

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GE HEALTHCARE LTD.,
Petitioner,

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner.

PGR2025-00059
Patent 12,115,233 B2

Before DEBRA L. DENNETT, DEVON ZASTROW NEWMAN, and
JAMIE WISZ, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

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

I. INTRODUCTION

GE Healthcare Ltd. (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting post-grant review of claims 1–4 (the “challenged claims”) of U.S. Patent No. 12,115,233 B2 (Ex. 1001, “the ’233 patent”). The Johns Hopkins University (“Patent Owner”) filed a Preliminary Response. Paper 7 (“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). After 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 1–4 of the ’233 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 GE Healthcare Ltd. as the real party-in-interest. Pet. 8. Patent Owner identifies The Johns Hopkins University as the real party-in-interest. Paper 5, 1.

B. Related Proceedings

Petitioner identifies related matters IPR2025-00808 and PGR2025-00012, both terminated, as related proceedings involving U.S. Patent No. 11,938,201, which claims priority and benefit to the same applications to which the '233 patent claims priority and benefit. Pet. 8. Patent Owner states that the '233 patent claims the benefit of pending U.S. Patent Application No. 16/758,182. Paper 5, 1.

C. The '233 Patent

The '233 patent issued October 15, 2024, from U.S. Application 18/585,905, filed February 23, 2024. Ex. 1001, codes (45), (21), (22). The '233 patent is a continuation of U.S. Application No. 18/354,282, filed on July 18, 2023, now Pat. No. 11,938,201, which is a continuation of 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 claim 1 issued Oct. 15, 2024. *Id.* at 43.

The '233 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 any 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, 1:65–2:5. The '233 patent depicts A, the FAP- α targeting moiety, and defines the possible subgroups. *Id.* at 2:6–3:13.

The '233 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, 1:25–40. FAP- α 's characteristics make it a potential imaging and radiotherapeutic target for cancer and inflammation diseases. *Id.* at 1:41–43.

The '233 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, 1:43–53. 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 '233 patent. *Id.* at 1:54–58.

Inhibitors selectively targeting FAP- α are known. Ex. 1001, 7:13–14. The '233 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

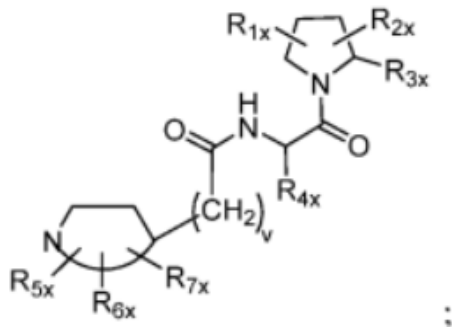
Independent claim 1 illustrates the challenged claims in the '233 patent, and is reproduced below.

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;



represents a quinolinyl ring having a point of attachment to a remainder of the FAP binding moiety at the 4-position of the 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 the grounds presented below.

Ground	Reference(s)/Basis	35 U.S.C. §	Claim(s) Challenged
1	US-633 ¹ , Meletta ² , Jansen ³	§ 103	1–4
2	US-122 ⁴ , Jansen	§ 103	1–4
3	Lack of Written Description	§ 112	1–4
4	Claims Not Enabled	§ 112	1–4

Pet. 8–9.

Petitioner also relies on the Declaration of Brian Zeglis, Ph.D. *See* Ex. 1003. Patent Owner relies on the Declaration of Henry VanBrocklin, Ph.D. *See* Ex. 2001.

III. PRELIMINARY MATTERS

A. Post-Grant Review Eligibility

As a threshold issue, we must determine whether the '233 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

¹ US 2010/0098633 A1, published Apr. 22, 2010 (“US-633”, Ex. 1004).

² R. Meletta et al., *Evaluation of the Radiolabeled Boronic Acid-Based FAP Inhibitor MIP-1232 for Atherosclerotic Plaque Imaging*, 20: MOLECULES, 2081–2099 (Jan. 27 2015), Ex. 1008 (“Meletta”).

³ K. Jansen, et al., *Extended Structure – Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP)*, 57 J. MED. CHEM., 3053–3074 (March 11, 2014). Ex. 1006 (“Jansen”).

⁴ US 2012/0009121 A1, published Jan. 12 2012, Ex. 1005 (“US-121”).

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 '233 patent's issue date. Pet. 7.

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 '233 patent do not include filings prior to March 16, 2013. Ex. 1001, codes (63), (60). The '233 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

- (i) an undergraduate and Ph.D. degrees in chemistry, biochemistry, medicinal chemistry or comparable fields and
- (ii) familiarity with chemical synthesis methods (including organic synthesis, radiometal chelation and radiohalogen labeling of prosthetic groups), assessment of cellular targets for radiopharmaceuticals, and other techniques relevant to the design, development, testing and/or evaluation of radiopharmaceuticals. The person would also be familiar with how radiopharmaceuticals are distributed and used in patients to perform therapy or imaging of diseases, including cancer.

Pet. 16 (citing Ex. 1003 ¶¶ 12–15).

Patent Owner does not proffer a description of a POSA. *See generally*, Prelim. Resp. For the purposes of this decision, on the record at

this time, we find that Petitioner’s definition appears consistent with the level of skill shown in the prior art references of record, and apply it herein. *See Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). We invite the parties to further address the definition of a POSA during trial should they find it necessary.

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) whether the claimed B and L moieties should be defined in functional terms.

1. “Low molecular weight”

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

a) Petitioner’s position

Petitioner asserts that “low molecular weight” need not be construed for two reasons. Pet. 20–25. First, Petitioner alleges that “low molecular weight” is not relevant to the present grounds because the compounds in the asserted obviousness grounds are “low molecular weight” compounds for the “same reasons the examples in the ’233 Patent are, and have molecular weights below or near 1500 Da, the (arbitrary) weight limit chosen by Dr. Pomper (an inventor) in a declaration he submitted during examination.”

Id. at 20 (citing Ex. 1002, 169 ¶ 17). However, Petitioner notes that the '233 patent discloses allowed components that, when combined into a B-L-A molecule, would exceed 1500 Da. Pet. 24 (citing Ex. 1001, 13:33–50, 14:56–16:14, 17:9–20).

