

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOF CORPORATION,
Petitioner,

v.

NEKTAR THERAPEUTICS,
Patent Owner.

IPR2019-01394
Patent 7,026,440 B2

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

TORNQUIST, *Administrative Patent Judge*.

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

I. INTRODUCTION

A. Background

NOF Corporation (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting an *inter partes* review of claims 1–20 and 29–35 of U.S. Patent No. 7,026,440 B2 (Ex. 1001, “the ’440 patent”). Nektar Therapeutics (“Patent Owner”) filed a Preliminary Response to the Petition. Upon review of the parties’ arguments and supporting evidence, on February 5, 2020, we instituted an *inter partes* review of all claims and grounds asserted in the Petition (Paper 22, “Institution Decision” or “Inst. Dec.”).

Patent Owner subsequently filed a Response (Paper 49, “PO Resp.”), Petitioner filed a Reply (Paper 53, “Pet. Reply”), and Patent Owner filed a Sur-Reply (Paper 57, “Sur-Reply”).

In support of its Petition, Petitioner originally relied upon the declaration testimony of Dr. Yuji Yamamoto. Ex. 1083. In light of scheduling difficulties caused by COVID-19, however, we authorized Petitioner to replace Dr. Yamamoto’s declaration with that of Dr. Todd Emrick (Ex. 1084¹), who also filed a reply declaration (Ex. 1095).

Patent Owner relies on the declaration testimony of Dr. Steven R. Little. Ex. 2036.

With authorization, Petitioner filed a motion requesting a good cause extension of the deadline for issuing a final written decision in this proceeding. Paper 39. Patent Owner opposed this motion. Paper 41. On July 31, 2020, a revised Due Date Appendix was issued and on January 29,

¹ In view of the replacement of Dr. Yamamoto’s 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.

2021, the time to administer the present proceeding was extended by up to six months, i.e., from February 5, 2021, up to August 5, 2021. Paper 48 (Revised Due Date Appendix); Paper 62, 2–3 (good cause extension granted by the Chief Administrative Patent Judge); Paper 63, 2–3 (Panel Order extending the current proceeding by up to six months).

An oral hearing was held on February 8, 2021, and a transcript of the hearing is included in the record. Paper 67 (“Tr.”).

B. Related Proceedings

Petitioner identifies *Nektar Therapeutics et al. v. Bayer Healthcare, LLC*, 1-18-cv-01355 (D. Del. August 31, 2018) as a related matter. Pet. 2. Patent Owner identifies *Baxalta Incorporated v. Bayer Healthcare LLC*, No. 17-1316 (D. Del.) (consolidated) as a related matter. Paper 6, 1.

Institution was granted with respect to related patents in IPR2019-01397 and IPR2019-01398 and denied with respect to related patents in IPR2019-01392, IPR2019-01395, and IPR2019-01396. Pet. 2; Paper 6, 1–2; IPR2019-01392, Paper 23; IPR2019-01395, Paper 27; IPR2019-01396, Paper 19.

C. The '440 Patent

The '440 patent discloses “branched, reactive water soluble polymers useful for conjugating to biologically active molecules” and “methods for making and utilizing such polymers.” Ex. 1001, 1:15–18. The '440 patent explains that it was known in the art that covalent attachment of hydrophilic polymer poly(ethylene glycol), or PEG, may increase water solubility and bioavailability of biologically active molecules, particularly hydrophobic molecules. *Id.* at 1:22–30 (citing Greenwald, et al., *J. Org. Chem.*, 60:331–336 (1995)). The total molecular weight of the attached polymers is chosen to provide the advantageous characteristics typically associated with PEG

polymer attachment, while at the same time avoiding “adversely impacting the bioactivity of the parent molecule.” *Id.* at 1:30–35.

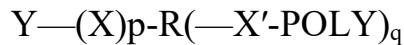
The ’440 patent discloses that methods for forming branched polymers attached to a central core and having a single reactive group for conjugation to a biologically active molecule were known in the art. *Id.* at 1:55–1:62. The ’440 patent states, however, that these known methods required “extensive purification of the PEG polymers prior to attachment to the core molecule” and removal of “partially pegylated polymer intermediates.” *Id.* at 1:62–2:3. Thus, according to the ’440 patent, there remained a need in the art for 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 2:4–9.

The ’440 patent instructs that the “branched reactive polymer of the invention will typically comprise at least two water-soluble and non-peptidic polymer arms, such as poly(ethylene glycol) arms, covalently attached to an aliphatic hydrocarbon core structure bearing a single functional group.” *Id.* at 7:18–22. “Typically, the total number average molecular weight of the branched reactive polymers of the invention will be about 500 to about 100,000 daltons (Da), preferably about 5,000 to about 60,000 Da, most preferably about 8,000 to about 40,000 Da.” *Id.* at 7:4–8. “Unless otherwise noted” in the ’440 patent, molecular weight is expressed “as number average molecular weight (M_n), which is defined $\frac{\sum N_i M_i}{\sum N_i}$, wherein N_i is the number of polymer molecules (or the number of moles of those molecules) having molecular weight M_i .” *Id.* at 4:51–63.

D. 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 water soluble and non-peptide polymer, wherein the molecular weight of each POLY is selected such that the total molecular weight or² the branched reactive polymer is independently selected from the group consisting of poly(alkylene glycol), poly(oxyethylated polyol), poly(olefinic alcohol), poly(vinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), polysaccharides, poly(α -hydroxy acid), poly(vinyl alcohol), polyphosphazene, polyoxazoline, poly(N-acryloylmorpholine), and copolymers, terpolymers, and mixtures thereof is at least about 5,000 Da;

X' is a heteroatom linkage;

X is a linker;

p is 0 or 1; q is 2 to about 10; and

² Although the claim uses the word “or,” this appears to be a typographical error and both parties asserts that the relevant claim language requires a branched reactive polymer with a “a total molecular weight of at least about 5,000 Da.” PO Resp. 3 (“However, Petitioner did not establish that the cited polymers had a total molecular weight of at least about 5,000 Da”), 47–48; Pet. 13, 19, 58; Ex. 2036 ¶ 383 (Little Declaration); *see Fitbit, Inc. v. Valencell, Inc.*, 964 F.3d 1112, 1119–20 (Fed. Cir. 2020) (holding the Board erred in not correcting a “conspicuous” and undisputed claim error related to antecedent basis).

Y is a functional group reactive with an electrophilic or nucleophilic group.

Ex. 1001, 24:7–30.

E. Prior Art and Instituted Grounds of Unpatentability

We instituted review of claims 1–20 and 29–35 of the '440 patent on the following grounds:

Claims Challenged	35 U.S.C. § ³	Reference(s)/Basis
1–16, 19, 20, 29–35	103(a)	Bentley ⁴
16–18, 30	103(a)	Bentley, Liebigs ⁵
1–3, 5, 7–10, 12–16, 20, 29–35	103(a)	Harris ⁶
29, 31	102(b)	Harris
1–15, 17, 19, 20, 29, 31–33, 35	102(b)	JP-542 ⁷
1–15, 17, 19, 20, 29, 31–35	103(a)	JP-542, MDD ⁸
16–18, 30	103(a)	JP-542, Bentley

II. ANALYSIS

A. Claim Construction

In this proceeding, the claims of the '440 patent are 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).” 37 C.F.R. § 42.100(b)

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 effective filing date of the challenged claims of the '440 patent is before this date, the pre-AIA version of these statutes apply. *See* 35 U.S.C. § 100(i)(2) (2018); Ex. 1001, code (22).

⁴ US 5,990,237, issued November 23, 1999 (Ex. 1015).

⁵ Edwin Weber, *Neutral ligands with surfactant structure – Synthesis, Complexation, Ion Transfer*, Liebigs Ann. Chem., 770–801, 1983 (Ex. 1019, English translation; Ex. 1020, original German language publication).

⁶ US 5,932,462, issued August 3, 1999 (Ex. 1016).

⁷ Sanchika et al., JP P2000-1542A, published January 7, 2000 (Ex. 1017).

⁸ Steven A. Charles, et al., *Improving Hepatitis C Therapy*, Modern Drug Discovery, September 2000 (Ex. 1029).

(2019). Under that standard, the words of a claim are generally given their “ordinary and customary meaning,” which is the meaning the term would have had to a person of ordinary skill at the time of the invention, in the context of the entire patent including the specification. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). The parties dispute the meaning of the term “functional group,” whether claim 1 requires a “functional group” that reacts readily with an electrophilic or nucleophilic group, and the correct method for determining the “total molecular weight of the branched reactive polymer.” We address these issues below.

1. “functional group”

Claim 1 requires that “Y is a functional group reactive with an electrophilic or nucleophilic group.” Ex. 1001, 24:29–30. Petitioner contends that the term “functional group” in claim 1 means “the portions of molecules that perform some function or activity and are reactive with other molecules, including protected functional groups.” Pet. 11. Patent Owner contends that “functional group” means “a distinct, definable portion or unit of a molecule that performs a function.” PO Resp. 7.

The written description of the ’440 patent explains that the terms ‘functional group,’ ‘active moiety,’ ‘reactive site,’ ‘chemically reactive group,’ and ‘chemically reactive moiety’ are used in the art and herein to refer to distinct, definable portions or units of a molecule. The terms are somewhat synonymous in the chemical arts and are used herein to indicate the portions of molecules that perform some function or activity and are reactive with other molecules.

Ex. 1001, 3:35–42.

Given the express definitions provided in the ’440 patent, we agree with Petitioner that a “functional group” is a portion of a molecule that

performs a function or activity and is reactive with other molecules, and with Patent Owner that a “functional group” is a “distinct, definable” portion of a molecule. *Id.* Accordingly, we construe the term “functional group” to mean the “distinct, definable portions of molecules that perform some function or activity and are reactive with other molecules.”⁹ We also agree with Petitioner that the term “functional group” includes “protected functional groups.” *See id.* at 3:35–42, 3:56–57 (“As used herein, the term ‘functional group’ includes protected functional groups.”); Pet. 11.

2. “*reactive . . . functional group*”

The preamble of claim 1 recites a “branched reactive polymer” and the ’440 patent instructs that “[t]he term ‘active,’ when used in conjunction with a functional group, is intended to include those functional groups that react readily with electrophilic or nucleophilic groups on other molecules.” Ex. 1001, 3:42–48, 3:56–57. Patent Owner contends that the term “reactive” in the preamble of claim 1 serves to describe the “functional group” in the body of the claim, and because the term “reactive” contains the word “active” one of ordinary skill in the art would have understood that the functional group of claim 1 must react readily with other chemical moieties. PO Resp. 10.

We are not persuaded by this argument because the ’440 patent expressly defines a “functional group” as being “reactive with other molecules.” Ex. 1001, 3:35–42 (“The terms are somewhat synonymous in

⁹ Neither party argues that defining the term “functional group” as “a portion of a molecule” or as a “distinct, definable” portion of a molecule will affect the outcome of this proceeding. Pet. 11; PO Resp. 6–11; Pet. Reply 3–4. We nevertheless provide an express construction to provide context to Patent Owner’s arguments, discussed below, that claim 1 requires a particular type of “functional group.”

the chemical arts and are used herein to indicate the portions of molecules that perform some function or activity and are reactive with other molecules.”), 10:55–59 (explaining that the Y functional group of the invention “can be any functional group suitable for reaction with a functional group on a biologically active molecule or a functional group that is a precursor thereof”); Pet. Reply 4. It is only when the term “active”—as opposed to “reactive”—is used to describe the “functional group” that it must react readily with electrophilic or nucleophilic groups on other molecules. Ex. 1001, 3:42–45. And because the term “active” is not used in claim 1 to refer to the recited “functional group,” we do not construe claim 1 to require a “functional group” that will react readily with electrophilic or nucleophilic groups.

3. *“total molecular weight of the branched reactive polymer”*

Claim 1 requires that the “total molecular weight o[f] the branched reactive polymer is . . . at least about 5,000 Da.” Ex. 1001, 24:15–24.

Molecular weight is calculated in the ’440 patent as follows:

Unless otherwise noted, molecular weight is expressed herein as number average molecular weight (M_n), which is defined “as number $\frac{\sum N_i M_i}{\sum N_i}$,”

wherein N_i is the number of polymer molecules (or the number of moles of those molecules) having molecular weight M_i .

Id. at 4:51–63.

Patent Owner contends that the ’440 patent defines molecular weight in terms of the polymeric backbone and thereby excludes the capping groups, aliphatic core, linker, heteroatom, and functional group from the calculation of molecular weight. PO Resp. 48 (citing Ex. 1001, 4:51–63).

In the Institution Decision, we found Patent Owner’s general argument persuasive in view of the formula provided in the ’440 patent and in view of the fact that Petitioner appeared to calculate molecular weight in the Bentley-based grounds using only the molecular weight of the polymer’s PEG arms. Inst. Dec. 33.

In its Reply, Petitioner contends that Patent Owner’s method of calculating total molecular weight is incorrect because all portions of the “branched reactive polymer” must be included in the calculation. Pet. Reply 22 (citing Ex. 1095 ¶¶ 229–233, 263–266). In support of Petitioner’s argument, Dr. Emrick testifies that the $\Sigma NiMi/\Sigma Ni$ formula set forth in the ’440 patent requires the inclusion of all molecules of the branched reactive polymer, which is consistent with the prosecution history of related U.S. Patent 8,808,453¹⁰ (“the ’453 patent”), in which the applicants included all portions of the branched reactive polymer in their calculation of molecular weight. Ex. 1095 ¶¶ 229–232.

When considering the meaning of a disputed claim term we look first to the intrinsic evidence of record, including the claims, written description, and, if in evidence, the prosecution history. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (“Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language.”).

a) Claims

Claim 1 recites a “branched reactive polymer having the structure: $Y-(X)_p-R-(X'-POLY)_q$,” and requires that the “total molecular weight

¹⁰ The ’453 patent is a continuing application of the ’440 patent. Ex. 1004, 4:53–63, code (60).

o[f] the *branched reactive polymer* . . . is at least about 5,000 Da.”

Ex. 1001, 24:7–24 (emphasis added). Because all of the constituents of the formula, including the linkers and the functional group, are part of the “branched reactive polymer,” claim 1 of the ’440 patent strongly suggest that all constituent parts of the branched reactive polymer are included in the calculation of total molecular weight.

b) Written Description

The written description is generally consistent with the conclusion that all constituent parts of the branched reactive polymer are used in calculating total molecular weight, explaining that the branched reactive polymers of the invention will “typically comprise at least two water-soluble and non-peptidic polymer arms, such as poly(ethylene glycol) arms, covalently attached to an aliphatic hydrocarbon core structure bearing a single functional group.” Ex. 1001, 7:18–38; *see id.* at 2:30–41.

Patent Owner’s conclusion that only the PEG arms are included in the calculation of total molecular weight is not, however, without some support in the ’440 patent. For example, the formula of the ’440 patent requires summing the number of “polymer molecules,” and the ’440 patent explains that the terms “polymer” and “polymer backbone” are used interchangeably to represent the repeating portions of, for example, the PEG arms. *Id.* at 4:40–48. The ’440 patent also discloses that the “number average molecular weight of the branched reactive polymers of the invention will be about 500 to about 100,000 daltons” and that each polymer arm “will typically have a molecular weight of about 250 Da to about 50,000 Da.” *Id.* at 7:4–10. The close alignment of these values suggests that molecular weight is primarily imparted by the polymer arms, and not by the linkers, core molecule, etc.

