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

PETITIONER'S OPPOSITION TO PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL OF INSTITUTION

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1003	Curriculum Vitae of Dr. Stephen F. Martin
1004	Prosecution History for U.S. Patent No. 11,938,201 (downloaded from USPTO Patent Center)
1005	U.S. Patent Publication No. 2011/0064657 to Pomper et al., published March 17, 2011 ("US '657")
1006	U.S. Patent Publication No. 2012/0009121 to Pomper et al., published Jan. 12, 2012 ("Pomper")
1007	U.S. Patent No. 9,346,814 to Jansen et al., issued May 24, 2016 ("Jansen I")

1008	Petra Dvořáková at al., *Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein*, 60 JOURNAL OF MEDICINAL CHEMISTRY 8385-8394 (2017), available at https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b00767 (last accessed Dec. 19, 2024) ("Dvořáková")
1009	U.S. Patent Publication No. 2010/0098633 to Zimmerman et al., published April 22, 2010 ("Zimmerman")
1010	Keon Jansen et al., *Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold*, 2013(4) ACS MEDICINAL CHEMISTRY, 491-96 (2013) ("Jansen II")
1011	*Product Information: ATTO 488*., ATTO-TEC GMBH (2024) available at https://www.atto-tec.com/fileadmin/user_upload/Katalog_Flyer_Support/ATTO_488.pdf (last accessed Dec. 18, 2024)
1012	*IVISense™ 680 NHS Fluorescent Labeling Kit: NEV11118*, REVVITY, INC., available at https://www.revvity.com/asset-search/tds?part_number=NEV11118 (last accessed Dec. 18, 2024)
1013	*Alexa Fluor™ 790 NHS Ester (Succinimidyl Ester)*, THERMOFISHER SCIENTIFIC, available at https://www.fishersci.com/shop/products/alexa-fluor-790-nhs-ester-succinimidyl-ester/A37569# (last accessed Dec. 18, 2024.
1014	IRDYE 700 DX, U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES, available at https://drugs.ncats.io/drug/C51A2YUX4N (last accessed Dec. 18, 2024)

1015	Ronnie C. Mease et al., *N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: A new Imaging probe for prostate cancer*, 14 CLIN CANCER RES 3036-43 (2008)
1016	Suzanne E. Lapi et al., *Assessment of an 18F-Labeled Phosphoramidate Peptidomimetic as a New Prostate-Specific Membrane Antigen–Targeted Imaging Agent for Prostate*, 50 J NUCL MED 2042-48 (2009)
1017	Ronny Rüger et al., *In Vivo Near-Infrared Fluorescence Imaging Of FAP-Expressing Tumors With Activatable FAP-Targeted, Single-Chain Fv-Immunoliposomes*, 186 JOURNAL OF CONTROLLED RELEASE 1-10 (2014)
1018	Zhi-Yi Chen et al., *Advance of Molecular Imaging Technology and Targeted Imaging Agent in Imaging and Therapy*, BIOMED RESEARCH INT'L 819324 (2014)
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1020	Mark Jordi, *Typical Molecular Weights of Common Polymers*, RQM+ (April 18, 2018), available at https://www.rqmplus.com/blog/typical-polymer-molecular-weights (last accessed Dec. 24, 2024)
1021	Anne Hellebust et al., *Advances in molecular imaging: Targeted Optical Contrast Agents For Cancer Diagnostics*, 7 NANOMEDICINE 429-45 (2012)
1022	Sumith A. Kularatne et al., *Prostate-Specific Membrane Antigen Targeted Imaging and Therapy of Prostate Cancer Using a PSMA Inhibitor as a Homing Ligand*, 6 MOLECULAR PHARMACEUTICS 780-89 (2009)

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I. INTRODUCTION

The Board should deny Patent Owner's request to discretionarily deny the Petition for Post-Grant Review (PGR) of U.S. Patent No. 11,938,201 ("the '201 patent") (EX1001). Several of the most common justifications for discretionary denial are not present here. There is no parallel litigation in any forum that would implicate *Fintiv* or otherwise inhibit the Board's objectives to advance "efficiency, fairness, and the merits." *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11, at 6 (P.T.A.B. Mar. 20, 2020) (precedential). Additionally, this is the first and only petition filed by Petitioner against the '201 patent. Thus, there is no reason to deny institution under *General Plastic*, as there is no risk of duplicating the PTAB's efforts or unduly prejudicing the Patent Owner. *Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 (P.T.A.B. Sept. 6, 2027) (precedential as to § II.B.4.i).

Patent Owner's Brief in Support of Discretionary Denial (Paper 9, hereinafter "Brief" or "Br.") chiefly asserts that the Director should exercise discretion to deny the Petition because it purportedly rehashes arguments considered and rejected by the Patent Office. But, as explained in the Petition and herein, the Patent Owner's allowance of the '201 patent claims was material error, and the *Advanced Bionics* factors weigh against discretionary denial here.

During prosecution, the Examiner recognized that the prior art taught each and every limitation of the claims and rejected them as obvious. Patent Owner only overcame this obviousness rejection through the submission of a declaration from one of the '201 patent's co-inventors, Dr. Pomper, who asserted the claimed compounds exhibited unexpectedly promising properties. But Dr. Pomper's assertion of unexpected results fails for several reasons.

First, it is based on only 11 examples and not even remotely commensurate with the extremely broad scope of the claims, which encompass thousands, if not millions or more, of possible compounds. Tellingly missing from the Pomper is a statement and rationale that the results observed with those 11 examples were representative of the full scope of that claim. Absent such a statement/rationale, no reasonable fact finder could have concluded that the properties observed for the 11 examples were somehow commensurate in scope with the extremely broad scope of the claims. Second, all 11 examples contain the same FAP inhibitor "A" structure, which Patent Owner concedes was known in the art and disclosed in Jansen I (*see* Br. at 39), and the "B" and "L" components' claimed functional language effectively captures all feasible options at those positions. Thus, any unexpected results are necessarily derived from the prior art and not any inventive aspects of the claims. The Examiner's reliance on this insufficient showing of unexpected results as

justification for allowing these *prima facie* obvious claims over the applied prior art was legally improper and a material error.

During prosecution, the Examiner also rejected the sole pending claim as anticipated by Dvořáková. In response, Patent Owner amended the claim to add the indefinite phrase "low molecular weight." But other references, including Dr. Pomper's own prior art Pomper reference cited by the '201 patent, taught that low molecular weight inhibitors may have better access to tumors than larger antibodies and that low molecular weight agents had shown promise in pre-clinical imaging studies. Apparently failing to recognize this teaching in the prior art, the Examiner withdrew the anticipation rejection and committed a material error by failing to enter an obviousness rejection based on Dvořáková and a prior art reference teaching the benefits of low molecular weight, such as Pomper.

The Examiner also failed to recognize that the '201 patent fails to comply with § 112's requirement of a fully and clearly described invention. Patent Owner submitted broad genus claims containing functional language of the exact type that has been invalidated by the Supreme Court in cases like *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023) and the Federal Circuit in cases like *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc) for failing to satisfy § 112's enablement and written description requirements. The Patent Owner also introduced the relative and undefined phrase "low molecular weight"—which Patent Owner

further convolutes by asserting that it is synonymous with "small molecule," which itself can have varied definitions depending on the context—into the claims. This violates § 112's requirement to inform those skilled in the art about the scope of the invention with reasonable certainty. Nevertheless, the Examiner allowed the '201 patent without a single rejection based on § 112. This, too, was a material error.

Instead of focusing on the merits of the Petition, Patent Owner attempts to advance an overly high standard of ordinary skill in the art in the hopes of disparaging Dr. Martin's credible expert declaration. But, as Dr. Martin explains in his declaration (EX1025), Patent Owner's offered definition is incorrect and, even if Patent Owner's definition is accepted, Dr. Martin meets that definition, and his opinions would not substantively change regardless of which POSA definition is applied. EX1025 at Section III.

Further, other considerations, such as public and economic policy and the expectations of the parties, weigh against a discretionary denial. Nuisance patents like the '201 patent stifle innovation and inflict large and unjustified healthcare costs on the public. The Director should thus decline to exercise its discretion to deny institution here.

II. THE PETITION PRESENTS ARGUMENTS WHICH WERE NOT PRESENTED DURING PROSECUTION AND IDENTIFIES ERRORS OF THE OFFICE WHICH ARE MATERIAL TO PATENTABILITY

The Director should not exercise its discretion under § 325(d) to deny institution. The Board has outlined factors it considers in determining whether to exercise discretion to deny institution under § 325(d). *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (P.T.A.B. Dec. 15, 2017) (precedential as to § III.C.5, first paragraph); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 8-11 (P.T.A.B. Feb. 13, 2020) (precedential).

Advanced Bionics explains how the six *Becton, Dickinson* factors fit into a two-part framework that examines:

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
> (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics at 8.

In evaluating the first factor, the Board looks to *Becton, Dickinson* factors (a), (b), and (d) to determine the similarities and differences between the asserted and prior art/arguments and both the cumulative nature and the extent of overlap of the two. *Id*. at 9-10. "If, after review of factors (a), (b), and (d), it is determined that the

same or substantially the same art or arguments previously were presented to the Office, then factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office." *Id*. at 10; *see also id.* at 9 n. 10 (describing the factors as (c) the extent to which the asserted art/arguments were evaluated, (e) whether petitioner sufficiently pointed out how the examiner erred in that evaluation, and (f) if additional evidence and facts from the petition warrant reconsideration of prior art/arguments).

The *Advanced Bionics* framework counsels against discretionary denial here.

