

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOF CORPORATION,
Petitioner,

v.

NEKTAR THERAPEUTICS,
Patent Owner.

IPR2019-01397
Patent 9,187,569 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and
JON B. TORNQUIST, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining Some Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

NOF Corporation (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting an *inter partes* review of claims 1–12 of U.S. Patent

No. 9,187,569 B2 (Ex. 1005, “the ’569 patent”). On February 10, 2020, we instituted trial to review the challenged claims. Paper 30¹ (“Dec.” or “Decision to Institute”). Thereafter, Nektar Therapeutics (“Patent Owner”) filed a Response to the Petition (Paper 51, “PO Resp.”), Petitioner filed a Reply (Paper 55), and Patent Owner filed a Sur-Reply (Paper 59). An oral hearing for this proceeding was held on February 8, 2021, and a transcript of that hearing is of record. *See* Paper 69 (“Tr.”).

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.² For the reasons provided below, we conclude Petitioner has established by a preponderance of the evidence that claims 1–3, 5, 7, 8, and 10–12 of the ’569 patent are unpatentable. Petitioner, however, has not shown that claims 4, 6, and 9 are unpatentable.

A. Related Matters

According to Petitioner, the ’569 patent is involved in *Nektar Therapeutics et al. v. Bayer Healthcare, LLC*, 1-18-cv-01355 (D. Del.). Pet. 3. According to Patent Owner, the ’569 patent is asserted in *Baxalta*

¹ The original, confidential version of the Decision to Institute was issued as Paper 24. We later issued Paper 30, the redacted, public version of the Decision to Institute.

² Although generally, a final written decision must be issued within one year of the institution date, the statute authorizes that the Director may, for good cause, extend that deadline by up to six months. 35 U.S.C. § 316(a)(11). Due to difficulties related to COVID-19, we authorized, and Petitioner filed, a motion requesting a good cause extension of the deadline for issuing a final written decision in this proceeding. Papers 40, 41. The Chief Administrative Patent Judge granted a good cause extension, and the time to administer the present proceeding was extended by up to six months, from February 10, 2021, up to August 10, 2021. Papers 64, 65.

Incorporated v. Bayer Healthcare LLC, No. 17-1316 (D. Del)
(consolidated). Paper 5, 1.

Petitioner also filed five additional petitions for *inter partes* review, challenging other patents by Patent Owner. Paper 5, 1–2. We instituted review in IPR2019-01394 and -01398 and denied the petitions in IPR2019-01392, -01395 and -01396. We have issued a Final Written Decision in each of IPR2019-01394 and -01398.

B. Background of Technology and the '569 Patent

The '569 patent discloses “branched, reactive water soluble polymers useful for conjugating to biologically active molecules.” Ex. 1005, 1:24–26.

Before the '569 patent, it was known that “[c]ovalent attachment of the hydrophilic polymer poly(ethylene glycol), abbreviated PEG, is a highly advantageous method of increasing water solubility and bioavailability and extending the circulation time of many biologically active molecules, particularly hydrophobic molecules.” *Id.* at 1:31–35. It was also known that the total molecular weight of the attached polymers should be sufficiently high to provide the advantageous characteristics typically associated with PEG polymer attachment without “adversely impacting the bioactivity of the parent molecule.” *Id.* at 1:38–44.

The '569 patent states that although branched polymers attached to a central core and having a single reactive group for conjugation to a biologically active molecule were known, the methods of forming those prior-art branched PEG molecules were difficult. *Id.* at 1:64–2:11. Thus, according to the '569 patent, “[t]here remain[ed] a need in the art for new branched polymer reagents that provide the benefits associated with branched polymers (i.e., high overall molecular weight in a single non-linear

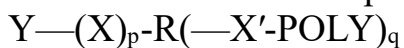
polymer molecule), but are easier to synthesize or provide more flexibility in their design than prior art reagents.” *Id.* at 2:12–16.

The ’569 patent discloses “branched reactive polymers comprising at least two polymer arms, such as PEG arms, attached to a central core through heteroatom linkages such as ether linkages.” *Id.* at 6:43–46. According to the ’569 patent, “[s]ince the branched polymers of the invention combine at least two polymer arms in a single molecule, a polymer with sufficient molecular weight to impart beneficial properties to a biologically active molecule, such as increased water solubility, can be formed using shorter, easier to prepare polymer chains.” *Id.* at 6:49–54.

C. Illustrative Claim

Claim 1 is illustrative of the challenged claims and is reproduced below:

1. A branched reactive polymer having the structure:



wherein:

R is an aliphatic hydrocarbon having a length of at least three carbon atoms;

each POLY is a poly(ethylene glycol) that terminates with a hydroxyl or methoxy group;

X' is a heteroatom linkage selected from –NH–, –O– or –S–;

X is a linker of 1 to ten atoms;

p is 0 or 1;

q is 2 to about 10; and

Y is a maleimide,

and further wherein the branched reactive polymer has a molecular weight of about 500 Da to about 100,000 Da.

D. Instituted Grounds of Unpatentability

We instituted trial to determine whether the challenged claims are unpatentable based on the following grounds:

Claim(s) Challenged	35 U.S.C. §³	Reference(s)
1–3, 5, 7, 8, 10, 11	103(a)	Harris ⁴
1–8, 10, 11	103(a)	Harris, Bentley ^{5,6}
9	103(a)	Harris, Choi ⁷
12	103(a)	Harris, Dalborg ⁸
9	103(a)	Bentley, Harris, Choi
12	103(a)	Bentley, Harris, Dalborg
1–7, 10, 11	103(a)	JP-674, ⁹ Harris
9	103(a)	JP-674, Harris, Choi
12	103(a)	JP-674, Harris, Dalborg

³ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the ’569 patent has an effective filing date prior to March 16, 2013, we apply the pre-AIA version of § 103.

⁴ Harris et al., U.S. Patent No. 5,932,462, issued August 3, 1999 (Ex. 1016).

⁵ Bentley et al., U.S. Patent No. 5,990,237, issued November 23, 1999 (Ex. 1015).

⁶ Petitioner argues that claims 4 and 6 would have been obvious over Harris in view of Bentley, whereas claims 1–8, 10, 11 would have been obvious over Bentley in view of Harris. Pet. 5–6. Despite the different orders of the two references, Petitioner’s arguments related to claims 4 and 6 are substantively the same. Thus, we consider these two grounds together. *See In re Mouttet*, 686 F. 3d 1322, 1333 (Fed. Cir. 2012) (“[W]here the relevant factual inquiries underlying an obviousness determination are otherwise clear, characterization . . . of prior art as ‘primary’ and ‘secondary’ is merely a matter of presentation with no legal significance.”).

⁷ Choi, International Publication No. WO 99/29759, published June 17, 1999 (Ex. 1032).

⁸ Dalborg et al., International Publication No. WO 97/11957, published April 3, 1997 (Ex. 1033).

⁹ Mitsuchika et al., Patent Application Publication No. P2000-44674, published February 15, 2000 (Ex. 1034) (“JP-674”).

In support of its patentability challenge, Petitioner originally relied on the Declaration of Yuji Yamamoto, Ph.D. (Ex. 1083). Because of scheduling difficulties caused by COVID-19, we authorized Petitioner to replace the Yamamoto Declaration with that of Todd Emrick, Ph.D. (Ex. 1084¹⁰), who also filed a reply declaration (Ex. 1095). Patent Owner relies on the Declaration of Steven R. Little, Ph.D. (Ex. 2005).

II. ANALYSIS

A. *Principles of Law*

To prevail in this *inter partes* review, Petitioner “shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.” 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d) (2019).

A patent claim is unpatentable under 35 U.S.C. § 103(a) 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) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR*, 550 U.S. at 406.

¹⁰ In view of the replacement of Yamamoto Declaration (Ex. 1083) with an essentially identical declaration from Dr. Emrick (Ex. 1084), we treat all citations to Exhibit 1083 in the Papers and Exhibits as citations to Exhibit 1084.

We analyze the instituted grounds of unpatentability in accordance with these principles.

B. Level of Ordinary Skill in the Art

Petitioner contends an ordinarily skilled artisan would have had a Ph.D. in chemistry, biochemistry, materials science, or a related field and 3–5 years of experience working in the field of synthesis of active PEG polymers for PEGylation of biological molecules. Pet. 25 (citing Ex. 1084 ¶¶ 7–13). Petitioner further contends that an ordinarily skilled artisan alternatively could have been a “highly skilled scientist having an advanced degree” other than a Ph.D., but with “additional years of experience working with PEGylation polymer synthesis and chemistries for modification of biomolecules.” *Id.* at 25–26.

Patent Owner contends a person of ordinary skill in the art would have had “at least a master’s degree in organic chemistry, biochemistry, or a comparable discipline with several years of experience with water-soluble polymers useful for conjugation to biologically active molecules, their synthesis, characterization, and/or application to biologically active molecules.” PO Resp. 6–7 (citing Ex. 2036 ¶¶ 54, 58).

We do not discern an appreciable difference in the parties’ respective definitions of the level of ordinary skill in the art, and any perceived distinction does not impact our Decision.¹¹ Nonetheless, we adopt Patent Owner’s definition of the skill level, as it is consistent with the ’569 patent

¹¹ Petitioner argues in its Reply that Patent Owner fails to account for the general knowledge of one of ordinary skill in the art. *See, e.g.*, Reply 10. Petitioner does not argue, however, that this general knowledge would differ between the two proffered definitions of the ordinary skill level.

disclosures and the prior art of record, and more inclusively describes the suitable experience for one of ordinary skill in the art.

We further note that, in this case, the prior art itself demonstrates the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

C. Claim Construction

In an *inter partes* review, a claim term “shall be construed 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), including construing 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.” 37 C.F.R. § 42.100(b); *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc) (holding that the words of a claim “are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application”) (citations omitted). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner proposes that we construe the term “aliphatic hydrocarbon.” Pet. 24–25. Patent Owner disagrees with Petitioner’s proposed construction. PO Resp. 6. Patent Owner also argues that the term does not need express construction because the patentability analysis does not turn on the definition of this term. *Id.* We agree with Patent Owner.

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to expressly construe any claim terms.

D. Obviousness of Claims 1–3, 5, 7, 8, 10, and 11 over Harris

Petitioner argues that claims 1–3, 5, 7, 8, 10, and 11 would have been obvious over Harris. Pet. 28–40. After reviewing the entire record, we conclude Petitioner has shown by a preponderance of the evidence that Harris renders these challenged claims obvious.

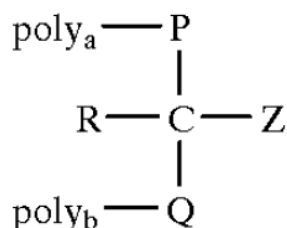
1. Harris

Harris teaches that although many enzymes and proteins are available for use as drugs or biocatalysts, limitations exist to use of these compounds, including “low stability and solubility in organic solvents.” Ex. 1016, 1:16–20. One approach to the problems that have arisen in the use of polypeptides as drugs or biocatalysts, according to Harris, is “to link suitable hydrophilic or amphiphilic polymer derivatives to the polypeptide to create a polymer cloud surrounding the polypeptide.” *Id.* at 1:36–40. Harris explains that “[i]f the polymer derivative is soluble and stable in organic solvents, then enzyme conjugates with the polymer may acquire that solubility and stability.” *Id.* at 1:40–42.

Harris teaches a branched or “multi-armed” amphiphilic polymer derivative that is monofunctional and hydrolytically stable. *Id.* at 7:33–35. “The derivative can include a single reactive site that is located along the polymer backbone rather than on the terminal portions of the polymer moieties.” *Id.* at 7:45–48.

Harris states that in this multi-armed polymer derivative, the single reactive site can be converted to a functional group for highly selective coupling to proteins and enzymes. *Id.* at 7:54–56. According to Harris, “[a] larger, more dense polymer cloud can be created surrounding a biomolecule with fewer attachment points to the biomolecule as compared to conventional polymer derivatives having terminal functional groups.” *Id.* at 7:56–60.

