

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. IPR2026-00069
U.S. Patent No. 11,938,201

PETITIONER'S REPLY

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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 No claim construction is necessary for the Board to determine that the claims are obvious. *See* III.

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, §§ III.H, IV.E; Pet., 85-86, 111-113.

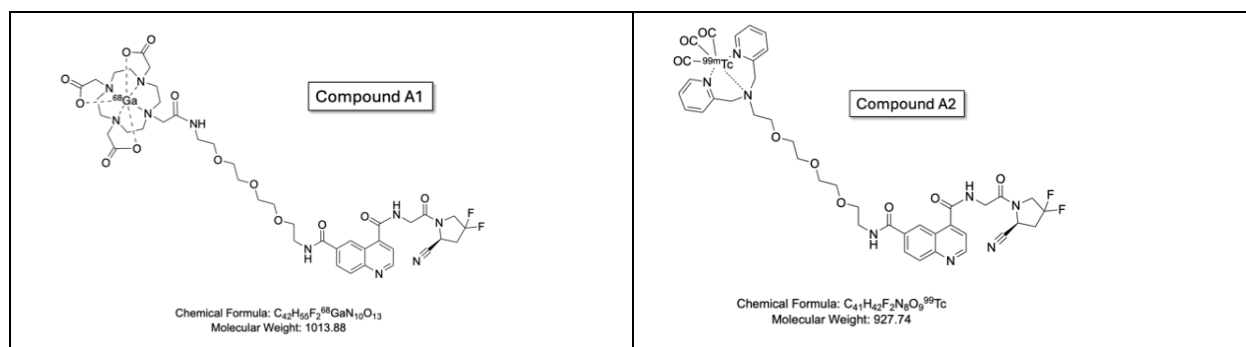
⁴ Pet., 83-93, 111-116; EX1003, ¶¶ 164-166, 213-215.

⁵ EX1069, 240:19-241:6, 237:12-238:11; EX1003, ¶ 177.

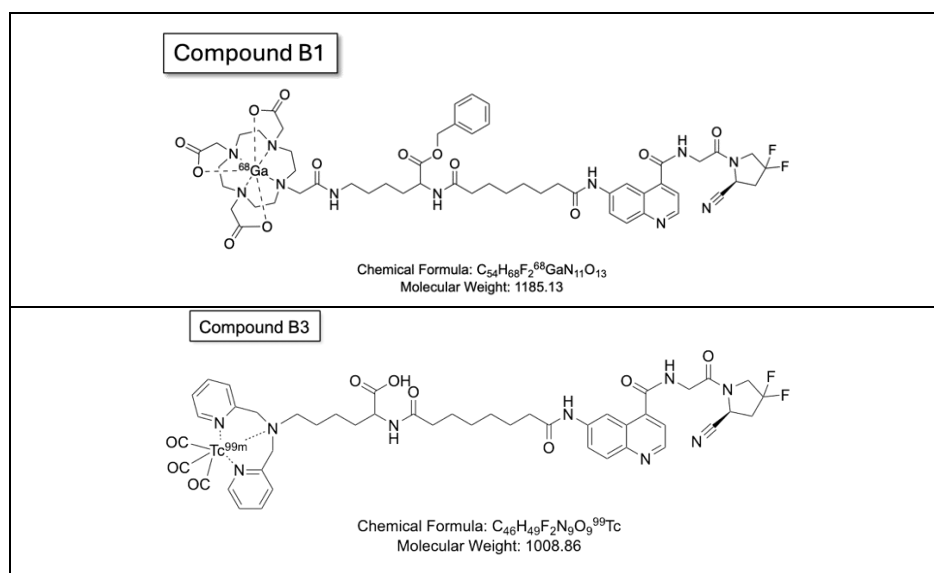
⁶ EX1003, ¶¶ 76-78, 83-87, 94, 97-101, 133, 144-155; EX1004, [0100], [0133], [0175]; EX1008, 2087-90.

⁷ EX1006, Abstract, 3062; EX1003, ¶¶ 112, 115.

