

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TRIPLET THERAPEUTICS, INC.
Petitioner,

v.

BOARD OF SUPERVISORS OF LOUISIANA STATE UNIVERSITY
AND AGRICULTURAL AND MECHANICAL COLLEGE,
Patent Owner.

PGR2021-00059
Patent 10,669,542 B2

Before SHERIDAN K. SNEDDEN, SUSAN L. C. MITCHELL, and
DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION
Denying Institution of Post-Grant Review
35 U.S.C. § 324

I. INTRODUCTION

Triplet Therapeutics, Inc., (“Petitioner”) filed a Petition pursuant to 35 U.S.C. §§ 321–329 (2018) requesting a post-grant review of claims 1–15 (“the Challenged Claims”) of U.S. Patent No. 10,669,542 (Ex. 1001, “the ’542 patent”). Paper 2 (“Pet.”). The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College (“Patent Owner”) filed a Patent Owner’s Preliminary Response. Paper 9 (“Prelim. Resp.”). With authorization, Petitioner filed a Sur-reply to Patent Owner’s Preliminary Response (Paper 10, “Reply”) and Patent Owner filed a Patent Owner’s Response to Petitioner’s Sur-reply (Paper 11, “Sur-reply”).

We have the authority and discretion to determine whether to institute a post grant review. 35 U.S.C. § 324; 37 C.F.R. § 42.4(a) (2021). We may not institute a post-grant review unless “the information presented in the petition . . . , if such information is not rebutted, would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” 35 U.S.C. § 324(a). After considering the briefing and the evidence of record, we conclude that Petitioner has failed to establish a reasonable likelihood of prevailing in demonstrating that the challenged claims are unpatentable over the cited prior art in asserted grounds 2–5. With regard to ground 1, Petitioner’s written description ground, we determine that Petitioner’s arguments are substantially the same as those previously presented to and considered by the Office, and we exercise our discretion under 35 U.S.C. § 325(d) and decline to institute post-grant review of the ’542 patent on that ground alone.

II. BACKGROUND

A. Related Matters

Petitioner states it is not aware of any related matters. Pet. 93. Patent Owner identifies three U.S. patent applications and issued patents that relate to the '542 patent: U.S. Patent Application No. 61/989,898, International Patent Application No. PCT/US2015/029724 (published as WO2015/171918), and U.S. Patent Application No. 16/889,050. Paper 4, 1.

B. Real Parties-in-Interest

Petitioner identifies itself, Triplet Therapeutics, Inc., as the real party-in-interest. Pet. 92. Patent Owner identifies the real party-in-interest as The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College” as owner of the '542 patent. Patent Owner states that Takeda Pharmaceuticals U.S.A., Inc., has been granted “the exclusive right to option an exclusive license to the '542 patent.” Paper 4, 1.

C. The '542 Patent

The '542 patent, titled “Compositions and Uses for Treatment Thereof” is directed to “oligonucleotide compositions for the treatment of DNA repeat expansion diseases” and “oligonucleotides directed to subunits of the DNA mismatch repair system.” Ex. 1001, code (57).

The '542 patent explains:

DNA mismatch repair (MMR) is essential for maintaining genome integrity. However, when it comes to certain types of repetitive DNA, MMR actually contributes to genome instability. MMR has been implicated in repeat expansions of numerous disorders including Huntington’s disease (HD) and myotonic dystrophy (DM). Friedreich ataxia (FRDA), the most common inherited ataxia, is a progressive neurodegenerative disorder caused by GAA•TTC repeat expansion in the first intron of the frataxin (FXN) gene.

Id. at 1:46–55.

In the MMR pathway, MutS heterodimers are responsible for identifying and binding mismatched bases and/or insertion/deletion loops of varying size. MSH2 (MutSHomologue 2) is a component of both MutS complexes and has consequently been implicated in DNA repeat expansion. Upon mismatch recognition by a MutS complex, a MutL heterodimer is recruited to make an incision near the lesion recognition site. Under physiologic conditions, binding of MutL initiates recruitment of the necessary machinery that will excise the lesion and synthesize the DNA patch . . . MLH1 (MutL Homologue 1) is the core subunit of known MutL complexes. MLH1 combines with one of three partners called PMS1 (post-meiotic segregation increased 1), PMS2, and MLH3 to form MutLb, MutLa, and MutLg, respectively.

Id. at 115:61–116:19 (internal citations omitted).

“MLH3 expression is key to GAA•TTC expansion in human cells. Manipulation of this minor component of MMR in a repeat expansion model may be a possible therapeutic target to limit DNA repeat expansion in FRDA patients.” *Id.* at 112:65–113:2. “MLH3 is expressed in humans as two isoforms, MLH3iso1 and MLH3iso2, resulting from alternative splicing. MLH3iso1 includes exon 7, which contains a highly conserved portion of an endonuclease domain, while MLH3 isoform 2 lacks this 72 base exon.” *Id.* at 112:51–55. The ’542 patent hypothesizes that “[f]orcing exclusion of exon 7 may approximate a functional knockout of the endonuclease activity of MLH3, which is critical for repeat expansion. Skipping exon 7 leaves MLH3 isoform 2 intact, so will not impact the total cellular ratios of MLH1 and its binding partners PMS2, PMS 1 and MLH3.” *Id.* at 113:7–12.

To enable forced exclusion, splice switching oligonucleotides (SSOs) comprising “a nucleic acid sequence that hybridizes to a complementary target nucleic acid sequence of a gene or gene product encoding a

component of a mismatch repair (MMR) complex” were “designed to mask the acceptor and donor regions of MLH3 exon 7, inducing skipping of exon 7 and the consequent production of MLH3iso2.” *Id.* at 2:9–13; 113:4–7.

The claims of the '542 patent are directed toward therapeutics useful to slow the expansion rate in repeat expansion diseases by forcing exclusion of exon 7 of MLH3 of MutLgamma.

D. Challenged Claims

Petitioner challenges claims 1–15 of the '542 patent. Claim 1 is independent and claims 2–6, and 15 depend from claim 1. Claims 7 and 9–11 are independent and claims 8 and 12–14 depend from those claims. Ex. 1001, 133:14–134:63. Claims 1, 7, and 9 are illustrative of the claimed subject matter and are reproduced below.

1. An isolated nuclease-resistant oligonucleotide comprising a nucleic acid sequence that hybridizes to a complementary target nucleic acid sequence of a gene or gene product to modulate the expression of a component of a mismatch repair (MMR) complex, wherein the component of the MMR complex comprises exon 7 of MLH3 of MutLgamma, further wherein the isolated nuclease resistant oligonucleotide does not impact the total cellular ratios of MLH1 and its binding partners.

7. A pharmaceutical composition comprising a nuclease-resistant oligonucleotide 15 to 30 nucleotide bases in length targeted to a complementary nucleic acid sequence of exon 7 a gene encoding a MLH3 subunit of MutLgamma, wherein the oligonucleotide hybridizes with and modulates the expression of the human MutL subunit by at least 20%, wherein the oligonucleotide comprises at least one modification, and further wherein the nuclease resistant oligonucleotide does not impact the total cellular ratios of MLH1 and its binding partners.

9. An oligonucleotide complex for modulating the expression or activity of a gene or gene product encoding a

component of a mismatch repair (MMR) system, the complex comprising a first oligonucleotide and a second oligonucleotide, wherein the first oligonucleotide comprises a sequence complementary to an acceptor region of exon 7 of a gene encoding a MLH3 subunit, and wherein the first oligonucleotide comprises a nuclease-resistant modification, and wherein the second oligonucleotide comprises a sequence complementary to a donor region of exon 7 of a gene encoding a MLH3 subunit, and wherein the second oligonucleotide comprises a nuclease-resistant modification.