Harris describes such a molecule as “having the structure



wherein Z is a moiety that can be activated for attachment to biologically active molecules such as proteins and wherein P and Q represent linkage fragments that join polymer arms poly_a and poly_b, respectively, to central carbon atom, C . . . R typically is hydrogen or methyl, but can be a linkage fragment that includes another polymer arm.

Id., Abstract.

2. Discussion

i. Law of Obviousness

One overarching dispute between the parties is how the law of obviousness applies in this case. Petitioner argues that we should apply standard principles of obviousness. Pet. 7–8; Reply 3–4. Patent Owner argues that we should apply the lead compound analysis when assessing whether the claimed genus of chemical compounds would have been obvious over the prior art of record. PO Resp. 1–2, 9; Sur-Reply 3–7.

The case law regarding “when a species is patentable over a genus claimed in the prior art is less than clear.” *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1364 (Fed. Cir. 2007) (Dyk, J., concurring). We look, therefore, to the general law of obviousness for guidance. When analyzing obviousness, we must take “an expansive and flexible approach,” focusing on “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 415, 419.

Thus, a party may take several different paths in establishing that a patent claim would have been obvious over the prior art. One of these paths is the lead compound analysis, which is based on structural similarity between a claimed chemical compound and a prior art compound. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012); *Eisai Co. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008). Under the lead compound analysis, the patent challenger must identify “some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound) in a particular way to achieve the claimed compound.” *Eisai*, 533 F.3d at 1357.

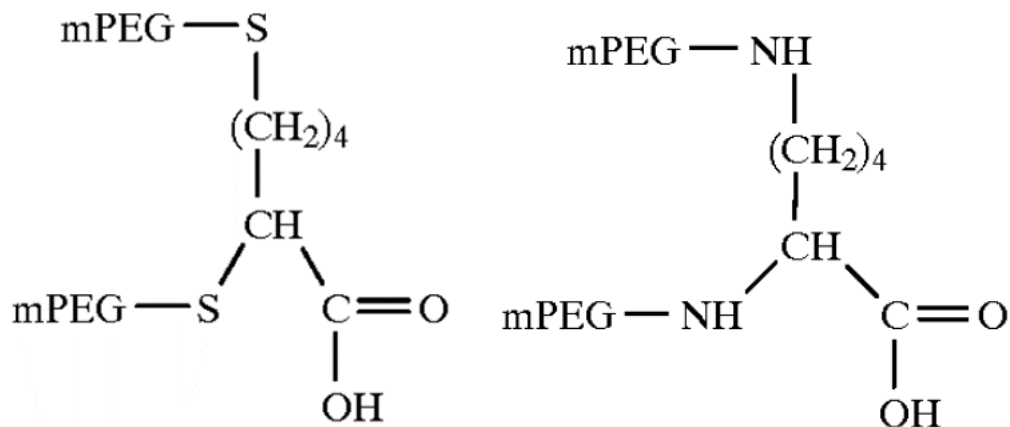
A lead compound analysis, however, is not the only way to demonstrate obviousness of a claimed compound or genus of compounds. *See Otsuka*, 678 F.3d at 1291 (“New compounds may be created from theoretical considerations rather than from attempts to improve on prior art compounds”). Indeed, any rigid application of the lead compound analysis risks running afoul of the broad, flexible obviousness test set forth by the Supreme Court in *KSR*. *See Altana Pharm. AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009) (noting that a “restrictive view of the

lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*”).

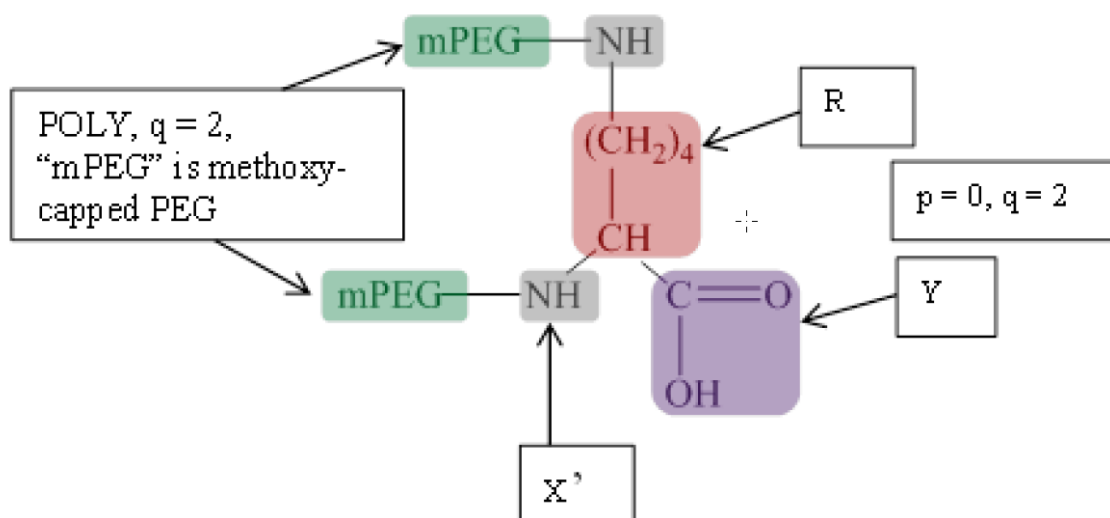
Because an obviousness challenge “may be based on the closest prior art, which may not have been a lead compound that the inventor had in mind” (*UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1329 (Fed. Cir. 2018)), we decline to apply the lead compound analysis as the exclusive test for obviousness in this case. Instead, we apply the standard principles of obviousness.

ii. *Claim 1*

Petitioner relies on two branched polymers exemplified in Harris:



The figures above depict two mPEG disubstituted lysine molecules, with a thioether linkage on the left, and an amine linkage on the right. Pet. 30 (citing Ex. 1016, 23:1–20, 37–45). Petitioner maps the structure of the molecule with the amine linkage to the formula of claim 1, as follows:



The figure above shows the amine-linked branched polymer of Harris, as annotated by Petitioner to show how the structure compares to the polymer recited in claim 1. *Id.* at 30 (citing Ex. 1084 ¶ 316).

Petitioner argues that this molecule meets all the structural elements of claim 1, except "the Y group as claimed is a maleimide rather than a carboxyl group." *Id.* at 31. The carboxyl group, according to Petitioner, "is the equivalent of the 'Y' functional group as claimed" and the $-Z$ moiety in Harris, which "can be converted to sites reactive toward nucleophilic moieties." *Id.* (quoting Ex. 1016, 8:19–25). Harris, Petitioner points out, expressly teaches maleimide as an exemplary active electrophilic moiety "useful for activating polymers or linking moieties for biological and biotechnical applications." *Id.* (quoting Ex. 1016, 23:44–52).

Regarding molecular weight, Petitioner refers to Harris for teaching branched polymers of 10,000 Da, 40,000 Da, at least about 50,000, about 40,000 to 50,000 Da, and from about 40,000 to 100,000 Da. *Id.* at 33–34 (citing, e.g., Ex. 1016, 11:2–7, 12:40–15:17, 15:55–17:2, 18:11–30, 37:62–65). Petitioner argues that each of these disclosures "falls within the

scope of the claim 1 limitation of ‘about 500 Da to about 100,000 Da.’” *Id.* at 34. Thus, according to Petitioner, Harris renders claim 1 obvious. *Id.*

Patent Owner does not dispute Harris’s teachings as Petitioner alleges. After reviewing the record, we agree with Petitioner that Harris teaches amine-linked and thioether-linked branched polymers, each of which meets the structural elements of claim 1, except maleimide at the Y position. Ex. 1016, 23:10–20, 36–43. We also agree with Petitioner that Harris teaches maleimide as “useful for activating polymers or linking moieties for biological and biotechnical applications.” *Id.* at 23:44–51. We further agree with Petitioner that Harris teaches branched polymers with molecular weight within the claimed range. *See, e.g., id.* at 18:15–25, 37:62–65. In other words, we find Harris teaches each limitation of claim 1.

This, however, does not end our inquiry. After all, “[a] patent composed of several elements is not proved obvious by merely demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. Instead, “it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does.” *Id.*

The questions we must answer, then, are whether Petitioner has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have had (1) a reason to select the amine- and thioether-linked polymers of Harris for further development, (2) a reason to modify those polymers to include a maleimide, and not a carboxyl, group at the Y position, and (3) a reasonable expectation of success of achieving the claimed invention. For the following reasons, we answer all three questions in the positive, despite Patent Owner’s contentions to the contrary.

a. Selecting Amine- and Thioether-Linked Polymers

As an initial matter, we reject Patent Owner's arguments that Petitioner fails to apply a lead compound analysis and this failure dooms the Petition. PO Resp. 11–21. As explained in Section II.D.2.i., the lead compound analysis is not an exclusive test for obviousness in this case. Instead, we accept Petitioner's analysis, applying the standard principles of obviousness, which require an “expansive and flexible” inquiry. *See* Pet. 7–8 (citing *KSR*, 550 U.S. at 415).

Patent Owner contends that Petitioner has not shown why an ordinarily skilled artisan would have selected the amine- and thioether-linked polymers of Harris for further development. PO Resp. 11–21. We find Patent Owner's argument unavailing.

According to Patent Owner, “Harris contains no data describing the properties of either amine or thioether compound.” *Id.* at 12. As Petitioner correctly points out, Harris claims “alternative linkages in a closed Markush group of only 11 members.” Pet. 29 (citing Ex. 1016, claim 9); Reply 9. Indeed, Harris's claim 9 recites linkages “selected from the group consisting of . . . amine, ether . . . thioether” and eight others. *See* Ex. 1016, 37:66–38:3. In other words, challenged claim 1 recites three out of the eleven linkages Harris specifically claims.

Harris describes these linkages as “hydrolytically stable.” Ex. 1016, 18:46–64. In our Decision to Institute, we found Petitioner's reliance on this property, among other reasons, persuasive to support the selection of the amine and thioether linkages. Dec. 19 (citing Pet. 29). Patent Owner asserts Petitioner “never argued that this characterization of linkers generally would have encouraged a POSA to pursue these specific polymers. Rather,

Petitioner simply states that Harris generally discloses that a number of linkages are ‘hydrolytically stable,’ including amines and thioethers.”

PO Resp. 14 n.5 (citing Pet. 14). We disagree.

When discussing challenged claim 1, Petitioner specifically points out that the linkages in Harris “can be selected from amine, ether, and thioether linkages, which are disclosed as hydrolytically stable.” Pet. 29. Petitioner later relies on this property again when discussing challenged claim 2, which limits the linkage to an ether. *See id.* at 34 (“Harris discloses that the linkage fragments P and Q can be selected from amine, ether, and thioether linkages, which are disclosed as hydrolytically stable.”). Certainly, any doubt around this issue is eliminated when Petitioner argues that “it would have been obvious for a POSA to select hydrolytically stable ether linkages from the disclosure of Harris to arrive at claim 2.” *Id.* at 35. Thus, we find Petitioner indeed relies on the property of hydrolytic stability to support the selection of amine, ether, and thioether linkages for further development.

Patent Owner also contends Petitioner’s argument “assumes that hydrolytic stability was a property that a POSA would have found desirable in the first place.” PO Resp. 14. According to Patent Owner, “[t]his basic premise fails.” *Id.* We, again, disagree.

Harris considers hydrolytic stability as one of the most important properties of the linkage. It repeatedly teaches that the polymer of its invention is hydrolytically stable. *See, e.g.*, Ex. 1016, Abstract, 7:33–35, 9:56–57, 11:44–48. Harris teaches it is the hydrolytically stable linkages that confer hydrolytic stability to the polymer. *See, e.g., id.*, Abstract, 8:10–14, 8:59–60. Specifically, Harris teaches an ordinarily skilled artisan to avoid hydrolytically unstable linkages, such as the ester linkage, because polymers

with such linkages “are quickly destroyed on injection into the blood stream,” and “[i]n vivo application is therefore limited.” *Id.* at 1:63–65, 7:14–17, 7:61–62, 11:63–64; *see also id.* at 10:67–11:2 (“The polymer backbone contains no hydrolytically weak ester linkages that could break down during in vivo applications.”). Thus, Harris indeed teaches that hydrolytic stability is a desirable property.