⁸ Pet., 85-86; EX1003 ¶¶ 146-158.



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. 95-98; EX1003, ¶¶ 205, 207; EX1070, ¶¶ 171-174.

¹⁰ Pet. 111-113.

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; EX2047, ¶¶ 43–46.

¹² Pet., 33, 94; EX1003, ¶¶ 30, 65, 71, 181-182, 184.

¹³ EX1001, 1:49-67; 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-affinity 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, 28-29; EX2047, ¶¶ 56-65, 72-73.

¹⁷ EX1069, 183:6-184:22; EX2047, ¶ 75.

¹⁸ EX1006, 3053, 3063-65; EX1003, ¶¶ 110-115; Pet. 59-65, 72; POR, 20-26.

¹⁹ EX1006, 3064; EX1003, ¶ 113.

²⁰ Pet. 70-74; EX1003, ¶¶ 115-118, 127, 133-134.

²¹ Pet. 59; EX1006, Abstract, 3053; EX1003, ¶ 112; EX1070, ¶141.

²² EX1006, 3062-64; EX1003, ¶¶ 112, 122-26, 142; EX1070, ¶ 141.

“important parameters” for successful FAP radiotracers.²³

[t]here are numerous important parameters which need to be taken into consideration for successfully developing *a FAP imaging agent*. Those parameters include, for example, affinity for FAP, *selectivity (specificity) for FAP*, ease of synthesis, and biodistribution, and the like. *It is important for the agent to have both high affinity and high specificity to bind to the target protein* that is associated with a medical condition. *The high specificity allows the imaging agent to bind selectively to the target protein* associated with the medical condition *but not other proteins* unrelated to the medical condition. *A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein.*²⁴

Even if a POSA intended to only use FAP radiotracers for *in vitro* uses, the knowledge that Compound 60 has a full suite of favorable attributes in *comparative* studies would have given a POSA confidence and motivation to use

²³ EX1002, 363 (¶31) (emphasis added); EX1070, ¶¶ 23, 141.

²⁴ EX1002, 172 (¶ 31) (emphasis added).

Compound 60.²⁵ A critical attribute of the claimed FAP radiotracers is their ability to measure *the spatial distribution* of the target within a sample, as the specification explains:

Images can be generated by virtue of *differences in the spatial distribution of the imaging agents* which accumulate at a site when contacted with FAP- α . *The spatial distribution may be measured* using any means suitable for the particular label, for example, a gamma camera, a PET apparatus, a SPECT apparatus, and the like.²⁶

As Jansen reported, Compound 60 demonstrated particular strength in traversing tissue environments, including *in vivo*, where it exhibited “the most extensive and prolonged inhibition of FAP in the PK studies.”²⁷

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.²⁸ Dr. VanBrocklin also includes Compound 60 in his table

²⁵ EX1003, ¶¶ 106-112; EX1070 ¶¶ 178-180.

²⁶ EX1070 (Zeglis II), ¶ 46. .

²⁷ (EX1006), 3064.

²⁸ EX1001, 13:33-14:15, 63:4-9, Claim 1; EX1006, Abstract, 3063-65; EX1070, ¶¶ 124-125; EX1003, ¶¶ 163-164; Pet., 76-77; EX1069, 92:12-93:4, 184:13-22.

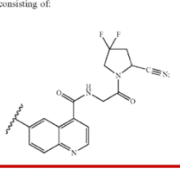
of “*TopPrior-Art FAPIs, ranked by selectivity....*”²⁹ Apparently being the 6th highest-performing FAP inhibitor is not enough for Dr. VanBrocklin. But to a POSA, Compound 60 was a *compelling* choice.³⁰

(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

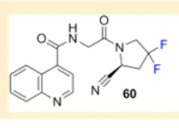
Jansen K, Heirbaut L, Verkerk R, Cheng JD, Joossens J, Costein (FAP). *J Med Chem.* 2014 Apr. 10; 57(7):3053-74.

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 (μM)	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.

²⁹ EX2047, ¶¶ 74-75.

