

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GE HEALTHCARE LTD.,
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner

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

**PATENT OWNER PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.107(a)**

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PATENT OWNER'S EXHIBIT LIST

Exhibit No.	Description
2001	Declaration of Dr. Henry VanBrocklin in Support of Patent Owner Preliminary Response
2002	<i>Curriculum vitae</i> of Dr. Henry VanBrocklin
2003	Jansen et al., "Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold," <i>MedChemComm</i> (August 2014) ("Jansen 2014")
2004	Sikkandhar et al., "Theranostic Probes for Targeting Tumor Microenvironment: An Overview," <i>International Journal of Molecular Sciences</i> (May 2017) ("Sikkandhar")
2005-2010	<i>Intentionally Left Blank</i>
2011	Slania et al., "Imaging of Fibroblast Activation Protein in Cancer Xenografts Using Novel (4-Quinolinoyl)-glycyl-2 cyanopyrrolidine-Based Small Molecules," <i>Journal of Medicinal Chemistry</i> (April 2021) ("Slania")
2012-2017	<i>Intentionally Left Blank</i>
2018	Bvumbi, M., "Activity of Riminophenazines against Mycobacterium tuberculosis: A Review of Studies that Might be Contenders for Use as Antituberculosis Agents," <i>ChemMedChem</i> 15(23):2207-2219 (December 2020) ("Bvumbi")
2019	Xu et al., "Discovery of potent and selective phenylalanine based dipeptidyl peptidase IV inhibitors," <i>Bioorganic & Medicinal Chemistry Letters</i> , 15:2533-2536 (May 2005) ("Xu 2005")
2020	Calcaterra et al., "Classics in Chemical Neuroscience: Diazepam (Valium)," <i>ACS Chemical Neuroscience</i> , 5:253-260 (February 2014) ("Calcaterra")

Exhibit No.	Description
2021	Lever, A.B.P., “Lewis Structures and the Octet Rule,” <i>Journal of Chemical Education</i> , 49(12):819-821 (December 1972) (“Lever”)

I. INTRODUCTION

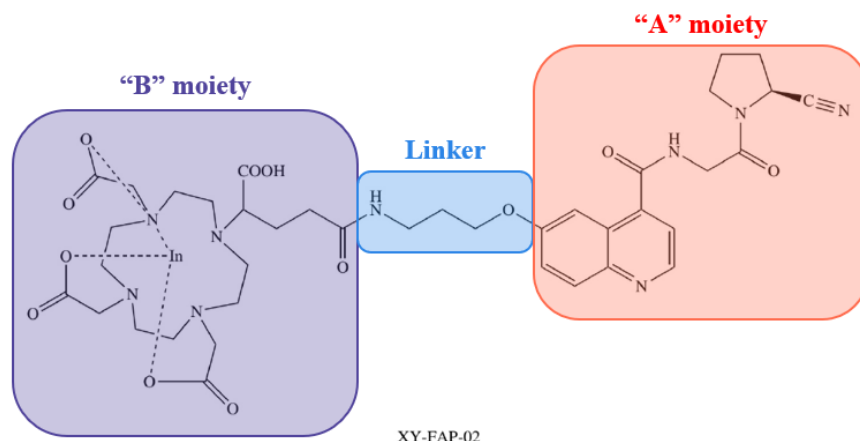
The challenged patent relates to innovative, low molecular weight imaging and radiotherapeutic agents (collectively, radiotracers) targeting fibroblast activation protein- α (FAP). EX1001, Abstract. These first-in-class radiotracers are useful in a wide range of applications, from *in vivo* treatment and diagnostics to *ex vivo* and *in vitro* applications. EX1001, 1:60-67, 7:46-54, 36:1-6.

In bringing this challenge and alleging that the claimed compounds would have been obvious, GE turns a blind eye to the state of the art before October 23, 2017. An objective review of the prior art shows that it was generally believed that FAP-based radiotracers provided only for *non-specific* binding thus “limit[ing] the fabrication of FAP targeted imaging probe[s].” EX2004, 11. Indeed, the single previous attempt to develop low molecular weight imaging agents for FAP resulted in failure: the radiotracer failed to “selectively accumulate in the atherosclerotic tissue” when tested for atherosclerotic plaque imaging by *in vitro* autoradiography. EX1008, 2089-2090.

In an advancement over the prior art compounds, the inventors have developed FAP-targeting compounds that can be used as imaging agents. The radiotracers of the challenged patent have a general formula “B-L-A,” where “A” is “a targeting moiety for FAP- α ,” “B” is an “optical or radiolabeled functional

group” suitable for imaging, and L is a linker connecting B and A. EX1001, 2:1-

12. An example of such a radiotracer is shown below:



EX1001, cols. 57-58 (annotated).

GE’s Petition challenging patentability of JHU’s claimed radiotracers suffers from multiple flaws warranting denial.

First, for its obviousness Grounds 1 and 2, GE fails to consider the art as a whole and uses impermissible hindsight to combine US-633, Jansen, and Meletta (Ground 1) or US-121 and Jansen (Ground 2) to arrive at the compounds of the Challenged Claims. GE “plucked one reference out of the sea of prior art ... and combined it with...[additional] elements to address some need present in the field.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016). In other words, GE ignores that the prior art as a whole would have presented a person of ordinary skill in the art (“POSA”) with a sea of FAP-targeting compounds

encompassing various, *better-performing* choices that would have led a POSA away from the claimed invention.

Rather than follow the path a POSA would have pursued, away from the claimed invention, GE impermissibly “cull[s] [components] from the prior art to fit the parameters of the patented invention.” *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998). GE’s hindsight infects both of the obviousness grounds and warrants denying the Petition. After all, “[a]ny compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound, with the benefit of hindsight, once one is aware of it does not render it obvious.” *Amerigen Pharmaceuticals Ltd. v. UCB Pharma GmbH*, 913 F. 3d 1076, 1089 (Fed. Cir. 2019).

Second, GE adds to its choice of a poorer performing FAPi compound by—without basis—choosing US-633’s poorer performing linker-containing radiotracers as a starting point. Indeed, US-633 discloses that its radiotracers *lacking* the linker “L” outperformed linker-containing radiotracers. GE provides no reason or evidence grounded in the prior art to select the *worse*-performing linker-containing radiotracers over US-633’s *better*-performing linker-less radiotracers, on top of selecting a FAP-targeting moiety that performed *worse* than many other known FAPis. As Patent Owner The Johns Hopkins University’s (“JHU”) expert Dr. Henry VanBrocklin (EX2001, ¶¶4-14) explains, selecting the better-performing

linker-less FAPi radiotracers would not have led to the claimed invention, revealing the additional hindsight GE used to develop its arguments. Rather than follow the path a POSA would have taken, GE used the claims as a roadmap.

GE should be held to its Petition's deficiencies because as the Petitioner, GE is the "master of its own petition." *Qualcomm, Inc. v. Apple LLC*, 134 F.4th 1355, 1367 (Fed. Cir. 2025). Accordingly, the deficiencies in GE's Petition warrant denial and IPR should not be instituted.

II. THE '201 PATENT

The invention of the '201 patent is directed to novel low molecular weight imaging and radiotherapeutic agents (collectively, radiotracers) targeting fibroblast activation protein- α (FAP). EX1001, Abstract; EX2001, ¶15. FAP is also referred to as seprase or FAP- α and is a transmembrane protein expressed on the stroma of cells, *i.e.*, the supportive framework of an organs or tissues. EX1001, Abstract, 1:30-48; EX1016, 259-260; EX2001, ¶15. FAP has been found to be overexpressed in diseases and disorders associated with activated stroma, such as wound healing, rheumatoid arthritis, osteoarthritis, cirrhosis, and pulmonary fibrosis. EX1001, Abstract, 1:30-48; EX1022, 124; EX1024, 456; EX1023, 288; EX1041, 2; EX2001, ¶15. The art also reported that FAP is overexpressed in cancer cells, where it has been detected in over 90% of cancer stroma examined. EX1001, Abstract, 1:30-48; EX1016, 260; EX1007, 491; EX2001, ¶15. In contrast,

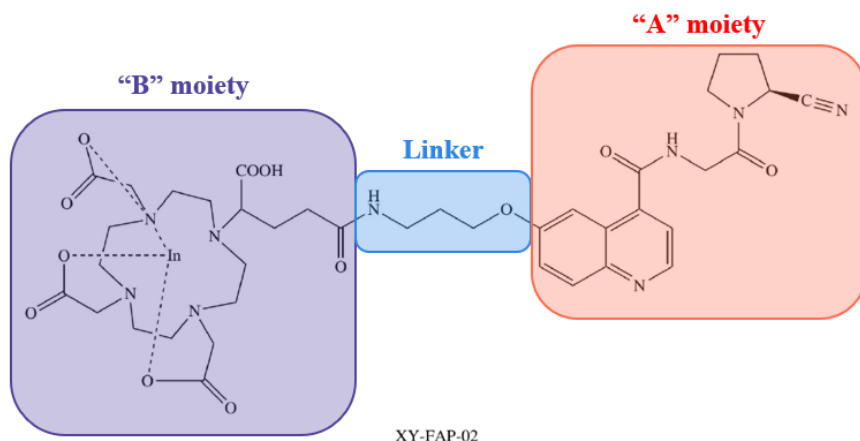
FAP has been found to be typically undetectable or low in healthy cell tissues.

EX1001, Abstract, 1:30-48; EX2001, ¶15.

