharomyces cerevisiae*. *Id.*; *see also* Spec. ¶ 94 (disclosing the same example species of yeast as a host organism); *see also* claim 307 (reciting *Saccharomyces* as a host yeast). Blanchard suggests that engineering a yeast cell as a host for bacteria genes of interest would be successful.

FF8. Blanchard discloses a successful example where

> *E.coli* are engineered to utilize cellobiose by expression of Cphy2464-2466, encoding an ABC transporter and Cphy0430, encoding a cellobiose phosphorylase that converts cellobiose into glucose and glucose-I-phosphate. The Cphy2464-2466 and Cphy0430 genes are expressed from a constitutive promoter on a plasmid. The signal sequence of Cphy2466 is replaced with the signal sequence of an endogenous *E. coli* ABC transporter periplasmic binding protein to direct expression of the protein in the periplasm. The engineered *E. coli* are able to grow using cellobiose as a sole carbon source.

Blanchard ¶ 252 (Example 7).

FF9. Thompson, similar to Blanchard, is directed to

> A genetically modified organism comprising: at least one nucleic acid sequence and/or at least one recombinant nucleic acid isolated from *Alicyclobacillus acidocaldarius* and encoding a polypeptide involved in at least partially degrading . . . [and] ***transporting . . . cellulose*** . . . [and] sugars, sugar oligomers, carbohydrates, [or] complex carbohydrates . . . ; and at least one nucleic acid sequence and/or at least one recombinant nucleic acid encoding a polypeptide involved in ***fermenting sugar molecules*** to a product.

Thompson Abstract, ¶¶ 7–8, 13 (emphasis added). One of the sugars specifically identified by Thompson is cellobiose, to be hydrolyzed by Cellobiose phosphorylases. *Id.* ¶ 13.

FF10. Thompson is directed to the fermentation of ethanol. Thompson ¶ 17.

FF11. Similar to Blanchard, Thompson discloses isolating genes of interest from various species of *Clostridium*. Thompson ¶¶ 30.

FF12. Similar to Blanchard, Thompson discloses incorporating isolated genes for expression in various host species of *Clostridium*, as well as species of *Saccharomyces*, *Zymomonas*, *Candida*, and *E. coli*, specifically *Saccharomyces cerevisiae* (yeast). Thompson ¶¶ 31, 48. Thompson, like Blanchard, suggests that engineering a yeast cell as a host for bacteria genes of interest would be successful.

FF13. GenBank XP discloses a hypothetical protein sequence of *Neurospora crassa*, a filamentous fungus; the protein being the product of the NCU00801 gene with an amino acid sequence identical to SEQ ID NO: 9. GenBank XP; *see also* Spec. ¶¶ 16, 106 (Tables 1 and 2), and Final Action 5.

FF14. GenBank XP discloses its sequenced protein is "similar to MFS lactose permease." GenBank XP; *see also supra* FF5 (suggesting transporters for lactose are also suitable transporters for cellobiose).

FF15. Strobel discloses the carbohydrate, e.g., cellobiose and glucose, uptake/transport system of *Clostridium thermocellum*, investigated in view of ethanol production from fibrous biomass. Strobel 4012.

FF16. Further to the preceding finding of fact, Strobel discloses observing "[h]igh levels of phosphoglucomutase activity [] in the cytosol fraction, while no activity was found in the membrane," which "confirmed that the membrane fraction was essentially free of contamination by cytosolic enzymes." Strobel 4014.

FF17. Strobel discloses that cellobiose and larger cellodextrins are transported intact across the cell membrane to then be subjected to phosphorylytic cleavage within the cell. Strobel 4014.

FF18. Strobel includes the following figure:

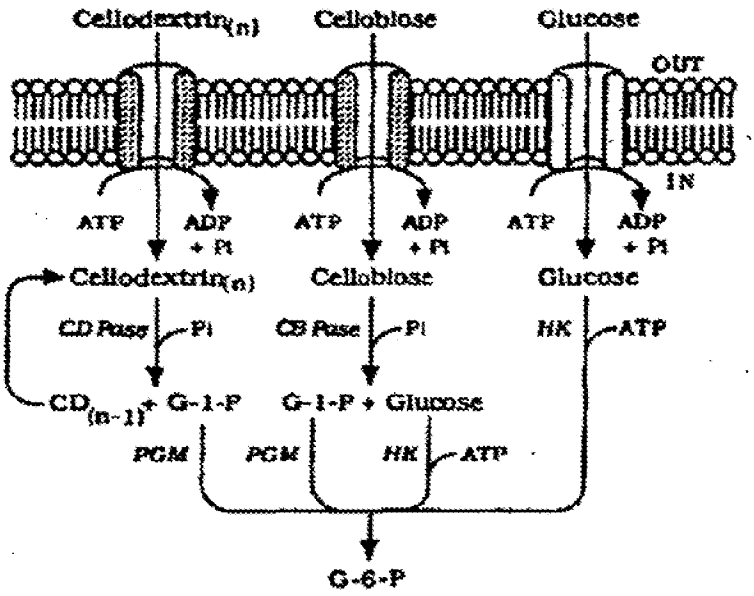

FIG. 5. Schematic model of carbohydrate uptake and phosphorylation by *C. thermocellum*. G-1-P, glucose-1-phosphate; G-6-P, glucose-6-phosphate; Pi, inorganic phosphate; CB Pase, cellobiose phosphorylase; CD Pase, cellodextrin phosphorylase; HK, hexokinase; PGM, phosphoglucomutase.

Strobel 4015 (Figure 5). Strobel Figure 5 (above) illustrates the transport of cellodextrin, cellobiose, and glucose across the cell membrane of *Clostridium thermocellum*, and shows that cellobiose, once so-transported, is metabolized with phosphoglucomutase (PGM) and hexokinase (HK), and that glucose, once transported is metabolized with hexokinase (HK). *Id.* Strobel suggests that, *inter alia*, sufficient levels of phosphoglucomutase and hexokinase are

required for the metabolism of cellobiose and glucose to produce ethanol.

FF19. Further to the preceding findings of fact, Strobel states, "[s]uch information may be useful in developing rational schemes (or manipulating the physiology of cellulolytic thermophiles and optimizing fermentation technology." Strobel 4015. Strobel suggests engineering microorganisms to ensure the presence of sufficient phosphoglucomutase and hexokinase.

FF20. Further to the preceding findings of fact, GenBank AAA91282.1 discloses the amino acid sequence of phosphoglucomutase of *Saccharomyces cerevisiae* (baker's yeast). GenBank AAA91282.1; *see also* Strobel Figure 5 (PGM).

FF21. Further to the preceding findings of fact, GenBank AAA34698.1 discloses the amino acid sequence of hexokinase (HXK1) of *Saccharomyces cerevisiae* (baker's yeast). GenBank AAA34698.1; *see also* Strobel Figure 5 (HK).

FF22. Brat discloses fermentation yeasts genetically engineered to include genes from *Clostridium phytofermentans* to enhance the fermentation of ethanol. Brat Abstract. Brat suggests engineering a yeast cell as a host for bacteria genes of interest would be successful.

FF23. Brat discloses that ordinary baker's yeast, *Saccharomyces cerevisiae*, has been used for fermentation for centuries, and discloses engineering yeast cells by introducing genes from bacteria (*Clostridium phytofermentans*) that, when expressed,

allowed the yeast to "efficiently metabolize xylose." Brat 1:36–39, 3:17–28, 4:16–22.

FF24. Further to the preceding finding of fact, Brat discloses that the engineered yeast cells can include host cells selected from *Saccharomyces, Kluyveromyces, Candida, Pichia, Schizosaccharomyces, Hansenula, Kloeckera, Schwanniomyces, Arxula* and *Yarrowia*," and filamentous cells selected from *Aspergillus, Trichoderma, Humicola, Acremonium, Fusarium* and *Penicillium.* Brat 5:50–6:62.

FF25. GenBank BAB discloses the amino acid sequence of cellodextrin phosphorylase of *Ruminiclostridium thermocellum.* GenBank BAB.

FF26. GenBank ABD discloses the amino acid sequence of cellobiose phosphorylase of *Saccharophagus degradans* 2–40. GenBank ABD.

Analysis

1. Rejection of Claims 286–298, 300, 307, 313, and 314 over Blanchard, Thompson, and GenBank XP

The Examiner determined that claim 286 would have been obvious over the Blanchard-Thompson-GenBank XP combination. Final Action 4–6; *see also supra* Findings of Fact. The Examiner cites Blanchard as disclosing using genes from bacteria, e.g., *Clostridium phytofermentens*, that, when expressed, promote the transport across the cell membrane and metabolism of cellobiose. *Id.* The Examiner points to an exemplary host cell being *E. coli*; however, Blanchard discloses a variety of host cells, including yeast cells. *Id.*; *see also* FF7, FF8 (disclosing using yeast cells as

hosts and suggesting the interchangeability of bacterial and yeast cells as hosts). The Examiner cites Thompson as additional, direct support that yeast cells would have been engineered as hosts for genes from bacterial cells relating to the transporting and metabolizing of cellobiose. Final Action 5–6; *see also* FF9–FF12. GenBank XP discloses a protein sequence identified as an MFS lactose permease and Blanchard suggests that such a protein would also be useful for transporting cellobiose; the Examiner cited GenBank XP as disclosing SEQ ID NO: 9, which is within the scope of the appealed claims. Final Action 5–6; *see also* FF13–FF14. The Examiner determined that it would have been obvious to combine the teachings of Blanchard, Thompson, and GenBank XP to improve ethanol production by applying the genetic engineering elements and steps disclosed by these references in the fashion taught by the references. Final Action 6. We discern no error in the Examiner's determinations.