Patent Owner points to the Emrick Declaration for stating that “[i]n some applications, it may be desirable that PEG chains be hydrolytically degradable.” PO Resp. 14 (quoting Ex. 1084 ¶ 87 n.6). Dr. Emrick cites Harris to support this testimony. Ex. 1084 ¶ 87 n.6 (citing Ex. 1016, 30:56–59). Patent Owner also points to Harris’s statement that “[i]t may be desirable in some instances to provide a linkage between, for example, a protein or enzyme and a multisubstituted polymer derivative that has limited stability in water.” PO Resp. 14 (quoting Ex. 1016, 25:42–45). A closer look into the language surrounding the quoted statement in Harris, however, casts doubt over whether it supports Patent Owner’s argument.

Harris teaches:

It should also be recognized that, although the linker fragments represented by P and Q should not contain aromatic rings or hydrolytically weak linkages such as ester linkages, such rings and *such hydrolytically weak linkages may be present in the moiety represented by –Z*. It may be desirable in some instances to provide a linkage between, for example, a protein or enzyme and a multisubstituted polymer derivative that has limited stability in water. Some amino acids contain aromatic moieties, and it is intended that the structure –Z include conjugates of multisubstituted monofunctional polymer derivatives with such molecules or portions of molecules.

Ex. 1016, 30:52–63 (emphasis added), *see also id.* at 25:37–49 (the same).

Read in such context, Harris permits the hydrolytically unstable linkages, not in the P and Q linkers (where the amine and thioether linkages are), but in the Z moiety, which, according to Petitioner's mapping, corresponds to the Y group in challenged claim 1. Such teaching is not inconsistent with Harris's preference for amine- or thioether-linked, hydrolytically stable polymers.

Moreover, even if an ordinarily skilled artisan understood Harris to suggest hydrolytically unstable linkages for P and Q linkers, it would not change our decision. After all, a prior art disclosure of "a multitude of effective combinations does not render any particular formulation less obvious." *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). Here, the teaching that hydrolytically unstable linkages may be useful in some instances would not render hydrolytically stable linkages less obvious.

Patent Owner further contends that hydrolytic stability "does not distinguish the cited amine- and thioether-linked polymers from any of the other compounds disclosed in Harris." PO Resp. 15. In addition, Patent Owner asserts that amine and thioether linkages would present "challenges," such as potential over alkylation for amine and susceptibility to oxidation for thioether. *Id.* at 16–17. In light of "these known issues," Patent Owner contends that an ordinarily skilled artisan would have looked instead to a carbamate linkage, which is "the focus of Harris's teaching." *Id.* at 16–20; *see also* Sur-Reply 10–12. Patent Owner's arguments are unavailing.

Harris teaches only five "[e]xamples of the . . . linkages and their formation from activated mPEG and lysine." Ex. 1016, 19:8–10. Amine and thioether linkages are among the five examples. *Id.* at 21:27–45, 23:1–20.

Amine and thioether linkages are also in a Markush group of merely eleven members Harris *claims. Id.*, claim 9. Thus, we agree with Petitioner that Harris, at a minimum, suggests amine and thioether linkages as suitable alternatives to the carbamate linkages. *See* Reply 9; *see also KSR*, 550 U.S. at 416 (“[W]hen a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.”).

We also find that the alleged “challenges” of over alkylation (amine related) and oxidation (thioether related) identified by Patent Owner, even if true,¹² would not have dissuaded an ordinarily skilled artisan from selecting the amine- or thioether-linked polymers for further development, because we are persuaded that one of ordinary skill in the art would have understood how to successfully overcome such challenges. *See* Reply 9 (citing Ex. 1095 ¶¶ 81–85). Our conclusion is further supported by the fact that the ’569 patent teaches using Harris’s method to prepare amine and thioether linkages. Ex. 1001, 8:27–55, 13:37–41. The ’569 patent not only teaches, but also claims, amine- and thioether-linked polymers, without any expressed concern regarding over alkylation or oxidation, and without suggesting any need for methods to avoid such reactions.

As noted by Patent Owner, Harris primarily focuses on carbamate-linked polymers and provides its only experimental results with these polymers. The fact that carbamate linkers may be preferred, however, does not diminish the fact that amine- and thioether-linked polymers are

¹² Petitioner disputes the existence of these challenges as applied to Harris. Reply 8–9 (citing Ex. 1095 ¶¶ 80, 84). We do not need to resolve this issue because we are persuaded by Petitioner’s other arguments.

taught and claimed in Harris. Indeed, “a finding that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed by the patent applicant is the preferred, or most desirable, combination.” *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004). And, as discussed above, we agree with Petitioner that amine and thioether linkages are at least acceptable substitutes for the carbamate linkage disclosed and tested in Harris. *See KSR*, 550 U.S. at 417 (“[A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.”).

In sum, we find Petitioner has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have had a reason to select the amine- and thioether-linked polymers of Harris for further development.

b. Reason to Modify Amine- and Thioether-Linked Polymers

Patent Owner contends that Petitioner has not shown why an ordinarily skilled artisan would have modified the amine- and thioether-linked polymers of Harris to include a maleimide at the Y position, instead of the carboxyl moieties Harris teaches. PO Resp. 21–28. We disagree.

As an initial matter, we reject Patent Owner’s assertion that Petitioner’s argument regarding the reason to modify Harris’s polymers “amounts to the mere possibility that a POSA could have selected a maleimide as a functional group.” PO Resp. 21–22. As discussed in the Decision to Institute, we understand Petitioner’s argument that “the carboxyl group of the branched reactive PEG polymers disclosed by Harris could be converted to a maleimide group” to be directed to the requirement of

reasonable expectation of success. Dec. 22 (quoting Pet. 31). The context of the statement supports our view. Indeed, continuing the sentence, Petitioner argues that this conversion is achieved “by means conventionally known in the art.” Pet. 31 (citing Ex. 1084 ¶ 317); *see also id.* at 32 (arguing maleimide “can be obtained from the carboxyl group shown in the structure above using means conventionally known in the art”) (citing Ex. 1084 ¶¶ 318–322).

On the reason to modify Harris’s polymers, “[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.” *See KSR*, 550 U.S. at 421. As Petitioner points out, Harris expressly teaches maleimide as one of ten examples of “active electrophilic moieties useful for activating polymers or linking moieties for biological and biotechnical applications in which the active moiety is reacted to form hydrolytically stable linkages.” Pet. 31 (quoting Ex. 1016, 23:44–52). Harris also *claims* polymers activated as maleimide, together with nine other moieties. Ex. 1016, claims 11, 38.

Moreover, Petitioner argues that an ordinarily skilled artisan would have modified the polymers to include “a maleimide for applications where the maleimide is selective for the available reactive site on a protein, such as a cysteine.” Pet. 41 (citing Ex. 1084 ¶ 336); *see also id.* at 54 (arguing that it would have been obvious to substitute functional groups and activate a polymer “as a maleimide, as taught by Harris, for applications in which a cysteine is available for conjugation using reactions commonly known in the art at the time of filing the ‘569 patent”) (citing Ex. 1084 ¶¶ 357–360);

Reply 10 (“Maleimide was well-known in the art as a cysteine-specific functional group.”) (citing Ex. 1045, 14:1–15, 20:30–21:5, 36:15–38:24; Ex. 1057, 157–58; Ex. 1058, 356–57; Ex. 1071; Ex. 1084 ¶¶ 280, 347; Ex. 1095 ¶¶ 91–94).

Patent Owner contends that Petitioner’s argument “rests on several layers of hindsight-driven assumptions.” PO Resp. 24. According to Patent Owner, Petitioner assumes (1) “a POSA would have been motivated to use PEG to create a polypeptide conjugate, rather than for any of the other myriad uses of PEG;” (2) “the target polypeptide would have one or more cysteine residues available for conjugation;” (3) “a POSA would have specifically targeted cysteine residues on the polypeptide for PEG attachment, as opposed to any other amino acid residue;” and (4) “a POSA would have used a maleimide to do so (and not, for example, any of the other cysteine-reactive functional groups cited in Harris, such as vinylsulfone).” *Id.* Patent Owner asserts that “[t]hese assumptions are not supported by the record.” *Id.* Patent Owner’s arguments are misguided.

Harris expressly teaches that “[t]he multi-armed polymer derivative of the invention having a single reactive site can be used for, among other things, protein modification with a high retention of protein activity.” Ex. 1016, 7:50–53; *see also id.* at 3:60–62 (stating that “[m]onofunctional PEGs are usually preferred for protein modification”). Although not all proteins have cysteine residues available for conjugation, many do.¹³ Even if

¹³ In fact, when “the native polypeptide does not contain any free cysteine residues,” the prior art teaches that “an altered polypeptide is produced to contain at least one free cysteine in the biologically active polypeptide.” Ex. 1045, 14.

other residues may be targeted for PEG attachment, prior art teaches that cysteine is a desired point of attachment for protein pegylation. Ex. 1037, 47.¹⁴ And even if other cysteine-reactive functional groups may be used, or even preferred, prior art teaches that “[m]aleimide-containing reagents are effective modifiers of free cysteinyl residues of polypeptides.” Ex. 1058, 356; *see also* Ex. 1057, 158 (teaching that “selective positioning of cysteine residues in polypeptide sequences, combined with their reactivity to maleimide-terminated PEG, offered an opportunity to assemble site-specifically modified PEG-proteins.”). In fact, prior art teaches that “[c]oupling of maleimide and thiol groups is one of the most useful reactions for bioconjugate preparation.” Ex. 1037, 33; Ex. 1038, 22.

As explained above, a prior art’s disclosure of “a multitude of effective combinations does not render any particular formulation less obvious.” *Merck*, 874 F.2d at 807. We read Patent Owner’s complaint about Petitioner’s “layers of hindsight-driven assumptions” (PO Resp. 24) as essentially arguing that the claimed approach should be the single preferred, or most desirable, approach. Alas, that is not the law. *See In re Fulton*, 391 F.3d at 1200.

In sum, Harris teaches maleimide as one of a handful “active electrophilic moieties useful for activating polymers or linking moieties for biological and biotechnical applications.” Ex. 1016, 23:44–52, claims 11, 38. In addition, Petitioner has persuasively shown that maleimide is well known for specifically modifying polypeptides having cysteine residues. Pet. 41, 45–47, 54. Thus, given the “finite number of identified, predictable

¹⁴ Unless otherwise noted, we cite to the original page number of the exhibits, not the number supplied by the parties.

solutions” in Harris, Petitioner has met its burden in showing that an ordinarily skilled artisan would have had a “good reason to pursue” maleimide, one of the known options. *See KSR*, 550 U.S. at 421.

c. Reasonable Expectation of Success

Patent Owner also argues that Petitioner has failed to demonstrate a reasonable expectation of success in modifying Harris to achieve the claimed maleimide functional group. PO Resp. 28–32. We disagree.

Petitioner refers to Harris for teaching that moiety Z, which corresponds to the Y group in challenged claim 1, “can be converted to sites reactive toward nucleophilic moieties,” such as maleimide. Pet. 31 (citing Ex. 1016, 8:19–25). Petitioner also refers to Harris for teaching that “there are a wide variety of functional moieties available for activation of carboxylic [sic] acid polymer moieties for attachment to various surfaces and molecules.” *Id.* at 32 (quoting Ex. 1016, 29:30–34). According to Petitioner, Harris teaches that “active electrophilic moieties useful for activating polymers or linking moieties for biological and biotechnical applications include[] both active ester, directly obtained from the carboxyl group and maleimide which can be obtained from the carboxyl group by means conventionally known in the art.” *Id.* (citing Ex. 1016, 23:44–52; Ex. 1084 ¶¶ 318–322), *see also id.* at 31 (citing Ex. 1084 ¶ 317) (“A POSA would recognize that the carboxyl group of the branched reactive PEG polymers disclosed by Harris could be converted to a maleimide group by means conventionally known in the art.”).

Patent Owner laments that Petitioner’s “generic statements fail to speak directly to the specific polymers from Harris and are, therefore, insufficient to support a reasonable expectation of success.” PO Resp. 29.

