

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GE Healthcare Ltd.,
Petitioner,

v.

Johns Hopkins University,
Patent Owner.

Case No. PGR2025-00059
U.S. Patent No. 12,115,233

PETITIONER'S REPLY

Table of Contents

I.	INTRODUCTION	1
II.	ALL CLAIMS ARE OBVIOUS	1
A.	Prior Art, Not Hindsight, Made Compound 60-Based B-L-A Radiotracers Obvious	2
B.	[REDACTED]	
	[REDACTED]	
1.	<i>Dr. Pomper and JHU Inflate Selectivity by Using the Wrong Comparator Compounds.....</i>	<i>7</i>
2.	[REDACTED]	
	[REDACTED]	
a)	[REDACTED]	11
b)	[REDACTED]	13
3.	[REDACTED]	18
C.	Disregard JHU's Mischaracterizations	21
III.	ALL CLAIMS ARE UNPATENTABLE UNDER § 112.....	21
A.	The Claims Require Compounds that Selectively Bind FAP	21
B.	The Claims Are Broad and Diverse,, the Disclosure Thin and Prophetic	25
C.	The Claims Are Not Enabled.....	27
1.	<i>The '233 Patent Provides No Guidance on the Vast Majority of Targeting Moieties Being Claimed.....</i>	<i>29</i>
2.	<i>The Disclosure Provides No Guidance on Overcoming Admitted Uncertainty.....</i>	<i>30</i>
3.	<i>The Scale of Experimentation Is Undue</i>	<i>31</i>
D.	The Claims Lack Written Description	33

1.	<i>No Common Structure or Representative Species</i>	34
2.	<i>The Claims Cover Non-Described Species JHU Maintains Are Patentably Distinct</i>	36
IV.	CONCLUSION	38

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Abbvie Deutschland GMBH & Co. v. Janssen Biotech, Inc.</i> , 759 F.3d 1285 (Fed. Cir. 2014)	33, 35
<i>Amgen Inc. v. Sanofi</i> , 598 U.S. 594 (2023)	25, 31
<i>Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010)	33
<i>Duke University v. Sandoz Inc.</i> , 160 F.4th 1305 (Fed. Cir. 2025)	33
<i>Fox Factory, Inc. v. SRAM, LLC</i> , 944 F.3d 1366 (Fed. Cir. 2019)	18, 21
<i>Fujikawa v. Wattanasin</i> , 93 F.3d 1559 (Fed. Cir. 1996)	34
<i>Regents v. University of Minnesota v. Gilead Sciences, Inc.</i> , 61 F.4th 1350 (Fed. Cir. 2023)	33, 34, 35
<i>WBIP, LLC v. Kohler Co.</i> , 829 F.3d 1317 (Fed. Cir. 2016)	18

I. Introduction

Patent Owner Johns Hopkins University (“JHU”) responds to the grounds with misdirection, mischaracterizations, and obstruction. It has no credible response on the merits. All claims are unpatentable.

II. All Claims Are Obvious¹

JHU contends that:²

- (i) the idea of arranging the targeting (“A”), imaging (“B”) and linker (“L”) moieties of a 3-component radiotracer into the “B-L-A” order was somehow inventive in 2017, and that Petitioner resorted to hindsight to arrive at Compound 60-based radiotracers that render the claims obvious, and
- (ii) B-L-A forms of an “A” moieties confer “unexpected” orders-of-magnitude increases in FAP selectivity.

Each point is false. The *prior art* made Compound 60-based B-L-A radiotracers obvious, [REDACTED]

[REDACTED]

[REDACTED]

¹ Claim construction (§ **Error! Reference source not found.**) is only implicated for the § 112 grounds.

² POR, 1-2, 51-54.

A. Prior Art, Not Hindsight, Made Compound 60-Based B-L-A Radiotracers Obvious

Dr. Zeglis identified *specific examples* of FAP-targeting radiotracers of B-L-A design made obvious from two sets of publications.³ Each meets every claim requirement.⁴ Dr. VanBrocklin agreed a POSA would have expected those examples to retain FAP binding, the only thing he believes the claims require.⁵ These facts are fatal to JHU’s response on obviousness.

First, US-633 taught FAP-targeting B-L-A radiotracers that combine well-known chelators or prosthetic groups [“B” moieties] with “short [PEG] diamine[]” linkers (*e.g.*, NH₂-(PEG)₃-NH₂) [“L” moieties] but used a targeting moiety Meletta taught was insufficiently selective.⁶ Jansen solved that problem with its highly FAP-selective Compound 60 [“A” moiety], showcased in a 2014 paper.⁷ Together, US-633, Meletta and Jansen render obvious several *specific* FAP-binding B-L-A radiotracers within the claim scope:⁸

³ EX1003, §§ IV.H, V.E; Pet., 77-78, 102-104.

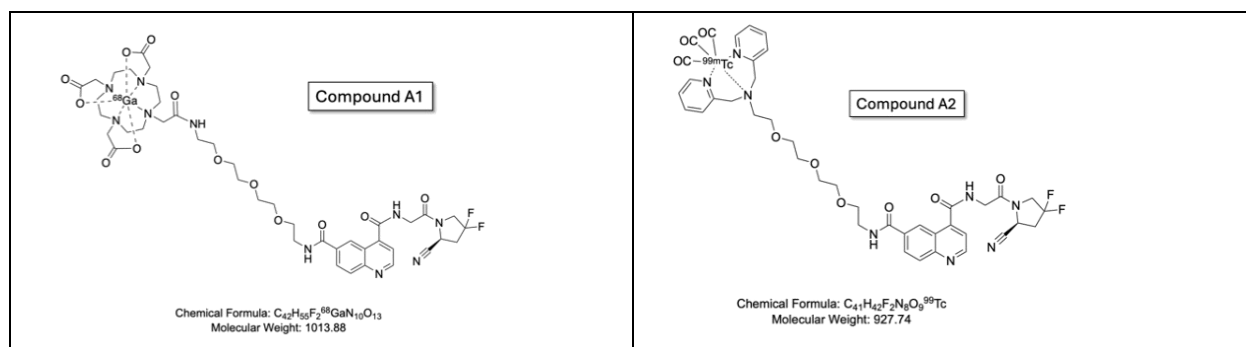
⁴ Pet., 77-85, 102-107; EX1003, ¶¶ 198-204, 241-245.