That said, the '440 patent goes on to instruct that the functional groups, linkers, and core molecule are part of the branched reactive *polymer* and the relevant formula requires summing the molecular weight of all polymer molecules. *Id.* at 4:49–63, 7:18–22, 10:30–33, 11:55–58. As such, the written description of the '440 patent is consistent with the conclusion that all portions of the branched reactive polymer are included in the calculation of molecular weight.

c) Prosecution History

Molecular weight calculations were discussed during prosecution of the '440 patent and the related '453 patent. During prosecution of the '440 patent, the applicants argued that a Shimomura reference did not anticipate the pending claims because “the total number of ethylene oxide groups on the adduct molecules must be between 15 and 90,” which would result in a “total polymer molecular weight” of less than about 4,000 Da. Ex. 2001, 692. Patent Owner calculates that if the non-PEG portions of Shimomura's compounds were included in the calculation, it would result in a total molecular weight of greater than 4,000 Da. PO Resp. 48 (citing Paper 8, 48–49) (Patent Owner's Preliminary Response). Upon review of this portion of the prosecution history, we agree with Patent Owner that the applicants' arguments during prosecution of the '440 patent are consistent with Patent Owner's argument that molecular weight is calculated based only on the PEG polymer chains. *Id.*

In contrast to the calculation method used during prosecution of the '440 patent, during prosecution of the '453 patent—which contains the same formula as the '440 patent for calculating molecular weight—the applicants expressly included the non-PEG portions of the compound in their calculation of molecular weight. Ex. 1011, 65 (noting that the mPEG arms

had a molecular weight of 5,000 Da (with a combined weight of 10,000 Da), and “[t]he remaining portion of the US-PEG (after coupling to erythropoietin) only contributes about ~230 Daltons to the molecular weight”); Ex. 1004, 4:53–63, code (60). This expressly supports Petitioner’s argument that all constituents of the branched reactive polymer should be considered in determining molecular weight. *See Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1349–50 (Fed. Cir. 2004) (noting that “the prosecution history of one patent is relevant to an understanding of the scope of a common term in a second patent stemming from the same parent application”).

Considering the relevant prosecution history as a whole, we find that the applicants’ arguments during prosecution support both Petitioner’s and Patent Owner’s arguments regarding how molecular weight should be calculated in the ’440 patent.

d) Conclusion

Upon consideration of the intrinsic record as a whole, we find that claim 1 of the ’440 patent strongly suggests that all the constituent parts of the “branched reactive polymer” are included in the calculation of molecular weight. We further find that this conclusion is consistent with the written description of the ’440 patent and the relevant prosecution history. Accordingly, we construe the term “total molecular weight of[f] the branched reactive polymer” in claim 1 to require inclusion of all components of the “branched reactive polymer” in the calculation of total molecular weight.

B. Principles of Law

To anticipate a claim under 35 U.S.C. § 102(b), a reference must disclose, explicitly or inherently, each and every element of the claimed

invention arranged or combined in the same way as in the claim. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009).

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. *See 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 ordinary skill in the art; and (4) if in the record, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

C. *Level of Ordinary Skill in the Art*

Petitioner contends a person of ordinary skill in the art 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. 12 (citing Ex. 1084 ¶¶ 45–48). Petitioner also contends that a person of ordinary skill in the art could alternatively have been “a highly skilled scientist having an advanced degree, but with additional years of experience working with PEGylation polymer synthesis and chemistries for modification of biomolecules in lieu of a Ph.D.” *Id.*

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 compatible 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. 11.

The parties’ definitions of the ordinarily skilled artisan are similar, requiring an advanced degree in a relevant field and several years of experience in synthesizing or applying water-soluble polymers, such as PEG, to biologic molecules. *Compare* Pet. 12, *with* PO Resp. 11. The parties’ definitions differ in that Petitioner requires experience working directly with active PEG polymers for conjugation to biological molecules, whereas Patent Owner’s definition allows for experience with the broader group of “water-soluble polymers useful for conjugation to biologically active molecules.” Pet. 12; PO Resp. 11. Upon review of the ’440 patent and the prior art of record, we adopt Patent Owner’s definition of one of ordinary skill in the art, as it is consistent with the disclosures of the ’440 patent and the prior art of record, and more inclusively describes the suitable experience for one of ordinary skill in the art. We note, however, that neither party asserts that selection between the two definitions of the level of ordinary skill in the art would impact any issue presented in this case.¹¹

D. Claims 1–15, 17, 19, 20, 29, 31–33, and 35 as Anticipated by JP-542

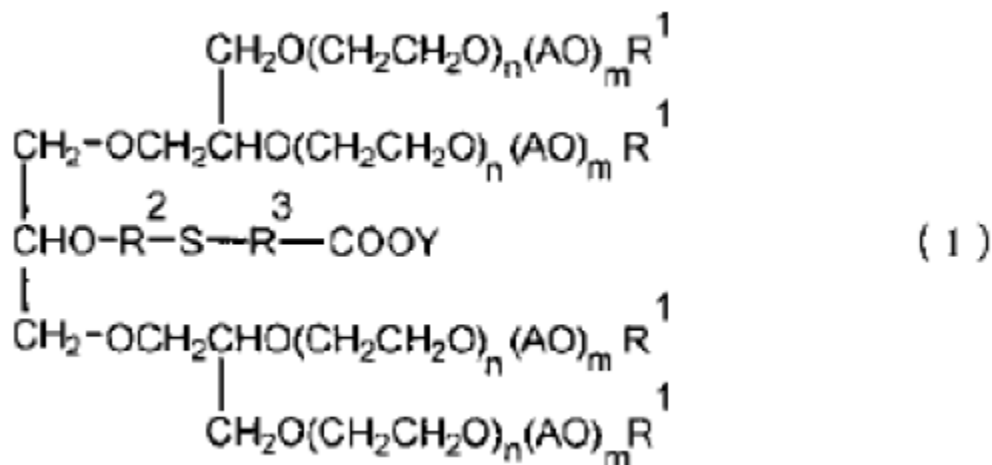
Petitioner contends that claims 1–15, 17, 19, 20, 29, 31–33, and 35 are anticipated by JP-542. Pet. 56–75.

¹¹ Petitioner argues in its Reply that Patent Owner fails to account for the general knowledge of one of ordinary skill in the art, but does not argue that this general knowledge would differ between the two proffered definitions of one of ordinary skill in the art. Pet. Reply 12–13 (citing Ex. 1084 ¶¶ 78, 208–210, 242–244).

1. JP-542

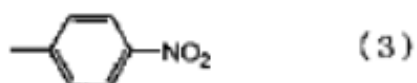
JP-542 discloses “a carboxyl-group-containing polyoxyalkylene compound that is used to modify a compound or a drug” in order to stabilize the drug, decrease its antigenicity, or prolong its residence time in the body. Ex. 1017, Abstract.

The polymer of formula (1) of JP-542 is reproduced below:



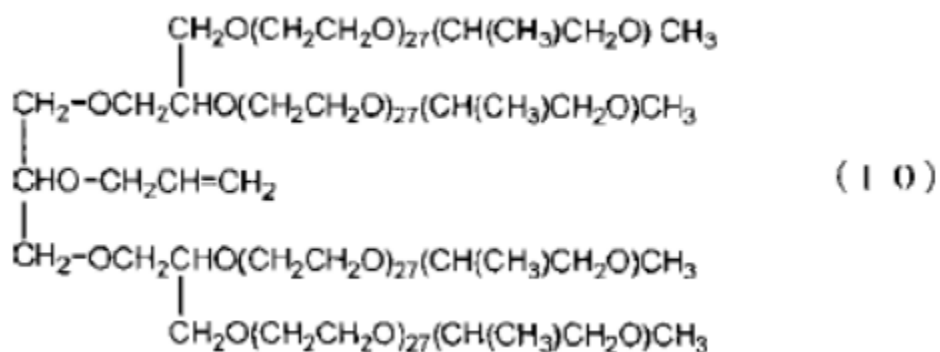
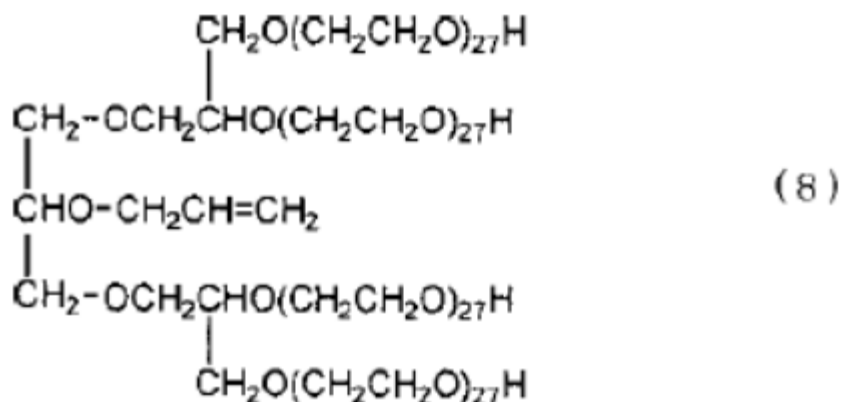
Formula (1) illustrates the general structure of the inventive polyoxyalkylene polymers of JP-542. *Id.* ¶ 6. In formula (1), R¹ is a hydrogen atom, a 1- to 24-carbon hydrocarbon group, or a 1- to 24-carbon acyl group; R² is a 3- or 4-carbon hydrocarbon group; R³ is a 1- to 10-carbon hydrocarbon group; AO is a 3- or 4-carbon oxyalkylene; Y is either a hydrogen atom or an active group illustrated by formula (2) or (3); n is 1 to 1000; m is 0 to 250; and n/(n+m) is no less than 0.8; wherein the oxyethylene and the 3 or 4 carbon oxyalkylene “may be added in blocks or randomly.” *Id.* ¶ 8.

Formulas (2) and (3) of JP-542 are reproduced below:



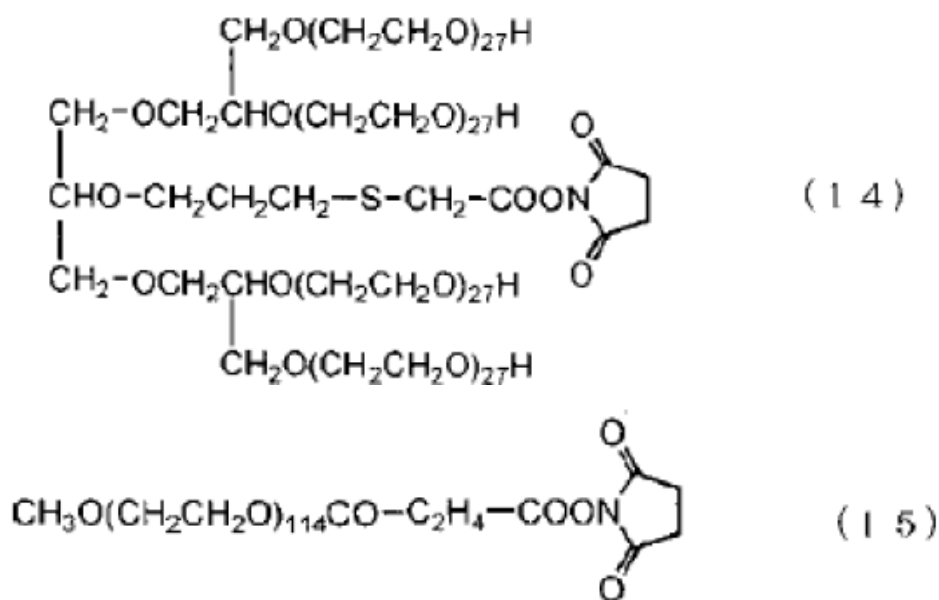
Formulas (2) and (3) represent preferred active groups for use in the compound of formula (1). *Id.* ¶ 17.

The polymers of formula (8) and (10) of JP-542 are reproduced below:



The polymers of formula (8) and (10) are intermediates used to synthesize various polymers disclosed in JP-542. *Id.* ¶¶ 33, 41, 44, 47.

JP-542 also discloses example polymer species falling within the scope of formula (1) that may be conjugated to a compound or drug, including the polymers of formula (14) and (15), which are reproduced below:



Formula (14) depicts a branched polyalkylene polymer and formula (15) depicts a linear polyalkylene polymer, both of which are conjugated to the active group illustrated in formula (2). *Id.* ¶¶ 9, 52, 56.

In Test Example 1 and Comparative Test Example 1 of JP-542, the compounds of formulas (14) and (15), respectively, were reacted with L-asparaginase. *Id.* ¶¶ 54–57. The resulting PEGlyated compounds were then tested for antigenicity and enzyme activity. *Id.* ¶¶ 57–58, Table 1. The results from these tests are reproduced below:

Table 1

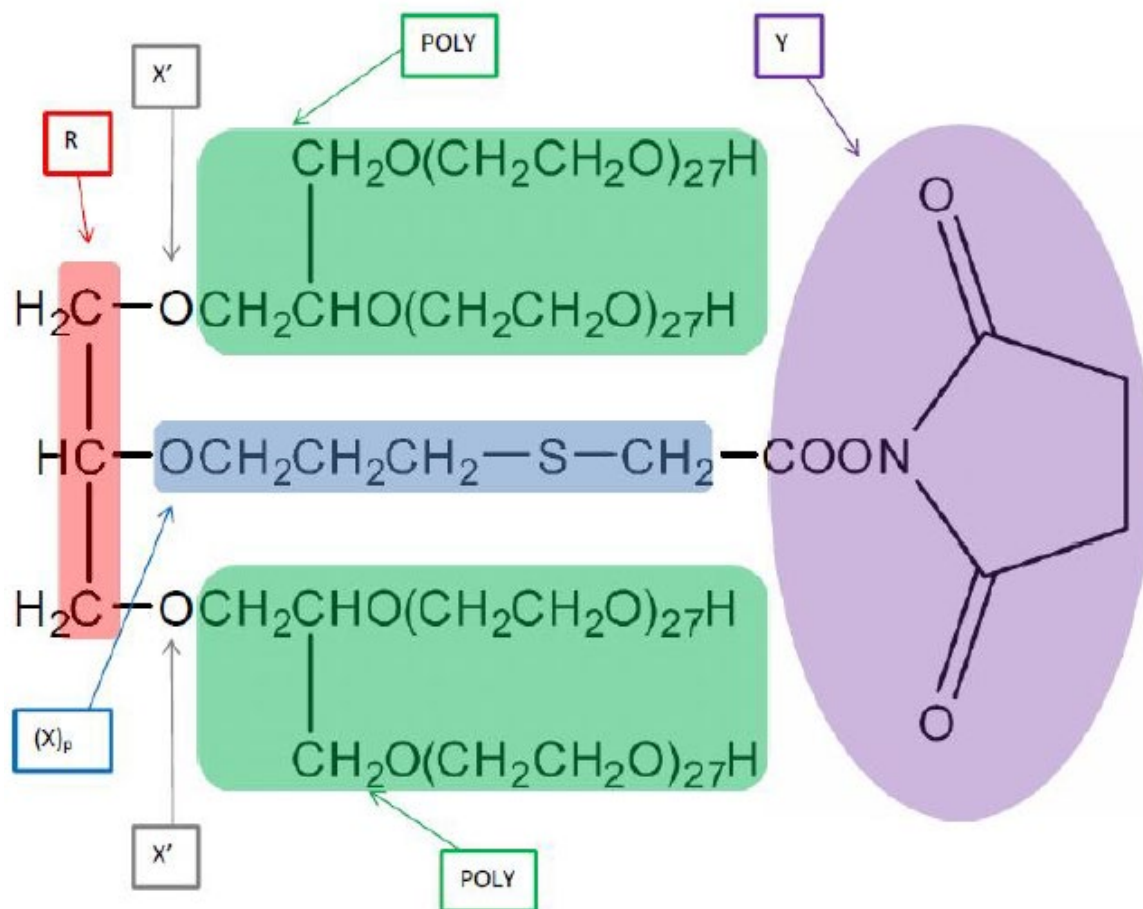
	PEG derivative (Mw)	No. of bound amino groups ^{a)}	Enzyme activity		Antibody binding capacity
			Method A	Method B	
Test example 1	5, 162	50	35	40	0
Comparative test example 1	5, 200	54	15	22	35

a) Number of amino groups bound to the compound among amino groups in asparaginase molecule (ninety-two)

Table 1 above provides the test results for Test Example 1 and Comparative Test Example 1. As shown in Table 1, the compound of Test Example 1 had zero antigenicity, yet still retained 35 to 40% of its enzyme activity. *Id.* ¶¶ 54, 58. Conversely, the compound of Comparative Test Example 1 had an antibody binding capacity of 35% (i.e., some level of antigenicity) and retained only 15 to 22% of its enzyme activity. *Id.* ¶¶ 54–58.