E. Asserted Grounds of Unpatentability and Declaration Evidence

Petitioner asserts that the Challenged Claims are unpatentable based on the following grounds:

Ground	Claims Challenged	35 U.S.C. §	References
1	1–15	112(a) (Written description)	
2	1–4, 6, 9–12	103	Fuselier, ¹ Morcos, ² Santucci-Darmanin ³
3	7, 8, 14, 15	103	Fuselier, Morcos, Santucci-Darmanin,

¹ Kayla Fuselier, *MLH3 isoform 2 does not make the cut in Friedreich ataxia GAA•TTC repeat somatic expansion*, 111 (Intl. Ataxia Res. Conf. Abstract, conference date March 25–28, 2015, Ex. 1014 ¶ 2. We note that the document is not dated, and the date of distribution is disputed by parties. Pet. 52–53; Prelim Resp. 60–62. (Ex. 1009).

² Paul A. Morcos, *Achieving targeted and quantifiable alteration of mRNA splicing with Morpholino oligos*, 358 BIOCHEM. & BIOPHYS. RES. COMMS., 521–527 (May 7, 2007) (Ex. 1010).

³ Sabine Santucci-Darmanin, et al., *The DNA mismatch-repair MLH3 protein interacts with MSH4 in meiotic cells, supporting a role for this MutL homolog in mammalian meiotic recombination*, 11(15): HUMAN MOL. GEN., 1697–1706 (May 15, 2002) (Ex. 1011).

Ground	Claims Challenged	35 U.S.C. §	References
			Wheeler ⁴
4	1–4, 6, 9–12	103	Pinto, ⁵ Santucci-Darmanin, Morcos
5	7, 8, 14, 15	103	Pinto, Santucci- Darmanin, Morcos, Wheeler

Pet. 24–25. Petitioner relies on the supporting declarations of Matthew Wood, D. Phil. (Ex. 1002) and Richard Fishel, Ph. D. (Ex. 1004).

III. ANALYSIS

As noted above, Petitioner asserts challenges for written description and obviousness against claims 1–15 of the '542 patent. Pet. 50–92. Patent Owner uses its Preliminary Response to make four arguments:

- (1) Petitioner's showing for all grounds is deficient because it relies on an improper claim construction (Prelim. Resp. 8–25; Sur-reply 3–5);
- (2) discretionary denial of this Petition is appropriate under 35 U.S.C. § 325(d) because Petitioner's arguments for invalidity are substantially similar to arguments addressed during prosecution and Petitioner has not demonstrated that the Office erred (Prelim. Resp. 26–42; Sur-reply 1–3);
- (3) Petitioner's arguments are conclusory and fail to establish unpatentability

⁴ Thurman M. Wheeler, et al, *Correction of ClC-1 splicing eliminates chloride channelopathy and myotonia in mouse models of myotonic dystrophy*, 117(12): J. CLIN. INVES., 3952–57 (December 2007). (Ex. 1013).

⁵ Ricardo Mouro Pinto, et al., *Mismatch Repair Genes Mlh1 and Mlh3 Modify CAG Instability in Huntington's Disease Mice: Genome-Wide and Candidate Approaches*, 9(10): PLOS GEN., 1–19 (October 2013) (Ex. 1012).

(Prelim. Resp. 43–60); and (4) Petitioner has not established that the Fuselier reference is prior art (Prelim. Resp. 60–78; Sur-reply 5–6).

Petitioner presents contrary arguments about why discretionary denial of the Petition is not appropriate (Reply 1–2), why the claim constructions are sound (*id.* at 2–5), and confirming Fuselier’s status as prior art (*id.* at 5–6).

After reviewing the record and the parties’ arguments, we find denial of post-grant review in this case is appropriate because, in the arguments presented in the Petition, Petitioner fails to establish that an ordinarily skilled artisan at the time of the invention would have had reason to combine the references as alleged in grounds 2–5 (§ 103) and because the Petition raises substantially the same arguments regarding ground 1 (§ 112) as those previously considered by the Office. Consequently, we confine our discussion to these issues and do not reach the claim construction issues raised by the parties, nor do we make findings or take any position about whether Fuselier is prior art to the ’542 patent.

A. Level of Ordinary Skill in the Art

Petitioner states that a person of skill in the art at the time of the invention in the field of antisense technology “would have had knowledge of the scientific literature and have skills relating to approaches for utilizing synthetic oligonucleotides to manipulate gene expression” and “have been well-experienced in laboratory techniques and strategies for designing and making SSOs, conducting *in vitro* and *in vivo* testing, and application of SSOs in research.” Pet. 18 (citing Ex. 1002 ¶¶ 30, 31). Petitioner adds that the artisan “would have had knowledge of laboratory techniques and strategies in creating nuclease-resistant SSOs, and using such SSOs to manipulate gene expression to force expression of selected isoforms of a

given protein.” *Id.* Petitioner states that the artisan “would have had an M.D. or a Ph.D. in physiological science, biochemistry, molecular biology, chemistry, or a related discipline, with at least five years of experience in SSOs design and manipulation” and may have “worked as part of a multidisciplinary team” to permit input by others on the team with specialized skills to assist in solving problems. *Id.*

Patent Owner does not contest the skill level provided by Petitioner for the purpose of deciding institution (Prelim. Resp. 4), and we adopt it as reasonably consistent with the level of skill represented by the ’542 patent and the art of record.

B. Eligibility for Post-Grant Review

The PGR provisions of the Leahy-Smith America Invents Act (“AIA”) apply only to patents subject to the first inventor to file provisions of the AIA. AIA § 6(f)(2)(A). Specifically, the first inventor to file provisions apply to any application for patent, and to any patent issuing thereon, that contains or contained at any time a claim to a claimed invention that has an effective filing date on or after March 16, 2013. AIA § 3(n)(1).

Furthermore, “[a] petition for a post-grant review may only be filed not later than the date that is 9 months after the date of the grant of the patent or of the issuance of a reissue patent (as the case may be).” 35 U.S.C. § 321(c); *see also* 37 C.F.R. § 42.202(a) (setting forth same).

Petitioner asserts that the ’542 patent is available for post-grant review. Pet. 92. Patent Owner does not challenge this assertion. *See generally* Prelim. Resp. The ’542 patent is a continuation-in-part of an application filed on May 7, 2015, and claims priority to a provisional application filed May 17, 2014. Ex. 1001 codes (63), (64). We agree that the ’542 application is eligible for post-grant review.

C. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.200(b) (2020). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

Petitioner proposes multiple terms for our interpretation. Pet. 19–24. Patent Owner contests Petitioner’s proposed interpretations for three terms: “complementary,” “isolated,” and “wherein the isolated nuclease resistant oligonucleotide does not impact the total cellular ratios of MLH1 and its binding partners.” Prelim. Resp. 8–22.

Upon review of the parties’ arguments and the evidence of record, we determine that no terms of the ’542 patent require express construction for purposes of this Decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”)).

D. Obviousness Challenges

1. Legal Principles

A claim is unpatentable for obviousness under 35 U.S.C. § 103 if the differences between the claimed subject matter and the prior art are “such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying

factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective indicia of nonobviousness, i.e., secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). Additionally, the obviousness inquiry typically requires an analysis of “whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue.” *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (requiring “articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”)); see *In re Warsaw Orthopedic, Inc.*, 832 F.3d 1327, 1333 (Fed. Cir. 2016) (citing *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006)).