A. Grounds I-II Pass the *Advanced Bionics* Framework Because They Demonstrate Specific Office Errors Material to Patentability of the '201 Patent Claims

Taking *Becton, Dickinson* factors (a), (b), and (d) together under *Advanced Bionics* Part 1, Grounds I and II do not constitute the "same or substantially the same" art or arguments previously presented to the Office. Both Grounds I and II rely on Pomper in establishing a *prima facie* case of obviousness over the '201 claims. *See* Pet. at Sections VII.A-B. While Pomper was cited in an IDS during prosecution, it was neither applied in a rejection nor cited of interest by the examiner. Moreover, Pomper is neither cumulative to the references relied upon in previous rejections nor do the arguments made during prosecution overlap with the key teachings of Pomper under factors (b) and (d), respectively.

First, and contrary to Patent Owner's assertion, Pomper is not cumulative to Zimmerman. Br. at 5. As discussed in the Petition and acknowledged by Patent Owner, Pomper provides express teachings regarding the benefits of "low molecular weight" radiopharmaceuticals—low molecular weight inhibitors have more access to tumors than larger antibodies and have shown promise in preclinical imaging studies. EX1006 at ¶¶ 8, 242; *see also* Pet. at 46, 56; Br. at 5. Although Zimmerman discusses small molecule compounds, it fails to provide any equivalent teaching related to tumor access, let alone any express benefit related to the size of its molecules.

In the seventeen pages of tables provided to allegedly demonstrate the cumulative nature of Pomper relative to Zimmerman, Patent Owner does not once identify any teaching, suggestion, or motivation related to the benefits of low molecular weight agents provided in Zimmerman which is the "same or substantially the same" as that of Pomper. *See* Br. 9 at 7-24. Indeed, in the row specifically addressing Pomper's statement regarding the benefit of low molecular weight agents for targeting tumors, Patent Owner cites only Zimmerman's general discussion of its "small molecule inhibitors of seprase that can be used as therapeutic agents" and therefore enable "delivering radiotherapy to tumor tissues that express seprase." *Id.* at 17-18 (citing EX1009 at ¶¶ 2, 7-8). Thus, from Patent Owner's own comparison,

it is plain that Zimmerman provides no teaching equivalent to Pomper's clear and explicit discussion of the benefits of low molecular weights on tumor access.

Second, this non-cumulative teaching of Pomper related to the benefits of "low molecular weight" agents—which is the operative teaching for which Petitioner relies on the reference—does not overlap with any argument made during examination. Nor can Patent Owner reasonably assert otherwise, for the claims were never rejected after the introduction of the "low molecular weight" limitation. *See generally* EX1004. Thus, on the whole, *Becton, Dickinson* factors (b) and (d) outweigh factor (a), and *Advanced Bionics* Part 1 is not met.

Even if the Director finds Part 1 of *Advanced Bionics* satisfied as to Grounds I and II, the analysis under Part 2 demonstrates that the Office erred in a manner material to the patentability of challenged claims and counsels against discretionary denial under § 325(d). *Advanced Bionics* at 8. To be sure, *Advanced Bionics* gives two examples of material errors pertinent in the Part 2 inquiry: the first being "misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims" and the second being "an error of law" (*e.g.*, misconstruing a claim term, where the construction impacts patentability). *Id.* at 8-9 n.9. Both categories of error are present here. Pet. at 100.

1. The Examiner's Failure to Identify Pomper's Specific Teachings Regarding the Benefits of Low Molecular Weight Radiopharmaceuticals Was Material Error

The Examiner overlooked Pomper's specific teaching regarding the benefits of "low molecular weight" agents on tumor access. Pet. at 100. When considered in light of *Becton, Dickinson* factors (c), (e), and (f), it is apparent that this failure to identify a teaching material to patentability of the claims is an error which militates against discretionary denial.

Factor (c) considers "the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection." *Id.* Patent Owner argues that "the art in Grounds I and II was extensively evaluated during Examination." Br. at 29. However, Pomper, which is relied upon in both Grounds I and II, was not used as the basis for an art rejection or even cited of interest. Patent Owner does not assert otherwise. This alone weighs against exercising discretion to deny institution under § 325(d). *See, e.g.*, *Therabody, Inc. v. Hyperice IP Subco, LLC*, PGR2024-00053, Paper 8 (P.T.A.B. Apr. 21, 2025). Furthermore, as established above, the teachings of Pomper related to the benefits of low molecular weight compounds are not cumulative to those of, *e.g.*, Zimmerman, which further discourages discretionary denial at this stage.

Factor (e) analyzes "whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art." *Advanced Bionics* at 9

n.10. The Petition points out with particularity the manner in which the Examiner erred—overlooking Pomper's express teaching that low molecular weight inhibitors have better access to tumors than larger antibodies and that low molecular weight agents had shown promise in pre-clinical imaging studies. Pet. at 2, 46, 61; EX1006 at ¶¶ 8, 126. Instead, as explained in Ground II of the Petition, the Examiner withdrew the rejection of the sole pending claim as anticipated by Dvořáková after Patent Owner amended the claim to add the phrase "low molecular weight." Pet. at 60; EX1004 at 1177-78 (Office Action), 1210 (Office Action Response), 1303-09 (Notice of Allowance). However, Dvořáková discloses every limitation of the claims except "low molecular weight." Pet. at 61; EX1002 at ¶ 138. A POSA reading Dvořáková in view of Pomper would have been motivated to modify Dvořáková's disclosed compounds to have a lower molecular weight based on Pomper's teachings about how such compounds have improved pharmacokinetic properties and have shown promise in preclinical studies (*see* Pet. at 61; EX1002 at ¶ 140), and the Examiner's failure to consider and/or appreciate these teachings of Pomper regarding the benefits of "low molecular weight" compounds is an error material to patentability.

Further, factor (f) considers "the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments." *Advanced Bionics* at 9 n.10. The Examiner's failure to appreciate the relevancy of

the Pomper reference to the claims is further highlighted and enhanced when considered in light of the Declaration of Dr. Martin, constituting new evidence that magnifies the Examiner's error in overlooking Pomper therefore warranting reconsideration. *See Therabody* at 10. For example, Dr. Martin's testimony explains that "a POSA would have readily understood how the molecular weight of Dvořáková's compounds could be lowered," "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," and "would have reasonably expected a low molecular weight version of iBody 1 to work for the desired purpose." EX1002 at ¶ 140; *see also* Pet. at 61. Each of these statements is probative to the issue of patentability and helpful in the consideration of the prior art combinations in Ground II. *See Therabody* at 10. As they were not considered by the Examiner, they provide facts which weigh against exercising discretion to deny institution under factor (f). *Id.* at 10-11.

In sum, each of *Becton, Dickinson* factors (c), (e), and (f) weigh against discretionary denial under *Advanced Bionics* Part 2. *See Advanced Bionics* at 9 n.10.

2. The Examiner's Acceptance of a Flawed Showing of Unexpected Results Was Material Error

The Examiner erroneously withdrew the obviousness rejection based on Jansen I, Jansen II, and Zimmerman based on a flawed showing of unexpected

results, which was clearly not commensurate in scope with the extremely broad '201 patent claims. Pet. at 100. Using *Becton, Dickinson* factors (c), (e), and (f) as a guide, this legal error amounts to a material error for which *Advanced Bionics* advises that discretionary denial is unfit.

It is true that, under factor (c), the pertinent art was evaluated during the single round of prosecution. Pet. at 100; *see generally* EX1004. However, factors (e) and (f) here outweigh whatever "extent" that evaluation constitutes.[1]

Under factor (e) the Petition again points out with particularity the manner in which the Examiner erred—improperly allowing the *prima facie* obvious claims of the '201 patent over the applied art based on "evidence of alleged unexpected results [that] was not even remotely commensurate with the extremely broad scope of the claims." Pet. at 47. Objective evidence of non-obviousness requires proof of a "nexus" with the claims and must be commensurate in scope with the claims. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Asyst Techs., Inc.* v. *Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

[1] Patent Owner characterizes "the art in Grounds I and II [as] *extensively* evaluated during Examination." Br. at 29 (emphasis in original). Whatever "extensively" means, it can hardly be used to characterize the original examination of the '201 patent, which merely involved a single Office Action and Examiner Interview, and should not hold any weight under the factor (c) analysis.

As explained in the Petition, "Patent Owner argued during prosecution that the 11 examples provided in the Pomper Declaration are evidence of unexpected results. Yet each of the 11 new examples, along with the two examples . . . in the '201 patent specification includes the same FAP inhibitor (A) structure." Pet. at 50 (citations omitted). Given the incredibly large scope of the FAP inhibitor (A) genus described in the claims, the Pomper Declaration's single FAP inhibitor (A) example does not provide evidence of unexpected results commensurate in the scope with the claims. Pet. at 58-59; EX1002 at ¶ 133; *see also In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003) (concluding that data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 714 F. Supp. 3d 652, 786 (N.D.W. Va. 2024) (rejecting evidence of secondary considerations that focused on narrow set of particular disorders because it was "insufficient to represent the full scope of the claimed genus").

Nor did Patent Owner assert or even explain how a mere 11 examples out of thousands, if not millions, of possible embodiments were representative of the full scope of the claims. Absent such a statement/rationale, no reasonable fact finder could have concluded that the properties observed for the 11 examples were somehow commensurate in scope with the extremely broad scope of the claims. *See Application of Lindner,* 457 F.2d 506, 508 (C.C.P.A. 1972) (affirming Patent

Office's determination that there was "no adequate basis for concluding that the great number and variety of compositions included by the claims would behave in the same manner as the tested composition") (citation omitted).

