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

Case PGR2025-00012
U.S. Patent No. 11,938,201

PATENT OWNER PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.207(a)

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I. INTRODUCTION

Johns Hopkins University's ("JHU") U.S. Patent No. 11,938,201 ("the '201 patent") claims low molecular weight compounds that are useful as imaging and radiotherapeutic agents targeting fibroblast-activation protein-α ("FAP-α"), "which plays a critical role in promoting angiogenesis, proliferation, invasion, and inhibition of tumor cell death." EX1001, Abstract, 1:30-39. The claimed compounds are defined structurally, being composed of a novel combination of moieties having the structure "B-L-A." EX1001, 64:45-65:63. ITM's Petition challenging JHU's claimed compounds suffers from multiple flaws warranting denial.

First, ITM and its declarant, Dr. Martin, commit an error that infects all five of the Petition's Grounds: the level of ordinary skill in the art is the "lens" through which the claimed invention must be viewed, *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001), yet ITM uses an incorrect POSA lens for its assessments in each Ground. Consequently, their unpatentability analyses are fundamentally flawed and warrant denying the Petition on at least that basis.

For instance, Grounds I and II allege obviousness of the challenged claims. But because ITM and Dr. Martin analyze the art and claims using the incorrect POSA lens, they propose modifications to prior art compounds that would likely eliminate the same beneficial properties that ITM asserts POSAs would have been

motivated to achieve. Grounds III and IV allege lack of enablement and written description, respectively, for the challenged claims. Yet, ITM's and Dr. Martin's incorrect POSA lens results in them failing to consider a POSA's ability to readily ascertain the full scope of the B and L moieties of the claimed compounds that are disclosed and incorporated by reference in the '201 patent specification. As a result, ITM and Dr. Martin overlook that the '201 patent specification adequately describes and enables the claimed compounds. As for Ground V, alleging indefiniteness of the claim term "low molecular weight," ITM and Dr. Martin fail to appreciate that a properly-defined POSA would have understood the '201 patent to use the term according to its plain and ordinary meaning in the field, and also would have reasonably understood its scope.

Second, ITM incorrectly construes the challenged claims, also infecting its unpatentability analyses and providing further basis for denial. For example, ITM treats the claimed compounds as if they are functionally-defined. But ITM does not undertake any claim construction analysis to support this interpretation. Contrary to ITM's unsupported position, the challenged claims are structural, reciting a "low molecular weight compound" of "Formula (I): B-L-A." ITM's improper view that the claimed genus of compounds is functionally-defined leads to it applying inapt analyses and case law to allege lack of enablement and written description in Grounds III and IV. When the challenged claims are analyzed correctly as

structural claims, they are sufficiently described and enabled by the specification.

ITM also incorrectly construes certain structures within the claimed A moiety to assert that the A moiety's scope is essentially limitless. But ITM fails to mention or address that the patent incorporates by reference a definition for these same structures that limits their scope. ITM's improper constructions should be rejected and provide a further basis to deny the Petition.

Third, for its obviousness Grounds I and II, ITM fails to use the lead compound analysis or explain why it is not required, when the claims here are directed to new chemical compounds and ITM's obviousness assertions rely on selecting and modifying prior art compounds. ITM also impermissibly uses hindsight with the claims as a roadmap to select and modify the prior art. Furthermore, when faced with evidence of the claimed compounds having unexpectedly superior results submitted during prosecution, ITM summarily dismisses that evidence as not commensurate in scope with the challenged claims. But ITM and Dr. Martin only provide conclusory assertions, which are not sufficient to address the evidence of unexpected results head-on. Each of those errors are fatal to Grounds I and II.

Lastly, ITM performs its § 112 enablement and written description analyses for Grounds III and IV using the wrong date. Under the law, a patent application should be assessed for compliance with § 112 as of that application's own filing

date. *See, e.g.*, *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345-46 (Fed. Cir. 2000). Here, ITM never assessed *any* application in the '201 patent family as of *that application's own filing date*. ITM has thus failed to meet its burden to demonstrate that it is more likely than not that the challenged claims lack enablement and written description under § 112.

Indeed, ITM should be held to its multiple deficiencies because as the Petitioner, ITM is the "master of its own petition." *Qualcomm v. Apple*, Nos. 2023-1208, 2023-1209, 2025 WL 1174161, at *22 (Fed. Cir. Apr. 23, 2025). Accordingly, the numerous deficiencies in ITM's Petition warrant denial and PGR should not be instituted.

II. ITM'S PETITION USES AN INCORRECT POSA LENS FOR EACH GROUND.

The level of ordinary skill in the art is "a prism or lens" through which the claimed invention must be viewed, and ITM uses an incorrect lens throughout its Petition. *Okajima*, 261 F.3d at 1355 (Fed. Cir. 2001). Such "prism or lens" must be applied to each of ITM's unpatentability Grounds. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007) (the question for obviousness is "whether the combination was obvious to a person with ordinary skill in the art"); *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006) (written description is "judged from the perspective of one of ordinary skill in the art"); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) ("[p]atents are written to enable those skilled in the

art to practice the invention"); *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 898-899 (2014) (to meet the definiteness requirement, a patent must "inform, with reasonable certainty, those skilled in the art about the scope of the invention"). ITM and its declarant, Dr. Martin, use an incorrect POSA lens for their analysis for each Ground—a lens that does not account for the training and practical experience the POSA would have had in imaging or radiotherapy. It is "not harmless" error to use an incorrect POSA perspective where it "affects the ultimate conclusion" of unpatentability. *Innovention Toys, LLC v. MGA Ent., Inc.*, 637 F.3d 1314, 1323-24 (Fed. Cir. 2011) (reversing obviousness finding "based on an inappropriately low level of skill in the art"). Because ITM's and Dr. Martin's use of the wrong POSA lens affects their ultimate conclusions of unpatentability for each Ground (*infra*), institution should be denied.

In determining the level of skill of a POSA, the Federal Circuit has long considered factors such as the "(1) [] educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field" as a guide in determining the level of ordinary skill in the art. *Env't Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 696–97 (Fed. Cir. 1983); *Okajima*, 261 F.3d at 1355 (Fed. Cir. 2001) (the prior art may reflect the appropriate skill level of a POSA). The Federal

Circuit has also held that "[t]he patent's purpose" and the prior art may reflect the appropriate skill level of a POSA. *Best Med. Int'l, Inc. v. Elekta Inc.*, 46 F.4th 1346, 1353 (Fed. Cir. 2022); *Okajima*, 261 F.3d at 1355 (Fed. Cir. 2001).

Here, the '201 patent abstract expressly states that "[i]maging and radiotherapeutics agents targeting fibroblast-activation protein-α (FAP-α) and their use in imaging and treating FAP-α related diseases and disorders are disclosed." EX2002, ¶¶22-23; EX1001, Abstract. The specification further discusses radiolabeled groups for these agents, and cites numerous references relating to imaging and radiotherapy; it also provides imaging quality testing for its inventive compounds. EX2002, ¶¶23-24; EX1001, 17:45-30:67, FIGs. 6-8 (providing nuclear imaging data for the disclosed compounds).

ITM also cannot deny that the prior art it uses for alleging obviousness here likewise discusses compounds with radiotherapeutics and imaging applications, and its art provides in vitro imaging quality testing results. *See, e.g.*, EX1009, Abstract; EX1008, 3, 5; EX2002, ¶¶25-27. ITM further concedes that "claimed subject matter of ... the '201 patent" is the creation of compounds "used in diagnostic imaging and radiotherapeutics." Pet., 1.

As JHU's expert, Dr. Henry VanBrocklin, explains, in view of the patent's and the cited prior art's overall focus on imaging and radiotherapeutic agents described above, 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).[1] EX2002, ¶28. This training and experience would have involved developing and evaluating agents for biomedical imaging or radiopharmaceuticals, and using molecular imaging techniques. *Id*. Indeed, without this training and practical experience, the POSA would not have had the skill to properly understand the image quality testing data for the compounds described in both the specification and in the prior art, discussed above. *Id.*, ¶¶24-25, 28. Nor would the POSA have had the skills required to perform the sorts of tests needed to evaluate the performance of imaging or radiotherapeutic agents targeting FAP, such as the

[1] As discussed below (§ VII), ITM's declarant, Dr. Martin, does *not* appear to have any formal training or practical experience in imaging or radiotherapeutics, and thus does not possess the level of skill of a POSA. JHU's expert, Dr. VanBrocklin, *does* have such training and experience—he has a Ph.D. in Radiopharmaceutical Chemistry and more than two decades of practical experience in molecular imaging and imaging agent development—and thus possesses more than the level of skill of a POSA. EX2002, ¶¶4-15.

claimed compounds. *Id.*, ¶¶24-25.

However, ITM's declarant, Dr. Martin, states only that POSAs would have had some undefined "*understanding* of processes employed for synthesis and evaluation of imaging and radiotherapeutic agents that selectively target a specific protein and would be able to evaluate published literature and patents to ascertain features of a molecule that contribute to its affinity and selectivity for a particular drug target." EX1002, ¶95 (emphasis added). Dr. Martin's definition thus fails to take into account the multiple years of *formal training* and *practical experience* in radiopharmaceuticals that the POSA would have, as discussed above.

ITM's and Dr. Martin's use of a POSA lens that does not take into account this requisite formal training and practical experience materially affects their unpatentability conclusions for each Ground. For example, as detailed below, ITM and Dr. Martin: (1) for obviousness Ground I, select Zimmerman's compounds of Formula I *with* linkers "L" for modification, but do not explain *why* POSAs would have selected Formula I compounds when Zimmerman reported they were overwhelmingly inferior as a class of compounds compared to compounds of Formula II *without* linkers; (2) for obviousness Ground II, erroneously assert POSAs would have been motivated to *remove* moieties from Dvořáková's high molecular weight iBody compound to create a low molecular weight compound, when Dvořáková instead reported the benefit of using a higher molecular weight,

polymeric compound *with* a multitude of moieties; (3) for written description and enablement, overlook the POSA's ability to ascertain the full scope of "B" and "L" moieties for use in the claimed compounds from the disclosures in the specification and incorporated references, and practice that full scope without undue experimentation; and (4) for claim construction and indefiniteness, erroneously assert "low molecular weight" is a relative term with no objective boundaries to a POSA, when POSAs instead would have reasonably understood its meaning and scope: namely, compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. *See* §§ III.C, IV, V, and VI, *infra*.

These failures alone justify denying the Petition. *See Innovention*, 637 F.3d at 1323.

III. ITM'S PETITION IS BASED ON INCORRECT CLAIM CONSTRUCTIONS, LEAVING THE PETITION DEFICIENT UNDER 37 C.F.R. § 42.204(B)(3)-(4).

ITM carries the burden to show that it is more likely than not that at least one construed claim is unpatentable. 37 C.F.R. §§ 42.204(b)(3)-(4) (petition must identify "[h]ow the challenged claim is to be construed"); *Orthopediatrics Corp. v. K2M, Inc.*, IPR2018-01548, Paper 9 at 10 (P.T.A.B. Mar. 1, 2019) ("our rules place an affirmative burden on [P]etitioners to 'set forth: … [h]ow the challenged claim is to be construed.'"); *Samsung v. Cobblestone Wireless*, IPR2024-00319, Paper 16 (P.T.A.B. June 24, 2024) at 20-21 ("Where a petitioner specifically relies

on a particular construction of a claim term … the petitioner must provide a sufficient basis to support that construction.").

ITM provides a claim construction analysis only for two claim terms: "C(O)Alkyl"/"Aryl" and "low molecular weight." Petition, 40-44, 90-97.[2] For the rest of the terms, ITM states it uses "the standard under *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005)." Petition, 40. Yet ITM's Grounds heavily rely on treating the claimed genus as though it is "defined by functional language" without undertaking any *Phillips* analysis justifying this (incorrect) construction. Petition, 87, 75-76, 80, 83, 90. Its purported constructions for the "C(O)Alkyl"/"Aryl" and "low molecular weight" terms are also wrong: contrary to ITM's assertions, POSAs would have recognized that "C(O)Alkyl"/"Aryl" are not limitless in scope, and "low molecular weight" is not indefinite but instead has a readily understandable plain meaning and scope.

[2] ITM and Dr. Martin assert in both their "Claim Construction" analysis and in unpatentability Ground V that "there is no clear definition" of "low molecular weight," and that the claims are therefore indefinite. EX1002, ¶¶105, 187; Petition, 40, 92. Thus, JHU addresses both claim construction and indefiniteness (Ground V) relating to "low molecular weight" in §III.C, below.

A. ITM Fails to Support its Construction that the Claimed Compounds Are Defined Functionally.

1. ITM's Failure to Conduct Any Claim Construction Analysis to Support its Functional Definition Renders the Petition Deficient.

The challenged claims recite a "low molecular weight compound" having a specific structure: "Formula (I): B-L-A," where A is a targeting moiety for FAP (a "FAP inhibitor" or "FAPi") of a particular structure, and B is an optical or radiolabeled functional group suitable for imaging or radiotherapy that is chemically bonded to A via the linker L. EX1001, 46-47. Although the claims as written utilize *structural* language to describe the claimed genus of compounds,[3] ITM's obviousness, written description, and enablement unpatentability Grounds hinge on interpreting the genus as "functionally-defined." Petition, 88. ITM asserts that because the claimed genus is defined functionally, the specification must adequately enable and describe compounds that "perform the claimed functions,"

[3] While the *specific* "B" and "L" moieties are defined in the claims as "suitable" for imaging or radiotherapy, and having bi-functionalization adapted to form a chemical bond, respectively, the plain language of the claims define *only* B and L as "suitable" for imaging/radiotherapy and having bi-functionalization, and not the recited *genus* of low molecular weight compounds of "Formula (I): B-L-A." EX1001, 46-47; EX2002, ¶¶44-50.

and that the evidence of unexpected results of non-obviousness is not commensurate with "the broad functional language of used in the claims." Petition, 59, 75, 76, 80, 83, 90.

However, ITM *does not undertake any claim construction analysis* justifying that the claimed genus is, in fact, functionally defined. ITM does not evaluate the language of the claims, the specification, or the file history, as is required under *Phillips. See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313, 1317 (Fed. Cir. 2005). ITM does not mention or address its purported functional definition for the claimed genus in its "Claim Construction" section. Petition, §VI. Indeed, throughout the Petition and Dr. Martin's declaration, the only functions ITM and Dr. Martin describe are the specific "B" moiety's "suitab[ility] for optical imaging [or] radiotherapy" and the specific "L" moiety's "bi-functionalization adapted to form a chemical bond with B and A." Petition, 75-76, 90; EX1002, ¶¶167, 171. Yet ITM and Dr. Martin fail to articulate whether it is their position that those functions must *also* be the "two claimed functions" of the claimed genus of compounds having the structure "Formula (I): B-L-A." Petition, 80, 83; EX1002, ¶¶176, 178.

Instead, ITM baldly asserts that the claimed genus is "defined by functional language" and must "perform the claimed functions" without articulating what the claimed functions of the genus even are, let alone why it must perform those

functions. Petition, 75-76, 83, 90. Thus, ITM's assertion the claimed genus is "functionally-defined" (Petition, 88) is not grounded in proper claim construction principles and should be rejected.

ITM's reliance on Dr. Martin's declaration for its functional definition for the claimed genus does not save its deficient claim construction analysis. Petition, 75-76, 83, 90 (citing EX1002, ¶¶167, 175-176, 178). Dr. Martin simply repeats ITM's assertions regarding the claimed genus's purported functional requirements, without any further explanation or support, and without any application of claim construction principles.

Compare Petition, 75-76, 80, 83, 90 *with* EX1002, ¶¶167, 171, 176, 178 (an example is shown below):

ITM's Petition	**Dr. Martin's Declaration**
"The '201 patent does not even describe why or how the two disclosed examples—XY-FAP-01 and XY-FAP-02—perform the claimed functions or why other compounds do not." Petition, 76.	"The '201 patent does not even describe why or how the two disclosed examples—XY-FAP-01 and XY-FAP-02—perform the claimed functions, or why other compounds do not." EX1002, ¶167.

Dr. Martin's testimony is thus entitled to little weight and cannot support ITM's unjustified assertion of a functional definition for the claims. *See Xerox*

Corp. v. Bytemark, Inc., IPR2022-00624, Paper 12, at 5 (P.T.A.B. Feb. 10, 2023) (Vidal, Dir.) (Board "correct in giving little weight" to expert declaration because it "merely offered conclusory assertions without underlying factual support and repeated, verbatim, [Xerox's] conclusory arguments."); *Deeper, UAB v. Vexilar, Inc.*, IPR2018-01310, Paper 7 at 26-27 (P.T.A.B. Jan. 24, 2019) ("This conclusory analysis[] in the Petition …, by itself, renders Petitioner's showing insufficient. But even if we were to go beyond the Petition and also consider the cited [expert] testimony …, Petitioner's showing would still be insufficient because that cited testimony is itself conclusory.").

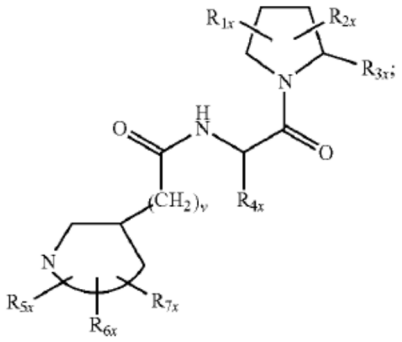
In sum, ITM's failure to explain how *the properly construed claims* are unpatentable warrants denial under 37 C.F.R. §§42.204(b)(3)-(4). *LG Display Co. v. Delaware Display Grp. LLC*, IPR2014-01359, Paper 12 at 6-7, 12-13 (P.T.A.B. Mar. 2, 2015) ("to evaluate Petitioner's challenges" regarding whether the prior art disclosed the term "relatively low angles," it was "necessary to determine the meaning" of the term, and denying institution because Petitioner failed to meet its burden to provide a construction).

2. Properly Construed under *Phillips*, the Claimed Compounds are Defined Structurally, Not Functionally.

When actually applying "the standard under *Phillips*" (Petition, 40), the plain language of the claims, in the context of the specification and prosecution history, shows that the recited "low molecular weight compound of Formula (I): B-

L-A (I)" is *not* "defined by functional language" as ITM incorrectly asserts. Petition, 87; EX2002, ¶¶43-53; *Phillips*, 415 F.3d at 1313.

It cannot be disputed that the challenged claims expressly recite a "low molecular weight compound" having a specific *structure*: "Formula (I): B-L-A (I)." EX1001, 46-47; EX2002, ¶¶44-45. It also cannot be disputed that the claims define "A" as having the following structure (*id.*):



wherein each of the R_{1x}, R_{2x}, R_{3x}, R_{4x}, R_{5x}, R_{6x}, and R_{7x} substituents also has a structural definition. EX1001, 46-47; EX2002, ¶¶44-45, 51-53; EX1002, ¶161 (Dr. Martin conceding "the A moiety is defined in [the] claims []as having the following *structure.*").

The *only* functional language present in the claims specifically defines the remaining "B" and "L" moieties within the genus of compounds—where "B" is "any optical or radiolabeled functional group suitable for" certain types of imaging or radiotherapy, and "L" is "a linker having bi-functionalization adapted to form a chemical bond with B and A." EX1001, 46-47; EX2002, ¶46. As explained by Dr.

VanBrocklin, POSAs—regardless of whether JHU's or ITM's POSA lens applies—would have understood that, because the "suitab[ility]" for imaging/radiotherapy and "bi-functionalization" claim language defines *specifically and only* "B" and "L," that language does *not* also define the claimed genus of low molecular weight compounds of formula B-L-A. EX2002, ¶¶46, 50, 53. And ITM and Dr. Martin fail to explain why POSAs would have read the "suitability" for imaging/radiotherapy" and "bi-functionalization" claim language defining "B" and "L" only, to also define the claimed genus of "B-L-A" compounds. Petition, 75-76, 80, 83, 90; EX1002, ¶¶167, 171, 176, 178. Instead, ITM itself states that "the claims of the '201 patent contain two functional limitations: (1) B is 'any optical or radiolabeled functional group suitable for optical imaging …; and (2) L is 'a linker having bifunctionalization adapted to form a chemical bond with B and A'"—likewise recognizing that the purported "two functional limitations" define *only* "B" and "L" and not "B-L-A." Petition, 74-75; EX1002, ¶171 (Dr. Martin stating the "B moiety [] *is defined*" as "suitable for" imaging or radiotherapy, and the "linker moiety [] *is defined*" as requiring "bi-functionalization"); EX2002, ¶¶47-50.

Indeed, reading the claims to somehow define the recited genus of "B-L-A" compounds with the "suitability" for imaging/radiotherapy and "bi-functionalization" definitions specific to "B" and "L," yields plainly incorrect

results. For example, requiring the function of the "L" moiety— "having bi-functionalization adapted *to form* a chemical bond with B and A"—to also define claimed genus of compounds is nonsensical. A compound comprising a linker L that forms a chemical bond linking B and A (i.e., the claimed B-L-A) cannot itself *also* be "adapted *to form* a chemical bond between A and B," as Dr. Martin alleged (EX1001, ¶160). EX2002, ¶50. The nonsensical result of ITM's claim construction renders it incorrect. *Becton, Dickinson & Co. v. Tyco Healthcare Grp., LP*, 616 F.3d 1249, 1255 (Fed. Cir. 2010) (constructions "that render [the] claims facially nonsensical 'cannot be correct.'").

The specification likewise defines the recited "compound of Formula (I): B-L-A" in structural terms, consistent with the plain language of the claims. *See, e.g.*, EX1001, 2:4-12, 4:30-51, 7:45-65, 8:14-24, 11:22-30, 12:40-50, 15:40-44; EX2002, ¶¶51-53. And during prosecution, the applicant distinguished the recited genus of compounds over the prior art on *structural* grounds: the applicant "define[d] the compound of formula (I) as being low molecular weight" to distinguish from Dvořáková's high molecular weight compounds, and pointed to the claimed structural combination of B, L, and A moieties to distinguish from Jansen I and II, and Zimmerman. EX1004, 1196-97 (Pomper Declaration, ¶8-29); EX2002, ¶¶52-53. ITM and Dr. Martin fail to point to any portion of the specification or the prosecution history that defines the claimed genus of "B-L-A"

compounds functionally rather than structurally. EX2002, ¶53.

In sum, POSAs reviewing the plain language of the claims in view of the specification and file history would have understood that the recited "low molecular weight compound of Formula (I): B-L-A (I)" is *not* defined functionally. EX2002, ¶53. Because ITM's Grounds heavily rely on the incorrect functional claim construction, institution should be denied.

B. The "C(O)Alkyl" and "Aryl" Terms in the R_{3x} substituent of "A" Are Not Unlimited.

ITM asserts that the "C(O)Alkyl" term in the R_{3x} substituent of the "A" moiety "should be construed as an 'acyl group comprising an alkyl group of *any length*.'" Petition, 44; EX1002, ¶¶110-111 (emphasis added). And while ITM does not offer any express construction for the "aryl" term in the R_{3x} substituent of the "A" moiety—failing to meet its burden to show that it is more likely than not that the *properly construed* claims are unpatentable under 37 C.F.R. §§42.204(b)(3)-(4)—ITM asserts that this term also "should not be limited to any particular length, size, or substitution." *Id.* However, ITM's assertion that these two terms are unlimited in scope is wrong, and cannot support its unpatentability Grounds.[4]

[4] ITM heavily relies on the alleged "unlimited" scope of the "alkyl" and "aryl" terms—per ITM, the specification does not enable and describe the "virtually infinite number of potential candidate structures" falling under the scope of the claims, and

As Dr. VanBrocklin explains, POSAs (under either JHU's or ITM's POSA definition) reviewing the claims and specification would have understood that JHU defined the recited "C(O)Alkyl" and "aryl" within the R_{3x} substituent of "A" *as claimed* are of *limited* length. EX2002, ¶¶54, 56, 58. The specification incorporates by reference in its entirety Jansen I (and its related applications with identical disclosures) and states that it provides "representative" FAP-α inhibitors of the recited structure "A" for "use with the presently disclosed subject matter." EX1001, 8:25-9:29; EX2002, ¶¶55-56. The Jansen I FAPi structures share *the same* R_{3x} substituent as the claimed "A" moiety. EX1007, 6:25-7:22, 98:45-99:35; EX2002, ¶¶57-58; EX1002, ¶115. POSAs would thus have turned to Jansen I's express definitions of the alkyl and aryl groups for use in the R_{3x} substituent of the claimed "A" moieties; these definitions state that these groups have *a specific, limited length, size, and substitution*. EX2002, ¶58; EX1007, 22:13-43.

Specifically, Jansen I provides "the following definitions" stating that "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

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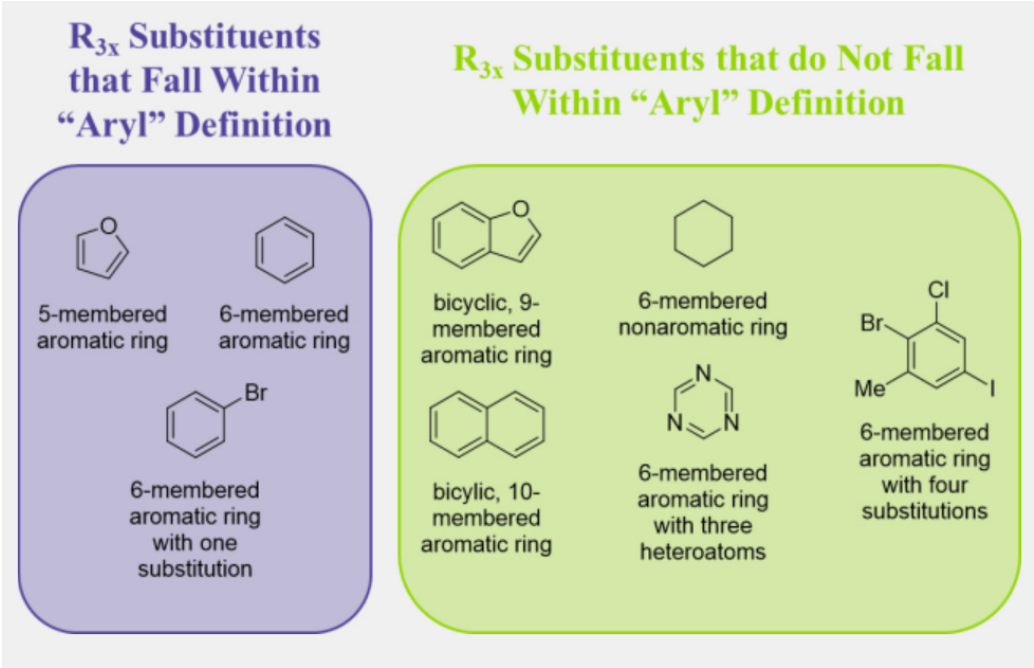
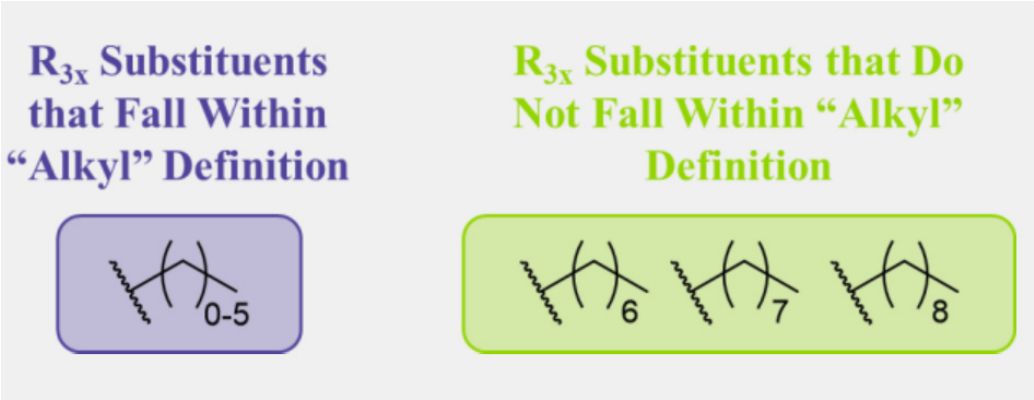
the evidence of unexpected results is also not commensurate with this purportedly "limitless" scope. Petition, 59, 75, 90; EX1002, ¶¶133-135, 162-163, 165, 167, 175, 178.

heteroatoms selected from O, N and S; said aryl further being optionally substituted with from 1 to 3 substituents." *Id*. Dr. VanBrocklin prepared the following graphics to illustrate how POSAs would have understood the definitions in Jansen I (EX2002, ¶58):





Thus, where, as here, the patentee acted as its own lexicographer to define "C(O)Alkyl" and "aryl" in the *claimed* R_{3x} substituent of "A" (via its incorporation of Jansen I) to be of limited length and size, ITM's constructions directly

contradictory to those definitions should be rejected. *Jack Guttman v. Kopykake Enterprises*, 302 F.3d 1352, 1361 (Fed. Cir. 2002) (where "the patentee has clearly defined a claim term, that definition usually is dispositive; it is the single best guide to the meaning of a disputed term"); *Finjan LLC v. ESET, LLC*, 51 F.4th 1377, 1382 (Fed. Cir. 2022) ("definitions in any incorporated patents or references are a part of the host patent.").

ITM never mentions Jansen's definitions for "C(O)Alkyl" and "aryl" *specifically when used* in the R_{3x} substituent of "A" as recited in the claims. Instead, ITM asserts that, because the specification's general definition for "alkyl" and "aryl" state that they have the number of carbons or rings "designated," yet the claims do not expressly include a numerical designation, the terms must somehow be unlimited. Petition, 43-44 (citing EX1001 at 39:43-50, 42:64-67). Not so. As discussed above, POSAs would have understood that the patentee had, in fact, designated *a specific* number of carbons (1 to 6 carbon atoms) or rings (5- or 6-membered aromatic *mono*cycle) for the "C(O)Alkyl" and "aryl" of R_{3x}. EX2002, ¶¶56, 58. ITM thus fails to account for the specification's incorporation of Jansen I's definition limiting the "alkyl" and "aryl" terms as used in the claims.

ITM's reliance on Dr. Martin's testimony that POSAs would have interpreted the alkyl and aryl claim terms as unlimited does not save its incorrect claim construction. Petition, 42-44 (citing EX1002, ¶¶108-111). For starters, Dr.

Martin applies the wrong POSA lens (§II, *supra*). Regardless, as exemplified below, Dr. Martin effectively repeats, verbatim, the Petition's discussion of the scope of the alkyl and aryl terms, failing to account for the definitions for the "C(O)Alkyl" and "aryl" of R_{3x} in the incorporated Jansen I.

Compare Petition, 43-44, *with* EX1002, ¶¶108-111 (an example shown below):

ITM's Petition	**Dr. Martin's Declaration**
"In other words, Patent Owner defined a particular nomenclature for situations where it wished to specify that an alkyl group was limited to a particular length or ranges of lengths. EX1002 at ¶108. An example of this nomenclature can be found in both claims 1 and 3, wherein Patent Owner specified that the R_{1x} and R_{2x} substituents can be chosen from a group that includes, for example, an alkyl chain containing between 1 and 6 carbon atoms, i.e., "$C_{1\text{-}6}$alkyl." EX1001, Certificate of Correction, claims 1, 3; EX1002 at ¶109." Petition, 43.	"In other words, Patent Owner defined a particular nomenclature for situations where it wished to specify that an alkyl group was limited to a particular length or ranges of lengths. Based on this definition, a POSA would understand the alkyl group of the —C(O)alkyl to be limited to the number of carbons designated in the term itself. For example, in both claims 1 and 3, R_{1x} and R_{2x} substituents can be chosen from a group that includes an alkyl chain containing between 1 and 6 carbon atoms, i.e., "C1-6alkyl." Id., Certificate of Correction, claims 1, 3." EX1002, ¶¶108-109.

See also id., 78-79 (citing EX1002, ¶¶162-163 (repeating similar statements effectively verbatim from the Petition)). Dr. Martin's testimony is thus entitled to little weight and cannot support ITM's incorrect claim construction. *Xerox*, Paper 12 at 15; *Deeper*, Paper 7 at 26-27.

C. A POSA Would Have Understood the Meaning and Scope of "Low Molecular Weight;" ITM Fails to Show That it is More Likely Than Not the Claims are Indefinite (Ground V).

Each of the challenged claims of the '201 patent requires that the compound of formula B-L-A is of "low molecular weight." EX1001, 46-47. ITM and Dr. Martin assert both in their "Claim Construction" analysis and unpatentability Ground V that the claims are indefinite because the meaning of low molecular weight allegedly "could vary based on the specific field of study and types of molecules" yet the specification does not state which specific meaning applies. EX1002, ¶¶19, 102, 105, 180, 184; Petition, 40-42, 95, § VII.E (Ground V: Indefiniteness). ITM and Dr. Martin are wrong.

1. A POSA Would Have Understood "Low Molecular Weight" Has its Plain and Ordinary Meaning.

Contrary to ITM's and Dr. Martin's assertions—who apply the wrong POSA lens (§II, *supra*)—that POSAs would not have understood the meaning of "low molecular weight," POSAs with the requisite training and experience in radiotherapeutics or imaging *would*, in fact, have understood the claim term's meaning in the context of the '201 patent. Indeed, the '201 patent itself makes

clear this ordinary meaning of "low molecular weight."

Because "the words of a claim are generally given their ordinary and customary meaning," "[t]he objective baseline from which to begin claim interpretation" under *Phillips* is "how a person of ordinary skill in the art understands [the] claim term." 415 F.3d at 1312-13, 1314. Here, as JHU's expert, Dr. VanBrocklin explains, POSAs would have understood the term "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. EX2002, ¶60.

POSAs would have specifically understood that the claims here recite the term "low molecular weight" according to this well-understood, ordinary meaning. The claims themselves do not ascribe any different definition to the term, and the specification discusses "low molecular weight" compounds consistent with their ordinary meaning. EX2002, ¶60; *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."). The specification incorporates by reference US2012/0009121 to Pomper, et al. (Pomper; EX1006), which (like the '201 patent) describes "targeting compounds" for "imaging [and] therapy." EX1001, 17:49-54; EX1006, Abstract. 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. EX1006, ¶¶12; EX2002, ¶¶61-62. Thus, the '201 patent shows "low molecular weight" is used according to its plain and ordinary meaning of compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. EX2002, ¶¶60-62.

The "prosecution history provides evidence of how the PTO and inventor understood the patent" and confirms that "low molecular weight" is used according to this ordinary meaning. *Phillips*, 415 F.3d at 1317. Specifically, during prosecution, Dr. Pomper submitted a declaration expressly stating that "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." EX1004, 1197-98; EX2002, ¶63.

2. A POSA Would Reasonably Understand the Scope of "Low Molecular Weight" And Thus The Claims are Not Indefinite

Relying heavily on its declarant, Dr. Martin, ITM asserts that the recited "low molecular weight" term is indefinite because it "has no objective boundaries to a POSA" as its meaning could "vary based on the specific field of study and types of molecules," yet the specification does not define the term, uses it "only three times," and also does not "provide numerical boundaries for the term." Petition, 40-42, 92-95; EX1002, ¶¶19, 99-105, 180-187. ITM is wrong.

At the outset, as discussed above, POSAs would have understood that "low molecular weight" has its plain and ordinary meaning of compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. EX2002, ¶¶60, 64. Further, ITM's focus on the mere amount of disclosure relating to "low molecular weight" within the specification and whether it provides precise numerical boundaries for the term is misplaced. 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. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 898–99 (2014); *Grace Instrument Indus., LLC v. Chandler Instruments Co., LLC*, 57 F.4th 1001, 1010-1011 (Fed. Cir. 2023) (rejecting indefiniteness finding even though the specification did not provide an "explicit definition" and only referred to the term "twice" because "the meaning may [still] be found in or ascertained by a reading of the patent documents"); *Niazi Licensing Corp. v. St. Jude Med. S.C., Inc.*, 30 F.4th 1339, 1347 (Fed. Cir. 2022) ("a patentee need not define his invention with mathematical precision in order to comply with the definiteness requirement"). That is precisely the case here.

As explained by JHU's expert, Dr. VanBrocklin, Dr. Martin is wrong to

assert that "low molecular weight" would not have had objective boundaries to any POSA—instead, POSAs would have reasonably understood the boundaries of the claims. EX2002, ¶¶64, 66. Specifically, because "low molecular weight" compounds (under their ordinary meaning) are those with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons (above), 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. EX2002, ¶66.

ITM's and Dr. Martin's other indefiniteness assertions are similarly wrong. *First*, ITM asserts that the prosecution history "attempts to exclude high relative molecule mass polymers from the claimed compounds" but "'the high relative molecule mass' of a polymer is not directly described as 'relative' to the allegedly 'low molecular weight compound as claimed." Petition, 97; EX1002, ¶186. But the specification does directly describe "molecules of low relative molecular mass" relative to "polymer[s] of high relative molecule mass." See EX1001, 48:18-21; EX2002, ¶64. And Dr. Martin himself concedes that polymers have molecular weights ranging from 8,000 to 400,000 Daltons (EX1002, ¶104), which is much higher than the molecular weights of typically from about 50 Daltons to about 1,500 Daltons that POSAs would have understood for the claimed low molecular

weight compounds. EX2002, ¶65.

Second, Dr. Martin states that the specification's mentions of "low molecular weight" are in relation to antibodies, which purportedly "introduces [] ambiguity." EX1002, ¶100, 182; Petition 41, 93. Not so. Dr. Martin concedes antibodies have molecular weights as high as 150,000 and 900,000 Daltons (EX1002, ¶104), and so POSAs also 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 with a much higher molecular weight. EX2002, ¶65.

Third, Dr. Martin wrongly asserts that the meaning of low molecular weight discussed during prosecution by Dr. Pomper is somehow unique to the field of metabolics and is unrelated to the field of the claimed invention. *See* EX1002, ¶¶102, 184; Petition, 40-41, 95. As discussed above, 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. EX2002, ¶¶59-62.

Finally, Dr. Martin asserts that if the claimed "low molecular weight" compounds have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons, then the patent "provides several examples of compounds" with B

moieties and linkers that otherwise would fall within the scope of the claims but have molecular weights exceeding about 1,500 Daltons. EX1002, ¶¶103, 185-186; Petition, 42, 96-97. This fails to show indefiniteness. There is an "extensive body of case law holding that a patentee may claim less" than what is disclosed. *Andrew Corp. v. Gabriel Elecs.*, Inc., 847 F.2d 819, 823 (Fed. Cir. 1988). POSAs reviewing the specification would have readily understood that any higher molecular weight B-L-A compounds described in the specification were not ultimately part of the claimed "low molecular weight" compounds. EX2002, ¶66. Indeed, the applicant specifically amended the '201 patent claims during prosecution to add the recitation of "low molecular weight" to "further define" the originally recited B-L-A compounds, confirming that the specification describes both low and higher molecular weight B-L-A compounds, but the claims were amended to recite only the low molecular weight compounds. EX1004, 1196.

ITM's flawed assertions thus cannot carry ITM's burden to establish indefiniteness here.

3. *Teva v. Sandoz* is Inapposite.

ITM also analogizes the claims to those invalidated as indefinite in *Teva v. Sandoz*. Petition, 98 (citing *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341-45 (Fed. Cir. 2015)). *Teva v. Sandoz* is inapposite. While the Court in *Teva v. Sandoz* found the term "molecular weight" indefinite, critically it did so in

the context of *polymers* that have a *range* of molecular weights, with a variety of distributions for those weights. *Id.* at 1338-39, 1341-45. *There,* the molecular weight of the polymer could vary depending on exactly how it was measured (e.g., measurements M_p, M_w, or M_n). *Id.* The Federal Circuit in *Teva* stated that "molecular weight" as used in those claims "could refer to M_p, M_w, or M_n [and] each of these measures is calculated in a different way and would typically yield a different result for a given polymer sample." *Id*. at 1341, 1344-45. But the patent in that case did not describe what specific measurement method to pick, resulting in the finding of indefiniteness. *Id*. ("the patentee has failed to inform with reasonable certainty those skilled in the art about the scope of the invention"). Here, the claimed compounds are low molecular weight, *non-polymeric* compounds (*supra*). Given the high precision of analytical techniques, such as mass spectrometry, that POSAs of any definition would have known how to use, POSAs would have had no trouble determining 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 (or not). EX2002, ¶66. *Teva v. Sandoz* fails to support indefiniteness.

IV. GROUNDS I & II: ITM FAILS TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS WOULD HAVE BEEN OBVIOUS.

A. Grounds I & II: ITM Fails To Use Lead Compound Analysis or, Alternatively, Explain Why it is Not Required.

When evaluating obviousness of new chemical compounds, the Federal Circuit has provided a generally applicable "two-prong analysis," often referred to as "lead compound analysis." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292-93 (Fed. Cir. 2012); *Mylan Pharms. Inc., v. Novo Nordisk A/S*, IPR2023-00722, Paper 9 (P.T.A.B. Oct. 2, 2023) at 13-14. The lead compound analysis requires, *first*, identifying "lead compounds or starting points" that POSAs "would have selected" as "most promising to modify" or were "a natural choice for further development efforts." *Id. Second*, like any other obviousness analysis, lead compound analysis requires providing a "reason or motivation to modify [the selected] lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292-93.

The lead compound analysis is especially applicable in cases where "the parties' arguments focus on selecting and modifying particular prior art compounds" and there were a "panoply of known compounds in the prior art" that potentially could be used as a starting point for modification. *Otsuka*, 678 F.3d at 1292; *see also Pfizer Inc. v. Teva Pharms. USA, Inc.*, 555 F. App'x 961, 970 (Fed. Cir. 2014) (applying lead compound analysis where there were "broad disclosures"

of possible starting compounds in the prior art). That is exactly the case here. ITM's obviousness arguments focus on selecting and modifying compounds from Jansen I, Jansen II, and Zimmerman (for Ground I) and Dvořáková (for Ground II) to arrive at the claimed compounds, and these references together broadly disclose *many dozens* of FAPi compounds. Petition, §§VII.A, B; EX1002, §§ VIII.A, B; EX2002, ¶¶72-73. ITM thus should have applied the lead compound analysis. *Otsuka*, 678 F.3d at 1292. It did not.

Instead, as set forth below, ITM and Dr. Martin fail to account for the fact that their own cited prior art contains many dozens of FAPi compounds with different properties,[5] and they do not articulate a reason why POSAs would have selected any of the disclosed FAPis as the "most promising to modify" for further development efforts, in view of the other disclosed compounds. Petition, 46-58,

[5] Prior to the October 2017 priority date of the '201 patent claims (and through to today), two metrics were generally used to assess performance of FAP-targeting molecules: affinity and selectivity. EX2002, ¶¶67-71. "Affinity" refers to how tightly the FAPi molecule binds to the target FAP enzyme, and "selectivity" refers to the FAPi molecule's ability to preferentially bind to and affect the targeted FAP enzyme. *Id*. Higher affinity and selectivity generally results in better performance of FAP-targeting molecules. *Id.*

60-71; EX1002, ¶112-130, 137-157; EX2002, ¶¶72-86; *Otsuka*, 678 F.3d at 1292-93; *Apotex Inc. v. Merck Sharp & Dohme Corp.*, IPR2015-00419, Paper 14 (P.T.A.B June 25, 2015) at 9-12 (rejecting petition where petitioner "does not explain sufficiently why a skilled artisan would have picked [the alleged lead compound] over hundreds of other compounds.").

For Ground I specifically, ITM relies on FAPi compounds disclosed in Jansen I, Jansen II, and Zimmerman. Petition, 48-55. However, as explained in §IV.C.1 below, ITM does not articulate whether it is Jansen I and II, or Zimmerman that provide the starting point compounds for modification. EX2002, ¶¶87-88. ITM thus does not even articulate *which reference* might provide the lead compounds or starting points most promising for further modification for Ground I, let alone articulate which *specific* compounds in those references would be lead compounds.

Further, as Dr. VanBrocklin explains, POSAs evaluating the most promising starting FAPi compounds for further development (i.e., selecting lead compounds) would have assessed their FAP affinity and selectivity data, and whether any FAPi compounds had a beneficial combination of affinity and selectivity. EX2002, ¶¶67-71, 76. ITM's Ground I art discloses many dozens of different FAPi compounds along with affinity (Zimmerman) or affinity *and* selectivity (Jansen I and II) data. *Id.*, ¶¶74-86. Yet ITM and Dr. Martin fail to even say *that* POSAs (under any

definition) would have evaluated the affinity and selectivity data amongst all the disclosed compounds, let alone articulate how POSAs would have evaluated the data to select the most promising compounds for further modification. Pet., 46-58; EX1002, ¶¶115-130; EX2002, ¶¶76-78, 83-84.

Zimmerman specifically discloses thirty-four different FAPi compounds of two different general formulas: Formula I and II. EX1009, Table 2; EX2002, ¶¶80, 81. Notably, while the Formula I compounds selected by ITM *do* have linkers attaching radiolabeled moieties, the Formula II compounds *do not* utilize linkers and so do not meet the "L" limitation of the claims (and ITM does not argue otherwise). EX1009, ¶¶8-28; EX2002, ¶¶82, 84-85. Zimmerman reports the best FAP affinities for the compounds of Formula II, *without* linkers: the two compounds that exhibited the best affinity were both of Formula II, and ten of the top eleven compounds with the best affinities were also of Formula II. EX1009, ¶185, Table 2; EX2002, ¶¶83-84. Thus, Zimmerman's data teaches toward selecting FAPi compounds of Formula II *without* linkers for further modification and development. EX2002, ¶84. But ITM and Dr. Martin do not even mention the compounds of Formula II, let alone explain why POSAs (under any POSA definition) would have selected the compounds of Formula I for further modification when the Formula II compounds exhibited better FAP affinity. Petition, 46-58; EX1002, ¶115-130; EX2002, ¶¶84-85. Nor can they, given their

use of an incorrect POSA lens.

Jansen I and II disclose various FAPi compounds—including forty-four that are in the genus of quinolone-modified FAPis that ITM relies on for Ground I—and also provide affinity and selectivity data for these compounds. EX1007, 5:35-55, Table 3; EX1010, Table 3; EX2002, ¶¶73-75. Jansen's data shows a variation of three to five orders of magnitude in both affinity and selectivity amongst the quinolone-modified FAPis, and report that some of the highest affinity compounds did not display high selectivity (and vice versa).[6] *Id.*, ¶¶74-75, 77. ITM and Dr. Martin fail to address the wide variation in the affinity and selectivity results for the dozens of disclosed compounds. Petition, 46-58; EX1002, ¶¶115-130; EX2002, ¶¶76-78. They do not explain how or why POSAs would have reconciled and

[6] For example, the worst affinity for quinolone-modified FAPis in Jansen II was an IC_{50} greater than 10 μM for compound 22, and the best affinity was an IC_{50} of 0.006 μM for compound 32 (a lower IC_{50} corresponds to higher affinity). EX1010, Table 3; EX2002, ¶74. The worst selectivity for those compounds was a FAP/PREP ratio of less than 0.1 for compound 22, and the best selectivity was a ratio of greater than 4500 for compound 26 (a higher FAP/PREP ratio corresponds to higher selectivity). *Id.* Notably, while compound 32 had the best FAP affinity, its selectivity was *twenty-three times worse* than compound 26 with the highest selectivity. *Id.*

balanced the variable affinity and selectivity properties of the different compounds to select one or more FAPis from the multitude of choices as lead compounds for further modification. *Id.* Nor can they, given their use of an incorrect POSA lens.

For Ground II specifically, neither ITM nor Dr. Martin articulate *why* POSAs would have selected Dvořáková's compounds as most promising to modify for further development in view of the other FAPi compounds in the prior art, including the many dozens of FAPis in Jansen I and II and Zimmerman. Petition, 60-71; EX1002, ¶¶137-157. Indeed, ITM and Dr. Martin never even mention the FAPi compounds described Jansen I, Jansen II, and Zimmerman in their Ground II arguments. *Id*. Thus, ITM and Dr. Martin fail to provide the required explanation of why POSAs would have picked Dvořáková's compounds over others disclosed in the prior art. And again, they cannot, because they apply the wrong POSA lens.

ITM also did not argue that the lead compound analysis should *not* be applied in this case. Nor can it. While the analysis need not apply in certain, limited fact-specific situations, none of those situations are at-issue here. *See Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876, 884-85 (Fed. Cir. 2024) (lead compound analysis not required because the prior art disclosed "a finite number of identified, predictable solutions" and "expressly suggest[ed] the proposed modification"); *NOF Corp. v. Nektar Therapeutics*, IPR2019-01394, Paper 68 (P.T.A.B. July 30, 2021) at 30-33 (declining to apply lead compound

analysis where the petitioner asserted "the overlap in the disclosed range [] with the claimed range [] renders the claimed range prima facie obvious"); *AlzheonInc. v. Risen (Suzhou) Pharma Tech Co., Ltd.*, IPR2021-00347, Paper 10 (P.T.A.B. July 14, 2021) at 26 (finding "the circumstances under which a 'lead compound' obviousness analysis should be employed" "do not apply" because the recited compounds were not actually "new chemical compounds" at all); *Shangai v Chemgene*, IPR2023-00490, Paper 35 (P.T.A.B. July 18, 2024) at 37 (declining to decide whether the lead compound analysis applied because the specific starting compound cited by petitioner "would have been an obvious starting point for modification.").

To start, ITM does not and cannot argue that there are "a finite number of identified, predictable solutions" or overlapping ranges in the art. *See Cytiva*, 122 F.4th at 884-85; *NOF Corp.*, Paper 68 at 30, 31. There are many dozens of FAPi compounds disclosed in ITM's cited art that could be selected for modification, and there are no prior art B-L-A compounds with molecular weight ranges that ITM asserts overlap with the claims. Petition, 46-58, 60-71; EX1002, ¶¶112-130, 137-157; EX2002, ¶¶73, 80.

ITM also does not assert that the recited genus of compounds is not actually new, as it concedes it must modify the FAPis of Jansen I, Jansen II, and Zimmerman (for Ground I) and Dvořáková (for Ground II) to arrive at the claimed

genus. Petition, 50, 56, 61; EX1002, ¶¶117-118, 139-140; *AlzheonInc.*, Paper 10 at 26. And ITM further does not assert that there would be a *specific* obvious starting compound given that it does not even select a specific compound from its cited art, but instead relies on dozens of compounds from Jansen I, Jansen II, Zimmerman and Dvořáková between its two Grounds (*supra*). *Shangai*, Paper 35 at 37.

Instead, as detailed above, ITM's obviousness Grounds I and II rely on selecting and modifying prior art compounds from many dozens disclosed in its cited art. Thus, ITM should have (but did not) apply the lead compound analysis or at least attempt to justify why it does not apply here. *Otsuka*, 678 F.3d at 1292 (rejecting assertion district court "erred by employing a 'lead compound' analysis" and finding lead compound analysis applied because challenger relied on modifying specific compounds, out of the "panoply" of known compounds). Grounds I and II should be denied.

B. Grounds I & II: ITM Uses Hindsight to Select Their Cited Compounds for Modification, Impermissibly Using the Claims as a Roadmap.

Under both lead compound analysis and any other obviousness analysis, it is impermissible to use the claims as a roadmap to engage in hindsight reconstruction of the claimed invention. *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991) ("[i]t is impermissible, however, simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting

elements from references to fill the gaps"); *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1275 (Fed. Cir. 2004) (prohibiting using "the invention as a roadmap" in an obviousness analysis); *Otsuka*, 678 F.3d at 1292-93 (requiring more than "mere structural similarity" to select lead compounds to avoid "the distortion caused by hindsight"). Yet that is exactly what ITM and Dr. Martin have done, rendering their obviousness analysis deficient, regardless of whether lead compound analysis applies.

For both Grounds I and II, ITM's and Dr. Martin's arguments show they impermissibly chose their cited compounds for modification simply because they were structurally similar *to the claims*. For Ground I, ITM and Dr. Martin fail to address Zimmerman's compounds of Formula II *without* linkers or their beneficial affinity data at all, and simply select the compounds of Formula *with* linkers for the sole reason that they "have a similar structure as the claims of the '201 patent." Petition, 53-55; EX1002, ¶¶118-124; EX2002, ¶¶84-86. ITM and Dr. Martin also fail to explain how POSAs would have reconciled the disparate FAP affinity and selectivity data reported amongst the various compounds disclosed in Jansen I and II to select any specific lead compounds for modification; they instead select the entire genus of "A" FAPis in Jansen I and II simply because they "fall[] within the scope of the claimed genus, A." Petition, 49; EX1002, ¶117; EX2002, ¶¶76, 78, 84.

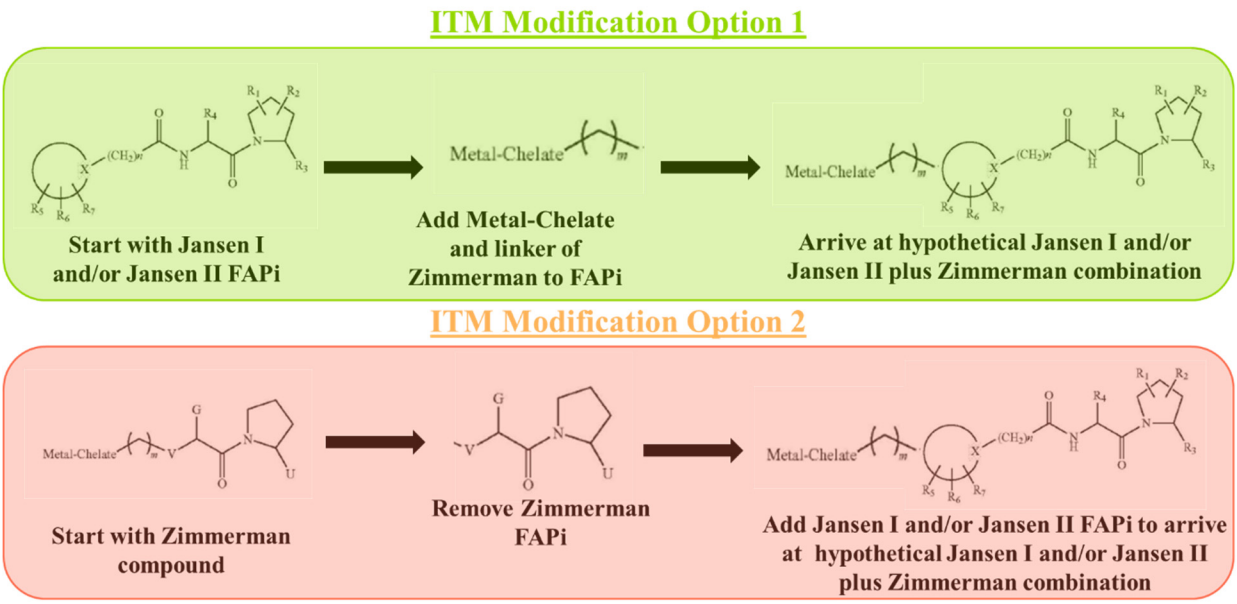
For Ground II, ITM and Dr. Martin do not explain why POSAs would have selected Dvořáková's compounds for further development in view of the many other FAPis in its Ground I art, but instead choose Dvořáková's compounds because their structure "overlaps with the compounds claimed in claim 1 of the '201 patent." Petition, 62-66; EX1002, ¶¶144-145. This is classic impermissible hindsight, and should be rejected.

C. Ground I: ITM Fails to Show That It is More Likely Than Not That The Claims Would Have Been Obvious in View of Jansen I and/or Jansen II in view of Zimmerman and Pomper.

