

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COMPLETE GENOMICS, INC.,
Petitioner,

v.

ILLUMINA CAMBRIDGE LTD.,
Patent Owner.

Case IPR2017-02174
Patent 7,566,537 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

MAJORS, *Administrative Patent Judge*.

DECISION
Denying Petitioner's Request for Rehearing
37 C.F.R. § 42.71(d)

I. INTRODUCTION

Complete Genomics, Inc. (“Petitioner”) filed a Petition (Paper 1, “Pet.”) to institute *inter partes* review of claims 1–6 and 8 of U.S. Patent No. 7,566,537 B2 (“the ’537 patent” (Ex. 1501)). Illumina Cambridge Ltd. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 6 (“Prelim. Resp.”). We entered a decision denying institution. Paper 20, (“Decision” or “Dec.”). Petitioner filed a request for rehearing of the Decision. Paper 21 (“Req. Reh’g” or “Request”). This paper addresses Petitioner’s Request.

In response to a request for rehearing, the panel reviews a decision whether to institute trial for an abuse of discretion. 37 C.F.R. § 42.71(c). “The burden of showing a decision should be modified lies with the party challenging the decision.” 37 C.F.R. § 42.71(d). Moreover, the request “must specifically identify all matters the [challenging] party believes the Board misapprehended or overlooked, and the place where each matter was previously addressed in a motion, an opposition, or a reply.” *Id.*

As discussed below, we deny the Request because Petitioner does not establish an abuse of discretion.

II. DISCUSSION

The Petition challenged claims 1, 2, 4–6, and 8 as unpatentable under 35 U.S.C. § 103 over the combined teachings of Dower, Church, and Zavgorodny. Pet. 8–9; Dec. 7–8. Claim 3 was challenged for obviousness based on the above prior art combination, in further view of Prober. Pet. 8–9; Dec. 7–8. Based on the information presented in the Petition and the Preliminary Response, we determined that Petitioner had not established a reasonable likelihood of prevailing with respect to at least one of the challenged claims on the grounds advanced and, accordingly, we denied the

Petition. Dec. 2, 16–38; 35 U.S.C. § 314(a) (authorizing trial only when Petitioner has made this necessary threshold showing). Among other things, we determined Petitioner had not made a sufficiently persuasive showing that the ordinarily skilled person would have combined Dower, Church, and Zavgorodny based on a “simple substitution” theory or the alleged “advantageous properties” of an azidomethyl protecting group as argued in the Petition. Dec. 25–38; Pet. 32–52.

Petitioner’s Request argues the Board (1) misapprehended or overlooked evidence concerning Zavgorodny’s use of co-solvents (Req. Reh’g 5–9); (2) misapprehended or overlooked evidence that amine group intermediates spontaneously collapse (*id.* at 9–11); (3) misapprehended or overlooked the nature of the azidomethyl group (*id.* at 11–13); and (4) improperly determined that an ordinarily skilled person would have been discouraged from applying Zavgorodny’s azidomethyl group to Dower’s methods (due to product yields reported in Loubinoux) (*id.* at 13–15).

A) Zavgorodny’s use of co-solvents

We turn to Petitioner’s first argument that the Board allegedly misapprehended or overlooked evidence related to Zavgorodny’s use of co-solvents. Req. Reh’g 5–9. According to Petitioner, the Board wrongly credited Patent Owner’s argument and evidence that an ordinarily skilled person would have been discouraged from using an azidomethyl protecting group and Zavgorodny’s deprotection conditions for such group. *Id.* at 5–6. Petitioner argues the “Board misapprehended or overlooked [Petitioner’s] arguments and evidence that a POSITA would not have had such concerns” and further, even if a POSITA would have been motivated to avoid pyridine (Zavgorodny’s co-solvent) as a DNA denaturant, “they would have found it

routine to modify Zavgorodny's deprotection conditions to remove pyridine." *Id.* at 6–7. More to this point, Petitioner contends, it would have been routine for the ordinarily skilled person to modify Zavgorodny's conditions to avoid pyridine as a co-solvent, and use other water soluble phosphines (i.e., TCEP) to cleave the azidomethyl group. *Id.* at 7–9.¹