2. *Ground 2: Obviousness of claims 1–4, 6, and 9–12 over the combination of Fuselier, Morcos, and Santucci-Darmanin*

Petitioner alleges that claims 1–4, 6, and 9–12 of the ’542 patent would have been obvious over the combination of Fuselier, Morcos, and Santucci-Darmanin.⁶

a) *Summary of Fuselier (Ex. 1009)*

Fuselier is an abstract in a “printed abstract booklet that contained information regarding delegates and speakers at the [International Ataxia Research] conference, as well as published abstracts relevant to the topics discussed by the speakers and to poster presentations given at the

⁶ Grounds 2 and 3 rely on Fuselier. The parties dispute whether Fuselier is prior art. (Prelim. Resp. 60–78; Prelim. Sur-Reply 5–6). Because we resolve this case on Petitioner’s alleged motivation to combine, we assume Fuselier is prior art for the purpose of this analysis only.

conference.” Ex. 1016 ¶ 6. “The printed abstract booklet was distributed to everyone who attended the conference.” *Id.*

Fuselier describes research regarding Friedreich ataxia (FRDA), a “progressive neurodegenerative disorder caused by GAA·TTC repeat expansion in the first intron of the frataxin (FXN) gene.” Ex. 1009, 111. Fuselier states that previous research showed that “the expansion rate is associated with transcription within the repeat and requires DNA mismatch repair enzymes, MutS β and the subsequent action of a MutL complex,” the “heterodimer of MutL Homologue one (MLH1) with MLH3, which is known as MutL γ .” *Id.* Fuselier discloses that one isoform of MLH3, MLHiso1, has a “pivotal role” in repeat expansion, while the second isoform, MLHiso2 “does not have an endonuclease domain and does not contribute to expansion in our human cell model.” Fuselier states that “FRDA patient derived cells . . . also express MLHiso1, and “[a]ll of the known MutL complexes require MLH1, while MLH3 is a constituent of only the MutL γ complex.” *Id.* Fuselier concludes, “when considering therapeutic targets to halt GAA·TTC expansion in FRDA, switching isoforms of MLH3 is much more attractive than targeting other DNA mismatch repair enzyme.” *Id.*

b) Summary of Morcos (Ex. 1010)

Morcos describes use of Morpholino oligonucleotides⁷ to alter the pattern of mRNA splicing in a targeted and quantifiable manner. Ex. 1010,

⁷ Morpholinos are synthetic antisense oligomers used to functionally inactivate specific genes. The genetic bases adenine (A), cytosine (C), guanine (G), and thymine (T) are each attached to morpholine rings, and these are linked in a specific order by nonionic phosphorodiamidate moieties. In spite of its altered backbone, a Morpholino still binds by Watson-Crick base-pairing to sequences of polynucleotides that have

521. Morcos discloses that Morpholinos, as steric-blocking antisense oligos, can be used to study the function of individual mRNA transcripts by “block[ing] RNA processing events, splicing events in particular, and thereby forc[ing] the expression of altered transcripts.” *Id.* Morcos discloses:

Morpholino oligos have been shown to be the most effective steric-block oligo type for splice modification, completely and specifically blocking splicing events. In splice-blocking, Morpholinos can be used as tools to characterize functions of alternatively spliced transcripts or generate “loss of function” (knockdowns) by means of exon deletion.

Id.

Morcos describes a method of targeting an exon for deletion: “targeting the splice-junctions on either side of an internal exon or the intronic snRNP binding site (branchpoint) just 5’ of the exon each yield deletion of the same targeted exon.” *Id.* at 525. Morcos states that the successful experimental results indicate a “simple model where targeting internal exon–intron or intron–exon boundaries results in exon deletion, and targeting the first exon–intron or last intron–exon boundary results in intron insertion.” *Id.* at 526.

With regard to hurdles in using the method, Morcos observes:

One should also be aware that even after the most careful targeting and oligo design, a splicing experiment can yield unexpected outcomes, such as activation of a cryptic splice site. These unexpected outcomes are difficult to guard against, but it

complementary base sequences. As they are not negatively charged, Morpholinos are less likely to interact nonselectively with charged proteins found within cells. Morpholinos are also not attacked by nucleases. Robert C. King et al, *A Dictionary of Genetics*, 8th ed., Oxford University Press, 2014.

is important to know that they can occur and to be able to identify them and find alternatives. For example, cryptic splice sites are often present and are not used unless a more-favorable splice site (snRNP binding site) is mutated or blocked. Highly conserved but different genes . . . may have similar splice sites, but a splice-blocking oligo may reveal differences that make one splicing event more favorable than another. Activation of a cryptic splice site illustrates how a lesser snRNP binding site that may not normally be utilized can end up dictating splicing.

And finally, there are ESEs, ISSs, and possibly other unidentified factors which may interfere with Morpholino targeting.

Id.

c) Summary of Santucci-Darmanin (Ex. 1011)

Santucci-Darmanin discloses that “[t]he role of role of hMutL homologs in reparation process is not clearly understood. However, it has been speculated that these proteins coordinate the interplay between the mismatch-recognition complex and other proteins necessary for MMR.” Ex. 1011, 1697. Santucci-Darmanin discloses that deficiencies in MMR “are associated with inherited and sporadic cancers” and that certain evidence points to a “loss of hMLH3 function being associated with colorectal cancer susceptibility.” *Id.* Santucci-Darmanin discloses that “Mlh3p plays an important role in meiotic recombination” in yeast, where “[f]unctional studies strongly suggest that Mlh1p and Mlh3p act as a heterodimeric complex to promote meiotic crossover.” *Id.* at 1698. In mice, “MSH4, MSH5 and MLH1, and also the MutL homolog PMS2, act during meiosis.” *Id.*

Santucci-Darmanin discloses that “studies concerning MLH3 function in mammals have focused on the possible involvement of this protein in the postreplicative MMR process” and investigated whether MLH3 participates

in mammalian meiotic recombination. *Id.* at 1698–99. Santucci-Darmanin “checked whether MLH3 interacts with the meiosis-specific MSH4 protein, which is known to be involved in different steps of meiotic recombination [by performing] co-immunoprecipitation assays using whole extracts from mouse meiotic cells” and observed co-immunoprecipitation of MLH3 and MSH4 proteins. *Id.* at 1659. GST pull-down assays using *in vitro* translated and radiolabeled human MLH3 protein and GST protein bound to sepharose beads confirmed that “radiolabeled hMLH3 protein was pulled down by GST–hMSH4 protein and, as expected, by GST–hMLH1,” suggesting that co-immunoprecipitation of murine MLH3 and MSH4 proteins may be due to a direct protein–protein association in meiotic cells.” *Id.* at 1700.

Santucci-Darmanin teaches that two “MLH3 mRNAs isoforms were found to be expressed in human testis, as in human somatic tissues” and that a separate study had found that “in contrast to the hMLH3 full-length protein, hMLH3 Δ 7 failed to interact with hMLH1, suggesting that the conserved C-terminal helix encoded by hMLH3 exon 7 is critical for the association with hMLH1.” *Id.* To confirm whether translated hMLH3 Δ 7 could interact with hMSH4, GST pull-down assays were performed, which confirmed that “hMLH3 Δ 7 was efficiently pulled down by GST-hMLH1 [and] precipitated by GST-hMSH4.” *Id.* Santucci-Darmanin concludes: “[t]hese findings suggest that the two hMLH2 isoforms potentially expressed in human testis could interact with hMSH4, and they further indicate that the C-terminal region encoded by nMLH3 exon 7 is not crucial for this interaction.” *Id.*

Santucci-Darmanin analyzed the expression of MLH3 gene in human testis using PCR amplification of the coding sequence. *Id.* at 1704. DNA sequencing revealed that the two hMLH3 mRNA isoforms are 1) a full-

length coding sequence, and 2) hMLH3 Δ 7 “resulting from alternative splicing, exhibits an inframe deletion of exon 7.” *Id.* at 1698.

d) Petitioner’s Obviousness Allegations

Petitioner, relying on the declarations of Dr. Fishel and Dr. Wood, contends that claims 1–4, 6, and 9–12 of the ’542 patent would have been obvious to the skilled artisan over the combination of Fuselier, Morcos, and Santucci-Darmanin. Patent Owner disagrees. Prelim. Resp. 43–78.