Patent Owner also faults Dr. Emrick for “postulat[ing] a reaction scheme to produce a branched maleimide compound based on the amine-linked PEG polymer as a starting material,” because he “fails to account for the possibility” of cyclization and does not propose a yield. *Id.* at 29–31 (citing Ex. 1084 ¶ 321; Ex. 2036 ¶ 196; Ex. 2040, 209:25–211:8, 211:22–24). Patent Owner does not dispute that claim 11 in Harris claims maleimide, but contends that fact cannot support Petitioner’s argument of reasonable expectation of success. *Id.* at 32 (citing *UCB*, 890 F.3d at 1327). Patent Owner’s arguments are unavailing.

Harris teaches that “[t]he skilled artisan should recognize that Z encompasses the *currently known activating moieties in PEG chemistry* and their conjugates.” Ex. 1016 at 25:35–37 (emphasis added). According to Harris,

It should be recognized that a number of activating groups can be used to activate the multisubstituted polymer derivatives for attachment to surfaces and molecules. Any of the *activating groups of the known derivatives of PEG* can be applied to the multisubstituted structure. For example, the mPEG-disubstituted lysine of the invention was functionalized by activation as the succinimidyl ester, which can be attached to protein amino groups. However, there are a wide variety of functional moieties available for activation of carboxylic [sic] acid polymer moieties for attachment to various surfaces and molecules. Examples of active moieties used for biological and biotechnical applications include . . . maleimide. . . .

Id. at 29:24–39.

Dr. Emrick testifies that “the chemistry for preparing maleimide groups, particularly maleimide groups on PEG polymers, was well known to a POSA at the time of filing the ‘569 patent.” Ex. 1084 ¶ 286. As support,

Dr. Emrick points to numerous prior art references, including Kogan.¹⁵ *Id.*

¶¶ 286–299; Ex. 1095 ¶¶ 99–101. According to Dr. Emrick,

Kogan is generally directed to the synthesis of mPEG derivatives, functionalized either as hydrazides for the selective attachment to carboxylate domains of glycoproteins, or as iodoacetamides and maleimides for the modification of free sulfhydryl groups. Ex. 1071, Abstract. In particular, Kogan discloses detailed reaction conditions for preparing a maleimide group by the reaction of maleic anhydride with an amine group. Ex. 1071, 2422. Kogan also discloses the conversion of mPEG-OH to mPEG-NH₂ by the method described in Zalipsky et. al. “via the intermediacy of the chloride and azide.” Ex. 1071, 2419.

Ex. 1084 ¶ 287; *see also* Ex. 1095 ¶ 100 (“Kogan shows the transformation from mPEG-OH to mPEG-NH₂ to mPEG-maleimide.”)

(citing Ex. 1071, 2419–20).

We find the teachings of Kogan support Dr. Emrick’s testimony that “the preparation of maleimide groups was well known to a POSA at the time of filing the ‘569 patent.” Ex. 1084 ¶ 286. The challenged ‘569 patent confirms this determination. Indeed, the ‘569 patent provides no examples of maleimide as the functional group. Instead, to support the claims to maleimide, the ‘569 patent relies exclusively on prior-art references. *See* Ex. 1005, 10:66–11:25 (incorporating by reference prior art describing exemplary functional groups, including “maleimide (see, e.g., Goodson et al. *Bio/Technology* 8:343 (1990) [Ex. 1072], Romani et al. in *Chemistry of Peptides and Proteins* 2:29 (1984) [Ex. 1073], and Kogan, *Synthetic Comm.* 22:2417 (1992) [Ex. 1071])”). In other words, the ‘569 patent relies on the

¹⁵ Kogan, *The Synthesis of Substituted Methoxy-poly(ethyleneglycol) Derivative Suitable for Selective Protein Modification*, 22 *SYNTHETIC COMM.* 2417–24 (1992) (Ex. 1071).

same prior-art references Petitioner and Dr. Emrick rely on to show that activation and use of maleimide were well-known in the art. Thus, we are persuaded that Petitioner has met its burden in showing a reasonable expectation of success in modifying Harris to achieve the claimed maleimide functional group.

Patent Owner's challenge of the allegedly "hypothetical" reaction scheme presented in the Emrick Declaration (PO Resp. 29–31 (citing Ex. 1084 ¶ 321)) does not change our determination. As an initial matter, we note that the cyclization reaction that Patent Owner criticizes Petitioner of failing to account for is hypothetical. *See id.* at 31 (arguing there is a "possibility" of such cyclization, which "*could* result in the formation of no maleimide whatsoever"). More importantly, "[t]he reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the *claimed invention*." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (emphasis added). Challenged claim 1 is directed to a branched reactive polymer (Ex. 1005, 24:18); it does not require any level of purity or yield, let alone "a pharmaceutical-grade end product," as Patent Owner asserts (PO Resp. 31).

Case law further supports our conclusion. *See Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1341–42 (Fed. Cir. 2006). In that case, Abbott Laboratories sued Teva Pharmaceuticals USA, Inc. for infringing patents relating to extended release formulations of clarithromycin. *Id.* at 1332. Abbott moved for a preliminary injunction, and Teva challenged the validity of the asserted claims for obviousness. *Id.* Concluding, among others, that "Teva had not raised a substantial question that a person of ordinary skill in

the art would have had a reasonable expectation of success in making the claimed invention,” the district court granted Abbott’s motion for a preliminary injunction. *Id.* at 1332, 1341. The Federal Circuit disagreed. *Id.* at 1341–42. The court pointed out that one of Abbott’s own prior-art patents, the ’190 patent, claims “[t]he composition of claim 4, wherein the macrolide is selected from the group consisting of erythromycin, dirithromycin, azithromycin, roxithromycin, and ABT–229.” *Id.* at 1341. According to the Federal Circuit,

This claim is relevant because it describes Abbott’s own view of the ordinary skill in the art at the time it filed the application that led to the ’190 patent and it does so not by what the ’190 patent discloses but by what it *does not* disclose. Claim 4 and 14 of the ’190 patent cover compositions that include azithromycin or clarithromycin. Despite these claims to varied compositions, the specification only explicitly describes compositions made from clarithromycin. We presume that Abbott filed and prosecuted the ’190 patent representing that claim 14 of the ’190 patent satisfies the written description and enablement requirements of 35 U.S.C. § 112. . . . Because the ’190 patent explicitly discloses only clarithromycin controlled release compositions, yet claims azithromycin compositions, we conclude that Abbott has represented to the U.S. Patent and Trademark Office (“PTO”) that the differences between clarithromycin and azithromycin were such that azithromycin could be substituted into a controlled release clarithromycin composition by a person of ordinary skill in the art without undue experimentation.

Id. at 1341–42. Thus, the court vacated the preliminary injunction, concluding that, “based on Abbott’s own ’190 patent, there exists a substantial argument that a person of ordinary skill in the art would [have had] a reasonable expectation of success” in making the claimed invention and therefore that the asserted claims would have been obvious. *Id.*

The facts are similar here. Harris claims a polymer activated as active ester or maleimide. Ex. 1016, claims 11, 38. Harris's specification, however, only explicitly describes the activation of mPEG-disubstituted lysine as an active ester. *Id.* at 28:31–29:12, 30:64–31:26. Harris, thus, describes Patent Owner's own view of the ordinary skill in the art in 1995, the priority date of Harris.¹⁶ It does so, as the Federal Circuit explained in *Abbott Laboratories*, not by what Harris discloses “but by what it does not disclose.” *See Abbott Labs., Inc.*, 452 F.3d at 1341. We presume that Patent Owner, as the applicant of Harris, filed and prosecuted Harris representing that claims 11 and 38 satisfy the written description and enablement requirements. In other words, Patent Owner must have viewed that the differences between active ester and maleimide were such that maleimide could be substituted into the active ester polymer by a person of ordinary skill in the art without undue experimentation. *See id.*

In sum, because Petitioner has persuaded us that preparing maleimide groups on PEG polymers was well known in the prior art, it has demonstrated, by a preponderance of the evidence, that an ordinarily skilled artisan would have achieved the claimed maleimide group with a reasonable expectation of success.

d. Conclusion

After reviewing the record, we determine that Petitioner demonstrates by a preponderance of the evidence that Harris teaches or suggests all of the

¹⁶ Petitioner states that Patent Owner “is the successor to Shearwater Polymers, Inc. and is the owner/author of each of Harris, Harris ‘221 and Bentley, as well as the Shearwater Catalogs (Ex-1037/Ex-1038).” Reply 1 n.1 (citing Exs. 1097–1101). Patent Owner does not dispute this assertion.

limitations of challenged claim 1, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of claim 1 of the '569 patent with a reasonable expectation of success.

iii. Claims 2, 3, 5, 7, 8, 10, and 11

Petitioner provides analysis and citations to record evidence to show where Harris teaches or suggests every limitation of claims 2, 3, 5, 7, 8, 10, and 11. Pet. 34–40. Patent Owner repeats its arguments in countering Petitioner's challenge of claim 1. PO Resp. 32. For the same reasons explained above, we find these arguments unavailing. *See* Section II.D.2.ii. Patent Owner also specifically disputes the asserted obviousness of claims 2, 8, and 10. PO Resp. 32–34. For the reasons below, we find those arguments unavailing as well.

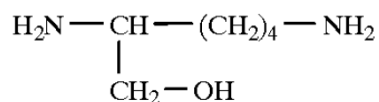
Claim 2 depends from claim 1, and further recites X' is –O–. Ex. 1005, 24:34–35. Petitioner refers to the specification and claims 9 and 35 for teaching the ether linkage. Pet. 34–35 (citing Ex. 1016, 18:46–64, claims 9, 35). Patent Owner contends that “the amine- and thioether- linked polymers relied upon by Petitioner do not contain this linkage at the alleged X' position.” PO Resp. 33. According to Patent Owner, “Petitioner points to generic disclosures in Harris of an ether as a possible linkage,” but “these generic disclosures do not answer the fundamental question of why a POSA would have included this linkage in the specific structure recited by claim 2.” *Id.* We disagree with Patent Owner.

In Harris, each of claims 9 and 35 recites ether as one of eleven choices of linkages. Ex. 1016, 37:66–38:3, 41:66–42:2. Harris also teaches ether as a hydrolytically stable linkage. *Id.* at 18:56–59. In view of these

specific teachings, we are persuaded that “it would have been obvious for a POSA to select hydrolytically stable ether linkages from the disclosure of Harris to arrive at claim 2.” Pet. 35.

Claim 8 depends from claim 1, and further recites “p is 1 and [linker] X is selected from the group consisting of . . . –alkylene . . .” Ex. 1005, 24:46–50. Acknowledging that this limitation is “not illustrated” in Harris, Petitioner nevertheless argues that “Harris teaches that the polymers may include a linkage fragment R_z (a “linker” X as claimed) that joins the reactive moiety –Z to the central carbon such that polymers where ‘p’ is 1 are described and would have been in the possession of [a] POSA.” Pet. 36–37 (citing Ex. 1016, 9:10–33, 24:6–26:18).

Harris teaches that “[t]he moiety –Z may also include a linkage fragment” R_z. Ex. 1016, 25:4–5. According to Harris, a suitable linker moiety is a diamino alcohol having the following structure:



The figure above is the structure of an exemplary diamino alcohol, in which R_z is CH₂. *Id.* at 24:19–23, 25:11–12.

Harris also teaches “[w]here a reactive group of the –Z moiety is carboxyl, for activation after substitution with nonpeptidic polymers, then the –Z moiety has the structure –R_z–COOH if the R_z fragment is present. For hydroxyl, the structure is –R_z–OH.” *Id.* at 25:7–11. Petitioner argues that “it would have been obvious to select a linker moiety of Harris having an –alkylene– linkage fragment R_z, such as –CH₂– in the diamino alcohol, thereby providing a –Z element of –CH₂–COOH or –CH₂–OH for further activation to a maleimide, as taught by Harris.” Pet. 38 (citing Ex. 1016, 39:54–57; Ex. 1084 ¶ 331); Ex. 1084 ¶¶ 329–330.