³⁰ EX1003 ¶¶ 115, 127; EX1070, ¶ 141; Pet. 72-74.

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

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.³³ 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.³⁴ 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 claimed compounds was **779** (below).³⁵ That omission suggested a non-existent numerical separation between the Reference Compounds and *all* the Representative Compounds.³⁶ But Compound D's (**403**) selectivity is

³² EX1070, ¶¶ 111-12, 116; Paper 19 (PGR2025-00059).

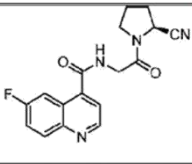
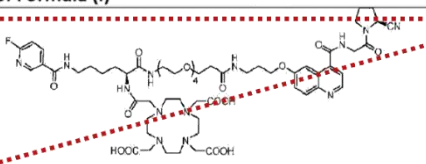
³³ EX1002, 367.

³⁴ EX1070, ¶ 101.

³⁵ EX1002, 365 (¶ 42).

³⁶ POR, 49-51; EX2047, ¶ 108; EX1070, ¶¶ 28, 101, 108.

indistinguishable from Compound 8's (407) (*i.e.*, 1.0099).³⁷

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	403		407
D		8	

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

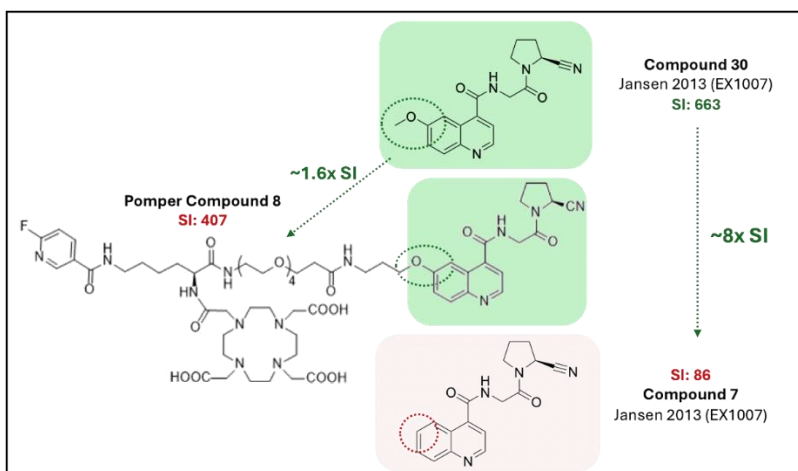
JHU and Dr. VanBrocklin amplify this distortion. They compare Dr. Pomper's 11 compounds to another low-selectivity "A" compound (Compound 7 of Jansen-2013) and contend it shows that B-L-A forms of A compounds "unexpectedly" demonstrate selectivity increases "several orders of magnitude greater than the ... corresponding "A" compounds alone.³⁸

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 (below, green).³⁹

³⁷ EX1002, 366-367; EX1070, ¶¶ 28, 101.

³⁸ EX2047, ¶¶ 103-105, 113; POR, 49-52.

³⁹ EX1070, ¶¶ 103-105; EX1007, 493.



Critically, this *one change alone* increases FAP selectivity *nearly 8-fold* over compound 7 (*i.e.*, 663 vs. 86).⁴⁰ 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).⁴¹