Petitioner alleges that the cited combination teaches every element of claims 1–4, 6, and 9–12. Pet. 54–72. Patent Owner responds that “Petitioner’s construction of core claim terms is demonstrably incorrect, and Petitioner fails to offer evidence of unpatentability for any of Grounds 1, 2, 3, 4, or 5 under the proper claim construction.” Prelim. Resp. 8. As stated above, we do not reach the issue of claim interpretation because, as we discuss below, we conclude Petitioner has not shown on this record that at least one claim is more likely than not to be found obvious for other reasons. Even assuming the claim limitations are taught as Petitioner alleges, Petitioner’s reasons that a skilled artisan would have had to combine the teachings of the references are stated in only cursory fashion and are insufficiently supported by evidence, particularly without Petitioner’s impermissible incorporation by reference. *See also* Prelim. Resp. 53–61. Without this evidence, Petitioner fails to demonstrate that it is more likely than not that at least one of the claims challenged in the petition is unpatentable.

Petitioner states its rationale for why the skilled artisan would have had reason to combine the teachings of Fuselier, Morcos, and Santucci-Darmanin as follows:

A POSA [person of ordinary skill in the related art] would have had a reason to combine Fuselier, Morcos, and Santucci-Darmanin because Fuselier expressly suggested “switching isoforms of MLH3,” which involves skipping exon 7 (per Santucci-Darmanin), to investigate potential therapeutic targets for FRDA, and Morcos would have provided a POSA with a “powerful” tool for doing so: morpholino SSOs. EX1009, 111; EX1010, 521, 525; EX1011, Abstract, 1700; EX1002, ¶212.

Pet. 58. Petitioner’s four citations are to the pages of Fuselier, Morcos, and Santucci-Darmanin containing the referenced teachings described above, and Dr. Wood’s testimony, which states nearly identical rationale:

A POSA would have had a reason to combine the teachings of Fuselier, Morcos, and Santucci-Darmanin to arrive at the claimed SSOs because Fuselier would have expressly suggested to the POSA to “switch[] isoforms of MLH3” from isoform 1 to isoform 2, which differ from each other by the presence or absence of exon 7 (as per Santucci-Darmanin); and Morcos would have provided the POSA with a “powerful” tool for doing so, which Morcos teaches are morpholinos. EX1009, 111; EX1010, 521, 525; EX1011, Abstract, 1700.

Ex. 1002 ¶ 212.

The Petition continues by reiterating the teachings of Fuselier concluding with the suggestion to switch isoforms of MLH3, and claims that the skilled artisan would have been motivated to pursue this course because MLH3 isoforms have “implications in human health.” Pet. 58. The Petition cites Dr. Wood’s testimony at ¶ 213, which is nearly identical to the above conclusory paragraph, and Dr. Fishel’s testimony at ¶¶ 49–53. Paragraphs ¶¶ 49–51 of Dr. Fishel’s declaration reiterate the statements above. Subsequent paragraphs 52 and 53 disclose:

52. Santucci-Darmanin teaches that “[t]wo MLH3 mRNA[] isoforms were found to be expressed in human testis, as in human somatic tissues.” EX1011, 1700. According to Santucci-Darmanin, one of the isoforms “contains the full length coding sequence, while the second isoform (hMLH3Δ7), resulting from alternative splicing exhibits an inframe deletion of exon 7.” EX1011, 1698. Therefore, Santucci-Darmanin discloses that hMLH3Δ7 lacks the region encoded by exon 7 of hMLH3.

53. As discussed above, it was known from Santucci-Darmanin that the two isoforms of MLH3 discussed in Fuselier are naturally expressed isoforms occurring in human tissues. EX1011, 1698, 1700. Because both Santucci-Darmanin and Fuselier report that there are two isoforms of MLH3, the POSA would have known that MLH3iso2 of Fuselier is the same as Santucci-Darmanin’s hMLH3Δ7. And because Santucci-Darmanin reports that hMLH3Δ7 lacks exon 7, the POSA would have known that the MLH3iso2 isoform described in Fuselier lacks exon 7.

Ex. 1004, ¶¶ 52, 53.

Among its responsive arguments, Patent Owner avers:

Petitioner’s arguments related to the alleged motivation to combine Petitioner’s cited references are conclusory and unexplained. For example, in its discussion of Claim 1 in Ground 2, Petitioner argues that a POSA would have had a reason to combine Fuselier, Morcos, and Santucci-Darmanin, stating, “As Dr. Wood explains, a POSA would have understood that Fuselier’s suggestion to ‘switch[] isoforms of MLH3’ could be accomplished by manipulating pre-mRNA splicing to delete exon 7.” Pet. at 59 (citing EX1002, ¶¶ 213–16). This conclusory statement masks that Petitioner provides no explanation for why a POSA would have had this understanding, why a POSA would have automatically elected to manipulate pre-mRNA splicing in view of other known options in 2014, or why “switching isoforms” would have necessarily meant skipping exon 7, leaving the Board and Patent Owner to turn to the Wood Declaration for further information. . . . But the Wood Declaration contains no

additional explanation. Instead, it simply repeats the same conclusory statement found in the Petition. EX1002, ¶ 214. These conclusory statements are insufficient to explain why a POSA would have been motivated to combine Fuselier, Morcos, and Santucci-Darmanin (and insufficient to show any expectation of success in that combination). Because this problem undermines Petitioner's obviousness argument for Claim 1 in Ground 2, it also undermines Petitioner's arguments for all other Claims in Grounds 2 and 3, which all rely on Petitioner's Claim 1 argument in Ground 2. *See* Pet. at 65–68, 71, 75, 79.

Prelim. Resp. 55–57 (footnotes omitted).

Petitioner does not respond to these critiques in its Reply to Patent Owner's Preliminary Response.

We agree with Patent Owner that Petitioner's allegations regarding the skilled artisan's reasons to combine are conclusory and insufficiently supported by evidence.

Petitioner cites Dr. Wood's testimony to explain why the skilled artisan would have understood that Fuselier's suggestion to “switch[] isoforms of MLH3” could be accomplished by manipulating pre-mRNA splicing to delete exon 7. Petitioner's discussion on pages 59–60 quotes phrases from Dr. Wood's referenced testimony, *see* Ex. 1002, ¶¶ 213–216, but the rationale appearing in the Petition merely comprises repetitive generalized statements akin to “Morcos is a powerful tool that can accomplish what Fuselier suggested.” *See* Pet. 59–60. Dr. Wood's underlying testimony lacks key explanation as to the understanding of the ordinary artisan at the time of the invention. What Petitioner has *not* provided, as Patent Owner argues, are the reasons 1) why Fuselier's suggestion to “switch[] isoforms” would have led the artisan to pursue deletion of exon 7; and 2) why the artisan would have selected Morcos'

technique of pre-mRNA splicing among the other options available at the time. *See* Prelim. Resp. 55–56.