Patent Owner asserts that an ordinarily skilled artisan “would have been wary of adding such a linker due to the possibility for antigenicity, toxicity, loss of activity, and hydrophilicity.” PO Resp. 33 (citing Ex. 2036 ¶ 220; Ex. 2040, 80:17–81:17). Patent Owner relies on the Shearwater catalog where it states that “our PEG maleimide has no linker segment between the PEG chain and the maleimide ring that could act as an antigenic or toxic site.” *Id.* at 33–34 (quoting Ex. 1037, 33).

The Shearwater catalog statement does not “criticize, discredit, or otherwise discourage” using a linker such that it would amount to teaching away. In fact, it states that “[w]e can make linked materials if desired.” Ex. 1037, 33. Moreover, Harris teaches avoiding “[l]arge linker fragments . . . so as to avoid an antigenic response in living organisms.” Ex. 1016, 7:63–64; *see also id.* at 10:64–66 (“Large spacer arms between the coupled polymer and protein are avoided to avoid introducing possible antigenic sites.”), 11:64–65 (the same). Harris, however, teaches that “[a] linker fragment length of from 1 to 10 carbon atoms or the equivalent has been determined to be useful to avoid a length that could provide an antigenic site.” *Id.* at 26:12–15. Thus, we are persuaded that Harris teaches or suggests all of the limitations of challenged claim 8, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of claim 8 with a reasonable expectation of success.

Claim 10 recites “[a] biologically active conjugate, comprising a biologically active molecule covalently attached to a branched reactive polymer of claim 1, wherein the biologically active molecule is a biologically active protein.” Ex. 1005, 24:53–56. Petitioner argues that “Harris describes its active branched polymers are prepared for conjugation

to biologically active molecules, where the biologically active molecule is a protein.” *Id.* Patent Owner faults Petitioner for relying on “general statements from Harris.” PO Resp. 34. According to Patent Owner, Petitioner has not shown that “a POSA could have made the recited conjugates using the specific maleimide PEG reagents recited by claim 10 with a reasonable expectation of success.” *Id.* We, again, disagree.

Harris teaches its “invention includes biologically active conjugates comprising a biomolecule, which is a biologically active molecule, such as a protein or enzyme, linked through an activated moiety to the branched polymer derivative of the invention.” Ex. 1016, 9:27–31. Harris also teaches examples of branched polymers conjugated to specific enzymes. *Id.* at 30:64–32:40. Although these examples relate to active esters, and not maleimide, we are satisfied that Petition has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have achieved the claimed maleimide group with a reasonable expectation of success. *See* Ex. 1084 ¶ 334 (citing Ex. 1016, 9:9–32, 30:64–32:41).

Patent Owner does not separately address Petitioner’s challenge of claims 3, 5, 7, and 11. After reviewing the record, we agree with Petitioner that Harris teaches or suggests all of the limitations of these claims, and adopt Petitioner’s mapping of the claim limitation to Harris’s teachings as our own finding. Pet. 35–36, 39–40.

In sum, we determine that Petitioner demonstrates by a preponderance of the evidence that Harris teaches or suggests all of the limitations of challenged claims 2, 3, 5, 7, 8, 10, and 11, and that an ordinarily skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of these claims with a reasonable expectation of success.

iv. Objective Indicia of Non-obviousness

Patent Owner contends that objective indicia demonstrate non-obviousness of the challenged claims. PO Resp. 52–56. We are not persuaded.

Objective indicia of non-obviousness guard against hindsight reasoning in an obviousness analysis, and are often “the most probative and cogent evidence in the record.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). As such, objective indicia of non-obviousness must be considered in every case in which they are presented. *Id.* Objective indicia of non-obviousness include commercial success, long-felt but unsolved needs, failure of others, copying, industry praise, unexpected results, and industry acceptance. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000).

a. Long-Felt Need

Patent Owner argues there was a “long-felt but unmet need for the claimed branched reactive polymer and biologically active conjugates thereof in the ’569 patent.” PO Resp. 53. According to Patent Owner, the ’569 patent expressly sets out this need as follows:

There remains a need in the art for new branched polymer reagents that provide the benefits associated with branched polymers (i.e., high overall molecular weight in a single non-linear polymer molecule), but are easier to synthesize or provide more flexibility in their design than prior art reagents.

Id. (quoting Ex. 1005, 4:2–8). Pointing to several other portions of the ’569 patent, Patent Owner argues that “the ’569 patent satisfied this long-felt but unmet need for a branched reactive polymer and biologically active conjugates thereof that are more easily synthesized and purified.” *Id.* at 53–55.

Patent Owner notes that Dr. Emrick testified that difficulties associated with high molecular weight polymers have been known for 80 years and that examples “where very high molecular weights are made with a low polydispersity are impressive.” Sur-Reply 23 (quoting Ex. 2040, 41:23–42:2). Patent Owner further notes that Dr. Little testified that overcoming polydispersity issues with high molecular weight polymers is precisely what the inventor’s claimed structure is designed to do. *Id.* at 23–24 (citing Ex. 1093, 118:18–123:7, 120:5–13).

We are not persuaded by Patent Owner’s evidence of long-felt need. First, Patent Owner’s evidence on this point stems primarily from self-serving statements in the ’569 patent, and not from independent sources. Second, as Petitioner correctly argues, to be relevant, the evidence of objective indicia must result from something that is “both claimed and novel.” Reply 23 (quoting *In re Kao*, 639 F.3d 1057, 1058 (Fed. Cir. 2011)). Polydispersity levels (as well as methods of producing the polymers) are not recited in the challenged claims, and Patent Owner presents no evidence that generally producing high molecular weight polymers was novel. Indeed, Harris specifically claims high molecular weight PEG polymers (up to about 100,000 Da) and states that these compounds can be formed using a “simple” method. Ex. 1016, 7:33–40 (“Relatively pure polymer molecules of high molecular weight can be created.”), 18:31–45, claims 7, 8.

Thus, we find that Patent Owner’s evidence of long-felt need is entitled to little, if any, weight.

b. Teaching Away

Patent Owner also contends that “[t]he 1997-1998 Shearwater catalog teaches away from using maleimide (i) with a linker and (ii) to provide

hydrolytic stability.” PO Resp. 55. On the linker, Patent Owner argues that “maleimide combined with a long chain between the PEG arm(s) and the maleimide was associated with increased antigenicity issues.” Sur-Reply 24 (citing Ex. 2036 ¶¶ 135–136; Ex. 2040, 81:9–23). On hydrolytic stability, Patent Owner points to the following statement in the Shearwater catalog:

The major advantages of VS [vinylsulfone]-PEG over the maleimide derivative is that VS PEG is stable in water and a stable linkage is produced from reaction with sulfhydryl groups. Maleimide is known to undergo slow addition of water across the double bond, and the amide linkages of the product can undergo slow hydrolysis.

Ex. 1037, 32 (citation omitted). Thus, Patent Owner concludes that “a POSA concerned about hydrolytic stability would view this as teaching away from maleimide for achieving hydrolytically stable attachment.”

We are not persuaded by Patent Owner’s evidence of teaching away. A reference teaches away “when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). The mere disclosure of alternative designs, however, does not teach away, and “just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.” *Mouttet*, 686 F.3d at 1334.

Here, the Shearwater catalog statement does not “criticize, discredit, or otherwise discourage” using maleimide, and therefore does not amount to teaching away. *Fulton*, 391 F.3d at 1201. On hydrolytic stability, it merely states that “[m]aleimide is known to undergo *slow* addition of water across the double bond.” Ex. 1037, 32 (emphasis added); *see also id.* at 38 (stating

both VS and maleimide groups are “especially useful” even though “maleimide shows *some* reactivity with water”). And on linker, it states that “[w]e can make linked materials if desired.”¹⁷ *Id.* at 33. Indeed, instead of discouraging an ordinarily skilled artisan from using maleimide, the same Shearwater catalog teaches that “[c]oupling of maleimide and thiol groups is one of the most useful reactions for bioconjugate preparation.” Ex. 1037, 33. This teaching appears valid even in 2000. *See* Ex. 1038, 22.

In view of the foregoing, we are not persuaded that Patent Owner’s evidence of objective indicia sufficiently demonstrates non-obviousness of the challenged claims.

v. Conclusion

Upon review of the record as a whole, including Patent Owner’s evidence of objective indicia, and for the reasons discussed above, we determine that Petitioner demonstrates by a preponderance of the evidence that the subject matter of claims 1–3, 5, 7, 8, 10, and 11 would have been obvious over Harris.

E. Obviousness of Claims 1–8, 10, and 11 over Harris and Bentley

Petitioner argues that claims 1–8, 10, and 11 would have been obvious over the combined teachings of Harris and Bentley. Pet. 40–42, 47–65. After reviewing the entire record, we conclude Petitioner has not shown by a preponderance of the evidence that Harris and Bentley render claims 1–8, 10, and 11 obvious.

¹⁷ Harris recognizes that lengthy linkage chains “could promote an antigenic response,” and thus, should be avoided. Ex. 1016, 11:64–65, *see also id.* at 26:12–15 (“A linker fragment length of from 1 to 10 carbon atoms or the equivalent has been determined to be useful to avoid a length that could provide an antigenic site.”).

1. Bentley

Bentley relates to methods of coupling a PEG polymer to a biomaterial. Ex. 1015, 1:8–10. Bentley explains that covalently attaching the PEG polymer to molecules and surfaces has several advantages, and thus, is important in biotechnology and medicine. *Id.* at 1:14–17, 1:60–2:11.

According to Bentley:

To couple PEG to a molecule such as a protein or a small drug molecule, it is necessary to use an “activated derivative” of the PEG having a functional group at the terminus suitable for reaction with a group on the other molecule. For example, the hydroxyl group of $\text{CH}_3\text{O}-\text{PEG}-\text{OH}$ can be converted to an aldehyde group, and this aldehyde group can then be covalently linked to a molecule or surface bearing one or more amine groups using the method of reductive amination.

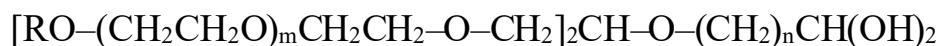
Id. at 2:12–20.

Bentley’s method “includes in situ preparation of PEG aldehyde hydrates, which can then be used in solution, without isolation, to form conjugates by reductive amination with a range of biologically active molecules, including proteins, peptides, polysaccharides, oligonucleotides, and small drug molecules.” *Id.* at 3:4–10. In Bentley, the PEG polymer is either linear or branched, and typically has an average molecular weight of from 200 to 100,000. *Id.* at 6:30–32, 35–36.

Bentley teaches that one form of activated PEG aldehyde is “dendritic activated PEG in which multiple arms of PEG are attached to a central core structure.” Ex. 1015, 6:64–66. These dendritic PEGs are commonly known as “star” molecules and can be represented by the formula $\text{Q}[\text{poly}]_y$, wherein Q is a branching core moiety and y is from 2 to about 100. *Id.* at 6:66–7:6.

Bentley teaches that

The aldehyde hydrate moiety can be used to provide an active, functional group on the end of the PEG chain extending from the core, or may act as a linker for joining a functional group to the star molecule arms. Additionally, the aldehyde hydrate moiety can also be linked directly to the core molecule having PEG chains extending from the core. One example of such a dendritic activated PEG has a formula of

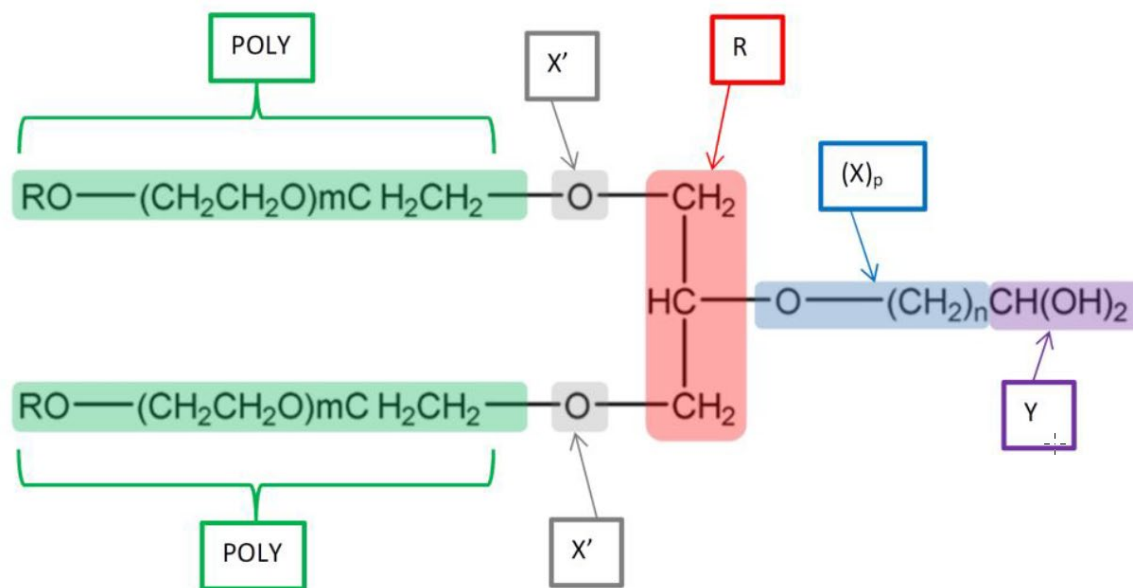


wherein R is H, alkyl, benzyl, or aryl; m ranges from about 5 to about 3000, [and] n ranges from 1 to 6.