As explained by JHU's expert, Dr. Henry VanBrocklin, a professor at the University of California, San Francisco, and an expert in radiopharmaceuticals and imaging with 35 years of experience in the field (EX2001, ¶¶4-14), before the October 23, 2017 priority date of the '201 patent, FAP molecular imaging had been plagued with challenges. EX2001, ¶16. The art reported that this was partially due to concerns associated with developing radiotracers with selectivity towards FAP. EX1008, 2089-2090; EX1016, 259; EX1044, ¶4; EX1007, 491; EX2001, ¶16. Indeed, FAP shares structural homology with several other proteins in its enzymatic family (prolyl oligopeptidase (PREP) and dipeptidyl peptidases (DPP) DPP^{IV}, DPP^{II}, and DPP^{IX}). EX1016, 259; EX1044, ¶4; EX1007, 491; EX2001, ¶16. Those structural similarities have resulted in FAP-targeting compounds having off-target activity against PREP and DPP peptidases. EX1016, 3; EX1044, ¶4; EX1007, 491; EX1007, 491-492; EX2001, ¶16. In fact, the only attempt to develop a low molecular weight FAP imaging agent before the '201 patent ended in a failure. EX1008, 2089-2090; EX2001, ¶16. That radiotracer failed to "selectively accumulate in the atherosclerotic tissue" when tested for atherosclerotic plaque imaging by *in vitro* autoradiography with human carotid plaques. EX1008, 2089-2090; EX2001, ¶16.

Consequently, the art generally believed that the non-specific binding of FAP due to sharing homology with other peptidases “limit[ed] the fabrication of FAP targeted imaging probe.” EX2004, 11; EX2001, ¶16. Imaging with more selective agents, such as anti-FAP antibodies, moreover, “suffer[ed] from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake.” EX1001, 1:56-60; EX2001, ¶16.

Against that background, the inventors of the '201 patent developed novel low molecular weight FAP-targeting imaging agents that addressed the selectivity and biodistribution issues seen with other FAP-targeting imaging agents. EX2001, ¶17. The '201 patent's radiotracers have the general formula “B-L-A,” where A is “a targeting moiety for FAP- α ,” B is an “optical or radiolabeled functional group” suitable for imaging, and L is a linker connecting B and A. EX1001, 2:1-12. An exemplary '201 patent radiotracer is shown below:



EX1001, cols. 57-58 (annotated); EX2001, ¶17.

The '201 patent's low molecular weight B-L-A radiotracers have "ideal properties for nuclear imaging of FAP- α ." EX1001, 1:65-67; EX2001, ¶18. The patent's radiotracers "demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration," and they "can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval." EX1001, 1:60-65; EX2001, ¶18.

The '201 patent demonstrates that its radiotracers, for example, have high selectivity and affinity for cell lines expressing FAP. *See, e.g.*, EX1001, 5:39-41 ("FIG. 3A, FIG. 3B, and FIG. 3C show the assessment of the *in vitro* binding ability and specificity of XY-FAP-01 and [^{111}In]-XY-FAP-02"); *see also id.*, 7:66-8:3 ("In a particular embodiment, an optical agent conjugated with IRDye-800CW (XY-FAP-01) was synthesized and showed selective uptake *in vitro* on a FAP- α + U87 cell line and *in vivo* on a FAP- α + U87 tumor and clearly detected the tumor"), 61:27-29 ("Taken together, these results support the specificity of XY-FAP-01 and ^{111}In -XY-FAP-02 in the engagement of FAP *in vitro*"); EX2001, ¶18. The '201 patent's radiotracers, moreover, exhibit "favorable biodistribution and retained uptake in the FAP-positive xenograft at various imaging time points." EX2011, Abstract, 8; EX2001, ¶18.

The '201 patent, therefore, describes innovative, highly selective radiotracers that can be used in various *in vivo*, *ex vivo*, and *in vitro* applications, such as imaging, diagnostic, and therapeutic applications. EX2001, ¶19.

III. CLAIM CONSTRUCTION

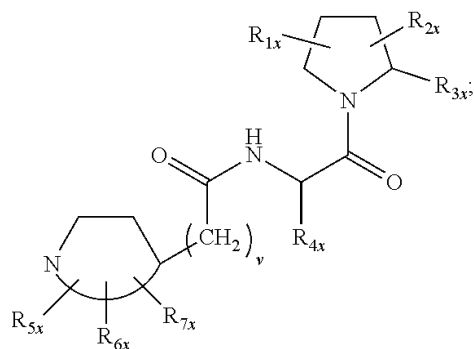
GE states that “[t]he terms in the claims generally employ objective language that requires no special construction.” Pet., 23. Yet, GE states that “[t]wo terms (*i.e.*, components ‘B’ and ‘L’) warrant observations to illustrate their breadth.” *Id.* And GE seeks to construe the phrase “low molecular weight,” because GE “anticipates [JHU] may contend the phrase ... requires a special construction.” *Id.* JHU addresses each of those points below.

A. Components “B” and “L” Do Not Render the Challenged Claim Functionally Defined

GE states that “[c]laims 1 to 3 use functional language (below) to define the ‘B’ and ‘L’ components of the claimed compounds.” Pet., 24. But GE does not explain how that has any impact on the analyses it provides in its Grounds. And JHU does not contend that “B” and “L” need to be construed to reach a decision on institution. To the extent the Director finds it necessary to construe “B” and “L” to reach a decision on institution, the Director should not import any functionality to the claimed compounds as a whole.

Here, the Challenged Claims are plainly structural. Indeed, independent claim 1 of the '201 patent recites “a low molecular weight compound of Formula (I): B-L-A,” wherein:

A is a targeting moiety for FAP- α , wherein A has the structure of:



wherein:

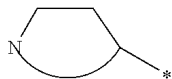
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C₁₋₆alkyl, —O—C₁₋₆alkyl, and —S—C₁₋₆alkyl;

R_{3x} is selected from the group consisting of H, —CN, —B(OH)₂, —C(O)alkyl, —C(O)aryl-, —C=C—C(O)aryl, —C=C—S(O)₂aryl, —CO₂H, —SO₃H, —SO₂NH₂, —PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

R_{5x}, R_{6x}, and R_{7x} are each H;

v is 0;



represents a quinolinyl ring;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

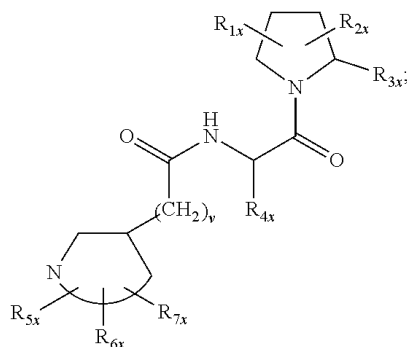
EX1001, 64:46-65:63, Certificate of Correction; EX2001, ¶32.

Claim 2 depends from claim 1 and further narrows B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.

EX1001, 65:64-67; EX2001, ¶33.

Claim 3 is also an independent claim and recites “[a] low molecular weight compound consisting essentially of components B-L-A,” wherein:

A is a targeting moiety for FAP- α , wherein A has the structure of:



wherein:

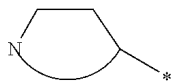
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

R_{3x} is selected from the group consisting of H, $-CN$, $-B(OH)_2$, $-C(O)alkyl$, $-C(O)aryl$, $-C=C-C(O)aryl$, $-C=C-S(O)_2aryl$, $-CO_2H$, $-SO_3H$, $-SO_2NH_2$, $-PO_3H_2$, and 5-tetrazolyl;

R_{4x} is H;

R_{5x} , R_{6x} , and R_{7x} are each H;

v is 0;



represents a quinolinyl ring;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography

(SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

EX1002, 509; EX2001, ¶34.

As can be seen from the elements of the challenged claims set forth above, they are plainly structural—the claims recite “a low molecular weight compound” having a specific structure: “Formula (I): B-L-A,” where A is a targeting moiety for FAP of a particular structure, and B is an optical or radiolabeled functional group suitable for imaging or radiotherapy that is chemically bonded to A via the linker L. EX1002, 508-509; EX2001, ¶35.

In fact, while the specific B and L moieties are defined in the claims as “suitable” for imaging or radiotherapy and having bi-functionalization adapted to form a chemical bond, respectively, the plain language of the claims define only B and L as “suitable” for imaging/radiotherapy and having bi-functionalization, and not the recited *genus* of low molecular weight compounds of “Formula (I): B-L-A.” EX1002, 508-509; EX2001, ¶35.

And “[w]here a claim uses clear structural language, it is generally improper to interpret it as having functional requirements,” especially when “nothing in the claim language itself [] requires [the claimed compounds] to perform [a] function.”

Schwing GmbH v. Putzmeister Aktiengesellschaft, 305 F.3d 1318, 1324 (Fed. Cir. 2002) (citing *Toro Co. v. White Consol. Indus., Inc.*, 266 F.3d 1367, 1371 (Fed. Cir. 2001) (“An invention claimed in purely structural terms generally resists functional limitation.”)); *see also Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (stating that it is improper to “import[] limitations from the specification into the claims”); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571 (Fed. Cir. 1988) (“Although the specification may aid the court in interpreting the meaning of disputed language in the claims, particular embodiments and examples appearing in the specification will not generally be read into the claims.”); *Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Research Found.*, PGR2022-00021, Paper 11 at 5-6 (P.T.A.B. Feb. 24, 2023) (Director Vidal finding that “the Board was correct to focus on whether the claims themselves were enabled and to find inapposite Petitioner’s arguments as to whether functional language—appearing only in the specification—was enabled.”).

The Board properly preliminarily decided that the claimed compounds should be treated as purely structural claims in a related proceeding, PGR2025-00012, involving the same ’201 patent, as well as in a related proceeding involving a child of the ’201 patent, PGR2025-00059. In PGR2025-00012, the Board explained: “The claims recite a compound, not a result. Although the B moiety must be suitable for specific imaging or radiotherapy uses, the claims do not

require that the claimed compound has this functionality. This is true of the L linker as well.” *ITM Isotope Techs. Munich SE v. The Johns Hopkins Univ.*, PGR2025-00012, Paper 12 at 54 (P.T.A.B. July 16, 2025); *see also GE Healthcare Ltd. v. The Johns Hopkins Univ.*, PGR2025-00059, Paper 8 at 13 (P.T.A.B. Jan. 14, 2026).