Petitioner’s case and the supporting testimony regarding Santucci-Darmanin’s teachings assumes that the skilled artisan would have believed that the MLH3 encoded by Fuselier’s “human cell model” of unidentified cell origin is the same MLH3 identified in human testis tissue by Santucci-Darmanin. *See* Ex. 1009, 111 (stating work performed in “human cell model” and “model cells”), Ex. 1011, 1753 (identifying inframe deletion of exon 7 in cDNA amplified from human testis). Although the Petition broadly discusses that MMR is “a highly conserved DNA repair system that plays an important role in maintaining genome stability,” (*see* Pet. 10, relying on statements in Dr. Wood’s declaration (¶¶ 16, 17) referring to single statements in a handful of references stating this same contention), Petitioner provides no evidence or explanation to substantiate Dr. Wood’s statement in paragraph 53 (copied above in full) that the artisan would have “known that MLH3iso2 of Fuselier is the same as Santucci-Darmanin’s hMLH3 Δ 7,” which lacks exon 7, and therefore, known to pursue deletion of exon 7.

For instance, Petitioner provides no evidence to support that the artisan would expect the existence of two isoforms to mean there are only two isoforms. As noted by Patent Owner, the NCBI listing for the MLH3 mL homolog 3 in humans as of 2008 showed multiple alternatively spliced transcript variants with only two transcript variants having identified full-lengths. Prelim. Resp. 56 n.15 (citing Ex. 2014, 1). Petitioner fails to explain what steps the artisan would have performed to convince herself of the identity of the isoforms, which would have supported Petitioner’s claims that 1) the POSA would have known that exon 7 of the hMLH3 gene

encoded the endonuclease domain (Ex. 1004 ¶ 42), or that 2) the POSA would have known that MLH3iso2 of Fuselier is the same as Santucci-Darmanin's hMLH3Δ7 . . . [a]nd because Santucci-Darmanin reports that hMLH3Δ7 lacks exon 7, the POSA would have known that the MLH3iso2 isoform described in Fuselier likewise lacks exon 7 (*Id.*, ¶¶ 52, 53). We have reviewed the testimony of Petitioner's experts but note that this testimony relied upon by Petitioner fails to disclose the underlying facts or data on which the opinion is based. Such "[e]xpert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." 37 C.F.R. § 42.65(a); *see Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473 (Fed. Cir. 1997) ("An expert's conclusory testimony, unsupported by the documentary evidence, cannot supplant the requirement of anticipatory disclosure in the prior art reference itself."); *see also* Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019), 36 available at <https://www.uspto.gov/TrialPracticeGuideConsolidated> ("Expert testimony . . . cannot take the place of a disclosure in a prior art reference, when that disclosure is required as part of the unpatentability analysis.").

The same gap exists for Petitioner's rationale as to why the artisan would have selected Morcos' technique of pre-mRNA splicing among the other options available at the time. As Patent Owner argues, Morcos discloses that morpholinos can also be used to generate "knockdowns" to demonstrate loss of function by deleting the exon at issue rather than directly altering splicing events by blocking binding sites and splice junctions (Ex. 1010, 521), and Santucci-Darmanin describes techniques for cloning and other manipulation of cDNA inserts using restriction endonucleases that could have been used in lieu of mRNA manipulation requiring design of

specific oligonucleotides (Ex. 1011, 1704). While we acknowledge that Petitioner's experts opine that Morcos' techniques provide a "powerful" tool that may indeed have been perceived as useful at the time, the Petition provides no basis for its contention that the ordinarily skilled artisan would have selected this tool above others available at the time. The Petition's background describing use of SSOs was a "well-established" and "powerful" technique to study individual transcripts by manipulating alternative splicing of pre-mRNA identifies four references that used SSOs prior to 2014.

Pet. 8–9. To the extent each references' use of SSO is briefly explained, three of the four uses of SSOs appear to have been in a different manner than suggested in the obviousness case here, with only one, Mercatante, appearing to cause a switch between natural isoforms. *Id.* at 8. We do not find such evidence persuasive to the question of whether a skilled artisan would have pursued use of Morcos' techniques as alleged.

In sum, we agree with Patent Owner that Petitioner's arguments, as stated, lack "an apparent reason to combine the known elements in the fashion claimed by the patent at issue," at the very least without significant sifting through the record to attempt to interpret the leaps presented in the conclusory statements regarding the skilled artisan's knowledge at the time of the invention. *KSR*, 550 U.S. at 418. *See also Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) ("We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention").

3. *Ground 3: Obviousness of claims 7, 8, 14, and 15 of the '542 patent over Fuselier, Morcos, Santucci-Darmanin, and Wheeler*

Petitioner alleges claims 7, 8, 14, and 15 of the '542 patent would also have been obvious to a skilled artisan over Fuselier, Morcos, Santucci-Darmanin, and Wheeler. Pet. 73.

a) Summary of Wheeler (Ex. 1013)

Wheeler hypothesized that “myotonia in the [mouse model of myotonic dystrophy] results from abnormal inclusion of exon 7a in the muscle-specific chloride channel (ClC-1) mRNA, owing to sequestration of MBNL1, a factor required for repression of exon 7a splicing in muscle fibers.” Ex. 1013, 3952. Wheeler discloses the use of morpholino antisense oligonucleotide (AON) targeting “for suppressing the inclusion of exon 7a” in the muscle-specific chloride channel (ClC-1) in mice. *Id.* “The morpholino AONs were complementary to the 3' or 5' splice sites of exon 7a in the ClC-1 pre-mRNA.” *Id.* The radiolabeled morpholinos were injected into TA muscle, and reverse transcriptase-PCR was used to quantitatively amplify the products at designated times from samples. *Id.* at 3956. Assay by gel and fluoro-imaging and statistical analysis was used to query if suppression was successful. *Id.* at 3956–57.

Wheeler concludes:

We postulated that exon 7a may show heightened susceptibility to AONs because splicing signals in alternative exons tend to be intrinsically weak and this exon is normally skipped in a fraction of ClC-1 transcripts (17). However, ClC-1 mRNAs that include exon 7a contain premature termination codons and undergo rapid degradation (17). Therefore, these splice products are underrepresented at steady state, and we cannot determine the exact efficiency of AON-induced exon skipping. Despite this limitation, the decrease of exon 7a+

isoforms to WT levels and the normalized activity of ClC-1 channels in treated muscle fibers suggest that this intervention is highly effective and surprisingly prolonged.

Id. at 3956.

b) Petitioner's Obviousness Allegations

Petitioner relies on the same contentions as it does for Ground 2 with regard to the skilled artisan's reasons to combine Fuselier, Morcos, and Santucci-Darmanin, and adds that the artisan "further would have formulated the SSOs for administering to mice, as taught by Wheeler." Pet. 74–76. Because Petitioner's case for Ground 3 provides no additional rationale that cures the defect in Ground 3, particularly with regard for why exon 7 should be targeted, Ground 3 fails for the same reasons.