Id. at 7:8–20.

2. Discussion

Petitioner argues that an ordinarily skilled artisan would recognize Bentley's formula above as:



The figure above shows Petitioner's depiction of the chemical structure identified at column 7, lines 16–20 of Bentley, as annotated by Dr. Emrick to show how the structure compares to that of the polymer recited in claim 1. Pet. 49–51 (citing Ex. 1015, 7:12–20; Ex. 1084 ¶¶ 350, 353).

According to Petitioner, Bentley teaches a branched PEG aldehyde hydrate polymer and claims a branched PEG aldehyde, each “meeting all of the structural elements” of challenged claim 1, except “group Y defined as a maleimide in claim 1.” *Id.* at 48 (citing, e.g., Ex. 1015, 7:12–20, 14:59–65). Petitioner relies on Harris for teaching the maleimide group. *Id.* at 52–54.

Petitioner refers to Bentley for teaching branched polymers with molecular weight from about 220 to 264,000 Da. *Id.* at 54 (citing Ex. 1015, 7:12–20, 14:59–65; Ex. 1084 ¶ 361). Bentley also teaches that “typical” molecular weight ranges from 200 to 100,000 Da, which, according to Petitioner, “is nearly identical to the claimed range.” *Id.* (citing Ex. 1015, 6:30–38). Thus, according to Petitioner, the combination of Bentley and Harris renders claim 1 obvious. *Id.*

Patent Owner does not dispute the prior art’s teachings as Petitioner alleges. After reviewing the record, we agree with Petitioner that the combination of Harris and Bentley teaches each limitation of claim 1.

Patent Owner contends that Petitioner has not shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have had (1) a reason to select the dendritic polymer of Bentley for further development, (2) a reason to combine the teachings of Harris and Bentley to modify Bentley’s dendritic polymer to include a maleimide at the Y position, and (3) a reasonable expectation of success of achieving the claimed invention. PO Resp. 34–45. We do not need to address the first argument, because we agree with Patent Owner on the latter two issues. Petitioner’s failure to demonstrate a reason to combine the relevant teachings and a reasonable expectation of success is fatal to this challenge.

i. Reason to Modify the Dendritic Polymer

Patent Owner argues that Petitioner has not shown that an ordinarily skilled artisan would have been motivated to modify Bentley's polymer to include a maleimide based on Harris's teaching. PO Resp. 39–43. We agree.

Petitioner argues that “[a] POSA would be motivated to combine Bentley and Harris because both references are in the same field of endeavor, namely the preparation of branched PEG polymers for conjugation to biologically active molecules, and a POSA *might* want to prepare an alternative branched PEG polymers for their particular application.” Pet. 47–48 (emphasis added); Ex. 1084 ¶ 349 (the same). The fact that Harris and Bentley are in the same field of endeavor, by itself, does not explain why an ordinarily skilled artisan would have combined the teachings. And that an ordinarily skilled artisan *might* have wanted to combine the teachings does not mean he or she would have combined the teachings.

Petitioner points out that Bentley cites to Harris. Pet. 48 n.8; *see also* Ex. 1015, 7:33–43. But, as Petitioner acknowledges, “Bentley cites to the Harris application in its disclosure as a source for *background information* known in the art regarding branched PEG polymers.” Pet. 48 n.8 (emphasis added). This general reference, thus, does not supply the requisite rationale to substitute the aldehyde or aldehyde hydrate of the asserted dendritic polymer in Bentley with a maleimide, as disclosed in Harris.

As Patent Owner argues, “Bentley's reference to Harris was made in the context of Bentley's invention (i.e. the use of an activated aldehyde hydrate as a functional group)—not the other way around.” PO Resp. 43. Bentley's invention centers on “[a]n activated PEG having an aldehyde

hydrate moiety.” Ex. 1015, Abstract, 3:17–24. In the Summary of the Invention, Bentley touts “[t]he great advantage of PEG aldehyde hydrates.” *Id.* at 3:9–15. It is within this context that Bentley cites to Harris for disclosing a branched form of PEG. *See id.* at 7:33.

Patent Owner points out that Bentley provides “a method of coupling PEG or related polymers to a substance by reductive amination” by using “[a]n activated PEG having an aldehyde hydrate moiety.” PO Resp. 39–40 (citing Ex. 1015, Abstract); *see also* Ex. 1015, code 54 (“Poly(ethylene glycol) aldehyde hydrates and related polymers and applications in modifying amines.”). The rest of Bentley’s specification as well as its claims are exclusively and repeatedly directed to aldehyde hydrates and reductive amination. *See, e.g.*, Ex. 1015, 3:42–48, 4:1–9, 4:13–15, 4:20–23, 5:3–5, 5:45–47, 5:60–62, 6:1–5, 6:15–18, 7:44–46.

We agree with Patent Owner that “Petitioner has not demonstrated that a POSA would have been motivated to modify the aldehyde hydrate because eliminating this group in favor of a maleimide would render Bentley inoperable for its intended purpose of coupling through reductive amination.” PO Resp. 39. Although an ordinarily skilled artisan would have had a reason to use a maleimide “for applications where maleimide is known in the art to be useful, such as cysteine conjugation” (Reply, 17–18 (citing Ex. 1084 ¶¶ 280, 284, 383)), “Petitioner does not explain why a POSA would have started with an amine-specific functional group only to replace it with functional group with another target altogether” (PO Resp. 42).

In sum, Petitioner has not shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have had a reason to convert Bentley’s aldehyde hydrate functional group to a maleimide.

ii. Reasonable Expectation of Success

Patent Owner also argues that Petitioner has failed to demonstrate a reasonable expectation of success in modifying Bentley to achieve the claimed maleimide functional group. PO Resp. 43–45. We, again, agree.

In the Petition, Petitioner asserts that maleimide “can be easily obtained from the aldehyde hydrate or aldehyde group . . . using means conventionally known in the art.” Pet. 54 (citing Ex. 1084 ¶¶ 357–360). In the Decision to Institute, we expressed doubt over whether the cited paragraphs of the Emrick Declaration actually support Petitioner’s position. *See* Dec. 27 n.12.

First, although claim 11 of Harris claims a polymer activated as, among others, aldehyde and maleimide, it is not apparent to us why an ordinarily skilled artisan would recognize that the claim “*equates* the aldehyde hydrate . . . with a maleimide.” *See* Ex. 1084 ¶ 357 (emphasis added). Dr. Emrick does not cite any support or otherwise explain this testimony.

Second, Dr. Emrick opines maleimide “can be easily obtained from the aldehyde hydrate group . . . using means conventionally known in the art.” *Id.* ¶¶ 357–358. According to Dr. Emrick, reduction of the aldehyde group “can be carried out using a well-known reducing agent, such as lithium aluminum hydride.” *Id.* ¶ 358 (citing Ex. 1081, 1219–20). But, even if a reducing agent is well-known, it does not follow it would be successful in every reaction, and Dr. Emrick does not show how easy or how conventional it is to reduce the aldehyde group using lithium aluminum hydride.

Alternatively, Dr. Emrick testifies that “an aldehyde group can be converted to an alcohol group according to the . . . scheme disclosed in Takahashi,”¹⁸ and the resulting hydroxyl group can then be converted an amine group, which can then be converted to a maleimide. *Id.* ¶¶ 359–360 (citing Exs. 1045, 1056, 1071). As discussed above, we agree with Petitioner that converting a hydroxyl group to a maleimide is well-known in the art. *See* Section II.D.2.ii.c.; Ex. 1071, 2419–22. It is, however, unclear how easy or conventional the “scheme disclosed in Takahashi” is.

Takahashi is an *untranslated* foreign document. Ex. 1056. Dr. Emrick plucks a chemical reaction from this document to support his opinion that an aldehyde group can be converted to an alcohol group. *Id.* ¶ 359 (citing Ex. 1056, 44). But without understanding how Takahashi describes this reaction, we cannot credit Dr. Emrick’s testimony on this issue. For all we know, Takahashi might be warning an ordinarily skilled artisan how difficult this reaction is. After all, we note Takahashi appears to be a 1975 document;¹⁹ yet, Petitioner does not present any other evidence from the last 46 years to show a similar reaction.

Even though we specifically expressed our doubt over the support for the issue of reasonable expectation of success (Dec. 27 n.12), neither Petitioner nor Dr. Emrick addresses our concern during trial. To the contrary, each gives the issue short shrift, touching on the topic in a short

¹⁸ Takahashi et al., *Structural Effects on the Properties of Nonionic Surfactants VI: Synthesis and Some Properties of Di-nhexyl- and Tri-n-butyl-carbinyl Polyoxyethylene Glycol Ethers*, 24 YUKAGAKU 43–49 (1975) (Ex. 1056).

¹⁹ We cannot discern the source of Takahashi on its face. Petitioner describes it as “Yukagaku.” Paper 56, 7. We do the same above in footnote 18.

paragraph with conclusory statements. Reply 18 (“As noted above with Harris, a POSA would have a reasonable expectation of success in substituting known functional groups using means conventionally known in the art. Dr. Emrick provided exemplar pathways.”); Ex. 1095 ¶ 172 (“A POSA would expect success in converting the Bentley ‘237 polymers to maleimide polymers because to do so uses methods commonly known in the art.”). Dr. Emrick also points out that the challenged patent “provides no greater teaching with respect to maleimide selection or activation, instead incorporating the same prior art reference I have relied upon to show maleimide synthesis.” Ex. 1095 ¶ 172.

Petitioner misunderstands the issue. For this ground of challenge, Petitioner directs us to start with the asserted polymer of Bentley, and then convert the aldehyde hydrate to a maleimide. This is a different reaction from the one in the ground based on Harris alone, where an ordinarily skilled artisan would have started with the asserted polymers of Harris, and convert the hydroxyl group to a maleimide. The latter is well-known; the former, Petitioner has not shown it is. Indeed, Petitioner has not demonstrated an alcohol group “can be easily obtained from the aldehyde hydrate group . . . using means conventionally known in the art.” Ex. 1084 ¶ 357. With this missing link, we are not persuaded that an ordinarily skilled artisan would have had a reasonable expectation of success in modifying the asserted polymer of Bentley.

iii. Conclusion

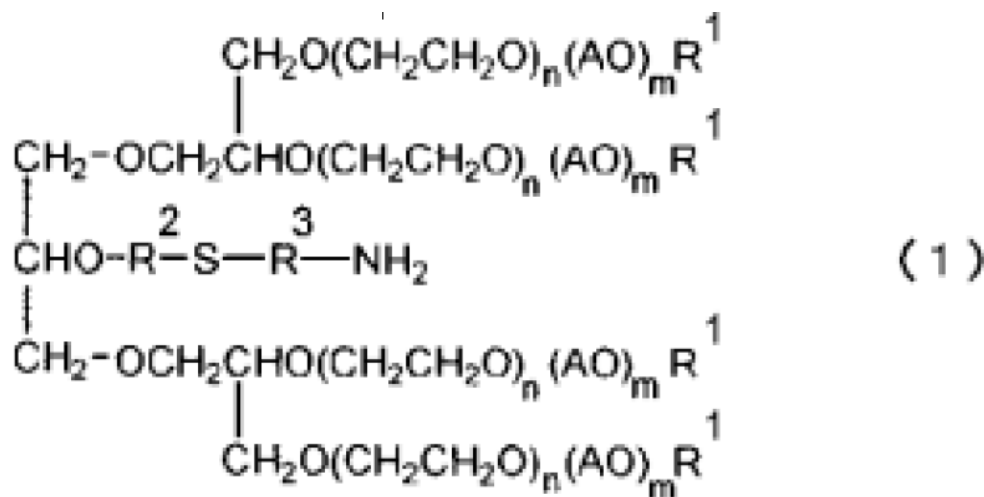
After reviewing the record, we determine that Petitioner has not demonstrated by a preponderance of the evidence that an ordinarily skilled artisan would have had a reason to combine the teachings of Bentley and

Harris, or would have had a reasonable expectation of success when doing so. Thus, Petitioner has not shown by a preponderance of the evidence that Harris and Bentley render claims 1–8, 10, and 11 obvious.