1. ITM Fails to Articulate the Specific Grounds on Which the Ground I Challenge to the Claims is Based.

For Ground I, ITM fails to explain how Jansen I and II, Zimmerman, and Pomper must actually be combined to arrive at each element of the claims, and so fails to explain for its "specific statutory [Ground I]" "where each element of the claim is found in the prior art" as required by 37 C.F.R. § 42.204. In particular, ITM makes two general assertions. ITM first asserts that Jansen I and II disclose quinolone-modified "A" FAPis but are missing the recited "B" and "L" moieties, which it asserts can be supplied via Zimmerman and Pomper. Petition, 48-51, 55; EX1002, ¶115-118, 127-128. Yet ITM and Dr. Martin *also* assert that Zimmerman discloses the use of "B" and "L" moieties with non-"A" FAPis, which can then be "swap[ped] with the "A" FAPis described in Jansen I and/or II. Petition 50-51, 54-55; EX1002, ¶¶118, 124, 128. The following chart demonstrates these two separate

paths available to a POSA within ITM's Ground I (EX2002, ¶¶87-89):



These two paths are in tension with one another. EX2002, ¶¶88-89. Is it ITM's position that POSAs would start with the "A" FAPis of Jansen I and/or II, and then *add* the "B" and "L" moieties from Zimmerman and Pomper? Or is it ITM's position that POSAs would *instead* start with Zimmerman's FAPi compound containing "B" and "L" moieties, and then swap the "A" FAPis of Jansen I and II for Zimmerman's non-"A" FAPi? Neither ITM nor Dr. Martin explain which of these two different arguments ITM is actually relying on here for obviousness. Petition, 50-56; EX1002, ¶115-118, 124, 128; EX2002, ¶¶87-89; *Johns Manville Corp., et al. v. Knauf Insulation, Inc., et al.*, IPR2018-00827, Paper 9 (P.T.A.B. Oct. 16, 2018) at 9-13 (agreeing with Patent Owner that the petition "fails to adequately explain its theory of obviousness, and picks and chooses binder

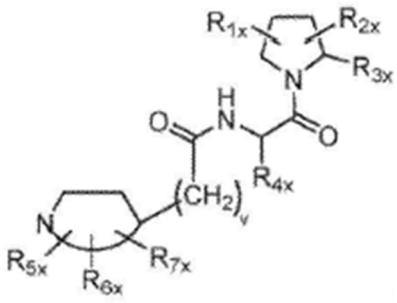
components [in the prior art] without explanation" and so denying institution).

ITM's failure 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, warrants denying Ground I under 37 C.F.R. § 42.204.

2. ITM Fails to Show There Would Have Been a Reason to Modify the FAPis of Jansen I and II to Arrive at the Claimed Invention.

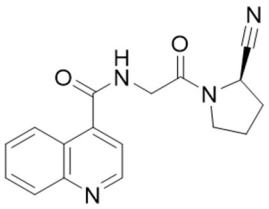
Under either lead compound analysis, or any other obviousness analysis, ITM's obviousness Ground I fails to carry its burden to show that POSAs would have been motivated to modify the any of the quinolone-modified FAPis disclosed Jansen I and II to create the claimed compounds. *Johns Manville Corp.*, Paper 9 at 13 ("it is Petitioner's burden to demonstrate 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention'"); *Otsuka*, 678 F.3d at 1292-93 (lead compound analysis requires showing that POSAs would have had "a reason or motivation to modify a lead compound to make the claimed compound.").

Specifically, the '201 patent claims recite that the "A" moiety has the following structure:

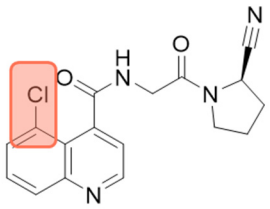


where (in relevant part), "R_{5x}, R_{6x} and R_{7x} are each H [and]

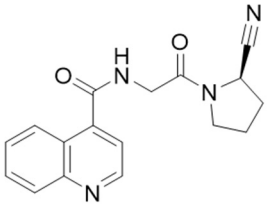
represents a quinolinyl ring[.]" EX1001, 46-47; EX2002, ¶¶90-91. The quinolone-modified portion of the *claimed* "A" moiety is thus *unsubstituted* other than by the linker "L." EX2002, ¶91. In contrast, Jansen I and II's genus of quinolone-modified FAPis includes compounds with both *unsubstituted* and *substituted* quinolinyl groups. Petition 49, EX1002, ¶115; EX1010, 4; EX2002, ¶¶90, 92. Jansen II teaches that the compounds with *substituted* quinolinyl groups had much higher selectivity compared to those with unsubstituted groups, teaching that "selectivity with respect to PREP of these inhibitors *sharply increases*" when substituted with Br or Cl in the 5-position, and showing a variety of compounds that performed with much higher selectivity when substituted compared to the naked quinolinyl groups, some examples of which are shown below. EX1010, 3; EX2002, ¶¶90, 92.



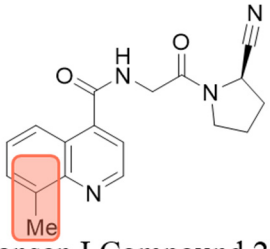
Jansen II Compound 7
FAP IC_{50} = 0.0103 µm
$SI_{[FAP/PREP]}$ = 83



Jansen II Compound 25
FAP IC_{50} = 0.010 µm
$SI_{[FAP/PREP]}$ = 1700

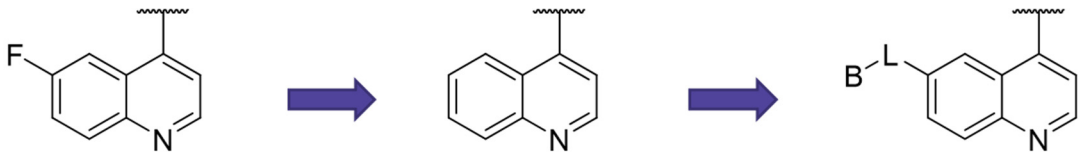


Jansen I Compound 2
FAP IC_{50} = 0.0103 µm
$SI_{[FAP/PREP]}$ = 83



Jansen I Compound 23
FAP IC_{50} = 0.0043 µm
$SI_{[FAP/PREP]}$ = 2100

Thus, if POSAs were to use Jansen I/Jansen II's compounds, they would have selected a *substituted* FAPi, given their significantly better selectivity properties. EX2002, ¶92. Then, to arrive at the claimed *unsubstituted* "A" FAPi moiety, POSAs would have had to *remove* the substituent before adding the linker and "B" radiolabeled moiety. *Id.*, ¶93.



POSA starts with substituted quinolinyl group

POSA removes substitution

POSA adds linker and "B" group

But POSAs would not have removed the substituent because Jansen II teaches that

removal would likely *destroy* the compound's beneficial selectivity. EX1010, Table 3; EX2002, ¶94. ITM and Dr. Martin fail to address these teachings of Jansen II, or show that POSAs would have been motivated removed the substituent and arrive at the claims. EX2002, ¶¶94-95. Nor can they, given their use of an incorrect POSA lens.

Because ITM's own cited prior art taught that removing the substituents on the quinolinyl ring would likely destroy the Jansen quinolone-modified FAPi compounds' beneficial selectivity, and ITM does not address these teachings, ITM cannot carry its burden to show that POSAs would have been motivated to remove those same substituents to prepare compounds "with high [] selectivity for FAP" (Petition, 46) and thus arrive at the claims. *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 69 F.4th 1341, 1349 (Fed. Cir. 2023) (affirming no motivation to remove an element from the prior art to arrive at the claimed invention where the removal "would undermine the goal [the prior art] *shares* with the challenged claims.").

3. ITM Fails to Show Reasonable Expectation of Success In Combining Jansen I and/or II, Zimmerman, and Pomper.

Under either lead compound analysis or any other obviousness analysis, ITM was required to show that there would have been a reasonable expectation of success to modify the compounds in its cited art to make the claimed compounds. *Otsuka*, 678 F.3d at 1292-93; *Eli Lilly v. Teva*, 8 F.4th 1331, 1348-49 (Fed. Cir. 2021) (it is, "at all times, [Petitioner]'s burden to show that the claims would have

been obvious, including that a skilled artisan would have had a reasonable expectation of success in achieving the claimed invention."). Thus, regardless of whether the lead compound analysis applies here (it does), ITM fails to meet its burden to show reasonable expectation of success. *Id.*

ITM provides the following analysis in its Petition for reasonable expectation of success for Ground I:

> The 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.
>
> …
>
> [A] POSA []would have been motivated to prepare the [FAPi] described in Jansen I and/or Jansen II [and] 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.

Petition, 46, 56; *see also id.*, 57 (providing *no* statement of reasonable expectation of success for claim 2, and, for claim 3, stating only that, "[a]s discussed above

with respect to claim 1," there would be a reasonable expectation of success). This analysis fails to provide the required reasonable expectation of success to support ITM's Ground I.

First, as discussed above (§IV.C.1), ITM's Petition fails to articulate *which* prior art compounds and moieties must be modified with the purported reasonable expectation of success. Thus, ITM's bare-bones discussion of reasonable expectation of success (shown above) does not explain whether POSAs would have had a reasonable expectation of success in: (a) adding Zimmerman's radiolabeled and linker moieties to the FAPis in Jansen I "and/or" II; (b) "swap[ping]" the FAPis in Jansen I "and/or" II into Zimmerman's compounds containing "B" and "L" moieties; or (c) both. Petition, 46, 56; EX2002, ¶¶96-97.

Second, ITM provides no explanation of why POSAs (under any POSA definition) would have had a reasonable expectation of even making the claimed compounds from ITM's prior art combinations without the '201 patent's guidance. EX2002, ¶97. *Third*, ITM asserts that POSAs would have had 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." Petition, 46, 56. Although the claimed compounds are defined structurally and so do not *require* a "high" level of affinity and selectivity for FAP, or any specific level of imaging or therapeutic utility (§III.A, *supra*), ITM is bound by its

obviousness theory. *Corephotonics v. Apple*, 84 F.4th 990, 1001-1002 (Fed. Cir. 2023). Thus, ITM needed to, but did not provide an explanation of why POSAs would have had a reasonable expectation that making *any* of ITM's potential prior art combinations would in fact result in compounds that work for the purposes *stated in the Petition*. *Eli Lilly*, 8 F.4th at 1348-49.

ITM's only other support for reasonable expectation of success is its citation to Dr. Martin's declaration. Petition, 46, 56, 57 (citing EX1002, ¶¶113-114, 126-130). However, like the Petition, the cited portions of Dr. Martin's declaration also fail to provide any explanation for why POSAs would have reasonably expected to make the claimed compounds without the '201 patent's guidance, or that combining the cited art would in fact result in compounds that work for the desired purposes that ITM asserts.

Dr. Martin first states that:

> The art, as exemplified by references like Jansen I, Jansen II, Zimmerman, and Pomper would have taught and motivated a POSA to design and prepare a potent and selective FAP inhibitor to serve as an imaging and therapeutic agent. The art would have further motivated a POSA to combine these known features into the compounds recited in the claims of the '201 patent. The art also would have provided a POSA with a reasonable expectation that such compounds would work for their desired purpose, particularly in view of the teachings of the prior art that the use of radiolabeled compounds presented advantages

> in diagnostic imaging and therapeutic treatment of diseases, and the teachings of the prior art that quinoline-modified FAP inhibitors have improved performance.

EX1002, ¶114, *see also id.* ¶113. Dr. Martin provides no evidentiary support for these assertions. *Id.* Dr. Martin also fails to explain *why* POSAs would have reasonably expected that combining the different FAPis, radiolabeled groups, and linkers disclosed in Jansen I, Jansen II, Zimmerman, and Pomper would result in new, modified compounds with "high affinity and selectivity for FAP" and that could "serve as [] imaging or therapeutic agent[s]" as ITM asserts. Petition, 46; EX1002, ¶¶113-114; EX2002, ¶¶96-97. Instead, Dr. Martin merely asserts the combination will work, without further explanation or support. *See id.*

Dr. Martin's remaining assertions fare no better as he provides the same non-rationale for reasonable expectation of success as he did in the paragraphs shown above. Dr. Martin states only that the prior art "touts the advantages" of using low molecular weight compounds, the specific "quinoline-modified" FAPis in Jansen I and/or II, and "radiolabeled compounds in diagnostic imaging, and therapeutic treatment of diseases." *See* EX1002, ¶¶126-130. Again, Dr. Martin fails to provide evidentiary support for his assertions or explain why POSAs would have reasonably expected that *combining* these purportedly advantageous FAPis, radiolabeled compounds, and linkers together would *actually* work to yield the claimed compounds. EX1002, ¶¶127-130; EX2002, ¶97.

Dr. Martin's conclusory, unsupported assertions are thus entitled to little or no weight. *See Zimmer v. Four Mile Bay*, IPR2016-00011, Paper 8 at 11 (P.T.A.B. Apr. 1, 2016) (Board has discretion to accord little weight to broad conclusory statements from expert witness); *Xerox*, Paper 9, at 15. They likewise fail to provide any actual support for ITM's own conclusory, unsupported opinions on reasonable expectation of success in the Petition. *See Deeper*, Paper 7 at 26-27.

Because ITM failed to provide the requisite reason to combine Jansen I and/or II, Zimmerman, and Pomper to arrive at the claimed invention with a reasonable expectation of success, ITM failed to meet its burden of showing that it is more likely than not that the claims would have been obvious. *Eli Lilly*, 8 F.4th at 1348-49.

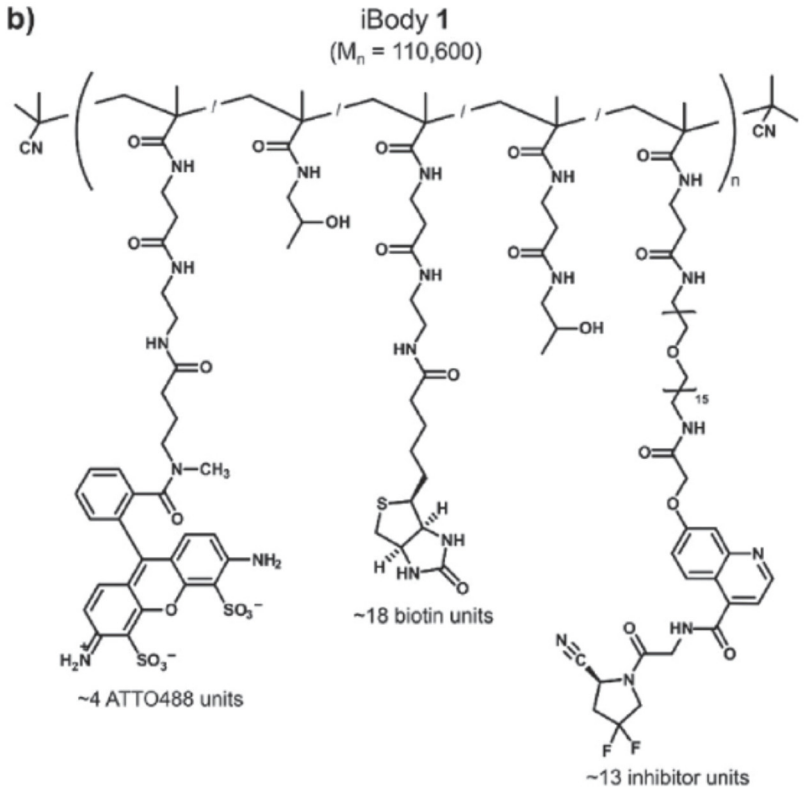
D. Ground II: ITM Fails to Show That It is More Likely Than Not That The Claims Would Have Been Obvious in View of Dvořáková and Pomper.