⁵ EX1069, 240:19-241:6, 237:12-238:11; EX1003, ¶ 205. *See also* § **Error! Reference source not found..**

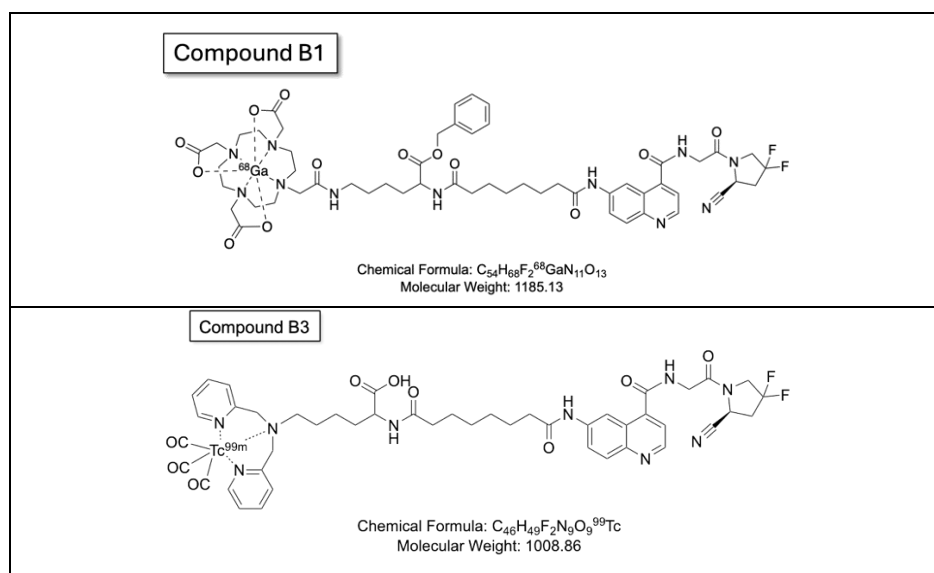
⁶ EX1003, ¶¶ 110-112, 117-121, 128, 131-135, 167, 180-191; EX1004, [0100], [0133], [0175]; EX1008, 2087-90.

⁷ EX1006, Abstract, 3062; EX1003, ¶¶ 146, 149.

⁸ Pet., 77-80; EX1003 ¶¶ 182-194.



Second, US-121 taught PSMA-targeting radiotracers with B-L structures useful for tumor imaging, and Jansen motivated adaptation of them to use Compound 60 to produce tumor imaging radiotracers that target FAP.⁹ Again, together they made obvious *specific* FAP-targeting B-L-A radiotracers being claimed:¹⁰



JHU responds first with misdirection, contending POSAs would have used

⁹ Pet. 87-90; EX1003, ¶¶ 233, 235; EX1070, ¶¶ 171-174.

¹⁰ Pet. 102-104.

antibodies, not small molecules, in FAP radiotracers.¹¹ The record uniformly refutes this theory.

- ***The prior art in the grounds*** (*i.e.*, US-633 and US-121) expressly taught use of small molecules as targeting moieties in B-L-A radiotracers for tumor imaging (including FAP targeting) ***5 to 7 years before*** the patent's earliest priority date.¹²
- The specification and Dr. VanBrocklin's ***pre-2017*** publications confirm what POSAs knew by 2017—small molecules had numerous advantages over antibodies for radiotracers (*e.g.*, better pharmacokinetics, easier manufacture, superior tumor penetration and accuracy).¹³

By October 2017, ***nearly every*** FDA-approved antibody-based radiotracer had been ***withdrawn from market***.¹⁴ Dr. VanBrocklin makes no mention of those product withdrawals, despite being aware of them.¹⁵

JHU next depicts a serendipitous path through the prior art, contending it would lead POSAs away from Compound 60 (but would still arrive at Jansen's

¹¹ POR, 12–14; EX2029, ¶¶ 58–61.

¹² Pet., 27, 87; EX1003, ¶¶ 40, 99, 105, 209-210, 212.

¹³ EX1001, 1:43-61; EX1065, 780-781; EX1069, 138:1-139:8; 143:2-144:13.

¹⁴ EX1070, ¶ 136, Appendix B.

¹⁵ EX1069, 145:5-146:9.

highest-selectivity FAP inhibitors).¹⁶ But Dr. VanBrocklin conceded ***Compound 60 is on that list of high-selectivity inhibitors.***¹⁷ And JHU ignores that Jansen (unlike JHU) ***actually traversed that path and arrived at Compound 60.***¹⁸ In **2017**, the POSA did not have to start where Jansen did in **2009**. And JHU makes no attempt to reconcile their **2026** theories with Jansen’s **2014** identification of Compound 60 as one of its “most promising FAP inhibitors.”¹⁹

Petitioner and Dr. Zeglis explained ***why*** POSAs would have focused on Compound 60.²⁰ First, it is ***literally showcased*** in Jansen’s abstract.²¹ Second, Jansen identifies numerous attributes that made it a compelling candidate for radiotracers, including (i) high selectivity for FAP over PREP, (ii) physiological stability, (iii) amenability to conjugation, and (iv) highly favorable pharmacokinetics (“the most extensive and prolonged inhibition of FAP in the PK studies”).²² In fact, Compound 60 checks every box of Dr. Pomper’s list of

¹⁶ POR, 27-28; EX2029, ¶¶ 71-79, 86-87.

¹⁷ EX1069, 183:6-184:22; EX2029, ¶ 88.

¹⁸ EX1006, 3053, 3063-65; EX1003, ¶¶ 144-149; Pet. 52-58, 65; POR, 20-25.

¹⁹ EX1006, 3064; EX1003, ¶ 147.

²⁰ Pet. 62-67; EX1003, ¶¶ 149-152, 161, 167-168.

²¹ Pet. 52; EX1006, Abstract, 3053; EX1003, ¶ 146; EX1070, ¶141.

²² EX1006, 3062-64; EX1003, ¶¶ 146, 156-60, 178; EX1070, ¶ 141.

“important parameters” for successful FAP radiotracers.²³

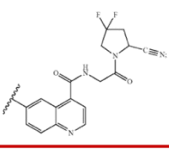
Jansen’s showcasing of Compound 60 was successful—it led *JHU in 2017* to incorporate Jansen wholesale into the disclosure and use Compound 60 as one of its two “A” examples.²⁴ Dr. VanBrocklin also includes Compound 60 in his table of “*Top prior-art FAPIs, ranked by selectivity....*”²⁵ Apparently being the 6th highest-performing FAP inhibitor is not enough for Dr. VanBrocklin. But to a POSA, Compound 60 was a *compelling* choice.²⁶

(10) Patent No.: **US 12,115,233 B2**
(45) Date of Patent: ***Oct. 15, 2024**

disclosed subject matter pertains. All publications, patent applications, patents, and other references (e.g., websites, databases, etc.) mentioned in the specification are herein incorporated by reference in their entirety to the same extent

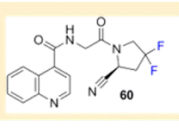
Jansen K, Heirbaut L, Verkerk R, Cheng J D, Joossens J, Costein (FAP). *J Med Chem.* 2014 Apr. 10; 57(7):3053-74.

In more particular embodiments, A is selected from the group consisting of:



Journal of Medicinal Chemistry

dx.doi.org/10.1021/jm500031w | J. Med. Chem. 2014, 57, 3053–3074



60

Top prior-art FAPIs, ranked by selectivity in Jansen, US-650, Jansen 2013, and Jansen 2014.