2. Analysis: Claim 1

Petitioner contends the polymer of formula (14) of JP-542 anticipates claim 1 of the '440 patent. Pet. 56–59. In support of this argument, Petitioner provides the following annotated version of the polymer of formula (14):



Pet. 56. In the figure set forth above, Petitioner included annotations and color coding to show its mapping of the constituents parts of the polymer of formula (14) to the limitations of claim 1. As shown in its annotated figure, Petitioner persuasively demonstrates that in the polymer of formula (14): R (red) is a three-carbon aliphatic hydrocarbon, POLY (green) consists of a branched poly(alkylene glycol) wherein q=2, X' (uncolored) constitute -O- linkages, X (blue) is an -OCH₂CH₂CH₂-S-CH₂ linker wherein p=1, and Y (purple) is an NHS "active ester" functional group. *Id.* at 56–58. With respect to molecular weight, Petitioner contends the polymer of formula (14) has a calculated molecular weight of 5,162 Da. *Id.* at 58.

Patent Owner does not expressly dispute that the polymer of formula (14) of JP-542 discloses the R, POLY, X', X, Y, p, and q limitations

of claim 1, but contends that Petitioner has not demonstrated that the 5,162 Da molecular weight reported in JP-542 was “calculated in the way required by the ’440 patent.” PO Resp. 47–49. According to Patent Owner, when only the polymer arms are considered in the calculation of molecular weight, the total molecular weight of the polymer of formula (14) is actually 4,752 Da, i.e., less than “about 5,000 Da.” *Id.* at 48–49.

As discussed in Section II.A.3, we construe claim 1 to require that all constituent parts of the “branched reactive polymer” be included in the calculation of “total molecular weight.” When this calculation method is used, Petitioner persuasively demonstrates that the total molecular weight of the polymer of formula (14) is 5,162 Da. Accordingly, Petitioner demonstrates by a preponderance of the evidence that the polymer of formula (14) discloses every limitation of claim 1 of the ’440 patent and therefore anticipates this claim.

3. *Analysis: Claims 2–8, 11–15, 17, 19, 20, 32, 33, and 35*

Petitioner persuasively identifies where every limitation of claims 2–8, 11–15, 17, 19, 20, 32, 33, and 35 is expressly or inherently disclosed by the polymers of formula (8) and/or formula (14) of JP-542. Pet. 59–70. For example, Petitioner demonstrates that in the polymer of formula (14) the X' heteroatom is an ether (–O–) (claim 2), $q = 2$ (claim 3), each POLY is symmetrically located on the aliphatic hydrocarbon (claim 4), R comprises three carbon atoms (claims 5 and 6), each POLY and the Y functional group are attached to different carbon atoms of R (claim 7), each POLY is covalently attached to a hydroxyl functional group (claims 8 and 11), the Y group is an “active ester” (claim 12), and each POLY is a branched poly(alkylene oxide) in the form of poly(ethylene glycol) (claims 13 and 14). *Id.* at 59–65. Petitioner further demonstrates that the polymer of

formula (14) was reacted to form a biologically active conjugate with asparaginase wherein X' is –O– (claim 20), the molecular weight of each poly of the polymer of formula (14) is selected to result in a total molecular weight for the branched reactive polymer (5,162 Da) that falls within the recited ranges of about 5,000 to about 60,000 Da (claim 33) and about 5,000 to about 100,000 Da (claim 32), and each POLY in the polymer of formula (14) has a molecular weight of 2,451 Da, which Petitioner contends is “about 2,500 to about 30,000 Da” (claim 35). *Id.* at 65–70.

With respect to the polymer of formula (8), Petitioner demonstrates that the –O– (ether linkage) of the polymer of formula (8)¹² is a heteroatom (claim 15) and that the polymer of formula (8) includes an allyl ether protecting group (claim 17). *Id.* at 65–67.

Finally, Petitioner demonstrates that the polymers of formula (8) and (14) have the structure depicted in claim 19. *Id.* at 68.

Patent Owner presents no evidence or argument, beyond its arguments related to claim 1, contesting Petitioner’s evidence and arguments with respect to dependent claims 2–8, 11–15, 17, 19, 20, 32, 33, and 35. *See generally* PO Resp. 47–49; Sur-Reply 23.

Upon review of Petitioner’s and Patent Owner’s arguments and supporting evidence, we find that Petitioner persuasively demonstrates that the polymers of formula (8) and/or formula (14) of JP-542 disclose every limitation of claims 2–8, 11–15, 17, 19, 20, 32, 33, and 35. Therefore, these claims are anticipated by JP-542.

¹² Petitioner persuasively demonstrates, and Patent Owner does not expressly dispute, that the polymer of formula (8) discloses every limitation of claim 1. Pet. 57.

4. *Analysis: Claims 9 and 10*

Claim 9 requires a capping group selected from the group “consisting of alkoxy, alkyl, benzyl, aryl, and aryloxy” and claim 10 requires a methoxy capping group. Ex. 1001, 24:47–51. The polymers of formula (8) and (14) do not have capping groups. Petitioner contends, however, that there is a general preference for methyl capping groups in the art, and JP-542 discloses that methyl groups are a preferred capping group. Pet. 62–63. In view of the general prevalence of methyl capped poly(alkylene oxide) chains in the PEGylation art, as well as the pattern of preference for methyl capped poly(alkylene oxide) chains in JP-542, Petitioner contends that one of ordinary skill in the art “would immediately envision and be in possession of the branched polymers of JP-542 formula (8) and formula (14) with methyl end-caps.” *Id.*

The polymers of formula (8) and (14) expressly include hydroxyl termini, not one of the recited capping groups. Petitioner’s arguments regarding the general preference for methyl capping groups expressed in the art and in JP-542 invoke the doctrine of obviousness, not anticipation. *Id.* at 62; *see NetMoney IN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008) (“But differences between the prior art reference and the claimed invention, however slight, invoke the question of obviousness, not anticipation.”). As such, we find claims 9 and 10 are not anticipated by JP-542.

5. *Analysis: Claims 29 and 31*

a) *Claim 29*

Independent claim 29 is similar to independent claim 1, but specifies that X' is –NH–, –O–, or –S–, and that Y can be any “functional group.” Ex. 1001, 26:14–35. Petitioner contends that the polymer of formula (10) of

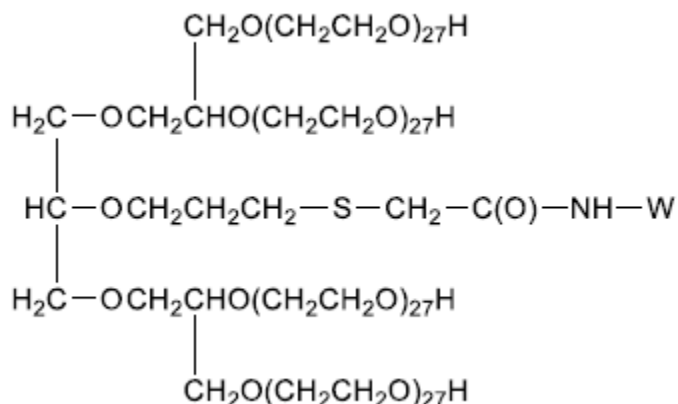
JP-542 discloses every limitation of claim 29, including an allyl ($\text{CH}_2\text{CH}=\text{CH}_2$) functional group. Pet. 70–73.

Patent Owner contends that claim 29 is not anticipated by JP-542 because “Petitioner has not shown that the allyl group will ‘react readily’ with any other molecule.” PO Resp. 50.

Upon review of the record as a whole, we find that Petitioner explains sufficiently where the polymer of formula (10) discloses every limitation of claim 29, including an allyl functional group. Patent Owner’s counter argument is not persuasive because we do not construe either claim 1 or claim 29 to require a functional group that “reacts readily” with any other molecule. *See* Section II.A.2. Accordingly, claim 29 is anticipated by JP-542.

b) Claim 31

Claim 31 is similar to claim 29, but requires covalent attachment of a biologically active molecule to the branched reactive polymer. Ex. 1001, 26:54–27:9. Petitioner contends that one of ordinary skill in the art would have understood that when the polymer of formula (14) was conjugated to L-asparaginase (a biologically active molecule) in JP-542 the resulting polymer had a structure that anticipates claim 31. Pet. 73–75. In particular, Petitioner contends that one of ordinary skill in the art would immediately understand and envisage that the resulting polymer had the following formula:



The above formula depicts Petitioner’s interpretation of the structure of the polymer of formula (14) when conjugated with L-asparaginase (identified as W in the above formula). *Id.* at 75 (citing Ex. 1084 ¶ 473).

Patent Owner contends JP-542 provides no formula for the polymer resulting from the conjugation of formula (14) with L-asparaginase and Petitioner’s conclusory statements regarding the polymer of Test Example 1 “do not meet the high bar of inherent anticipation.” PO Resp. 51–52.

JP-542 discloses the formula for the polymer of formula (14), discloses reacting the polymer of formula (14) with L-asparaginase, and provides the reaction conditions for this conjugation. Ex. 1017 ¶ 54. Although JP-542 does not provide a figure, formula, or description of the resulting branched polymer, Dr. Emrick testifies that one of ordinary skill in the art would understand that the resulting polymer would be represented by the formula set forth above. Ex. 1084 ¶ 473. This testimony is credible and Patent Owner provides no persuasive argument or evidence to call into question Mr. Emrick’s conclusions. Thus, we credit the testimony of Dr. Emrick that one of ordinary skill in the art would immediately envisage the formula for the conjugate of L-asparaginase and the polymer of formula (14) expressly discussed in JP-542 and his testimony that the resulting structure anticipates claim 31. *See Kennemetal, Inc. v. Ingersoll Cutting*

Tool Co., 780 F.3d 1376, 1381 (Fed. Cir. 2015) (noting that a reference may anticipate a claim “if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination” (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962))). Accordingly, Petitioner demonstrates by a preponderance of the evidence that claim 31 is anticipated by JP-542.

6. Conclusion

For the reasons set forth above, Petitioner demonstrates by a preponderance of the evidence that JP-542 anticipates claims 1–8, 11–15, 17, 19, 20, 29, 31–33 and 35 of the ’440 patent. Petitioner has not demonstrated by a preponderance of the evidence, however, that claims 9 and 10 are anticipated by JP-542.

E. Obviousness of Claims 1–16, 19, 20, and 29–35 over Bentley

Petitioner contends the subject matter of claims 1–16, 19, 20, and 29–35 of the ’440 patent would have been obvious over the disclosures of Bentley. Pet. 17–31.

1. Bentley

Bentley discloses a method of coupling a poly(ethylene glycol) polymer (PEG) to a biomaterial. Ex. 1015, 1:8–11. Bentley explains that both linear and branched PEG molecules had been used in the art to improve the solubility of “water insoluble compound[s],” without altering the compound’s biological activity. *Id.* at 1:60–2:1. Bentley further explains that conjugation of PEG to a drug molecule may result in enhanced blood circulation lifetime for the conjugated drug due to reduced kidney clearance and reduced immunogenicity. *Id.* at 2:6–11.

Bentley explains that conjugation of PEG to a drug molecule requires the use of an activated derivative “having a functional group at the terminus

suitable for reaction with a group on the other molecule.” *Id.* at 2:12–15. For example, a hydroxyl group on the PEG compound can be converted to an aldehyde group (forming PEG acetaldehyde) and then this aldehyde group can be covalently linked to an amine group on a target molecule in a process called reductive amination. *Id.* at 2:15–20.

Bentley indicates that one problem reported in the art with respect to the use of PEG acetaldehyde is its high reactivity, “which leads to condensation side reactions.” *Id.* at 2:42–45. Bentley also reports that PEG acetaldehyde is “difficult to prepare in high purity,” requiring additional purification steps that result in the “loss of valuable bioactive molecules, such as proteins.” *Id.* at 2:46–54. To overcome these difficulties, Bentley discloses the use of activated PEG molecules having an aldehyde hydrate moiety. *Id.* at 3:2–9. According to Bentley, the use of an aldehyde hydrate moiety to conjugate PEG to a target molecule avoids the condensation and oxidation reactions that hindered prior art conjugation methods. *Id.* at 3:9–15.

The activated PEG polymer of Bentley may be linear or branched and typically has an average molecular weight of from 200 to 100,000 Da. *Id.* at 6:35–36. As biological properties may vary based on molecular weight and the degree of branching, Bentley discloses that “not all” of the disclosed derivatives “may be useful for biological or biotechnical applications.” *Id.* at 6:35–39.

Bentley reports that “[f]or many biological and biotechnical applications, substantially linear, straight-chain PEG acetaldehyde hydrate is useful.” *Id.* at 6:40–42. This linear PEG may be capped on one end with a relatively nonreactive moiety, such as methyl, benzyl and aryl moieties, and conjugated to either a “surface” or a “substance” “selected from, e.g.,

proteins, peptides, oligonucleotides, polysaccharides and small drug molecules.” *Id.* at 6:12–15, 6:44–52, 7:44–46. According to Bentley, “[b]roadly speaking, any material having a reactive amine group accessible to the activated polymer having an aldehyde hydrate group can be used in the present invention.” *Id.* at 6:15–18.