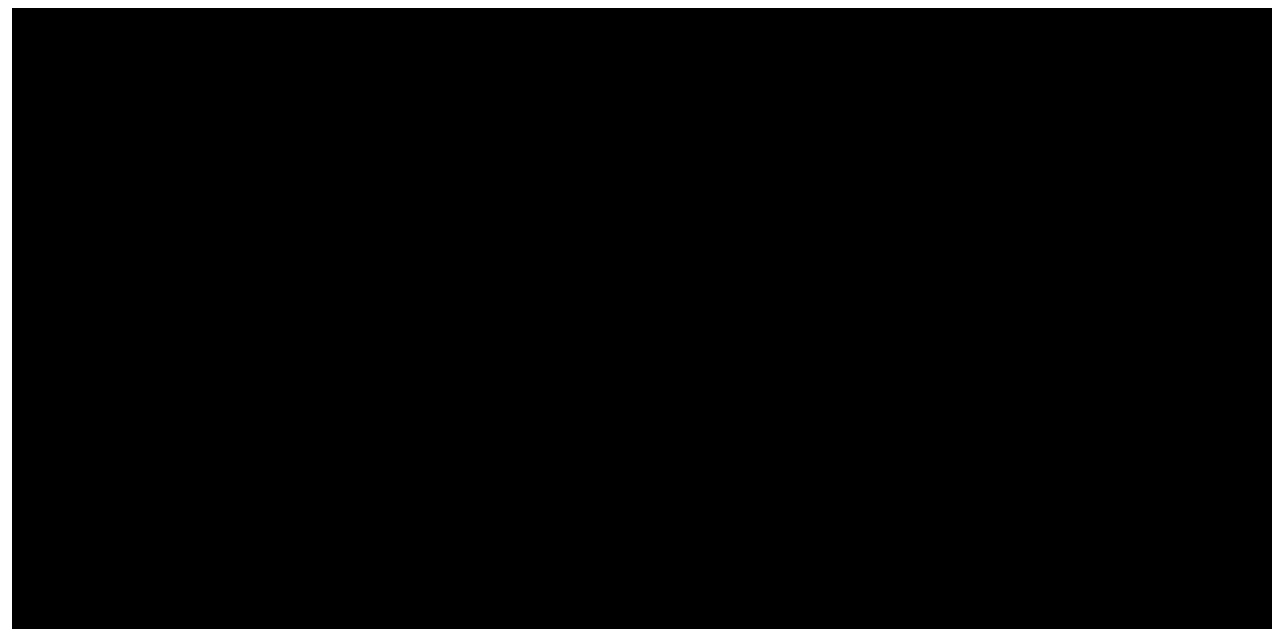
	Compound 30	Compound 7	Pomper Reference Compounds							
			A	B	C	D	E	F	G	H
SI (PREP/FAP)	663	86	32	152	20	403	15.70	241	17	3
% of Compound 30 SI	100%	13.0%	4.8%	22.9%	3.0%	60.8%	2.4%	36.3%	2.6%	0.5%

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

⁴⁰ EX1007, 493; EX1070, ¶ 104.

⁴¹ EX1070, ¶¶ 101, 107-108.

narrative (below, red = $SI_A > SI_{B-L-A}$).⁴²



It is a substantial oversight for Dr. VanBrocklin to not use Compound 30 as the comparator in his analysis.⁴³ He does not reveal why he ignored it. He certainly was familiar with Compound 30—it is on his list of “Top prior-art FAPi's” and, relative to Compound 60, he said “...*Compound 30 of Jansen 2013*[/]exhibit[s] *superior selectivity and affinity for FAP*.”⁴⁴ 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

⁴² EX1070, ¶¶ 107, 109. [REDACTED]

⁴³ EX1070, ¶¶ 104-106, 108-109.

⁴⁴ EX2047, ¶¶ 74-75.

alone.⁴⁵

2.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

a)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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

⁴⁶ Paper 19; EX1070, ¶¶ 82-89, 111-112.

⁴⁷ EX1070, ¶¶ 111-112, 116; EX1057, 134-141 (Table 3), 141-143 (Table 4), Appx. C-9.

⁴⁸ EX1070, ¶¶ 94-96, 111-112, 116-117.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁴⁹ EX1070, ¶¶ 111-112, Appx. C-3, C-9.

⁵⁰ EX1070, ¶¶ 69-75, 110-112, 118, Appx. C-4.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

b) [REDACTED]

[REDACTED]

[REDACTED]

(i) [REDACTED]

[REDACTED]

(ii) [REDACTED]

⁵¹ EX1070, ¶ 112.

⁵² EX1070, ¶¶ 91, 93.

⁵³ EX1070, ¶ 76.

54

(iii)

(iv)

⁵⁴ EX1070, ¶¶ 58-61, 64-66, 70.