Petitioner's argument fails to meet the burden in showing the Board overlooked or misunderstood relevant matters, and abused our discretion in denying institution based, in part, on the Board's determination that an ordinarily skilled person would have been discouraged from using an azidomethyl protecting group and Zavgorodny's deprotecting conditions in Dower's DNA sequencing methods. Dec. 30–33. As explained in the Decision, Zavgorodny does not disclose any specific use for its protected molecules, much less disclose or suggest a use in DNA sequencing methods like disclosed in Dower. Dec. 18; Dec. 27–28. Petitioner admitted (and the art reflected) that potential harm to the DNA was a key consideration in selecting suitable protecting groups. Dec. 23. And, as discussed in the Decision, the evidence of record persuaded us that the skilled person would not have been motivated to use Zavgorodny's deprotection conditions

¹ Petitioner also contends the Board appears to have misunderstood the word "very specific" in relation to Zavgorodny's reaction conditions. Req. Reh'g 8 n.1 (citing Dec. 30 n.22). According to Petitioner, Zavgorodny used the term to describe the specificity of the reaction, not to suggest that the reaction must use the specific conditions recited. *Id.* Assuming, for argument's sake, Petitioner is correct, we are unpersuaded the Decision should be modified. The fact remains that even nearly 10 years after the initial Zavgorodny publication, Zavgorodny '00 does not disclose any other suitable removal conditions. Dec. 30 n.22. We were unpersuaded those conditions would be considered suitable for Dower's DNA sequencing methods as discussed in the Decision. Dec. 30–33.

(including the use of triphenylphosphine and pyridine) for DNA sequencing reactions because pyridine is a well-known DNA denaturant. Dec. 28 (discussing references describing pyridine as one of the “most effective” DNA denaturants); *see also id.* at 31 (discussing the Board’s determination that conditions disclosed as mild in some contexts does not demonstrate those conditions are mild and suitable in other contexts). That the Board found persuasive the evidence clearly and explicitly disclosing that pyridine is an especially effective DNA denaturant, over the opinion of Petitioner’s expert that such solvents would not be a concern does not constitute an abuse of discretion. Req. Reh’g 6–7.

As for Petitioner’s argument that, putting aside whether Zavgorodny’s conditions would risk harming DNA, a skilled person would just use other conditions until sufficiently suitable conditions for DNA sequencing were achieved (Req. Reh’g 7–9), we remain unpersuaded that the Board abused its discretion for at least two reasons. First, as explained in the Decision, it was “unclear if Petitioner is actually proposing [in the Petition] to further modify the method based on the combination of Dower, Church, or Zavgorodny with specific conditions” from other references. Dec. 31–32 (“If Petitioner is making such a proposal, it fails to do so clearly and persuasively.”). Alluding to other potential agents, solvents, etc. in the Petition, without specifying what conditions and agents are being proposed and used to modify the relied-upon combination of prior art is insufficient to show particular subject matter allegedly misapprehended or overlooked by the Board. *See* Req. Reh’g 7 (citing Pet. 41–45 & n. 7). And, insofar as Petitioner was suggesting to further modify the Dower/Church/Zavgorodny combination to omit pyridine and use tetrahydrofuran or TCEP in DNA

sequencing methods, those conditions were not overlooked — the Decision addressed such modifications. Dec. 32–33.