“Another form of activated PEG aldehyde is dendritic activated PEG in which multiple arms of PEG are attached to a central core structure.” *Id.* at 6:64–66. These dendritic PEGs are commonly known as “star” molecules and can be represented by the formula $Q[\text{poly}]_y$, wherein Q is a branching core moiety and y is from 2 to about 100. *Id.* at 6:66–7:6. Bentley notes that such “star” molecules are generally described in Merrill (U.S. Patent No. 5,171,264), which is incorporated by reference in Bentley. *Id.* at 7:5–8.

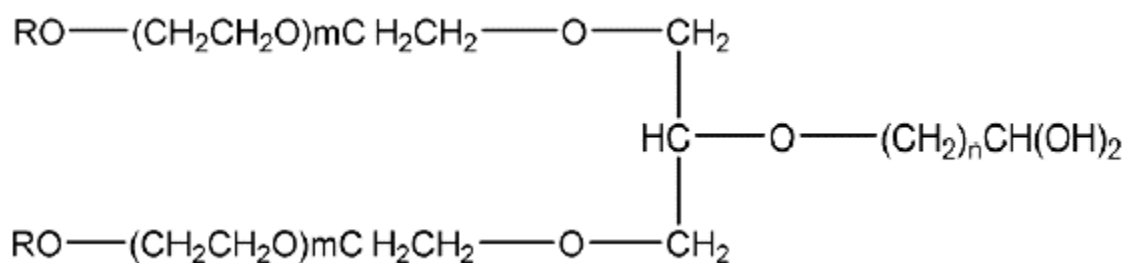
Bentley discloses that the aldehyde hydrate moiety on the “star” molecules can be used to provide an active functional group on the end of the PEG chain extending from the core, or may act as a linker for joining a functional group to the star molecule arms. *Id.* at 7:8–12.

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
$$[\text{RO}-(\text{CH}_2\text{CH}_2\text{O})_m\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2]_2\text{CH}-\text{O}-(\text{CH}_2)_n\text{CH}(\text{OH})_2$$
wherein R is H, alkyl, benzyl, or aryl; m ranges from about 5 to about 3000, [and] n ranges from 1 to 6.

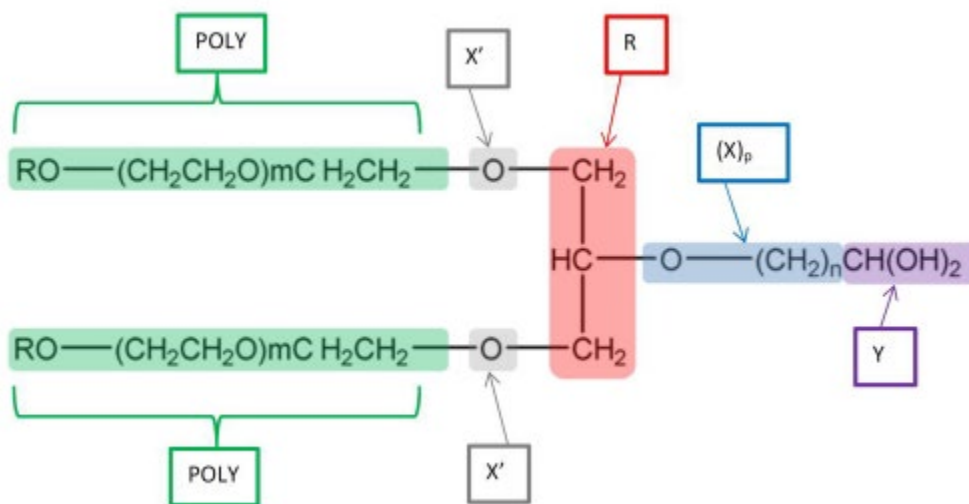
Id. at 7:12–20.

2. Analysis: Claim 1

Petitioner contends the dendritic “star” molecule of Bentley identified above may be drawn as follows:



Pet. 18. The figure above is Petitioner’s depiction of the chemical structure identified at column 7, lines 16–20 of Bentley.¹³ *Id.* (citing Ex. 1015, 7:12–20). Petitioner maps the limitations of claim 1 to this structure in the following annotated figure:



The figure reproduced above is an annotated and color-coded depiction of Bentley’s star molecule. *Id.* at 17–18. Referring to its annotated figure, Petitioner persuasively demonstrates that Bentley discloses a branched reactive poly(alkylene glycol) polymer having the formula $\text{Y}-(\text{X})_p\text{-R}-($

¹³ We refer to the polymer described at column 7, lines 16–20 of Bentley alternatively as “Bentley’s star molecule” or “Bentley’s genus.”

X'-POLY)_q (Pet. 13–14), wherein R is an aliphatic hydrocarbon having three carbon atoms (red) (*id.* at 14–15), each POLY chain is composed of “poly(alkylene glycol),” a water soluble and a non-peptide polymer (green) (*id.* at 15), X' is an ether (–O–) heteroatom linkage (grey) (*id.* at 16), X is a linker (–O–(CH₂)_n–) wherein p is 1 (blue) (*id.*), q (the number of polymer arms) is 2 (*id.*), and Y is an aldehyde hydrate functional group (–CH(OH)₂) (purple) that is reactive with an electrophilic or nucleophilic group (*id.* at 17).

With respect to the requirement that the total molecular weight of the branched reactive polymer is “at least about 5,000 Da,” Petitioner contends that “m” in Bentley’s star molecule ranges from about 5 to about 3,000, which describes a molecular weight range of about 220 Da to about 132,000 Da for each PEG chain (POLY), and results in a total polymer molecular weight range for the branched reactive polymer of at least 440 to about 264,000 Da. *Id.* at 18–19 (citing Ex. 1015, 7:12–20, 14:59–65; Ex. 1084 ¶¶ 305–306). Petitioner further contends that the overlap in the disclosed range (at least 440 to about 264,000 Da) with the claimed range (at least about 5,000 Da) renders the claimed range *prima facie* obvious. *Id.* at 19 (citing *In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003); Ex. 1084 ¶¶ 307–309).

Petitioner contends that one of ordinary skill in the art “would have had a reasonable expectation of success in preparing polymers of different [molecular weights] above 5,000 Da and within Bentley’s suggested ranges by increasing the length of the PEG polymer arms through polymerization or substitution of large PEG chains as known in the art.” *Id.* (citing Ex. 1015, 1:14–47, 14:59–65 (Claim 21); Ex. 1084 ¶ 308; Exs. 1016–17).

Patent Owner asserts that Petitioner's arguments with respect to claim 1 fail because: (1) Petitioner fails to apply a "lead compound" analysis, (2) Petitioner fails to demonstrate that the reasoning of *Peterson* applies to the facts of this case, (3) Petitioner has not shown that one of ordinary skill in the art would have selected the identified genus of polymers in Bentley for further development, (4) Petitioner has not shown that one of ordinary skill in the art would have selected individual species of polymers from Bentley's genus having the claimed molecular weight ranges, (5) Petitioner has not demonstrated a reasonable expectation of success in achieving the claimed invention, and (6) indicia of non-obviousness rebut any prima facie case of obviousness. PO Resp. 14–29, 57–60. We address these arguments below.

a) 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. 18–19; Pet. Reply 1–2. Patent Owner argues that we must (or at least should) apply a "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, 14; Sur-Reply 9.

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. In *KSR*, the Supreme Court instructed that we must take "an expansive and flexible approach to the obviousness question," 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. In conducting this analysis, we must “consider all disclosures of the prior art” (*In re Young*, 927 F.2d 588, 591 (Fed. Cir. 1991)), and we do not require that a petitioner “prove that a person of ordinary skill would have been motivated to select one prior art disclosure over another.” *Infineum USA L.P. v. Chevron Oronite Co.*, 2021 WL 210722, at *6 (Fed. Cir. Jan. 21, 2021)(non-precedential). Nor must a petitioner demonstrate that the “prior art suggests that the combination claimed” in the patent “is the preferred, or most desirable, combination.” *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004); *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (noting that in an obviousness inquiry “all disclosures of the prior art, including unpreferred embodiments, must be considered”).

Applying these general principles, a party may take many different paths in establishing that a patent claim would have been obvious over the prior art. One of these paths 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. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008). When a party chooses to argue that a patent claim would have been obvious based on structural similarity to a known compound, this can be proven “by identification of 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 is not the only way to demonstrate obviousness of a claimed compound or genus of compounds, however, and any rigid application of the lead compound doctrine risks running afoul of

the broad, flexible obviousness test set forth by the Supreme Court in *KSR*. See *Otsuka*, 678 F.3d at 1291 (noting that new compounds may be made out of theoretical concerns “rather than from attempts to improve on prior art compounds”); *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*”). Here, Petitioner argues that the genus of Bentley, in view of its disclosure of molecular weight ranges that overlap the claimed range, renders claim 1 obvious. This analysis relies upon established case law regarding obviousness based on overlapping ranges. See *Peterson*, 315 F.3d 1329–30. Thus, we find that a “lead compound” analysis is not the most appropriate analytical framework in this case.

b) Overlapping Ranges

(1) The Parties’ Arguments

As noted above, relying on the reasoning set forth in *Peterson*, Petitioner contends that the 440 to about 264,000 Da molecular weight range taught or suggested in Bentley renders the claimed molecular weight range of “at least about 5,000 Da” *prima facie* obvious. Pet. 19.

Patent Owner argues that, unlike the ranges of a single composition at issue in *Peterson*, claim 1 “does not recite a single composition but rather a set of chemical compounds,” i.e., “the group of branched reactive polymers having the structure $Y-(X)_p-R-(X'-POLY)_q$.” PO Resp. 14–15. And because Bentley discloses “a genus covering a different set of polymers, which includes between about 5 and 3,000 ethylene glycol subunits,” Patent Owner contends that *Peterson* is inapposite. *Id.* at 15.

Patent Owner further argues that even if *Peterson* applied to the facts of this case, *Peterson* is limited to selecting a narrow range from within a somewhat broader range, and Dr. Little determined that the cited genus of Bentley is not narrow, covering at least 300,000 distinct species. *Id.* at 16–17. Patent Owner contends that the facts of this case are therefore more similar to those addressed in *In re Baird*, 16 F.3d 380 (Fed. Cir. 1994) and *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992), where it was found that a prior art genus does not, by itself, render obvious specific compounds that fall within that prior art genus. PO Resp. 15–16.

In response, Petitioner argues that Bentley’s genus, in the context of the claimed chemical formula, “is tantamount to a species” because Y, X, R, X’, POLY, and q are fixed, and the only claim limitation not expressly disclosed in Bentley is the overlapping molecular weight ranges. Pet. Reply 6. Petitioner further argues that molecular weight is known to be a result-effective variable for PEG polymers and, when “the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *Id.* at 6–7 (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)).

Patent Owner contends Petitioner’s assertion that Bentley’s genus is tantamount to a species is an improper new argument that “is designed to excuse Petitioner’s failure to account for the complexity of the chemical arts.” Sur-Reply 15. Patent Owner further contends that Petitioner’s “attempts to minimize the tremendous structural variety associated with the different molecular weights” ultimately fail because Petitioner does not rebut Dr. Little’s calculation that the genus of Bentley encompasses more than 300,000 distinct species. *Id.*

(2) *Analysis*

In the context of the formula of claim 1, Petitioner persuasively demonstrates—in both the Petition and the Reply—that the variables Y, (X)_p, R, X', POLY, p, and q are fixed and result in a polymer that falls within the structural formula of claim 1 of the '440 patent. Pet. 13–18; Pet. Reply 6. In particular, R is a three carbon aliphatic hydrocarbon (Pet. 14–15), POLY is poly(alkylene glycol) (*id.* at 15), X' is –O– (*id.* at 16), X is –O–(CH₂)_n– (wherein n is 1–6) (*id.*), p=1 (*id.*), q is 2 (*id.*), and Y is an aldehyde hydrate functional group (*id.* at 17).

The only variable set forth in Bentley that could potentially result in a species outside the scope of claim 1 is molecular weight. The claimed molecular weight range (“at least about 5,000 Da”) is, however, obvious over the range disclosed in Bentley (between about 440 and 264,000 Da) for at least two interrelated reasons. First, when a variable is “result-effective” and “the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Applied Materials*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) (quoting *Aller*, 220 F.2d at 456). It is undisputed that the molecular weight range recited for Bentley’s polymers overlaps the claimed range of “about 5,000 Da,” thereby disclosing the “general conditions of the claim.” *Id.* (noting that any overlap between the claimed and disclosed ranges serves to disclose the “general conditions” of the claim).

The evidence of record also persuasively demonstrates that molecular weight is a result-effective variable for PEG polymers, whether they are attached to a biologically active molecule or to surfaces, such as in a

hydrogel.¹⁴ Ex. 1015, 6:35–37; Ex. 1016, 32:52–33:7, 35:54–57; Ex. 2020, Table 1 (Merrill polyethylene oxide star molecule patent); Ex. 1029, 4; Ex. 1095 ¶ 227; *see E.I. DuPont de Nemours & Co. v. Synvina CV*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (noting that a variable is “result-effective” if it was recognized in the prior art that a “property is affected by the variable”). For example, Bentley discloses that the biological properties of a PEG conjugated compound “can vary with molecular weight” (Ex. 1015, 6:35–37), MDD found that the size and branching of PEG polymers “directly influenced the pharmacokinetic properties and biological activity” of a protein drug (Ex. 1029, 4), and Merrill discloses that the properties of a hydrogel depend on the molecular weight of each individual polymer arm and the total molecular weight of the PEG molecule (Ex. 2020, Table 1; PO Resp. 25–26 (Patent Owner asserting that optimal properties were achieved with lower molecular weights for each polymer arm)).

Given that molecular weight is a result-effective variable and the general conditions of the claim are disclosed in Bentley, Petitioner has satisfied its burden to show that it would not have been inventive to optimize molecular weight within the range recited in claim 1.

Second, “even a slight overlap in range establishes a *prima facie* case of obviousness.” *Peterson*, 315 F.3d at 1329. The burden of production then shifts to Patent Owner to demonstrate that the invention would not in fact have been obvious, “generally by showing that the claimed range achieves unexpected results relative to the prior art.” *Id.* at 1330 (quoting *In*

¹⁴ The parties vigorously dispute whether Bentley’s genus of polymers is intended for attachment to biologically active molecules or to surfaces, such as the hydrogels of Merrill. Pet. 19; PO Resp. 22–26; Pet. Reply 8–15. In either case, though, molecular weight is a result-effective variable.

re Geisler, 116 F.3d 1465, 1469–70 (Fed. Cir. 1997)). Patent Owner does not attempt to demonstrate that the claimed molecular weight range achieves unexpected results relative to Bentley, or any other piece of prior art. Accordingly, we find that claim 1 would have been *prima facie* obvious over Bentley.¹⁵

We disagree with Patent Owner that the reasoning of *Peterson* is inapplicable in this case. PO Resp. 14–15. *Peterson* applies the decades-old legal principle that in cases involving overlapping ranges “even a slight overlap in range establishes a *prima facie* case of obviousness.” *Peterson*, 315 F.3d at 1329. This legal principle is not restricted to certain types of technologies or claims, e.g., claims reciting a single composition versus a set of chemical compounds. *See E.I. DuPont*, 904 F.3d at 1006.

Patent Owner further asserts that even if the reasoning of *Peterson* is applicable, it is limited to situations where a narrow range is selected from within a somewhat broader range, and Dr. Little determined that the cited genus of Bentley is not narrow, covering at least 300,000 distinct species. PO Resp. 16–17. Patent Owner contends the facts of this case are similar to those in *Genetics Institute v. Novartis Vaccines and Diagnostics*, 655 F.3d 1291, 1306 (Fed. Cir. 2011), where the prior art disclosed “a large breadth of possible protein variants” and provided “no motivation to optimize for some value within” the disclosed range. *Id.* at 17; *Genetics Institute*, 655 F.3d at 1306.

Patent Owner’s argument is unavailing because *Peterson* focuses on whether the disclosed *range* is “somewhat broader” than the claimed range,

¹⁵ Patent Owner asserts that the prior art would have discouraged selection of molecular weights within the claimed range. PO Resp. 25. We address and reject this argument in Section II.E.2.(c).(2) below.

and Dr. Little does not assert that the molecular weight range of Bentley is broader than the molecular weight range recited in claim 1 of the '440 patent. *See Peterson*, 315 F.3d at 1329–30. Indeed, the unbounded range of “at least about 5,000 Da” recited in claim 1 appears to be much broader than the bounded range of Bentley.¹⁶ Moreover, Dr. Little’s calculation of over 300,000 potential species within Bentley’s formula takes into account the possibility of varying R, m, and n in Bentley’s formula. Ex. 2036 ¶¶ 235–239. Petitioner persuasively demonstrates, however, that the calculations based on varying R and n utilize a false reference point, as all of these polymers fall within the scope of the genus of claim 1.

Genetics Institute does not suggest a different conclusion because the disclosed polymers of Bentley differ (in relevant part) only in the molecular weight of the polymer arms, and the evidence of record demonstrates that there was ample reason to optimize within the molecular weight range set

¹⁶ As generally alluded to by Patent Owner, a prior art range may be so large that it effectively does “not teach any specific amounts or combinations.” *See Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015). In that case, the burden of producing evidence of teaching away, unexpected results, and other pertinent secondary considerations does not shift to Patent Owner. *Id.* The evidence of record, however, demonstrates that the 5 to 3,000 range of ethylene glycol subunits in Bentley, resulting in a total molecular weight for the polymer of between 440 and 264,000 Da, is not so large as to effectively not teach any specific amounts. For example, Merrill discloses molecular weight ranges of 100,000 to 300,000 Da for star molecules, as well as specific examples having molecular weights from 79,000 to 229,000 Da for Type I stars and 190,000 to 371,000 Da for Type II stars. Ex. 2020, 3:61–64, Table I. Likewise, Harris discloses multi-armed PEG polymers with molecular weights from about 100 to 100,000 Da, and specifically claims two-armed PEG polymers having a molecular weight from about 40,000 to 100,000 Da. Ex. 1016, Abstract, 37:18–38, 37:62–65, 40:27–36 (Claims 1, 8, 19).

forth in Bentley. *See Genetics Institute*, 655 F.3d at 1306 (noting that the prior art reference provided a motivation to make smaller, truncated proteins, not the larger truncated proteins recited in the claim at issue); Ex. 1015, 6:35–36 (“PEG typically has average molecular weights of from 200 to 100,000.”); Pet. Reply 8.

In view of the foregoing, we find that the case law regarding overlapping ranges, as set forth in *Peterson* and *Applied Materials*, applies in this case and that the molecular weight range of claim 1 is prima facie obvious over the overlapping molecular weight range disclosed in Bentley.

c) Selecting the Genus and Sub-Genus of Bentley

Applying a lead compound analysis, Patent Owner contends that Petitioner fails to adequately demonstrate that one of ordinary skill in the art would have (1) selected Bentley’s genus from the within the other classes of molecules disclosed in Bentley, and (2) selected polymer species from within Bentley’s genus that have a molecular weight that is within the claimed range. PO Resp. 1–2, 18–26 (citing *Otsuka*, 678 F.3d at 1291).

(1) Selection of Bentley’s Genus

Patent Owner argues that Petitioner fails to identify any reason that one of ordinary skill in the art would have selected the specific genus of Bentley relied upon by Petitioner as a lead compound from among the numerous disclosures of Bentley. PO Resp. 19–20. According to Patent Owner, “[b]y focusing on the cited dendritic genus versus the other embodiments [disclosed in Bentley], it is apparent that Petitioner’s reliance on the asserted Bentley polymers is the product of hindsight.” *Id.* at 20.

For the reasons discussed above, we do not apply a “lead compound” analysis in this case. Accordingly, Petitioner need not show that one of ordinary skill in the art would have selected Bentley’s genus over all other

disclosures in the reference, or all other disclosures in the prior art. *See Infineum USA*, 2021 WL 210722, at *6. In any event, Merrill provides a utility for star molecules in general and Dr. Emrick persuasively explains why one of ordinary skill in the art would have understood that Bentley's star molecules are in fact useful for conjugation to biologically active molecules. Ex. 1015, 6:64–7:20; Ex. 1084 ¶ 308; Ex. 1095 ¶¶ 156–162 (Dr. Emrick testifying that the use of inert end-capping indicates that Bentley's genus of polymers is not limited to use in hydrogels); *see also* PO Resp. 30–31 (Patent Owner asserting that use of inert end-capping would render the star molecules of Bentley “ineffective for their intended purpose”). Thus, the evidence of record provides sufficient reason to select the particular genus of Bentley for further development and optimization.

(2) *Selection of a Sub-Genus with Molecular Weights of “at least about 5,000 Da”*

Patent Owner asserts that even if one of ordinary skill in the art would have selected the particular genus of Bentley relied upon by Petitioner, Petitioner has not demonstrated that one of ordinary skill in the art would have selected from within this disclosure the sub-genus of compounds having molecular weights of “at least about 5,000 Da.” PO Resp. 25–26. Patent Owner reasons that “Merrill contains experimental data that would have discouraged” a person of ordinary skill in the art from selecting “polymers corresponding to the claimed molecular weight.” *Id.* at 25. In particular, Patent Owner contends Merrill teaches that it “is desirable to have a high value of [OH] and a low swelling ratio q in order that the biomaterial remain approximately in the shape in which it was cast” *Id.* at 25–26 (quoting Ex. 2020, 7:37–40). And, according to Patent Owner, Merrill's experimental data indicates that the greatest value of [OH] was exhibited by

star molecules with individual arms having a molecular weight (^MP EO) of 3,460 Da. *Id.* at 26 (citing Ex. 2020, Table 1).

Patent Owner's arguments are based on a lead compound analysis, which for the reasons discussed above, we do not apply in this case. That said, the prior art must be considered for all that it teaches, including teachings that may lead towards or away from the claimed invention. *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). On this point, we are not persuaded that Merrill teaches away from total molecular weights above "about 5,000 Da."

Similar to the genus disclosed in Bentley, each of the star molecules tested in Merrill had at least two arms. Ex. 2020, Table 1; Ex. 1015, 7:17–18. Applying Patent Owner's argument that 3,460 Da polymer arms are preferred in Merrill, this results in minimum total molecular weight of at least 6,920 Da (3,460 x 2) for the star molecules of Bentley, which falls squarely within the claimed range of "at least about 5,000 Da." Moreover, Patent Owner does not assert that Merrill teaches away from using two-armed star molecules for conjugation to biologically active molecules, or using total molecular weights above "at least about 5,000 Da" for such conjugates. Thus, regardless of whether the genus of Bentley is used as a star molecule for a hydrogel or for conjugation to a biologically active material, we find that Merrill does not teach away from total molecular weights above "about 5,000 Da."

Patent Owner also argues that the genus of polymers disclosed in Bentley are merely intermediates that would have to be coupled to the core of an undisclosed star molecule. PO Resp. 20–21. Absent some motivation for doing so, Patent Owner contends "it cannot be said that it would have been obvious to stop the process for synthesizing the disclosed end product

and isolate the claimed intermediate.” *Id.* at 21 (quoting *In re Gyurik*, 596 F.2d 1012, 1018 (CCPA 1979)).

Petitioner argues in response that Bentley’s molecules are not intermediates, but instead fully-activated derivatives in which the aldehyde hydrate moiety is “linked directly to the core molecule having PEG chains extending from the core.” Pet. Reply 11–12.

As noted by Petitioner, Bentley describes the claimed genus as having PEG chains extending from the core, which requires that the core be part of the recited, activated compounds. Ex. 1015, 7:12–14; Pet. Reply 11–12. Thus, we agree with Petitioner that Bentley’s polymers are fully-activated derivatives ready for use. Pet. Reply 11. We note, however, that even if the recited genus was an intermediate or precursor for formation of a completed star molecule, this is reason enough for one of ordinary skill in the art to form such compounds, i.e., for their subsequent attachment to a core molecule. *See Gyurik*, 596 F.2d at 1019 (Baldwin, J., concurring) (noting that it is irrelevant that a chemical compound is an intermediate or precursor if “some practical reason were provided for recovering the claimed precursor”).

(3) *Conclusion with Respect to Reason to Select the Genus and Sub-Genus of Bentley*

For the reasons set forth above, we find that Petitioner demonstrates by a preponderance of the evidence that one of ordinary skill in the art using routine optimization would have selected a subgenus of polymers from within Bentley’s genus that reads on every limitation of claim 1 of the ’440 patent.

d) Reasonable Expectation of Success

To demonstrate obviousness, Petitioner has the burden to demonstrate both that a skilled artisan would have been motivated to combine the teachings of the prior art and that the skilled artisan would have had a reasonable expectation of success in so doing. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (“The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention.”).

Petitioner contends that one of ordinary skill in the art “would have had a reasonable expectation of success in preparing polymers of different [molecular weights] above 5,000 Da and within Bentley’s suggested ranges by increasing the length of the PEG polymer arms through polymerization or substitution of larger PEG chains as known in the art.” Pet. 19 (citing Ex. 1084 ¶¶ 308; Ex. 1015, 1:14–47, 14:59–65 (Claim 21); Ex. 1016; Ex. 1017).

Patent Owner contends Petitioner “must do more than generally assert that a [person of ordinary skill in the art] knew how to lengthen PEG arms.” PO Resp. 27. Rather, according to Patent Owner, “Petitioner must explain with specificity how such teachings would have been applied to the polymer genus that Petitioner relies upon.” *Id.* On this point, Patent Owner contends that Dr. Emrick admitted that “issues arise” as you get to high molecular weights, including “unwanted termination reactions that will interrupt molecular weight growth for some chains but not for others.” *Id.* at 28 (citing Ex. 2040, 43:8–23 (Emrick deposition)). Patent Owner contends these effects may “lead to increases in polydispersity” and “may well” constitute a negative effect. *Id.*

Petitioner argues in its Reply that the expectation of success need only be reasonable, not absolute, and this “claim element is directed to a well-known, result-effective variable (MW) in overlapping ranges.”

Pet. Reply 16. Petitioner also contends that Bentley is presumed enabled and Patent Owner’s polydispersity arguments “are misplaced because there are no polydispersity limitations in the claims.” *Id.* (citing Ex. 1095 ¶¶ 51, 141, 219).

As noted above, molecular weight is a result-effective variable for PEG polymers and it was well known in the art that the length of PEG arms of a branched polymer could be successfully extended over a broad range of molecular weights. For example, Harris discloses two-armed PEG polymers with molecular weights as low as 100 and as high as 100,000 Da that “can be prepared in a simple, one-step reaction.” Ex. 1016, 7:33–40 (“Relatively pure polymer molecules of high molecular weight can be created.”), 18:31–45, 37:58–65 (Claims 7, 8). Consistent with these disclosures, the ’440 patent acknowledges that Harris’s methods are “useful for attaching a high molecular weight polymer to a molecule at a single attachment site.” Ex. 1001, 1:55–2:3. Although the methods of Harris may be more difficult than those disclosed in the ’440 patent, we credit the testimony of Dr. Emrick that one of ordinary skill would have reasonably expected success in using such methods to achieve molecular weights within the range recited in claim 1 of the ’440 patent. Ex. 1084 ¶ 308; Ex. 1095 ¶ 220.

This conclusion is further supported by the fact that Bentley is presumptively enabled, is Patent Owner’s own patent (*see* Exs. 1096–1101), and claim 21 of Bentley provides for the same number of extensions of the PEG polymer as are recited in claim 1 of the ’440 patent and Bentley discloses no concerns with being able to successfully extend the PEG arms

without undue experimentation. *See Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1341–42 (Fed. Cir. 2006) (presuming that a party that filed and prosecuted a prior art reference represented to the Patent and Trademark Office that its claims satisfy “the written description and enablement requirements of 35 U.S.C. § 112”).

In view of the foregoing, we find that Petitioner sufficiently demonstrates that one of ordinary skill in the art would have had a reasonable expectation of success in producing the polymers of Bentley’s genus.

e) Secondary Indicia of Non-Obviousness

Objective indicia of non-obviousness, or “secondary considerations,” 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) (citations omitted). As such, objective indicia of non-obviousness must be considered in every case in which they are presented. *Id.* (citing *Transocean Offshore Deepwater Drilling Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012)).

Objective indicia of non-obviousness include: (1) commercial success; (2) long-felt but unsolved needs; (3) failure of others; (4) copying; (5) praise in the art; (6) unexpected results; and (7) industry acceptance. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000) (citing *Graham*, 383 U.S. at 17 and *Allen Archery, Inc. v. Browning Mfg. Co.*, 819 F.2d 1087, 1092 (Fed. Cir. 1987)).

Patent Owner contends that there was a “long-felt but unmet need for the claimed branched reactive polymer and biologically active conjugates

thereof in the '440 patent.” PO Resp. 58. According to Patent Owner, the '440 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. 1001, 2:4–9). Pointing to several other portions of the '440 patent, Patent Owner argues that the '440 patent satisfied this long-felt need by providing “a branched reactive polymer and biologically active conjugates thereof that are more easily synthesized and purified.” *Id.* at 58–60.

In its Sur-Reply, 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 24–25. 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.* (citing Ex. 1093, 120:5–13, 118:18–123:7 (Little deposition); Ex. 2040, 41:23–42:2 (Emrick deposition)).

Patent Owner’s evidence of long-felt need is not persuasive for at least two reasons. First, Patent Owner’s evidence of long-felt need stems primarily from self-serving statements in the '440 patent, and not from independent sources. PO Resp. 58–60. Second, as Petitioner notes, to be relevant, the evidence of secondary considerations must result from something that is “both claimed and novel.” Pet. Reply 24 (citing *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, Bentley discloses every limitation of claim 1, either expressly or via overlapping ranges, and claims polymers with a molecular weight of over 200,000 Da. *Id.* at 24–25.

Likewise, Harris specifically claims high molecular weight PEG polymers (100,000 Da) and indicates 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, 37:58–65 (Claims 7, 8).

In view of the foregoing, we find that Patent Owner’s evidence of secondary considerations is entitled to little, if any, weight. Each of our obviousness analyses below are made in view of this conclusion.

f) Conclusion with Respect to Claim 1

Upon consideration of Petitioner’s and Patent Owner’s arguments and supporting evidence, including Patent Owner’s evidence of secondary considerations, we determine that Petitioner demonstrates by a preponderance of the evidence that claim 1 would have been obvious over Bentley.