Compound Number	Structure	FAP Affinity (pM)	FAP Selectivity	Fall within scope of claimed "A" structure?
1 US 650: 22 Jansen 2013: 26 Jansen: 5		0.011	>4500	N
2 US 650: 23 Jansen: 53		0.0043	2100	N
3 US 650: 21 Jansen 2013: 25		0.0099	1700	N
4 US 650: 24 Jansen: 61		0.0085	970	N
5 US 650: 11 Jansen 2013: 30		0.0092	677	N
6 US 650: 1 Jansen: 60		0.0032	562	Y

B.

²³ EX1002, 172 (¶¶31); EX1070, ¶¶ 23, 141.

²⁴ EX1001, 13:33-14:15, 62:31-36, Claim 1; EX1006, Abstract, 3063-65; EX1070, ¶¶ 124-125; EX1003, ¶¶ 202-203; Pet., 69; EX1069, 92:12-93:4, 184:13-22.

²⁵ EX2029, ¶¶ 88-89.

²⁶ EX1003 ¶¶ 149, 161; EX1070, ¶ 141; Pet. 65-67.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

1. Dr. Pomper and JHU Inflate Selectivity by Using the Wrong Comparator Compounds

Dr. Pomper's § 1.132 declaration portrays test results for eleven B-L-A compounds relative to eight "A" compounds as showing "surprising" selectivity increases due to the "B-L-A" design.²⁹ But the "A" compounds used to paint this picture were all *low-selectivity compounds* (3-403, mean of 41); using them as comparators inflated the perceived selectivity increases of the other compounds.³⁰ That is not a surprise. It is math.

Notably, Dr. Pomper omitted Compound 8's selectivity value (**407**) when he told the PTO the *lowest* selectivity index ("SI") value for his 11 compounds

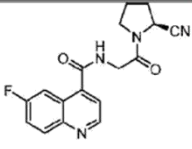
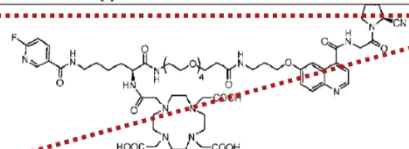
²⁷ EX1070, ¶¶ 27-31, 91, 93, 101, 104-110, 116; *generally* §§ III-IV.

²⁸ EX1070, 111-12, 116; Paper 19.

²⁹ EX1002, 176.

³⁰ EX1070, ¶ 101.

claimed compounds was **779** (below).³¹ That omission suggested a non-existent numerical separation between the Reference Compounds and *all* the Representative Compounds.³² But Compound D's (**403**) selectivity is indistinguishable from Compound 8's (**407**) (*i.e.*, 1.0099).³³

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	403		407
Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for the representative compounds			

EX1002, 175-176

JHU and Dr. VanBrocklin amplify this distortion. They compare Dr. Pomper's 11 compounds to another low-selectivity "A" compound (Compound 7 of Jansen-2013) and contend it shows that B-L-A forms of A compounds "unexpectedly" demonstrate selectivity increases "several orders of magnitude greater than the ... corresponding "A" compounds alone.³⁴

But Compound 7 is *not* the correct comparator—**Compound 30** of Jansen-2013 is. As Dr. Zeglis explains, Compound 30 contains the same alkoxy substitution at position 6 of the quinolinyl ring found in *every* Pomper Compound

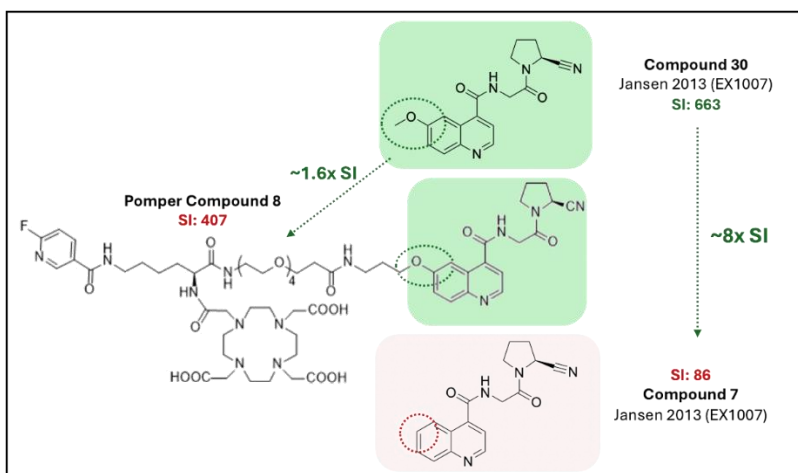
³¹ EX1002, 174 (¶ 42).

³² POR, 49-50; EX2029, ¶¶ 118; EX1070, ¶¶ 28, 101, 108.

³³ EX1002, 175-176; EX1070, ¶¶ 28, 101.

³⁴ EX2029, ¶¶ 116-118, 123; POR, 49-52.

(below, green).³⁵



Critically, this *one change alone* increases FAP selectivity *nearly 8-fold* over compound 7 (*i.e.*, 663 vs. 86).³⁶ Compound 30 also exhibits *1.6 times* the selectivity of *Pomper Compound 8*, a *B-L-A form of Compound 30*, and all 8 Pomper Reference Compounds have a fraction of Compound 30’s selectivity (below).³⁷

	Compound 30	Compound 7	Pomper Reference Compounds							
			A	B	C	D	E	F	G	H
SI (PREP/FAP)	663	86	32	152	20	403	15.70	241	17	3
% of Compound 30 SI	100%	13.0%	4.8%	22.9%	3.0%	60.8%	2.4%	36.3%	2.6%	0.5%