⁵⁵ EX1070, ¶¶ 67, 72.

56 EX1070, ¶¶ 80-90.

⁵⁷ EX1070, ¶¶ 77-79, 82, 90.

⁵⁸ EX1070, ¶¶ 58-60, 69-75, 87.

(i) [REDACTED]

[REDACTED]

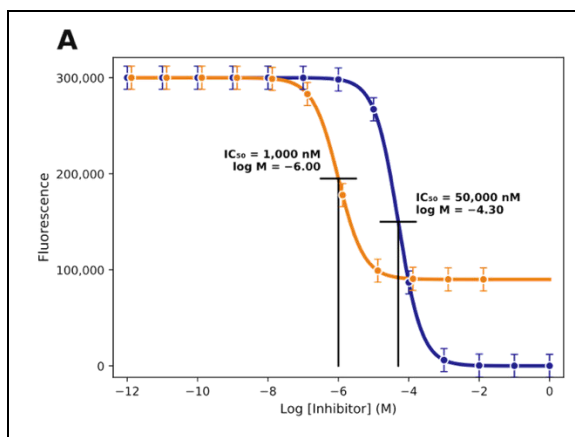
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]

(ii) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- (iii) [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁵⁹ EX1070, ¶¶ 87 & n.116.

⁶⁰ EX1070, ¶ 91.

[REDACTED]

[REDACTED]

[REDACTED]

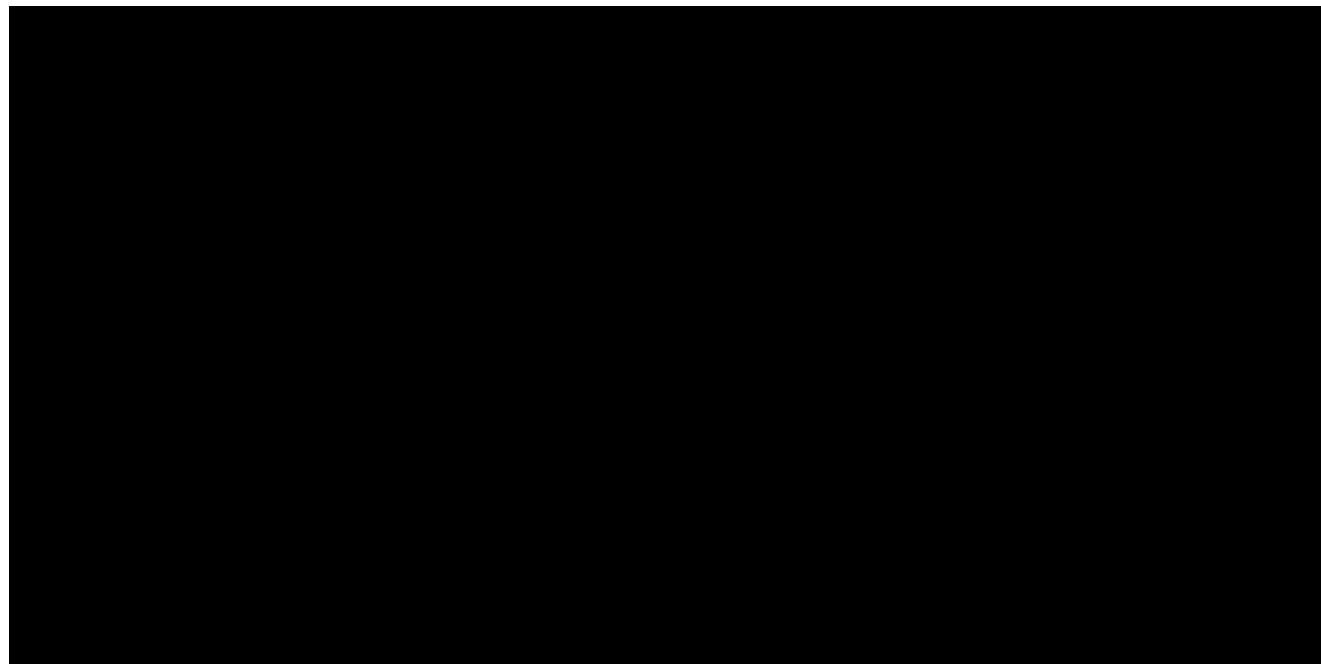
[REDACTED]

[REDACTED]

[REDACTED]

⁶¹ EX1070, ¶¶ 91, 110.

⁶² EX1070, ¶¶ 75, 111.



Dr. VanBrocklin did not review *any* experimental records before signing his declaration.⁶³ At his deposition, prompted by JHU counsel, Dr. VanBrocklin stated he did review some experimental records but none changed his opinions.⁶⁴ 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.

⁶³ EX1069, 17:6-17, EX1070, ¶¶ 99, 118.

⁶⁴ EX1069, 268:1-269:15.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

⁶⁵ EX1070, ¶¶ 98, 114-115.

⁶⁶ EX1070, ¶¶ 116-118.

Relevant here, the Jansen publications show significant unpredictability in the selectivity of chemically similar "A" moieties with minor changes.⁶⁸ Even crediting published examples, nothing is known about ~30,000 other "A" choices being claimed.⁶⁹

JHU and its expert identify no scientific theory a POSA could employ to predict the selectivity effects on *unknown and uncharacterized* "A" choices when paired with (literally) any "B" and any "L" moiety.⁷⁰ 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*."⁷¹

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

⁶⁷ *Id.*

⁶⁸ EX1070, ¶¶ 178-180, Appx. D; EX1003, ¶¶ 141-143.

⁶⁹ EX1070, ¶ 117..

⁷⁰ EX1070, ¶¶ 116, 119-122; EX1069, 127:17-128:9; 132:17-135:2.

⁷¹ EX1002, 363 (¶¶ 31-32).

⁷² EX1070, ¶¶ 28, 75, 111-112, 116; EX1002, 367 (¶ 43); EX2047, ¶ 104.

Fourth, despite saying the claims are defined in "purely structural terms," Dr. VanBrocklin admitted he only considered *functional* issues for his opinions.⁷³ 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).⁷⁴ Although he recognized the challenges of inhibitors differentiating 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.⁷⁵

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.⁷⁶

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

⁷³ EX1069, 127:17–128:9, 132:17-135:2.

⁷⁴ EX1070, ¶¶ 119-122; EX1069, 121:9-135:2.

⁷⁵ EX2047, ¶¶ 36, 111; EX1070, ¶¶ 119-122; EX1069, 122:4-124:8, 127:17-128:9.

⁷⁶ *Fox Factory*, 944 F.3d 1373-74, EX1070, ¶¶ 116-117; EX1003, ¶ 162.

second Declaration.⁷⁷

III. The Claims Require BLA Compounds that Selectively Bind FAP and are Suitable for Imaging and Radiotherapy

A. The Claims Require Compounds that Selectively Bind FAP

JHU's expert confirmed that a POSA would have a reasonable expectation of producing a radiotracer based on compound 60 and using a particular linker and imaging moiety combinations. There is no dispute these compounds are within the scope of the claims. No claim construction is necessary to resolve obviousness. For completeness, Petitioner provides the basis for claim construction if a construction is determined to be necessary by the Board. JHU argues its claims define "B-L-A" compounds in "purely structural terms" and thus impose no functional requirements.⁷⁸ 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 most obvious way conceivable (*i.e.*, "B-L-A").⁷⁹

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.

⁷⁷ EX1070, ¶¶ 135, 54, 170, 138-139.

⁷⁸ POR, 3-7; EX2047 ¶¶ 24-29.

⁷⁹ EX1002, 363 (¶ 32); EX1003, ¶¶ 138, 142-143.

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).⁸⁰

The claims thus require B-L-A compounds that *are* “FAP-targeting” and *are* “suitable for” PET/SPECT/optical imaging or radiotherapy.⁸¹ Both experts agreed that the “A” and “B” *functions* must persist in the ***assembled*** B-L-A compound.⁸²

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***.”⁸³

⁸⁰ EX1001, Claim 1; Pet., 24-25.