Appellants argue that the Examiner's determination that

> [i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the recombinant ABC transporter and the recombinant cellobiose phosphorylase gene described by Blanchard et al., or to have incorporated the GenBank MFS permease, in the *Saccharomyces cerevisiae* or *Candida shehatae* host cells described by Thompson et al. because Thompson et al. generically describe the use of any transporter or carbohydrate metabolizing enzymes in *Saccharomyces cerevisiae* or *Candida shehatae* host cells to produce fermentation products such as ethanol and the enzymes described by Blanchard et al. and GenBank Accession No. XP_963801.1 are merely alternatives within the generic teachings of Thompson et al.

(Final Action 6), is incorrect because bacteria (e.g., *Clostridium phytofermentens*) and yeast (e.g., *Saccharomyces cerevisiae*) are so different ("widely diverged") that the skilled artisan would expect that transferring components (genes) between them would not work. Appeal Br. 3–4. Appellants argue that only their research discovered that such a transfer, particularly for MFS transporters, could work; arguing that only improper hindsight on the part of the Examiner could have led to combining the cited prior arts' teachings. *Id.* at 4–5 (citing Cate Declaration).[12] In the Reply Brief, Appellants argue that the Examiner's case for obviousness has changed in that the rejection "seeks now to spotlight Thompson." Reply Br. 2. The Reply Brief also states "Blanchard and Thompson both teach away from our invention," but offers no persuasive supporting evidence for the statement. *Id.* at 4.

These arguments are not persuasive. Appellants' primary argument, that the skilled artisan would not have engineered a host yeast cell with genes from a bacterial cell, is not supported by a preponderance of the evidence. Appellants' Cate Declaration concludes that "because such bacterial and fungal host cells [disclosed by Blanchard and Thompson] are so widely diverged [] persons skilled in the art would reasonably expect that transferring the components would not work"; however, this statement is not supported by data or any other evidence, but amounts to only the Professor's opinion. *See* Cate Declaration ¶ 2. This point is mirrored in Appellants'

[12] Declaration of James H. Doudna Cate, dated Dec. 7, 2016 ("Cate Declaration").

arguments in the Appeal Brief (for each rejection). *See, e.g.*, Appeal Br. 4, 5, 7, 8, 10, 12, 14, 15, 17–20.

This conclusory statement and argument is not persuasive in the face of the Blanchard and Thompson references' disclosures and suggestions that it is possible, and would have been obvious, to transfer the claimed components between bacteria and yeast cells. *See supra* FF1–FF12; *see also* FF22–FF24 (Brat, cited by the Examiner in other obviousness rejections, also suggests that this is a known technique). The mere suggestion of unpredictability cannot overcome this evidence suggesting a reasonable expectation of success.

Appellants' arguments that the Examiner's focus shifted from Blanchard to Thompson in the Answer, and that these references teach away from the invention, are also not persuasive. Thompson was always a part of the prior art combination cited by the Examiner in the final rejection; there was no error in the Examiner's further explaining its relevance. Further, Appellants do not identify where or how Blanchard or Thompson teach away from the claims, as contended.

Regarding claim 297, Appellants argue, similarly, that absent their discovery that bacterial genes could work effectively in fungal cells, there would have been no motivation to combine the cited references and employ a mutated transporter, as claimed. Appeal Br. 5.

As discussed above, Blanchard and Thompson both suggest engineering yeast cells with genes from bacteria that are useful with respect to transporting and metabolizing cellobiose. Appellants do not argue the

Examiner's understanding of the claimed "mutant" is incorrect. *See* Appeal Br. 5; Reply Br. 5. Appellants' argument is not persuasive.

2. Rejection of Claims 286–298, 300, 307, 309, 310, 313, and 314 over Blanchard, Thompson, GenBank XP, Strobel, and GenBank AAA91282.1

The Examiner determined that the Blanchard-Thompson-GenBank XP-Strobel-GenBank AAA91282.1 combination would have rendered the claims obvious. Final Action 6–7. Blanchard, Thompson, and GenBank XP were cited by the Examiner here, and in each obviousness rejection (discussed below), for the same reasons as set forth above for the first (1) obviousness rejection. The Examiner cited Strobel as teaching the importance of phosphoglucomutase in metabolizing cellobiose and glucose once these molecules are transported into the cell. *Id.* at 7; *see also* FF15–FF19. The Examiner cited GenBank AAA91282.1 as disclosing the amino acid sequence of phosphoglucomutase of *Saccharomyces cerevisiae* (baker's yeast). Final Action at 7; *see also* FF20. We discern no error in the Examiner's determinations.