Accordingly, to the extent the Director determines that there is a need to construe the Challenged Claims, the Director should reach the same conclusion as the Board did in the earlier proceeding and find that no functional requirement should be imported into the claims as a whole. *Schwing GmbH*, 305 F.3d at 1324; *Phillips*, 415 F.3d at 1323; *Advanced Micro-Devices*, 848 F.2d at 1571; *Boehringer*, Paper 11 at 5-6.

B. “low molecular weight”

Each of the Challenged Claims of the ’201 patent requires that the compound of formula B-L-A is of “low molecular weight.” EX1002, 508-509. JHU provides a construction for “low molecular weight,” to the extent the Director finds it necessary to reach a decision on institution.

GE has submitted that the ’201 patent’s intrinsic evidence demonstrates that this term allegedly should mean “having a molecular weight at least an order of magnitude less than an antibody-based radiopharmaceutical.” Pet., 27-28. This interpretation is flawed, however, because it ignores that Dr. Martin Pomper, one

of the inventors of the '201 patent, defined the term “low molecular weight” during prosecution of the '201 patent.

Indeed, during the prosecution of the '201 patent, Dr. Pomper submitted a declaration to define how he viewed the scope of the term “low molecular weight” to mean “about 50 Daltons to about 1,500 Daltons.” EX1002, 360; EX2001, ¶¶36-37. In doing so, Dr. Pomper acted as his own lexicographer to define the scope of the claim term “low molecular weight.”

In fact, “a patentee is free to be his own lexicographer, so long as the special definition of a term is made explicit in the patent specification or *file history*.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1327 (Fed. Cir. 2001). Furthermore, “[a]ny explanation, elaboration, or qualification presented by the inventor *during patent examination* is relevant, for the role of claim construction is to ‘*capture the scope of the actual invention*’ that is disclosed, described, and patented.” *Fenner Invs., Ltd. v. Cellco P’ship*, 778 F.3d 1320, 1323 (Fed. Cir. 2015).

Here, Dr. Pomper did just that by providing his understanding of the scope of the term “low molecular weight” as related to his invention when submitting his declaration during prosecution. Based on Dr. Pomper speaking as a co-inventor, a POSA would have understood him to be providing the inventors’ explanation, elaboration, and qualification regarding the scope of the invention the inventors

sought to capture with the term “low molecular weight.” EX1002, 360; EX2001, ¶¶36-37.

Because Dr. Pomper, moreover, was acting as his own lexicographer it is perfectly fine that the evidence cited by Dr. Pomper in his declaration during prosecution was related to the field metabolomics, rather than that of radiotherapy. As a co-inventor, Dr. Pomper chose how he was “explain[ing], elaborat[ing], or qualif[ying]” the claim term in his declaration. *Fenner*, 778 F.3d at 1323. A POSA, therefore, would have understood Dr. Pomper’s comparison to metabolites to be providing a reference for the molecular weight range Dr. Pomper was ascribing to the compounds of his invention. EX2001, ¶¶36-37. The fact that the claimed compounds are not derived from metabolites would thus have been irrelevant. *Id.* Rather, Dr. Pomper’s comparison is analogous to a POSA referring to the molecular weight of antibodies and polymers to establish a range of molecular weights that would fall within the scope of “high molecular weight.” *Id.* Consequently, Dr. Pomper did not need to limit himself to a specific field to define the term “low molecular weight.” *Id.*

It also does not matter whether the definition Dr. Pomper offered during the prosecution history would exclude certain B moieties in the specification. Patentees are permitted to claim less than what is disclosed, even if embodiments are excluded. *Sinorgchem Co., Shandong v. Int’l Trade Comm’n*, 511 F.3d 1132,

1138 (Fed. Cir. 2007) (“Where ... multiple embodiments are disclosed, we have previously interpreted claims to exclude embodiments where those embodiments are inconsistent with unambiguous language in the patent’s specification or prosecution history.”).

In PGR2025-00059, the Board preliminarily found not persuasive the definition Dr. Pomper put forth in his declaration because it would allegedly “exclude[s] examples disclosed in the specification.” PGR2025-00059, Paper 8 at 10 (citing *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1305 (Fed. Cir. 2007)). But any reliance here on *Verizon* would be misguided. *Verizon* concerned the exclusion of *preferred* embodiments. 503 F.3d at 1305 (“A claim interpretation that excludes a *preferred* embodiment from the scope of the claim is rarely, if ever, correct.”). The B moieties of VivoTag-680, AlexaFluor790, and IRDye 700DX identified in the specification that would be excluded by a range of “about 50 Daltons to about 1,500 Daltons” are *not* identified as preferred embodiments in the ’201 patent.¹ Their exclusion, moreover, cannot outweigh the definitional language provided in the prosecution history. *N. Am. Container, Inc. v.*

¹ VivoTag-680, AlexaFluor790, and IRDye 700DX are listed once in the detailed description as possible B embodiments without being referred to as “preferred.” EX1001, 25:25-26:23.

Plastipak Packaging, Inc., 415 F.3d 1335, 1346 (Fed. Cir. 2005) (“[L]imitations may be construed to exclude a preferred embodiment if the prosecution history compels such a result.”); *Pacing Techs., LLC v. Garmin Int’l, Inc.*, 778 F.3d 1021, 1026 (Fed. Cir. 2015) (stating that “where the patent describes multiple embodiments, every claim does not need to cover every embodiment”).

Accordingly, Dr. Pomper’s statement that “low molecular weight” should be understood to be “about 50 Daltons to about 1,500 Daltons” should be credited and controlling. *Mycogen*, 243 F.3d at 1327; *Fenner*, 778 F.3d at 1323; *Sinorgchem*, 511 F.3d at 1138; *N. Am. Container*, 415 F.3d at 1346.

IV. GROUNDS 1 & 2: GE FAILS TO SHOW THAT IT IS REASONABLY LIKELY TO PREVAIL IN ESTABLISHING THAT THE CHALLENGED CLAIMS WOULD HAVE BEEN OBVIOUS.

To prevail as to the Petition’s obviousness grounds (Grounds 1 and 2), GE “must show that ‘a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention’” without resorting to hindsight. *NetScout Sys., Inc. v. Longhorn HD LLC*, IPR2021-01258, Paper 11 at 8-9 (P.T.A.B. Feb. 10, 2022) (quoting *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016)); *Grain Processing Corp. v. Am. Maize-Prod. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) (“Care must be taken to avoid hindsight reconstruction by using ‘the patent in suit as a guide through the maze of

prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.””).

Here, GE’s Petition fails on this account in both Grounds 1 and 2.

A. Ground 1: GE Uses Hindsight to Arrive at the Claimed Invention in View of the Combination of US-633, Jansen, and Meletta, and Thus Fails to Demonstrate Obviousness of the Challenged Claims.

In Ground 1 of the Petition, GE and Dr. Zeglis fail to consider the art as a whole and use impermissible hindsight to combine US-633, Jansen, and Meletta to arrive at the compounds of the Challenged Claims. But, a “[d]etermination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention.” *ATD Corp.*, 159 F.3d at 546. Rather, “[t]here must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.” *Id.* As discussed herein, Dr. Zeglis’s analysis ignores that the prior art as a whole would have presented a POSA with a sea of choices for the claimed “A” moiety and directed a POSA away from the claimed B-L-A structure, both of which would have led a POSA away from the claimed invention, rather than pursue Dr. Zeglis’s path that “cull[s] [components] from the prior art to fit the parameters of the patented invention.” *Id.*

Ground 1 should, therefore, be found legally and factually deficient and rejected.

1. GE and Dr. Zeglis’s incorrectly allege that a POSA would have arrived at the Challenged Claims based on the combination of US-633, Jansen, and Meletta.

Dr. Zeglis grounds the starting point for his obviousness analysis in his opinion that a POSA allegedly would have developed a FAP-targeting radiotracer having “a modular three-component design,” such as the claimed “B-L-A” structure. EX1003, ¶¶28, 71, 90; EX2001, ¶¶38-40. With that as his starting basis, Dr. Zeglis next alleges that a POSA would have purportedly been motivated to improve “the entire class of radiotracers described in US-633” by swapping out the corresponding FAPi of US-633’s compounds with a “new, more selective small molecule FAP inhibitor as the targeting moiety.” EX1003, ¶133; EX2001, ¶39. Dr. Zeglis then lands on Jansen’s Compound 60 as the “new, more selective” FAPi that a POSA would have allegedly selected to arrive at a claimed “B-L-A” compound. EX1003, ¶¶134-135; EX2001, ¶40.

But Zeglis’s analysis relying on linker-*containing* radiotracers is fundamentally flawed because he overlooks the fact that US-633 provides both linker-containing FAPi radiotracers (B-L-FAPi) *and* linker-less FAPi radiotracers (B-FAPi), and that a POSA would have favored the linker-*less* FAPi radiotracers based on the disclosures of US-633. EX1004, Abstract; EX2001, ¶¶41-49; *see*

§IV.A.1(a). Indeed, US-633 discloses that its linker-less compounds outperformed the linker-containing compounds in terms of FAP affinity. EX1004, Abstract; EX2001, ¶¶50-53; *see* §§IV.A.1(b)-(c). A POSA following Dr. Zeglis's path, therefore, would have had to start their alleged path to arriving at the claimed invention by first selecting the *worse*-performing linker-*containing* radiotracers from US-633 over the better-performing linker-*less* radiotracers. EX1004, Table 2, p. 34; EX2001, ¶¶54-66; *see* §§V.A.1(b)-(c). Yet, as discussed below and as Dr. VanBrocklin explains, Dr. Zeglis fails to show that a POSA would have had a reason to follow such a path. EX2001, ¶¶54-74; *see* §§IV.A.1(b)-(c).