⁸¹ EX1070, ¶¶ 33-39; EX1003, ¶¶ 163.

⁸² EX1069, 95:12-97:16, 115:16-116:13; EX1070, ¶¶ 13-20, 32-39; EX1003, ¶¶ 163, 139-142.

⁸³ EX1002, 364-366 (¶¶ 41,43 (“specificity/selectivity” determined as IC₅₀PREP/IC₅₀FAP in Jansen (EX1007)); EX1070, ¶¶ 28-30.

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:⁸⁴

The following is an examiner's statement of reasons for allowance: the low molecular weight quinoliny- 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..."⁸⁵ Then, addressing the precise embodiment claimed here:

...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*

⁸⁴ EX1002, 442; EX1070, ¶ 31

⁸⁵ EX1001, 7:41-42. *Also* EX1002, 168 (¶12)(citing passage as claim support); EX1070, ¶¶ 18-20.

SPECT), and *radiotherapy* targeting FAP- α .⁸⁶

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).⁸⁷ 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”⁸⁸ That is textually and substantively incorrect. The claims require not only compounds with the “X” structure but which “target” FAP (*i.e.*, are selective for FAP over PREP).⁸⁹ Jansen's work demonstrates most “X” compounds are not—even modest structural changes can destroy selectivity.⁹⁰ And selectivity is necessary for *any* type of imaging or radiotherapy—including “in

⁸⁶ EX1001, 7:41-66, 59:35-57, 61:4-28; EX1070, ¶¶ 18-20.

⁸⁷ EX1002, 367 (¶ 43); EX1070, ¶¶ 28, 38-39, 101; POR, 2; EX2047, ¶¶ 103-105.

⁸⁸ POR, 4-7; EX2047, ¶ 24-27.

⁸⁹ EX1070, ¶¶ 38-39, 178; EX1003, ¶¶ 45, 60; EX1002, 363-365 (¶¶ 31, 39, 41), 367 (¶ 43); EX2047, ¶¶ 33, 108; EX2001, ¶¶ 63-67.

⁹⁰ EX2047, ¶¶ 94-97; EX1070, ¶¶ 175-178; EX1003, ¶ 139.

vitro.”⁹¹ If the B-L-A compound cannot distinguish FAP from PREP, it is not a “targeting moiety for FAP- α .”⁹² 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.⁹³ That is not this disclosure.

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.⁹⁴ The description does not identify what constitutes sufficient selectivity or requisite IC₅₀

⁹¹ Imaging requires spatial identification of FAP, not just its presence in a solution. EX1070, ¶¶ 45-48.

⁹² EX1070, ¶¶ 38-39; EX1002, 363 (¶ 31).

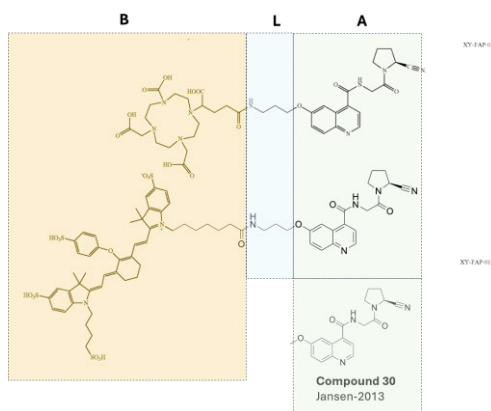
⁹³ *Amgen*, 598 U.S. at 610; EX1070, ¶¶ 117.

⁹⁴ EX1070 ¶¶ 124-125.

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).⁹⁵

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.⁹⁶

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.⁹⁷



IV. Conclusion

All claims are unpatentable under the grounds.

⁹⁵ EX1003, ¶¶ 91-92; EX1070 ¶¶ 38-39.

⁹⁶ EX1001, 14:16-55; 14:56-31:55.

⁹⁷ EX1003, ¶¶ 166-167.

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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 4,127 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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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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