Second, Petitioner asserts that Grounds 3 and 4, relating to § 112(a) are unaffected by the definition of “low molecular weight.” Pet. 21. Petitioner asserts that, should we find it necessary to construe “low molecular weight,” “the intrinsic evidence demonstrates it means ‘*having a molecular weight at least an order of magnitude less than an antibody-based radiopharmaceutical*’” based upon the Specification’s distinguishing of “low molecular weight” agents from anti-FAP antibodies “based on their behavior *in vivo*, ease of synthesis and ability to get approved by the FDA.” Pet. 21–22 (citing Ex. 1001, 1:53-61, 7:46-54). Petitioner also criticizes Dr. Pomper’s selection of weights below or near 1500 Da as valid criteria to distinguish “low molecular weight” compounds from antibodies and anti-FAP antibodies. Pet. 21–24.

b) Patent Owner’s position

Patent Owner asserts that Dr. Pomper, in submitting a declaration regarding the scope of the term “low molecular weight” to mean “about 50 Daltons to about 1,500 Daltons” properly acted as his own lexicographer in doing so, and his definition should be adopted. Prelim. Resp. 19–20. Patent Owner further asserts that the scope of the invention claimed by reciting “low molecular weight” compounds permissibly excludes non-preferred embodiments that are larger than 1,500 Da because the prosecution history supports this result. *Id.* at 21–22 (citing cases).

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 to define “low molecular weight” as a term well accepted in the chemical arts relates to metabolomics and metabolites. *See* Ex. 1002, 169, (specifically, ¶ 17 of Dr. Pomper’s declaration). Patent Owner admits that Dr. Pomper’s testimony is about molecules that differ from the claimed imaging and radiotherapeutic agents targeting FAP- α , but argues that the testimony is still relevant for purposes of explanation. Prelim Resp. 21. While it may be relevant, the testimony is not persuasive in light of the Specification. We find the uncontested fact that several of the B moieties alone—without the A moiety or L linker—specifically identified in the ’233 patent fall outside of Patent Owner’s proposed definition persuasive, 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). The cases cited by Patent Owner supporting that a claim term may be construed to exclude embodiments where the prosecution history supports such construction are factually distinguishable from the instant case as they regard instances of specific prosecution history disclaimer, clear prosecution disavowal, or relate to a specific definition of the terms in the Specification for the term being construed. Here, “low molecular weight” is not defined in the Specification, but, as Petitioner argues (*see* Pet. 21–25) is characterized as “demonstrat[ing] faster pharmacokinetics and a higher specific signal within

clinically convenient times after administration” and that it “can be synthesized in radiolabeled form more easily.” Ex.1001, 13:33–50, 14:56–16:14, 17:9–20. We are persuaded by the testimony of Dr. Zeglis, Petitioner’s declarant, that compounds weighing over 1500 Da may share those same behaviors, along with certain identified B moieties disclosed as embodiments. *See* Ex. 1003 ¶ 83.

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 from 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 (“[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.”)

US-121, of which Dr. Pomper is lead inventor, 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. 1006, ¶ 12. In

addition, Patent Owner's definition does not appear to apply to all compounds claimed in US-121.⁵

Because we agree with Petitioner that the compounds in the asserted obviousness grounds have molecular weights below or near 1500 Da, which Patent Owner alleges is a "low molecular weight" molecule, we apply 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 invite the parties to further address construction of "low molecular weight" in future briefing to the extent needed to clarify this issue at trial.

2. *Whether moieties "B" and "L" are defined in functional terms*

a) Petitioner's Position

Petitioner argues that the claims use "functional language" to define moieties "B" and "L" of the claimed compounds because only the purpose of the moiety within the compound is identified, not structure. Pet. 18–19. Petitioner argues that the non-limiting portions of the claims illustrating each of the three identified classes of "B" compounds, (i) "radiolabeled prosthetic groups comprising a radioisotope" (e.g., 18F, 123I), (ii) "chelating agent[s]" and (iii) an "optical dye", reinforce that the definitions must be functional. *Id.* at 19 (citing Ex. 1003 ¶ 75). Regarding the linker "L", Petitioner argues that no structural or size or other limitations are provided.

b) Patent Owner's Position

Patent Owner argues that requiring functionality in the definition is an impermissible importation of functional limitations into the claims. Prelim.

⁵ See, e.g., claim 113 of Ex. 1006.

Resp. 13. Patent Owner argues that the claims are “plainly structural” and cites cases in support of its position that including functional requirements is improper where nothing in the claim language requires the function. Prelim. Resp. 15–16.

c) Analysis

On this preliminary record, we find Patent Owner has the better position. The claims recite a compound, not a result. Moieties B and L must be suitable for specific purposes, but are not required by the claim language to accomplish these functions. We invite the parties to further address this issue in future briefing to the extent needed to clarify this issue at trial.

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 four asserted grounds of unpatentability.

A. Ground 1: Alleged Obviousness over US-633, Meletta, and Jansen

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) US-633 (Ex. 1004)

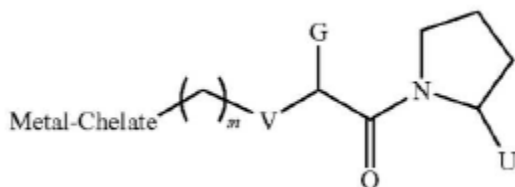
US-633 (U.S. Patent Publication No. 2010/0098633 A1), titled “Selective Seprase Inhibitors,” was published on Apr. 22, 2010.

Ex. 1004, codes (10), (43), (54). Seprase is also known as FAP- α . *Id.*, ¶ 3.

US-633 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 US-633 have the following general structure:

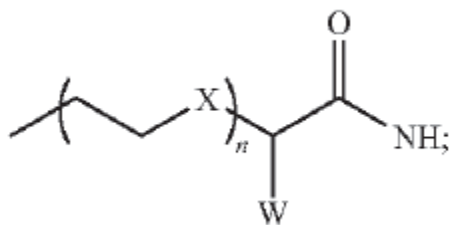


wherein:

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;

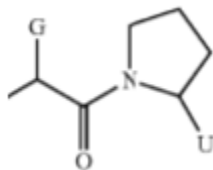
m is an integer ranging from 0 to 6;

Metal represents a metallic moiety comprising a radionuclide; and

Chelate represents a chelating moiety that chelates to said Metal.

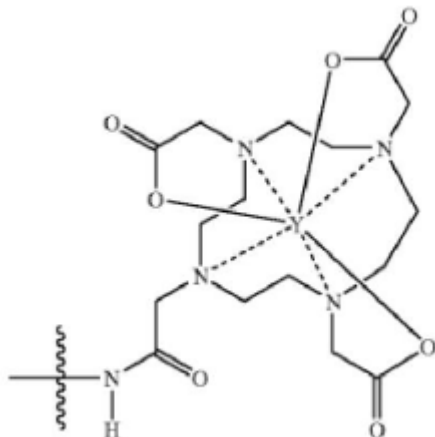
Ex.1004, ¶¶ 8–20.

In the general structure, a proline moiety as shown below



is attached via tether  to a Metal-Chelate. Ex. 1004, ¶ 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.* at ¶ 7.

US-633 discloses numerous Metal-Chelate moieties, including the following:



Id., ¶ 193, Table 4.

b) Meletta (Ex. 1008)

Meletta, titled “Evaluation of the Radiolabeled Boronic Acid-Based FAP Inhibitor MIP-1232 for Atherosclerotic Plaque Imaging,” published January 27, 2015. Ex. 1008, 2081.

Meletta disclosed that FAP- α “was recently proposed as [an] inflammation-induced protease involved in the process of plaque vulnerability” and had been identified in elevated levels in tissues having advanced atherosclerotic plaques. *Id.* at 2081, 2089. Meletta disclosed that, due to a need for FAP-selective radiotracer to image atherosclerotic plaques, FAP inhibitor MIP-1232 was made and radiolabeled with iodine-125 for potential use. *Id.* at 2081, 2083.

Meletta disclosed that MIP-1232 was 32-fold more potent in inhibiting FAP than inhibiting the closely related dipeptidyl peptidase, prolyl endopeptidase, citing an abstract that reported assay-measured IC₅₀ values of the [¹²⁵I]MIP-1232. *Id.* at 2083.

Meletta concluded that the data indicated [¹²⁵I]MIP-1232 was insufficiently selective for FAP, and identified a need for more selective targeting moieties for FAP-targeting radiopharmaceuticals. *Id.* at 2089–2090.

c) Jansen (Ex. 1006)

Jansen, titled “Extended Structure–Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP)” published March 11, 2014 Ex. 1006, 3053.

Jansen discloses that FAP- α , seprase, is a prolyl oligopeptidase that cleaves peptides preferentially after proline residues. *Id.* Jansen discloses that FAP- α is also highly expressed on activated fibroblasts in over 90% of epithelial cancers and inflammation diseases, making it appealing for evaluation as a drug target. *Id.* However, Jansen noted that while it was possible to obtain inhibitors for enzymes in this family, it was “far more challenging” to obtain inhibitors possessing selectivity for FAP. *Id.*

Jansen disclosed synthesis of around 60 novel inhibitors to attempt synthesis of a better FAP inhibitor. *Id.* at 3055. Jansen disclosed analysis and testing of multiple synthesized compounds found to be promising, resulting in identification of compound 60 as the most promising FAP inhibitor and a candidate for use as a FAP-targeting moiety in nuclear imaging. *Id.* at 3057–3062.⁶

3. *Petitioner’s Position*

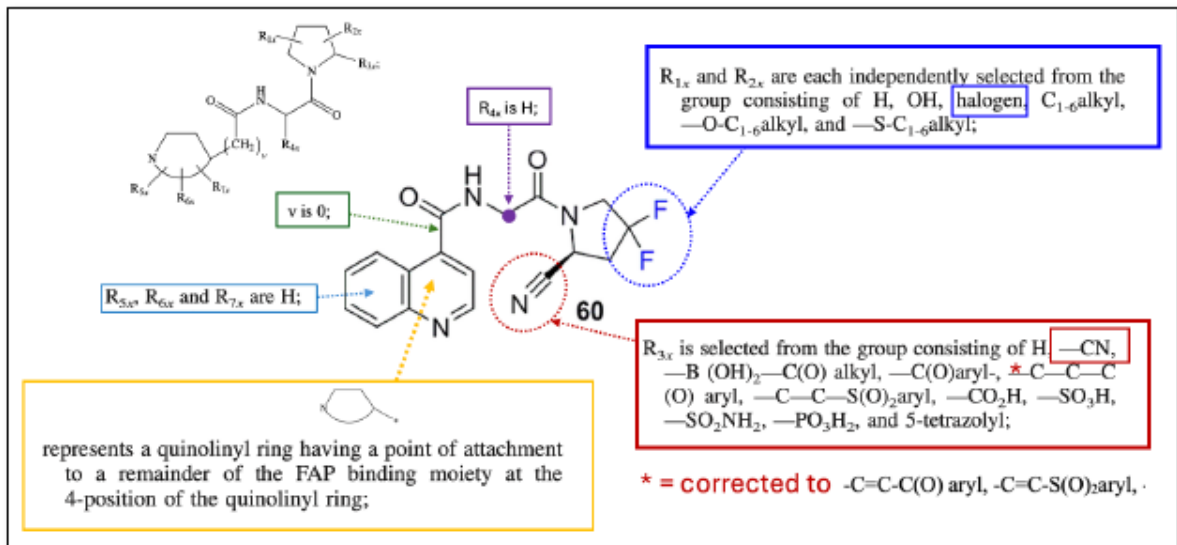
Petitioner argues that the claims of the ’233 patent would have been obvious over the teachings of US-633, Meletta, and Jansen. Pet. 25. Petitioner contends that, of the claimed compound Formula (I) having a B-L-A structure, only the identity of the targeting moiety “A” differs from the small molecule inhibitor of seprase (FAP- α) disclosed in US-633 for use in targeting radiopharmaceuticals. *Id.* at 25–26, 59–61. Petitioner argues that a skilled artisan aware of the teachings of US-633 would have learned from Meletta that the boronic acid pyrrolidine targeting moiety in compounds disclosed in US-633 was insufficiently selective for FAP, and thus there was a need for “new compounds exhibiting greater selectivity for

⁶ See also Ex. 1003 ¶¶ 145–150, 157–161.

FAP,” giving the artisan motivation to look for “more FAP-selective small molecule FAP-inhibitor compounds to use in FAP-targeting radiotracers.” *Id.* at 46; *see also* Ex. 1003, ¶¶ 135–138. Petitioner alleges that the artisan would have found Jansen and understood from it that Jansen’s “highly selective FAP inhibitor” identified as compound 60 could be used as a superior targeting moiety to solve the problem Meletta identified. *Id.* at 26–27; *see also* Ex. 1003, ¶¶ 167–169, 144–147, 149. Due to compound 60’s favorable high selectivity, Petitioner alleges, the artisan would have been motivated to replace the targeting moiety of the radiotracers described in US-633 with Jansen’s more selective compound 60 *Id.* at 62–67 (citing Ex. 1002, 172–173 (¶¶ 32–37); Ex. 1003, ¶¶ 68–69, 71–72, 101, 103–105, 132–135, 134–138, 140, 144–149, 157–160, 167–169, 182, 194; Ex. 1004, ¶¶ 5, 7, 169–170, 178–180, 185; Ex. 1006, 3053–3055, 3063–3064 (Table 5); Ex. 1008, 2089–90; EX1022, 123, 125; Ex. 1024, 454, 455. Ex. 1026, 1, 8; Ex. 1046, 26).

Petitioner argues that compound 60 meets the structural requirements of the “A” component in the claimed “Formula (I)” of “B-L-A” as

represented in Petitioner's annotated diagram below:



Pet. 68. Reproduced above is Petitioner's annotated diagram explaining its assertions that compound 60 meets the structural requirements of the "A" component in the claimed "Formula (I)."

Petitioner provides, with the support and explanatory testimony of Dr. Zeglis, the steps that the ordinarily skilled artisan would have taken to replace the "A" component of US-633 with Jansen's compound 60 and argues that the artisan would have found it obvious to do so. *Id.* at 70–78, 85–86 (citing Ex. 1003 ¶¶ 33–38, 42–43, 45–46, 49–53, 105–106, 105, 112–119, 122–123, 127, 163–164, 166, 167, 171, 174–176, 178–179, 183–184, 187–188, 190, 192–193, 195, 197–199, 202, 204–205, 211, 213; Ex. 1001 ¶¶ 8, 21, 101; Ex. 1004 ¶¶ 8, 12–20, 48–49, 100–101, 117–118, 130, 131, 133; Ex. 1006, 3053, 3062). Petitioner summarizes these steps as follows:

- (i, ii) used the modular three-component design known in the art and taught by US-633 to replace the boronic acid pyrrolidine targeting moiety of the radiotracers in US-633 with compound 60 with compound 60 from Jansen (see § V.D);
- (iii) select a radionuclide and its suitable chelator or prosthetic group for a desired imaging platform (PET or

SPECT) pursuant to US-633 and knowledge they possessed in 2017, such as by matching the prosthetic group's radioactive half-life to the pharmacokinetic half-life of the radiotracer;

(iv) select a linker pursuant to the guidance in US-633 to connect compound 60 to the radiolabeling moiety (*e.g.*, a 3-monomer functionalized PEG) so as to separate the reporter and targeting moieties by ~10-20 bonds to avoid causing steric or chemical interference between the radiolabeling and targeting moieties; and

(v) construct the compound by conventional synthetic steps (*e.g.*, functionalize compound 60 at position C⁶ with a carboxylic group, attach PEG linker via amide bond, attach chelator/prosthetic group via amide bond).

Pet. 77–78 (internal references removed). Petitioner provides four compounds, A1–A4, as compounds falling within the scope of claim 1 that could be made following these steps. *Id.* at 78–85 (citing Ex. 1003 ¶¶ 171, 185–190; 192–199, 201–202, 204; Ex. 1004 ¶¶ 8, 19–21, 28, 48–49, 100, 111, 116–118, 130, 133; Ex. 1006, 1053, 3061–3062).

4. *Patent Owner's Position*

Patent Owner argues some of Grounds 1 and 2 together, and provides no separate discussion in relation to claims 2–4 in either ground.

Specifically, Patent Owner contends that Petitioner's analysis for both Grounds 1 and 2 uses hindsight to arrive at the claimed invention and that secondary considerations are inappropriately dismissed. Prelim. Resp. 23–27, 35–41, 48–61. We address all of Patent Owner's arguments relating to Ground 1 below. We do not repeat and separately address the issues of hindsight or objective indicia of nonobviousness in our discussion of Ground 2 beginning at § IV.B.

For Ground 1, Patent Owner argues that the prior art as a whole would have presented an ordinarily skilled artisan with numerous choices that

would have led them away from the claimed invention, and that the directions and conclusions reached by Petitioner's declarant, Dr. Zeglis, reflect the use of hindsight to construct a prima facie case of obviousness. Prelim. Resp. 23–63.

Patent Owner argues, through its declarant Dr. VanBrocklin, that Dr. Zeglis erred in identifying linkers in certain molecules in Jansen, overlooked possible sites for moiety conjugation, and that Dr. Zeglis's conclusions about certain teachings of Jansen are incorrect. *Id.* at 27–35 (citing Ex. 2001 ¶¶ 52–58). Dr. VanBrocklin opines that Jansen discloses both linker-containing radiotracers (B-L-A) and linker-less radiotracers (B-A), and that the concerns articulated by Dr. Zeglis regarding the needs expressed by the prior art would have driven the POSA to select B-A (linker-less) rather than B-L-A compounds for use. *Id.* at 23–27, 36–41 (citing Ex. 2001 ¶¶ 59–62). Patent Owner argues that US-633 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 39. Patent Owner also argues that Dr. Zeglis's selection of linker-containing compounds ignored art showing increased FAPi selectivity and affinity through halogenation. *Id.* at 46–48 (citing Ex. 2001 ¶¶ 66–69).

Patent Owner further argues that Dr. Zeglis's chosen method requires adding a linker in addition to using the inferior B-L-A structure, which a POSA would not have been motivated to do, including technically incorrect assumptions by Dr. Zeglis in the method itself. Prelim. Resp. 41–46 (citing Ex. 2001 ¶¶ 50–58). Patent Owner contends that Petitioner and Dr. Zeglis used hindsight to select its cited compounds for modification by

impermissibly choosing compounds for modification because the compounds were structurally similar to the claims. *Id.*, *e.g.* at 48.

Patent Owner further faults Dr. Zeglis's ultimate selection of Compound 60 from Jansen as the best candidate for moiety A because: 1) other, more suitable FAPis were known in the art, including other art authored by Jansen, and Dr. Zeglis did not explain why these other FAPis were not selected; 2) Dr. Zeglis's own analysis, performed correctly, would not have arrived at Compound 60 as the best moiety A; and 3) Dr. Zeglis eliminated Jansen compounds 51 and 61 as potential A moieties without correct justification when the art showed they could have been conjugated at other positions on the quinolyl ring and Dr. Zeglis failed to explain his threshold for hydrophobicity concerns that caused him to exclude these compounds. Prelim. Resp. 48–63 (citing Ex. 2001 ¶¶ 70–86). According to Patent Owner, a non-hindsight motivated criteria would have led Dr. Zeglis to a different end product not within the scope of claim 1. *Id.* For this reason, Patent Owner argues that Dr. Zeglis's assertions are conclusory and unsupported, and are entitled to little or no weight.

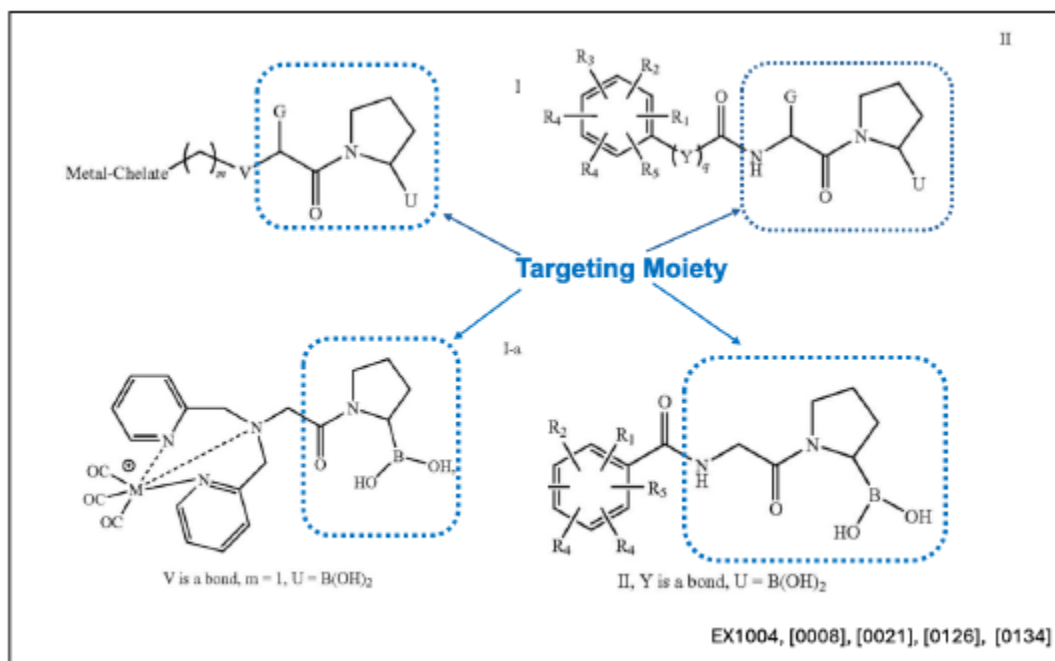
With regard to objective indicia of nonobviousness, Patent Owner alleges that the Petition is fatal as it did not “address the known evidence of the unexpected results of the claimed compounds that were submitted during prosecution of the '233 patent.” Prelim. Resp. 66. Patent Owner provides no further analysis of this issue.

5. *Analysis*

Based on this preliminary record, we find that Petitioner has established that it is more likely than not that the claims are obvious over the cited art. Petitioner has established that US-633 taught small molecule

radiopharmaceuticals that target FAP and are used in diagnostic imaging and radiotherapy of tumors and tissues. Pet 25–26, 59–61. Petitioner additionally establishes that Meletta discloses that the boronic acid pyrrolidine targeting moiety in compounds disclosed in US-633 was insufficiently selective for FAP, and thus there was a need for more selective targeting moieties for FAP-targeting radiopharmaceuticals. *Id.* at 26, 62; *see also* Ex. 1003, ¶¶ 132–134. Petitioner further establishes that Jansen discloses Compound 60 as an improved FAP-selective inhibitor that could be used as a superior targeting moiety to solve the problem Meletta identified. *Id.* at 26–27; *see also* Ex. 1003, ¶¶ 167–169, 144–147, 149. While Petitioner and Patent Owner’s declarants may disagree on molecule development strategy and particular disclosures of Jansen, Petitioner’s case for *prima facie* obviousness beginning with compounds in a B-L-A configuration is documented in the prior art, and Patent Owner does not directly address it.

We further note that Petitioner’s 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., to improve inhibition of FAP- α ’s enzymatic activity. 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. It is clear that Petitioner looked to FAP- α targeting moieties disclosed in US-633, having a particular boronic acid pyrrolidine moiety as the FAP-targeting moiety in most of its examples as the starting point of the obviousness determination for Ground 1. *See* Pet. 39–40. Petitioner specifically identified the following targeting moiety structure disclosed on multiple compounds in US-633 as the FAP inhibitor of interest:



Shown above is Petitioner’s annotated diagram of four compounds disclosed in US-633 at paragraphs 8, 21, 126, and 134. Petitioner’s application of Meletta and Jansen’s disclosures to lead an ordinarily skilled artisan to replace the targeting moiety of the radiotracers described in US-633 and shown above with the more selective Compound 60 of Jansen is a reasonable solution that we are persuaded, on this record, would have motivated one of skill in the art to pursue, for the reasons given by Petitioner and Dr. Zeglis. We acknowledge that Patent Owner’s critiques of particular statements and decisions made by Dr. Zeglis (*see, e.g.*, Ex. 2001 ¶¶ 52–58) may be individually valid, but these critiques largely relate to specific disclosures in Jansen and other prior art and ignore the broader disclosures referenced in the asserted art by Petitioner, including that the starting compound 60 is already in B-L-A form. Moreover, Petitioner’s case need not be the best option to establish obviousness. “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) (citing *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 alleges that any possible assertion of secondary indicia would relate to prior art elements, not the claims. Pet. 106. Patent Owner contends that “GE fails to make a case of obviousness as a matter of law because it does not address known objective indicia of nonobviousness, namely unexpected results of the claimed compounds.” Prelim. Resp. 64. Patent Owner does not identify the “known objective indicia of nonobviousness.” On this preliminary record, we are unable to determine whether such objective indicia exists or is commensurate with the broad scope of the claims.⁷ 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

⁷ We note that in a related case, PGR2025-00012, the Board concluded that evidence related to examples tested and reported in Dr. Pomper’s declaration during prosecution of the 11,938,201 B2 patent was found to be “plainly not commensurate with the much broader scope of the claims,” which are similar in scope to the currently challenged claims. *ITM Isotope Tech. Munich SE v. The Johns Hopkins Univ.*, PGR2025-00012, Paper 12, 36 (PTAB July 16, 2025).

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.’”). We encourage the parties to address any such evidence at trial.

On this preliminary record, we find that Petitioner demonstrates sufficient argument and evidence to show it is more likely than not that at least one claim would have been obvious over US-633, Meletta, and Jansen.

B. Ground 2: Alleged Obviousness over US-121 and Jansen

Petitioner argues that claims 1–4 are unpatentable over the combination of US-121 and Jansen. Pet. 86.

1. Overview of Asserted Art

a) US-121 (Ex. 1005)

US-121 (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. 1005, (10), (43), (54), (60). PSMA is prostate-specific membrane antigen. *Id.*, Abst.

US-121 describes imaging and therapeutic compounds that target and bind PSMA expressed in prostate cancer. Ex. 1005, ¶ 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.

US-121 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. 1005, ¶ 8. US-121 provides compounds with greater cellular retention and low molecular weight. *Id.*, ¶ 12.

b) Jansen

Jansen is summarized above at IV.A.2.(c).

2. *Petitioner’s Position*

Petitioner alleges that the challenged claims would have been obvious over the teachings of US-121 and Jansen. Petitioner alleges that US-121 discloses advantages of its “low molecular weight” compounds used as radiotracers and therapeutic radiopharmaceuticals, including better contrast between target and non-target tissues and better tumor penetration. Pet. 87 (citing Ex. 1005 ¶¶ 8–9, 12, 188). Petitioner alleges that US-121 discloses examples of radiotracer designs that target a protein called prostate-specific membrane antigen (PSMA) and can be used for imaging cancerous cells and tumors. Petitioner alleges that US-121 discloses that PSMA is a transmembrane (cell-surface) enzyme with an extracellular active site that is selectively expressed in epithelial cancers. Pet. 88 (citing Ex. 1005 ¶ 12).

Petitioner alleges that US-121’s radiotracers have a modular, three-component design, with its targeting moiety having comparable molecular weight to Jansen’s Compound 60. *Id.* at 89 (citing Ex. 1005 ¶¶ 166, 169; Ex. 1003 ¶¶ 211, 233). Petitioner alleges that US-121 discloses benefits of its design, from allowing optimization of the linker chelate complex to improve pharmacokinetics to detection of its radiolabeled tracers by PET and SPECT devices. *Id.* at 90 (citing Ex. 1005 ¶¶ 11, 103, 184, 207, 214, 225, 242, 244, 249–250, 279; Ex. 1003, ¶ 212, 215–216). Petitioner alleges that US-121 discloses that its chelating moieties are interchangeable, and that linkers can be selected to improve hydrophobicity to promote

circulation time. *Id.* at 91 (citing Ex 1005 ¶¶ 12, 27, 102, 187, 214, 231, Fig. 4; Ex. 1003 ¶¶ 217, 221, 225–226, 235).

Petitioner alleges that an ordinarily skilled artisan would have considered US-121 and Jansen together due to the similarity of the size of their targeting molecules and their uses, and both references' emphasis on use of small molecules to target cell-surface enzymes. *Id.* at 93 (citing Ex. 1003 ¶¶ 207, 233, 227, 229; Ex. 1036, 226–27; Ex. 1005 ¶¶ 7, 240; Ex. 1006, 3053, 3065). Petitioner argues that the similarity would have prompted the artisan to develop a compound 60-based radiopharmaceutical using the guidance in US-121 to replace the urea-based targeting moiety in US-121's radiotracers with compound 60 of Jansen. *Id.* at 93–94 (citing Ex. 1006, 3053, 3065; Ex. 1003, ¶¶ 227–228, 230–232, 234). In particular, Petitioner alleges that US-121's guidance to use specific linkers “to improve the performance of radiotracers in tumor imaging” would have guided the artisan to use US-121's particular combinations of linkers and chelators to produce FAP-targeting radiotracers based on compound 60. *Id.* at 97 (citing Ex. 1003 ¶¶ 234–236). Petitioner further alleges that the artisan would have selected small molecule radiotracers taught in US-121 such as ^{68}Ga and $^{99\text{m}}\text{Tc}$ as radionuclides to use in a compound 60-based radiotracer, and would have used correspondingly appropriate chelators from US-121. *Id.* at 98 (citing Ex. 1003 ¶¶ 40, 217, 232, 237).