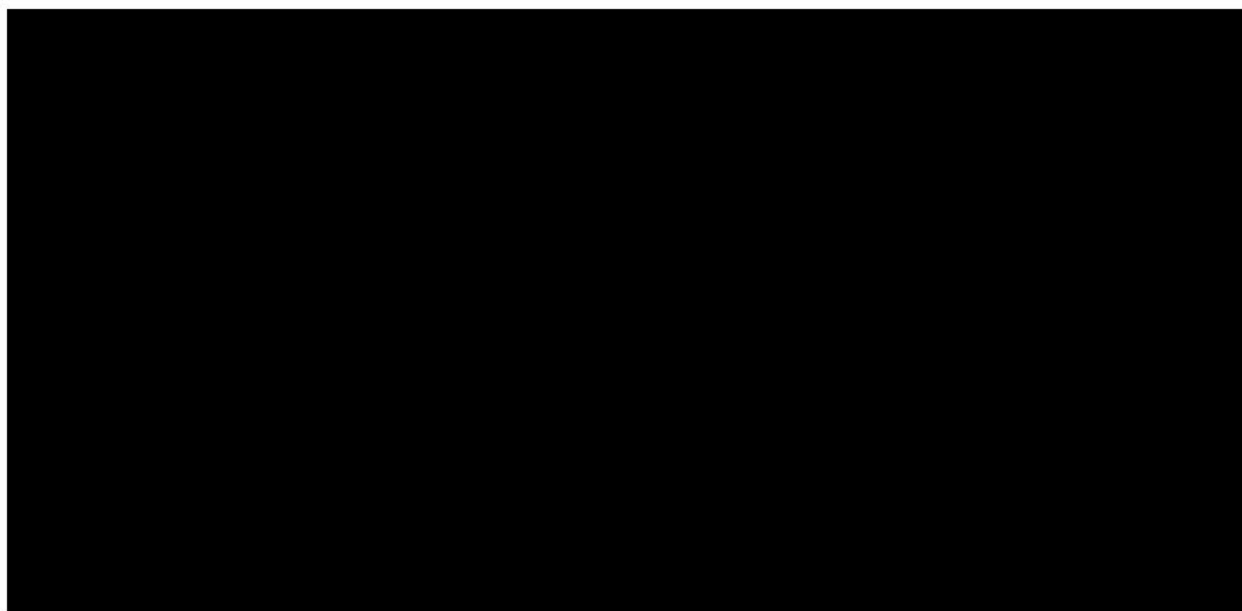
Measuring the Pomper Compounds against *any* of Jansen’s “higher selectivity” A moieties destroys JHU’s “B-L-A always increases selectivity of A”

³⁵ EX1070, ¶¶ 103-105; EX1007, 493.

³⁶ EX1007, 493; EX1070, ¶ 104.

³⁷ EX1070, ¶¶ 101, 107-108.

narrative (below, red = $SI_A > SI_{B-L-A}$).³⁸



It is a substantial oversight for Dr. VanBrocklin to not use Compound 30 as the comparator in his analysis.³⁹ He does not reveal why he ignored it. He certainly was familiar with Compound 30—it is on his list of “Top prior-art FAPis” and, relative to Compound 60, he said “...*Compound 30 of Jansen 2013*[/exhibit[s] *superior selectivity and affinity for FAP.*”⁴⁰ Using a compound known to be *less selective* and *less chemically relevant* perpetuates the false impression that B-L-A compounds are uniformly more active than A compounds

³⁸ EX1070, ¶¶ 107, 109. [REDACTED]

³⁹ EX1070, ¶¶ 104-106, 108-109.

⁴⁰ EX2029, ¶¶ 88-89.

alone.⁴¹

2.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

a)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁴¹ EX1070, ¶¶ 104, 106, 108, 111-112; Appendix C-1.

⁴² Paper 19; EX1070, ¶¶ 82-89, 111-112.

⁴³ EX1070, ¶¶ 111-112, 116; EX1057, 134-141 (Table 3), 141-143 (Table 4), Appx. C-9.

⁴⁴ EX1070, ¶¶ 94-96, 111-112, 116-117.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁴⁵ EX1070, ¶¶ 111-112, Appx. C-3, C-9.

⁴⁶ EX1070, ¶¶ 69-75, 110-112, 118, Appx. C-4.

[REDACTED]

⁴⁹ EX1070, ¶ 76.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(iv) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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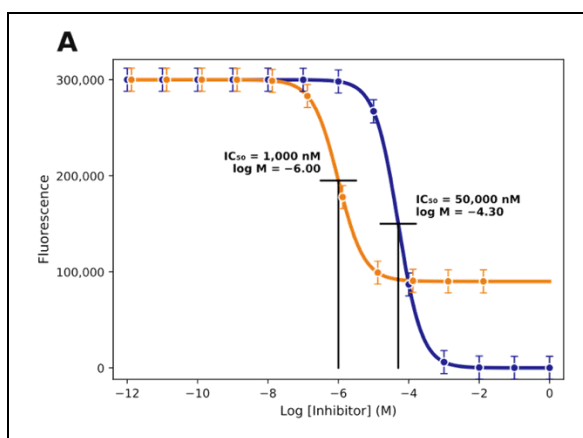
⁵⁰ EX1070, ¶¶ 58-61, 64-66, 70.

⁵¹ EX1070, ¶¶ 67, 72.

⁵² EX1070, ¶¶ 80-90.

⁵³ EX1070, ¶¶ 77-79, 82, 90.

(i)



(ii)

⁵⁴ EX1070, ¶¶ 58-60, 69-75, 87.

[REDACTED]

(iii) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED],

[REDACTED]

⁵⁵ EX1070, ¶¶ 87 & n.116.

⁵⁶ EX1070, ¶ 91.

⁵⁷ EX1070, ¶¶ 91, 110.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Dr. VanBrocklin did not review *any* experimental records before signing his

⁵⁸ EX1070, ¶¶ 75, 111.

declaration.⁵⁹ At his deposition, prompted by JHU counsel, Dr. VanBrocklin stated he did review some experimental records but none changed his opinions.⁶⁰ If anything, that answer makes his opinions even less credible.

3. No Nexus and No Credible Unexpected Results

Unexpected results must be “the direct result of the unique characteristics of the claimed invention” (*i.e.*, attributable to the claimed combination rather than to prior art features in isolation or to unclaimed features). *Fox*, 944 F.3d at 1373-74, 1378; *WBIP*, 829 F.3d 1317, 1329-32 (Fed. Cir. 2016). The evidence disproves that here—it is not credible and has no nexus to the claims.

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

⁵⁹ EX1069, 17:6-17, EX1070, ¶¶ 99, 118.

⁶⁰ EX1069, 268:1-269:15.

⁶¹ EX1070, ¶¶ 98, 114-115.

⁶² EX1070, ¶¶ 116-118.

§ II.B.2.b).

Relevant here, the Jansen publications show significant unpredictability in the selectivity of chemically similar “A” moieties with minor changes.⁶⁴ Even crediting published examples, nothing is known about ~30,000 other “A” choices being claimed.⁶⁵

JHU and its expert identify no scientific theory a POSA could employ to predict the selectivity effects on *unknown and uncharacterized* “A” choices when

⁶³ *Id.*

⁶⁴ EX1070, ¶¶ 241-244, Appx. D; EX1003, ¶¶ 291, 299-302.

⁶⁵ EX1070, ¶ 117; EX1003, ¶¶ 91-94.

paired with (literally) any “B” and any “L” moiety.⁶⁶ Instead, Dr. Pomper testified that “affinity and specificity of the medical imaging agent are *highly dependent on the molecular structure of the agent*” and that “the art of developing a medical imaging agent is *highly unpredictable*.”⁶⁷

Third, Dr. Pomper and Dr. VanBrocklin said 11 Pomper compounds had selectivity several orders of magnitude (i.e., 1000x) greater than reference compounds. [REDACTED]

[REDACTED]

Fourth, despite saying the claims are defined in “purely structural terms,” Dr. VanBrocklin admitted he only considered *functional* issues for his opinions.⁶⁹ For example, he did not consider PREP’s sterically restricted active site which, unlike FAP, impairs its ability act on large bulky substrates. That could cause PREP (but not FAP) to exhibit reduced binding to bulky B-L-A compounds, and if PREP binding goes down while FAP stays constant, selectivity increases (i.e., PREP/FAP).⁷⁰ Although he recognized the challenges of inhibitors differentiating

⁶⁶ EX1070, ¶¶ 116, 119-122; EX1069, 127:17-128:9; 132:17-135:2.

⁶⁷ EX1002, 172 (¶¶ 31-32); EX1001, 36:20-29; EX1070, ¶¶ 45-48, 226-228.

⁶⁸ EX1070, ¶¶ 28, 75, 111-112, 116; EX1002, 176 (¶ 43); EX2029, ¶ 117.

⁶⁹ EX1069, 127:17–128:9, 132:17-135:2.

⁷⁰ EX1070, ¶¶ 119-122; EX1069, 121:9-135:2.

FAP from structurally-similar enzymes, Dr. VanBrocklin made no attempt to decipher *why*, in his opinion, every B-L-A will exhibit increased selectivity for FAP over PREP.⁷¹

Finally, it is irrelevant that *some* species of B-L-A compounds might exhibit unexpected selectivity. To be credited, the claims must correlate to what is unexpected. They do not by any measure.⁷² *Fox*, 944 F.3d 1373-74.

C. Disregard JHU's Mischaracterizations

The remainder of JHU's Response consists of mischaracterizations of Dr. Zeglis's opinions or record evidence. Examples are identified by Dr. Zeglis in his second Declaration.⁷³

III. All Claims Are Unpatentable Under § 112

A. The Claims Require Compounds that Selectively Bind FAP

JHU argues its claims define “B-L-A” compounds in “purely structural terms” and thus impose no functional requirements.⁷⁴ But even the briefest inspection of the claims, specification and prosecution history demonstrates the claims require more than just joining three parts of a compound together in the

⁷¹ EX2029, ¶¶ 51, 121; EX1070, ¶¶ 119-122; EX1069, 122:4-124:8, 127:17-128:9.

⁷² EX1070, ¶¶ 116-117, 138-148; EX1003, ¶ 94.

⁷³ EX1070, ¶¶ 135, 181, 222, 54, 170, 138-139.

⁷⁴ POR, 4-7, 93-94; EX2029 ¶¶ 41-44.

most obvious way conceivable (*i.e.*, “B-L-A”).⁷⁵

As explained below, the claim language and intrinsic evidence are fully aligned in requiring B-L-A compounds (i) that *selectively* bind (*i.e.*, “target”) FAP and (ii) are suitable for specific types of imaging and radiotherapy.

First, the claims require the B-L-A compound to have

- an “A” moiety that *is* a *targeting moiety for FAP-α*;
- a “B” moiety that *is* any optical or radiolabeled functional group that *is* “*suitable* for optical *imaging*, ... PET, or ... SPECT *imaging*, or *radiotherapy*”; and
- an “L” moiety that *is* a linker with bi-functionalization that forms chemical bonds with B and A (only in the full compound are those bonds formed).⁷⁶

The claims thus require B-L-A compounds that *are* “FAP-targeting” and *are* “suitable for” PET/SPECT/optical imaging or radiotherapy.⁷⁷ Both experts agreed that the “A” and “B” *functions* must persist in the *assembled* B-L-A compound.⁷⁸

⁷⁵ EX1002, 172 (¶ 32); EX1003, ¶¶ 273-275.

⁷⁶ EX1001, Claim 1; Pet., 19-20.

⁷⁷ EX1070, ¶¶ 33-39; EX1003, ¶¶ 74, 275.

⁷⁸ EX1069, 95:12-97:16, 115:16-116:13; EX1070, ¶¶ 13-20, 32-39; EX1003, ¶¶ 74-75, 273-275.

The prosecution history makes crystal clear what functional properties the *claimed* compounds must possess. They are what JHU and Dr. Pomper said (under oath) to secure allowance of the claims: “*the claimed compounds have specificity for FAP several orders of magnitude higher than other known FAP inhibitors*:”⁷⁹

43. Surprisingly, the specificity of the 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 particular, as shown in the Table below, MIP-1232,

That is precisely *why* the examiner allowed these claims:⁸⁰

The following is an examiner’s statement of reasons for allowance: the low molecular weight quinolinyl-containing compounds of the instant claims surprisingly have a specificity (PREP/FAP ratio) for FAP that is several orders of magnitude higher than other small molecule FAP inhibitors found in the prior art.

The specification is consistent with the claims and the prosecution history. It states: “the *highly potent and specific binding moiety targeting FAP- α* enables its use in nuclear imaging and radiotherapy...”⁸¹ Then, addressing the precise embodiment claimed here:

⁷⁹ EX1002, 173-176 (¶¶ 41,43 (“specificity/selectivity” determined as IC₅₀PREP/IC₅₀FAP in Jansen (EX1007)); EX1070, ¶¶ 28-30.

⁸⁰ EX1002, 213; EX1070, ¶ 31

⁸¹ EX1001, 7:41-42. *Also* EX1002, 168 (¶12) (citing passage as claim support); EX1070, ¶¶ 18-20.

...the presently disclosed subject matter provides *potent and selective* low-molecular-weight (LMW) ligands of FAP- α , *i.e., an FAP- α selective inhibitor, conjugated* with a targeting moiety feasible for modification with optical dyes and radiolabeling groups...which enable *in vivo optical imaging, nuclear imaging (optical, PET and SPECT)*, and *radiotherapy* targeting FAP- α .⁸²

The intrinsic record could not be clearer that a “targeting moiety for FAP- α ” requires a compound that exhibits *selective* binding to FAP over PREP, which JHU and Dr. Pomper portrayed being *several magnitudes* greater than selectivity of prior art compounds (~32 to 403).⁸³ In this proceeding, it is unnecessary to define how much, as just the requirement for some selective binding imposes impossible obstacles for the claims under § 112.

JHU simply ignores the term “targeting moiety for FAP- α ” and maintains the claims are “plainly structural”⁸⁴ That is textually and substantively incorrect. The claims require not only compounds with the “X” structure but which “target”

⁸² EX1001, 7:46-54, 58:61-66, 60:29-47; EX1070, ¶¶ 18-20.

⁸³ EX1002, 176 (¶ 43); EX1070, ¶¶ 28, 38-39, 101; POR, 2; EX2029, ¶¶ 116-117, 120.

⁸⁴ POR, 4-7; EX2029, ¶ 41-44.

FAP (*i.e.*, are selective for FAP over PREP).⁸⁵ Jansen’s work demonstrates most “X” compounds are not—even modest structural changes can destroy selectivity.⁸⁶ And selectivity is necessary for *any* type of imaging or radiotherapy—including “in vitro.”⁸⁷ If the B-L-A compound cannot distinguish FAP from PREP, it is not a “targeting moiety for FAP- α .”⁸⁸ The intrinsic evidence compels reading these claims as requiring compounds that exhibit selective binding for FAP.

B. The Claims Are Broad and Diverse, the Disclosure Thin and Prophetic

The claims capture immense genera of chemical compounds. Each can have (i) one of 31,000+ choices for the “A” moiety, plus any chemical structure that (ii) can function as imaging or radiotherapeutic moiety “B” and (iii) a bifunctional linker. Immensely broad claims like these require a robust and diverse disclosure reflecting the diversity of structures and activities being claimed.⁸⁹ *Amgen*, 598 U.S. at 610. That is not this disclosure.

⁸⁵ EX1070, ¶¶ 38-39, 178, 223; EX1003, ¶¶ 55, 70, 288; EX1002, 172-174 (¶¶ 31, 39, 41), 176 (¶ 43); EX2029, ¶¶ 22, 118; EX2001, ¶¶ 71-75.

⁸⁶ EX2029, ¶¶ 108-111; EX1070, ¶¶ 241-244; EX1003, ¶¶ 290-293, 175.

⁸⁷ Imaging requires spatial identification of FAP, not just its presence in a solution. EX1070, ¶¶ 45-48, 227-228.

⁸⁸ EX1070, ¶¶ 38-39; EX1002, 172 (¶ 31).

⁸⁹ EX1003, ¶¶ 91-94; EX1070, ¶¶ 117, 216-217.

For the “A” moiety, the disclosure describes *two* examples of targeting moieties for FAP- α compounds, both from the prior art. It then points to the Jansen papers, without explaining what features (structural or functional) of the 100+ compounds they disclose make one a FAP- α targeting moiety.⁹⁰ The description does not identify what constitutes sufficient selectivity or requisite IC₅₀ values for PREP and FAP. It lists dozens of substituent choices throughout the Structure X architecture but does not correlate which combinations yield sufficient selectivity (other than two).⁹¹

The description of “B” and “L” moieties similarly are laundry lists of options, presented as isolated parts. Again, no direction is given as to how to combine them—*all* choices are equivalently proposed.⁹²

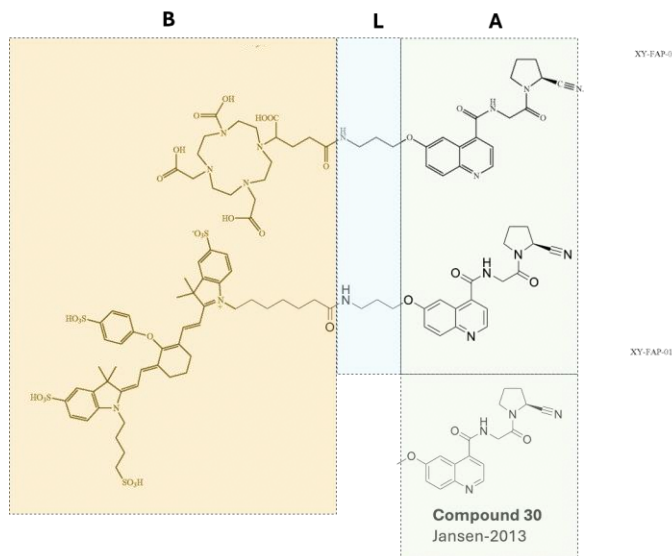
As to B-L-A compounds, there are two, with one shared FAP- α targeting moiety and linker, and two options for “B” illustrated (one chelator, one optical dye). Less exemplification is hard to imagine.⁹³

⁹⁰ EX1003, ¶ 249; EX1070 ¶¶ 124-125.

⁹¹ EX1003, ¶¶ 91-92; EX1070 ¶¶ 38-39, 216-217, Pet., 112-118.

⁹² EX1001, 14:16-55; 14:56-29:55; EX1070, ¶¶ 205-207; EX1003, ¶¶ 76-78.

⁹³ EX1003, ¶¶ 249-252.



C. The Claims Are Not Enabled

The Board correctly found the claims non-enabled. Nothing JHU has said changes this correct conclusion.⁹⁴

JHU's arguments are irreconcilable. On the one hand, it strains to read out of the claims any requirement that might yield a useful invention, dumbing down the supposed invention to simply assembly any of 10^{27} possible combinations. On the other, it argues the disclosure provides "guidance to preserve FAP-binding functionality."⁹⁵ Is that "functionality" FAP-selectivity? If it is only FAP-binding, why add "functionality"?⁹⁶

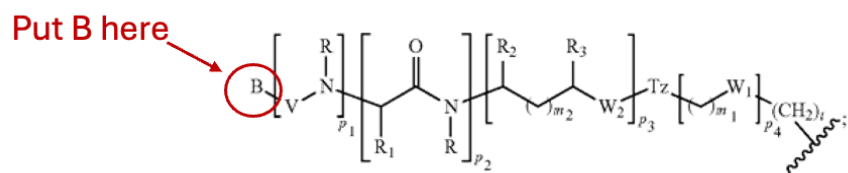
JHU's supposed "guidance" on "A" moieties consists of identifying the

⁹⁴ Paper 8, 34.

⁹⁵ POR, 77, 92-95.

⁹⁶ EX1069, 237:12-238:11; EX2029, ¶¶ 41-45.

available positions on the X structure Jansen invented, and telling the POSA to try different options at them. One example is “any of the carbon atoms of the 5 to 10 membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle of A.”⁹⁷ That is not guidance, it is simply enumerating available positions on a complex ring structure. Another example is “direction on how to conjugate L and B.”⁹⁸ That direction apparently is to form any chemical bond between B and L:

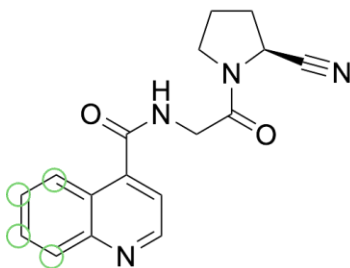


Another example is “directing” the POSA to “carbons 5 to 8 of the quinolinyl ring”(below). To do what? A POSA already knows the available positions where substituents can be attached on the quinolinyl ring. What they do not know is *which* substituents at *which* of those positions will yield a **FAP-targeting** moiety.⁹⁹

⁹⁷ POR, 76-77; EX1001, 3:10-13; EX1070, ¶ 216.

⁹⁸ POR, 76-77; EX1070 ¶¶ 205-207.

⁹⁹ EX1070, ¶¶ 241-244; EX1003, ¶¶ 290-291.