4. Grounds 4 and 5: Obviousness of claims 1–4, 6, and 9–12 over Pinto, Morcos, and Santucci-Darmanin and obviousness of claims 7, 8, 14, and 15 over Pinto, Morcos, Santucci-Darmanin, and Wheeler

Petitioner contends that claims 1–4, 6, and 9–12 of the '542 patent would have been obvious to the skilled artisan over the combination of Pinto, Morcos, and Santucci-Darmanin, and that claims 7, 8, 14, and 15 would have been obvious over Pinto, Morcos, Santucci-Darmanin, and Wheeler. Pet. 80–92. Patent Owner raises no arguments specific to Pinto, but its arguments discussed earlier with regard to improper claim construction, conclusory arguments, and improper incorporation of evidence (*see generally* Prelim. Resp. 43–78) extend to Grounds 4 and 5.

a) Summary of Pinto (Ex. 1012)

Pinto discloses that MLH1 and MLH3, which are involved in MutLgamma are "absolutely required for somatic HTT CAG instability in B6.*HdhQ111* mice. Ex. 1012, 4, 7. Pinto discloses that "both *Mlh1* and

Mlh3 are critical novel modifiers of *HTT* CAG instability,” and the “identification of *Mlh1* and *Mlh3* as modifiers of CAG instability in *Hdh*^{Q111} mice suggests that variation in the human *MLH1* and *MLH3* genes may contribute to differences in somatic *HTT* CAG expansion that occurs between [Huntington’s Disease] HD patients. *Id.* at 14. Pinto discloses:

given their minor roles in human tumorigenesis, both MLH3 and MSH3 currently stand as the most promising targets of the MMR proteins that have been identified as modifiers of the *HTT* CAG pathogenic process to date. Further delineation of the factors involved in somatic instability and the pathway(s) involved are likely to increase the ability to specifically intervene in the process of CAG/CTG expansion in HD as well as other trinucleotide repeat disorders.

Id.

b) Petitioner’s Obviousness Allegations

Petitioner alleges that the cited combination teaches every element of claims 1–15.⁸ Pet. 81, 86, 89, 90. Once again, we do not reach the issue of claim interpretation because, as we discuss below, we conclude Petitioner has not shown on this record that at least one claim is more likely than not to be found obvious. Even assuming the claim limitations are taught as Petitioner alleges, Petitioner’s reasons that a skilled artisan would have had to combine the teachings of the references are stated in only cursory fashion and are insufficiently supported by evidence, particularly without

⁸ As above, in its statement of Grounds 4 and 5, Petitioner improperly incorporates information into the Petition without explanation. *See, e.g.*, Pet. at 81, incorporating an entire claim chart analysis: “Pinto, Santucci-Darmanin, and Morcos teach each and every limitation of claims 1-4. EX1002, §XI.A.1. Appendix IV. The teachings of Santucci-Darmanin and Morcos are discussed in Ground 2 and are not repeated here” (referring back to prior references to the same Appendix, containing information not explained in Ground 2).

Petitioner's impermissible incorporation by reference. *See also* Prelim. Resp. 53–61, the reasoning of which at least in part extends to Grounds 4 and 5. Without this evidence, Petitioner fails to demonstrate that it is more likely than not that at least one of the claims challenged in the petition is unpatentable.

Petitioner states its rationale for why the skilled artisan would have had reason to combine the teachings of Pinto, Morcos, and Santucci-Darmanin as follows:

As Drs. Wood and Fishel confirm, a POSA would have had a reason to investigate the role of MLH3's endonuclease domain in trinucleotide repeat instability, which a POSA could have done by investigating “functional specificity” of the two known MLH3 isoforms. EX1012, 13; EX1002, ¶301; EX1004, ¶48. A POSA, thus, would have had a reason to combine Pinto, Santucci-Darmanin, and Morcos to skip exon 7 (i.e., SEQ ID No. 2) of human MLH3 to manipulate expression of the two isoforms, as Dr. Wood confirms. EX1002, ¶¶301-303.

In 2013, Pinto showed that MLH3 “plays a major role” in expansion of CAG repeats within the huntingtin protein gene (HTT), a process implicated in the fatal neurodegenerative Huntington's disease. EX1012, 1, 6-7, Figure 6; EX1004, ¶37; EX1002, ¶302. Using a trinucleotide disease mouse model, Pinto showed, “for the first time,” that “both Mlh1 and Mlh3 genes enhance HTT CAG expansion.” EX1012, 13; EX1004, ¶37; EX1002, ¶302. Given the human health implications, Pinto suggested conducting “[f]urther delineation of factors involved in somatic instability,” with MLH3 being one of “the most promising targets.” EX1012, 14; EX1004, ¶37, 48; EX1002, ¶302. What's more, Pinto provided a concrete direction for future research: determining “whether MLH3's putative endonuclease domain is required for CAG expansion in vivo.” EX1012, 13; EX1004, ¶¶37, 48; EX1002, ¶302. Thus, before 2014, Pinto pointed a spotlight on MLH3—with a special interest on its putative endonuclease domain—as the

prime candidate for future studies related to trinucleotide repeats instability. EX1004, ¶¶37, 48; EX1002, ¶302.

Pet. 81–82 (emphasis omitted).

We find Petitioner’s reasoning with regard to why the artisan would have had reason to combine the teachings of Pinto with Santucci-Darmanin to pursue deletion of exon 7 through pre-mRNA splicing unpersuasive. Here, Petitioner alleges that Pinto suggests “determining whether MLH3’s putative endonuclease domain is required for CAG expansion *in vivo*.” *Id.* But the offered explanation as to what the artisan should have known is, again, too far a leap without additional supporting evidence. Dr. Wood testifies:

Dr. Fishel explains, and I confirm, that the hMLH3 Δ 7 isoform of Santucci-Darmanin lacks a putative endonuclease domain. EX1043, 34; EX1011, Abstract, 1698, 1700. The putative endonuclease domain missing from the hMLH3 Δ 7 isoform (also known as MLH3 isoform 2) is the same endonuclease domain that Pinto expressly encourages a POSA to investigate. A POSA would have recognized that one way to address Pinto’s suggestion was to apply Morcos’s SSO technology to effect alternative splicing of MLH3’s pre-mRNA.

Ex. 1002, ¶ 303. The deficiencies highlighted above with regard to the skilled artisan’s reasons for identifying exon 7 of Santucci-Darmanin as the focus for deletion and the stated reasons to use Marcos’ technology in Grounds 2 and 3 are similarly unsupported here (*see* III.B(1)(d)). Thus, we conclude that Petitioner has not established that the skilled artisan would have had reason to combine the references as alleged; rather Petitioner’s arguments lack sufficient reasoning to combine the known elements in the fashion claimed. *KSR*, 550 U.S. at 418.

As with Ground 3, Petitioner’s case for Ground 5 including the Wheeler reference provides no additional rationale that cures the defect in Ground 4,

particularly with regard for why exon 7 should be targeted. Accordingly, Ground 5 fails for the same reasons.

E. Ground 1: Written Description

Petitioner contends that claims 1–15 of the ’542 patent lack written description support because the claim scope is far broader than taught by the examples in the specification. Pet. 25–50; Reply 1–2. Patent Owner disagrees, and argues that post-grant review should be denied under 35 U.S.C. § 325(d) because “the Examiner previously advanced substantially the same arguments as those raised by Petitioner in Ground 1 during prosecution of the ’542 patent” and Petitioner has not demonstrated that the Office erred in its examination of the patent. Prelim. Resp. 23–43; Sur-Reply 1–3. Under § 325(d), the Director⁹ has discretion to deny review when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). In that respect, § 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the Office. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

1. Legal Principles

In evaluating matters under § 325(d), the Board uses the following two-part framework: (1) determine whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office;

⁹ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a); *Advanced Bionics*, Paper 6 at 7 n.7.

and (2) if either condition of the first part of the framework is satisfied, determine whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, Paper 6 at 8. In applying the two-part framework, we consider several nonexclusive factors, including:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;
- (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

Advanced Bionics, Paper 6 at 9–11; *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) (“*Becton, Dickinson*”).