Through Dr. Zeglis, Petitioner provides a specific method of modification of four radiotracers depicted in US-121 to replace the urea-based targeting moiety with compound 60 of Jansen, resulting in compounds B1–B4. Pet. 99–102 (citing Ex. 1002 ¶¶ 223–226, 237–239). Petitioner alleges that each of B1–B4 falls within the scope of claims 1–4. Pet. 103–

104 (citing Ex. 1002 ¶¶ 202, 242–243, 245). Finally, Petitioner argues that US-121 provides descriptions of “straightforward synthetic procedures” that would have guided the artisan to make compounds B1–B4, which are within the scope of claims 1–4, and which would have been expected to retain the selectivity and affinity of compound 60 based on their size and experimentation disclosed in Jansen. Pet. 105 (citing Ex. 1003 ¶¶ 178, 246).

3. Patent Owner’s Position

We do not repeat Patent Owner’s arguments regarding hindsight or secondary indicia of nonobviousness already addressed in relation to Ground 1 (*see* § IV.A.4., *supra*).

Patent Owner alleges that, similar to Ground 1, Petitioner does not consider the prior art as a whole and uses hindsight to guide its obviousness allegations. Prelim. Resp. 63. Patent Owner alleges that Dr. Zeligs’s “selection of Jansen’s Compound 60 ignores the prior art as a whole by failing to factor Jansen 2013, US-650, and Jansen 2014 in his analysis.” *Id.* (citing Ex. 2001 ¶¶ 70–87). Patent Owner alleges that Petitioner’s use of hindsight analysis is a sufficient basis to reject Ground 2.

4. Analysis

On the record at this stage of the proceeding, we find that Petitioner demonstrates sufficient argument and evidence to show it is more likely than not that at least one claim would have been obvious over USU-121 and Jansen.

We agree with Petitioner that US-121 teaches a modular, B-L-A “low molecular weight” compound used as a radiotracer with a targeting moiety designed to target an enzyme with an extracellular active site, similar to FAP- α . *See* Pet. 87. As in Ground 1, Petitioner relies on Jansen to teach

compound 60 as the most promising FAP inhibitor and a candidate for use as a FAP-targeting moiety in nuclear imaging. *See* Pet. 93. Petitioner relies on specific disclosures in US-121 that suggest to an ordinarily skilled artisan that its chelating moieties can be altered to improve performance of radiotracers in imaging. *See* Pet. 97. Once again, Petitioner’s motivation for the proposed combination is documented in the prior art.

Patent Owner’s objections are based, as with Ground 1, on failing to consider the teachings of the prior art as a whole and allegations of hindsight used to guide its allegations of obviousness. *See* Prelim. Resp. 62.

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 develop a compound 60-based radiopharmaceutical using the guidance in US-121 to replace the urea-based targeting moiety in US-121’s radiotracers with compound 60 of Jansen. The artisan would have reasonably expected success in creating compounds B1–B4 based on guidance in US-121 to use specific linkers “to improve the performance of radiotracers in tumor imaging”, providing options for small molecule radiotracers, and illustrating synthetic procedures to make its radiotracer molecules. Ex. 3053, 3065. Patent Owner provides no separate discussion in relation to claims 2 and 3 and does not oppose Petitioner’s allegation that compounds B1–B4 are within the scope of challenged claims 1–4.

On the current record, we find that Petitioner has demonstrated that it is more likely than not that the combination of US-121 with Jansen would have rendered claims 1–4 obvious.

C. Ground 3: 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 that contain options for the three functional groups of the B-L-A formula, permitting “immense structural diversity, particularly in the B and L components.” Pet. 107. Petitioner cites Dr. Pomper’s statement in the prosecution history that “developing a medical imaging agent is highly unpredictable” and summarizes the multiple options for each component in contrast to the Specification’s disclosures regarding each. Pet. 108–109

(citing Ex. 1001, 14:57–15:48, 15:49–17:54; Ex. 1002, 172 ¶¶ 30–32; Ex. 1003 ¶¶ 85–89, 91–92. Appxs. A, B).

As such, Petitioner argues, the '233 patent must disclose “a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.”” Pet. at 118–119 (citing *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (quoting *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993))).

Despite this broad diversity of combinations of components, Petitioner argues, the Specification describes but two examples of FAP-targeting compounds having the B-L-A formula. *Id.* at 121. Petitioner alleges that the two examples provided “plainly are not representative of the immense diversity of B-L-A compounds within the claimed genera.” *Id.* at 122. Petitioner notes that both examples were made from a single intermediary compound, and lack examples of multiple options that fall within the scope of the claims. *Id.* at 122–123 (citing Ex. 1001, 53:53–5:60; Ex. 1003 ¶¶ 93, 178, 250–253, 261). Petitioner further argues that the '233 patent disclosure fails to identify compounds outside the provided B-L-A options that could be used and fails to identify a structure-function relationship that would aid an ordinarily skilled artisan in identifying low molecular weight FAP-targeting compounds being claimed by claims 1-4 that have the disclosed diagnostic or therapeutic utility. *Id.* at 124–131 (citing Ex. 1001, 14:57–15:65, 15:1–6, 26–27; Ex. ¶¶ 85(b), 93, 178, 248, 251, 253–257, 266, 270; Ex. 1019, 479–81).

3. *Patent Owner's Position*

Patent Owner points out that Petitioner's written description arguments are predicated on the claimed genus purportedly needing to meet diagnostic or therapeutic utility defined by the Specification. Prelim. Resp. 66 (citing Pet. 107; Ex. 2001 ¶¶ 89–92). 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 for use in the recited compounds based on their individual functional characteristics.” *Id.* at 66–67. Patent Owner argues that numerous examples of suitable B and L moieties are listed in and incorporated by reference into the Specification, along with two working examples. *Id.* at 69. 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* have this functionality. Likewise, the L moiety must have the capability to form a chemical bond with B and A, but the claims do not require that the claimed compound have this function. The case law argued by Petitioner that addresses functionally-defined claims is not relevant here. On this record, we agree with Patent Owner that the '233 patent describes a common modular structure containing a targeting moiety, a reporter moiety, and a linker, and provides exemplary moieties for each, including incorporating by

reference other publications disclosing numerous moieties falling within the claims. *See* Prelim. Resp. 70–71 (citing Ex. 2001 ¶¶ 89–97, 102–103).