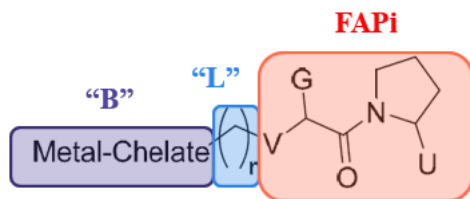
In selecting Jansen's Compound 60, moreover, Dr. Zeglis ignores other prior art publications presenting a multitude of FAPi candidates from which a POSA would have selected several other better-performing FAPis over Compound 60. EX1007, Tables 2-3; EX2003, Abstract, 1706; EX1044, Table 4; EX2001, ¶¶62-66, 77-79; *see* §§IV.A.2-IV.A.3.

In view of the above, Dr. Zeligs has improperly "selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp.*, 159 F.3d at 546; *WBIP*, 829 F.3d at 1337; *Amerigen*, 913 F. 3d at 1089.

- a. **Dr. Zeglis wrongly equates the two different radiotracer types disclosed in US-633 to erroneously arrive at selecting a linker-containing FAPi compound for further development.**

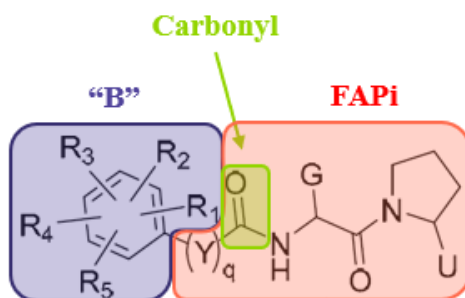
As discussed, Dr. Zeglis alleges that a POSA would have purportedly developed a FAP-targeting radiotracer having “a modular three-component design,” *i.e.*, the claimed B-L-A design, based on the FAPi radiotracers of US-633. EX1003, ¶¶28, 71, 90; EX2001, ¶¶38-40. In doing so, Dr. Zeglis incorrectly treats all of US-633’s radiotracers as having a modular three-component design. EX1003, ¶¶28, 71, 90; EX2001, ¶¶38-40.

In fact, US-633 discloses two sets of radiotracers: (i) radiotracers that have linkers (linker-containing) conjugated to a FAPi (that, importantly, is not the same as the claimed “A” moiety) and (ii) radiotracers that lack linkers (linker-less). EX1004, Abstract; EX2001, ¶¶41-42. It is only US’633’s linker-containing radiotracers that have the modular B-L-FAPi design, as shown by the annotation of a Formula I radiotracer from US-633:



Formula I
US-633, Abstract.

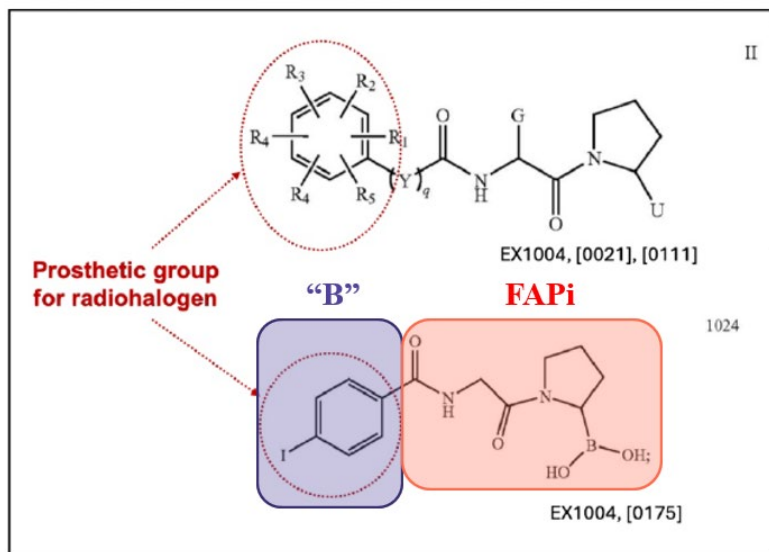
EX1004, Abstract; EX2001, ¶41. And US-633 discloses linker-less compounds, with radiohalogens directly conjugated to the aryl group of the FAPi and only a B-FAPi design, as illustrated below with the generic Formula II formula from US-633:



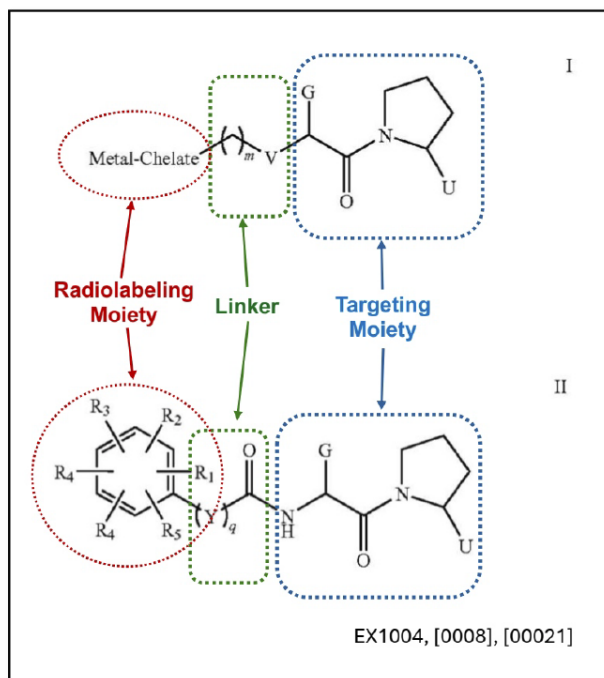
Formula II
US-633, Abstract.

EX1004, Abstract; EX2001, ¶42. For the Formula II compounds shown above, the substituent (Y)_q is depicted as a potential linker. EX2001, ¶42. But in 22 of the exemplified Formula II radiotracers, 20 have q=0, and the carbonyl is directly conjugated to the radioprosthetic "B" group. EX1004, ¶¶171-175, 178-180 (Compounds 1023-1033, 1039-48); EX2001, ¶42.

In discussing the radiotracers of US-633, Dr. Zeglis discussed Compound 1024, which is linker-less, as an example of a compound of Formula II.



EX1003, ¶156 (annotations added); EX2001, ¶43. In Dr. Zeligs's relied-upon example shown above, the iodine-containing radioprosthetic group corresponds to the B moiety. EX2001, ¶43. No linker component is present because the B moiety is directly conjugated to the FAPI. *Id.* Yet, Dr. Zeglis argues that the carbonyl group of Compound 1024 is a linker "L," as indicated by his green annotation in the figure below (EX1003, ¶71):



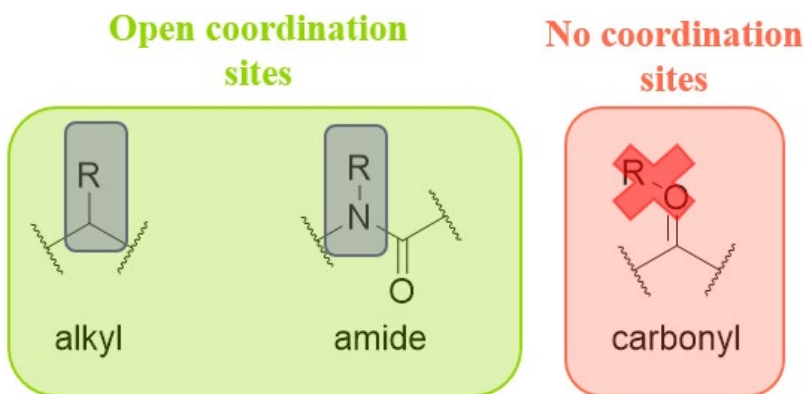
EX1003, ¶71; EX2001, ¶43. But, as Dr. VanBrocklin explains, Dr. Zeglis is incorrect; the carbonyl group in Compound 1024, and in other similar carbonyl containing compounds of US-633, is not a linker. EX2001, ¶¶44-47.

First, as Dr. Zeglis admits, a linker should “spatially separate the radiolabeling moiety from the targeting moiety.” EX1003, ¶35; EX2001, ¶44. But, a POSA would have known that the carbonyl group is one-carbon long. EX2001, ¶44. And a POSA would have understood that a one-carbon long “linker” would not have been able to serve this purpose: it would not have been long enough to spatially separate two groups from one another. *Id.*

Second, Dr. Zeglis alleges that “[l]inkers can be selected or designed to influence the biochemical and pharmacokinetic characteristics of the

radiopharmaceutical. For example, a radiopharmaceutical chemist can introduce hydrophobic character into a radiopharmaceutical by incorporating one or more benzyl groups into the linker moiety.” EX1003, ¶36; EX2001, ¶45. A POSA would have understood that a carbonyl group, however, *could not have served that purpose* of controlling the characteristics of a compound, because a carbonyl group cannot support additional bonds from the oxygen or carbon atoms of the group and thus cannot be modified. EX2021, 819; EX2001, ¶45. Indeed, the carbonyl cannot be removed because it is integrated into the B moiety. EX1004, ¶134, Scheme 5; EX2001, ¶45. And one cannot add a different group to replace the carbonyl. EX2001, ¶45.