Factors (a), (b), and (d) of the *Becton, Dickinson* factors relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 10. Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we

then consider whether petitioner has demonstrated a material error by the Office. *Id.*

2. *Relevant Prosecution History of the '542 Patent*

During prosecution of the application leading to the '542 patent, the Examiner issued three rejections under 35 U.S.C. § 112, first paragraph,¹⁰ for lack of enablement. Each rejection was premised on the Examiner's interpretation that the claims were overbroad with respect to the guidance provided in the specification.

In the first rejection, the Examiner claimed that the specification was not enabling because the intended oligonucleotide target was to a very large region of the MutS or MutL subunit. The Examiner stated:

The claims are so broad to embrace and encompass any subunit of MutS or MutL, where the art is clear that certain exon deletions of these subunits cause cancer. . . . There is no guidance or working examples for targeting acceptor and donor regions of any other subunit or exon.

The amount of direction or guidance is limited to a specific MMR subunit and exon. In view of the above, undue experimentation is necessary to practice the invention over the full scope claimed.

Ex. 1006, 623–624.

Applicant responded by amending the claims to limit the oligonucleotide sequence to only those complementary to the acceptor and donor regions from “an exon of a gene encoding a MutS or MutL subunit” to “exon 7 of a gene encoding a MLH3 subunit” (MLH3 is a portion of MutL).

¹⁰ Although the Examiner issued rejections under 35 U.S.C. § 112, first paragraph, for purposes of this decision, we apply post-AIA 35 U.S.C. § 112(a).

Id. at 1157. The Examiner withdrew this rejection following the amendment. *Id.* at 1178–79.

In the second rejection, again under 35 U.S.C. § 112, first paragraph, for lack of enablement, the Examiner stated that

the specification, while being enabling for an isolated nuclease-resistant splice switching oligonucleotide (SSO) comprising a nucleic acid sequence that hybridizes to a complementary target nucleic acid sequence of a gene to modulate the expression of a component of a mismatch repair (MMR) complex, wherein the component of the MMR complex comprises exon 7 of MLH3 of Mutly, further wherein the isolated nuclease resistant SSO does not impact the total cellular ratios of MLH1 and its binding partners, does not reasonably provide enablement for an isolated nuclease resistant oligonucleotide comprising a nucleic acid sequence that hybridizes to a complementary target nucleic acid sequence of a gene or gene product to modulate the expression of a component of a mismatch repair (MMR) complex, wherein the component of the MMR complex comprises Mutl, further wherein the isolated nuclease resistant oligonucleotide does not impact the total cellular ratios of MLH1 and its binding partners.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

Id. at 1180–81.

Applicant responded by amending then-pending claim 1 to limit the target of the modulated gene expression, the MMR complex, from “MutL” to “exon 7 of MLH3 of MutLgamma.” *Id.* at 1194. The Examiner withdrew this rejection following the amendment, which also addressed the third simultaneously-issued rejection, discussed below. *Id.* at 1204.

In the third rejection, again under 35 U.S.C. § 112, first paragraph, for lack of enablement, the Examiner stated that

the specification, while being enabling for a pharmaceutical composition comprising a nuclease-resistant splice switching oligonucleotide (SSO) 15 to 30 nucleotide bases in length targeted to a complementary nucleic acid sequence of exon 7 of a gene encoding a MLH3 subunit of MutL, wherein the SSO hybridizes with and modulates the expression of the human MutL γ by at least 20%, and wherein the SSO comprises at least one modification, and further wherein the nuclease resistant SSO does not impact the total cellular ratios of MLH1 and its binding partners, does not reasonably provide enablement for a pharmaceutical composition comprising a nuclease-resistant oligonucleotide 15 to 30 nucleotide bases in length targeted to a complementary nucleic acid sequence of a gene or gene product encoding a MutL subunit, wherein the oligonucleotide hybridizes with and modulates the expression of the human MutL subunit by at least 20%, and wherein the oligonucleotide comprises at least one modification, and further wherein the nuclease resistant oligonucleotide does not impact the total cellular ratios of MLH1 and its binding partners. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

Id. at 1183–84.

Applicant's amendment to limit the target of the modulated gene expression, the MMR complex, from "MutL" to "exon 7 of MLH3 of MutL γ ," was likewise made to other pending claims to address this rejection. *Id.* at 1200. In response to Applicant's amendment, a Notice of Allowability of the pending claims was issued. *Id.* at 1204.

3. *Same or Substantially the Same Arguments Previously Presented to the Office*

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office.

Advanced Bionics, Paper 6 at 8.

Petitioner contends that claims 1–15 of the '542 patent lack written description support

[b]ecause the claims (i) allow for nearly any combination of various nuclease-resistant modifications (sugars and/or a backbone) across a wide range of oligonucleotide lengths (limited to “15 to 30 nucleotide basis in length” only in claims 7, 8, and 14; unlimited otherwise); and (ii) are further broad with respect to oligonucleotide sequences and the environment in which they perform the claimed function, a POSA would understand that the structural limitations of claims 1–15 are met by an almost incalculable number of oligonucleotides.

Pet. 26.

Petitioner’s declarant, Dr. Wood, opines:

the claims are directed to vast genera of nuclease-resistant oligonucleotides. However, the specification shows possession of, at most, four SSOs, all of the same type, that modulate the expression of the MLH3 gene. It is my opinion that this handful of working oligonucleotides does not convey to a POSA that the inventors possessed the tremendously large genera of oligonucleotides claimed, at the time they filed their patent applications.

Ex. 1002 ¶ 16. Dr. Wood’s testimony regards the scope of the claimed oligonucleotides using the claim constructions Petitioner proposes. *Id.* ¶¶ 99–143.

Patent Owner argues that we should exercise our authority to reject Ground 1 under § 325(d) because the Examiner “previously advanced

substantially the same arguments” as argued in Ground 1 during prosecution of the ’542 patent.¹¹ Prelim. Resp. 26. Patent Owner argues that

[t]he Petitioner contends that “Claims 1-15 encompasses [sic] myriad possible oligonucleotides—an enormous genus—because the claims are open to various combinations of nuclease-resistant modifications.” *Id.* at 27. Petitioner’s argument is the same issue raised and overcome during prosecution, i.e., that the claims allegedly broadly encompass “any nuclease-resistant oligonucleotide.”

Id. at 29 (emphasis omitted). Patent Owner argues that, during prosecution, the Examiner “thoroughly considered whether the specification provided sufficient support for the proposed claims, issuing three separate rejections of the pending claims on grounds that, as then drafted, the claims were not enabled pursuant to § 112.” *Id.* at 30. Patent Owner argues that each rejection was addressed by the Examiner during careful analysis, and was overcome when Patent Owner amended the claims “to narrowly encompass only that which the Examiner expressly stated was supported by the specification.” *Id.* at 30.

Patent Owner argues that Ground 1 “now asserts that the issued claims are overly broad for the same reasons previously raised and overcome before the Examiner during prosecution.” *Id.* at 35. Patent Owner argues that our case law under § 325(d) commends we exercise our discretion to deny institution because Petitioner has not demonstrated “that the Office

¹¹ Patent Owner also argues that Petitioner’s arguments for Ground 1 are deficient because they rely on an improper claim construction. Prelim. Resp. 1–2; 8–25; Sur-reply 3–5. Patent Owner argues that, under the correct interpretation, Petitioner’s calculations are incorrect and Petitioner offers no argument or evidence supporting lack of written description under the correct claim interpretation. *Id.* We do not reach this argument as we decide this matter under § 325(d).

erred in previously concluding that the Patent Owner had overcome substantially the same arguments as Petitioner now presents in the Petition” or “substantively addressed any particular differences between the enablement and reframed written description arguments.” *Id.* at 38–39, 41.