3. Analysis: Claims 2–15 and 32–35

With respect to dependent claims 2–15, 19, and 32–35, Petitioner identifies where Bentley teaches or suggests every limitation of these claims. Pet. 20–30. Patent Owner does not expressly contest Petitioner’s arguments, apart from its arguments with respect to claim 1. Upon review of Petitioner’s arguments and supporting evidence, we find that Petitioner demonstrates by a preponderance of the evidence that claims 2–15, 19, and 32–35 would have been obvious over Bentley.

4. *Analysis: Claims 16, 20, and 29–31*

Patent Owner contests whether Petitioner sufficiently demonstrates that the subject matter of dependent claims 16, 20, and 29–31 is taught or suggested in Bentley. PO Resp. 29–30. In view of our determinations (discussed above and below) that claims 16–18 and 30 would have been obvious over Bentley and Liebigs, that claims 16, 20, and 29–31 would have been obvious over Harris, and claims 20, 29, and 31 are anticipated by JP-542, we decline to address the parties’ dispute here as to whether claims 16, 20, and 29–31 would also have been obvious over Bentley alone. *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.*, Nos. 2019-1594, -1604, -1605, 2020 WL 2071962, at *4 (Fed. Cir. Apr. 30, 2020) (non-precedential) (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”).

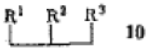
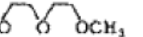
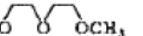
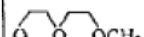
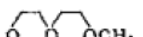
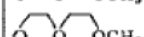
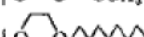
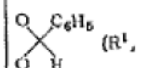
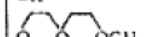
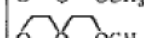
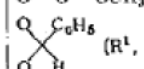
F. *Obviousness of Claims 16–18 and 30 over Bentley and Liebigs*

Claim 16 depends from claim 1 and further requires that “p is 0 and Y is a hydroxyl,” claim 17 depends from claim 1 and further requires that “Y has the structure –O-Gp, wherein Gp is a protective group,” and claim 18 depends from claim 17 and further requires that “Gp is selected from the group consisting of benzyl, acetal and dihydropyranyl.” Ex. 1001, 25:10–16. Independent claim 30 is similar to claim 1, but requires a polymer that has a terminal hydroxyl moiety. *Id.* at 26:36–38.

Petitioner contends the subject matter of claims 16–18 and 30 would have been obvious over the combined disclosures of Bentley and Liebigs. Pet. 31–35.

1. Liebigs

Liebigs is an article titled “Neutral ligands with surfactant structure – Synthesis, Complexation, Ion Transfer.” Ex. 1019, 770.¹⁷ Liebigs discloses several starting materials and associated ligands for forming the disclosed compounds, including “biologically interesting” polymers based on glycerol. *Id.* at 770–774. The following table shows various glycerol ether compounds and synthesis pathways set forth in Liebigs.

	R ¹	R ²	R ³
10			
a			
b			
c			
d			
e			
f	OH	OH	OCH ₂ C ₆ H ₅
g			OCH ₂ C ₆ H ₅
h			OH
i			OCH ₂ C ₆ H ₅
j			OH
k	 (R ¹ , R ²)	OH	--
l	OH	OCH ₂ C ₆ H ₅	OH
m		OCH ₂ C ₆ H ₅	
n		OH	
o	 (R ¹ , R ²)		--
p	OH		OH

¹⁷ Our citations are to the original page numbers of Liebigs.

The table above shows the possible combinations of R¹, R², and R³ for attachment to the compound of formula 10. In the pathway depicted in 10l, 10m, and 10n, the hydroxyl groups of 10l (2-benzyl-1,3-glycerol) are used to couple mPEG arms at positions R¹ and R² (as depicted in 10m). *Id.* at 775. The –O–benzyl group at R² (10m) is then deprotected to provide a hydroxyl at R² (10n). Ex. 1084 ¶ 366.

2. Analysis

Bentley does not describe a specific synthesis pathway for forming its star molecules, but does provide general guidance on forming its disclosed polymers. In particular, Bentley explains that PEG polymers are formed from a central core molecule, such as glycerol, and that the disclosed polymer relied upon by Petitioner has a three-carbon core molecule. Ex. 1015, 1:38–54, 7:1–20; Pet. 31. Bentley further explains that the starting molecule should have at least one hydroxyl moiety (–OH) available to participate in chemical reactions and that a –O–benzyl group may be used to protect a PEG hydroxyl. Ex. 1015, 4:25–32, 10:55–11:32; Pet. 31–32.

Given these disclosures, Petitioner contends one of ordinary skill in the art seeking to prepare the branched PEG of Bentley would have searched for a suitable glycerol core upon which to link two PEG chains at the 1 and 3 positions, “while preserving a hydroxyl at the central carbon atom (2-position) for the subsequent reaction with the halide-substituted compound.” Pet. 32. Dr. Emrick testifies that Liebigs expressly discloses an appropriate glycerol core (2-benzyloxy-1,3-propanediol), as well as a synthesis pathway (10l, 10m, and 10n) that one of ordinary skill in the art would have understood could be used to create the activated PEG of Bentley. *Id.* at 32–33 (Ex. 1084 ¶¶ 366–367). Dr. Emrick further testifies that the intermediary form having mPEG arms at positions 1 and 3 and –O–benzyl (the claimed

“–O–Gp”) at position 2 (10m) satisfies the limitations of claims 17 and 18. Pet. 34–35 (Ex. 1084 ¶ 369). Then, once the protecting –O–Gp (OCH₂C₆H₅ (a benzyl group)) is removed (10n), the deprotected form with –OH at position 2 satisfies the limitations of claims 16 and 30. *Id.*

Patent Owner contends Petitioner’s arguments fail because Liebigs discloses compounds promising for use as catalysts, lipophilic ionophores, and molecular aggregates, and Petitioner does not sufficiently explain why one of ordinary skill in the art would have looked to such disclosures when producing the PEG polymers of Bentley. PO Resp. 32. Patent Owner further contends that the pathway and synthesis steps set forth by Petitioner are hypothetical, as neither Liebigs nor Bentley discloses taking these particular steps to form the polymers of Bentley’s genus. *Id.* at 31–32.

Bentley does not describe how to form its PEG polymers. Thus, one of ordinary skill in the art seeking to produce the activated PEG polymers of Bentley would have needed to purchase or synthesize these compounds. Given that the genus of Bentley has a three-carbon core with PEG arms extending from positions 1 and 3, we find persuasive Petitioner’s argument that one of ordinary skill in the art looking for suitable glycerol-based starting materials would have looked to Liebigs’s three-carbon core molecule, i.e., 2-benzyloxy-1,3-propanediol. Pet. 31.

Although Liebigs is focused on producing compounds for use as phase transfer catalysts, etc., and not for use as PEG polymers, we credit the testimony of Dr. Emrick that one of ordinary skill in the art would have understood that Liebigs provides a three-carbon core molecule and synthesis pathway that are particularly useful for producing the branched reactive polymer disclosed in Bentley. Ex. 1084 ¶¶ 191–192, 362–367. We also find that Liebigs is reasonably pertinent to one of the problems facing the

inventors of the '440 patent, i.e., providing an appropriate starting material for synthesis of the branched reactive polymers. Ex. 1001, 2:18–24 (disclosing the need to provide suitable aliphatic core structures for the synthesis of the disclosed polymers), 2:34–35 (“The central core molecule is an aliphatic hydrocarbon having a length of at least three carbon atoms.”), 17:55–58 (using the same commercially available starting core material as disclosed in Liebigs (2-benzyloxy-1,3-propanediol)).

Having chosen the glycerol-based compound of Liebigs, Petitioner persuasively explains both how and why one of ordinary skill in the art following the general synthesis pathway of Liebigs would have produced the claimed –O–Benzyl intermediate (claims 17 and 18) and the deprotected form having an –OH group at position 2 (claims 16 and 30). Pet. 34–35. Although the use of Liebigs’s pathway to produce the genus of Bentley is hypothetical in the sense that it is not expressly disclosed in either Bentley or Liebigs, Petitioner persuasively explains why one of ordinary skill in the art would have followed the general pathway disclosed in Liebigs to produce that activated PEG polymers disclosed in Bentley. *Id.* at 32–35.

In view of the foregoing, we find that Bentley and Liebigs teach or suggest the subject matter of claims 16–18 and 30 of the '440 patent and that Petitioner persuasively explains why one of ordinary skill in the art would have combined the teachings of Bentley and Liebigs to arrive at the claimed invention. Accordingly, Petitioner demonstrates by a preponderance of the evidence that claims 16–18 and 30 would have been obvious over Bentley and Liebigs.

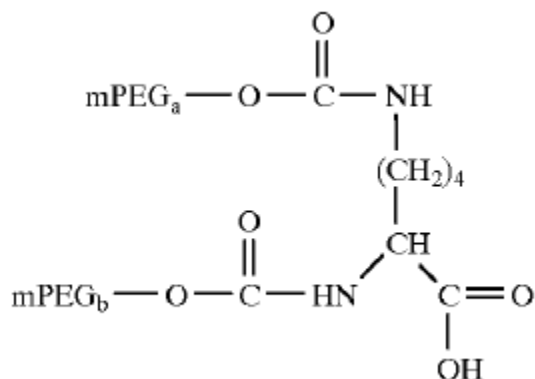
G. Obviousness of Claims 1–3, 5, 7–10, 12–16, 20, and 29–35 over Harris

Petitioner contends the subject matter of claims 1–3, 5, 7–10, 12–16, 20, and 29–35 would have been obvious over the disclosures of Harris. Pet. 39–53.

1. Harris

Harris discloses “[m]ulti-armed, monofunctional, and hydrolytically stable polymers” having two polymer arms. Ex. 1016, Abstract. A functional group on the polymer may be used to link this polymer to a drug, protein, enzyme, or a surface. *Id.* at 1:36–40, 7:50–57 (“The 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.”).

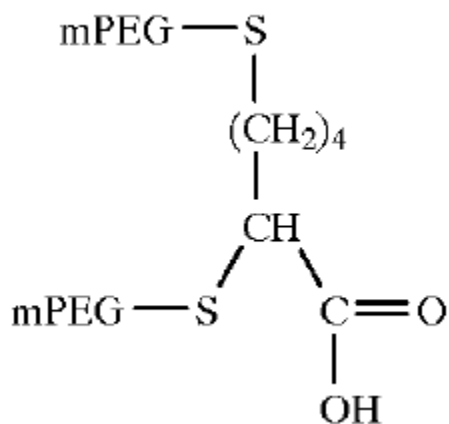
One embodiment of the polymer of Harris is reproduced below:



The figure above depicts one embodiment of Harris that is based upon the “hydrolytically stable coupling of mPEG to lysine” and contains a carbamate linkage. *Id.* at 9:35–55, 20:34–55. In this embodiment, the mPEG arms consist of $\text{CH}_3\text{O}-(\text{CH}_2\text{CH}_2\text{O})_n\text{CH}_2\text{CH}_2$ and the reactive carboxyl moiety provides a linkage to reactive sites on proteins, enzymes, nucleotides, lipids, liposomes, and other materials. *Id.* at 9:20–22, 9:35–55.

Harris explains that the mPEG disubstituted lysine of the invention may be made using a one-step method or a two-step method. *Id.* at 11:46–58, 18:15–22. The mPEG disubstituted lysine made by the one-step method typically has a molecular weight of 40,000 Da and the mPEG disubstituted lysine made by the two-step method typically has a molecular weight of 10,000 Da. *Id.* at 18:11–22. Harris notes, however, that mPEG disubstituted lysines may have molecular weights as high as about 100,000 and as low as about 100 to 200 Da. *Id.* at 18:31–45.

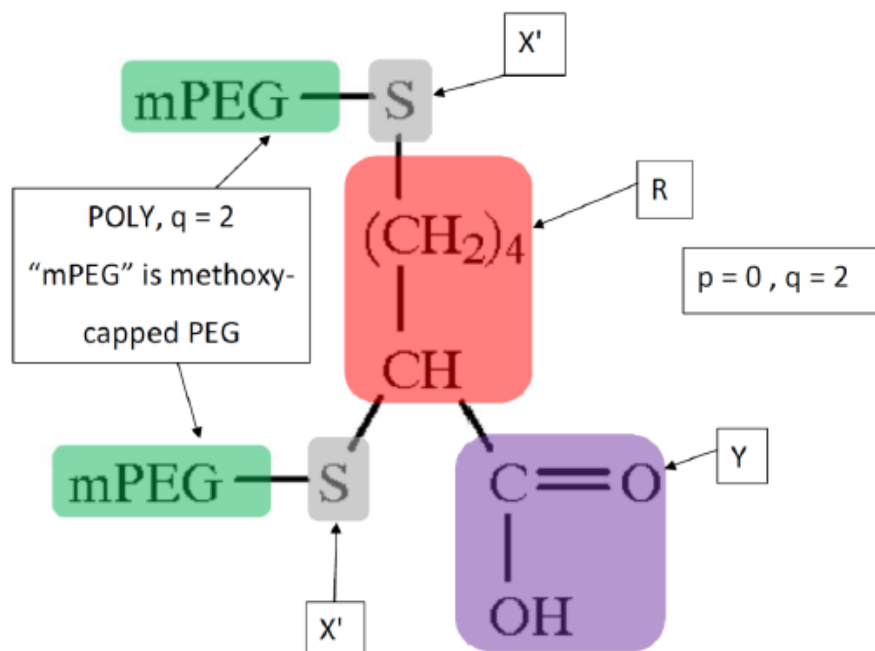
Harris discloses that a wide variety of other hydrolytically stable linkages may be used, including amine and thioether linkages, “although not necessarily with equivalent results.” *Id.* at 18:46–48, 18:56–62, 19:12–23:20. The formula of a polymer having a thioether linkage is reproduced below:



In the figure above, the mPEG disubstituted lysine is depicted having two mPEG arms, attached using thioether linkages, and a reactive carboxyl moiety. *Id.* at 9:56–60, 12:10–16, 23:11–20. The amine-linked polymer of Harris is similar in configuration to the thioether-linked polymer, but uses an amine linkage as opposed to a thioether linkage. *Id.* at 21:28–45.

2. Analysis: Claim 1

Petitioner maps the structure of the thioether-linked PEG polymer to the formula of claim 1, as follows (Pet. 40):



The figure above is an annotated and color-coded version of the thioether-linked polymer of Harris. Dr. Emrick testifies this polymer satisfies the claimed formula $Y-(X)_p-R-(X'-POLY)_q$, wherein R (red) is a five carbon residue $-(CH_2)_4CH$ of the branching core precursor (Ex. 1084 ¶ 376), POLY (green) consists of two “mPEG” chains (corresponding to $q=2$) composed of “poly(alkylene oxide),” a water soluble non-peptide polymer (*id.* ¶¶ 377, 380), X' (grey) is a thioether linkage ($-S-$) (*id.* ¶ 378), Y (purple) is a carboxyl group ($-COOH$) that is reactive with an electrophilic or nucleophilic group (*id.* ¶ 381), and X is not present, such that $p=0$ (*id.* ¶ 379).