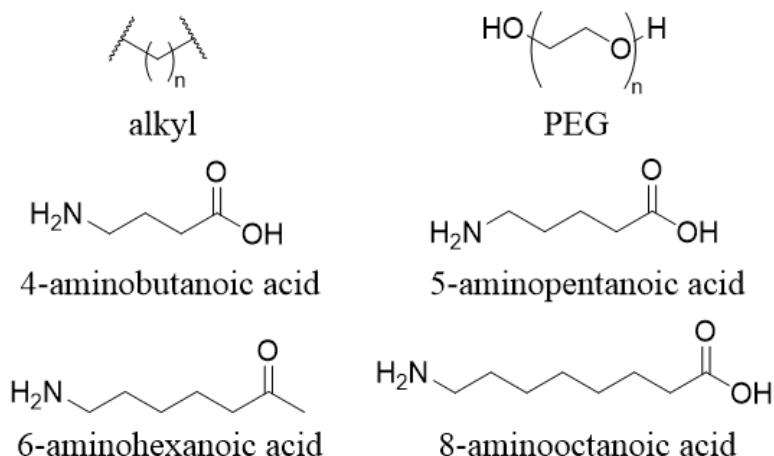
Dr. VanBrocklin shows in the figures provided below that the carbonyl group has no open sites for conjugation thus preventing a POSA from “introduc[ing] hydrophobic character” or any other substituent group that would “influence the biochemical and pharmacokinetic characteristics of the compound,” which Dr. Zeglis incorrectly states linkers would allow. *Id.*



Id. The carbonyl group's lack of coordination (bond-forming) sites stands in direct contrast to the linker groups US-633 discloses, such as alkyl or amide linkers, which would have allowed for modification of the physical properties of the compound via conjugation. *Id.*

Third, US-633 provides no disclosure that a carbonyl group could have been used as a linker, including not listing carbonyl groups among the numerous potential linkers US-633 discloses.² EX1004, ¶130 (listing the following groups as potential linkers: “a simple alkyl chain ..., a PEG (CH₂CH₂O)_n, a polyethylene amine ((CH₂CH₂NH)_n), or the like. Terminal aminoalkanoic acids (such as (β-alanine, 4-aminobutanoic acid, 5-aminopentanoic acid, 6-aminohexanoic acid and the 8-aminooctanoic acid) or amino-PEG-acids (NH₂–(CH₂CH₂O)_n–CH₂–COOH, e.g. 2-(2-(3-aminopropoxy)ethoxy)acetic acid).” EX2001, ¶46. Exemplary structures of the above linkers disclosed in US-633 are shown below, in which $n \geq 1$.

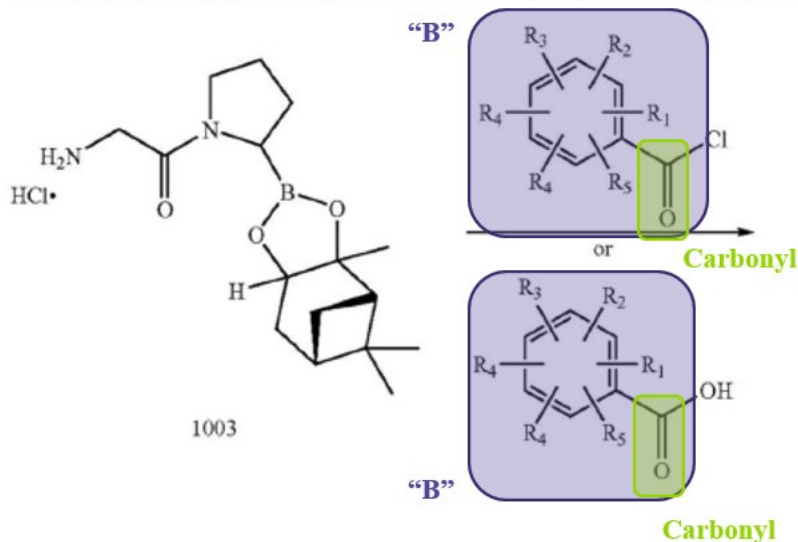
² Nor is a carbonyl listed as a potential linker in the '201 patent. *See, e.g.*, EX1001, 17:45-54; EX2001, ¶46, fn. 2.



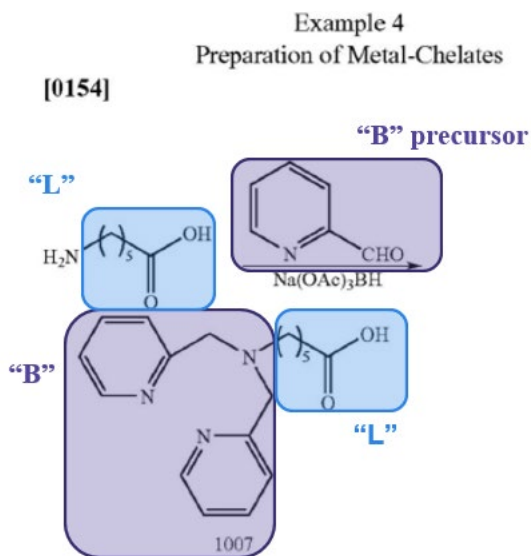
EX1004, ¶130; EX2001, ¶46.

Fourth, as discussed above, Dr. Zeglis states that linkers can be “selected or designed” to influence the properties of a compound. EX1003, ¶36; EX2001, ¶47. But a carbonyl group that is integrated into the B moiety, as US-633 discloses for its linker-less radiotracers, cannot be selected or designed because the B moiety is directly conjugated to the FAPi. EX2001, ¶47. Consequently, there is no potential for other selections in between the two groups. *Id.* As illustrated below, because the carbonyl group is directly integrated into the B moiety, a POSA would have understood that such a configuration would not have allowed for selecting other linking groups or “design[ing]” the compound differently:

Scheme 5: General synthesis of substituted benzamide glycineboronopropine seprase inhibitors, Formula II



EX1004, ¶134 (annotated); EX2001, ¶47. As shown above, the carbonyl of the linker-less radiotracers is already present as part of the B moiety prior to the B moiety's conjugation to the FAPi. EX2001, ¶¶47-48. In contrast, the syntheses disclosed in US-633 for the linker-containing radiotracers involve adding the linker to the B moiety before the step of conjugating the newly joined B-L structure to the FAPi. As an example, Example 4 of US-633 involves adding an alkyl linker to B before conjugating the B-L structure to the FAPi, as illustrated below:



EX1004, ¶154 (annotated); EX2001, ¶48.

US-633 also never discusses its “tethers,” *i.e.*, linkers, in the context of the Formula II compounds. EX1004, ¶¶101, 130, 133; EX2001, ¶49. Rather, each time the word “tether” appears in US-633, it is in reference *only* to the compounds of Formula I. EX1004, ¶¶101, 130, 133; EX2001, ¶49. Examples of such disclosures include the following statements:

- “The distance between the Metal-Chelate moiety and the pyrrolidine moiety of the complex *represented by Formula I can be varied by altering the tether and/or expanding the length of the tether* between them...” EX1004, ¶101;
- “Scheme 3 [describing the synthesis of a compound of Formula I] can be utilized to synthesize functionalized proline- $M^+(CO)_3$ complexes to

explore the effect of more significant variations of the distance of the metal chelator from the proline moiety by incorporating a tether into these structures.” *Id.*, ¶130; and

- “The above reaction scheme [Scheme 4, describing the synthesis of a compound of Formula I] is applicable to any modification of the tether.” *Id.*, ¶133.

EX2001, ¶49.

Accordingly, a POSA viewing US-633’s disclosures would have understood that US-633 discloses two classes of radiotracers: those having the B-L-FAPi design (linker-containing) and those having the B-FAPi design (linker-less). And, therefore, not all of US-633’s radiotracers employ a modular B-L-FAPi design that is required by each of the Challenged Claims. EX2001, ¶50.

- b. GE fails to show that a POSA would have started with US-633’s linker-containing radiotracers or added a linker to US-633’s linker-less radiotracers in view of US-633’s linker-less radiotracers showing greater affinity for FAP.**

As part of his hindsight-focused argument, Dr. Zeglis alleges that “a skilled artisan would have found it obvious to replace the boronic acid pyrrolidine targeting moiety in the FAP-targeting radiotracers described in US-633 with

compound 60 from Jansen” to arrive at the claimed modular B-L-A radiotracers.

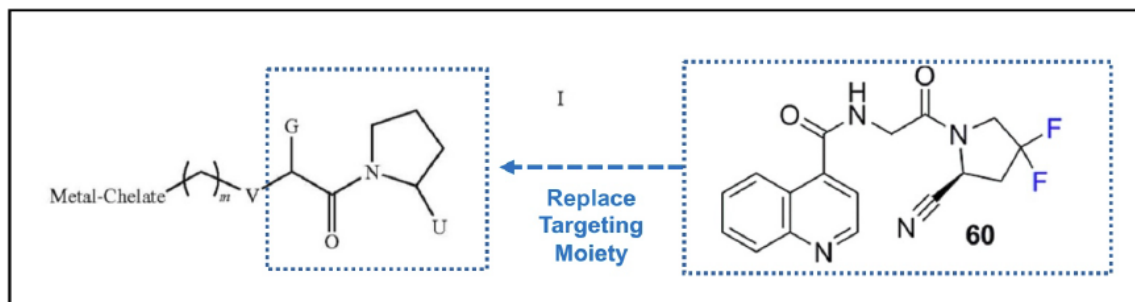
EX1003, ¶146; EX2001, ¶51.

For US-633’s linker-containing radiotracers, Dr. Zeglis alleges that a POSA would have proceeded with those radiotracers and swapped in Jansen’s Compound 60 for US-633’s FAPi to arrive at the claimed B-L-A. EX1003, ¶146; EX2001, ¶¶51-54. And for US-633’s linker-less radiotracers, Dr. Zeglis alleges that a POSA would have *added* a linker and also swapped in Jansen’s Compound 60 for US-633’s FAPi to arrive at the claimed B-L-A. EX1003, ¶146; EX2001, ¶¶55-59. Given the worse performance of US-633’s linker-containing FAPi radiotracers, a POSA would not have had a reason to start their development of a FAPi radiotracer by pursuing either path.³

i. GE fails to show that a POSA would have started with US-633’s linker-containing radiotracers for modification with Jansen’s Compound 60.