1. ITM Fails to Show POSAs Would Have Been Motivated to Modify Dvořáková with Pomper to Create a Low Molecular Weight Compound.

As with Ground I, under either lead compound analysis, or any other obviousness analysis, ITM fails to meet its burden to show that POSAs would have been motivated to modify Dvořáková with Pomper to create the claimed low molecular weight compounds. *Johns Manville Corp.*, Paper 9 at 13; *Otsuka*, 678 F.3d at 1292-93. The teachings of Dvořáková itself contradict ITM's assertion that

POSAs would have been "motivated to modify Dvořáková's disclosed compounds"—the high molecular weight iBody compounds, and specifically the iBody 1 compound—"to have a lower molecular weight." Petition, 61; EX1002, ¶140.

Dvořáková's iBody 1 contains FAPis of compound 1, ATO488 fluorophores (dyes), and the affinity anchor biotin that are "conjugated to the HPMA copolymer carrier[7]" in the following structure:



EX1008, 3-4, 7, FIG. 2 (b); EX2002, ¶¶98-99. Notably, iBody contains

[7] HPMA is an "N-(2-hydroxypropyl)methacrylamide," polymer. EX1008, 2.

approximately *four* ATT00488 (or dye) units, *thirteen* inhibitor (or FAPi) units, and *eighteen* biotin units,[8] along with an HPMA copolymer backbone. *Id.* Dvořáková reports that compound has a total molecular weight of *110,600* Daltons, which POSAs would have understood was due to the multiple dye units, affinity units, and FAPis, plus the HPMA copolymer backbone. EX1008, FIG. 2 (b); EX2002, ¶¶99-100. iBody's molecular weight is thus *two orders of magnitude* higher than low molecular weight FAPi compounds, including those disclosed in Zimmerman, Jansen I and II, and Pomper, and the compounds recited in the claims. EX2002, ¶100.

Dvořáková specifically touts the benefits of its high molecular weight compound, and POSAs 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. EX2002, ¶¶102, 103. Dvořáková states that iBody is: "suitable for the specific targeting and visualization of FAP as well as the inhibition of its enzymatic activity," "highly selective for FAP," and "suitable for a

[8] These numbers are approximations because polymeric compounds like iBody, unlike the claimed low molecular weight compounds, are heterogeneous, with variable structures, and the unit values are thus average numbers. EX2002, ¶100.

broad spectrum of biochemical and biomedical applications." EX1008, Abstract, 2-4, 7; EX2002, ¶99. Notably, Dvořáková provides data showing its polymeric compound with multiple FAPis and affinity anchors had better FAP targeting than a compound with a single FAPi unit[9]—POSAs would have understood that the multiple affinity anchors and FAPis resulted in this better FAP targeting. EX2002, ¶¶103-105. Dvořáková also praises iBody's high molecular weight HPMA copolymer backbone because it has "enhanced permeability and retention (EPR) effect" and "can be easily adjusted to specifically tailor the pharmacokinetic properties" of the compound. EX1008, 2; EX2002, ¶105. POSAs reviewing Dvořáková would thus have understood that it is precisely the use of *multiple* such moieties, and a higher molecular weight HPMA copolymer backbone in iBody—resulting in the compound's high molecular weight—that also results in its overall beneficial properties. EX2002, ¶¶98-100, 103-105.

Notably, other art—consistent with Dvořáková—reports that high molecular weight compounds with multiple functional moieties like iBody exhibited better

[9] Dvořáková reports that iBody had a 5-fold increase in affinity compared to compound 1 with a single FAPi unit; Dvořáková also provides data showing that iBody also had better selectivity than compound 1 (765 for compound 1, greater than 4500 for iBody). EX1008, 4; EX2002, ¶100.

targeting results than lower molecular weight compounds. For example, Carlucci reported that high molecular weight peptide-based ligands "may improve binding characteristics," and Tweedle reported that "biological activity was evident" in high molecular weight, polymeric compounds, "where none or very little existed" in low molecular weight, monomeric compounds. EX2010, 1; EX2009, 1; EX2002, ¶101. Likewise, Tassa stated that multivalent conjugation of low molecular weight targeting compounds into a higher molecular weight nanoparticle resulted in "enhance[d] binding to the desired target." EX2008, 1; EX2002, ¶101. Dr. Martin is silent on this art. Dr. Martin is also silent on the results in Meletta that showed that the preferred, *low molecular weight* FAPi compound disclosed in Zimmerman (MIP-1232) failed in the clinic due to poor FAP selectivity. EX2006, 1, 9-10; EX2002, ¶102; *Novo Nordisk A/S v. Caraco Pharma. Lab'ys, Ltd.*, 719 F.3d 1346, 1365 (Fed. Cir. 2013) ("it is necessary to consider prior art that supports unobviousness of the claimed invention, as well as that which weighs against it.").

ITM's sole basis for asserting that POSAs still would have been motivated to modify the iBody compound into a low molecular weight version of that compound is that Pomper teaches that low molecular weight compounds have improved pharmacokinetic properties and have shown promise in preclinical studies. Petition, 61-62, 70; EX1002, ¶¶140-141, 157. But Dvořáková already

taught that iBody had beneficial pharmacokinetic properties by virtue of its HPMA copolymer backbone which could be "easily adjusted to specifically tailor the pharmacokinetic properties" of the compound, and that allowed for "enhanced permeability and retention" of iBody over single FAPi moiety compounds. EX1008, 2, 4; EX2002, ¶105. Dvořáková likewise already taught that iBody was "a useful tool" and "suitable for a broad spectrum of biochemical and biomedical applications." EX1008, Abstract, 4; EX2002, ¶99.

Since Dvořáková's iBody already solved the only purported issues that ITM asserts would have motivated POSAs to modify iBody, ITM cannot carry its burden to show there was any motivation to modify Dvořáková, let alone combine it with the teachings of Pomper to create the claimed low molecular weight compounds. *See Apotex Inc. v. Wyeth LLC*, 657 F. App'x 998, 1003 (Fed. Cir. 2016) (affirming lack of motivation where the prior art compounds already had favorable properties and there was nothing in the record to show that the proposed modifications would solve any other problem).

2. ITM Fails to Establish a Reasonable Expectation of Success in Creating a Low Molecular Weight Compound From the Teachings of Dvořáková and Pomper.

As with Ground I, under either lead compound analysis, or any other obviousness analysis, ITM fails to meet its burden to show there would have been any reasonable expectation of success to arrive at the claimed low molecular

compounds from modifying Dvořáková in the way ITM asserts. *Eli Lilly*, 8 F.4th at 1348-49 (Fed. Cir. 2021).

ITM and Dr. Martin provide only the following, effectively *identical* assertions for reasonable expectation of success for Ground II: "a POSA would have recognized that a low molecular weight version of iBody 1 could be synthesized by using fewer inhibitor and ATTO488 units and using a linker with a lower molecular weight … [b]ased on Pomper's teachings about the benefits of a low molecular weight compound, a POSA would have reasonably expected a low molecular weight version of iBody 1 to work for the desired purpose," having "high affinity and selectivity for FAP [and] serv[ing] as an imaging or therapeutic agent." *Compare* Petition, 61-62 with EX1002, ¶¶140-141; *see also* Petition, 70; EX1002, ¶¶155, 157. This fails to provide the required reasonable expectation of success to support ITM's Ground II.

First, ITM provides *no* explanation for why POSAs (under any POSA definition) 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. Petition, 61-62. And in view of ITM's assertions that POSAs would have been motivated to create compounds with a "high" level of affinity and selectivity for FAP, and that would be useful for imaging/radiotherapy

(Petition, 62), ITM fails to provide any explanation for why POSAs would have reasonably expected that a low molecular weight version of iBody resulting from its proposed modifications would actually exhibit those properties. Petition, 61-62.

Second, because Dr. Martin testimony simply repeats, essentially verbatim, the conclusory and unsupported statements in ITM's petition (as discussed above), it is thus entitled to little weight and cannot provide the requisite support for reasonable expectation of success either. *See Xerox*, Paper 9 at 15; *Deeper*, Paper 7 at 26-27.

Third, ITM and Dr. Martin ignore the compelling evidence that there would have been *no* reasonable expectation that "using fewer inhibitor and ATTO488 units and using a linker with a lower molecular weight" in Dvořáková's iBody compound would yield a compound that still had "high" FAP affinity/selectivity and would serve as an imaging and therapy agent, as ITM asserts. Petition, 61-62; EX1002, ¶¶140-141. As discussed above (§ IV.D.1), 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. EX2002, ¶¶100-105. 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 ITM asserts. EX2002, ¶¶104, 105.

In fact, POSAs would have expected that such modifications would far more likely *destroy* iBody's beneficial properties. EX2002, ¶¶100, 102, 104, 105, 107. POSAs would have expected that reducing the number of moieties would likely result in significantly less FAP affinity and selectivity, and be detrimental to its function as an imaging agent. EX2002, ¶¶100, 102, 104, 107. POSAs would also have expected that replacing the HPMA copolymer backbone with a low molecular weight linker (as ITM asserts) would, if anything, significantly reduce the compound's beneficial pharmacokinetic properties as Dvořáková expressly touts the HPMA copolymer's pharmacokinetic benefits. EX2002, ¶¶105, 107.

Thus, ITM fails to provide the requisite reason to combine Dvořáková and Pomper to arrive at the claimed invention with a reasonable expectation of success and so fails to meet its burden of showing that it is more likely than not that the claims would have been obvious. *Eli Lilly*, 8 F.4th at 1348-49.

E. ITM Inappropriately Dismisses Relevant Secondary Considerations Evidence.

During prosecution of the '201 patent, named inventor Dr. Martin Pomper submitted a declaration providing 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 ITM 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.

Neither ITM nor Dr. Martin actually contest that the significantly improved FAP specificity of the claimed compounds was unexpected and superior. Petition, 1-2, 21-22, 46-48, 58-59, 100; EX1002, ¶¶16, 89, 90-92, 131-136. Instead, ITM and Dr. Martin assert only that the unexpected results are not commensurate in scope with the claims, and therefore cannot support non-obviousness. *Id.* However, ITM's and Dr. Martin's assertions are conclusory and fail to "address the [unexpected] results head-on," thus "fall[ing] short of [ITM's] burden to establish a likelihood of success in prevailing on its [obviousness] challenge." *Gilead Sci., Inc. v. U.S.*, IPR2019-01456, Paper 17 (P.T.A.B. Feb. 5, 2020) at 53 (denying institution where "evidence of unexpected results [was] part of the public prosecution of the patent" and played a "pivotal role [] in securing allowance of the claims," yet petitioner simply made "vague assertions about the results being attributable to the prior art and a lack of nexus.").

Specifically, ITM and Dr. Martin state that there are "thousands, if not millions or more" possible compounds falling under the scope of the claims, and therefore examples tested by Dr. Pomper are "insufficient" to represent that full scope. Petition, 2, 47, 58-59; EX1002, ¶¶133-134. But neither ITM nor Dr. Martin provide any calculation, evidence, or other support for this assertion of "thousands, if not millions or more" possible compounds falling under the full scope of the claims. *Id*. ITM and Dr. Martin also fail to identify even a single compound, or A, L, or B moiety that would not behave similarly to those in Dr. Pomper's declaration. *Id.*; *see also* EX2002, ¶110; *see In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (tests showing unexpected results of not every compound covered by the claim scope were representative where "there was no factual basis to expect the [untested claimed] compounds to behave differently in different environments.").

Because ITM incorrectly dismissed the evidence of unexpected results showing non-obviousness of the claims, ITM has not shown that the claims are more likely than not unpatentable, and both of the Petition's obviousness Grounds I and II should be rejected. *Gilead Sci*, Paper 17 at 53; *see also Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) ("[o]bjective indicia of nonobviousness must be considered in every case where present" and it is "error to reach a conclusion of obviousness" until these indicia are considered).

V. GROUND IV: ITM FAILS TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS LACK WRITTEN DESCRIPTION.

A. ITM's Written Description Analysis Hinges on an Incorrect Functional Definition and Inapplicable Case Law.

ITM's written description arguments are predicated on the claimed genus purportedly being "defined by functional language." Petition, 87, 89. But, the "scope of what is claimed (and must be adequately described) is, in turn, determined through claim construction." *In re Entresto*, 125 F.4th 1090, 1098 (Fed. Cir. 2025); *Phillips*, 415 F.3d at 1312.

Indeed, in *Entresto*, the Federal Circuit expressly held that a patent needs only to describe and enable what the claim *requires* as ascertained via claim construction, and *not* what the claim simply *covers*. *Entresto*, 1097−1100. There, the challenged claims recited administering two pharmaceutical agents "in combination." *Id.*, 1097. The district court construed "in combination" to have its plain and ordinary meaning over the defendant's proposed construction that the two agents must be to separate components, as opposed to a "complex." *Id.*, 1095, 1098. The Federal Circuit affirmed the district court's construction, stating it would have been error to construe the patent as claiming complexes because the "complex" form of the claimed composition was not what was claimed. *Id.* at 1098. The court, therefore, held that the patent did not need to describe a complex. *Id.*

Here, ITM's written description wrongly focuses entirely on whether the '201 patent describes claim scope that is *not* actually required by the claims: ITM wrongly alleges that the claims recite a functionally-defined genus. But as explained in §III.A., the claimed compounds are defined *structurally*, i.e., having formula B-L-A. It is only the specific "B" and "L" moieties that must be selected for use in the recited compounds based on their individual functional characteristics—i.e., suitability for imaging/radiotherapy and bi-functionalization, respectively. *Id.* As ITM *concedes*, the specification is replete with examples of such B and L moieties (both expressly listed in the specification and incorporated by reference into the specification), along with two working examples of compounds with the claimed structure. EX1001, cols. 16-30; EX1001, cols. 16-30; EX2002, ¶¶112-116; Petition, 5-6 (conceding the specification contains *eighteen* columns describing "examples of moiety B" as well as incorporating extensive information regarding L moieties), 75 (admitting the specification incorporates a "diverse list of examples" for B and L).

By incorrectly framing the claims as reciting a functionally-defined genus, ITM relies on inapposite case law. When the claims are properly viewed as reciting low molecular weight compounds that are structurally-defined, the appropriate case law applied to the facts here instead supports a finding of written description.