Moreover, while the structures of the linkers (L) and optical dyes or radiolabeling groups (B) vary in the 11 examples provided, it is certainly insufficient to represent the thousands, if not millions or more, of possible FAP inhibitors, linkers, optical dyes, radiolabeling groups, and combinations thereof encompassed by the broad functional language used in the claims. Pet. at 59; EX1002 at ¶¶ 134-35. Indeed, because B and L are defined using such broad functional language that effectively captures all feasible options at those positions, any unexpected results are necessarily derived from the prior art and not any inventive aspects of the claims. Thus, the Examiner's reliance on the Pomper Declaration's insufficient evidence of unexpected results constitutes a material error of law under *Advanced Bionics* Part 2. *Advanced Bionics* at 9 n.9.

Furthermore, the Declaration of Dr. Martin again constitutes new evidence that was not presented to the Examiner and therefore warrants reconsideration under factor (f). *See Therabody* at 10. In particular, Dr. Martin analyzed the breadth of the claims and the relatively few examples provided by Applicant. EX1002 at ¶¶ 134-35. Furthermore, he explained why the evidence is not commensurate with the scope of the claims by pointing out that all of the examples relied upon as a basis for

unexpected results use the same "A" structure. EX1002 at ¶ 133. Thus, and contrary to the Patent Owner's assertion, Dr. Martin's testimony is not "conclusory and unsupported" on the point of unexpected results but rather is highly probative of the issue. Br. at 26. Because it was not considered by the Examiner, the testimony thus provides facts which weigh against discretionary denial under factor (f). *Therabody* at 10-11.

In summary, weighing the *Becton, Dickinson* factors pertinent to Part 2 of the *Advanced Bionics* framework, discretionary denial is inappropriate for Grounds I and II and the Director should decline to exercise such discretion.

B. Grounds III-V Pass the *Advanced Bionics* Framework Because They Are Each Premised on New Arguments Never Presented to the Office

35 U.S.C. § 325(d) states, in pertinent part, that "[i]n determining whether to institute or order a proceeding . . . the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." *See also Advanced Bionics* at 7 ("Under § 325(d), the art and ***arguments must have been previously presented to the Office*** during proceedings pertaining to the challenged patent.") (emphasis added). Thus, discretionary denial under Section 325(d) requires an affirmative showing that an argument was previously presented to the Office. *Id.* Presumptions about what an Examiner may have considered off the record do not suffice. *See*

Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Rsch. Found., PGR2022-00021, Paper 13, 3 (P.T.A.B. Mar. 22, 2023) (holding that § 325(d) does not apply where a challenge was based on a statutory ground which was not the basis of a rejection); *see also* 35 U.S.C. § 326(e) (establishing that no presumption of validity applies in post-grant reviews, which instead examine "[]patentability").

Patent Owner's assertion that Grounds III-V "present the same arguments previously presented to the Office" is wholly unsupported by both the prosecution history and its arguments in the Request for Discretionary Denial, which amount to no more than presumptions—and unsubstantiated ones at that—about what the Examiner may have considered. Br. at 30-32. Where, as here, grounds are focused on § 112 issues which are entirely absent from the prosecution history, they do not trigger Part 1 of the *Advanced Bionics* framework, nor do they implicate matters of efficiency with which § 325(d) is concerned. *See Boehringer*, Paper 13 at 3 ("§ 325(d) does not apply to Petitioner's enablement challenge . . . because an enablement rejection was not made during the prosecution . . . .").

1. An Examiner's Mere Compliance with Examination Guidelines Does Not Satisfy *Advanced Bionics* Part 1

Concerning Ground III (lack of enablement) and Ground IV (lack of written description), Patent Owner does not point to even a single instance in the prosecution history to support that Part 1 of the *Advanced Bionics* framework is satisfied. Br. at

31-32. Rather, Patent Owner relies solely on an extrapolation of the Examination Guidelines to craft a narrative that Examiner "should be presumed to have considered enablement and written description for challenged claims during prosecution and found them compliant because enablement and written description rejections were never raised." *Id.* This presumption is neither logically nor practically sound.

Patent Owner bases this presumption on two portions of the Manual of Patent Examining Procedure ("M.P.E.P.") which do not themselves recite, let alone compel, any presumption. *Id.* (citing M.P.E.P. §§ 1302.01, 2103 (2024)). While Patent Owner contends that, based on these sections, the Examiner is presumed to have considered the claims for compliance with § 112, it notably omits the operative term from its quotations: "should." *See* M.P.E.P. § 2103 ("Under the principles of compact prosecution, each claim ***should*** be reviewed for compliance with every statutory requirement for patentability. . . .") (emphasis added); *id.* § 1302.01 ("When an application is apparently ready for allowance, it ***should*** be reviewed by the examiner to make certain that . . . the language of the claims is enabled by, and finds adequate descriptive support in, the application disclosure . . . .") (emphasis added). What the M.P.E.P. states that the Examiner should do is hardly equivalent to a presumption that they actually did so.

And even if, *arguendo*, Patent Owner is correct that the Examiner is presumed to have considered the application for compliance with § 112, this does not, by the plain text of § 325(d), satisfy *Advanced Bionics* Part 1. Consideration of an application for enablement and written description support cannot, by any stretch of the imagination, constitute "arguments previously . . . presented to the Office," where neither Applicant nor the Examiner made any such arguments about such issues. *See Boehringer*, Paper 13 at 3. Holding otherwise would mean that every issued patent challenged on § 112 (or § 101) grounds would satisfy Part 1 of *Advanced Bionics*, regardless of whether any rejection on those Sections was made, merely by virtue of the fact that it was subject to examination. This interpretation cannot be correct. Therefore, the Director should decline to adopt Patent Owner's radical position regarding applicability of *Advanced Bionics* to Grounds III and IV and find instead that discretionary denial under § 325(d) does not apply here, where neither enablement nor written description rejections were made during prosecution. *See Boehringer*, Paper 13 at 3; *see generally* EX1004.

2. Arguments About Written Description Support for a Limitation Are Not the Same or Substantially the Same as Arguments About Indefiniteness of that Limitation and Therefore Do Not Satisfy *Advanced Bionics* Part 1

Regarding Ground V (indefiniteness of the phrase "low molecular weight"), Patent Owner has again failed to show that any arguments about indefiniteness were

previously presented to the Office. Rather, Patent Owner conflates arguments about claim interpretation and written description support (*i.e.*, new matter) with arguments about indefiniteness. Br. at 30-31. Each are different requirements, involving different considerations, such that an argument made regarding one does not necessarily equate to an argument made regarding another. *See Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Rsch. Found.*, PGR2022-00021, Paper 11, 2-3 (P.T.A.B. Feb. 24, 2023) (declining "as a matter of principle and law" to find that an enablement challenge constituted the same or substantially the same arguments as previously presented to the Office on written description).

The indefiniteness arguments as presented in Ground V do not constitute the same or substantially the same arguments as those previously made relating to claim interpretation, including the declaration of Dr. Pomper "explaining how the term 'low molecular weight' should be understood in the context of the claimed invention" and the "discussion of this phrase during an Examiner's interview." *Compare* Br. at 30-31 *with* Pet. at 90-98 (arguing that the phrase "low molecular weight" is indefinite for failing to provide reasonable certainty where, *inter alia*, it could have different meanings depending on the field of study and where the specification does not define the term). While, conceivably, arguments about claim interpretation and indefiniteness overlap, they do not necessarily equate for the purposes of § 325(d). *C.f. Boehringer*, Paper 11 at 2-3 ("While 'written description

and enablement often rise and fall together,' . . . an argument made regarding one requirement does not necessarily equate to an argument made regarding the other.").

Here, Patent Owner previously argued that "one of ordinary skill in the art would recognize that low molecular weight compounds would have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons." Pet. at 94; EX1004 at 1215 (Office Action Response); *see also id.* at 1198 (Pomper Declaration), 1273 (Supplemental Amendment). That is not the same or substantially the same as the specific arguments in Ground V, *i.e.*, that the phrase "low molecular weight" is indefinite at least because, while it may include the "non-limiting 'typical' general range of about 50 Da to about 1500 Da," a POSA would understand the phrase to be relative to the field of study which is different between the '201 patent and the references cited in support for the range. Pet. at 90-96. Nor is it the same or substantially the same as the specific argument in Ground V that the '201 patent specification itself demonstrates the ambiguity and indefiniteness of the phrase by way of "several examples of moiety B that have molecular weights greater than 1,500 Da by themselves." *Id.* at 96. That is also not the same or substantially the same as the specific argument in Ground V that "[t]he claim term 'molecular weight' has already been considered—and found indefinite—by the Federal Circuit" and "[t]he '201 patent claims provide no greater certainty than those in *Teva* because the claims introduce the additional, relative modified 'low' without sufficiently

explaining what molecular weights the claims compounds are lower than." *Id.* at 97-98 (citing *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341-45 (Fed. Cir. 2015)).

Likewise, the indefiniteness arguments as presented in Ground V do not constitute the same or substantially the same arguments as those previously made relating to written description support (*i.e.*, new matter). Just as written description and enablement are two separate requirements involving different considerations, so too are written description and indefiniteness, such that arguments relating to one do not necessarily equate to arguments relating to the other. *See Boehringer*, Paper 11 at 2-3. *Google LLC v. Ecofactor, Inc.*, as relied upon by the Patent Owner, is inapposite. Br. at 31 (citing IPR2022-00535, Paper 7 at 13 (P.T.A.B. Aug. 1, 2022)). *Ecofactor* did indeed "hold[] that the same arguments were previously before the Office when patent owner presented arguments concerning support for [a] claim limitation during examination." *Id.* (second alteration in original) (internal quotation marks omitted); *see also Ecofactor* at 13. However, the "same arguments" at issue in *Ecofactor* were Petitioner's ***support*** arguments—not indefiniteness arguments as at issue here. *Ecofactor* at 13. Indeed, indefiniteness arguments by Petitioner could not have been an issue in the IPR in *Ecofactor*. 35 U.S.C. § 311(b).