Dr. Zeglis provided the following figure showing his proposed modification of US-633’s linker-containing radiotracers, shown below:

³ As discussed below in §§IV.A.2.-IV.A.3., a POSA would not have been motivated to implement Jansen’s Compound 60 in US-633’s radiotracers in view of the prior art as a whole or even when following the criteria set forth in Dr. Zeglis’s analysis.



EX1003, ¶146; EX2001, ¶51.

Dr. Zeglis has not shown that a POSA would have begun their development of a FAPi radiotracer by making the first poor choice of selecting one of US-633's compounds *with* linkers for further modification in view of US-633's disclosures. EX2001, ¶¶52-54. Rather, a POSA would have understood US-633 to **discourage** using a FAP-targeting radiotracer with a linker. *Id.* GE's and Dr. Zeglis's proposed modifications of US-633's compounds, therefore, are incorrect and based on hindsight used to arrive at the claimed B-L-A structure. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) ("A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.").

Indeed, as Dr. Zeglis states, FAP affinity, *i.e.*, how tightly a FAP-targeting molecule binds to FAP, is "paramount" in choosing "the targeting moiety of a radiopharmaceutical." EX1003, ¶45. Yet, US-633 discloses that radiotracers

comprising a boronic acid pyrrolidine targeting moiety *and a linker*, i.e., those in B-L-FAPi format, performed *worse* in terms of FAP affinity compared to those comprising *the same boronic acid pyrrolidine target moiety without a linker*.
EX1004, Table 2, p. 34; EX2001, ¶¶51-54.

Table 2 from US-633, reproduced and annotated below, illustrates the inferior performance of US-633's linker-containing radiotracers compared to those without a linker, with the top performing radiotracers indicated with blue boxes:

TABLE 2	
Summary of in vitro data against seprase	
Compound No.	FAP (IC ₅₀ nM)
1010	2,540
1014	21
1016	3,533
1018	20
1020	4
1022	236
1023	7
1024	3
1025	2
1026	3
1027	5
1028	5
1029	8
1030	2
1031	262
1032	11
1033	500
1034	11
1035	340
1036	37
1039	511
1040	35
1041	692
1042	785
1043	115
1044	23,680
1045	1,437
1046	970
1048	7,414
1049	953
1050	1152
1051	67
1060	41,300
1061	24,540

Contain
Linkers

No Linkers

Contains Linkers

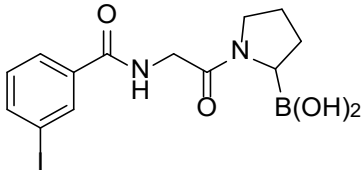
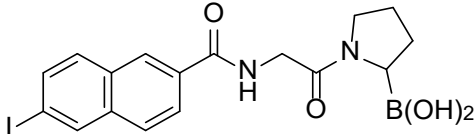
No Linkers

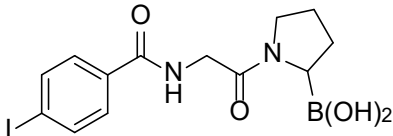
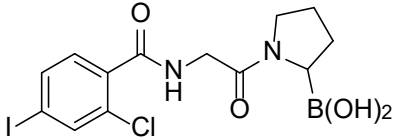
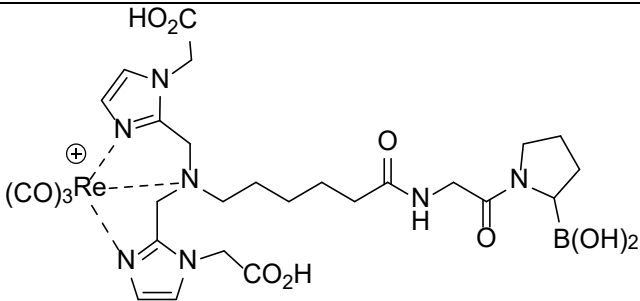
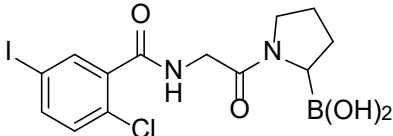
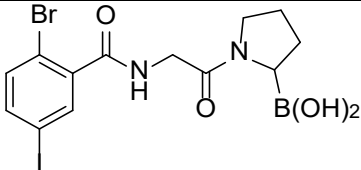
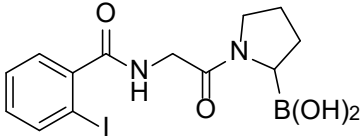
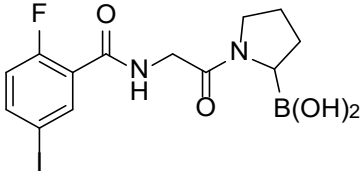
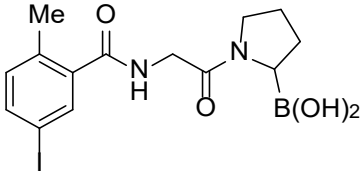
EX1004, Table 2, p. 34 (annotated); EX2001, ¶52.

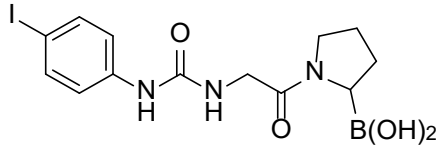
As shown in the annotated version of Table 2 from US-633, above, the linker-less radiotracers overall had the best FAP affinity. EX1004, Table 2, p. 34 (annotated); EX2001, ¶¶52-53. For instance, linker-less radiotracers 1025 and 1030 displayed the best FAP affinity—an IC_{50} of 2 nM. EX1004, Table 2, p. 34 (annotated); EX2001, ¶53. Table 2 of US-633 also discloses that nine of the top eleven radiotracers with the highest FAP affinities are achieved with linker-less radiotracers, rather than with linker-containing radiotracers. EX1004, Table 2, p. 34 (boxes); EX2001, ¶53.

The structures of those eleven radiotracers with the highest FAP affinity are shown in the table below. EX1004, Table 2, p. 34 (annotated); EX2001, ¶53. As Dr. VanBrocklin explains, a POSA would have been able to easily identify these compounds from a review of the data in US-633's Table 2 and comparing the IC_{50} values, with the lower IC_{50} values meaning better affinity:

Tabulated highest affinity radiotracers of US-633.

US-633 Compound No.	IC_{50} (nM)	Formula	Structure
1025	2	II (linker-less)	
1030	2	II (linker-less)	

US-633 Compound No.	IC ₅₀ (nM)	Formula	Structure
1024	3	II (linker-less)	
1026	3	II (linker-less)	
1020	4	I (linker-containing)	
1027	5	II (linker-less)	
1028	5	II (linker-less)	
1023	7	II (linker-less)	
1029	8	II (linker-less)	
1032	11	II (linker-less)	

US-633 Compound No.	IC ₅₀ (nM)	Formula	Structure
1034	11	II (linker- containing)	

EX1004, Table 2; EX2001, ¶53.

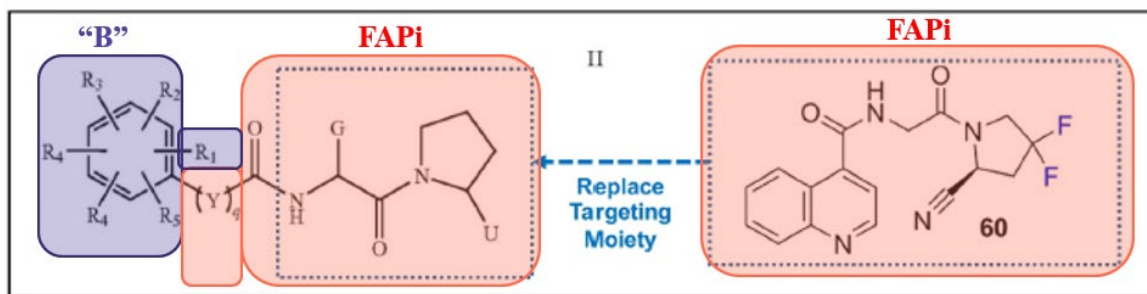
Consequently, only two of the B-L-FAPi (i.e., linker-containing) radiotracers in US-633 had high FAP affinity, whereas the remainder of the top performers were linker-less radiotracers (nine linker-less radiotracers). EX2001, ¶¶53-54. And given that, Dr. Zeglis's claim that a POSA would have begun their development of a FAPi radiotracer by moving forward with modifying a linker-containing radiotracer is driven by the hindsight-based desire to arrive at the claimed B-L-A formula, rather than by US-633's teachings as a whole.

ii. A POSA would not have added a linker to US-633's linker-less radiotracers for modification with Jansen's Compound 60.

In addition to erroneously arguing that a POSA would have chosen US-633's linker-containing compounds for modification with Jansen's Compound 60, Dr. Zeglis alleges that a POSA would have also begun their development of a FAPi radiotracer by selecting US-633's linker-less compounds to arrive at the claimed compounds. EX1003, ¶146; EX2001, ¶¶55-57. But to do so and then arrive at the claimed invention, a POSA would have had to make the additional modification of

adding a linker, which as discussed above US-633 discloses as being detrimental to activity. *See* §IV.A.1(a); EX2001, ¶¶55-59.