F. Obviousness of Claims 1–7, 10, and 11 over JP-674 and Harris

1. JP-674

JP-674 teaches “a polyoxyalkylene compound containing an amino group, that minimizes toxicity and produced few byproducts in liposomes and fat emulsions used for modifying phospholipids, for the purpose of not only reducing and stabilizing the antigenicity of the compound or drug, but also to extend the retention time in the body.” Ex. 1034, Abstract. The compound of JP-674 is represented by formula (1), reproduced below:



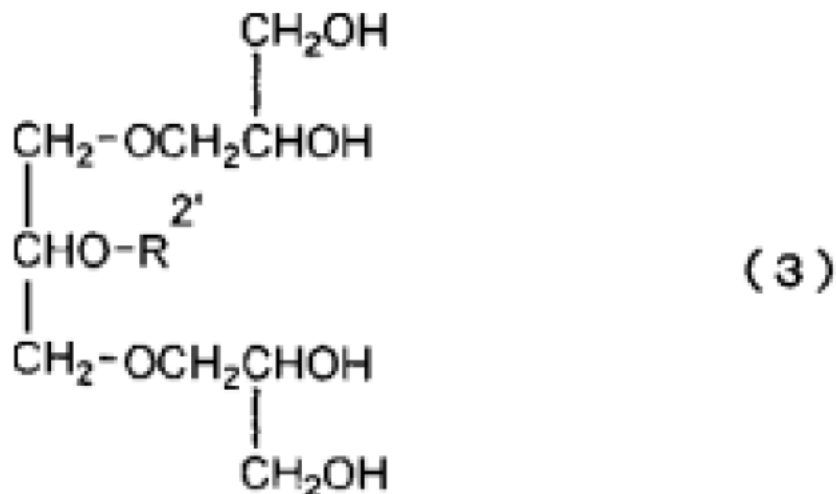
Formula (1) illustrates the general structure of the polyoxyalkylene compounds of JP-674. *Id.* ¶ 6. In formula (1),

R¹ represents a hydrogen atom, a hydrocarbon group with 1 to 24 carbon atoms or an acyl group with 1 to 24 carbon atoms; R² represents a hydrocarbon group with 3 or 4 carbon atoms, R³ represents a hydrocarbon group with 1 to 10 carbon atoms; AO represents an oxyalkylene group with 3 or 4 carbon atoms; n represents the average number of added moles of oxyethylene and is 1 to 1000; m represents the average number of moles of added moles of oxyalkylene with 3 or 4 carbon atoms and is 0-

250; $n/(n+m)$ is 0.8 or higher; where the addition state of the oxyethylene group and the oxyalkylene group having 3 or 4 carbon atoms can be either block or random.

Id. ¶ 7.

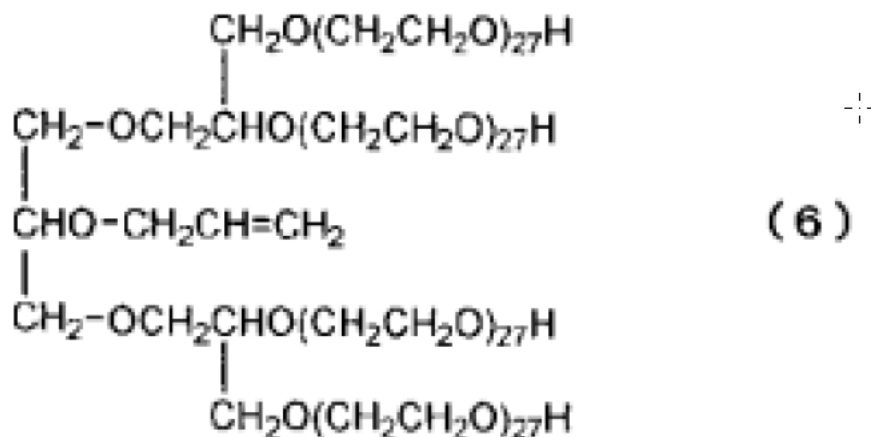
JP-674 teaches how to make the compound of formula (1). *Id.* ¶¶ 14–24. Specifically, it teaches a compound represented by formula (3):



Formula (4) depicts the chemical structure of the compound used as the starting material for the compound of formula (1). *Id.* ¶¶ 14, 15. JP-674 explains that “ $\text{R}^{2'}$ ” represents a hydrocarbon group having a polymeric unsaturated group, preferably an alkyl group having a double bond and having 3 or 4 carbon atoms such as and an allyl group, methallyl group, or the like.” *Id.* ¶ 16.

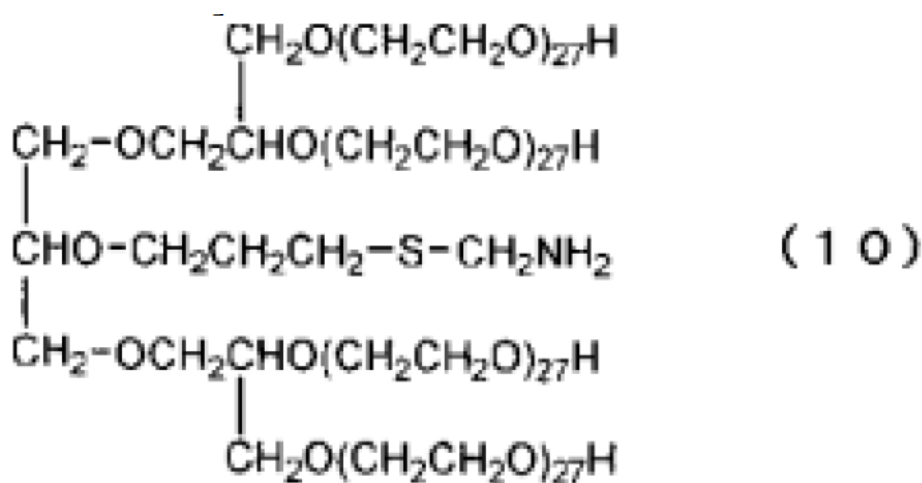
According to JP-674, first, ethylene oxide alone or ethylene oxide and an alkylene oxide having 3 or 4 carbon atoms are added to the compound of formula (3). *Id.* ¶¶ 14, 16, 17. Next, if necessary, a hydrocarbon group is introduced to the terminal hydroxyl groups by alkylation or acylation. *Id.* ¶ 19. Then, an amino group is introduced by adding the compound expressed by formula (5) $\text{HS}-\text{R}^3-\text{NH}_2 \cdot \text{HCl}$ to complete the reaction. *Id.* ¶ 21. R^3 represents a hydrocarbon group with 1 to 10 carbon atoms. *Id.* ¶¶ 7, 21.

In Manufacturing example 1, JP-674 describes obtaining a compound of formula (6):



Formula (6) illustrates the compound obtained by polymerizing ethylene oxide onto triglyceryl monoallyl ether. *Id.* ¶¶ 26, 27.

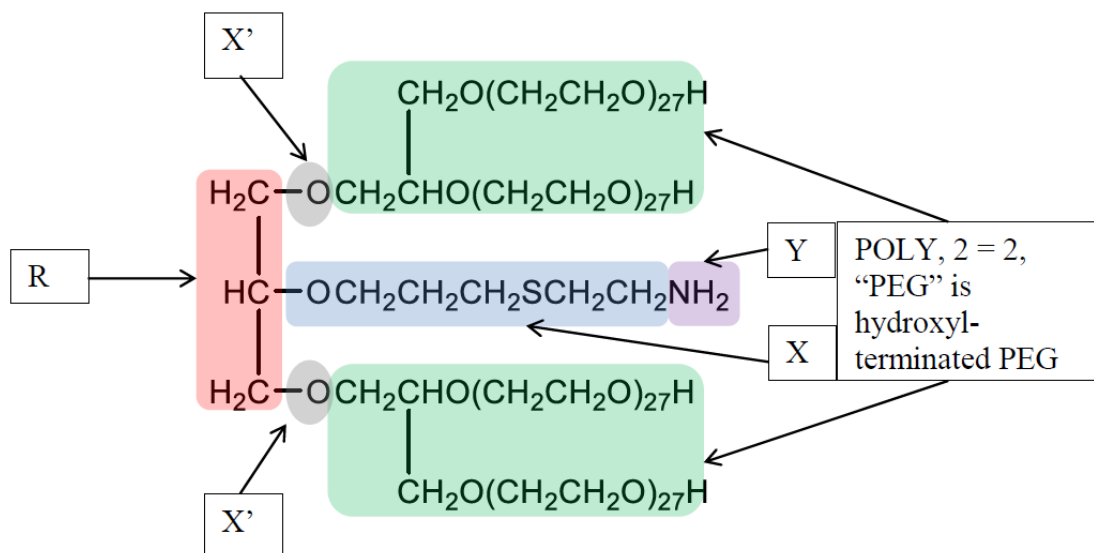
In Example 2, JP-674 teaches adding aminomethanethiol ($\text{HSCH}_2\text{NH}_2 \cdot \text{HCl}$) as compound of formula (5) to compound of formula (6). *Id.* ¶ 34. The resulting compound is depicted in formula (10):



Formula (6) illustrates the compound obtained from Example 2 in JP-674. *Id.* ¶ 35.

2. Discussion

Petitioner maps JP-674's formula (6) compound above as:



The figure above shows Petitioner's depiction of the chemical structure of JP-674's formula (6), as annotated by Dr. Emrick to show how the structure compares to that of the polymer recited in claim 1. Pet. 66–67 (citing Ex. 1084 ¶ 386).

According to Petitioner, the branched polymer of JP-674's formula (6) “meets the structural limitations of claim 1, except the amine functional group is replaced with a maleimide in claim 1.” Pet. 67. Petitioner then relies on Harris for teaching the maleimide group. *Id.* at 67–68.

Petitioner asserts that an ordinarily skilled artisan would have been motivated to combine JP-674 and Harris because they are “in the same field of endeavor, namely the preparation of branched PEG polymers for conjugation to biologically active molecules.” Pet. 65–66; Reply 18. Being in the same field of endeavor may suggest that an ordinarily skilled artisan would have considered the teachings of both references. It, however, does not explain why the artisan would have ultimately modified those teachings

in the manner proposed by Petitioner. Thus, Petitioner has not shown by a preponderance of the evidence that JP-674 and Harris render claims 1–7, 10, and 11 obvious.

G. Obviousness of Claim 9 over Harris, Choi, and Other References

1. Choi

Choi relates to star-shaped PEGs bearing heterofunctional end groups and methods of making them. Ex. 1032, Abstract. According to Choi, these polymers can be used for conjugation with proteins. *Id.*

Choi's polymers are represented by the formula $[X-(CH_2CH_2O)_m]_a-Z-[(CH_2CH_2O)_n-OH]_b$, "wherein X is amine, carboxyl, aldehyde, thiol, halogen, or epoxide; Z represents amide, carbamate, or ester bonds; m and n are integers ranging from about 10 to 2,000; a is an integer from about 1 to 5; and b is an integer from about 1 to 100." *Id.* at 4:25–28.