1. ITM's reliance on cases involving functionally-defined genera is misplaced.

Each of the cases that ITM cites for its written description arguments involve claims reciting functionally-defined genera. Petition, 86-89 (citing *Ariad*, *AbbVie*, *Regents of the Univ. of California*, *Idenix*, *Novozymes*, *Boston Scientific*, *Enzo Biochem*). The specifications in those cases also lacked sufficient representative examples of structures that could achieve the expressly claimed functionality in view of the scope of the claimed genera. *Id.* They are thus inapposite.

Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010) involved claims that expressly "recite[d] methods encompassing a genus of materials achieving a stated useful result, i.e., reducing NF-κB binding to NF-κB recognition sites in response to external influences" yet "the specification [did] not disclose a variety of species that accomplish the result," and so the claims lacked written description. *Id.* at 1350; *see also Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1163-64 (Fed. Cir. 2019) (no written description for claims defining the genus of compounds as "effective in treating HCV," yet the specification did not provide "any indication as to *which* of th[e] undisclosed [compounds] would be effective.").

Likewise, *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014) involved claims reciting "a genus using functional

language to define a desired result," namely, antibodies that "bind[] to human IL–12 and dissociate[] from human IL–12." *Id.* at 1292, 1299. Yet, the specification described only "one type" of antibody that fell under the scope of the claims. *Id.*

In *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997) the claims were defined by the function of "requir[ing] human insulin-encoding cDNA," but the specification only provided a disclosure of *rat* insulin-encoding cDNA. *Id.* at 1567-68. *See also Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1363-1364 (Fed. Cir. 2011) (claims recited "macrocyclic triene analogs" of rapamycin in drug-eluting stents to prevent restenosis, yet the specification contained "no examples" and "virtually no information" regarding compounds meeting the claimed function); *Enzo Biochem., Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 961, 963, 967-968 (Fed. Cir. 2002) (holding recited nucleotide compositions were "defined only by a statement of function or result," specifically "specific for *Neisseria gonorrhoeae*" but remanding to consider whether such compositions were adequately defined).

In contrast here, the claims do not define the *structural* low molecular weight B-L-A compounds by their ability to achieve any particular function or level of functionality. *See* §III.A.

ITM's attempt to also analogize this case to *Novozymes* is also clearly misplaced. Petition, 88-89 (citing *Novozymes A/S v. DuPont Nutrition Biosciences*

APS, 723 F.3d 1336 (Fed. Cir. 2013)). In sharp contrast to this case, the claims in *Novozymes* not only defined the recited genus of enzymes functionally ("increased thermostability"), but the specification also "contain[ed] *no* disclosure of *any* variant that actually satisfies the claims." *Id.* at 1341, 1348 ("one searches the [specification] in vain for the disclosure of even a single species that falls within the claims"). In *Novozymes*, moreover, the *only* enzyme disclosed in the specification and otherwise falling within the scope of the claims was not actually thermostable, and was thus not representative of the claimed genus. *Id.* at 1349. Here, in contrast, the '201 specification discloses actual examples of the claimed compounds and numerous examples of A, B, and L moieties that a POSA would have considered when making the claimed compounds. EX1001, cols. 8-30; EX2002, ¶¶113-118.

In sum, all the cases ITM cites for its written description arguments involve functionally-defined genera and specifications containing effectively *no* examples of suitable structures for achieving those functions, with the holdings all turning on those specific facts. That is not the case here. Because no law supports ITM's written description arguments, Ground IV fails for this reason alone.

2. The claimed low molecular weight compounds are properly described in view of apposite case law.

In contrast to the above, the Federal Circuit has repeatedly recognized that where, as here, the claims recite a novel combination of otherwise known

elements, the patent specification need not re-describe these known elements and "add unnecessary bulk to the specification." *Falko-Gunter*, 448 F.3d at 1368. That is the case here with the claimed low molecular weight compounds. As such, cases such as *Daiichi v. Seagen*, *Falko-Gunter*, and *Capon v. Eschar* are appropriately applicable here.

Daiichi Sankyo, Inc. v. Seagen Inc., PGR2021-00030, Paper 57 (P.T.A.B. Jan. 16, 2024), is instructive. There, the claims recited an antibody-drug conjugate comprising a "drug moiety" conjugated to an antibody via a novel linker. *Id.* at 8-9. The Petitioner challenged the written description support for the claimed "drug moiety." *Id.* at 31-32. The Petitioner alleged that the patent specification only provided limited examples with a single type of drug moiety and did not provide a representative number of species because "'drug moiety … is broad enough to encompass all drug moieties.'" *Id.* at 31. The Board disagreed with the Petitioner and found adequate written description.

In so finding, the Board stated that "the prior art is aware of a number of chemotherapeutic drug compounds and the use of antibody-drug conjugates." *Id.* at 37. The Board also found that the challenged patent recited "dozens, if not hundreds of different chemotherapeutic agents" and "an extensive list of known chemotherapeutic agents whose structures were all known in the prior art." *Id.*at 38. Analogizing the facts to *Falko-Gunter*, the Board held that because "the claims

[] are not focused on the particular cancer drug selected from the large number of known cancer drugs or the antibody used, but rather focus entirely on the linker joining a drug moiety and an antibody or other ligand moiety" the specification's alleged failure to describe 'other known cancer drugs' did not render the disclosure inadequate for written description." *Id.* at 39 (citing *Falko-Gunter*, 448 F.3d at 1367).

Similarly, in *Falko-Gunter*, the claims at issue in the count of an interference proceeding involved novel poxvirus vaccines made from known DNA elements. *Id.* at 1360−61. The junior party argued that the senior party's patent specification did not describe "'essential regions'" of any poxviruses sufficient to provide written description. *Id.* at 1367. The Federal Circuit rejected that argument because the claimed DNA elements were known and "recit[ing] known DNA structures … would serve no goal of the written description requirement." *Id.* Thus, where POSAs would understand from the specification what DNA elements to use and would know their structure from knowledge in the art, the full scope of elements that could be used need not be disclosed to find adequate written description. *Id.* at 1367−68.

Likewise, in *Capon*, the challenged claims recited known DNA segments linked by known methods to create "a novel combination of the DNA segments to achieve a novel result." *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005).

The Federal Circuit held that the specification need not recite those known elements to provide adequate written description. *Id.*

Here, as with *Daiichi*, *Falko-Gunter*, and *Capon*, the specification makes clear that the invention is a novel combination of known A FAPi moieties, B radiolabeled groups, and L linkers, and then provides *dozens* of columns of exemplary A, B, and L moieties that a POSA would have considered when making the claimed compounds. EX1001, cols. 8-30; EX2002, ¶¶113-118. The specification also incorporates by reference a multitude of other references that provide even further examples of such moieties. EX1001, 17:45-54; EX2002, ¶116. Indeed, ITM admits the specification contains these extensive disclosures and incorporated examples. Petition, 5-12. Dr. Martin, moreover, admits that the claims are directed to a combination of known B, L, and A moieties. EX1002, ¶112. POSAs who had extensive practical experience in developing and evaluating imaging or radiotherapeutic agents would thus have readily ascertained from the specification's disclosures known A, B, and L moieties for use in the recited novel compounds combining these moieties—and would thus likewise have readily understood that the inventors of the '201 patent possessed the recited subject matter. EX2002, ¶¶117-118.

Thus, there is no need for the '201 patent specification to provide any disclosure beyond that which it already provides. *Daiichi*, Paper 57 at 31−39;

Falko-Gunter, 448 F.3d at 1367−68; *Capon*, 418 F.3d at 1358. For the individual B and L moieties of the recited compounds—those that are suitable for imaging/radiotherapy and have bi-functionalization, respectively—the specification indisputably *does* "disclose a variety of species" of such B and L moieties, as discussed above. EX1001, cols. 16-30; EX2002, ¶¶114-116. And the specification also provides the two examples that ITM incorrectly decries as not being sufficient. EX1001, 51:5-61:62; EX2002, ¶113. The specification here is thus in sharp contrast to the specifications at-issue in ITM's cited cases. *Cf. Ariad*, 598 F.3d at 1350 (relying on the specification's *failure* to disclose "a variety of species that accomplish the result" for lack of written description). ITM burdens the inventors with describing known prior art concepts by failing to consider the disclosures of the specification and existing knowledge in the field of suitable A, B, and L moieties. This is improper because POSAs would have been able to readily discern what the inventors possessed (*see* §II)).

B. ITM Fails to Show There is a Lack of Representative Species Disclosed in the Specification.

ITM also asserts that the claims lack written description because they recite "a structurally and functionally huge, if not unlimited, genus of compounds" that "perform the claimed functions," yet the specification contains "only two working examples" of such compounds. Petition, 89-90. But, *first*, ITM's misconstruing of the claims infects its belief that the claims recite a "functionally huge" and

"unlimited" genus of compounds. *Second*, ITM is wrong that the examples of the '201 patent are not sufficiently representative of the claimed genus.

1. ITM Misconstruing the Claims Infects ITM's Allegations that the '201 Patent Fails to Describe a Representative Number of Species.

ITM fails to support its assertion that the claims recite "a structurally and functionally huge, if not unlimited genus of compounds." Petition, 90. ITM generally points to §§II and VII.C. of its Petition and Dr. Martin's declaration in making this assertion. But neither of those portions, nor any other portion, of the Petition or Dr. Martin's declaration ever actually provide the basis for ITM's assertion of "huge, if not unlimited" claim scope—e.g., they provide no explanation, no calculations, no examples, no citations to literature, or the like. *Id.* Yet, it is ITM that ultimately bears the burden of proving unpatentability by a preponderance of the evidence. *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1375 (Fed. Cir. 2016). ITM provides no evidence here, and Dr. Martin only provides conclusory assertions without underlying factual support, warranting denial. *Xerox*, Paper 12 at 5.

ITM's claim construction that relies on the recited alkyl and aryl terms being purportedly "limitless"—as ITM's written description arguments here seem to imply, but never affirmatively state—does not rescue ITM's lack of evidence. Those constructions are unsupported and wrong. *See* §III.B. ITM's written

description arguments premised on the same reasoning should thus be rejected. *Intellectual Ventures I LLC v. Motorola Mobility LLC*, 870 F.3d 1320, 1325–26 (Fed. Cir. 2017) (rejecting written description challenge predicated on an incorrect claim construction).

ITM also asserts that the recited compounds are required to "perform the claimed functions." Petition, 90. They do not, as explained in §III.A. ITM and Dr. Martin are inappropriately conflating what the claim *requires* (as ascertained via claim construction) and thus must be adequately described, with what it simply *covers*. *Entresto*, 125 F.4th at 1097-1098.

Thus, ITM's assertions based on the idea that the specification must provide adequate written description support for performing some unspecified "claimed functions" (Petition, 90) and achieve some unspecified functionality, are wrong and not what the claims require.

2. The Specification Is Not Limited to Only "Two Working Examples" and Contains Other Disclosures POSAs Would Readily Discern Adequately Describe the Claimed Compounds.

ITM's assertion that the specification's support for the claimed genus comes from "only two working examples" somehow means there is inadequate written description is likewise wrong. Petition, 89, 90.

To start, there is no requirement (as ITM implies) that the specification contain *any* working examples to satisfy written description, let alone some

minimum number beyond two. *See Falko-Gunter*, 448 F.3d at 1366-67 ("examples are not necessary to support the adequacy of a written description"). Indeed, specifications disclosing only limited working examples have been held to provide adequate written description for a recited genus when viewed in light of the claims at issue, the specifications' disclosures as a whole, and knowledge in the art. *See, e.g., Sandoz Inc. v. Boehringer Ingelheim Int'l*, PGR2022-00037, Paper 11, 23−24 (P.T.A.B. Nov. 7. 2022) (adequate written description with only two working examples when "the ordinary artisan was provided with guidance in making [the claimed formulations] from the teachings of the specification and ha[d] additional knowledge from the art" and the claims recited "specific structures") ("*Sandoz*"); *Alcon*, 745 F.3d 1180, 1190−1192 (Fed. Cir. 2014) (adequate written description with three working examples each using the same type of polyethoxylated castor oil ("PECO") in combination with prostaglandins, yet the claims encompassed a genus of formulations comprising combinations of numerous PECOs and prostaglandins).

ITM and Dr. Martin also fail to mention or dispute that POSAs with knowledge of the prior art and reviewing the extensive disclosures as to the B and L moieties in the specification would "readily discern that other members of the [B and L moieties] would perform similarly to the disclosed members" in the specification. *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004);

EX2002, ¶¶117-118. Indeed, ITM and Dr. Martin provide zero explanation or evidence to support their assertion that POSAs would somehow need additional guidance to know what A, B, and L moieties would be suitable for use in the recited low molecular weight compound of formula B-L-A. Petition, 90; EX1002, ¶178; EX2002, ¶¶117-118. ITM and Dr. Martin, moreover, do not provide even a single example of any A, B, or L moieties, or low molecular weight compounds of formula B-L-A that POSAs purportedly would *not* believe were possessed by the inventors or would otherwise be inoperable. *Id*. ITM and Dr. Martin thus fail to show that "the difference between members of the group is such that the person skilled in the art would not readily discern that other members of the genus would perform similarly to the disclosed members." *Bilstad*, 386 F.3d at 1125.

ITM's unsupported and conclusory assertions of lack of written description should be rejected. *See, e.g.*, *Sandoz*, Paper 11 at 23 (rejecting argument of lack of written description for claimed genus of formulations where petitioner failed to introduce evidence even a single formulation falling under the claim scope that would not work).

C. ITM's Written Description Analysis Fails under Binding Precedent.

The '201 patent issued from Appl. No. 18/354,282 ("the '282 application") filed on July 18, 2023. The '282 application is a continuation of Appl. No. 16/758,182 ("the '182 application"), which is the United States National Stage

entry of PCT/US2018/057086, filed on October 23, 2018, which claims priority benefit to a provisional application filed on October 23, 2017. EX1001, Face page at (63), (60).

Indisputably, ITM and Dr. Martin assess the written description of the claims based on the disclosures of the '201 patent specification. Petition, 90 (citing EX1001 at Examples 1.1-1.2); EX1002, ¶¶177-179. But ITM and Dr. Martin never actually state what date they used to assess written description; it appears that—if they used *any specific* date for the analysis—ITM and Dr. Martin used October 23, 2017.[10] *See, e.g.*, Petition, 27-40; EX1002, ¶¶32-68, 95 (citing and discussing *only* pre-October 23, 2017 art and POSA understanding).