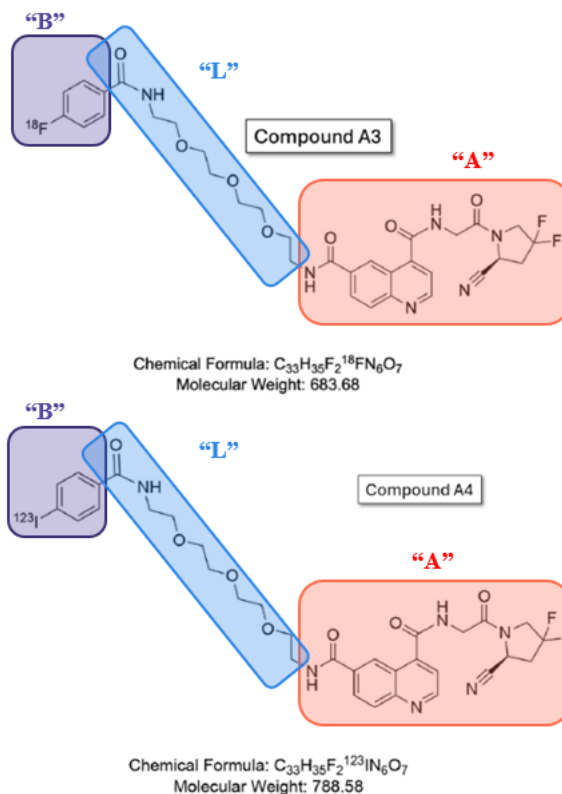
In advancing this argument, Dr. Zeglis, however, does not state that his proposed modification would require adding a linker between the corresponding B moiety and the FAPi of US-633's linker-less radiotracers. EX1003, ¶146; EX2001, ¶55. Indeed, reproduced below is an annotated version of the figure provided by Dr. Zeglis that depicts his proposed modification:



EX1003, ¶146 (purple and red annotations added); EX2001, ¶55. As discussed in §IV.A.1(a), the B moiety in the radiotracer depicted above is directly conjugated to the FAPi moiety.

Dr. Zeglis's declaration also makes evident that he understands that a linker would have had to be introduced into US-633's linker-less compounds, although he does not articulate it. EX2001, ¶56. In discussing his proposed modification of US-633's linker-less radiotracers, Dr. Zeglis provides hypothetical Compounds A3 and A4 that would have been the supposed result of his proposed modification of US-633's radiotracers with Jansen's Compound 60. EX1003, ¶161; EX2001, ¶¶56-

57. Dr. Zeglis's hypothetical Compounds A3 and A4 are reproduced below,
annotated by Dr. VanBrocklin:

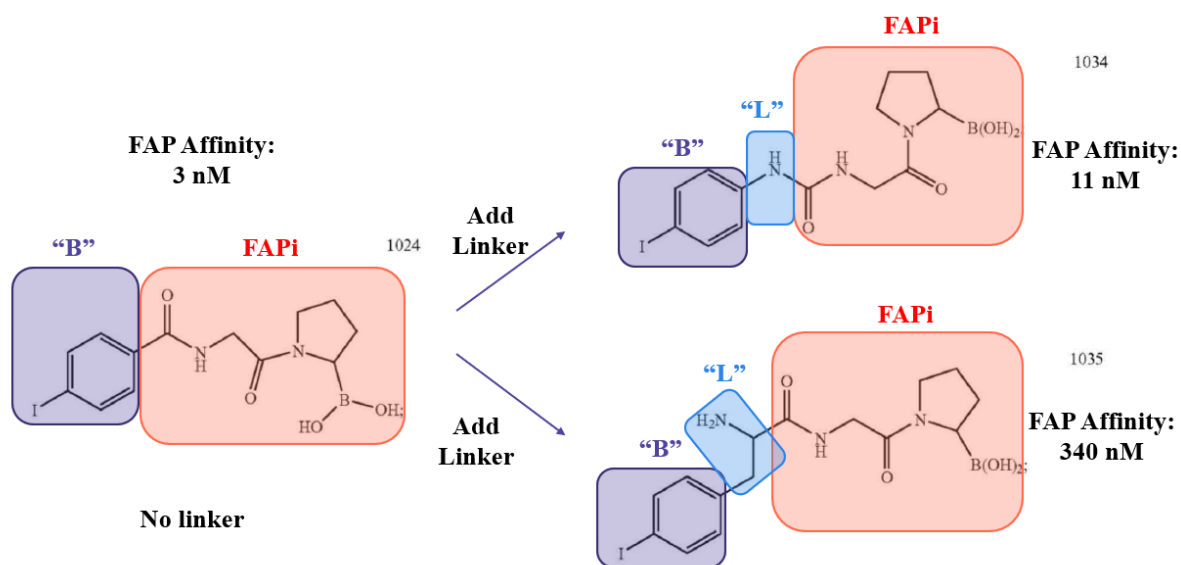


EX1003, ¶161 (annotations added); EX2001, ¶56.

To arrive at the compounds Dr. Zeglis proposed above, a POSA would have had to not only replace US-633's FAPi with Compound 60, but also add a linker (depicted in blue) between the B (the radioprosthetic group) and the A (Compound 60). EX1003, ¶161; EX2001, ¶57. But in view of US-633's disclosures, a POSA would not have been directed to add a linker and create a linker-containing compound because those were inferior to the linker-less compounds in terms of FAP affinity. EX1004, Table 2; EX2001, ¶57. To the extent that the Board

determines that US-633's teachings do not rise to the level of teaching away from employing a linker (which US-633's teachings do), the evidence demonstrates that US-633 provides substantial evidence that would have discouraged a POSA from pursuing linker-containing radiotracers. *Arctic Cat Inc. v. Bombardier Recreational Prods. Inc.*, 876 F.3d 1350, 1363 (Fed. Cir. 2017) (even if “evidence may not rise to the level of teaching away ... reasons to combine cannot be viewed in a vacuum apart from evidence suggesting reasons not to combine”); *Lab’y Corp. of Am. Holdings v. Ravgen, Inc.*, No. 2023-1342, 2025 WL 32904, at *4 (Fed. Cir. Jan. 6, 2025) (“Even if evidence does not ‘rise to the level of teaching away,’ it is still proper for the Board to consider evidence that ‘suggests reasons that a skilled artisan would be discouraged from pursuing such a combination.’”).

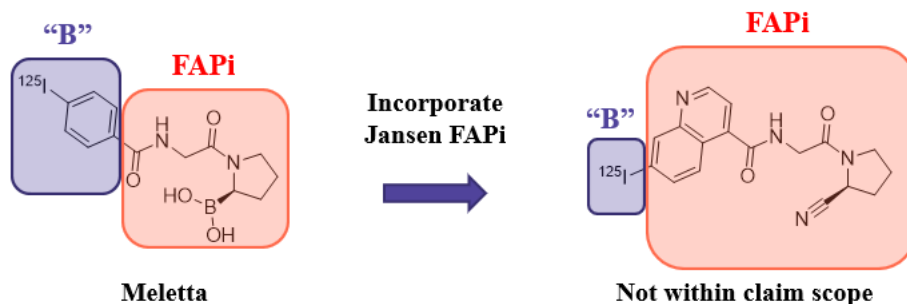
Indeed, US-633 discloses that adding a linker to the linker-less compounds of US-633 reduces FAP affinity, as the figure below shows:



EX2001, ¶57. The figure above shows that taking linker-less Compound 1024, with a FAP affinity of 3 nM, and adding a linker to arrive at Compounds 1034 and 1035 with linkers resulted in a reduction of FAP affinity: FAP affinity is reduced to 11 nM and 340 nM, respectively. EX1004, Table 2; EX2001, ¶57.

What is more, as Dr. VanBrocklin explains, were a POSA to “replace[] the boronic acid pyrrolidine targeting moiety in [the linker-less radiotracers] of US- 633 [] with compound 60,” as Dr. Zeglis suggested (EX1003, ¶146), a POSA would have arrived at compounds that *do not fall* within the scope of the challenged claims because they do not have the claimed “B-L-A” formula.

EX2001, ¶¶58-59. This is illustrated below:



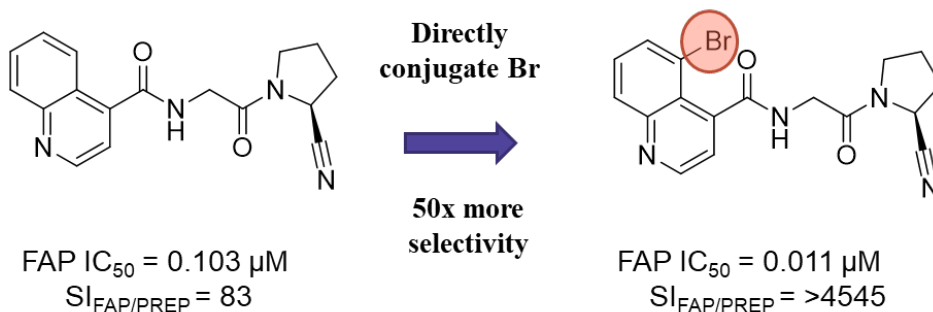
EX2001, ¶58. The above compound has formula B-FAPi, not B-L-A as required by the claims. *Id.*

c. Known structure-activity relationship (SAR) for quinolinyl-based FAPis would not have directed a POSA to linker-based radiotracers.