1. The '233 Patent Provides No Guidance on the Vast Majority of Targeting Moieties Being Claimed

Unlike JHU, the Jansen group spent 5+ years making and testing FAP inhibitors to discover those that are FAP-targeting.¹⁰⁰ Jansen's group methodically explored different substituents throughout the N-4-quinolinoyl-Gly-(2S)-cyanoPro scaffold, ultimately testing ~60 such compounds.¹⁰¹ What Jansen discovered was *tremendous unpredictability* associated with *modest structural changes*. Jansen's work documented numerous instances where the same substituent (*e.g.*, halogen, a methoxy group, etc.) introduced at **all** of the positions the '233 Patent points to caused wildly different effects, altering selectivity by several orders of magnitude with one change, or even with subtle changes like chirality.¹⁰²

The disclosure provides no answers to this documented unpredictability in producing the claimed "A" moieties. It just incorporates but does not explain

¹⁰⁰ EX1006, 3053, 3057-62; EX1007, 493-94.

¹⁰¹ EX1006, 3054.

¹⁰² EX1003, ¶¶ 152, 178, 290-291, 298-302; EX1070, ¶¶ 242-245; Appendix D.

Jansen’s findings.¹⁰³ Jansen also did not describe the 31,000+ “A” moieties JHU now claims, much less say all were FAP-selective. It reported many exhibited no selectivity, low affinity, or being unstable in solution.¹⁰⁴ Dr. Pomper’s declaration likewise distinguished the Pomper Compounds from *insufficiently selective* Reference Compounds with selectivity values between 32 and 403.¹⁰⁵ Only 6 of Jansen’s 60 compounds clear that threshold in Dr. VanBrocklin’s “Top prior-art FAPis” table. That is only 10% of a refined collection of compounds identified over years of work. By contrast, the patent claims provide only an unfocused research plan.¹⁰⁶

2. The Disclosure Provides No Guidance on Overcoming Admitted Uncertainty

Dr. Pomper, in his declaration, not only confirmed the claims require highly selective and highly potent FAP-targeting B-L-A compounds, but that making them requires navigating tremendous uncertainty:¹⁰⁷

¹⁰³ EX1001, 62:31-36.

¹⁰⁴ EX1006, 3063 (Table 7).

¹⁰⁵ EX1002, 173-76 (¶ 42).

¹⁰⁶ EX2029, ¶¶ 88-89.

¹⁰⁷ EX1002, 172 (¶ 31); EX1070, ¶¶ 23-25, 211-215.

The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

As he points out, the molecular structure of the prospective imaging agent is critical, but deciphering what it must be “is highly unpredictable” (plus he associates imaging with only *in vivo* applications).¹⁰⁸ His views are echoed by many others working in this field.¹⁰⁹ JHU’s position on what it takes to practice the claimed invention cannot be reconciled with Dr. Pomper’s testimony.

3. The Scale of Experimentation Is Undue

JHU does not dispute the claims encompass 10²⁷+ different B-L-A compounds. They respond by claiming their disclosure provides “sufficient guidance so that POSAs can identify workable embodiments.”¹¹⁰ But JHU ignores the central holding of *Amgen*, which affirmed the century-old principle of enablement that “[t]he more one claims, the more one must enable.” *Amgen*, 598 U.S. at 610 (2023). It also misdescribes the guidance their disclosure provides.

JHU identified *two* “workable embodiments” that share the same targeting

¹⁰⁸ EX1002, 172 (¶ 31).

¹⁰⁹ EX1070, ¶¶ 211-212; EX1029, 3412; EX1003, ¶¶ 55-58, 299.

¹¹⁰ POR, 92.

moiety and linker.¹¹¹ The rest of their disclosure is an inventory of known B and L components that a POSA must figure out how to combine. To identify other candidates involves straightforward but time-consuming synthesis and testing of compounds, especially given the absence of guidance on combinations.¹¹²

The problem here is the unknown, not the known. A POSA only would have high expectations for producing combinations using A moieties *known* to have high affinity and selectivity (*i.e.*, the 6 compounds discovered by Jansen).¹¹³ The vast majority of the claimed genus is on a different footing. Discovering the others requires overcoming the unpredictability in finding highly selective N-4-quinolinoyl-Gly-(2S)-cyanoPro compounds (as Jansen demonstrated), as well as converting them into highly selective imaging agents (as Dr. Pomper admits). That requires making and testing “A” moieties and combinations of them without any direction from the patent.¹¹⁴

Jansen’s experiences illustrate the time and effort required for the “A” part (e.g., producing ~60+ candidates over several years to yield 6 with promise). Dr. VanBrocklin’s publications illustrate similar challenges for B-L-As—they require

¹¹¹ EX1001, Col. 31-32.

¹¹² EX1003, ¶¶ 249-252; EX1070, ¶¶ 205-207, 216-217.

¹¹³ EX1070, ¶¶ 216-217, 245-246; EX1003, ¶¶ 247-248.

¹¹⁴ EX1070, ¶¶ 213-215, 241-244; EX1003, ¶¶ 290-291.

empirical, iterative synthesis and testing.¹¹⁵ Even though these procedures can be carried out by the POSA, probing even a tiny fraction of $10^{27}+$ compounds being claimed would require an impossible (and thus undue) scale of work.¹¹⁶ The claims are not enabled.

D. The Claims Lack Written Description

To satisfy § 112’s written description requirement, the specification must contain a “description not only of the outer limits of the genus but also of either a representative number of members of the genus or structural features common to the members of the genus, in either case with enough precision that a relevant artisan can visualize or recognize the members of the genus.” *Regents*, 61 F.4th 1350, 1356 (Fed. Cir. 2023) (citing *Ariad*, 598 F.3d 1336, 1350-52 (Fed. Cir. 2010) (en banc)).

In other words, regardless whether the claimed genus is defined in structural or functional terms, the specification must show possession of the “full scope” of the claims (i.e., the “breadth of the genus”) and “not just a species” therein, particularly where a “variety of materials constitut[e] the genus” of the claims (i.e., the claimed genus is heterogeneous). *Ariad*, 598 F.3d at 1349-50; *Duke*, 160 F.4th 1305, 1310 (Fed. Cir. 2025); *Abbvie*, 759 F.3d 1285, 1299-1300 (Fed. Cir. 2014).

¹¹⁵ EX1070, ¶¶ 236-237.

¹¹⁶ EX1070, ¶ 217; EX1003, ¶¶ 94, 247.

Written description of a claimed chemical genus also “requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials.” *Fujikawa*, 93 F.3d at 1571; *Regents*, 61 F.4th at 1357. A “‘laundry list’ disclosure of every possible moiety for every possible position” in a molecule cannot “constitute a written description of every species in the genus,” because it does not “‘reasonably lead’ those skilled in the art to any particular species.” *Fujikawa*, 93 F.3d at 1571; *Regents*, 61 F.4th at 1357.