Whether a given application satisfies 35 U.S.C. § 112, including written description, "is determined *as of the filing date of each application*." *Chiron v. Genentech*, 363 F.3d 1247, 1254 (Fed. Cir. 2004); *Merck v. Wyeth*, PGR2017-

[10] Here, the October 23, 2017 written description disclosure is only relevant to determining priority to the provisional application, as any failure of that 2017 application to meet the requirements of Section 112 would not render the claims unpatentable. ITM has not assessed the disclosure in JHU's October 23, 2017 priority application, and JHU maintains that the October 23, 2017 provisional application meets the written description requirement.

00016, Paper 9 at 14 (P.T.A.B. Oct. 20, 2017) ("Petitioner's failure to address *each relevant date* bolsters our holding that Petitioner fails to [make the necessary showing under §112]"); *Reiffin*, 214 F.3d at 1345 ("the sufficiency [of a disclosure] under § 112, first paragraph must be judged *as of its filing date*."); *Sandoz Inc. v. Biogen MA Inc.*, PGR2022-00054, Paper 16, 25-28 (P.T.A.B. Feb. 2, 2023) ("Petitioner did not specifically address the sufficiency or insufficiency of the written description *at each relevant priority date* in view of the changing state of the art."); *see also* M.P.E.P. §2164.05(a) ("…the state of the prior art must be evaluated for *each application based on its filing date.*").

As is discussed above, the law is clear that an application must be assessed for compliance with §112 as of that application's own filing date. ITM never assessed *any* application in the '201 patent family as of *that application's own filing date*. Here, ITM assessed only the '201 patent's specification, but did not do so as of its filing date—July 18, 2023. No case law allows ITM to mix and match applications and filing dates to assess §112 compliance, as ITM has done here. ITM's written description assessment is therefore deficient and does not meet ITM's burden to show it is more likely than not that the challenged claims lack written description support.

VI. GROUND III: ITM FAILS TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS LACK ENABLEMENT.

A. ITM's Enablement Analysis—and Heavy Reliance on *Amgen*—Hinges on ITM's Incorrect Functional Definition for the Claims.

ITM first argues that there is a lack of enablement under the Supreme Court's framework in *Amgen*. Petition, 73-75 (citing *Amgen*, 598 U.S. 594 (2023)). ITM's attempt to analogize to *Amgen* is predicated on the claims purportedly being defined by their ability to "perform the claimed functions." Petition, 76. Yet, "a specification must only enable the *claimed* invention," as determined via claim construction. *Entresto*, 125 F.4th at 1099 (citing *Amgen*, 598 U.S. at 610). Here, the claimed compounds are defined and construed *structurally*—i.e., they have a common quality of being a low molecular compound having formula B-L-A. *See* §III.A; EX2002, ¶¶44-53, 119. The specification need only, and did, enable the *claimed* structural compounds and suitable moieties; it need not enable some further undefined "claimed functions."

Amgen is thus inapposite. In *Amgen*, the claims 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." *Amgen*, 598 U.S. at 599. The Supreme Court thus recognized that "Amgen seeks to monopolize an entire class of things defined by their *function*" and Amgen itself "freely admit[ted] that it seeks to claim for itself an

entire universe of antibodies" defined by that function. *Id.* at 613. That is not the case here, as the '201 patent claims do not seek to claim an entire universe of compounds defined solely by their ability to perform a certain function; instead, they are limited to a genus of compounds defined by their structure. *See* §III.A; EX2002, ¶¶44-53, 119-120.

Amgen itself confirms that ITM's attempts to apply the framework of that case to the claims of the '201 patent are misguided. *Amgen* expressly held that the level of disclosure provided in the specification in that case "might suffice to enable other claims in other patents" where the claims were not entirely functionally defined, as is the case here. *Id.* at 614.

ITM thus has not and cannot show that "*Amgen* [] dictates cancelation of claims 1-3 of the '201 patent." Petition, 76.

B. ITM Fails to Show Undue Experimentation Would Be Required.

1. ITM Misconstrues the "Full Scope of the Asserted Claims" that Must be Enabled.

ITM first asserts that the scope of the claimed invention under *Wands* Factor 7 is "virtually infinite." Petition, 77-79. But ITM's assertion of purportedly infinite claim scope is premised on Dr. Martin's statements that POSAs would understand that the recited "alkyl" and "aryl" groups "have a virtually infinite number of possible carbon atoms." *See id.* (citing EX1002, ¶¶162-163). For starters, as discussed above in §III.B., any assertion that the recited alkyl and aryl

groups are unlimited is wrong, given the express statements and definition in the specification limiting their scope. EX2002, ¶¶54-58, 119, 123. Furthermore, as explained in §§III.A. and V.A., ITM wrongly implies that the claimed compounds are themselves *required* to achieve some specific level of suitability for imaging/therapy and bi-functionalization. EX2002, ¶¶120-121.

Thus, ITM's assertions based on a purported lack of enablement for "virtually infinite" compounds that are *required* to perform some level of undefined functionality are wrong and should be rejected. *Entresto*, 125 F.4th at 1098-99 (rejecting lack of enablement arguments where they focused on whether the specification enabled what the claims *covered*, not what they required); *Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Research Found.*, PGR2022-00021, Paper 11 (P.T.A.B. Feb. 24, 2023), at 5-6 ("the Board was correct to focus on whether the claims themselves were enabled and *to find inapposite Petitioner's arguments as to whether functional language*—appearing only in the specification—was *enabled*.").

2. ITM Underestimates the Level of Skill of a POSA.

ITM's and Dr. Martin's analysis underestimates the level of skill of POSAs here. Petition, 81 (citing EX1002, ¶¶170-174). As discussed above in §II, ITM and Dr. Martin do not account for the fact that POSAs would have both formal training and practical experience in nuclear imaging or radiotherapeutics, as well as in

radiotherapeutic development, and in using molecular imaging techniques. EX2002, ¶¶19-28, 124. Their failure to account for the high level of skill of POSAs here entirely undermines their assertion that POSAs would be required to perform undue experimentation to determine whether the claims are satisfied, as detailed both in §II above and further below. *Id.*

3. ITM Underestimates the Predictability of the Invention and Level of Guidance Provided by the Specification Showing No Undue Experimentation Would Be Required.

The remainder of ITM's and Dr. Martin's *Wands* analysis is predicated on the assertions that the specification discloses only "two working examples" along with a "trial-and-error" or "make-and-screen" approach requiring "an unfathomably large exercise in making and testing" to achieve the full scope of the claimed invention. Petition, 80-86; EX1002, ¶165-176. ITM's assertions are again conclusory, unsupported, and wrong.

First, like with written description, there is no requirement for *any* working examples in the specification, let alone some number beyond "only two," in order to adequately enable the claims. *Alcon*, 745 F.3d at 1190 ("a patentee is not required to provide actual working examples" to satisfy enablement). And, as discussed above in §V for written description, not only does the specification disclose two working examples of compounds exhibiting FAP inhibition and suitability for imaging, it is also replete with *dozens* of columns of disclosures, and

incorporated materials providing exemplary A, B, and L moieties. EX2002, ¶¶113-116, 124-130. POSAs with multiple years of formal training and practical experience in the field and knowledge of the art, reviewing the specification, would have had ample guidance for selecting such moieties for use in low molecular weight compounds of the recited structure. EX2002, ¶¶124-130.

Indeed, ITM and Dr. Martin never actually assert that it would require undue experimentation for POSAs to *make* the claimed low molecular weight compounds of formula B-L-A, nor do they establish that *practicing* the full scope of the claims would somehow have required undue experimentation. Petition, 80-86; EX1002, ¶¶165-176; EX2002, ¶¶128-130. ITM and Dr. Martin merely state that the specification discloses simply a "trial-and-error" or "make-and-screen" approach to practice the claimed invention, but they fail to explain *why*. Petition, 75, 76, 80, 81, 84; EX1002, ¶¶167-174; EX2002, ¶¶128-130. Neither ITM nor Dr. Martin provide *any* evidence regarding what the iterative trial-and-error or make-and-screen approach actually would be, let alone what POSAs would even be "screen[ing]" for. EX2002, ¶¶128-130. ITM and Dr. Martin also fail to explain why engaging in this unspecified approach would somehow require POSAs to engage in undue experimentation, rather than simply the routine tasks of selecting and adjusting the disclosed types of moieties for creating and using the claimed compounds. EX2002, ¶¶127-130; *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d

1330, 1338–39 (Fed. Cir. 2013)("[u]nsubstantiated statements indicating that experimentation would be 'difficult' and 'complicated' are not sufficient."); *Fresenius Kabi USA, LLC v. Coherus Biosciences, Inc.*, PGR2019-00064, Paper 10, 17-18 (P.T.A.B. March 20, 2023) (rejecting petitioner's enablement challenges where petitioner failed to "explain sufficiently why a POSA would not have known how to adjust or select [adequate] ingredients in order to achieve the claimed stable aqueous pharmaceutical composition.").

ITM and Dr. Martin also fail to point to *any* specific embodiments of the recited low molecular weight compounds that would require undue experimentation to make and use, or that are otherwise inoperable. Petition, 73-86; EX1002, ¶¶158-176; EX2002, ¶¶128-130. ITM's and Dr. Martin's failure dooms ITM's assertions of lack of enablement. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984) (upholding enablement of claims directed to an emulsion blasting agent comprising an emulsifying agent when the defendant failed to identify any emulsifiers that are inoperable); *Sandoz*, Paper 11 at 28 (same).

Nor does ITM's (and Dr. Martin's) reliance on Dr. Pomper's prosecution declaration that the field is allegedly "unpredictable" support a finding of non-enablement. Petition, 80; EX1002, ¶171 (citing EX1004, 1201). The Federal Circuit expressly recognizes that testimony discussing "difficulties . . . before [the

inventor] disclosed his invention" is immaterial to whether "undue experimentation would be necessary once the teachings in the patents-in-suit were known." *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1291-92 (Fed. Cir. 2012); *BASF Plant Sci., LP v. Commonwealth Sci. & Indus. Rsch. Org.*, 28 F.4th 1247, 1265 n.4 (Fed. Cir. 2022) ("[w]hat the specification at issue *describes* to a relevant artisan . . . presents a distinct question from what a relevant artisan would have found obvious from the prior art without the specification.").

ITM lastly tries to assert that, in addition to *Wands*, the *Amgen, Baxalta*, and *ALZA* cases "compel[] a finding of no enablement." Petition, 84-86. ITM is wrong as *each* of these cases involved claims that were either defined solely functionally or *required* certain functionality that was not adequately enabled. For example, the claimed antibodies in *Baxalta*—like those in *Amgen* (discussed above)—were solely defined by the function of "bind[ing] Factor IX or Factor IXa and increas[ing] the procoagulant activity of Factor IXa." *Baxalta Inc. v. Genentech, Inc.*, 81 F.4th 1362, 1363 (Fed. Cir. 2023). And in *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935 (Fed. Cir. 2010), the claims expressly *required* that the administered dosage form of methylphenidate "treat[] ADD or ADHD … and provid[e] an ascending release rate over an extended period of time." *Id.* at 937-939. And in each of *Amgen*, *Baxalta*, and *ALZA*, the holdings of lack of enablement were expressly predicated on the fact that the specification did not

adequately enable POSAs to practice the full scope antibodies and dosage forms that would perform the explicitly *required* functionality. *Amgen*, 598 U.S. at 612-16; *Baxalta*, 81 F.4th at 1366-67; *ALZA*, 603 F.3d at 940-43. In contrast here, the claimed compounds are defined structurally and do not recite any specific level of functionality be attained. *See* §II. ITM cites no other law "compel[ling] a finding of no enablement" and so its lack of enablement ground should be rejected. Petition, 84.

C. ITM Enablement Analysis Fails under Binding Precedent.

As discussed above for written description, the law is clear that an application must be assessed for compliance with §112 as of that application's own filing date. *See, e.g.*, *Reiffin*, 214 F.3d at 1345-46. Again ITM never assessed *any* application in the '201 patent family as of *that application's own filing date*. ITM's assessment of the adequacy of enablement therefore is deficient and does not meet ITM's burden to show it is more likely than not that the challenged claims lack enablement.

VII. THE BOARD SHOULD GIVE DR. MARTIN'S TESTIMONY LITTLE TO NO WEIGHT.

As discussed in §II, POSAs here would have years of practical experience in radiotherapeutics or imaging. Nothing in Dr. Martin's CV or discussion of his "Qualifications" indicates that he has *any* formal training or practical radiotherapeutic or imaging experience. EX1003, 1-45; EX1002, ¶¶4-14. Dr.

Martin's lack of experience undermines the reliability of his testimony regarding, e.g., how POSAs would have interpreted the claims, reasons to modify the art, the purported expectations of success when "swap[ping]" one moiety in the art for another, and the purported complex and unpredictable process to determine suitable "B" and "L" moieties that may be used within the claimed genus of compounds. His opinions should be given little to no weight.

"[A]n expert must at a minimum possess ordinary skill in the art." *Osseo Imaging v. Planmeca*, 116 F.4th 1335, 1340 (Fed. Cir. 2024); *Kyocera v. ITC*, 22 F.4th 1369, 1376–77 (Fed. Cir. 2022); *Avail MedSystems, v. Teladoc Health*, IPR2022-00444, Paper 10 at 24-28 (P.T.A.B. July 21, 2022) ("it would be inappropriate for us to consider any testimony by [the inexperienced expert] on any issue that is analyzed through the lens of [a POSA]"). A person of ordinary skill *in this art* would have practical experience with radiotherapeutics and imaging. In contrast to Dr. Martin, JHU's expert Dr. VanBrocklin is a leading expert in radiopharmaceuticals, and his testimony should be given more weight than Dr. Martin's. EX2002, ¶¶4-14; EX2003.

VIII. CONCLUSION

The Petition fails to show a reasonable likelihood that any of the challenged claims is unpatentable and, therefore, the Board should deny institution.

Respectfully submitted,

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CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))

1. This Patent Owner Preliminary Response complies with the type-volume limitation of 18,700 words, comprising 18,505 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

I certify that the above-captioned **PATENT OWNER PRELIMINARY RESPONSE UNDER 37 C.F.R. § 42.207(a)** and associated Exhibits 2001-2018 were served in their entireties on April 28, 2025, upon the following parties via electronic mail:

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