Second, Petitioner’s argument about optimizing the conditions for an azidomethyl protecting group presumes there was sufficient motivation for the ordinary artisan to use that group in DNA sequencing methods to begin with. As we explained throughout the Decision, we were unpersuaded for many reasons that the evidence of record provided an adequate motivation to do so. *See, e.g.*, 21–38. There may well be conditions under which a 3'-O-azido protecting group is usable in DNA-sequencing methods. Indeed, that is the invention claimed. But it is impermissible hindsight to start with the end result and work backwards, asserting that whatever roadblocks are reflected in the art or that might arise in relation to the use of that protecting group, the skilled person would just work around them by changing the conditions to yield the claimed invention. As we explained in the Decision, in the years before the invention there were numerous known protecting groups described in the art for DNA sequencing methods like Dower (e.g., 3'-O-allyl, tBOC, 3'-O-acetyl). Dec. 26. Why choose an azido or azidomethyl group for this purpose when there is no indication in the art to have done so, and ample evidence suggests selection of such a group would be accompanied by a host of discouraging factors (e.g., DNA-denaturing conditions, low yields, steric bulk)? *See* Dec. 26–37. For reasons discussed in the Decision, the Petition failed to provide a sufficiently persuasive answer to this question.

B) Amine Group Intermediates

Petitioner argues the Board “improperly determined that a POSITA would have been discouraged from applying Zavgorodny to Dower’s DNA

sequencing methods due to concerns that ‘the amine group formed by the reaction of a phosphine with an azido group would cleave the phosphate ester backbone of DNA.’” Req. Reh’g 9–10 (citing Dec. 33). As Petitioner notes, the Board found that formation of those intermediates, such as by the use of TCEP as an alternative phosphine to that disclosed in Zavgorodny, would have discouraged the use of azido protecting groups and TCEP in Dower’s DNA sequencing methods. *Id.* According to Petitioner, in making its determination, the Board “overlooked evidence presented in the Petition that POSITAs would not view the creation of an amine as problematic” because the amines would spontaneously collapse and result in a free hydroxyl group. *Id.* at 10 (citing Pet. 40 n.5 and Ex. 1601, ¶ 36).²

Here too, we disagree that the Board abused its discretion. Patent Owner presented persuasive argument and evidence related to the use of TCEP in the proposed further modification to the Dower, Church, and Zavgorodny combination. Prelim. Resp. 41–43. As described in the Decision, Stanton discloses that the amine group formed from the reaction of TCEP with an azido-modified polynucleotide will spontaneously attack and cleave the DNA backbone. Dec. 33 (citing Ex. 1546). Petitioner admitted that the proposed reaction produces such amines, but Petitioner contends the amines will subsequently collapse and therefore cannot harm the DNA. Req. Reh’g 11 (“Thus a POSITA would not have viewed the creation of a

² Petitioner’s citation to paragraph 36 of Exhibit 1601 (Sutherland Decl.) appears to be incorrect as that paragraph relates to a description of Greene & Wuts. Petitioner may have intended to cite to paragraph 136. But even the footnote to which Petitioner cites in the Petition (Pet. 40 n.5) in support is unclear because it cites to paragraph 136 of Exhibit 1615, which exhibit does not exist in this record.

hemiaminal intermediate as problematic because the surrounding media would cause it to decompose long before it could cleave the DNA backbone of the template.”). After considering the information in the Petition and the Preliminary Response, however, we were persuaded that the intermediate amine products would be considered potentially harmful to the DNA backbone in view of at least Stanton. Dec. 33. Petitioner’s contentions (primarily made in a footnote) failed to address Patent Owner’s argument and evidence on this point in a sufficiently clear, direct, and persuasive way. Nor does Petitioner’s expert squarely address Stanton (and the relevant disclosures cited by Patent Owner) in the portion of the declaration cited.³

C) Nature of the Azidomethyl Group

We turn to Petitioner’s argument that “the Board gave inappropriate weight to Patent Owner’s misleading and factually incorrect assertions” about the size, rigidity, and steric bulk of the azidomethyl group and contention that the Board “inappropriately resolved the factual dispute in favor of Patent Owner in violation of 37 C.F.R. § 42.108(c).” Req. Reh’g 11–13; *see also id.* at 5. Rule 42.108(c) provides, in pertinent part, that:

The Board’s [institution] decision will take into account a patent owner preliminary response where such response is filed, including any testimonial evidence, but a genuine issue of material fact created by such testimonial evidence will be viewed in the light most favorable to the petitioner solely for purposes of deciding whether to institute an inter partes review.