The discussion above illustrates the nuance that Patent Owner overlooks in attempting to fault ITM for allegedly contradicting itself. Br. at 30. It can be true

that "[t]he phrase 'low molecular weight' was . . . discussed during prosecution" and was, in part, the basis for allowance of the '201 patent's claims, while also true that "'the prosecution history does not reflect that the Examiner ever appreciated or considered the § 112 issues' discussed in Ground V." *Id.* (citing Pet. at 93-94, 100). Put differently, the former truth does not negate the latter truth where the previous arguments related to different requirements than those presented in the Petition. *Compare Boehringer*, Paper 11 at 2-3 *with Ecofactor* at 13. And, for the reasons discussed in Section II.B.1 above, any presumption that the Examiner's entrance of the claim amendment was a determination that the phrase "low molecular weight" is definite (*see* Br. at 31) does not constitute the same or substantially the same arguments under *Advanced Bionics* Part 1 and § 325(d).

3. Overlooking Issues of Patentability Under § 112 Constitutes Material Error Under *Advanced Bionics* Part 2

Only after it is established that the same or substantially the same arguments were previously presented to the Office must the Director consider whether Petitioner has demonstrated a material error by the Office. *Advanced Bionics* at 8. For the reasons described above in Sections II.B.1 and II.B.2, the Director need not consider *Advanced Bionics* Part 2 here for Grounds III-V. Nevertheless, Petitioner briefly responds to Patent Owner's allegations regarding a lack of material error. *See* Br. at 32-33.

Concerning Grounds III and IV, Patent Owner facially asserts only that "ITM has made no effort to demonstrate an error material to patentability." *Id.* at 32. This argument plainly ignores the twenty pages of the Petition that specifically address the manner in which the claims lack both enablement and written description under § 112. Pet. at 71-90. Nor does this argument make any attempt to substantively rebut Petitioner's positions. That silence is telling. The Examiner's failure to identify the enablement and written description problems plaguing the claims is, to all reasonable minds, material to patentability. *See Advanced Bionics* at 9 n.9.

Concerning Ground V, Patent Owner alleges that "ITM erroneously concludes" that the Examiner did not appreciate or consider indefiniteness and alleges that this "position is merely a disagreement with the Examiner's allowance in view of JHU's arguments during prosecution." Br. at 32. But, as outlined in Section II.B.2 above, JHU's arguments during prosecution related to claim interpretation and new matter support, not indefiniteness. Thus, Gound V is not merely a "disagree[ment] regarding the purported treatment of the art or arguments." *Advanced Bionics* at 9. Instead, Ground V presents a concrete error related to the indefiniteness of an amended limitation for which the claims were erroneously deemed allowable. *See* Pet. at 90-98; EX1004 at 1308 (Notice of Allowance) (reciting the indefinite "low molecular weight" phrase in the Reasons for

Allowance). Overlooking or misapprehending the indefiniteness of the claims is therefore hardly immaterial to patentability. *See Advanced Bionics* at 9 n.9.

III. THE MERITS OF THE PETITION ARE STRONG

The merits of the Petition are strong and warrant institution. A denial of institution here would harm the public's interest and the patent system by preventing the review of a patent that has been credibly shown to have at least one invalid claim.

The strength of the Petition's merits are confirmed by Patent Owner's analysis, which primarily rests on its unfounded and incorrect assertion that Petitioner and Dr. Martin have applied the wrong POSA standard. *See* Br. at 33-37. But Patent Owner has proffered an unreasonably high POSA standard that is divorced from the state of the art in the hopes of excluding Dr. Martin's declaration. These arguments should be disregarded because Dr. Martin's definition most faithfully provides the level of ***ordinary*** skill in the art, consistent with both the '201 patent's purpose and the prior art, while Dr. VanBrocklin's definition requires a level of skill beyond ordinary and approaching ***extraordinary***. *See* EX1025 at ¶¶ 7-13. Furthermore, even if Patent Owner's standard is applied, Dr. Martin qualifies as an expert and his opinions do not substantively change. *See id.* at ¶¶ 14-16.

A. Under Either Petitioner's or Patent Owner's POSA Lens, Dr. Martin Possesses the Requisite Skill

Patent Owner alleges that Petitioner uses an incorrect POSA lens which "does not account for the training and practical experience the POSA would have had in imaging or radiotherapy." Br. at 34. In particular, Patent Owner and its expert Dr. VanBrocklin contend:

> [I]n view of the patent's and the cited prior art's overall focus on imaging and radiotherapeutic agents . . . POSAs would, critically, have had ***multiple years of both formal training and actual practical experience*** in i) nuclear or optical imagining, or ii) radiotherapeutics (collectively, radiopharmaceuticals), as well as in radiopharmaceutical development, and in using molecular imagining techniques . . . .

Br. at 36 (emphasis in original). This is a blatant attempt to craft an erroneously high POSA standard in the hopes of excluding the credible opinions advanced by Petitioner's expert. Because it is neither the proper standard, nor does it actually impeach Dr. Martin's testimony, the Director should give this argument by Patent Owner no credence.

1. Petitioner's POSA Standard is Proper, as it Defines the Level of Ordinary—Not Extraordinary—Skill

A person of ordinary skill in the art possesses an ordinary, not expert or genius, level of skill in the art. *See Env't Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 697 (Fed. Cir. 1983) (holding that a person of "ordinary skill in the art" is not a person "skilled in remote arts" or a "genius[] in the art at hand"). Petitioner's

POSA lens most faithfully provides the level of ***ordinary*** skill, while Patent Owner's lens requires something beyond ordinary and approaching ***extraordinary*** (*i.e.*, expert or genius) skill.

As Dr. Martin previously explained, considering such factors as (1) the type of problems encountered in the art, (2) the prior art solutions to those problems, (3) the rapidity with which inventions are made, (4) the sophistication of the technology, and (5) the educational level of active workers in the field, a POSA considering the '201 patent "would comprise a person possessing a Bachelor's degree in organic chemistry or a related field such as medicinal chemistry and two to five years of experience employing organic chemistry as a tool for the development of molecules with targeted biological activity." EX1002 at ¶¶ 94-95. "A POSA would also have an understanding of processes employed for synthesis and evaluation of imaging and radiotherapeutic agents that selectively target specific protein and would be able to evaluate published literature and patents to ascertain those features of a molecule that contribute to its affinity and selectivity for a particular drug target." *Id.* at ¶ 95.

This lens complies with the test allegedly performed by Patent Owner—"that '[t]he patent's purpose' and the prior art may reflect the appropriate skill level of a POSA." Br. at 35 (alteration in original) (citing *Best Med. Int'l, Inc. v. Elekta Inc.*, 46 F.4th 1346, 1353 (Fed. Cir. 2022)). Here, the '201 patent abstract expressly states that "[i]maging and ***radiotherapeutics agents targeting fibroblast-activation-α***

(FAP-α) and their use in imaging and treating FAP-α related diseases and disorders are disclosed" and the prior art "likewise discusses ***compounds with radiotherapeutics*** and imaging ***applications***." Br. at 35 (all emphases added).

A POSA with a degree in chemistry or a related field (*e.g.*, medicinal chemistry), two to five years' experience employing organic chemistry as a tool for developing molecules with targeted biological activity, "an understanding of processes employed for synthesis and evaluation of imaging and ***radiotherapeutic agents that selectively target specific protein***," and an ability "to evaluate published literature and patents to ascertain those features of a molecule that contribute to its affinity and selectivity for a particular drug target" has a level of skill which aligns with the both the patent's purpose and the prior art. EX1025 at ¶¶ 9-12. Requiring any more than this, such as requiring multiple years of formal training and practical experience in radiopharmaceuticals specifically, is unnecessary and extends the level of skill beyond ordinary and into the realm of expert or genius. *See Environmental Designs*, 713 F.2d at 697; *see also* EX1025 at ¶ 13.

2. Dr. Martin is a POSA Under Patent Owner's Standard

Even if, *arguendo*, Patent Owner's heightened POSA standard is the correct standard, Dr. Martin still qualifies as an expert under that standard. EX1025 at ¶ 14.

As defined by Patent Owner, the requisite "training and experience would have involved developing and evaluating agents for biomedical imaging or

radiopharmaceuticals, and using molecular imagining techniques." Br. at 36. Contrary to Patent Owner's assertion, Dr. Martin has practical experience in radiotherapeutics, including ^{3}H- and ^{11}C-labeled therapeutic agents for treatment of, *e.g.*, traumatic brain injury, and in using proton emission tomography (PET) as a molecular imaging technique to evaluate those agents. EX1025 at ¶¶ 14-15. Therefore, under either POSA standard, Dr. Martin's testimony should not be discounted and should, at a minimum, be given the same weight as Dr. VanBrocklin's.

B. The Strength of the Unpatentability Grounds Warrants Institution[2]

1. Claim Construction

Patent Owner asserts that ITM's proposed constructions for the terms "C(O)Alkyl"/"Aryl" and "low molecular weight" are incorrect "because ITM and Dr. Martin use the incorrect POSA lens." Br. at 38. However, Patent Owner does not explain how the parties' competing POSA standards impact the construction of these terms, and this conclusory and unsupported assertion should be disregarded.