1. No Common Structure or Representative Species

The '233 Patent's claimed universe of $10^{27}+$ “B-L-A” compounds encompass many heterogeneous sub-genera.¹¹⁷ That results from (i) compound “A” having at least 6 chemically-distinct locations available for attachment of the linker; (ii) the existence of heterogeneous classes and sub-classes of optical or radiolabeled functional groups (e.g., chelators, prosthetic groups) and (iii) the limitless diversity structural diversity of the “L” linker.¹¹⁸ The particular selections of (i) “A” moiety, (ii) binding location on “A”, (iii) functional moiety “B”, and (iv)

¹¹⁷ EX1003, ¶¶ 94-96, 251, App’x A, B; EX1070 ¶¶ 56; EX1069, 108:16-109:4.

¹¹⁸ EX1003, ¶¶ 84-94; EX1070 ¶¶ 188-190, 204-205; EX1001, 15:50-30:65.

linking structure “L” each can have significant impacts on the compound’s selectivity and suitability for imaging or therapy.¹¹⁹

The two examples of B-L-A compounds cannot come close to being considered representative. The claims capture $\sim 10^{27}+$ B-L-A combinations. The linker can be attached at *any* of six “A” positions, and evidence shows different positions cause unpredictable effects when conjugated.¹²⁰ The two examples probe only one position, only one linker structure and one type of change (alkoxy). That is not representative of other positional changes, bond types and linker characteristics.¹²¹ They are just two species residing within “a corner of the genus,” with the remaining “unknown contours of the claimed genus” left to be explored by others. *Abbvie*, 759 F.3d at 1299-1300.¹²²

The specification’s remaining disclosures are “laundry list[s]” of “different moieties for every possible side chain or functional group” such that “it is quite unclear how many compounds actually fall within the described genera.” *Regents Univ. Minn.*, 61 F.4th at 1357. The specification does not contain any disclosure

¹¹⁹ EX1003, ¶¶ 290-291; EX1070 ¶¶ 111-112, 207, 242-245; EX1069, 72:16-73:4.

¹²⁰ EX1070 ¶¶ 242-245; EX1003 ¶ 178.

¹²¹ EX1001, Col. 31-32; EX1070 ¶ 117.

¹²² EX1003, ¶ 249; EX1070, ¶¶ 124-125.

leading the POSA to particular species across the heterogeneous scope of the claims (e.g., different “A”s with different “B”s and “L”s attached at all available locations on “A”) that will have sufficient selectivity, or for identifying and distinguishing molecules within the claim that lack such selectivity and are inoperative species.¹²³ The disclosure thus lacks the “blaze marks” required under § 112. *Id.*

2. The Claims Cover Non-Described Species JHU Maintains Are Patentably Distinct

The disclosure describes only one formula for the claimed compounds: “B-L-A.”¹²⁴ As Dr. VanBrocklin testified, in this formula, B forms one bond with the linker (L), and A forms a second bond with the other end of the linker.¹²⁵ It (and Dr. VanBrocklin) also identify several specific structures as prosthetic groups and chelators.¹²⁶

During examination, JHU and Dr. Pomper portrayed the 11 Pomper Compounds as being covered by the claims.¹²⁷ But many of those compounds

¹²³ EX1001, 14:60-16:8, 16:15-18:34; EX1003, ¶¶ 248-252; EX1070 ¶¶ 205-207.

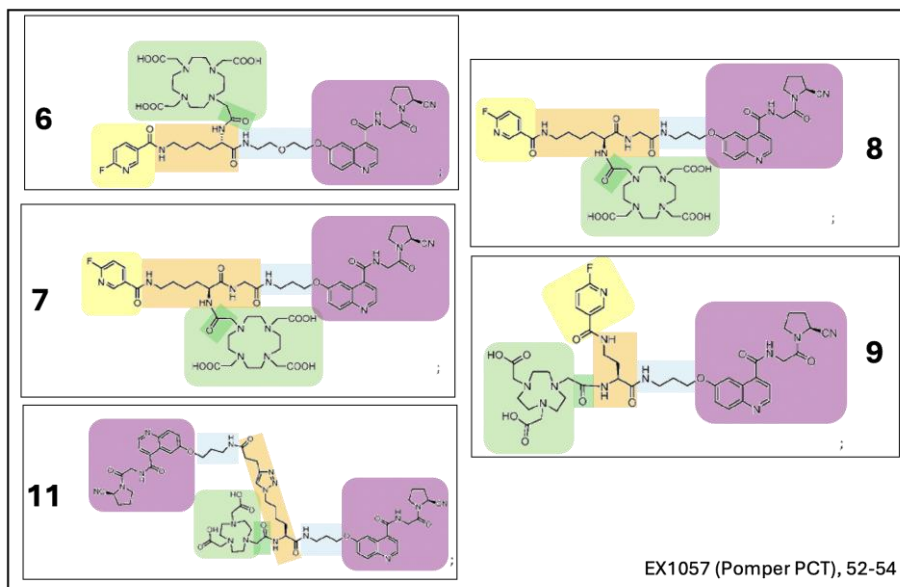
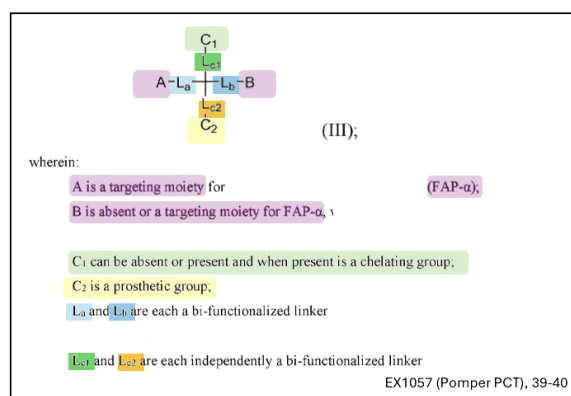
¹²⁴ EX1001, 1:65-67.

¹²⁵ EX1069, 85:14-86:1; EX1070, ¶¶ 184-187.

¹²⁶ EX1070, ¶¶ 188-190.

¹²⁷ EX1002, 174-175 (¶¶ 42-43).

have a very distinct structure nowhere described in the specification, which use two different imaging groups in one compound, up to four distinct linkers and even have two FAP-targeting moieties. Their architecture (Formula III) is illustrated and explained in a PCT JHU filed in 2021 (below, colors map elements to Formula III).



JHU portrays these unique structures as being patentably distinct from prior

art imaging agents, *which include* the B-L-A compounds in the '233 Patent.¹²⁸ A POSA likewise would view them as structurally and functionally distinct, and from a review of the disclosure, a POSA would conclude the inventors of the '233 patent did not have possession of these structures.¹²⁹ Because the claims capture structures nowhere described in the disclosure, the claims lack written description and are unpatentable.

IV. Conclusion

All claims are unpatentable under the grounds.

Dated: August 20, 2026

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¹²⁸ EX1070, ¶¶ 194-202.

¹²⁹ EX1070, ¶¶ 199-202.

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 5,577 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 20th day of August, 2026, I caused to be served a true and correct copy of the foregoing by e-mail on the following counsel of record for Patent Owner:

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