³ In relevant portions of the Request, Petitioner cites to paragraphs 135–136 of the Sutherland Declaration (Ex. 1601). Req. Reh’g 9–11. Stanton (Ex. 1546, which is an exhibit originally introduced by Petitioner) is not addressed at all in the Petition.

Under that rule, when a patent owner submits testimonial evidence with the preliminary response, the Board views “genuine issue[s] of material fact created by such testimonial evidence” in the light most favorable to petitioner for institution purposes. This does not, however, mean that the Board must institute trial in every instance where the preliminary record includes conflicting opinion testimony. Petitioner directs us to no binding Board decisions applying Rule 42.108(c) so broadly. The conflicting testimony must be sufficient to raise a “genuine” and “material” dispute of fact. Moreover, Rule 42.108(c) does not supersede the Board’s statutory mandate that precludes institution of trial where, as here, the information presented in the Petition fails to satisfy the threshold showing for review. 35 U.S.C. § 314(a) (authorizing institution of trial only upon a showing of “a reasonable likelihood that petitioner would prevail with respect to at least 1” challenged claim); Dec. 25–38 (explaining numerous reasons why Petitioner did not demonstrate that it was reasonably likely to prevail in this case). A reading of the rule that would require the Board to institute trial whenever the preliminary record includes differing expert opinion on an issue is an untenable result that is inconsistent with § 314(a).

The applicability of Rule 42.108(c) on this record, and specifically the question of whether the skilled person would have believed the size, rigidity, and steric bulk of an azidomethyl moiety to be unfavorable for use as a protecting group, is a closer call. On one hand, as Petitioner points out, its expert opined that although the azide ($-N_3$) portion is linear and rigid, “the additional methyleneoxy moiety would allow the azidomethyl group to adopt rotamers that minimize steric bulk.” Ex. 1601, ¶ 144; Req. Reh’g 12. This opinion is, however, conclusory, and Petitioner’s expert provides insufficient evidentiary support for it, much less support showing that the

asserted rotameric character would project the rigid and sterically bulky azide sufficiently away from that polymerase active site to facilitate further nucleotide incorporation. *See, e.g.*, Ex. 1601, ¶ 143; Dec. 35–36 (“Petitioner fails to support this assertion [regarding adoption of rotameric states and minimizing steric interference] with sufficiently persuasive evidence.”).

On the other hand, Patent Owner’s expert (Dr. Romesberg) opined that the linear, “cylindrical shape makes it difficult for a 3’-O-protecting group having an azido group to avoid steric clashes in the polymerase active site.” Ex. 2024, ¶ 25. This too is somewhat conclusory. But Patent Owner went further, citing evidence that we found persuasive in the Decision, such as a study from Boyer showing that size and steric bulk of the azido moiety alone was known to fully occupy the enzyme active site. Dec. 34–35. Moreover, Patent Owner’s rebuttal argument and evidence demonstrated that known protecting moieties (such as cited in Metzker) were non-polar and included long and flexible chemical arms that served to keep bulkier groups away from the enzyme active site — and thus included materially different structures than an azidomethyl group. Dec. 35–36. Moreover, as explained in the Decision, Patent Owner cited evidence that a small size of a protecting group was not predictive of incorporation because even small molecular changes, such as an additional oxygen atom at the binding site can make the difference between incorporation and non-incorporation. *Id.* at 35 (discussing Metzker); *see also id.* at 35 n.24 (discussing Ex. 1526).