[2] In the interest of efficiency and the spirit of the Office's Memorandum on Interim Processes for PTAB Workload Management, dated March 26, 2025, Petitioner has limited its rebuttal discussion of the merits to only those arguments raised by Patent Owner in its Discretionary Denial Brief. This is not an acquiescence to any of the additional arguments made by Patent Owner in its Preliminary Patent Owner Response and Petitioner reserves the right to respond to such arguments if PGR is instituted.

As discussed above, Section III.A.1, *supra*, Petitioner and Dr. Martin applied the correct POSA standard, although Petitioner submits that its proposed constructions are correct under both Petitioner's and Patent Owner's proposed POSA standard.

a. "C(O)Alkyl"/"Aryl"

Patent Owner takes issue with Petitioner's assertion that the claim terms "C(O)alkyl" and "aryl" are not limited to any particular length or size. Br. at 39. In support, Patent Owner alleges that the patentee, through incorporation of Jansen I, "designated a specific number of carbons (1 to 6 carbon atoms) or rings (5- or 6-membered aromatic monocycle) for the recited 'C(O)Alkyl' and 'aryl' within the R_{3x} substituent of "A" as claimed." Br. at 39. But the imprecise and broad language in the '201 patent and Jansen I that Patent Owner relies on is insufficient to define these terms under established claim construction canons, particularly where this language is contradicted by the definitions provided in the '201 patent itself.

Patent Owner asserts that the specification of the '201 patent incorporates Jansen I by reference and that Jansen I defines these terms therein. However, the passage of the '201 patent that Patent Owner relies upon states that "***[r]epresentative*** targeting moieties for FAP-α are disclosed in [Jansen I] . . . which [is] incorporate[d] by reference in [its] entirety." EX1001 at 8:25-32 (emphasis added); EX1025 at ¶ 24. Moreover, Patent Owner neglects to mention that the definition of "alkyl" in Jansen I is expressly non-limiting. *See* EX1007 at 22:18-20 ("***Generally***, alkyl groups of

this invention comprise from 1 to 6 carbon atoms") (emphasis added); EX1025 at ¶ 24. The bar for lexicography is exacting and applies only where the patentee "clearly set[s] forth a definition of the disputed claim term" and "clearly express[es] an intent" to redefine the term. *Thorner v. Sony Comput. Ent. Am. LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012) (first quoting *CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002); and then quoting *Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1381 (Fed. Cir. 2008)). Imprecise and non-limiting language like "representative" and "generally" fails to meet this standard, particularly where the alleged definition is incorporated by reference.

This is especially true where the proposed construction is contradicted by the plain text of the specification. As discussed in the Petition, the '201 patent provides a definition of alkyl:

> The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent groups, ***having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons)***.

EX1001 at 39:43-50 (emphasis added); Pet. at 42-43; EX1025 at ¶ 24. Patent Owner's proposed construction of "1 to 6 carbons" cannot be correct because it is contradicted by the definition of alkyl provided in the '201 patent and its

accompanying example, which explicitly contemplates alkyls having between 1 and 10 carbons and, by its plain language, allows for alkyl chains having even more than 10 carbons. *See Thorner*, 669 F.3d at 1365 ("It is likewise not enough that the only embodiments, or all of the embodiments, contain a particular limitation. We do not read limitations from the specification into claims; we do not redefine words. Only the patentee can do that."); *see also* EX1025 at ¶ 24.

Patent Owner's proposed construction would also render the term "$C_{1\text{-}6}$alkyl," which appears several times in claims 1 and 3, superfluous, as it would have an identical meaning as "alkyl." Such a construction is highly disfavored. *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 801, 810 (Fed. Cir. 2021) ("It is highly disfavored to construe terms in a way that renders them void, meaningless, or superfluous."); *Thorner*, 669 F.3d at 1368 ("If the applicant had redefined the term 'attached' to mean only 'attached to an outer surface,' then it would have been unnecessary to specify that the attachment was 'to [an] outer surface' in the specification. We conclude that the term attached should be given its plain and ordinary meaning. The specification does not redefine attached nor is there any disavowal.").

Patent Owner's proposed construction for "aryl," based on the same alleged incorporation by reference of Jansen I and similar language in Jansen I about how the term is "generic" for "a 5- or 6-membered aromatic monocycle" is likewise contradicted by the plain language of the '201 patent. Like "alkyl," the term "aryl"

is defined in the '201 patent. The '201 patent defines "aryl" as "an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently." EX1001 at 42:64-67; EX1002 at ¶ 111; EX1025 at ¶ 25. Patent Owner's proposed construction of "a 5- or 6-membered aromatic monocycle" cannot be correct because the '201 patent explicitly describes aryls having at least 1 to 3 rings. *See Thorner*, 669 F.3d at 1365; *see also* EX1025 at ¶ 25.

b. "Low Molecular Weight"

In its discretionary denial briefing, Patent Owner disputes that "low molecular weight" "could vary based on the field of study and types of molecules" and that "the term has no objective boundaries to a POSA." Br. at 40. But Patent Owner's protestations only further demonstrate the lack of objective boundaries provided for one of skill in the art with respect to this phrase. *See Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014).

For example, Patent Owner and its declarant, Dr. VanBrocklin, assert that "low molecular weight" has a "well-understood, ordinary meaning in the field—namely compounds with a molecular weight of ***typically*** from about 50 Daltons to about 1,500 Daltons." Br. at 40 (emphasis added). But even here, Patent Owner uses the imprecise term "typically," in recognition of the inherent uncertainty in the phrase "low molecular weight."

Patent Owner also asserts that "low molecular weight" and "small molecule" are synonymous. *See, e.g.*, EX2001 at ¶ 41; Br. at 5 n.1. If taken as true, this casts even more uncertainty on the meaning of the phrase "low molecular weight." EX1025 at ¶ 19. Those working in the art and analogous fields have recognized that the term "small molecule" "means different things to different scientists and the meaning has also changed over time." Paul J. Trim et al., *Small Molecule MALDI MS Imaging: Current Technologies and Future Challenges*, 104 Methods 127, 129 (2016) ("Trim") (EX1028); EX1025 at ¶ 19. Indeed, definitions of "small molecule" vary throughout the prior art. *See, e.g.*, *id.* ("Here [small molecule] is taken to be any molecule with a molecular weight under 2000 g/mol in its native form."); Isotta Chimenti et al., *Biochemistry and Biology: Heart-to-heart to Investigate Cardiac Progenitor Cells*, 1830 Biochimica et Biophysica Acta 2459, 2465 (2013) ("Chimenti") (EX1029) ("A small molecule, in the fields of pharmacology and biochemistry, is a low molecular weight organic compound . . . . Their molecular weight is approximately 800 Da . . . ."); Erica J. Carbone et al., *Small Molecule Delivery Through Nonfibrous Scaffolds for Musculoskeletal Regenerative Engineering*, 19 Nanomedicine 1691 (Nov. 2014) ("Carbone") (EX1030) ("In biomedical sciences, small molecule refers to a non-peptide biologically active organic compound with a molecular size usually less than 1,000 Da."); *see also* EX1025 at ¶ 19.

The indefiniteness of the phrase "low molecular weight" is further demonstrated by Patent Owner's reliance on Pomper. *See* Br. at 40-41; EX2002 at ¶¶ 59-64; EX1025 at ¶¶ 20-23. Patent Owner does not assert that Pomper, which is incorporated by reference into the '201 patent, expressly defines "low molecular weight" as "about 50 Daltons to about 1,500 Daltons." Instead, Patent Owner points to 17 compounds disclosed in Pomper and having molecular weights between 642.3 and 1586.6 g/mol, and asserts that this confirms Patent Owner's proposed definition—with some heavy reliance on the word "about." *See* Br. at 40-41; EX2002 at ¶¶ 59-64. But Pomper does not expressly refer to these 17 compounds as "low molecular weight," nor does Pomper suggest that these 17 compounds are intended to exemplify "low molecular weight" compounds or that compounds having molecular weights above 1586.6 g/mol (or "about 1500 g/mol") could fall within the scope of Pomper's intended invention. EX1025 at ¶ 21.

Application of the various definitions in the art for the synonymous term "small molecule" to Pomper's example compounds demonstrates the lack of reasonable certainty that Section 112 demands. *Id.* at ¶ 22. For example, according to Chimenti's definition of the synonymous phrase "small molecule" as "less than 800 Da," only 2 of 17 Pomper compounds would be considered "low molecular weight." *See* EX1029 at 2465 (defining "small molecule" as less than 800 Da); EX2002 at ¶ 61; EX1025 at ¶ 22. Similarly, under Carbone's definition of "less than

1,000 Da," only 5 of 17 Pomper compounds would be considered "low molecular weight." *See* EX1030 at 2 (defining "small molecule" as less than 800 Da); EX2002 at ¶ 61; EX1025 at ¶ 22. And, under Trim's broader definition of "under 2000 g/mol," all 17 of Pomper's compounds would be considered "low molecular weight." EX1028; EX1025 at ¶ 22. Section 112 requires that a patent claim "must be precise enough to afford clear notice of what is claimed, thereby 'appris[ing] the public of what is still open to them.'" *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 909 (2014) (alteration in original) (quoting *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996)); *see also Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 369 (1938) ("The limits of a patent must be known for the protection of the patentee, the encouragement of the inventive genius of others, and the assurance that the subject of the patent will be dedicated ultimately to the public."). A skilled artisan, reading the claims of the '201 patent would be unable to make an informed and confident determination of what infringes and what does not. *See Interval Licensing*, 766 F.3d at 1371; *see also* EX1025 at ¶¶ 18-19, 22-23.