Appellants present the same arguments over this rejection as presented over Rejection 1 and discussed above. Appeal Br. 6–8. These arguments remain unpersuasive.

Regarding claims 309 and 310, Appellants argue that without their discovery that phosphoglucomutase, required for glucose conversion, can be downregulated during glycolytic growth or otherwise effected by other cellular conditions, there would have been no motivation to express the recited recombinant phosphoglucomutase. Appeal Br. 8–9.

This argument is not persuasive. Strobel teaches the importance of phosphoglucomutase (and hexokinase) in metabolizing cellobiose (and glucose) and suggests using this knowledge when engineering microorganisms to perform this function. FF15–FF19. Therefore, even without Appellants' disclosure, the claimed invention would have been obvious.

3. Rejection of Claims 286–298, 300, 307, and 311–314 over Blanchard, Thompson, GenBank XP, Strobel, and GenBank AAA34698.1

The Examiner determined that the Blanchard-Thompson-GenBank XP-Strobel-GenBank AAA34698.1 combination would have rendered the claims obvious. Final Action 8–9. Blanchard, Thompson, and GenBank XP, and Strobel were cited by the Examiner here for the same reasons as set forth above for the previous obviousness rejections (1 and 2). The Examiner cited Strobel as teaching the importance of hexokinase, in particular. *Id.* at 8; *see also* FF15–FF19. The Examiner cited GenBank AAA34698.1 as disclosing the amino acid sequence of hexokinase of *Saccharomyces cerevisiae* (baker's yeast). Final Action at 8; *see also* FF21. We discern no error in the Examiner's determinations.

Appellants present the same arguments over this rejection as presented over Rejection 1 and discussed above. Appeal Br. 9–12. These arguments remain unpersuasive.

Regarding claims 311 and 312, Appellants argue that without their discoveries that hexokinase, required for glucose conversion, may not be sufficiently expressed and that its expression may be effected by other

cellular conditions, there would have been no motivation to express the recited recombinant hexokinase. Appeal Br. 12.

As with the prior rejection (2) and for the same reasons discussed above, this argument is not persuasive.

4. Rejection of Claims 286–298, 300, 307, 308, 313, and 314 over Blanchard, Thompson, GenBank XP, and Brat

The Examiner determined that the claims would have been obvious over the Blanchard-Thompson-GenBank XP-Brat combination, citing the Blanchard, Thompson, and GenBank XP references for the same teachings as discussed above. The Examiner cited Brat as teaching engineering filamentous fungal cells as hosts in the manner taught by Blanchard and Thompson. Final Action 9–10; *see also* FF22–FF24. We discern no error in the Examiner's determinations.

Appellants present the same arguments over this rejection as presented over Rejection 1 and discussed above. Appeal Br. 12–15. These arguments remain unpersuasive.

5. Rejection of Claims 286–302, 305, 307, 313, and 314 over Blanchard, Thompson, GenBank XP, and GenBank BAB

The Examiner determined that the claims would have been obvious over the Blanchard-Thompson-GenBank XP-GenBank BAB combination, citing the Blanchard, Thompson, and GenBank XP references for the same teachings as discussed above. The Examiner cited GenBank BAB as teaching the amino acid sequence of SEQ ID NO: 184, which is within the scope of the claims. Final Action 10–11; *see also* FF25. We discern no error in the Examiner's determinations.

Appellants present the same arguments over this rejection as presented over Rejection 1 and discussed above. Appeal Br. 15–18. These arguments remain unpersuasive.

6. Rejection of Claims 286–298, 300, 301, 303, 304, 306, 307, 313, and 314 stand rejected under 35 U.S.C. § 103(a) over Blanchard, Thompson, GenBank XP, and GenBank ABD

The Examiner determined that the claims would have been obvious over the Blanchard-Thompson-GenBank XP-GenBank ABD combination, citing the Blanchard, Thompson, and GenBank XP references for the same teachings as discussed above. The Examiner cited GenBank ABD as teaching the amino acid sequence of SEQ ID NOs: 158 or 12, which are within the scope of the claims. Final Action 11; *see also* FF26. We discern no error in the Examiner's determinations.

Appellants present the same arguments over this rejection as presented over Rejection 1 and discussed above. Appeal Br. 18–21. These arguments remain unpersuasive.

SUMMARY

The obviousness rejections are each affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED