

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ITM ISOTOPE TECHNOLOGIES MUNICH SE,
Petitioner,

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

PGR2025-00012
Patent 11,938,201 B2

Before JEFFREY N. FREDMAN, JAMES A. WORTH, and DEBRA L.
DENNETT, *Administrative Patent Judges*.

DENNETT, *Administrative Patent Judge*.

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

I. INTRODUCTION

ITM Isotope Technologies Munich SE (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting post-grant review of claims 1–3 (the “challenged claims”) of U.S. Patent No. 11,938,201 B2 (Ex. 1001, “the ’201 patent”). The Johns Hopkins University (“Patent Owner”) filed a Preliminary Response. Paper 8 (“Prelim. Resp.”).

We have authority to determine whether to institute a post-grant review under 35 U.S.C. § 324. Institution of a post-grant review is authorized by statute when “the information presented in the petition . . . would demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable.” 35 U.S.C. § 324(a). A post-grant review may also be instituted when “the petition raises a novel or unsettled legal question that is important to other patents or patent applications.” *See id.* § 324(b). Applying that standard on behalf of the Director (37 C.F.R. § 42.4(a)) and in consideration of the Petition, Preliminary Response, and the evidence of record, we determine that the information presented shows that it is more likely than not that Petitioner would prevail in establishing unpatentability of claims 1–3 of the ’201 patent.

This decision to institute trial is not a final decision as to patentability of claims for which post-grant review is instituted. Our final decision will be based on the full record developed during trial.

II. BACKGROUND

A. *Real Parties-in-Interest*

Petitioner identifies ITM Isotope Technologies Munich SE as the real party-in-interest. Pet. 101. Patent Owner identifies The Johns Hopkins University as the real party-in-interest. Paper 4, 1.

B. Related Proceedings

Petitioner states, regarding related matters, “Petitioner is not aware of any related matters that would affect or be affected by this proceeding.” Pet. 101. Patent Owner states that the ’201 patent claims the benefit of pending U.S. Patent Application No. 16/758,182. Paper 4, 1.

C. The ’201 Patent

The ’201 patent issued March 26, 2024, from U.S. Application 18/354,282, filed July 18, 2023. Ex. 1001, codes (45), (21), (22). The ’201 patent is a continuation of U.S. Application No. 16/758,182, filed as application No. PCT/US2018/057086 on Oct. 23, 2018, which claims the priority benefit of provisional application No. 62/575,607, filed on Oct. 23, 2017. *Id.*, codes (63), (60). A Certificate of Correction (“Certif. Corr.”) of claims 1 and 3 issued Sept. 24, 2024.

The ’201 patent is drawn to compounds of Formula (I): B-L-A in which A is a targeting moiety for fibroblast-activation protein- α (FAP- α) and has a specified structure, B is an optical or radiolabeled functional group suitable for various kinds of imaging, and L is a linker having bi-functionalization adapted to form a chemical bond with B and A. Ex. 1001, 2:3-29.

FAP- α is a type II integral membrane serine protease predominately expressed by activated fibroblasts. The ’201 patent teaches that FAP- α expression has been detected on the surface of fibroblasts in the stroma surrounding greater than 90% of epithelial cancers and inflammation diseases, with nearly no expression in healthy adult tissues. Ex. 1001, 6:64–7:9. FAP- α ’s characteristics make it a potential imaging and radiotherapeutic target for cancer and inflammation diseases. *Id.* at 1:46–48.

The '201 patent teaches that because FAP- α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmuno-targeting of malignancies and inflammation, but their use as molecular imaging agents suffers from pharmacokinetic limitations. Ex. 1001, 1:49–58. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration, and can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval, according to the '201 patent. *Id.* at 1:60–64.

Inhibitors selectively targeting FAP- α are known. Ex. 1001, 7:13–14. The '201 patent teaches a FAP- α selective targeting moiety that can be modified with an optical dye, a radiometal chelation complex, and other radiolabeled prosthetic groups to provide a compound that can be used for both imaging and radiotherapy based on targeting FAP- α . *Id.* at 7:16–21.

D. Illustrative Claim

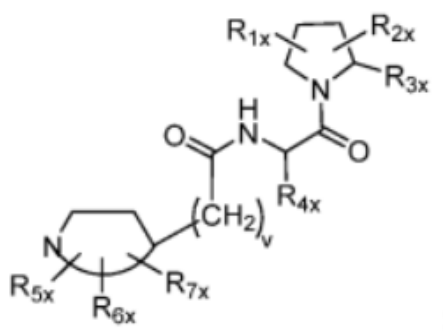
Claim 1 illustrates the challenged claims in the '201 patent, and is reproduced below.

1. A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP- α , wherein A has the structure of:



wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

R_{3x} is selected from the group consisting of H, $-CN$, $-B(OH)_2$, $-C(O)alkyl$, $-C(O)aryl$ -, $-C=C-C(O)aryl$, $-C=C-S(O)_2aryl$; $-CO_2H$, $-SO_3H$, $-SO_2NH_2$, $-PO_3H_2$, and 5-tetrazolyl;

R_{4x} is H;

R_{5x} , R_{6x} and R_{7x} are each H;

v is 0;



represent a quinolinyl ring;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

Ex. 1001, Certif. Corr.

E. Asserted Grounds

Petitioner contends that the challenged claims are unpatentable based on several grounds that are presented below.

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged
I	Jansen I ¹ and/or Jansen II, ² Zimmerman, ³ Pomper ⁴	§ 103	1–3
II	Dvořáková, ⁵ Pomper	§ 103	1–3
III	Enablement	§ 112	1–3
IV	Written Description	§ 112	1–3
V	Indefiniteness	§ 112	1–3

Petitioner also relies on the Declaration of Stephen F. Martin, Ph.D. *See* Ex. 1002. Patent Owner relies on the Declaration of Henry VanBrocklin, Ph.D. *See* Ex. 2002.

III. PRELIMINARY MATTERS

A. Post-Grant Review Eligibility

As a threshold issue, we must determine whether the '201 patent is eligible for post-grant review. There are two requirements that must be met for post-grant review to be available. First, post-grant review is only available if the petition is filed within nine months of the issuance of the challenged patent. 35 U.S.C. § 321(c). Petitioner certifies that the petition was filed within nine months of the '201 patent's issue date. Pet. 102.

¹ US 9,346,814 B2, issued May 24, 2016 (Ex. 1007, "Jansen I").

² K. Jansen et al., *Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold*, 2013(4) ACS MEDICINAL CHEMISTRY, 491-96 (2013) (Ex. 1010, "Jansen II").

³ US 2010/0098633, published Apr. 22, 2010 (Ex. 1009, "Zimmerman").

⁴ US 2012/0009121, published Jan. 12, 2012 (Ex. 1006, "Pomper").

⁵ P. Dvořáková et al., *Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein*, 60 JOURNAL OF MEDICINAL CHEMISTRY 8385–8394 (2017), available at <https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b00767> (Ex. 1008, "Dvořáková").

Second, post-grant review is available only for patents that issue from applications that at one point contained at least one claim with an effective filing date of March 16, 2013, or later. *See* Pub. L. No. 112-29, §§ 3(n)(1), 6(f)(2)(A). Here, the priority dates recited for the '201 patent do not include filings prior to March 16, 2013. Ex. 1001, codes (63), (60).

The '201 patent is eligible for post-grant review as the effective filing date is no earlier than Oct. 23, 2017, the filing date of the provisional application. Ex. 1001, code (60).

B. Level of Ordinary Skill in the Art

We consider the grounds of unpatentability in view of the understanding of a person of ordinary skill in the art (sometimes referred to herein as “POSA”) as of the effective filing date of the challenged claims.

Petitioner contends that one of ordinary skill in the art would have had

a Bachelor's degree in organic chemistry or a related field such as medicinal chemistry and two to five years of experience employing organic chemistry as a tool for the development of molecules with targeted biological activity. EX1002 at ¶ 95. A POSA could also include individuals with a Master's degree or a Ph.D. in chemistry or a related field with comparatively less experience. *Id.* A POSA would have an understanding of processes employed for synthesis and evaluation of imaging and radiotherapeutics agents that selectively target a specific protein and would be able to evaluate published literature and patents to ascertain those features of a molecule that contribute to its affinity and selectivity for a particular drug target. *Id.*

Pet. 26.

Patent Owner contends that this definition is insufficient in view of the '201 patent's and the cited prior art's overall focus on imaging and radiotherapeutic agents. Prelim. Resp. 6. Patent Owner argues that

POSAs would, critically, have had *multiple years of both formal training and actual, practical experience* in i) nuclear or optical

imaging, or ii) radiotherapeutics (collectively, radiopharmaceuticals), as well as in radiopharmaceutical development, and in using molecular imaging techniques (such as positron emission tomography and single photon emission computed tomography).

Id. at 6–7. Patent Owner argues that Petitioner’s declarant, Dr. Martin, does not appear to possess the level of skill of a POSA. *Id.* at 7.

At this stage of the proceedings, neither Petitioner’s nor Patent Owner’s proffered definitions of the level of skill appear appropriate. Petitioner’s proposal requires as little as a bachelor’s degree in organic chemistry and two years of experience as a laboratory technician working on development of molecules with targeted biological activity, and an ambiguous “understanding” of certain processes. Patent Owner’s proposal, other the other hand, requires multiple years of both formal training and actual, practical experience in highly specialized fields that involve *detection* of optical or radiolabeled compounds and *use* of molecular imaging techniques such as PET and SPECT.

For the purposes of this decision, on the record at this time, we find that a POSA would have had a Ph.D. in chemistry, biochemistry, or a comparable field or an M.D., and at least four years of experience in chemical synthesis of compounds that may be used to target biologically-significant tissues. This definition appears consistent with the level of skill shown in the prior art references of record. *See Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007).

The parties will have the opportunity to cross-examine Dr. Martin and Dr. VanBrocklin in this proceeding to develop a full record for us to determine the weight that each expert’s testimony should be given. We invite the parties to further brief the definition of a POSA here, and whether we should discount either experts’ testimony due to lack of qualifications.

C. Claim Construction

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

The parties dispute the construction of (1) low molecular weight, and (2) C(O)alkyl / aryl.

1. low molecular weight

The preamble of independent claims 1 and 3 begins: “[a] low molecular weight compound.” Ex. 1001, Certif. Corr.

a) Petitioner’s position

Petitioner asserts that “low molecular weight” is “a relative term that is not defined in the specification and has no objective boundaries to a POSA.” Pet. 40. Petitioner argues that “‘low molecular weight’ appears only three times in the [S]pecification of the ’201 patent, and its use is not tied to any particular defined range.” *Id.* at 41 (citing Ex. 1001, 1:60-67, 7:44-54; Ex. 1002 at ¶¶ 99-100). Petitioner argues that, during prosecution, in an attempt to overcome the prior art, Patent Owner added “low molecular weight” to the claims, arguing that a POSA “would recognize that low molecular weight compounds would have a molecular weight of typically from ***about 50 Daltons to about 1,500 Daltons***,”⁶ citing literature related to metabolites. *Id.* (citing Ex. 1004 at 1215 (Office Action Response); Ex. 1004 at 1198 (Pomper Declaration); Ex. 1004 at 1273 (Supplemental

⁶ “Dalton” is often abbreviated as “Da.”

Amendment); Ex. 1002, ¶ 101). Petitioner argues that the subject matter of the '201 patent, however, is unrelated to metabolites and the general, non-limiting statement about what is “typical” would not have defined or otherwise informed a POSA as to the scope of the term “low molecular weight” as used in the claims. *Id.* (citing Ex. 1002, ¶ 102).

Petitioner additionally argues that construing the phrase “low molecular weight” as from “about 50 Daltons to about 1,500 Daltons” would improperly exclude several disclosed embodiments of the '201 patent, each having a molecular weight greater than 1,500 Da. Pet. 42; *see also* Ex. 1002, ¶ 103. Petitioner notes that courts have routinely rejected narrow claim constructions that improperly read disclosed embodiments out of the claim. *Id.*

b) Patent Owner’s position

Patent Owner asserts that “POSAs with the requisite training and experience in radiotherapeutics or imaging *would*, in fact, have understood [low molecular weight’s] meaning in the context of the '201 patent.” Prelim. Resp. 23. Patent Owner asserts that the well-accepted, plain and ordinary meaning in the field would have been compounds with a molecular weight of typically from about 50 Da to about 1,500 Da. *Id.* at 24 (citing Ex. 2002, ¶ 60).

The specification of the '201 patent incorporates by reference US 2012/0009121 to Pomper (Ex. 1006). Ex. 1001, 17:45–53. Patent Owner argues that Pomper expressly describes its targeting compounds for imaging and therapy as “low molecular weight” and discloses a variety of such compounds with molecular weights up to about 1,586 Da. Prelim. Resp. 24–25 (citing Ex. 1006, ¶ 12 and Ex. 2002, ¶¶ 61–62). Patent Owner contends

that incorporation of Pomper in the '201 patent shows that “low molecular weight” is used according to its plain and ordinary meaning. *Id.* at 25.

Patent Owner further argues that the prosecution history of the '201 patent provides evidence on the meaning of “low molecular weight.” Prelim. Resp. 25. Patent Owner refers to a declaration submitted by Dr. Pomper, one of the inventors on the '201 patent, in which Dr. Pomper states that he distinguishes between the low molecular weight compounds of the then-pending claims and larger biologic compounds such as antibodies and high relative molecular mass polymers, and that the term is “well accepted in the chemical arts.” *Id.*; Ex. 1004, 1197–98. Dr. Pomper testified that “low molecular weight compounds would have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons.” Ex. 1004, 1197–98; *see also* Prelim. Resp. 25.

c) Analysis

On the present record, we find that “low molecular weight” is not limited to Patent Owner’s proposed “from about 50 Daltons to about 1,500 Daltons.” The cited evidence relied on in the Pomper Declaration all concerns metabolomics and metabolites, and we find no reason that even a vague definition of metabolites applies to the claimed compounds. *See* Ex. 1002, ¶ 102. Moreover, the uncontested fact that several of the B moieties *alone*—without the A moiety or L linker—specifically identified in the '201 patent fall outside of Patent Owner’s proposed definition is persuasive (*see id.*, ¶ 103), as we normally do not interpret claim terms in a way that excludes examples disclosed in the specification. *See, e.g., Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1305 (Fed. Cir. 2007) (rejecting proposed claim interpretation that would exclude disclosed examples in the specification).

In addition, the opinion stated in the Pomper Declaration that “the term of ‘low molecular weight’ is well accepted in the chemical arts” and the declarant “recognize[s] that low molecular weight compounds would have a molecular weight of typically form about 50 Daltons to about 1,500 Daltons” is offered by a co-inventor. We, as factfinder, have discretion to weigh the credibility of expert witnesses and to give each item of evidence such weight as appropriate. *See In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) (“[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations.”). In this case, we find that the published references on metabolites do not support the opinion. *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d at 1368 (Fed. Cir. 2004) (“[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations.”)

The Pomper reference (Ex. 1006) also uses the term “low molecular weight”—without further characterization of the term—and is uninformative as to the meaning of the term. *See* Ex. 2002, ¶ 60; Ex. 1006, ¶ 12. The table giving the molecular weight of a “selection of compounds disclosed by Pomper” (*see* Ex. 2002, ¶ 62) is not persuasive in defining “low molecular weight,” as it does not explain how those included were “selected” and does not include molecular weights for all of the examples.⁷ In addition, Patent Owner’s definition does not appear to apply to all claimed compounds.⁸

⁷ At least one of the examples (SRV73) not included in the table appears to have a molecular weight well over “about 1,500 Daltons.”

⁸ *See, e.g.*, claim 113 of Ex. 1006.

Patent Owner's arguments distinguishing "low molecular weight compounds" from "polymers" do not support an upper limit for low molecular weight compounds as "about 1,500 Daltons," given Petitioner's un rebutted evidence that polymers typically range in weight from 8,000 to 400,000 Daltons. *See id.*, ¶ 104. The same is true of contrasting low molecular weight agent with antibodies, which typically have a molecular weight of about 150,000 Daltons.⁹

We invite the parties to further address construction of "low molecular weight" in future briefing.

We will employ Patent Owner's proposed definition of "about 50 Daltons to about 1,500 Daltons" *only for the purposes of addressing the alleged obviousness grounds*. We discuss whether "low molecular weight" is indefinite in § IV.E., *infra*.

2. C(O)alkyl / aryl

The claims of the '201 patent recite that R_{3x} is selected from the group consisting of one of several options, including "C(O)alkyl" and "C(O)aryl." Ex. 1001, Certif. Corr.

a) Petitioner's position

Petitioner asserts that "alkyl" in C(O)alkyl is not limited in the number of carbon atoms present in the alkyl chain. Pet. 43 (citing Ex. 1002, ¶ 110). Petitioner points out that the '201 patent defines alkyl as follows:

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or

⁹ *See, e.g.*, C.A. Janeway, Dr. et al, Immunobiology: The Immune System in Health and Disease, 5th ed., Chap. 3, sec. 3.1 (accessed June 30, 2025), <https://www.ncbi.nlm.nih.gov/books/NBK10757/>

polyunsaturated and can include di- and multivalent groups, ***having the number of carbon atoms designated (i.e., C₁–C₁₀ means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons).***

Id. (quoting Ex. 1001, 39:43-50) (emphasis added by Petitioner). Petitioner notes that the claims recite “R_{1x} and R_{2x} are . . . selected from the group consisting of . . . C₁₋₆alkyl, –O-C₁₋₆alkyl.” *Id.* Petitioner concludes that this demonstrates that Patent Owner knew how to claim alkyl chains of a particular range of lengths when desired. *Id.*

Petitioner argues that “–C(O)aryl” is defined in the ’201 patent as “an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently.” Pet. 44 (quoting Ex. 1001, 42:64–67).

Petitioner argues that –C(O)alkyl and –C(O)aryl, as well as other alkyl and aryl options in the group of R_{3x} in the claims, should not be limited to any particular length, size, or substitution. Pet. 44.

b) Patent Owner’s position

Patent Owner asserts that POSAs reviewing the claims and specification would have understood the recited “C(O)alkyl” and “aryl” in the R_{3x} substituent of “A” to be of limited length. Prelim. Resp. 19. As support for this argument, Patent Owner points to the ’201 patent’s incorporation by reference of Jansen I and its related applications, which the ’201 patent describes as providing representative FAP- α inhibitors suitable for use with the disclosed subject matter. *Id.* (citing Ex. 1001, 8:25–9:28). Petitioner argues that Jansen I defines “alkyl groups of this invention comprise from 1 to 6 carbon atoms,” and “‘aryl’ [is] generic for a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms

selected from O, N and S; said aryl further being optionally substituted with from 1 to 3 substituents.” *Id.* at 19–20 (quoting Ex. 1007, 13–43).

Patent Owner argued that it acted as its own lexicographer to define (C(O)alkyl” and “aryl” in the claimed R_{3x} substituent of “A” via its incorporation by reference of Jansen I to be of limited length and size. Prelim. Resp. 20 (citing Ex. 2002, ¶ 58).

c) Analysis

The present record does not support Patent Owner’s position that C(O)alkyl in position R_{3x} should be construed as limited to “from 1 to 6 carbon atoms” or to any unspecified limited length and size. Prelim. Resp. 19.

The ’201 patent defines “alkyl” as “a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof” “ that has “the number of carbon atoms designated (i.e., C_1 – C_{10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons)” and “[i]n particular embodiments, the term ‘alkyl’ refers to C_{1-20} inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons” “unless otherwise stated.” Ex. 1001, 39:44–58. Although substituents at the R_{1x} position in the claims are limited to “ C_{1-6} alkyl,” those at position R_{3x} are not. Ex. 1001, Certif. Corr.

Patent Owner’s representation that “Jansen I provides ‘the following definitions’ stating that ‘alkyls groups of this invention comprise from 1 to 6 carbon atoms’” is inaccurate. *See* Prelim. Resp. 19. In fact, Jansen I states:

The term “alkyl” by itself or as part of another substituent refers to a fully saturated hydrocarbon of Formula C_xH_{2x+1} wherein x is a number greater than or equal to 1. *Generally*, alkyl groups of this invention comprise from 1 to 6 carbon atoms. Alkyl groups may be linear or branched and may be substituted as indicated herein. *When a subscript is used* herein following a carbon atom,

the subscript refers to the number of carbon atoms that the named group may contain.

Ex. 1007, 22:16–23 (emphasis added). Neither the '201 patent nor its incorporation by reference of Jansen I would have conveyed to a POSA that the “(CO)alkyl” of the substituent in the R_{3x} position in the claims is intended to comprise from one to six carbon atoms or is limited to any particular length and size.

“(C(O)alkyl,” having no number of carbon atoms designated, means “a fully saturated hydrocarbon of Formula C_xH_{2x+1} wherein x is a number greater than or equal to 1.” *Id.*

“Aryl” is defined by the '201 patent as “an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently.” Ex. 1001, 42:64–67. In contrast, Jansen I defines “aryl” as “a group of part of a group is generic for a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; said aryl further being optionally substituted with from 1 to 3 substituents as defined herein.” Ex. 1007, 22:39–43. These two definitions of “aryl” are in conflict. Patent Owner urges that the definitions in Jansen I applies, in spite of the clear distinction from the definition in the '201 patent. *See* Prelim. Resp. 19–21. “[A] claim term may be clearly redefined without an explicit statement of redefinition” and “[e]ven when guidance is not provided in explicit definitional format, the specification may define claim terms by implication such that the meaning may be found in or ascertained by a reading of the patent documents.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1320-21 (Fed. Cir. 2005) (en banc). However, Patent Owner fails to address the issue raised by defining “aryl” one way in the '201 patent, and urging a conflicting definition via the incorporation of Jansen I.

Although a patentee may, indeed, act as its own lexicographer (*see Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)), it may not define a single term in two conflicting ways. *See id.* (“[W]ords in a claim are generally given their ordinary and customary meaning, [but] a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the term is clearly stated in the patent specification or file history.”). The conflicting definitions here “fail[] to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

We encourage Patent Owner to address the conflict in future briefing.

For the purpose of addressing Petitioner’s grounds asserting obviousness, we use the definition provided in the ’201 patent, i.e., “an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently.”

IV. ANALYSIS

In a post grant review, “the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.”

Harmonic Inc. v. Avid Tech., Inc., 815 F.3d 1356, 1363 (Fed. Cir. 2016).

The petitioner ultimately bears the burden of persuasion to prove unpatentability of each challenged claim by a preponderance of the evidence. 35 U.S.C. § 326(e). This burden never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). The Board may authorize a post grant review if we determine that the information presented in the record shows that it is more likely than not that the petitioner will prevail with respect to at least one of

the claims challenged in the petition. 35 U.S.C. § 324(a). We now turn to analyzing each of Petitioner's five asserted grounds of unpatentability.

A. Ground I: Alleged Obviousness over Jansen I/II in view of Zimmerman and Pomper

1. Principles of Law

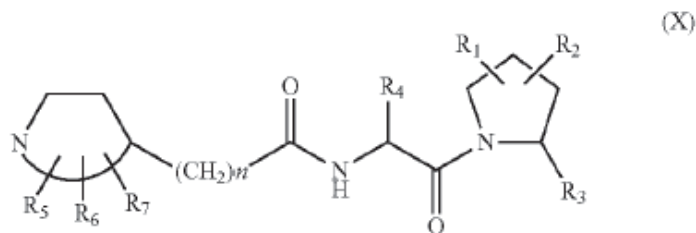
Under 35 U.S.C. § 103, a claim is unpatentable as obvious if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. 35 U.S.C. § 103; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on 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) any objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). An obviousness determination requires finding a reason to combine accompanied by a reasonable expectation of achieving what is claimed in the challenged patent. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). “[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *KSR*, 550 U.S. at 419–20.

2. Overview of the Asserted Prior Art

a) Jansen I (Ex. 1007)

Jansen I (U.S. Patent No. 9,346,814), titled “FAP Inhibitors,” issued on May 24, 2016, and claims priority to applications filed in 2012. Ex. 1007, (30), (45), (54).

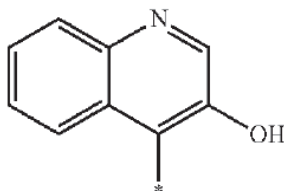
Jansen I relates to the development of inhibitors having high selectivity and specificity for FAP. Ex. 1007, Abst. Jansen I claims a compound of Formula X:



Id., 98:51–57. Jansen I discloses that n may be 0. *Id.*, 99:24. Jansen I discloses that the position of nitrogen in the substituent



is of pivotal importance to FAP affinity, with the 4-quinolinoyl ring

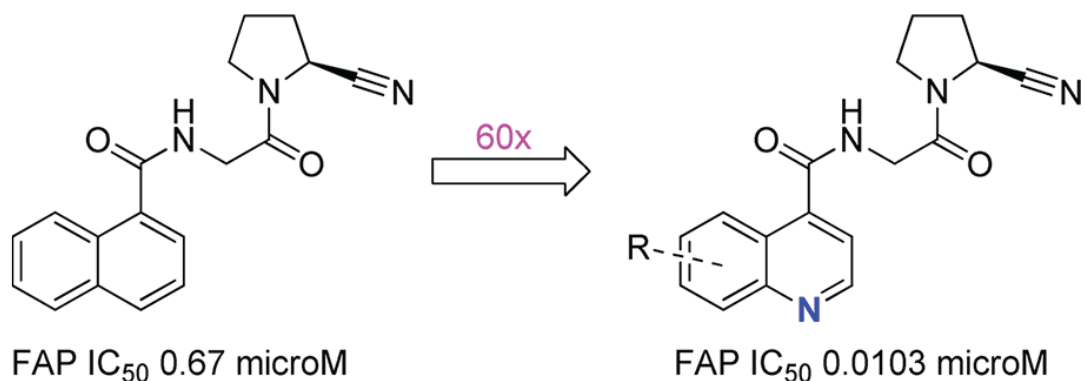


displaying the best results of those compounds studied. *Id.* at 78:24–29.

b) Jansen II (Ex. 1010)

Jansen II, titled “Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold,” was published March 18, 2013. Ex. 1010, 1.

Jansen II discloses that the *N*-(4-quinolinoyl) substituted compound had about 60 times more affinity than the base compound *N*-(1-naphthoyl):



Ex. 1010, Abst., 492 rt col.

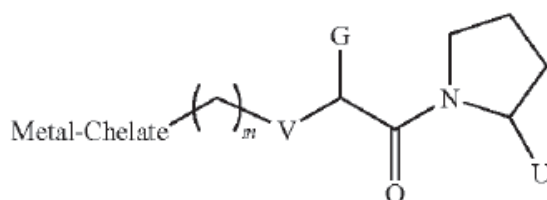
c) Zimmerman (Ex. 1009)

Zimmerman (U.S. Patent Publication No. 2010/0098633 A1), titled "Selective Seprase Inhibitors," was published on Apr. 22, 2010.

Zimmerman, (10), (43), (54). Seprase is also known as FAP- α . *Id.*, ¶ 3.

Zimmerman discloses small molecule inhibitors of seprase that can be used as therapeutic agents through inhibition of seprase's enzymatic activity, or as radiopharmaceuticals that bind to seprase to enable imaging of tissues expressing seprase, or for delivering radiotherapy to tumor tissues expressing seprase. Ex. 1009, ¶ 2. The radiopharmaceuticals include complexes or compounds that contain a functionalized proline moiety which is capable of selectively inhibiting seprase, and a radionuclide adapted for radioimaging and/or radiotherapy. *Id.*, ¶ 7.

The compounds described in Zimmerman have the following general structure:

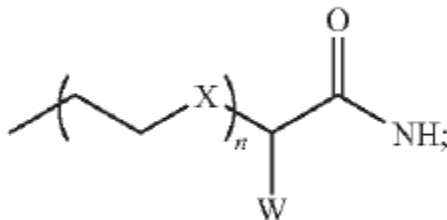


wherein:

U is selected from the group consisting of —B(OH)_2 , —CN , $\text{—CO}_2\text{H}$ and P(O)(OPh)_2 ;

G is selected from the group consisting of H, alkyl, substituted alkyl, carboxyalkyl, heteroalkyl, aryl, heteroaryl, heterocycle and arylalkyl;

V is a bond, O, S, NH, $(\text{CH}_2\text{—CH}_2\text{—X})_n$ or a group of



X is O, S, CH_2 , or NR;

R is H, Me or $\text{CH}_2\text{CO}_2\text{H}$;

W is H or NHR' ;

R' is hydrogen, acetyl, t-butyloxycarbonyl (Boc), 9H-fluoren-9-ylmethoxycarbonyl (Fmoc), trifluoroacetyl, benzoyl, benzyloxycarbonyl (Cbz) or substituted benzoyl;

n is an integer ranging from 0 to 6;

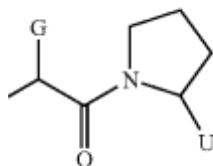
m is an integer ranging from 0 to 6;

Metal represents a metallic moiety comprising a radionuclide; and

Chelate represents a chelating moiety that chelates to said Metal.

Ex.1009, ¶¶ 8–20.

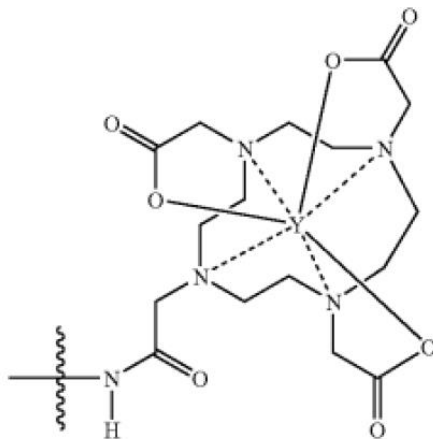
In the general structure, a proline moiety as shown below:



is attached via tether  to a Metal-Chelate. Ex. 1009, ¶ 87, claim 1. The proline moiety is capable of selectively inhibiting seprase, and the metal-

chelate or radionuclide is adapted for radioimaging and/or radiotherapy. *Id.*, ¶ 7.

Zimmerman discloses numerous Metal-Chelate moieties, including the following:



Id., ¶ 193, Table 4.

d) Pomper (Ex. 1006)

Pomper (U.S. Patent Publication No. 2012/0009121 A1), titled “PSMA-Targeting Compounds and Uses Thereof,” was published on Jan. 12, 2012, and claims priority to provisional applications filed in 2009. Ex. 1006, (10, (43), (54), (60). PSMA is prostate-specific membrane antigen. *Id.*, Abst.

Pomper describes imaging and therapeutic compounds that target and bind PSMA expressed in prostate cancer. Ex. 1006, ¶ 12. These compounds include PSMA inhibitors used to treat cancer linked to a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. *Id.*, ¶¶ 31–34.

Pomper teaches that labeled monoclonal antibodies against PSMA are clinically available, but “antibodies may have less access to tumor[s] than low molecular weight agents, which can be manipulated

pharmacologically.” Ex. 1006, ¶ 8. Pomper provides compounds with greater cellular retention and low molecular weight. *Id.*, ¶ 12.

3. *Petitioner’s Position*

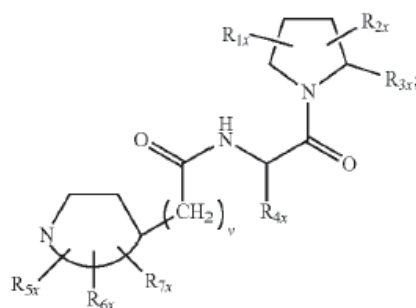
Petitioner argues that the claims of the ’201 patent are nothing more than the obvious combination of known elements. Pet. 45. Petitioner contends that Jansen I and II teach the genus of targeting moieties for FAP- α (i.e., FAP- α inhibitors A in Formula I), Zimmerman discloses components that meet “the broad functional language specified for B and L” in Formula I, and Pomper teach that low molecular weight inhibitors may have better access to tumors than larger antibodies, and low molecular weight agents had shown promise in pre-clinical imaging studies. *Id.* at 46. According to Petitioner, the art would have motivated a POSA to design and prepare low molecular weight compounds with high affinity and selectivity for FAP that would serve as imaging or therapeutic agents with a reasonable expectation of success. *Id.*

Petitioner contends that the Examiner recognized the teachings and motivations disclosed in Jansen I and II and Zimmerman, and the Examiner rejected the claims as obvious over these references. Pet. 46. *Id.* Petitioner argues that Patent Owner responded by submitting a declaration from one of the ’201 patent’s co-inventors, Dr. Martin Pomper (“Pomper Declaration, Ex. 1004, 1195–1206). Pet. 46. The Pomper Declaration asserts that the claimed compounds unexpectedly demonstrated a specificity for FAP that was several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds. Ex. 1004, 1203–05 (Pomper Decl.). Petitioner argues that Patent Owner’s unexpected results are based on only eleven examples, although the claims encompass “thousands, if not millions or more, of possible FAP inhibitors, linkers, optical dyes,

radiolabeling groups, and combinations thereof.” Pet. 47. Thus, argues Petitioner, the results shown in the Pomper Declaration are not commensurate in scope with the extremely broad claims. *Id.*

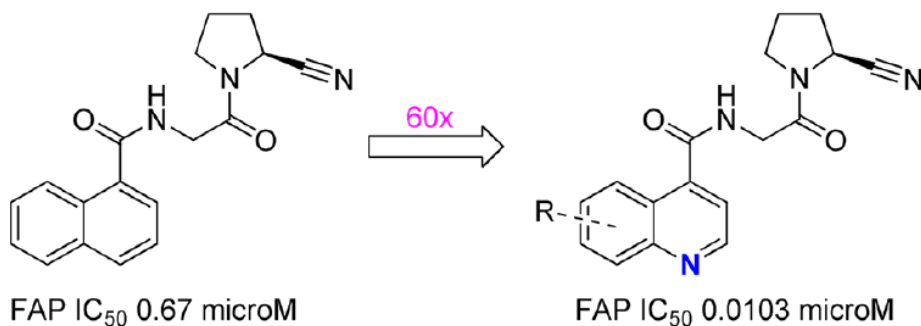
a) Claim 1

Addressing claim 1 specifically, Petitioner argues that the claimed genus of FAP- α targeting moieties, A, is not new, but rather is disclosed in Jansen I. Pet. 48. Petitioner notes that the '201 patent explains that Jansen I discloses FAP- α inhibitors with the following general structure:



Id. at 48; *see also* Ex. 1001, 8:33-52. This structure is included in the only two embodiments disclosed in the '201 patent, and in all eleven examples in the Pomper Declaration. Pet. 49.

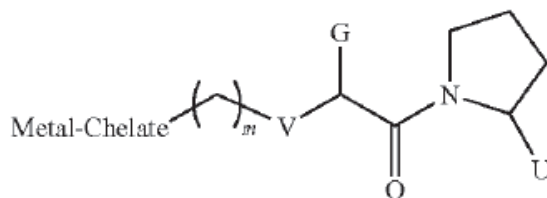
Petitioner contends that Jansen II discloses that FAP- α inhibitors containing quinoline have 60 times more FAP-affinity than N-(1-naphthoyl) based FAP inhibitors:



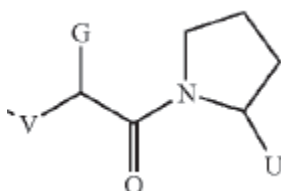
Pet. 49; *see also* Ex. 1010, Abst.

Petitioner acknowledges that neither Jansen I nor II disclose the FAP inhibitor may be attached via a linker to “any optical or radiolabeled functional group” as claimed, but alleges that Zimmermann teaches small molecular FAP- α inhibitors for use as therapeutic medicines or as radiopharmaceuticals. Pet. 50–51. Petitioner argues that “[t]he radiopharmaceuticals disclosed in Zimmerman include “complexes or compounds that contain *a functionalized proline moiety which is capable of selectively inhibiting seprase [FAP- α], and a radionuclide adapted for radioimaging and/or radiotherapy.*” *Id.* at 51 (quoting Ex. 1009, ¶ 7 (emphasis added)). Petitioner contends that Zimmerman thus “discloses the use of ‘any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy’ with a FAP inhibitor, as recited in claim 1.” *Id.* Zimmerman teaches that expression of FAP- α on tumors makes it attractive target to exploit for imaging and targeted radiotherapy. Ex. 1009, ¶ 5.

According to Petitioner, Zimmerman discloses a linker (tether) having bi-functionalization adapted to form a chemical bond with substituents A and B of Formula I. Pet. 52. Zimmerman claims a complex of Formula I:



which has a FAP- α inhibitor including a proline moiety:



that is attached via linker  to a Metal-Chelate. Ex. 1009, claim 1. The linker, per Petitioner, is not limited to any particular structure, and meets the parameters of the linker in claim 1 of the '201 patent. Pet. 52–53. Petitioner contends that Zimmerman teaches a metal-chelate moiety that is similar to the B group in XY-FAP-02-[In] disclosed in the '201 patent. *Id.* at 54. Accordingly, Zimmerman discloses components B and L of the '201 patent. *Id.* at 54–55.

Petitioner relies on Pomper, incorporated by reference in the '201 patent, for teaching the benefits of low molecular weight compounds in new imaging and therapeutic compounds targeting cancer and cancer angiogenesis. Pet. 55. Pomper discloses that antibodies used to target cancers have less access to tumors than low molecular weight agents and can be manipulated pharmacologically. Ex. 1006, ¶ 8. Petitioner argues that a POSA would have been motivated by Pomper to develop a targeting compound with a low molecular weight. Pet. 56.

According to Petitioner:

In summary, a POSA at the time of filing the '201 patent application would have been motivated to prepare the FAP- α inhibitor described in Jansen I and/or Jansen II. Ex. 1002 at ¶ 127. A POSA also would have been motivated to attach the FAP- α inhibitor of Jansen I and/or Jansen II to a radiolabeled compound via a linker for diagnostic imaging based on Zimmerman and Pomper, which teach the advantages of low molecular weight compounds, diagnostic imaging, and therapeutic treatment of diseases, to form the compound of claim 1 of the '201 patent, with a reasonable expectation of success.

Pet. 56. Dr. Martin testifies:

A POSA would expect to succeed because Jansen II clearly teaches that the quinoline-modified FAP inhibitors have improved performance over the proline-based FAP inhibitors. EX1010 at Table 1, Table 4. Thus, a POSA would be motivated

to swap the proline-based FAP inhibitor of Zimmerman with the higher performing quinoline-modified FAP inhibitors or Jansen I and/or Jansen II, to form a compound including a quinoline-modified FAP inhibitor attached via a linker to a radiolabeled compound.

Ex. 1002, ¶ 128.

b) Claim 2

Claim 2 depends from claim 1 and further recites “wherein B is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.” Ex. 1001, claim 2.

Petitioner argues that claim 2 would have been obvious over Jansen I and II in view of Zimmerman and Pomper for the same reasons as provided for claim 1. Pet. 56–57.

c) Claim 3

Claim 3 is similar to claim 1, but differs in reciting “[a] low molecular weight compound consisting essentially of components B-L-A.”¹⁰ Ex. 1001, Certif. Corr.

Petitioner argues that “consisting essentially of” does not change the motivation of a POSA to combine the teachings with a reasonable expectation of success. Pet. 57–58.

d) Secondary Indicia

Petitioner asserts that the eleven examples provided in the Pomper Declaration during prosecution of the application leading to the ’201 patent are inadequate as proof of unexpected results. Pet. 58–59. Petitioner points out that all eleven examples in the Pomper Declaration, as well as the two

¹⁰ Claim 1 recites “[a] low molecular weight compound of Formula I: B-L-A.”

examples disclosed in the '201 patent (XY-FAP-01 and XY-FAP-02-[In]) have the same FAP inhibitor (A) structure, yet the structure of A as claimed is vast as a result of substituent R_{3x} reciting “-C(O)alkyl” and “aryl.” *Id.* at (citing Ex. 1002, ¶ 133); *see also* § III.C.2., *supra*). Petitioner further argues that the structures of linker (L) and optical dyes or radiolabeling groups (B) are claimed much more broadly than the very few structures identified in the eleven examples. Pet. 59.

4. Patent Owner's Position

Some of Patent Owner's arguments regarding Grounds I and II are argued together. *See* Prelim. Resp. i–ii. Specifically, Patent Owner contends that in both Ground I and II a lead compound analysis was required, hindsight infects the grounds, and secondary considerations are inappropriately dismissed. *Id.* at 31–40, 58–60. We address all of Patent Owner's arguments relating to Ground I in the next pages. We do not repeat and separately address the lead compound analysis, hindsight, or secondary considerations in our discussion of Ground II beginning at § IV.B.

For Ground I, Patent Owner argues that Petitioner failed to make a lead compound analysis or explain why it is not required. Prelim. Resp. 31. Patent Owner contends that the references cited by Petitioner broadly disclose many dozens of FAPi compounds, and Petitioner should have identified those that were “most promising to modify” or were “a natural choice for further development efforts.” *Id.* at 31–32. Patent Owner argues that Petitioner failed to articulate any reason why a POSA would have selected any of disclosed FAPi compounds as the most promising to modify for further development efforts. *Id.* at 32.

According to Patent Owner, a POSA identifying a lead compound would have assessed the compound's FAP affinity and selectivity data, and

looked for a beneficial combination of these properties. Prelim. Resp. 33. Using this premise, Patent Owner argues that Zimmerman teaches that Formula II compounds *without* linkers have better affinity (lower IC₅₀) than Formula I compounds *with* linkers, and would have been chosen for further modification. *Id.* at 34. Patent Owner also argues that affinity and selectivity among quinolone-modified FAPis vary by three to five orders of magnitude in Jansen I and II. *Id.* at 35.

Patent Owner contends that Petitioner used hindsight to select their cited compounds for modification. Prelim. Resp. 38. According to Patent Owner, Petitioner impermissibly chose compounds for modification because the compounds were structurally similar to the claims, which Patent Owner charges is impermissible hindsight. *Id.* at 39–40.

Patent Owner argues that Petitioner fails to explain how the references would have been combined to arrive at the compounds claimed. Prelim. Resp. 40. Patent Owner argues that Petitioner is unclear on whether a POSA would have started with (1) a FAPi of Jansen I and/or II, and then added Zimmerman’s Metal-Chelate and linker, or (2) Zimmerman’s FAPi compound containing “B” and “L” moieties, and then replaced Zimmerman’s FAPi with the FAPi disclosed in Jansen I and II. *Id.* at 40–41. Patent Owner contends that Petitioner thus fails “to state with particularity which references it relies on for Ground I or how those references are to be combined to provide each element of the claims.” *Id.* at 42.

Patent Owner next argues that Petitioner provides no reason to modify the FAPis of Jansen I and II to arrive at the claimed invention. Prelim. Resp. 42. Patent Owner argues that “[t]he quinolone-modified portion of the *claimed* ‘A’ moiety is thus *unsubstituted* other than by the linker ‘L,’” but “Jansen I and II’s genus of quinolone-modified FAPis includes compounds

with both *unsubstituted* and *substituted* quinolinyl groups.” *Id.* at 43. According to Patent Owner, Jansen II teaches that the compounds with substituted quinolinyl groups had much higher selectivity compared to those with unsubstituted groups, and thus a POSA would have used a substituted FAPi of Jansen, then had to remove the substitute before adding L and B to achieve the claimed compounds. *Id.* at 43–45. Contending that removing substitutes from the quinolinyl groups would likely have destroyed the compound’s beneficial selectivity provided by substitution, Patent Owner argues that a POSA would have had no motivation to modify Jansen I or II. *Id.* at 44–45.

In addition, according to Patent Owner, a POSA would have had no reasonable expectation of success in combining Jansen I and/or II, Zimmerman, and Pomper. Prelim. Resp. 45–46. Patent Owner bases this argument first on its position stated above that Petitioner fails to articulate which prior art compounds and moieties would be modified. *Id.* at 47. Patent Owner next argues that Petitioner provides no explanation for why a POSA would have had a reasonable expectation of success of making the claimed compounds without the ’201 patent’s guidance. *Id.* Patent Owner also argues that Petitioner asserted a reasonable expectation of success in making the claimed compounds that would have “high affinity and selectivity for FAP [and] serve as an imaging or therapeutic agent,” and Petitioner must therefore provide evidence to show that the compounds would have worked for such purposes. *Id.* at 47–48.

Patent Owner asserts that Petitioner’s witness, Dr. Martin, fails to provide evidentiary support that a POSA would have had a reasonable expectation of success in making the claimed compounds, or that they would have worked for the purposes stated in the Petition. Prelim. Resp. 48–49.

Patent Owner argues that Dr. Martin's assertions are conclusory and unsupported, and are entitled to little or no weight. *Id.* at 49.

During prosecution of the '201 patent, one of the named inventors, Dr. Pomper, submitted a declaration in support of then-pending claim 29. *See* Ex. 1004, 1195. Patent Owner submits that the declaration provided

FAP selectivity data for nearly a dozen FAPi compounds covered by the claims of the '201 patent as compared to FAP selectivity data for a number of prior art FAPi compounds, including those from Zimmerman that [Petitioner] cites here. *See* EX1004, 1195, 1203-1205. As explained by Dr. Pomper, "[s]urprisingly, the specificity of the compounds covered by the pending claims for FAP is general several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds" in the prior art. *Id.* Some of the claimed FAPi compounds had a FAP selectivity *five* orders of magnitude higher than that of the prior art, reference compounds. *Id.* This heightened FAP specificity was an unexpected and highly beneficial result over the prior art showing non-obviousness of the claimed invention. EX1004, 1195, 1203-1205; EX2002, ¶¶108-111.

Prelim. Resp. 58-59. Patent Owner argues that neither Petitioner nor its declarant, Dr. Martin, contest that the results were unexpected and superior, but only that the unexpected results were not commensurate in scope with the claims. *Id.* at 59. Patent Owner contends that Petitioner's and Dr. Martin's assertions are conclusory and fail to provide "any calculation, evidence, or other support for [the] assertion of 'thousands, if not millions or more' possible compounds fall[] under the full scope of the claims." *Id.* at 60 (quoting Pet. 2, Ex. 1002, ¶¶ 133-134).

5. *Analysis*

Based on this preliminary record, we find that Petitioner has the better position.

We first address Patent Owner’s position that Petitioner did not identify a lead compound, which is allegedly fatal to the petition. *See* Prelim. Resp. 31–38.

We are not convinced that a lead compound analysis was required here. Our reviewing court has explained “[a] lead compound . . . is ‘a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity.’” *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012) (quoting *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)). The court in *Otsuka* noted

In recent cases involving the alleged obviousness of a new chemical compound in which the parties have frequently focused upon the notion that a chemist must select one or more lead compounds. . . . In such cases our analysis focuses on those proposed lead compounds that the alleged infringer has attempted to prove, by clear and convincing evidence, that the skilled artisan would have had a reason to select from the panoply of known compounds in the prior art. . . .

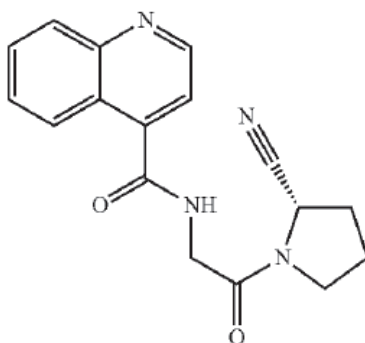
In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound’s pertinent properties. . . . Such properties may include positive attributes such as activity and potency, . . . adverse effects such as toxicity, . . . and other relevant characteristics in evidence. . . . Absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection.

Otsuka, 678 F.3d at 1291–92. The court also noted, however, that “structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, *where the prior art gives reason or motivation to make the claimed compositions*, creates a *prima facie* case of

obviousness.” *Id.* at 1292 (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc) (emphasis added)).

Unlike in *Otsuka*, here the suggested modification of a FAP- α inhibitor was not to improve on the activity of the FAP- α inhibitor *as a FAP- α inhibitor*, i.e., improve its affinity and selectivity for targeting FAP- α . Rather, the modifications were to create a new compound of a FAP- α inhibitor linked to an optical or radiolabeled functional group suitable for use in imaging or radiotherapy. Under these circumstances, a lead compound analysis is not applicable, making Patent Owner’s “most promising to modify” and “natural choice for further development efforts” arguments (*see* Prelim. Resp. 31–36) unavailing.

Moreover, contrary to Patent Owner’s contention that Petitioner asserts a POSA would have relied on Zimmerman as a starting point, and “swapped” Zimmerman’s proline-based FAP inhibitors with Jansen I/II’s quinoline-modified inhibitors (*see* Prelim. Resp. 40–42), it is clear that Petitioner looked to FAP- α targeting moieties disclosed in Jansen I and/or II as the starting point of the obviousness determination for Ground I. Petitioner specifically identified the following structure disclosed in Jansen I as the FAP inhibitor included in the only two embodiments in the ’201 patent specification:



Pet. 48–49 (citing Ex. 1007, 47:5–18). Petitioner also noted that Jansen II teaches that quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) based FAP inhibitors:



Id. at 49 (citing Ex. 1010, Abst.). A POSA would have recognized these structures as superior, tantamount to a lead compound.

Patent Owner’s contention regarding “swapping” Zimmerman’s proline-based FAP inhibitors with Jansen I/II’s quinoline-modified inhibitors is based on Petitioner’s arguments made regarding a reasonable expectation of success, and do not address how the references are to be combined. *See* Pet. 51–52, Ex. 1002, ¶¶ 118, 124, 128.

Patent Owner argues that a POSA would have selected Jansen II’s FAPi compounds with a chlorine or bromine substituent at the 5-position of the quinoline ring due to higher selectivity with respect to PREP, in comparison to FAPi compounds with substituted and unsubstituted groups, as a starting point for modifying with L and B. Prelim. Resp. 43–44. This argument focuses on a single sentence in Jansen II, and ignores the broader disclosures in Jansen I and II referenced by Petitioner.

Patent Owner further argues that a POSA “would not have removed the substituent because Jansen II teaches that removal would likely *destroy* the compound’s beneficial selectivity.” *Id.* at 44–45 (citing Ex. 1010, Table 3). “Our precedent, however, does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach

away.” *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014) (*Intel Corp. v. PACT XPP Schweiz AG*, 61 F.4th 1373, 1381 (Fed. Cir. 2023) (“And contrary to the Board’s suggestion, Intel never had to show that replacing Kabemoto’s secondary cache with Bauman’s secondary cache was an “improvement” in a categorical sense. . . . Intel just had to show that Bauman’s secondary cache was a “suitable option” to replace Kabemoto’s secondary cache.”). Petitioner explains that

[T]he art would have taught and motivated a POSA to design and prepare a low molecular weight compound with high affinity and selectivity for FAP that would serve as an imaging or therapeutic agent, and the art would have further motivated a POSA to combine these known features into the compounds recited in the claims of the ’201 patent with a reasonable expectation that such compounds would work for their desired purpose.

Pet. 46 (citing Ex. 1002, ¶ 114). Overall, Patent Owner’s argument is not persuasive.

Patent Owner contends that Petitioner failed to meet its burden to show a reasonable expectation of success in relation to Ground I. Prelim. Resp. 46. We disagree. Petitioner explained that the a POSA would have had a reasonable expectation of success based on Zimmerman’s disclosure of a proline moiety linked to a radionuclide adapted for radioimaging and/or radiotherapy (Ex. 1009, Abst.), and Pomper’s disclosure of the benefits of low molecular weight compounds in accessing tumors (Ex. 1006, ¶ 6). Pet. 46.

Patent Owner provides no separate discussion in relation to claims 2 and 3, other than asserting Petitioner provides no statement of reasonable expectation of success for these claims. Prelim. Resp. 46–47. We disagree, as Petitioner explicitly relied on arguments made in relation to claim 1. Pet. 56–58.

As to the issue of secondary indicia of nonobviousness, Petitioner has the burden to show the evidence of unexpected results is not commensurate with the scope of the claims. *FanDuel, Inc. v. Interactive Games LLC*, 966 F.3d 1334, 1341 (Fed. Cir. 2020) (“In an inter partes review, the burden of persuasion is on the petitioner to prove ‘unpatentability by a preponderance of the evidence,’ 35 U.S.C. § 316(e), and that burden never shifts to the patentee.”). On the current record, Petitioner has met that burden.

As Petitioner explained, and Patent Owner does not dispute, all of the examples tested in the Pomper declaration as well as the two examples in the ’201 patent include the same FAPi (A) structure, i.e., R_{3x} is $-CN$ in all compounds tested. Pet. 58. The claimed structure of A is significantly broader due to the possibilities included in R_{3x} . In addition, “B” is claimed broadly as “any optical or radiolabeled functional group suitable for” several imaging uses or radiotherapy, and “L” is claimed broadly as “a linker having bi-functionalization adapted to form a chemical bond with B and A,” but the Pomper Declaration provides results on very limited examples for B and L. The evidence of unexpected results is plainly not commensurate with the much broader scope of the claims.

On this preliminary record, we find that Petitioner demonstrates sufficient argument and evidence to show it is more likely than not that claims 1–3 would have been obvious over Jansen I and/or II, Zimmerman, and Pomper.

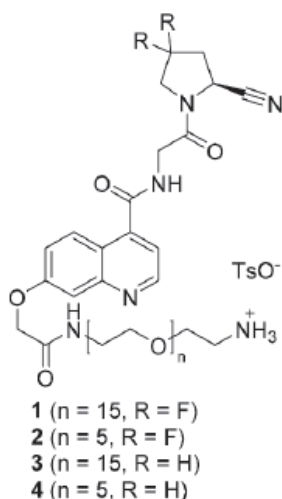
B. Ground II: Alleged Obviousness over Dvořáková in view of Pomper

Petitioner argues that claims 1–3 are unpatentable over the combination of Dvořáková with Pomper. Pet. 60.

1. Overview of Asserted Art

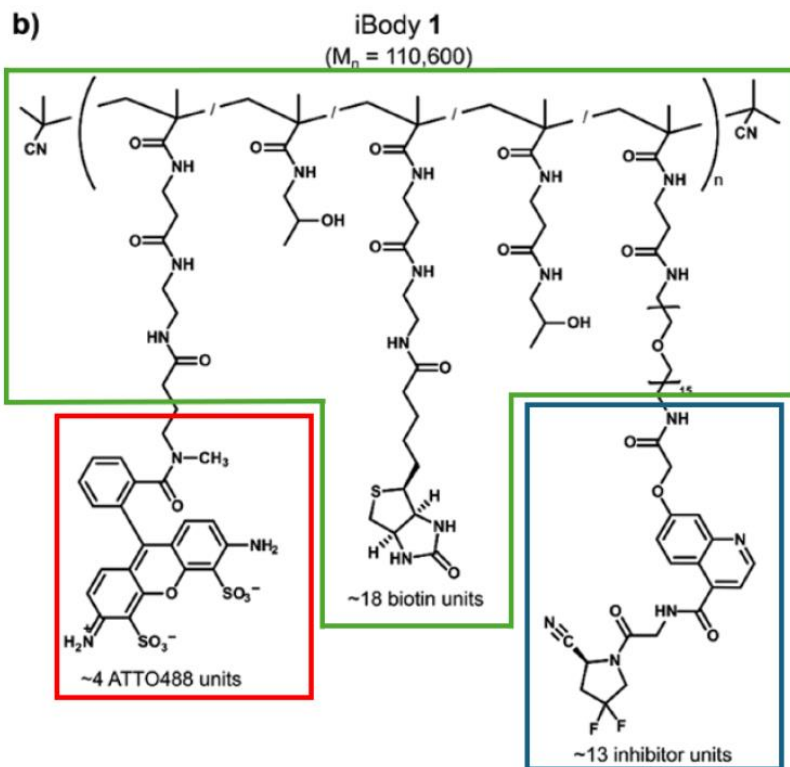
a) Dvořáková (Ex. 1008)

Dvořáková, titled “Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein,” was published Sept. 27, 2017. Ex. 1008, 8385. Dvořáková relates to developing polymer conjugates (iBodies) containing a FAP-specific inhibitor as a targeting ligand. *Id.*, Abst. Dvořáková discloses “[s]pecific [i]nhibitors of FAP modified with PEG [l]inkers” (Compounds 1-4) having the following structures:



Id., Scheme 1, 8388.

Dvořáková discloses attaching its Compounds 1–4 to an ATTO488 fluorophore via a N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer resulting in the following structure:



Ex. 1008, Fig. 2b (as annotated by Petitioner). Petitioner identifies the ATTO488 dye units in red, the FAP inhibitor units in blue, and the linker in green. *See* Pet. 29.

Dvořáková concludes that the developed inhibitor-decorated polymer conjugate can be used as a tool for the specific imaging of FAP-positive cells. Ex. 1008, 8387. The conjugate binds only to FAP-expressing cells and not to cells lacking FAP, and the conjugate without incorporation of FAP inhibitor does not bind to cells. *Id.* Upon binding to FAP on the cell surface, the conjugate undergoes slow internalization, resulting in an optical signal from the ATTO488 dye inside the cell. *Id.*

Dvořáková concludes that molecules including FAP inhibitors and optical imaging agents can be used for in vivo imaging and selective drug delivery into the tumor microenvironment. Ex. 1008, 8391.

2. *Petitioner's Position*

During prosecution of the application for the '201 patent, the Examiner rejected the only pending claim as anticipated by Dvořáková. Ex. 1004, 1177–78 (Non-Final Office Action). Thereafter, Patent Owner amended the claim to overcome the Dvořáková-based anticipation rejection by adding “low molecular weight” to the preamble, arguing that the amendment distinguished the claim from large molecule imaging agents containing anti-FAP moieties. *Id.*, 1209–13. Patent Owner noted that Dvořáková's compound 1 had a molecular weight of 149,900 g/mol. *Id.* at 1214.

As discussed in § III.C.1., *supra*, Petitioner contends that “low molecular weight” is indefinite. Pet. 40–42. Should we determine a POSA would have understood “low molecular weight” with reasonable certainty, however, Petitioner argues that Dvořáková discloses all limitations of the claims except “low molecular weight.” *Id.* at 60–61.

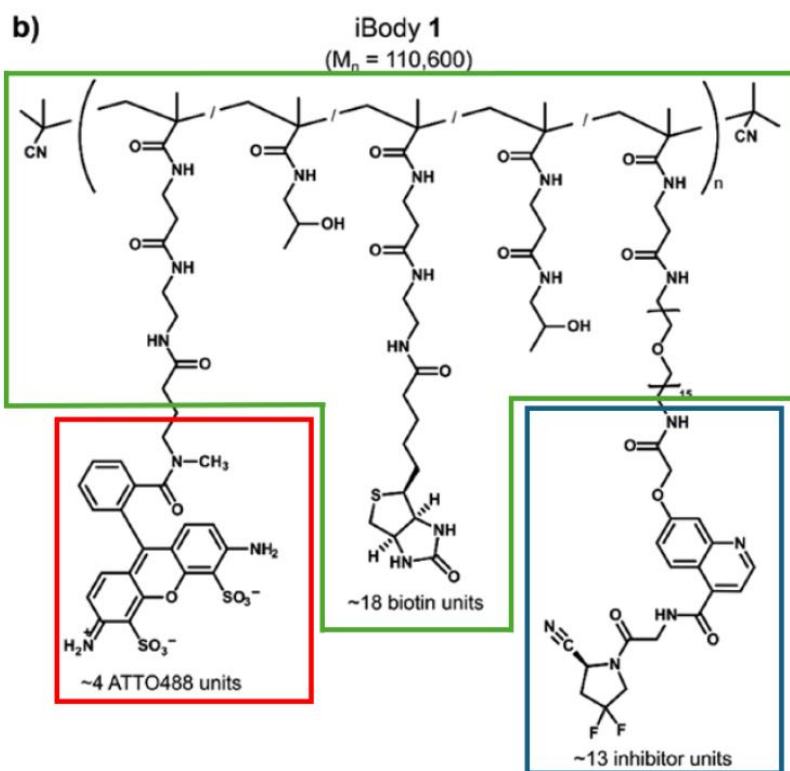
Petitioner argues that Pomper teaches the benefits of low molecular weight compounds, noting that Pomper discusses how “antibodies may have less access to tumor[s] than low molecular weight agents, which can be manipulated pharmacologically” (Ex. 1006, ¶ 8), and how low molecular weight inhibitors have “shown promise in preclinical imaging studies” (*id.* at ¶ 242). Pet. 61.

According to Petitioner, a POSA reading Dvořáková in view of Pomper would have been motivated to modify Dvořáková's disclosed compounds to have a lower molecular weight based on Pomper's teachings about how such compounds have improved pharmacokinetic properties and have shown promise in preclinical studies. Pet. 61 (citing Ex. 1002, ¶ 140). Petitioner contends that a POSA would have readily understood how the

Pet. 62–63 (citing Ex. 1008, 8388). Petitioner contends that Dvořáková’s compounds overlap with compounds claimed in the ’201 patent. *Id.* at 63–64, providing illustrations). In addition, Petitioner argues, the only two examples in the ’201 patent (XY-FAP-01 and XY-FAP-02-[In]) have the same targeting moiety for FAP- α as Dvořáková’s Compounds 3 and 4. *Id.* at 65–66.

- (3) [1c] “B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy”

Petitioner contends that Dvořáková discloses attaching its Compounds 1–4 to an ATTO488 dye via a HPMa copolymer, resulting in the following structure:



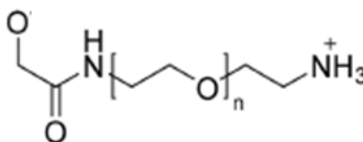
Pet. 66–67 (citing Ex. 1008, Fig. 2b). ATTO488 dye is said to be a fluorophore that contains a rhodamine-based structure and is known to be

“highly suitable for single-molecule detection applications and high-resolution microscopy.” *Id.* at 67 (quoting Ex. 1011). Petitioner argues that “[a] POSA would have recognized ATTO488 dye as an ‘optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.’” *Id.* Accordingly, per Petitioner, Dvořáková discloses the B moiety as recited in claim 1. *Id.* at 68.

Petitioner argues that Pomper also discloses the B moiety as recited in claim 1 because the reference discloses inhibiting compounds used to treat cancer coupled with a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. Pet. 68.

(4) [1d] “*L is a linker having bi-functionalization adapted to form a chemical bond with B and A*”

Petitioner asserts that there is no explicit limitation to the structure or atoms of the linker in claim 1. Pet. 68. Petitioner argues that the structure of Compounds 1–4 (*see* § IV.B.1.a, *supra*) includes the following structure:



Pet. 68 (citing Ex. 1008, 8388 and Ex. 1002, ¶ 151). According to Petitioner, Dvořáková discloses using a linker (specifically, a PEG linker) as shown above to form a chemical bond between a targeting moiety for FAP- α and an optical functional group. *Id.*; *see also* Ex. 1002, ¶ 151–152. Thus, Petitioner argues that Dvořáková discloses the claimed linker. Pet. 68–69.

Petitioner also argues that Pomper discloses suitable linkers for coupling an inhibiting moiety and an optical or radiolabeled moiety, including “linking groups having alkyl, aryl, combination of alkyl and aryl,

or alkyl and aryl groups having heteroatoms.” Pet. 69 (citing Ex. 1006, ¶¶ 102, 129).

(5) [1e] “or a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof”

Petitioner contends that, in considering whether a prior art reference renders a claim obvious, courts do not consider whether that reference includes optional elements of the claim, like the optional claim element 1e.

Petitioner contends that claim 1 would have been obvious to a POSA at the time of invention over the combination of Dvořáková and Pomper.

b) Claims 2 and 3

Petitioner argues that claims 2 and 3 would have been obvious over the combination of Dvořáková and Pomper for the same reasons discussed regarding claim 1. Pet. 70–71.

3. *Patent Owner’s Position*

We do not repeat Patent Owner’s arguments regarding lead compounds, hindsight, or secondary indicia of nonobviousness already addressed in relation to Ground I (*see* § IV.A.4., *supra*).

Challenging Ground II, Patent Owner argues that Petitioner fails to show that a POSA would have been motivated to modify Dvořáková with Pomper to create a low molecular weight compound. Prelim. Resp. 50. Patent Owner contends that Dvořáková, disclosing iBody 1 (*see* § IV.B.1.a, *supra*) containing ~13 inhibitor units, ~ four ATO488 units (dyes), and ~18 affinity anchor biotin units conjugated to the HPMA copolymer carrier with a molecular weight of 110,600 Daltons, “touts the benefits of its high molecular weight compound.” *Id.* at 51–52. According to Patent Owner, a POSA would have understood that the multiple moieties and polymeric backbone (resulting in the compound’s high molecular weight) would be the

reason for these benefits. *Id.* at 52. Patent Owner argues that Dvořáková provides data showing its polymeric compound with multiple FAPis and affinity anchors had better FAP targeting than a compound with a single FAP unit, meaning a POSA would have understood that the multiple FAPis and affinity anchors resulted in better FAP targeting. *Id.* at 53.

According to Patent Owner, other art is consistent with Dvořáková, and “reports that high molecular weight compounds with multiple functional moieties like iBody exhibited better targeting results than lower molecular weight compounds.” *Id.* at 53–54 (citing Ex. 2002, ¶ 101 discussing Carlucci, Tweedle, and Tassa)). Patent Owner criticizes Dr. Martin for failing to provide testimony on this and other art, that it alleges show better biological activity in high molecular weight, polymeric compounds in comparison to low molecular weight, monomeric compounds or poor performance of a low molecular weight FAPi compound disclosed in Zimmerman. *Id.* at 54.

Patent Owner asserts that Petitioner’s only alleged motivation for a POSA to modify Dvořáková’s iBody—to improve pharmacokinetic properties in products showing promise in preclinical studies—had been solved already by Dvořáková’s iBody, which had beneficial pharmacokinetic properties by virtue of its HPMA copolymer backbone. Prelim. Resp. 54–55.

According to Patent Owner, Petitioner fails to provide a reasonable expectation of success to support Ground II. Prelim. Resp. 56. Patent Owner contends that Petitioner provides no explanation for why a POSA would have had “a reasonable expectation that it could even ‘synthesize’ the claimed low molecular weight compounds by ‘using fewer inhibitor and ATTO488 units and using a linker with a lower molecular weight’ without

the '201 patent's guidance," i.e., why a low molecular weight version of iBody would exhibit the properties of high affinity and selectivity for FAP and be useful for imaging or radiotherapy. *Id.* at 56–57. Patent Owner contends that, because Dvořáková teaches POSAs that it is precisely the use of a multitude of these moieties and the higher molecular weight backbone that resulted in iBody's beneficial FAP targeting and suitability for imaging and therapy, "POSAs would not have expected that *removing* these beneficial moieties and using a different linker would allow the modified compound to work for the purposes [Petitioner] asserts." *Id.* at 57. More likely, according to Patent Owner, Petitioner's proposed modifications would have destroyed iBody's beneficial properties. *Id.*

Patent Owner repeats its arguments regarding secondary indicia of nonobvious. *See* Prelim. Resp. 58–60.

4. *Analysis*

On the record at this stage of the proceeding, Petitioner's arguments prevail over those of Patent Owner.

We agree with Petitioner that Dvořáková teaches the "B", "L", and "A" of the claims, but does not teach "low molecular weight." *See* Pet. 28–30, 61. Patent Owner does not argue otherwise. *See generally* Prelim. Resp. Dvořáková discloses iBody can be used as a tool for the specific imaging of FAP-expressing cells. Ex. 1008, 8387.

As in Ground I, Petitioner relies on Pomper to teach the benefits of low molecular weight compounds in imaging and therapeutic compounds for targeting cancer and cancer angiogenesis. *Id.* at 39–40. Pomper teaches using prostate-specific membrane antigen (PSMA) inhibitors, rather than the claimed FAPi, to treat cancer, where PSMA inhibitor is linked to a

fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. Ex. 1006, ¶¶ 31–34, 279.

Patent Owner argues that Dvořáková’s iBody has a molecular weight “*two orders of magnitude* higher than low molecular weight FAPi compounds” and that “Dvořáková specifically touts the benefits of its high molecular weight compound.” Prelim. Resp. 52. We interpret Dvořáková as reporting success with its iBody in targeting FAPi, not that high molecular weight compounds are inherently superior to low molecular weight compounds for such use.

A POSA is “a person of ordinary creativity, not an automaton.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). The record before us indicates that a POSA would have been motivated to alter Dvořáková’s iBody to create a low molecular weight compound of B-L-A based on Pomper’s teaching of the benefits of low molecular weight compounds for imaging and therapeutic use. A POSA would have reasonably expected success in modifying the HPMA backbone disclosed in Dvořáková to a low molecular weight based on Dvořáková’s disclosure that “[i]mportantly, the molecular weight of the HPMA backbone can be easily adjusted to specifically tailor the pharmacokinetic properties.” Ex. 1008, 8386.

Patent Owner provides no separate discussion in relation to claims 2 and 3.

On the current record, we find that Petitioner has demonstrated that it is more likely than not that the combination of Dvořáková with Pomper would have rendered claims 1–3 obvious.

C. Ground III: Alleged Lack of Enablement

1. Principles of Law

“[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.” *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1362 (Fed. Cir. 2018) (internal quotations omitted). That is, “there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill [in the art] how to make and how to use the invention as broadly as it is claimed.” *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

A claim is not enabled where the specification discloses only a starting point for further iterative research in an unpredictable and poorly understood field. *Wyeth and Cordis Corp. v. Abbott Labs.*, 720 F.3d at 1380, 1386 (Fed. Cir. 2013); *Enzo Life Sciences v. Roche Molecular Sys.*, 928 F.3d 1340, 1345-46 (Fed. Cir. 2019) (where claims require both a particular structure and functionality, no enablement where specification fails to teach which of the many embodiments of the broad claims would exhibit that required functionality of being both hybridizable and detectable upon hybridization).

2. *Petitioner's Position*

Petitioner first argues that the claims of the '201 patent lack enablement at least because the facts are analogous to those in *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023). Pet. 74. Petitioner argues that, like *Amgen*, the claims contain two functional limitations: (1) B is “any optical or radiolabeled **functional group suitable for** optical imaging, positron-emission tomography (PET) imaging, single-photon emission computer tomography (SPECT) imaging or radiotherapy; and (2) L is “a linker having **bi[-]functionalization adapted to form** a chemical bond with B and A.” *Id.* at 74–75 (quoting Ex. 1001, Certif. Corr. (emphasis added)). Petitioner contends that these “limitations encompass a virtually infinite number of potential candidate structures, EX1002 at ¶¶ 160–163, but the specification provides only two examples falling within the scope of the claims: XY-FAP-01 and XY-FAP-02.” *Id.* at 75. Petitioner argues that the '201 patent specification fails to direct a POSA to a method for determining which B moieties are suitable and which linkers have the required bi-functionalization. *Id.*

Petitioner also argues the claims lack enablement under the *Wands* factors. Regarding the scope of the claimed invention, Petitioner argues that the B moiety and L linker are defined using broad functional language that permits a virtually infinite number of potential candidate compounds, and A permits, due to its substituent R_{3x} , alkyls and aryls with a virtually infinite number of possible carbons. *Id.* at 77–79. Petitioner further argues that Patent Owner admitted during prosecution of the '201 patent application that “the art of developing a medical imaging agent is highly unpredictable art as it involves optimizing numerous parameters including the specificity of the compound.” *Id.* at 80. Petitioner argues that “the functional limitations . . .

would require a POSA to perform undue experimentation to determine whether the claims are satisfied,” “[t]he ’201 patent provides only two work working examples falling within the scope of the claims,” and does not describe how to determine if a B moiety of linker is suitable for the claimed function. *Id.* at 80–82. Petitioner argues that the amount of testing and experimentation would have been undue. *Id.* at 82. Petitioner argues that weighing the *Wands* factors shows a lack of enablement of the claims. *Id.* at 82–86.

3. Patent Owner’s Position

Patent Owner argues that the claimed compounds are defined and construed *structurally*, having the common quality of being a low molecular weight compound having formula B-L-A. Prelim. Resp.76. Patent Owner distinguishes the claims from *Amgen*, which “recited ‘all antibodies’ *defined only* by their ability to ‘bind to specific amino acids’ and ‘block’ a certain protein ‘from impairing the body’s mechanism for removing LDL cholesterol from the bloodstream.’” *Id.* Patent Owner argues that *Amgen*, unlike the ’201 patent claims, sought to monopolize and entire class of things defined by their function, rather than their structure. *Id.* at 76–77.

Patent Owner argues that Petitioner fails to show undue experimentation would be required, challenging Petitioner’s contentions that “alkyl” and “aryl” as recited in the claims “have a virtually infinite number of possible carbon atoms,” and that the claimed compounds are themselves required to have some specific level of suitability for imaging/therapy and bi-functionalization. Prelim. Resp. 77–78. Addressing *Wands* factors, Patent Owner argues that level of skill of a POSA is high, the invention is predictable, and the level of guidance provided in the specification is adequate given that two working examples are disclosed although none is

required. *Id.* at 79. According to Patent Owner, the specification is “replete with dozens of columns of disclosures, and incorporated materials providing exemplary A, B, and L moieties.” *Id.* at 79–80.

Patent Owner criticizes Petitioner’s contention that the specification simply discloses a trial-and-error or make-and-screen approach in order to practice the claimed invention as unsubstantiated and insufficient. Prelim. Resp. 80–81.

Patent Owner argues that statements in the Pomper Declaration that the field of the invention is “unpredictable” should be disregarded in considering enablement, as “testimony discussing ‘difficulties . . . before [the inventor] disclosed his invention’ [are] immaterial to whether ‘undue experimentation would be necessary once the teachings in the patents-in-suit were known.’” Prelim. Resp. 81–82 (citing *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1291–92 (Fed. Cir. 2012)).

Finally, Patent Owner distinguishes other cases cited by Petitioner as supporting enablement, asserting that each of those cases involved claims that were either defined solely functionally or required certain functionality that was not adequately enabled. Prelim. Resp. 82.

4. Analysis

We first address Petitioner’s argument that the ’201 patent claims lack enablement because they are analogous to those in *Amgen*, determining that they are not, based on the preliminary record. The claims do not require that the claimed compound is suitable for specified imaging or radiotherapy uses.

We next address the parties’ arguments with respect to various of the *Wands* factors.

Regarding the breadth of the claims, at this stage of the proceedings we agree with Petitioner that the claims are very broad due to the B moiety

and L linker, and due to the construction of “alkyl” in the A moiety (*see* § III.C.2.c, *supra*) as “a fully saturated hydrocarbon of Formula C_xH_{2x+1} wherein x is a number greater than or equal to 1.

We view the relative level of skill in the art as high, and have addressed this issue in § III.B, *supra*.

Unsurprisingly, the parties have very different views on the predictability or unpredictability of the art. *Compare* Pet. 80, *with* Prelim. Resp. 81–82. Petitioner, quoting the Pomper Declaration describing “the high unpredictability of the medical imaging art,” is more convincing at this stage of the proceeding. We do not agree with what we view as Patent Owner’s interpretation of *Streck* as holding that all statements regarding the state of the art made in the course of prosecution are immaterial to consideration of predictability. *See* Prelim. Resp. 81–82 (citing *Streck*, 665 F.3d at 1291–92 (Fed. Cir. 2012)). In *Streck*, the testimony held to not establish undue experimentation concerned the difficulties of making the claimed invention in the first place, not whether undue experimentation was required once the invention was known. *See Streck*, 665 F.3d at 1291. Availability of the ’201 patent would not have altered the predictability of the medical imaging art, and thus the evidence is not immaterial.

How much experimentation would have been required, and whether it would have been routine depends on how broadly the claims are construed. Given the breadth of the claims, a very substantial amount of experimentation would have had to take place for a POSA to make and use the full scope of the claimed invention. However, given the relatively high level of skill in the field, the experimentation would have been routine.

Working examples in the specification are not required, as long as the invention is otherwise disclosed in such a manner that a POSA will be able

to practice the claim without undue experimentation. *See* MPEP § 2164.02. Working examples are more important in unpredictable fields. *Id.* The '201 patent's disclosure of two working examples does not entirely fall on the side of enablement, however, as both examples employ the same FAPi (the A moiety), although the structures covered by the A moiety are voluminous, due to the breadth of "alkyl" included in substituent R_{3x}.

Although Patent Owner urges that the '201 patent "provides *dozens* of columns of exemplary A, B, and L moieties that a POSA would have considered when making the claimed compounds" (Prelim. Resp. 68), the disclosures are countered by the even broader scope of the claims.

Weighing the *Wands* factors, we find that the totality of the evidence shown in the current record better supports Petitioner's position that undue experimentation would have been required to enable the broad scope of the claims, and that the claims therefore fail to comply with the enablement requirement of 35 U.S.C. § 112(a).

That said, enablement is a highly fact-dependent issue that will benefit from further expert testimony and evidence at trial. The key issues at trial for enablement will be the scope of the claims and whether a POSA would have understood how to make and use the full scope of the claimed invention. As the Federal Circuit has repeatedly instructed, although the specification need not describe "how to make and use every possible variant of the claimed invention, when a range is claimed, there must be reasonable enablement of the scope of the range." *McRo, Inc. v. Bandai Namco Games Am. Inc.*, 959 F.3d 1091, 1100 (Fed. Cir. 2020).

D. Ground IV: Alleged Lack of Written Description

1. Principles of Law

Section 112(a) requires that “[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.” 35 U.S.C. § 112(a). The written description requirement is separate and distinct from the enablement requirement. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). “A specification that ‘reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date’ has adequate written description of the claimed invention.” *Novartis Pharm. Corp. v. Accord Healthcare, Inc.*, 21 F.4th 1362, 1368 (Fed. Cir. 2022) (citing *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc)). “[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.” *Id.* at 1368–69.

2. Petitioner’s Position

Petitioner argues that the claims are broad functional genus claims. Pet. 76, 87. As such, Petitioner argues, the ’201 patent must disclose “either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.” *Id.* at 87. (quoting *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1164 (Fed. Cir. 2019)). Petitioner urges that “the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and

do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.” *Id.* at 88 (quoting *Ariad*, 598 F.3d at 1349. Petitioner argues that the ’201 patent fails to disclose sufficient species within the broadly claimed genus. *Id.* at 89.

3. *Patent Owner’s Position*

Patent Owner points out that Petitioner’s written description arguments are predicated on the claimed genus purportedly being “defined by functional language.” Prelim. Resp. 61 (citing Pet. 87, 89). Patent Owner argues that the claimed compounds are defined structurally as having formula B-L-A, and only B and L moieties must be selected by on individual functional characteristics. *Id.* at 62. Patent Owner argues that numerous examples of suitable B and L moieties are listed in the specification and incorporated by reference into the specification, along with two working examples. *Id.* Patent Owner contends that by incorrectly framing the claims as reciting a functionally-defined genus, Petitioner relies on inapposite case law. *Id.*

4. *Analysis*

On this preliminary record, Petitioner fails to demonstrate that the claims lack written description. The claims recite a compound, not a result. Although the B moiety must be suitable for specific imaging or radiotherapy uses, the claims do not require that the claimed compound has this functionality. This is true of the L linker as well. The case law argued by Petitioner that addresses functionally-defined claims is not relevant here.

E. Ground V: Alleged Indefiniteness

1. Petitioner’s Position

Petitioner argues that “low molecular weight” recited in the preamble of claims 1 and 3 is indefinite. Pet. 90–92.

Petitioner argues that the '201 patent uses the term “low molecular weight” three times throughout the specification, with two of those times being in the “Background” section:

Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal [than anti-FAP antibodies] within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. . . . To date, however, no *LMW* ligand has been reported with ideal properties for nuclear imaging of FAP- α .

Pet. 93 (quoting Ex. 1001, 1:60–67) (emphasis by Petitioner). The remaining instance of low molecular weight states:

Accordingly, in some embodiments, the presently disclosed subject matter provides potent and selective *low-molecular-weight (LMW)* ligands of FAP- α , i.e., an FAP- α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable in vivo optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP- α .

Ex. 1001, 7:46–54 (emphasis added). Petitioner contends that these uses of “low molecular weight” in the specification provide no insight as to definition or range. Pet. 93. According to Petitioner, interpretation of “low molecular weight” would be relative to the field of study and the type of experiments to be performed. *Id.* at 95.

Petitioner discounts the references regarding metabolites and metabolomics that Patent Owner uses to define “low molecular weight” as “typically from about 50 Daltons to about 1,500 Daltons.” Pet. 94–96. Petitioner notes that each of the references is related to the field of metabolomics or the scientific study of metabolites, but the only mention in the '201 patent specification clarifies that “the injected compound is *not*

metabolized by the body prior to excretion.” *Id.* at 95 (quoting Ex. 1001, 35:66–97).

Petitioner points to the ’201 patent as disclosing several examples of moiety B that have a molecular weight greater than 1,500 Da by themselves. Pet. 96. Petitioner specifically identifies fluorescent dyes VivoTag-680 (now named IVISense 680) (molecular weight 1,856 g/mol), AlexaFluor790 (molecular weight about 1,750 g/mol), and IRDye 700DX (molecular weight about 1,954 g/mol), which fall within claimed moiety B, explaining that the claimed compound would include the A moiety and the L linker, making the molecular weight even higher. *Id.* (citing Ex. 1001, 25:19–25, 26:19–24). Petitioner contends that “[t]hese contradictory disclosures further demonstrate the ambiguity and indefiniteness of the term ‘low molecular weight.’” *Id.*

Petitioner contends that the ’201 patent specification discloses a polymer can be used in the claimed compounds via its incorporation by reference of Pomper, which describes “suitable” embodiments of linker L as including a poly(ethyleneglycol) linker. Pet. 97. According to Petitioner, polyethyleneglycol can have a molecular weight varying from 62 Daltons to over 35,000 Daltons. *Id.* (citing Ex. 1006, ¶ 129, Ex. 1024, Abst.).

Petitioner argues that “low molecular weight” is closely analogous to the phrase “molecular weight” that was examined and found indefinite in *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335 (Fed. Cir. 2015). In *Teva*, according to Petitioner, the Federal Circuit affirmed an indefiniteness finding where the prosecution history and specification contained contradictory statements and an alleged infringer would not know whether it fell within or outside the scope of the claims. Pet. 92, 98. Petitioner urges that “[t]he same result of indefiniteness is warranted here.” *Id.* at 92.

2. *Patent Owner's position*

Patent Owner argues that a POSA would have understood “low molecular weight” to have its “well-accepted, plain and ordinary meaning in the field—namely, compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons.” Prelim. Resp. 24. Patent Owner contends that “the specification discusses ‘low molecular weight’ compounds consistent with their ordinary meaning,” and quotes *Phillips*, 415 F.3d at 1315: “the specification is always highly relevant to the claim construction analysis [and] usually it is dispositive; it is the single best guide to the meaning of a disputed term.” Prelim. Resp. 24.

Patent Owner states that the '201 patent incorporates Pomper by reference, and argues that Pomper describes its targeting compounds as “low molecular weight.” Prelim. Resp. 24 (citing Ex. 1006, Abst., ¶ 12). Patent Owner contends that Pomper discloses a variety of low molecular weight targeting compounds with molecular weights up to about 1,586 Da. *Id.* at 24–25 (citing Ex. 2002, ¶¶ 61–62).

Patent Owner also points to Dr. Pomper's Declaration, submitted during prosecution of the '201 patent, as evidence that “low molecular weight” is used according to the ordinary meaning of “typically from about 50 Da to about 1,500 Da.” Prelim. Resp. 25. The declaration states: “the term of ‘low molecular weight’ is well accepted in the chemical arts” and “low molecular weight compounds would have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons.” *Id.* (citing Ex. 1004, 1197–98).

Patent Owner argues:

There is no requirement that the specification must expressly define a claim term, use it a minimum number of times,

or provide absolute, numerical boundaries for that term to be definite.

Instead, all the law requires is that the claims, when read in light of the specification, inform POSAs with reasonable certainty about the meaning and scope of the claimed invention.

. . . POSAs would have had reasonable certainty that a given compound of formula B-L-A with a molecular weight from about 50 to about 1,500 Daltons would fall within the scope of the claims, and B-L-A compounds with higher molecular weights would fall outside the scope of the claims.

Prelim. Resp. 26–27.

Patent Owner also counters Petitioner’s arguments. First, Patent Owner argues that the specification directly describes “molecules of low relative molecular mass” relative to “polymer[s] of high relative molecule mass,” and Dr. Martin concedes that polymers have molecular weights ranging from 8,000 to 400,000 Dalton, “which is much higher than the molecular weights of typically from about 50 Daltons to about 1,500 Daltons.” Prelim. Resp. 27. In response to Dr. Martin’s statement that “antibodies have molecular weights as high as 150,000 and 900,000 Daltons,” Patent Owner argues “POSAs would have reasonably been able to distinguish a compound of low molecular weight typically from about 50 Daltons to about 1,500 Daltons from an antibody.” *Id.* at 28. And, contending that Dr. Martin is wrong in criticizing the Pomper Declaration (and Patent Owner) for relying on references related to the field of metabolics to define “low molecular weight,” Patent Owner claims “the patent specification itself (by incorporating Pomper) makes clear to POSAs that low molecular weight imaging and targeting compounds, including the ones claimed, are ones with molecular weights typically from about 50 to about 1,500 Daltons.” *Id.*

Patent Owner also contests Dr. Martin's criticism that the '201 specification provides examples of B moieties and linkers that would result in a compound including them to exceed about 1,500 Da. Prelim. Resp. 28–29. Patent Owner argues that a patentee may claim less than what is disclosed. *Id.* Specifically, Patent Owner argues that a POSA would have understood that any higher molecular weight B-L-A compounds described in the '201 patent specification were not ultimately part of the claimed “low molecular weight” compounds. *Id.* at 29.

Finally, Patent Owner contends that *Teva v. Sandoz* does not apply to the facts here. Prelim. Resp. 29. According to Patent Owner, the court in *Teva* found “molecular weight” to be indefinite in the context of polymers, where the molecular weight of the polymer could vary depending on exactly how it was measured (e.g., measurements Mp, Mw, or Mn, each method yielding different results), but the patent did not describe what specific measurement method to pick, resulting in the finding of indefiniteness. *Id.* at 29–30. Patent Owner distinguishes over *Teva*, arguing that the claimed compounds are low molecular weight, non-polymeric compounds, and POSAs of any definition would have known how to use high precision analytical techniques to determine the molecular weight of a given B-L-A compound to see if it falls under the typical “from about 50 to about 1,500 Dalton” scope of “low molecular weight” as claimed. *Id.*

3. Analysis

On the preliminary record before us, we find that Petitioner has the better arguments.

The Supreme Court in *Nautilus* instructed that § 112(b) (§ 112, ¶ 2 at the time) “require[s] that a patent’s claims, viewed in light of the specification and prosecution history, inform those skilled in the art about

the scope of the invention with reasonable certainty. The definiteness requirement, so understood, mandates clarity, while recognizing that absolute precision is unattainable.” *Nautilus*, 572 U.S. 898, 901 (2014). Terms of degree are not inherently indefinite, but “will fail for indefiniteness unless they ‘provide objective boundaries for those of skill in the art’ when read in light of the specification and the prosecution history.” *Liberty Ammunition, Inc. v. United States*, 835 F.3d 1388, 1396 (Fed. Cir. 2016) (cleaned up). “Terms of degree are problematic if their baseline is unclear to those of ordinary skill in the art.” *Id.* at 1395.

“Low molecular weight” is a term of degree; it requires a comparison against some baseline in order to give it meaning. *See id.* In *Liberty*, the court found that, although the claim term “reduced area of contact” provided no clue as to “what the area of contact was reduced *from*,” the specification saved the term from indefiniteness “by disclosing that the patent’s proposed projectile has ‘a reduced contact area as compared to conventional projectiles,’” although the question of “What constitutes a conventional projectile?” remained. *Id.* The court noted that “the Background of the Invention identifies the M855 round as a specific conventional projectile that the invention seeks to improve upon,” and held that the M855 round was the proper baseline for the term “reduced area of contact.” *Id.*

The ’201 patent does not define “low molecular weight.” *See generally* Ex. 1001. In fact, in the specification, low molecular weight is only mentioned as an alternative to antibodies for use in radioimaging. *See* Ex. 1001, 1:56–64. Antibodies typically have a molecular weight of about

150,000 Daltons.¹¹ Therefore, applying *Liberty*, lower than about 150,000 Da would appear to be the only baseline suggested by the '201 patent.

The '201 patent incorporates Pomper by reference, and Patent Owner argues that Pomper “expressly describes its targeting compounds for imaging and therapy as ‘low molecular weight’ and discloses a variety of such compounds with molecular weights up to about 1,586 Daltons.” Prelim. Resp. 24–25 (citing Ex. 1006, ¶ 12; Ex. 2002, ¶¶ 61–62). This is not entirely accurate. Regarding “low molecular weight,” Pomper states “[t]he invention also provides compounds with greater cellular retention and low molecular weight” (¶ 12), “[t]he development of low molecular weight radiotherapeutic agents is much different from developing radio-pharmaceuticals for imaging in that longer tumor residence times may be important for the former” (¶ 188); and “¹⁸F-labeled, low molecular weight PSMA inhibitors have shown promise in preclinical imaging studies” (¶ 242), “a wide variety of low molecular weight PSMA-based imaging agent have been synthesized” (¶ 279). Ex. 1006. Pomper does not define “low molecular weight,” and neither all of the examples or all of the specifically claimed compounds are limited to “from about 50 Da to about 1,500 Da.”

The prosecution history fares no better in clarifying the meaning. “Low molecular weight” became significant during prosecution of the '201 patent application when the applicant sought to overcome an anticipation rejection based on Dvořáková. *See* Ex. 1004, 1196–98 (Pomper Decl.); Ex. 1004, 1213–15 (Response to Non-Final Action). Dvořáková concerns developing polymer conjugates decorated with FAP inhibitors for use in

¹¹ *See, e.g.*, C.A. Janeway, Dr. et al, *Immunobiology: The Immune System in Health and Disease*, 5th ed., Chap. 3, sec. 3.1 (accessed June 30, 2025), <https://www.ncbi.nlm.nih.gov/books/NBK10757/>

imaging FAP expressing cells. Ex. 1008, 8385. As detailed in § IV.B.1.a. and 4, Dvořáková discloses a compound (“iBody”) comprising B-L-A wherein A is a targeting moiety for FAP, L is a linker, and B is a dye. *See also* Ex. 1004, 1178 (Non-Final rejection of claims as anticipated by Dvořáková, explaining that the reference teaches an anti FAP-iBody FAP inhibitor comprising a targeting moiety that anticipates A, a moiety bound to HMPA that anticipates L, and a dye that anticipates B). Dvořáková’s iBody has a molecular weight of 149,900 Da. Ex. 1008, 8387. The applicant (Patent Owner) amended the preamble to the claims to “[a] low molecular weight compound” to avoid anticipation by Dvořáková. *See* Ex. 1004, 1210 (Response to Non-Final Action). This evidence also suggested a baseline lower than 150,000, but does not provide further guidance on how much lower is necessary to be “low molecular weight”.

On the present record, the ’201 patent fails to inform those skilled in the art about the scope of the invention with reasonable certainty. *See Nautilus*, 572 U.S. at 901. The evidence does not show that “low molecular weight” is limited to Patent Owner’s proposed “from about 50 Daltons to about 1,500 Daltons.” The evidence relied on in the Pomper Declaration concerns metabolomics and metabolites, and we find no reason that even a vague definition of metabolites applies to the claimed compounds.

Patent Owner’s contention that “low molecular weight” intentionally excluded the B moieties identified in the ’201 patent that fall outside of Patent Owner’s proposed definition is not convincing, as Patent Owner also argues that all of the compounds in the ’201 patent and in Pomper are of low molecular weight. In addition, Patent Owner’s effort to distinguish “low molecular weight compounds” from “polymers” does not support an upper limit for low molecular weight compounds as “about 1,500 Daltons,” given

Petitioner's un rebutted evidence that polymers typically range in weight from 8,000 to 400,000 Daltons.

V. CONCLUSION

Petitioner has, at this stage, established that it will more likely than not prevail in showing that at least one of the challenged claims is unpatentable. This determination is, however, based on a preliminary record and is not final on any issues of patentability. We will make a final determination on the patentability of the challenged claims, as necessary and applying the preponderance of the evidence standard, based on a fully developed record through trial.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 324(a) post grant review of claims 1–4 and 8–21 of the '600 patent is hereby *instituted* on the grounds set forth in the Petition, commencing on the entry date of this Order, and

PGR2025-00012
Patent 11,938,201 B2

pursuant to 35 U.S.C. § 324(d) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; and

FURTHER ORDERED that the trial will be conducted in accordance with a separately issued Scheduling Order.

PGR2025-00012
Patent 11,938,201 B2

For PETITIONER:

David Kohn
LEWIS KOHN & WALKER LLP
dkohn@lewiskohn.com

Bryan Diner
Justin Hasford
Matthew Hlinka
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
bryan.diner@finnegan.com
justin.hasford@finnegan.com
matthew.hlinka@finnegan.com

For PATENT OWNER:

Eldora Ellison
Olga Partington
Christopher Gallo
STERNE, KESSLER, GOLDSTEIN & FOX PLL
Cellison-ptab@sternekessler.com
opartington-ptab@sternekessler.com
cgallo-ptab@sternekessler.com