Patent Owner first cites *Novartis Pharmaceuticals Corp. v. Plexxikon, Inc.*, IPR2018-01287, Paper 17, at 8–12 (PTAB Jan. 16, 2019). Prelim Resp. 37. In *Novartis*, the Petitioner’s anticipation challenge required the Board to conclude that the patent was not entitled to its priority claim because the challenged claims did not have sufficient written description to support the priority claim. *Novartis* at 10. The Board declined to institute under § 325(d), concluding that Petitioner’s arguments on written description were substantially similar to the Examiner’s rejection under 35 U.S.C. § 112, first paragraph, which were overcome by narrowing the claims to a more focused genus of compounds. *Id.* at 14–15.

Patent Owner also cites *Starbucks Corp. v. Ameranth, Inc.*, CBM2017-00053, Paper 7 at 20–21 (PTAB Dec. 4, 2017). The Petitioner in *Starbucks* raised a lack of enablement challenge. *Id.* at 14. The Board concluded that the arguments on enablement that Petitioner raised were substantially similar to the lack of written description arguments the Examiner had raised during prosecution. *Id.* at 15–17. The Board concluded that discretionary denial under 35 U.S.C. § 324(a) was appropriate due to the similarity of the arguments as weighed with the other *Becton, Dickinson* factors. *Id.* at 21–22.

Petitioner responds that Patent Owner’s argument is legal error because written description is not the same legal inquiry as enablement, and the cited prosecution history “does not demonstrate that the Examiner ever

considered written description for the full scope of the '542 patent claims in the specification or in the priority documents.” Reply 1.

We agree with Patent Owner that Petitioner’s arguments regarding whether the '542 patent provides § 112 written description support for the challenged claims are substantially the same as those considered by the Examiner during the prosecution of the '542 patent. As set forth above, the Examiner repeatedly rejected the pending claims because (1) the claims were overly broad in light of the guidance provided in the specification that was limited to the working examples specific to exon 7 of a gene encoding a MLH3 subunit (Ex. 1006, 623–24); (2) the claims did not enable the oligonucleotides to “hybridize[] to a complementary target nucleic acid sequence of a gene or gene product to modulate the expression of a component of a mismatch repair (MMR) complex” based on the disclosure of the specification, which was limited to the working examples (*id.*); and (3) the claims did not enable a pharmaceutical composition of the recited nucleotide base length range for the entire scope of the claims based on the disclosure of the specification, which was limited to the working examples (*id.* at 1183–84). The rejections were based on a broad reading of the claims as interpreted by the ordinarily skilled artisan, and required analysis of whether there is sufficient support in the specification for the entire scope of the claims. Applicant overcame these issues by narrowing the claims until the Examiner agreed that the support present was sufficient.

Here, Petitioner argues that (1) the claims “allow for nearly any combination of various nuclease-resistant modifications . . . across a wide range of oligonucleotide lengths” (Pet. 26); (2) “a POSA would understand that the structural limitations of claims 1–15 are met by an almost incalculable number of oligonucleotides” (*id.*); and (3) “the specification

shows possession of, at most, four SSOs, all of the same type, that modulate the expression of the MLH3 gene” (Ex. 1002 ¶ 16). As with the Examiner’s rejections above, Petitioner’s arguments are based on a broad reading of the claims as interpreted by the ordinarily skilled artisan, and would require us to analyze whether there is sufficient support in the specification for the entire scope of the challenged claims. Hence, we agree that the holdings in *Novartis* and *Starbucks* as cited by Petitioner are analogous to the issues in this case, because those cases concluded that the petitioner’s arguments on whether the teachings in a specification were sufficient to support the scope of the challenged claims was substantially similar to the then-presented challenge requiring the same inquiry. *Novartis* at 10; *Starbucks* at 15–17.

Having found that the Petition raises substantially the same arguments regarding § 112 as those previously considered by the Office, we move on to the second part of the *Advanced Bionics* framework.

4. *Whether the Office Erred in a Manner Material to Patentability*

Because we find that substantially the same arguments previously were presented to the Office, we turn to whether Petitioner demonstrates that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, Paper 6 at 8, 10; *see Becton, Dickinson*, Paper 8 at 24.

Patent Owner argues that “Petitioner makes no effort to demonstrate that the Office erred in previously concluding that the Patent Owner had overcome substantially the same arguments as Petitioner now presents in the Petition,” conducts no analysis under § 325(d), and provides no “expla[nation] why—in Petitioner’s view—Patent Owner’s narrowing claim amendments (which were enough to satisfy the Examiner) should now be

deemed insufficient.” Prelim. Resp. 39. According to Patent Owner, Petitioner’s failure to substantively address any differences between the enablement and “reframed written descriptions arguments” supports our exercise of discretion, which would avoid reconsideration of substantially the same arguments already addressed by the Office. *Id.* at 39–43.

Petitioner argues that it is not required to identify Examiner error because its allegations are a separate legal inquiry. Reply 1. Petitioner argues that there is no evidence the Examiner ever considered written description support. *Id.* Petitioner concludes that because it “does not revisit **any** of the Examiner’s arguments[,] it is therefore is not required to demonstrate ‘that the Office erred’” and that factor (e) of *Becton, Dickinson* does not favor denial. *Id.* at 1–2.

Patent Owner notes that Petitioner does not refute that the arguments are substantially similar, and that the *Novartis* and *Starbucks* decisions exercising discretionary denial of review have clarified that although enablement and written description are distinct legal theories, the question at issue in a § 325(d) or § 324(a) analysis focuses on the identity of the arguments raised, which in this case are substantially similar. Sur-reply 1–2. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“Advanced Bionics”).

We conclude that Petitioner has not made a sufficient showing that the Examiner erred in the examination of the ’542 patent.

As discussed above, Petitioner relies on substantially the same arguments with respect to whether the specification provides written description support for the challenged claims as those considered by the Examiner during the prosecution of the ’542 patent. Petitioner does not

present any argument distinguishing the *Novartis* and *Starbucks* cases finding that issues similar to those addressed here were substantially similar for the purposes of the exercise of discretion to deny review or provide a compelling reason why we should readjudicate substantially the same arguments considered by the Examiner during prosecution. The Declaration of Dr. Wood (Ex. 1002), which Petitioner submitted to support the challenges presented in the Petition, does not provide additional evidence or facts that warrant reconsideration of the disclosures in the specification that are substantially the same as the disclosures already considered by the Office.

We recognize that Petitioner has a direct interest in pursuing the instant Petition, but we also recognize the burden and expense to Patent Owner in having to defend the '542 patent based on substantially the same arguments already considered by the Office. We find that the disclosures in the specification were substantively considered by the Examiner with respect to whether the challenged claims met the requirements of § 112, and that we have been shown no reason sufficient to reevaluate those disclosures with respect to any of the challenged claims. Consequently, we exercise our discretion and decline to institute review of claims 1–15 under 35 U.S.C. § 112 as lacking written description support.

IV. CONCLUSION

Based on the arguments in the Petition, Preliminary Response, Reply, Sur-reply, and the evidence of record, we conclude that Petitioner has failed to establish a reasonable likelihood of prevailing in demonstrating that the challenged claims are unpatentable over the cited prior art in asserted grounds 2–5. With regard to ground 1, Petitioner's written description

ground, we determine that Petitioner's arguments are substantially the same as those previously presented to and considered by the Office, and we exercise our discretion under 35 U.S.C. § 325(d) and decline to institute post-grant review of the '542 patent on that ground alone.

V. ORDER

Accordingly, it is

ORDERED that the Petition is *denied* as to all challenged claims, and no trial is instituted.

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