D. Ground 4: 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 argues that the Specification of the '233 patent fails to enable the challenged claims because it does not sufficiently guide one of skill in the art to practice the full scope of the invention without undue experimentation, particularly as the FAP-targeting compounds require potent and specific binding to FAP along with stability and sufficient bioavailability. Pet. 132–135. Petitioner alleges that the variety of options provided for each B-L-A component in combination with the lack of guidance in the Specification regarding selection, arrangement and assembly to “yield compounds with the diagnostic or therapeutic utilities identified in the specification” is an absence of meaningful guidance. *Id.* at 107–108, 135.

Through Dr. Zeglis' testimony, Petitioner argues that the diversity of choices, including, e.g., options for different substituents and numerous positions, and arrangement of different sections in any order with optional repeating segments, renders the process of creating a B-L-A molecule disclosed by the patent unpredictable. *Id.* at 108–109 (citing Ex. 1001, 14:57–15:48, 15:49–17:54 Ex. 1003 ¶¶ 85–86. Appendix B). Petitioner argues that the diversity of the choices available creates “substantial uncertainty” about whether the B-L-A compound resulting from the various compounds could have affinity for and be selective for its molecular target. *Id.* at 112 (citing Ex. 1003 ¶¶ 59(b), 96–96). As an example, Petitioner points to examples in Jansen reflecting reduction in FAP affinity and selectivity from substitution of components. *Id.* at 113–114 (citing Ex. 1003, ¶¶ 174, 178; Ex. 1006, 3056, 3061–3062).

Petitioner argues that it is important for the B-L-A compounds to maintain potency and selective binding, remain stable in bodily fluids and *in vivo*, and be sufficiently bioavailable. *Id.* at 115 (citing Ex. 1001, 7:41-43, 7:46-56, 34:63-35:52, 35:42-46, 38:65-39:9; Ex. 1003 ¶¶ 59, 133, 275, 277). Petitioner argues that, based on the lack of guidance provided in the Specification of the '233 patent, an ordinarily skilled artisan would have needed to synthesize and test compounds “to determine if any (i) retained high affinity and selectivity for FAP, (ii) was stable, and (iii) had adequate bioavailability.” *Id.* at 116-118 (citing Ex. 1001, 4:27-51, Ex. 1002, 172-173, ¶¶ 30-37; Ex. 1008, 2089, 2095; Ex. 1003, ¶¶ 275-277).

Petitioner argues that '233 patent Specification does not enable the full scope of the claimed invention due to the “immense and diverse” genera of B, L, and A components claimed, the high unpredictability of the art, as supported by the testimony of Dr. Pomper as addressed above, and the limited guidance provided by two examples in the Specification. Petitioner offers Dr. Zeglis’s testimony that he identified four compounds that, based on their structural characteristics, would not have been predicted by an ordinarily skilled artisan to “retain high affinity and selectivity for FAP, [be] stable under physiological conditions (*e.g.*, in plasma), and ha[ve] adequate bioavailability.” Pet. 140-141 (citing Ex. 1003 ¶¶ 276, 279). Dr. Zeglis references data in Jansen that show substitutability of certain positions on the quinoliny ring, the glycine α -carbon, and the open positions on the pyrrolidine ring is inconsistent. *Id.* at 141-143 (citing Ex. 1003 ¶ 290). Petitioner acknowledges that the artisan “would not have believed that testing was necessary for every B-L-A compound,” but that “innumerable compounds within the claimed genera” would not have been reasonably

predictable. Petitioner argues that the amount of testing and experimentation would have been undue. *Id.* at 145. Petitioner argues that weighing the *Wands* factors shows a lack of enablement of the claims. *Id.* at 145–146.

3. Patent Owner’s Position

Patent Owner argues that the claimed compounds are defined and construed *structurally*, and that Dr. Zeglis’s opinion regarding enablement is incorrect because it relies on his understanding that the compound must be viable *in vivo*. Prelim. Resp.78. Patent Owner argues that the claims do not require an ordinarily skilled artisan to make and use the compounds *in vivo*, and there is no other such requirement. Patent Owner argues that the compounds meet the utility requirement of 35 U.S.C. § 101, e.g., because the Specification discloses uses such as “*in vitro* or *ex vivo* by introducing, and preferably mixing, the compound and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube” and also *ex vivo* or *in vivo* imaging. *Id.* at 81 (citing Ex. 1001, 35:4–9, 37:22–25; Ex. 2001 ¶ 105). Patent Owner argues that Dr. Zeglis’s focus on *in vivo* uses results in a failure to show lack of enablement because *in vitro* uses would not require the same amount of labor and time as alleged with *in vivo* uses. *Id.* at 82 (citing Ex. 2001 ¶ 106). Patent Owner provides additional critiques of Dr. Zeglis’s testimony that undue experimentation would be required to obtain highly selective FAP-binding compounds because poorly selective compounds would still have utility and could be usable in certain circumstances. *Id.* at 84 (citing Ex. 2001 ¶ 108). Patent Owner concludes that Dr. Zeglis’s analysis of enablement under the wrong lens fails to establish a lack of enablement of the claims.

4. *Analysis*

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

The extent of experimentation that 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, on the current record, we determine that 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 a specification are not required where the invention is otherwise disclosed in such a manner that an ordinarily skilled artisan will be able to practice the claim without undue experimentation. *See* MPEP § 2164.02. However, working examples are more important in unpredictable fields, as in the technology of the '233 patent. *Id.* Petitioner's quotation of the Pomper Declaration describing "the high unpredictability of the medical imaging art" is particularly persuasive at this stage of the proceeding. The two working examples in the '233 patent's Specification employ the same FAPi (the A moiety), despite the fact that the options for structures covered by the A moiety are voluminous due to the breadth of the "alkyl" limitation included in substituent R_{3x}. Moreover, both examples are derived from a single precursor. Ex. 1003 ¶ 250. This limited disclosure weighs towards non-enablement.

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. On this record, it is more likely than not that Petitioner will prevail in showing that one or more claims fails 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.

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 of the '233 patent is hereby *instituted* on the grounds set forth in the Petition, commencing on the entry date of this Order, and 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.

PGR2025-00059
Patent 12,115,233 B2

For PETITIONER:

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