Petitioner and Dr. Emrick concede that the molecular weight of the mPEG arms of the polymer is not shown in the annotated figure, but contend that one of ordinary skill in the art would have formed this molecule with a

total molecular weight of either 10,000 Da or 40,000 Da based on Harris's express disclosures of achieving these molecular weights using its one- or two-step methods. Pet. 40–41. Petitioner further contends that one of ordinary skill in the art would have found it obvious to use a total molecular weight of 10,000 Da based on Harris's disclosure that a 10,000 Da polymer conjugated to asparaginase provided an increase in blood circulation half-life from 27 minutes to 2,600 minutes. *Id.* at 41 (citing Ex. 1016, 30:66–31:27, 31:65–32:40, 35:40–57).

Patent Owner contends that Petitioner's evidence and arguments are insufficient to demonstrate the unpatentability of the challenged claims because: (1) the carboxyl group of the recited polymers is not a "functional group" as claimed (PO Resp. 33); (2) Petitioner has failed to establish that one of ordinary skill in the art would have selected the amine- or thioether-linked polymers for further development (*id.* at 34–41); (3) Petitioner has not shown that Harris would have supplied a reason to select a polymer within the recited molecular weight range (*id.* at 41–42); and (4) Petitioner has not shown that one of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention (*id.* at 42–43). We address these arguments in turn.

a) "functional group"

Patent Owner contends that Petitioner's arguments relying on the amine- and thioether-linked polymers of Harris fail because the carboxyl group (-COOH) of Harris "is not a functional group" as claimed. PO Resp. 33. This argument is not persuasive because Petitioner demonstrates that Harris's carboxyl group is a "functional group" under our construction of that term, i.e., a distinct, definable portion of a molecule that performs some function or activity and is reactive with other molecules. Ex. 1084 ¶ 381;

Pet. Reply 4 (citing Ex. 1001, 9:19–23, 10:55–11:61, 15:3–40), 18 (citing Ex. 1084 ¶¶ 381, 401; Ex. 1095 ¶¶ 15–18, 253). Indeed, the ’440 patent specifically identifies “alkanoic acids having a carbon length (including the carbonyl carbon) of 1 to about 25 carbon atoms (e.g., carboxylic acid[])” as suitable functional groups for the inventive polymers. Ex. 1001, 10:59–11:2.

b) Selection of Amine and Thioether Linkages

(1) The Parties’ Arguments

Petitioner contends one of ordinary skill in the art would have selected and used the amine- and thioether-linked polymers of Harris in view of Harris’s disclosure that such polymers are hydrolytically stable alternatives to the carbamate-linked polymers discussed at length in Harris. Pet. 41.

Patent Owner contends that a “lead compound” analysis is “guided by evidence of the compound’s pertinent properties,” and Harris does not describe properties specific to these polymers, such as their “stability, reactivity, toxicity” or yield. PO Resp. 34–35. According to Patent Owner, without taking these factors into account “it cannot be said that a [person of ordinary skill in the art] would have expected similar results for the amine-, thioether-, and carbamate-linked polymers.” *Id.* at 36–37. Patent Owner further argues that in some applications it may be desirable to have a hydrolytically degradable molecule and not the hydrolytically stable amine- and thioether-linked polymers of Harris. *Id.* at 36 (citing Ex. 1084 ¶ 87).

With respect to the properties of amine- and thioether-linked polymers, Patent Owner asserts that these linkages would have presented “challenges.” *Id.* at 37. In particular, Patent Owner contends that reacting an amine with a haloalkane is not a “clean” reaction and thioether linkers are a potential site of oxidation. *Id.* at 37–38 (citing Ex. 2036 ¶ 178; Ex. 2037,

950; Ex. 2038, 843–44 (organic chemistry textbooks)). In view of these known disadvantages, Patent Owner contends that one of ordinary skill in the art would have looked instead to the carbamate linkage described in Harris, which is discussed throughout the reference and represents “the only experimental data in Harris regarding branched PEG conjugates.” *Id.* at 38–39.

Petitioner asserts that Patent Owner’s arguments are unavailing because Harris identifies the amine and thioether linkages as suitable alternatives to the carbamate linkages, claim 9 of Harris includes both the amine and thioether linkages in a Markush group of only eleven members, and the ’440 patent itself claims amine, ether, and thioether linkages as alternatives, without any comparative data. Pet. Reply 19 (citing Ex. 1016, 7:30–65, 9:20–33, 10:55–11:7, 36:27–29, 37:18–39:57, 39:63–40:8 (Claims 1–11, 13–17); Ex. 1095 ¶¶ 86–89).

With respect to Patent Owner’s expressed concerns with over alkylation of amine linkages, Petitioner asserts that Harris does not describe using a haloalkane, but in any event one of ordinary skill in the art knew how to either “suppress over-alkylation, use alternative methods (e.g., reductive amination) and/or separate reaction product.” *Id.* (citing Ex. 1095 ¶¶ 81–83, 85). With respect to oxidation of thioether linkages, Petitioner contends that one of ordinary skill in the art would have been aware of the issue and been able to select appropriate conditions to avoid oxidation, as evidenced by the fact that the ’440 patent specifically discloses that amine and thioether linkages can be prepared using Harris’s technique. *Id.* at 19–20 (citing Ex. 1001, 8:30–59, 13:49–53; PO Resp. 38; Ex. 1095 ¶ 84).

In its Sur-Reply, Patent Owner contends that it is undisputed that amine linkages can result in overalkylation and that thioether linkages can

result in oxidation, whereas carbamate-linked polymers were actively and successfully commercialized. Sur-Reply 19. Given these known problems, Patent Owner contends that Petitioner fails to show that one of ordinary skill in the art would have selected either an amine or thioether linkage for further development, especially when carbamate-linked polymers were the most promising compounds disclosed in Harris for further development. *Id.* at 20 (citing *Takeda*, 492 F.2d at 1357).

(2) *Analysis*

Harris expressly discloses and claims the use of carbamate-, amine-, and thioether-linked polymers. Ex. 1016, 8:59–67, 17:61–18:2, 20:34–56, 21:28–45, 23:3–20, 37:66–38:3. These disclosures would have, at a minimum, suggested that amine- and thioether-linked polymers could be used successfully to achieve the benefits discussed in Harris. *See 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.”).

Although the use of either amine- or thioether-linked polymers may present overalkylation (amine) or oxidation (thioether) challenges, Petitioner persuasively demonstrates that one of ordinary skill in the art would have understood how to successfully overcome such challenges. Pet. Reply 19–20. This conclusion is further supported by the fact that the ’440 patent discloses and claims amine- and thioether-linked polymers without any expressed concern regarding overalkylation or oxidation, and without providing any express methods for avoiding such reactions. Thus, we find that the overalkylation and oxidation issues identified by Patent Owner would not have taught away from or counseled against the use of Harris’s amine- or thioether-linked polymers.

As noted by Patent Owner, Harris focuses significant attention on carbamate-linked polymers and provides its only experimental results with these polymers. The fact that carbamate linkers may be preferred, or the primary subject of focus, however, does not diminish the fact that amine- and thioether-linked polymers are taught and claimed in Harris. And, as discussed above, we reject Patent Owner's contention that Petitioner must show that such linkages were the most promising for use or further development, as opposed to being acceptable substitutes for the carbamate-linked polymers disclosed and tested in Harris. *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 view of the foregoing, we find that Harris expressly teaches or suggests the use of amine- and thioether-linked polymers for use in its multi-armed polymer derivatives.

c) Selection of a Molecular Weight of at Least 5,000 Da

Harris expressly discloses every limitation of claim 1 of the '440 patent, except the molecular weight of the mPEG arms on its amine- and thioether-linked polymers. As noted above, the record clearly demonstrates that the molecular weight of mPEG arms is a result-effective variable, and Harris discloses both a general range of molecular weights from 100 to 100,000 Da and a typical molecular weight range of 40,000 to 50,000 Da. Ex. 1016, 18:31–45 (“Polymerization of ethylene oxide to yield mPEGs usually produces molecular weights of up to about 20,000 to 25,000 g/mol. Accordingly, two-armed mPEG disubstituted lysines of molecular weight of about 40,000 to 50,000 can be made according to the invention.”). The typical range falls squarely within the claimed range of “at least about 5,000 Da” and the general range significantly overlaps the claimed range,

rendering the claimed range prima facie obvious. *See Peterson*, 315 F.3d at 1329.

In addition, Harris discloses that a carbamate-linked polymer with two 5,000 Da mPEG arms conjugated to asparaginase provided increased blood circulation half-life compared to unmodified asparaginase, and Dr. Emrick persuasively testifies that one of ordinary skill in the art would have expected similar properties would be achieved when using the alternative amine and thioether linkers disclosed in Harris. Ex. 1016, 30:66–31:27, 31:65–32:40, 35:40–57; Ex. 1084 ¶ 387. This provides another independent reason for selecting mPEG arms that would provide an overall molecular weight of “at least about 5,000 Da.”

Patent Owner contends that although Harris generally contemplates mPEG arms with molecular weights from “44 to 55,600 Da,” it also allows for molecular weights down to 100 to 200 Da. PO Resp. 41–42. Patent Owner further contends that Harris recognizes that “[t]ypically, mPEG polymers are linear polymers of molecular weight in the range of from about 1,000 to 5,000.” *Id.* at 42 (citing Ex. 1016, 4:14–15). Thus, absent evidence that the teachings regarding carbamate-linked polymers would have been applied to other linkages, Patent Owner contends that “Petitioner has failed to carry its burden to show the claims obvious in light of Harris.” *Id.*

The case law contemplates that an overlapping range will have some values within and some values outside the claimed range, i.e., an overlapping range as opposed to a fully encompassed range. *See Peterson*, 315 F.3d at 1329–30. Thus, it is of limited significance in this case that Harris allows for molecular weights down to 100 to 200 Da. In addition, Patent Owner presents no persuasive evidence to rebut the prima facie case of obviousness presented by the overlapping molecular weight ranges. For

example, Patent Owner identifies no reference that teaches away from the claimed molecular weight ranges or any evidence that the claimed molecular weight ranges provide unexpected results. Accordingly, we agree with Petitioner that the claimed molecular weight range of “about 5,000 Da” would have been *prima facie* obvious over the broad range of molecular weights recited in Harris, as well as the typical molecular weight range disclosed in the reference. *See id.* at 1329.

d) Reasonable Expectation of Success

Although Harris teaches, suggests, and claims the use of amine and thioether linkages for its disclosed multi-armed polymers, Patent Owner contends that there is insufficient evidence of record that these polymers would have similar properties to the carbamate-linked polymers disclosed in Harris. PO Resp. 42–43. Patent Owner further contends that it was understood in the art, and expressly described in the ’440 patent, that Harris’s methods are difficult and require extensive purification. *Id.* at 43 (citing *Endo Pharms., Inc. v. Actavis LLC*, 922 F.3d 1365, 1375 (Fed. Cir. 2019) (Patent Owner asserting that technological difficulties are “relevant to a reasonable expectation of success”)). Thus, Patent Owner contends that one of ordinary skill in the art would not have had a reasonable expectation of success in achieving the claimed invention. *Id.* at 42.

The claims of the ’440 patent do not require any particular level of activity or purity for the claimed polymers, and the ’440 patent and Harris both expressly disclose that the compounds claimed in Harris are useful and could be formed successfully. Ex. 1001, 1:55–2:3 (noting that Harris discloses “branched polymers [that] are useful for attaching a high molecular weight polymer to a molecule at a single attachment cite,” but noting the need in the art for easier and more flexible methods than those disclosed in

Harris); Ex. 1016, 7:33–37 (Harris disclosing that its “invention provides a branched or ‘multi-armed’ amphiphilic polymer that is monofunctional, hydrolytically stable, can be prepared in a simple, one-step reaction, and possess no aromatic moieties in the linker fragments forming the linkages with the polymer moieties”), 37:18–65 (Claims 1–8). That the process for forming Harris’s polymers is more difficult or time consuming than the later-disclosed methods of the ’440 patent does not suggest that the various disclosures of Harris identified by Petitioner could not have been implemented successfully to form the claimed polymers. Moreover, we credit the testimony of Dr. Emrick that one of ordinary skill in the art would have expected that the amine- and thioether-linked polymers of Harris would have similar properties to the carbamate-linked polymers described and tested in Harris. Ex. 1084 ¶¶ 387–388; Ex. 1095 ¶¶ 76–79, 86. Thus, we find one of ordinary skill in the art would have had a reasonable expectation of success in applying the express teachings of Harris to arrive at the claimed invention.

e) Conclusion

Petitioner persuasively explains where Harris teaches or suggests every limitation of claim 1 of the ’440 patent. Petitioner also persuasively explains why one of ordinary skill in the art would have followed the teachings of Harris to arrive at the invention recited in claim 1 with a reasonable expectation of success.

As noted above with respect to the Bentley grounds, Patent Owner’s evidence of secondary considerations is entitled to little, if any, weight.

Considering Petitioner’s obviousness arguments in combination with Patent Owner’s evidence of secondary considerations, we determine that

Petitioner demonstrates by a preponderance of the evidence that claim 1 is unpatentable as having been obvious over Harris.

3. *Analysis: Dependent Claims 2, 3, 5, 8–10, 12–14, 20, and 29–35*

With respect to claims 2, 3, 5, 8–10, 12–14, 20, and 29–35, Petitioner persuasively demonstrates that Harris teaches or suggests: (1) a thioether (–S–) linkage (claim 2) (Pet. 42 (citing Ex. 1084 ¶ 390)); (2) two mPEG arms (q=2) (claim 3) (*id.* (citing Ex. 1084 ¶ 391)); (3) an aliphatic hydrocarbon core (R) with five carbon atoms (claim 5) (*id.* (citing Ex. 1084 ¶ 392)); (4) POLY arms that are covalently attached to a methoxy capping group (claims 8, 9, and 10) (*id.* at 44–45 (citing Ex. 1084 ¶¶ 398–400)); (5) activating the carboxyl functional group to form active carbonates, etc. (claim 12) (*id.* at 45–46 (citing Ex. 1084 ¶¶ 401–402)); (6) two linear poly(ethylene glycol) (mPEG) arms (claims 13 and 14) (*id.* at 46 (citing Ex. 1084 ¶¶ 404–405)); (7) using the disclosed polymers to form a biologically active conjugate (claim 20) (*id.* at 48–49 (citing Ex. 1084 ¶ 413)); (8) a branched reactive polymer having the structure –HO–R[–X' – POLY]_q (claim 30) (*id.* at 49–50 (citing Ex. 1084 ¶¶ 416–418)); and (9) a range of molecular weights that fall within or overlap with the claimed ranges of “at least about 5,000 to about 100,000 Da” (claim 32), “at least about 5,000 to about 60,000 Da” (claim 33), “at least about 8,000 to about 40,000 Da” (claim 34), and “about 2,500 to about 30,000 Da” (claim 35) (*id.* at 51–52 (citing Ex. 1084 ¶¶ 420–426)).