Upon considering the evidence of record, which included more than simply conflicting testimonial evidence, we determined that Petitioner had not met its burden on a key issue of “explain[ing] adequately why, at the time of the invention, the *larger* azidomethyl moiety . . . would have been expected to fit within the enzyme active site.” Dec. 35. On the record

before us, we were unpersuaded that a genuine dispute of material fact on the size, rigidity, and steric bulk of an azidomethyl group arose sufficient to justify institution of trial. But even if we agreed with Petitioner on this point — and the evidence demonstrated sufficiently for institution purposes that a skilled person would not have seen the rigidity, bulk, etc. of an azidomethyl moiety as a negative relative to its use as a protecting group for DNA sequencing methods — the record reflects several other discouraging factors with the use of an azidomethyl group (e.g., DNA-harmful conditions, low yields). Dec. 25–33, 36–38. And, as explained in the Decision, we denied institution based on our review of the entire Petition and its apparent deficiencies. We are, accordingly, unpersuaded that the Board abused its discretion or that the Decision should be changed to institute trial.

D) Loubinoux's Reported Yields

Finally, we turn to Petitioner's argument that the Board "erroneously concluded" that an ordinarily skilled person would have been discouraged from using an azidomethyl group in Dower's DNA sequencing methods based on reported yields in the art, particularly those reported in Loubinoux. Req. Reh'g 13–14. According to Petitioner, "the Board improperly credited Patent Owner's arguments and evidence over [Petitioner's] evidence" and, in particular, Petitioner's evidence related to the use of the solid phase with excess reactants to drive the reaction and improve yields. *Id.* at 14. Petitioner argues "because a POSITA would have known that solid phase immobilization would greatly increase yields as compared to the liquid phase techniques of Loubinoux, the Board must have misapprehended or overlooked this evidence," when it concluded Loubinoux's low yields would have been discouraging. *Id.* at 15.

We disagree. As an initial matter, that the Board, upon reviewing the evidence, arrived at a conclusion different from the one urged by Petitioner does not demonstrate that the Board overlooked matters or abused its discretion. On the issue of the low yields reported in the art when azidomethyl protecting groups were used, Petitioner simply failed to present sufficiently persuasive evidence that those low yields would not have been discouraging for use in high yield/efficiency DNA sequencing methods. Dec. 36–38.

Petitioner’s argument that the use of the solid phase would have been expected to improve yields relative to the liquid phase in Loubinoux failed to grapple adequately with the fact that the yields reported in Loubinoux were for deprotected phenols — a different type of, and more easily deprotected, molecule than simple aliphatic alcohols like the 3' hydroxyl of the molecules used in DNA sequencing methods. *See* Dec. 11, 14, 37. As explained in detail in the Decision discussing Greene & Wuts (which we found authoritative on the use of protecting groups), phenols are known to be better leaving groups and more easily deprotected than simple alcohols. *Id.* at 26–27. And, although Greene & Wuts devotes entire chapters to protecting groups for both phenols and aliphatic alcohols, only the chapter on phenols mentions the use of an azidomethyl group. *Id.*; *see also id.* at 32, 36–37. So, although the skilled person might have expected some improved yield by using the solid phase and excess reactants compared to Loubinoux as Petitioner asserts, the skilled person would conversely have expected lower efficiency/yield than Loubinoux inasmuch as Loubinoux was using more easily deprotected phenols. Dec. 37 (“Petitioner fails to make a sufficient evidentiary showing that efficiencies expected or observed with deblocking of phenols would have been expected with deblocking of an

azidomethyl protecting group from the relevant nucleotides here.”). The Petition failed to persuade us otherwise on this point. Moreover, Petitioner’s argument suffers from similar hindsight problems as noted above. That is, the Petition is premised on the ordinarily skilled artisan choosing a protecting group that carried expected inefficiencies (and other problems) and seeking to work around such downsides rather than using protecting groups (e.g., 3'-O-allyl) known to be suitable for DNA labeling and sequencing methods. Dec. 26, 36–37.

III. CONCLUSION

Under these circumstances, and for the reasons explained above, Petitioner has not met its burden in demonstrating that the Board abused its discretion in the Decision. We therefore deny Petitioner’s request for rehearing of our decision declining to institute *inter partes* review.

IV. ORDER

It is

ORDERED that Petitioner’s request for rehearing is *denied*.

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