Choi describes "the preparation of a 3-arm star-shaped PEG having a carboxyl group at an end," in which 2-amino-1,3-propanediol is used as the core structure. *Id.* at 9:25–26, 10:1–26.

2. Discussion

Claim 9 depends from claim 1, and further specifies that p is 0. Ex. 1005, 24:51–52. According to Petitioner, claim 9 is directed to "a branched reactive polymer wherein there is no linker between the maleimide and the aliphatic hydrocarbon core structure." Pet. 42.

Petitioner argues that claim 9 would have been obvious over Harris in view of Choi (*id.* at 44), Bentley, Harris, and Choi (*id.* at 61–62), or JP-674, Harris, and Choi (*id.* at 72–73). Petitioner asserts that an ordinarily skilled artisan would have selected 2-amino-1,3-propanediol disclosed in Choi as "a

starting core structure” for preparing branched PEG polymers of Harris, Bentley, or JP-674. *Id.* at 44, 62, 73.

Petitioner argues that “[a] POSA would be motivated to combine Harris and Choi because both references are in the same field of endeavor, namely the preparation of branched PEG polymers for conjugation to biologically active molecules.” Pet. 43, *see also id.* at 61 (the same for combining Bentley, Harris, and Choi), 72 (the same for combining JP-674, Harris, and Choi). We are not persuaded.

The fact that Harris, Bentley, JP-674, and Choi are in the same field of endeavor, by itself, does not explain why an ordinarily skilled artisan would have selected 2-amino-1,3-propanediol disclosed in Choi as a starting core structure. And Petitioner has not explained how the proposed core structure relates to the branched PEG polymers of Harris, Bentley, or JP-674. That was our view at the institution stage (*see* Dec. 33); it remains our position now.

In the Decision to Institute, we also stated:

Harris, as Petitioner points out, teaches that “[l]arge spacer arms between the coupled polymer and protein are avoided to avoid introducing possible antigenic sites.” [Pet.] 43 (citing Ex. 1016, 10:64–66); *see also* Ex. 1016, 7:63–64 (“Large linker fragments can be avoided so as to avoid an antigenic response in living organisms.”). Thus, Petitioner argues, an ordinary artisan “would find it obvious to prepare an alternative branched PEG polymer having no linker to avoid possible antigenicity or toxicity sites in the polymer.” Pet. 43 (citing Ex. 1083 ¶ 341). We find this argument reasonable. Indeed, a 1997–1998 catalog from Shearwater Polymers, Inc. states that its “PEG maleimide has no linker segment between the PEG chain and the maleimide ring that could act as an antigenic or toxic site.” *Id.* at 43 n.7 (quoting Ex. 1037, 33). During trial, the parties may discuss whether Harris alone renders claim 9 obvious, and whether the teachings

of the other references would negate that obviousness determination.

Dec. 33–34.

Patent Owner argues that “Petitioner does not contend that ‘Harris alone’ renders claim 9 obvious,” and “[t]he Board does not have discretion to institute review based on a ground of challenge not advanced in the Petition.” PO Resp. 47–48 (citing *Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1335 (Fed. Cir. 2020)). We agree with Patent Owner.

In all three grounds, Petitioner argues 2-amino-1,3-propandiol disclosed in Choi is the starting material. Pet. 44, 62, 73. This is different from a challenge based on, for example, the teachings from Harris,²⁰ as suggested in the Decision to Institute (*see* Dec. 33–34), with Choi merely supplying further evidence to confirm the obviousness of claim 9. Because it is “the petitioner’s contentions, not the Director’s discretion, [that] define the scope of the litigation all the way from institution through to conclusion,” we cannot instead consider the obviousness of claim 9 based on Harris alone for these three grounds. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355 (2018).

In sum, Petitioner has not sufficiently shown that an ordinarily skilled artisan would have had a reason to start with Choi, and combine its teachings with those of Harris, Bentley, or JP-674 to arrive at the subject matter of claim 9. Thus, Petitioner has not demonstrated, by a preponderance of the evidence, that claim 9 would have been obvious as asserted.

²⁰ We observe that when annotating the structure of the amine-linked branched polymer of Harris, Petitioner notes that “p=0.” Pet. 30 (citing Ex. 1084 ¶ 316).

H. Obviousness of Claim 12 over Harris and Dalborg

1. Dalborg

Dalborg teaches conjugates of a polypeptide and a biocompatible polymer, and use of the conjugates as medicaments. Ex. 1033, 1:10–12. According to Dalborg, “[t]he invention is particularly advantageous for conjugates where the polypeptide is factor VIII with a high specific activity using mono-methoxy polyalkyleneoxide (mPEG) as the biocompatible polymer.” *Id.* at 1:12–15.

2. Discussion

Claim 10 and its dependent claim 12 are reproduced below:

10. A biologically active conjugate, comprising a biologically active molecule covalently attached to a branched reactive polymer of claim 1, wherein the biologically active molecule is a biologically active protein.

12. The biologically active conjugate of claim 10, wherein the biologically active protein is a biologically active fragment of Factor VIII.

Petitioner challenges claim 12 as obvious over the combination of Harris and Dalborg. Pet. 45–46. Petitioner refers to Dalborg for teaching that “[t]he biocompatible polymer must be activated prior to the coupling reaction, to make possible the formation of covalent bonds.” *Id.* at 45 (quoting Ex. 1033, 10:29–30). Dalborg states “[t]here are several ways of activating the biocompatible polymer depending on the amino acid selected for covalent binding.” *Id.* at 46 (quoting Ex. 1033, 11:2–3). Dalborg specifies that cysteine residues can be conjugated with mPEG maleimide. *Id.* (citing Ex. 1033, 11:14).

According to Petitioner, Harris teaches that “maleimide can be used as the reactive functional group on the branched PEG polymer for conjugation

to a protein.” *Id.* (citing Ex. 1016, 23:44–55, 29:23–42; 39:54–57). Harris also teaches that “there are thousands of proteins and enzymes that can be usefully modified by attachment to the polymer derivatives” of Harris. *Id.* (quoting Ex. 1016, 36:27–29). Petitioner argues that it would have been obvious for an ordinarily skilled artisan to select a Factor VIII fragment as the protein for conjugation. *Id.* (citing Ex. 1084 ¶ 347). In other words, an ordinarily skilled artisan would have had a reason to “combine the disclosures of Harris (branched reactive PEG activated as a maleimide) and Dalborg (Factor VIII fragments and PEG-maleimide) to prepare an alternative branched polymer having an alternative protein, i.e. a biologically active fragment of Factor VIII.” *Id.*; *see also id.* at 74 (arguing that an ordinarily skilled artisan would “want to prepare alternative branched PEG polymers for their particular application, particularly in view of Harris’ teaching that branched polymers provide benefits”) (citing Ex. 1016, 7:33–64; 7:50–65; 11:2–4, 33:18–22, 34:52–56, 35:11–23, 35:54–57).

Patent Owner repeats its arguments as presented in responding to the ground based on Harris alone. PO Resp. 50. For the same reasons as explained above, we reject those arguments. *See* Section II.D.2.ii.

Patent Owner also argues that “nothing in Harris itself that would have suggested conjugating any polymer to Factor VIII.” PO Resp. 50. “[N]on-obviousness cannot be established by attacking references individually where the [challenge] is based upon the teachings of a combination of references.” *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). Here, Petitioner relies on Dalborg for teaching conjugating Factor VIII with mPEG. Pet. 45–46 (citing Ex. 1033, 1:10–15, 9:10–26, 10:13–26, 10:29–11:3, 11:14–18, 15:3–15).

Harris teaches that many proteins can be conjugated to the branched polymer of Harris. Ex. 1016, 36:27–29. Dalborg teaches that Factor VIII is an important protein. Ex. 1033, 4:6–19. According to Dalborg, “[t]he B-domain of factor VIII seems to be dispensable as regards the factor VIII cofactor function while the A and C domains have several interaction sites for other macromolecules playing a role in the hemostasis.” *Id.* at 4:17–19.

Dalborg also teaches that “factor VIII is a protein with several interaction sites, each responsible for a specific function. Therefore, it is difficult to modify factor VIII with fully retained biological function.” *Id.* at 5:17–19. Given that the branched polymer of Harris can be used for “protein modification with a high retention of protein activity” (Ex. 1016, 7:50–53), an ordinarily skilled artisan would have had a reason to combine the teachings of Harris (branched PEG polymer) and Dalborg (biologically active fragment of factor VIII). The fact that many other proteins may be similarly conjugated with the branched PEG polymer of Harris, or that factor VIII may be conjugated with other polymers, does not negate the obviousness of conjugating factor VIII with mPEG maleimide. *See Merck*, 874 F.2d at 807 (stating that a prior art’s disclosure of “a multitude of effective combinations does not render any particular formulation less obvious”).

In sum, Petitioner has demonstrated, by a preponderance of the evidence, that claim 12 would have been obvious over the combination of Harris and Dalborg.²¹

²¹ Petitioner also argues that claim 12 would have been obvious over the combined teachings of Bentley, Harris, and Dalborg (Pet. 62–64), or JP-674, Harris, and Dalborg (*id.* at 74–76). Having determined that Petitioner has

III. CONSTITUTIONAL CHALLENGE

Patent Owner contends subjecting the '569 patent to *inter partes* review violates its constitutional rights. PO Resp. 56–60. Patent Owner's arguments on this issue are foreclosed by the decisions in *Celgene Corp. v. Peter*, 931 F.3d 1342, 1362–63 (Fed. Cir. 2019) and *United States v. Arthrex, Inc.*, 141 S. Ct. 1970, 1986–87, 1997 (2021). As such, we do not further consider or address Patent Owner's arguments.

IV. CONCLUSION²²

After reviewing the entire record and weighing evidence offered by both parties, we determine that (1) Petitioner has demonstrated by a preponderance of the evidence that claims 1–3, 5, 7, 8, 10, and 11 of the '569 patent would have been obvious over Harris, and claim 12 would have

shown claim 12 would have been obvious over Harris and Dalborg, we do not address the other two challenges of claim 12. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding a petitioner “is entitled to a final written decision addressing all of the claims it has challenged”); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App'x 984, 990 (Fed. Cir. 2020) (recognizing that the “Board need not address issues that are not necessary to the resolution of the proceeding” and, thus, agreeing that the Board has “discretion to decline to decide additional instituted grounds once the petitioner has prevailed on all its challenged claims”).

²² Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

been obvious over Harris in view of Dalborg; and (2) Petitioner has not shown that claims 4, 6, and 9 would have been obvious under any of the grounds challenging these claims.

In summary:

Claims	35 U.S.C. §	Reference(s)/ Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–3, 5, 7, 8, 10, 11	103	Harris	1–3, 5, 7, 8, 10, 11	
1–8, 10, 11	103	Harris, Bentley		1–8, 10, 11
9	103	Harris, Choi		9
12	103	Harris, Dalborg	12	
9	103	Bentley, Harris, Choi		9
12	103	Bentley, Harris, Dalborg		
1–7, 10, 11	103	JP-674, Harris		1–7, 10, 11
9	103	JP-674, Harris, Choi		9
12	103	JP-674, Harris, Dalborg		
Overall Outcome			1–3, 5, 7, 8, 10–12	4, 6, 9

V. ORDER

Accordingly, it is

ORDERED that claims 1–3, 5, 7, 8, and 10–12 of the '569 patent are held unpatentable;

FURTHER ORDERED that Petitioner has not demonstrated by a preponderance of the evidence that claims 4, 6, and 9 are unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2019-01397
Patent 9,187,569 B2

PETITIONER:

Thomas Donovan
Mark Hagedorn
Vincent Liptak
BARNES & THORNBURG LLP
thomas.donovan@btlaw.com
mhagedorn@btlaw.com
vincent.liptak@btlaw.com

PATENT OWNER:

Edgar Haug
Brian Murphy
Angus Chen
Andrew Wasson
Kaitlin Abrams
Erika V. Selli
Andrew Roper
HAUG PARTNERS LLP
ehaug@haugpartners.com
bmurphy@haughpartners.com
achen@haugpartners.com
awasson@haughpartners.com
kabrams@haughpartners.com
eselli@haugpartners.com
aroper@haugpartners.com