Petitioner also persuasively demonstrates that Harris teaches or suggests every limitation of claim 29, including wherein X' = (–S–) (*id.* at 49 (citing Ex. 1084 ¶¶ 414–415)), as well as every limitation of claim 31, wherein the thioether-linked polymer of Harris is conjugated to a biologically active material (*id.* at 50 (citing Ex. 1084 ¶ 419)).

Patent Owner does not dispute Petitioner's arguments with respect to claims 2, 3, 5, 8–10, 12–14, and 29–35, apart from its arguments with respect to independent claim 1 discussed above.

Upon review of Petitioner's arguments and supporting evidence, we find that Petitioner demonstrates by a preponderance of the evidence that the subject matter of claims 2, 3, 5, 8–10, 12–14, 20, and 29–35 would have been obvious over Harris. Pet. 42, 44–46, 48–53.

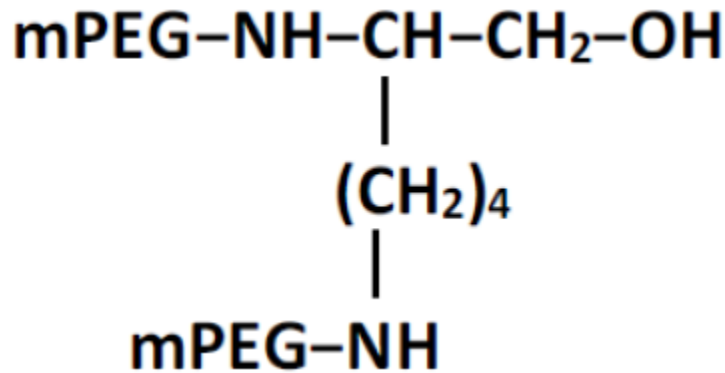
4. *Dependent claims 7, 15, and 16*

Petitioner also contends that claims 7, 15, and 16 would have been obvious over Harris. Pet. 42–44, 46–48. Patent Owner disputes Petitioner's arguments with respect to these claims. PO Resp. 44–47. We address the parties' arguments below.

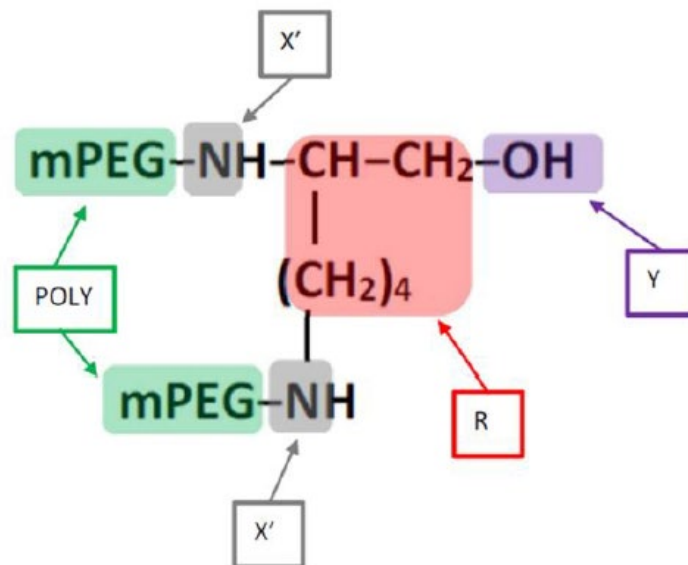
a) *Analysis: Claims 7 and 16*

Claim 7 depends from claim 1 and further requires “wherein each POLY and the Y functional group are attached to different carbon atoms of R.” Ex. 1001, 24:41–43. Claim 16 depends from claim 1 and further requires “wherein p is 0 and Y is a hydroxyl.” *Id.* at 25:10–11.

Petitioner contends that Harris teaches substitution of diamino alcohol linkers in place of lysine linkers and that such linkers may be disubstituted at the amines with activated mPEG. Pet. 42–43 (citing Ex. 1016, 23:66–25:3, 25:52–61). Petitioner contends such a heteroatom branched polymer would have the following structure:



The figure above is Petitioner's depiction of the diamino heteroatom of Harris. *Id.* at 43. Petitioner maps this structure to the limitations of claims 1, 7, and 16, as follows:



The figure above is annotated by Petitioner to identify the X', R, Y, and POLY limitations of claims 1, 7, and 16. As shown in the figure, Petitioner contends Harris discloses a diamino polymer with two (q=2) POLY (poly(alkylene glycol)) arms (green), a X' (-NH-) heteroatom linkage (grey), no linker (p=0), and a Y functional group in the form of a hydroxyl group (-OH) (purple). *Id.* at 43, 47. With respect to molecular weight, Petitioner repeats its arguments set forth above for claim 1, i.e., that the molecular weight ranges expressly disclosed and used in Harris either fall entirely

within or substantially overlap the range recited in claim 1. *Id.* In view of these disclosures, Petitioner contends the subject matter of claims 7 and 16 would have been obvious over the diamino heteroatom branched polymer of Harris. *Id.* at 42–44, 47–48.

Patent Owner contends Petitioner’s arguments “start[] from scratch” to build a new molecule off a completely different linker moiety, yet “Petitioner fails to explain why a [person of ordinary skill in the art] would have pursued the diamino alcohol polymer over a disubstituted lysine,” or pursued a synthesis that would produce amine linkages versus the carbamates depicted by Harris. PO Resp. 44–45.

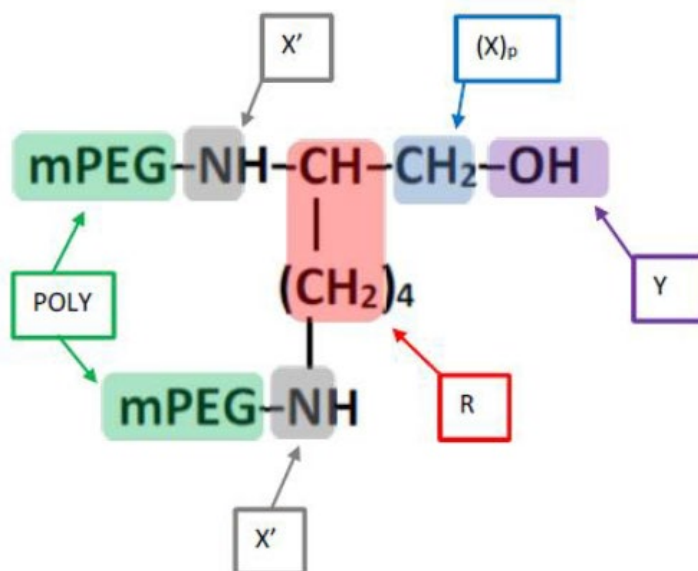
Harris expressly discloses the use of disubstituted, diamino alcohol polymers and the use of amine linkages, and Petitioner explains sufficiently why the combined polymer renders claims 7 and 16 obvious. Although we agree with Patent Owner that Harris does not disclose that diamino alcohol-linked polymers are preferred or superior to carbamate-linked polymers, Petitioner need not show that a disclosed alternative is the most preferred embodiment in order to render the claimed polymers obvious. *See Fulton*, 391 F.3d at 1200 (“Thus, 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.”). Accordingly, Petitioner demonstrates by a preponderance of the evidence that claims 7 and 16 would have been obvious over Harris.

b) Analysis: Claim 15

Claim 15 depends from claim 1 and further requires “wherein p is 1 and X is selected from the group consisting of a heteroatom, -alkylene, -O-

alkylene-O-, -alkylene-O-alkylene, -aryl-O-, -O-aryl, (-O-alkylene-)*m*, and (-alkylene-O-)*m*, wherein *m* is 1–10.” Ex. 1001, 25:5–9.

Petitioner contends that the diamino alcohol polymer described above with respect to claim 7 is a polymer wherein *p* is 1 and the heteroatom *X* is an alkylene. Pet. 46–47. In mapping the diamino alcohol polymer structure to the limitations of claim 15, Petitioner alters its identification of (*X*)_{*p*} and *R*, as follows:



The annotated and color coded figure above depicts Petitioner’s mapping of the diamino alcohol structure of Harris to the limitations of claim 15. As shown in the figure above, Petitioner identifies five carbons (red) as *R* and CH₂ (blue) as the (*X*)_{*p*} linker. *Id.* at 47. This mapping differs from that for claims 7 and 16 in that Petitioner does not identify the CH₂ group (blue) as part of the aliphatic carbon core (*R*), but instead as a linker moiety wherein *p*=1.

Patent Owner contends that Petitioner arbitrarily identifies the linker as CH₂ in its arguments against claim 15, and asserts that one of ordinary skill in the art “would have been wary of adding such a linker due to the

possibility for antigenicity, toxicity, loss of activity, and hydrophilicity.”
PO Resp. 45 (citing Ex. 2036 ¶ 220; Ex. 2040, 80:17–81:17).

Contrary to Patent Owner’s argument, Petitioner does not seek to add an additional CH₂ to the diamino alcohol polymer taught or suggested in Harris. Pet. Reply 21–22. Rather, Petitioner simply notes that one can change the claim mapping to identify CH₂ as a linker instead of as part of the aliphatic carbon R. As such, Patent Owner’s arguments regarding the addition of a linker are unavailing.

Upon review of the parties’ arguments and supporting evidence, we determine that Petitioner demonstrates by a preponderance of the evidence that claim 15 would have been obvious over Harris.

c) Conclusion

For the reasons set forth above, we find that Petitioner demonstrates by a preponderance of the evidence that claims 7, 15, and 16 would have been obvious over Harris.

H. Anticipation of Claims 29 and 31 by Harris

Claim 29 is independent and differs from claim 1 in relevant part in that “X’ is –NH–, –O–, or –S–,” no molecular weight is recited for the branched reactive polymer, and each POLY is “covalently attached to a methoxy capping group.” Ex. 1001, 26:14–35. Claim 31 is similar to claim 29 but requires a “biologically active conjugate, comprising a biologically active molecule covalently attached to a branched reactive polymer,” and the POLY need not include a methoxy capping group. *Id.* at 26:54–27:8.

In addition to its arguments with respect to claim 1, Petitioner contends that claim 29 is anticipated by Harris because Harris’s mPEG arms have methoxy capping groups. Pet. 54 (citing Ex. 1016, 3:62–4:3, 8:37–49, 11:50–53, 18:11–37). Petitioner further contends that claim 31 is anticipated

by Harris because Harris is directed to branched polymers that are intended “for attachment to biologically active molecules such as proteins.” *Id.* at 55 (citing Ex. 1016, 9:10–33, 10:48–64, 11:66–12:16, 25:26–51, 28:31–29:12, Abstract).

Patent Owner contends that claim 29 is not anticipated by Harris because Petitioner has not demonstrated that the carboxyl moiety of Harris (–COOH–) will react readily with another chemical moiety. PO Resp. 46. Patent Owner’s counter-argument is unavailing because the claims do not require that the functional group “react readily” with another chemical moiety. Thus, because Harris’s mPEG arms have a methoxy capping group, we determine that Petitioner demonstrates by a preponderance of the evidence that claim 29 is anticipated by Harris.

With respect to claim 31, Patent Owner argues that Harris fails to teach or disclose conjugating either amine- or thioether-linked polymers to a biologically active molecule, and the general statements of Harris referring to biologically active conjugates are not sufficient to show that the cited polymers “necessarily existed as conjugates to a biologically active molecule.” PO Resp. 46–47.

Although we are directed to no express disclosure or description of the specific amine- or thioether-linked polymers of Harris being attached to a biologically active molecule, this is one of the primary intended purposes for Harris’s polymer derivatives. Ex. 1016, 7:50–54 (“The 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.”), 9:27–31 (“The invention includes biologically active conjugates comprising a biomolecule, which is a biologically active molecule, such as a protein or enzyme, linked through an active moiety to the branched polymer

derivative of the invention.”). Harris also provides an express disclosure of attaching one disclosed multi-armed polymer to a biologically active material. *Id.* at 30:64–35:23. As such, we agree with Petitioner that one of ordinary skill in the art would immediately understand that the amine and thioether linkages of Harris were intended for conjugation to a biologically active molecule. Accordingly, claim 31 is anticipated by Harris. *See Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1344 (Fed. Cir. 2016) (noting that a reference need not “include an express discussion of the actual combination to anticipate . . . if that reference teaches that the disclosed components or functionalities may be combined and one of ordinary skill in the art would be able to implement the combination.”); *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995).

I. Remaining Grounds

Having determined that all challenged claims of the ’440 patent would have been obvious over, or are anticipated by, one or more of Bentley, Harris, and JP-542, we do not address Petitioner’s arguments that claims 1–15, 17, 19–20, 29 and 31–35 would also have been obvious over the combination of JP-542 and MDD or the combination of JP-542 and Bentley. Pet. 53–55, 75–80. *See SAS Inst.*, 138 S. Ct. at 1359; *Boston Sci.*, 2020 WL 2071962, at *4.

III. CONSTITUTIONAL CHALLENGE

Patent Owner contends subjecting the ’440 patent to *inter partes* review violates its constitutional rights. In particular, Patent Owner contends (1) that subjecting a patent effectively filed before September 16, 2012 to *inter partes* review “is an impermissibly retroactive, unconstitutional taking”; (2) subjecting a pre-AIA patent to *inter partes* review “violates the Due Process Clause of the Fifth Amendment by

eviscerating the Patent Owner’s substantive vested rights”; and (3) *inter parties* review violates the “Appointments Clause, rendering it constitutionally impermissible for the PTAB to order the cancellation of any patent claims.” PO Resp. 60–64.

Patent Owner’s arguments 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. CONCLUSION¹⁸

Petitioner has shown by a preponderance of the evidence that claims 1–8, 11–15, 17, 19, 20, 29, 31–33, and 35 are anticipated by JP-542 and claims 29 and 31 are anticipated by Harris. Petitioner has also shown by a preponderance of the evidence that the subject matter of claims 1–20 and 29–35 would have been obvious over one or more of Bentley, Harris, and Bentley in view of Liebig.

¹⁸ 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).

In summary:

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–15, 19, 32–35	103(a)	Bentley	1–15, 19, 32– 35	
16, 20, 29– 31	103(a)	Bentley ¹⁹		
16–18, 30	103(a)	Bentley, Liebig's	16–18, 30	
1–3, 5, 7– 10, 12–16, 20, 29–35	103(a)	Harris	1–3, 5, 7–10, 12–16, 20, 29–35	
29, 31	102(b)	Harris	29, 31	
1–15, 17, 19, 20, 29, 31–33, 35	102(b)	JP-542	1–8, 11–15, 17, 19, 20, 29, 31–33, 35	9, 10
1–15, 17 19, 20, 29, 31–35	103(a)	JP-542, MDD ²⁰		
16–18, 30	103(a)	JP-542, Bentley ²¹		
Overall Outcome			1–20, 29–35	

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–20 and 29–35 of U.S. Patent

No. 7,026,440 B2 are unpatentable; and

¹⁹ For the reasons discussed above, we do not address obviousness of claims 16, 20, and 29–31 over Bentley.

²⁰ For the reasons discussed above, we do not address obviousness of claims 1–15, 17, 19, 20, 29, 31–35 over JP-542 and MDD.

²¹ For the reasons discussed above, we do not address obviousness of claims 16–18, 30 over JP-542 and Bentley.

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.

IPR2019-01394
Patent 7,026,440 B2

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