2. Ground I: Claims 1-3 Would Have Been Obvious Over Jansen I and/or Jansen II Taken In View of Zimmerman and Pomper

With respect to both obviousness grounds, Patent Owner first contends that because Petitioner and Dr. Martin applied a lower level of skill in the art, these

grounds "are weak on the merits." As discussed above, Petitioner disputes Patent Owner's proposed level of ordinary skill in the art and disputes that Dr. Martin does not meet Patent Owner's POSA standard. However, if Patent Owner's proposed level of skill is accepted, it would only strengthen the merits of Petitioner's obviousness grounds, as even more would be obvious to such a person. *See, e.g.*, *Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1338 (Fed. Cir. 2004) (holding that something rendered obvious to a person with less than ordinary skill is probative to what would be obvious to someone having ordinary skill in the art).

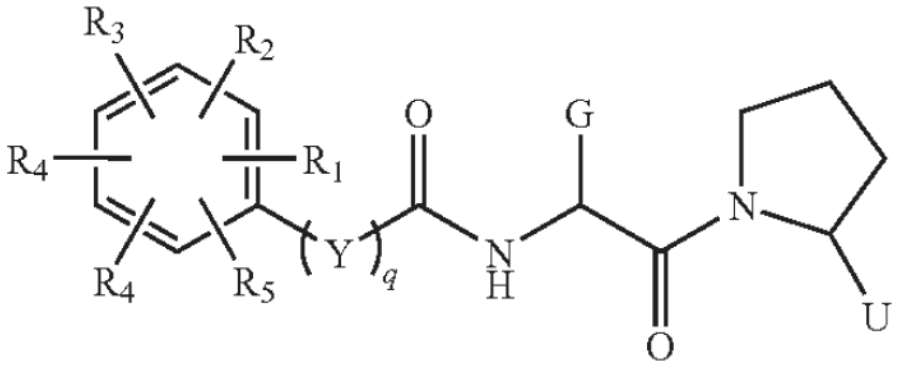
With respect to Ground I—the combination of Jansen I and/or Jansen II taken in view of Zimmerman and Pomper—Patent Owner does not dispute (1) that Zimmerman and Pomper both disclose low molecular weight compounds, to the extent the scope of that phrase can be ascertained; (2) that the claims are directed to "low molecular weight" compounds having the formula B-L-A; (3) that Jansen I and Jansen II disclose the claimed genus of A; and (4) that Zimmerman discloses components meeting the broad functional language specified in the claims for B and L. This, combined with the motivations for combining these references with a reasonable expectation of success as articulated in the Petition and Dr. Martin's declaration, is more than sufficient to establish a *prima facie* case of obviousness

justifying institution of PGR. *See* Pet. at 44-48; EX1002 at ¶¶ 112-14; EX1025 at ¶ 31.

The only rebuttal to this *prima facie* case that Patent Owner presents in its Brief in Support of Discretionary Denial is an assertion that Zimmerman discloses compounds of Formula I having linkers and compounds of Formula II without linkers, and that "Zimmerman's data show that compounds of Formula II without linkers exhibited overwhelmingly better FAP targeting properties." Br. at 49. But Patent Owner's reading of Zimmerman is flawed and overly narrow. EX1025 at ¶¶ 27-30.

As an initial matter, Dr. VanBrocklin's classification of the compounds of Formula II as being without linkers is erroneous. *Id.* at ¶ 28. As shown below, the genus of Zimmerman's Formula II includes a linker, as represented by at least the designation Y_q:

II



where:

U is —$B(OH)_2$, —CN, —CO_2H, or —$P(O)(OPh)_2$;

> G is H, alkyl, substituted alkyl, carboxyalkyl, heteroalkyl, aryl, heteroaryl, heterocycle, or arylalkyl;
>
> Y is a bond, —O—, —CH_2—, —OCH_2—, —CH_2O—, NR, —NR—CH_2, or CH_2—NR—, wherein R is H, Me or CH_2CO_2H;
>
> q is an integer ranging from 0 to 24; and
>
> R_1, R_2 , R_3 , R_4 and R_5 are independently hydrogen, halogen, cyano, carboxyl, alkyl, alkylamino, alkoxy, or substituted or unsubstituted amino, provided that at least one of R_1, R_2, R_3, R_4 and R_5 is a radiohalogen.

EX1009 at ¶¶ 111-17; EX1025 at ¶ 28. Zimmerman also teaches that "glycine and/or other appropriate amino acid can be incorporated as a linker," and Zimmerman's Scheme 4 depicts the synthesis of a functionalized proline-$M^+(CO)_3$ Complex utilizing an amino acid linker. EX1009 at ¶¶ 131-32; EX1025 at ¶ 28. Each compound included in Dr. VanBrocklin's Table 5—including all the compounds of Formula II in Table 5—include a glycine moiety. EX1025 at ¶ 28. This demonstrates that Dr. VanBrocklin's characterization of the compounds of Formula II is erroneous. *Id.*

The data relied upon by Patent Owner and Dr. VanBrocklin is also overstated. *Id.* at ¶¶ 27, 29. In support of Patent Owner's interpretation of Zimmerman, Dr. VanBrocklin asserts that ten of the eleven compounds with the highest reported affinities fall within Formula II. *See* EX2002 at ¶ 83. Implicit in this, however, is that one of the compounds with the highest affinities falls within Formula I

(Compound 1020; IC_{50} = 4 nM; fifth highest of compounds in Table 2).[3] *See* EX1009 at ¶ 185, Table 2; EX2002 at ¶ 83; EX1025 at ¶ 29. Additionally, other compounds with high reported affinities, such as Compound 1014 (IC_{50} = 21 nm) and Compound 1018 (IC_{50} = 20 nm), are of Formula I. *See* EX1009 at ¶ 185, Table 2; EX2002 at ¶ 83; EX1025 at ¶ 29. Moreover, several compounds of Formula II, including Compound 1061 (IC_{50} = 24,540 nm), Compound 1044 (IC_{50} = 23,680 nm), Compound 1048 (IC_{50} = 7,414 nm) have very poor affinities. EX1025 at ¶ 29.

Zimmerman does not expressly disparage compounds with linkers, of the compounds of Formula I, and the data is certainly not "overwhelmingly" in favor of the compounds of Formula I. *Id.* at ¶ 30. A POSA reading Zimmerman would understand that its disclosed linkers are viable and certainly would not have believed that Zimmerman taught away from using a linker. *Bayer Pharma AG v. Watson Lab'ys., Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017) ("[T]he teaching away inquiry does not focus on whether a person of ordinary skill in the art would have merely favored one disclosed option over another disclosed option."); *Syntex (U.S.A) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) ("[T]hat a particular

[3] Notably, a POSA would understand that the limitations of this *in vitro* assay, including experimental error, are such that one could not definitely determine whether Compound 1020 (IC_{50} = 4 nm) has lower affinity than the compounds such as 1025 (IC_{50} = 2 nm) or 1030 (IC_{50} = 2 nm).

combination is not a preferred embodiment does not teach away absent clear discouragement of that combination."); *see also* EX1025 at ¶ 30.

3. Ground II: Claims 1-3 Would Have Been Obvious In View of Dvořáková and Pomper

With respect to Ground II—the combination of Dvořáková and Pomper—Patent Owner's Brief only disputes the motivation to synthesize low molecular weight versions of Dvořáková's iBody. *See* Br. at 42-43. In support, Patent Owner asserts that "Dvořáková would have taught a POSA that iBody exhibited beneficial FAP targeting and imaging properties because it used multiple such moieties and a higher molecular weight linker, causing iBody to have high molecular weight." Br. at 43. But this is an improper reading of Dvořáková. EX1025 at ¶ 34. Dvořáková does not attribute its beneficial properties to its high molecular weight. *Id.* To the contrary, Dvořáková touts the "highly module and versatile" nature of the iBody. EX1008 at 8386; EX1025 at ¶ 34. Dvořáková also states that "conjugates containing virtually any desired compound can be easily prepared" and that "[i]mportantly, the molecular weight of the HMPA backbone can be easily adjusted to specifically tailor the pharmacokinetic properties." EX1008 at 8386; EX1025 at ¶ 34. These teachings in Dvořáková would not have taught away from low molecular weight compounds and, in fact, would have encouraged a POSA to take advantage of the high affinity FAP binding molecule, a linker, and an imaging or radiolabeled moiety to synthesize

and test a low molecular weight compound according to the teachings of Pomper. *See* Pet. at 60-62; EX1002 at ¶¶ 137-41; EX1025 at ¶ 34-35.

4. Ground III: The Claims Lack Enablement

Patent Owner's rebuttal to the Petition's Ground III focuses on the POSA standard applied by Petitioner and Dr. Martin. Br. at 43-44. As discussed above , Petitioner applied the correct standard and the analysis would not change even under Patent Owner's proposed standard. *See supra* Sections III.A.1-2.

Patent Owner also asserts that Petitioner did not "explain why or how the specification would have required the POSA to engage in 'countless lengthy, sometimes challenging' experimentation." Br. at 44. This is incorrect. The Petition discusses in detail the unpredictability of the art (Pet. at 80), the level of skill (Pet. at 80-81), and the insufficient level of guidance provided in the '201 patent (Pet. at 75-76, 80-82). *See also* EX1002 at ¶¶ 158-76.

Patent Owner also asserts that the Petitioner is flawed because it needs to point to an inoperable embodiment. Br. at 44. But this is legally incorrect. Indeed, the Supreme Court has cautioned against patents that provide nothing more than iterative, trial-and-error methods that call for POSAs to "engage in 'painstaking experimentation' to see what works" and what does not. *Amgen*, 598 U.S.at 614 (quoting *Consol. Elec. Light Co. v. McKeesport Light Co.*, 159 U.S. 465, 475 (1895)). That "is not enablement." *Id.*

Additionally, as discussed above, Patent Owner's proposed constructions of the claim terms "C(O)Alkyl" and "Aryl" are an erroneous and improper attempt to limit the vast number of compounds falling within the scope of the claimed genus. Because Patent Owner's enablement analysis is based on this improperly narrow interpretation of the claims, it should be given little to no weight at this stage, and the panel should be permitted to decide whether to institute based on the compelling merits of the Petition.

5. Ground IV: The Claims Lack Written Description

Like with Ground III (enablement), Patent Owner's rebuttal to the Petition's Ground IV (written description) focuses on the POSA standard applied by Petitioner and Dr. Martin (Br. at 45), and should be disregarded for the same reasons. *See supra* Section III.B.4.

Patent Owner further alleges that the analysis presented in the Petition is defective because "ITM and Dr. Martin fail to point out any 'B' or 'L' moieties that would not be suitable for the recited B-L-A compounds, and they again fail to point to even a single inoperative embodiment." Br. at 45. It is apparent from this argument that Patent Owner misunderstands the scope of its own claims and their Section 112 deficiencies. Because B and L are claimed with such broad, functional language, the scope of the claims is coterminous with the full universe of B and L moieties and effectively captures all feasible options at those positions. The breadth of these

claims, combined with the generic and insufficient guidance provided in the specification of the ’201 patent, fails to demonstrate that the inventors had possession of the claimed compounds. *See* Pet. at Section VII.D.

With respect to the guidance provided by the ’201 patent, Patent Owner asserts that the patent specification “provides multiple working examples.” Br. at 45. While it is technically true that the ’201 patent discloses “multiple working examples,” the ’201 patent and its ***two*** working examples clears this threshold by the thinnest of margins. Only two working examples, and in the absence of any additional guidance permitting a skilled artisan to determine what characteristics are most likely to meet to claimed functional language, is insufficient written description support given the vast breadth of the claims. *See* Pet. at Section VII.D.

6. Ground V: The Phrase “Low Molecular Weight” Is Indefinite

As discussed above in Section III.B.1.b, the meaning of the phrase “low molecular weight”—and the synonymous phrase “small molecule”—vary based on the field of study and the types of molecules. Even Patent Owner’s attempts to further define the phrase only introduce more uncertainty. *See supra* Section III.B.1.b. The definiteness requirement is clear: “When a claim term ‘depend[s] solely on the unrestrained, subjective opinion of a particular individual purportedly practicing the invention,’ without sufficient guidance in the specification to provide

objective direction to one of skill in the art, the term is indefinite." *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1260 (Fed. Cir. 2014) (alteration in original) (quoting *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1350 (Fed. Cir. 2005)).

7. Dr. Martin's Credible Opinions Further Support the Strength of the Petition's Merits

Patent Owner alleges that "Dr. Martin himself mostly parrots the language of the Petition" and that his opinions therefore show that the Petition's unpatentability grounds are weak. Br. at 47. But Patent Owner has reached the incorrect conclusion. Similarities between the Petition and Dr. Martin's declaration are not because Dr. Martin "parrots the language of the Petition," but because the Petition has incorporated the opinions upon which it relies. All that Patent Owner has established is that the Petition is well supported by credible expert testimony.

Indeed, the rules governing the conduct of AIA trial proceedings prohibit incorporating expert testimony by reference and encourage expert testimony to be integrated into petitions, as Petitioner has done. *See* 37 C.F.R. § 42.6(a)(3); PTAB, *Consolidated Trial Practice Guide* at 35 (Nov. 2019). Moreover, this is common practice, as evidenced by a comparison of Patent Owner's Preliminary Response (POPR) and Dr. VanBrocklin's declaration submitted in support (EX2002):

Level of Ordinary Skill

Patent Owner Preliminary Response	Dr. VanBrocklin's Declaration
"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)." POPR at 6.	**"[T]he '201 patent explicitly 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.'** EX1001, Abstract. The '201 patent also contains significant description regarding nuclear imaging and radiotherapy from the research lab to the clinic, and the '201 patent **cites numerous references relating to imaging and radiotherapy.** EX1001, 62:20-64:38. For example, more than 10 references cited plainly relate to radiopharmaceutical development, targeted imaging or radiotherapeutics in their title. EX1001, 62:20-64:38

	(containing more than 10 references mentioning PET, SPECT, or other imaging techniques in their titles); EX1001, 62:20-64:38." EX2002 at ¶ 23.
"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**	"[A] POSA for the '201 patent would have an advanced degree, typically a Ph.D. and/or an M.D., and also have **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). This training and experience would involve developing and evaluating**

emission computed tomography). EX2002, ¶28. **This training and experience would have involved developing and evaluating agents for biomedical imaging or radiopharmaceuticals, and using molecular imaging techniques.** *Id.*" POPR at 6-7.	**agents for biomedical imaging or radiopharmaceuticals, and using molecular imaging techniques.**" EX2002 at ¶ 28.

Claim Construction

Patent Owner Preliminary Response	**Dr. VanBrocklin's Declaration**
"**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**	"**The only functional language that appears in the claims is with regard to the "B" and "L" subgroups**: **'B' as 'any optical or radiolabeled functional group suitable for** optical imaging, positron emission tomography (PET) imaging, singlephoton emission computed tomography (SPECT) imaging, or radiotherapy' and **'L' as a**

to form a chemical bond with B and A.' EX1001, 46-47; EX2002, ¶46." POPR at 15.	**'linker having bi-functionalization adapted to form a chemical bond with B and A.'** EX1001, Certificate of Correction, 1-2." EX2002 at ¶ 46.
"**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 . . . ." POPR at 17.	"**And during the prosecution history** of the '201 patent, one of the inventors, Dr. Pomper, **defined the invention in structural terms over the cited prior art, citing the structural feature of 'low molecular weight.'** EX1004, 1196-97 (Pomper Declaration)." EX2002 at ¶ 52.
"**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*	"**A POSA, thus, would have looked to the Jansen FAP-α documents to understand the meaning of "C(O)alkyl" and "C(O)aryl" in the context of the claimed R_{3x} substituent.**" EX2002 at ¶ 58.

length, size, and substitution. EX2002, ¶58; EX1007, 22:13-43." POPR at 19.	
"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*." POPR at 73.	"Dr. Martin argues that '[t]he '201 patent also fails to provide any additional guidance permitting a POSA to determine what characteristics are most likely to meet these functional limitations [for the B and L moieties].' EX1002, ¶178. However, **Dr. Martin fails to provide any evidence to show that such teaching would be necessary** for a POSA to understand that the specification describes the claimed invention, **nor does he point out any "B" or "L" groups that allegedly would not perform imaging/therapeutic or linking functions, respectively**." EX2002 at ¶ 118.

Grounds I & II

Patent Owner Preliminary Response	**Dr. VanBrocklin's Declaration**
"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. . . . But POSAs would not have removed the substituent because Jansen II teaches that removal would likely *destroy* the compound's beneficial selectivity." POPR at 44-45.	"Furthermore, if a POSA would have selected one of the better performing compounds from Jansen I/Jansen II, such as compounds 22 or 23 from Jansen I, or compound 25 from Jansen II, **to arrive at the claimed invention, the POSA would have then had to remove the substituent first, before adding the linker and 'B' moiety**. . . . **Removing the substituent completely from this position (Jansen II compound 7) destroys selectivity**. . . ." EX2002 at ¶ 93-94.
"Dr. Martin's declaration also **fail[s] to provide any explanation for why POSAs would have reasonably**	"Dr. Martin **fails to explain why a POSA would have reasonably expected that combining the different**

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." POPR at 48.	**FAPis , radiolabeled groups, and linkers** disclosed in Jansen I, Jansen II, Zimmerman, and Pomper **could even have been done without the guidance in the patent**, or would have resulted in the claimed compounds." EX2002 at ¶ 96.
"**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,**	"**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 comparisons to Zimmerman**. EX1004, 1195-1206. **According to Dr. Pomper, '[s]urprisingly, the specificity of the**

'[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." POPR at 58-59.	**compounds covered by the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds' in the prior art**. EX1004, 1195-1206. In fact, as reported by Dr. Pomper, **some of the claimed FAPi compounds had a FAP selectivity *five* orders of magnitude higher than that of the prior art, reference compounds**. EX1004, 1195-1206. **The 'higher specificity of the compounds' was an unexpected and highly beneficial result over the prior art, showing nonobviousness of the claimed invention**. EX1004, 1195-1206." EX2002 at ¶ 108.

Grounds III & IV

Patent Owner Preliminary Response	Dr. VanBrocklin's Declaration
"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.*" POPR at 62.	"Dr. Martin's **written description analysis solely depends on whether the '201 patent provides sufficient description for 'the broad functional language recited in the claims.'** EX1002, ¶¶177-178. . . . **But as explained in Section VII.A above, the claims recite low molecular weight compounds that are defined structurally, having formula B-L-A. It is only the specific "B" and "L" moieties that must be selected based on their individual functional characteristics—i.e., suitability for imaging/radiotherapy and bifunctionalization adapted to form a chemical bond between A and B,**

	respectively. EX1001, 46-47." EX2002 at ¶ 112.

Ground V

Patent Owner Preliminary Response	**Dr. VanBrocklin's Declaration**
"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." POPR at 24; *see also id.* at 26.	"**A POSA would have understood the term 'low molecular weight' to have its well-accepted, plain and ordinary meaning in the field: compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons.**" EX2002 at ¶ 60.
"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**	"In light of this disclosure, a POSA would have understood the meaning of the term 'low molecular weight' as referring to compounds with a **molecular weight of typically from**

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." POPR at 27.	**about 50 Daltons to about 1,5000 Daltons**, even under Dr. Martin's wrong POSA definition. It then follows that Dr. Martin fails to show that the '201 patent claims are indefinite, as a **POSA would readily have been able to understand the bounds of the claimed invention as compounds of the formula B-L-A from about 50 to about 1,500 Daltons, and that a compound with higher molecular weight than about 1,500 Daltons would fall outside the scope of the claims**." EX2002 at ¶ 66.
"**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**	"In addition, **given the high precision of analytical techniques that a POSA under either** Dr. Martin's or my **definition would have known how to use, such as mass spectrometry,**

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." POPR at 30.	EX2013, 5-8, **a POSA would have had no trouble determining the molecular weight of a given B-L-A compound to see if it falls under the typical about 50 to about 1,500 Da scope of 'low molecular weight.**'" EX2002 at ¶ 66.

Patent Owner attempts to hold Petitioner to a higher standard than even itself has met in this proceeding. Dr. Martin's opinions are credible, supported, reasoned, and not conclusory. Patent Owner's baseless attempts to disparage Dr. Martin's opinions instead of responding to the substance of those opinions demonstrates the strength of the merits of the Petition and reinforces why the Director should not discretionarily deny institution here.

IV. COMPELLING ECONOMIC, PUBLIC HEALTH, AND NATIONAL INTERESTS STRONGLY FAVOR INSTITUTION

The public and economic policies of fostering innovation and decreasing drug prices through competition, particularly in view of the overly broad and obvious claims present in the '201 patent, strongly weighs against the Director exercising its discretion to deny institution.

"[T]he patent system represents a carefully crafted bargain that encourages both the creation and the public disclosure of new and useful advances in technology,

in return for an exclusive monopoly for a limited period of time." *Pfaff v. Wells Elecs., Inc*., 525 U.S. 55, 63 (1998). The patent claims at issue here do not comport with the patent bargain. Patent Owner made the choice to seek a monopoly over compounds comprising the obvious combination of three known elements, two of which are claimed using broad functional language. Moreover, Patent Owner has not invented all compounds that perform these two claimed functions; instead it has, at most, discovered and disclosed only a handful of them. Nonetheless, it seeks a decades-long monopoly over every compound falling within the broad claims of the '201 patent. Patent Owner's gambit must be rejected because the '201 patent does not meet the requirements of § 103 or § 112 and its overbroad claims deprive the public—specifically, American patients—of access to valuable medical innovations. The public has an interest in ensuring that patents confer monopolies on novel, non-obvious inventions—and nothing more.

Innovative pharmaceutical companies, like Petitioner, expend considerable time, effort, and resources on research and development to find the most effective treatments. These innovative companies not only provide consumers with improved products, but also save consumers money by increasing competition in drug markets. Overbroad patents allow their owners to suppress competition by discouraging potential competitors from developing alternative, competing treatments for fear of

potential infringement, thereby raising costs for consumers and often depriving them of access to potentially lifesaving treatments.

Recognizing these externalities, on April 18, 2025, the White House issued Executive Order 14273 titled "Lowering Drug Prices by Once Again Putting Americans First." EX 1031. The Executive Order states that "[i]t is the policy of the United States that Federal health care programs, intellectual property protections, and safety regulations are optimized to provide access to prescription drugs at lower costs to American patients and taxpayers." *Id*. at Section 2.

Similarly, Senators Amy Klobuchar (D-MN) and Chuck Grassley (R-IA), Chairman of the Senate Judiciary Committee, introduced two bipartisan bills to reduce drug prices by promoting competition. EX1032. In support of this proposed legislations, Senator Klobuchar explains that "[p]rescription drug prices are too high—driven up by excessive consolidation in the pharmaceutical industry and abusive business tactics that keep more affordable medications off the market and out of reach for far too many Americans." *Id*. at 1. Senator Grassley also asserted: "The shady efforts of some drug companies to block competition and keep drug costs high are greedy and wrong. Across the country, consumers are suffering because of it. Our bipartisan bills will help tackle these abuses and make prescription drugs more affordable for Americans." *Id.*

Although the White House's Executive Order and these legislative efforts are primarily focused on generic and biosimilar pharmaceutical products, they also support a public and economic policy of enabling innovative competitors—like Petitioner—to enter the market. Denying institution in situations like this only encourages entities like the Patent Owner to seek overly-broad patents directed to obvious combinations of the prior art with the knowledge that they can avoid PTAB scrutiny of dubious claims and discourage competitors.

Petitioner is a leading international radiopharmaceutical theranostics company with an established expertise in developing and providing radionuclide therapies and diagnostics to patients in need. EX1033 at 1. Petitioner's extensive research and development efforts have led to the discovery of ITM-74, an innovative diagnostic radiopharmaceutical. EX1034. ITM-74 is currently in phase 1 clinical trials, as Petitioner seeks FDA approval to market ITM-74 in the United States. In anticipation of Petitioner's increased activities in the United States, including the marketing of ITM-74 if approved by FDA, Petitioner recently opened its United States headquarters in Princeton, New Jersey. EX1033 at 1. Petitioner's United States headquarters will further strengthen Petitioner's capabilities to serve the American healthcare community and American consumers, while creating jobs in the domestic pharmaceutical industry. *Id.*

Patent Owner's discretionary denial brief vastly overstates the economic and national interests implicated by the '201 patent. While Petitioner does not dispute that Patent Owner is a large and accomplished university and research institution, the '201 patent is not, as Patent Owner insinuates, essential to the financial well-being of JHU and the State of Maryland. Patent Owner points to JHU's total employment, estimated economic impact, and awards won by JHU associates, Br. at 60, yet Patent Owner fails to even attempt to apportion any of these figures to the '201 patent, as opposed to the thousands of other patents owned by Patent Owner or Patent Owner's numerous other activities. The reason for this is obvious—the public interests implicated by the '201 patent alone are minimal. Indeed, Patent Owner does not identify a single commercial product—actual or planned—that embodies the '201 patent claims. Moreover, despite Patent Owner's attempted characterization of Petitioner as a "foreign actor," Patent Owner neglects to mention that at least one of the '201 patent's licensees—Bracco S.p.A.—is itself an Italian company headquartered in Milan. EX1035.

For the reasons articulated in the Petition and herein, the '201 patent claims nothing more than an obvious combination of known elements in a way that fails to comply with § 112's requirements. The public and economic policies of increasing patient access to innovative pharmaceutical products while decreasing prices

through competition strongly weighs against the Director exercising its discretion to deny institution here.

V. OTHER FACTORS

In addition to the factors discussed above, additional factors weigh against discretionary denial, including whether the PTAB or another forum has already adjudicated the validity or patentability of the challenged claims and the settled expectations of the parties, such as the length of time the claims have been in force.

First, aside from the Office's initial determination of patentability during examination as addressed under the *Advanced Bionics* framework in Section II above, neither the PTAB nor another forum have already adjudicated, or are currently adjudicating,[4] the validity or patentability of the '201 patent's claims. Thus, the administrative concerns as considered in *General Plastic* are inapplicable here. *General Plastic* at 9-10 (considering, *inter alia*, the finite resources of the Board). Likewise, those same concerns as considered in *Fintiv* are similarly inapplicable. *Fintiv* at 6 (describing issues of efficiency and fairness implicated by parallel proceedings which may warrant discretionary denial).

[4] IPR2025-00808, filed March 28, 2025 by a petitioner with no relationship with the real parties of interest here and challenging the '201 patent on materially different grounds, is currently stayed pending resolution of the present proceeding. IPR2025-00808, EX3101 (May 2, 2025).

Second, the claims of the ’201 patent have only been in force since March 26, 2024. Given this short lifetime, Patent Owner cannot reasonably be said to have any settled expectations surrounding the ’201 patent, nor has it asserted otherwise. This is consistent with Congress’s expectations when creating the post-grant review process: the PGR window was “designed as an extension of the examination process” and was intended to balance concerns of patent owner’s certainty with the need for valid patents. *See* S. Rep. No. 110-259, at 20-21 (2008) (discussing AIA’s predecessor Patent Reform Act of 2007). Thus, the America Invents Act created PGRs as a “streamlined mechanism for third parties who want to challenge recently issued, low-quality patents that should never have been issued in the first place.” 157 Cong. Rec. S1034, at 1036-37 (2011) (statement of Sen. Amy Klobuchar). “No patent holder has a right to an invalid patent, however long that patent holder may have enjoyed that right inappropriately.” S. Rep. No. 110-259, at 21. And where, as here, that misgiven right has only been enjoyed for a short period, no minimal amount of Patent Owner certainty should outweigh Petitioner’s interest in review of an invalid patent.

VI. CONCLUSION

For the reasons discussed above, the Director should not exercise its discretion to deny institution of PGR here.

Respectfully submitted,

Dated: May 28, 2025 By: /David M. Kohn/

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CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

The undersigned hereby certifies that the foregoing **PETITIONER'S OPPOSITION TO PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL OF INSTITUTION** contains 13,982 words as measured by the word-processing system used to prepare this paper, and is in compliance with the word limit set forth in 37 C.F.R. § 42.24.

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CERTIFICATE OF SERVICE

The undersigned certifies that on May 28, 2025, a copy of the foregoing **PETITIONER'S OPPOSITION TO PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL AND EXHIBITS 1025 TO 1035** have been served on Patent Owner's counsel of record via electronic mail as follows:

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