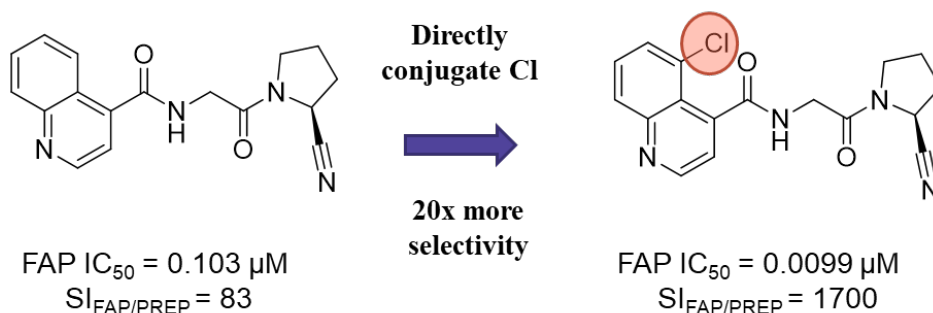
In addition to the above, Dr. Zeglis's opinion that a POSA would have chosen to begin its alleged path to the claimed invention by pursuing linker-containing compounds ignores known structure-activity relationship (SAR) data for quinolinyl-based FAPis that were present in the prior art. Without considering the prior art as a whole, Dr. Zeglis argues that a POSA "would have viewed use of a linker in a radiotracer based on compound 60 to be preferable to direct attachment of a radiohalogen to the quinolinyl ring of compound 60" purportedly because (1) "it would allow use of a radiometal as a radionuclide;" and (2) "some adverse effects on selectivity/affinity were observed when a halogen (e.g., bromine) was attached to C⁵ position of the quinolinyl ring of [Jansen's] compound 60 (forming compound 62)." EX1003, ¶139; EX2001, ¶60.

But, as illustrated below, the prior art had disclosed by 2017 that adding halogen substituents to the 6 and 7 positions of a FAPi's quinolinyl ring ***dramatically increased*** both FAPi selectivity and affinity. *Id.* As the figure below illustrates, adding a bromine or chlorine to the 6 position of the quinolinyl ring increases selectivity by 50x and 20x, respectively:

Jansen 2013 teaches that direct conjugation of halogens
to the quinolinyl group increases selectivity:



Jansen 2013 teaches that direct conjugation of halogens
to the quinolinyl group increases selectivity:



EX2003, Tables 2-3; EX2001, ¶60.

Thus, as Dr. VanBrocklin explains, a POSA would not have viewed using a linker in a FAPi-based radiotracer to be “preferable to direct attachment of a radiohalogen to the quinolinyl ring” because *direct halogenation* of the quinolinyl ring actually *benefited* FAPi’s selectivity and affinity. EX1003, ¶139; EX2001, ¶61. Yet because direct halogenation would have resulted in a compound outside the claim scope, Dr. Zeglis instead relies on a hindsight-driven path that lacks scientific justification in view of the art, so as to arrive at using a linker to make the B-L-A compounds. EX2001, ¶¶60-61. Indeed, Dr. Zeglis does not explain why

a POSA would have ignored the known SAR data in the art discussed above for quinolinyl-based FAPis. EX2001, ¶61.

In sum, given the art as a whole, had a POSA wanted to add a radiohalogen to Jansen's FAPis, a POSA would not have selected a linker to do so, contrary to Dr. Zeglis's argument. EX2001, ¶¶55-61. A POSA, therefore, would not have arrived at the claimed B-L-A compounds for at least this reason. *Id.*

2. Dr. Zeglis ignores the FAPi prior art as a whole in focusing on Jansen's Compound 60 over other known FAPis with better FAP selectivity that do not fall within the scope of the Challenged Claims, demonstrating his use of hindsight.

In alleging that a POSA would have combined US-633, Jansen, and Meletta, GE relies on Dr. Zeglis's opinion that a POSA would have supposedly selected Jansen's Compound 60, which the prior art did not disclose as being in a B-L-A structured radiotracer,⁴ to modify US-633's compounds. Pet., 65; EX1003, ¶134; EX2001, ¶62. Yet, as set forth below, in doing so, Dr. Zeglis ignores numerous other FAPis disclosed in other prior art references that had better FAP selectivity, which Dr. Zeglis opines is "ultimately the most important factor" in selecting a

⁴ In PGR2025-00059, the Board erroneously preliminary concluded that Jansen discloses that "compound 60 is already in B-L-A form [i.e., B-L-FAPi]."

PGR2025-00059, Paper 8 at 25. In fact, no FAPis encompassed by the claimed A moiety were disclosed as being B-L-FAPi structured radiotracers. EX2001, ¶21.

FAPi. EX1003, ¶45, fn. 50; EX2001, ¶¶62-67. Dr. Zeglis’s cherry-picking of the art demonstrates his hindsight reconstruction of the art to arrive at the challenged claims. *Impax Lab’s Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379-80 (Fed. Cir. 2018) (the court not finding claims obvious when it “properly considered additional record evidence to make findings *on the state of the prior art as a whole*,” and stating that “in an obviousness analysis, prior art should be viewed as a whole”); *WBIP*, 829 F.3d at 1337 (the court finding claims nonobvious while noting that “[w]hether a skilled artisan would be motivated to make a combination includes whether he would select particular references in order to combine their elements”). Indeed, Dr. Zeglis’s analysis is flawed and hindsight-driven because after making the choice of selecting the worse performing linker-containing FAPi radiotracer structure, he overlooks other references in the art that disclosed copious known FAPis. EX2001, ¶63. And those overlooked references include numerous FAPis that performed better than Jansen’s Compound 60, yet Dr. Zeglis does not explain why he ignored them. *Id.*

For instance, Meletta selected for evaluation one of US-633’s linker-less Formula II compounds as “a target for atherosclerosis imaging” because of its “high binding affinity to FAP,” its favorable selectivity profile (“MIP-1232 was 32-fold more potent in inhibiting FAP than PREP”), and “the possibility to radioiodinate MIP-1232 without altering its structure.” EX1008, 2083; EX2001,

¶63. Based on *in vitro* studies that found Meletta's compound to not selectively accumulate in target tissue, Dr. Zeglis alleges a POSA would have been led to look for "new, more selective FAP inhibitors, ... [to] invariably discovered the compounds characterized in Jansen." EX1008, 2089; EX1003, ¶134; EX2001, ¶¶62-63. But Dr. Zeglis fails to provide any reason why a POSA would have looked to Jansen in particular over all the other available references disclosing more selective FAPis, *including other references from Jansen's research group*, for a suitable FAPi to use in modifying Meletta's [¹²⁵I]MIP-1232 that failed to selectively accumulate in target tissue. EX2001, ¶¶62-63.

In fact, after describing the shortcomings of US-633's Compound [¹²⁵I]MIP-1232, Meletta states: "[t]o overcome limitations in specificity, novel lead structures and the use of antibodies and fusion proteins was proposed to minimize off-target effects." EX1008, 2090; EX2001, ¶¶62-63. And at the end of that sentence, Meletta cites three references: Jansen 2013 (EX1007), a reference pertaining to an anti-FAP antibody, and Jansen. EX1008, 2090, fn. 24, 34, and 44; EX2001, ¶63.

Skipping over Jansen 2013, Dr. Zeglis jumps straight to Jansen with no explanation. *See, e.g.*, EX1003, ¶¶104-105; EX2001, ¶63. But that lack of explanation as to why Dr. Zeglis ignored Jansen 2013 is glaring when (1) one notes that Dr. Zeglis indicates that he considered Jansen 2013 (EX1003, ¶¶142, fn. 166,

167. C-3); and, as discussed below, (2) Jansen 2013 is considered in context with Jansen and other publications disclosing FAPis. EX2001, ¶63.

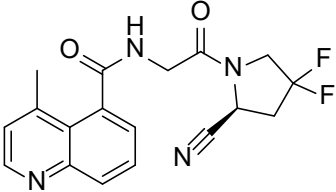
Jansen 2013 investigated the FAP and PREP affinities (and, therefore, the FAP selectivity) of 36 FAPi compounds. EX1007, Tables 2-3; EX2001, ¶64. And given that both Jansen 2013 and Jansen are directed to FAPis, and the fact that both Jansen's and Jansen 2013's FAPis are cited in Meletta, a POSA would have considered the FAPis of Jansen 2013 alongside those of Jansen. EX2001, ¶¶63-64. But Dr. Zeglis's obviousness analysis does not indicate that he evaluated Jansen 2013's compounds in selecting FAPis for modifying US-633's compounds, nor does he state why rejected the compounds of Jansen 2013, some of which were more selective than Compound 60, in favor of Jansen's Compound 60. EX1007, Tables 2-3; EX2001, ¶64.

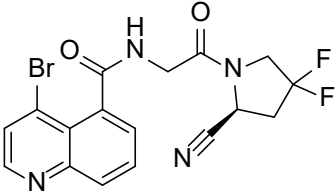
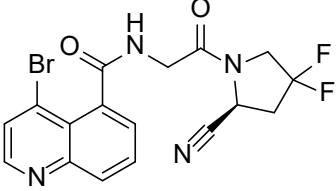
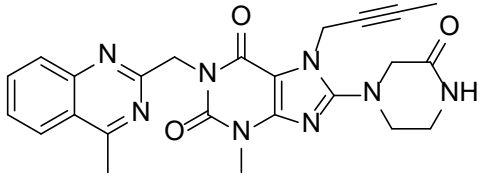
Dr. Zeglis also indicates that he considered US-650 (EX1044), also by Jansen. EX1003, ¶142, fn. 165, C-6; EX2001, ¶66. But, Dr. Zeglis's obviousness analysis does not indicate that he evaluated the compounds of US-650 for modifying US-633's compounds, nor does he state why he rejected the compounds of US-650 in favor of Jansen's Compound 60. EX2001, ¶66. In fact, US-650 discloses 43 FAPi compounds, many of which are highly selective for FAP and out-performed Jansen's Compound 60. EX1044, Table 4; EX2001, ¶66.

Also missing from Dr. Zeglis’s analysis is any discussion of another publication by Jansen (“Jansen 2014”; EX2003), describing a host of non-quinolinyl based FAP inhibitors that also do not fall within the scope of the claimed compounds. EX2003, Abstract, 1703, Tables 3-6; EX2001, ¶65. A POSA would have been aware of these 33 FAPis with xanthine scaffolds disclosed in Jansen 2014. EX2003, Abstract, 1703, Tables 3-6; EX2001, ¶65. And Jansen 2014 discloses that those 33 FAPis “display affinities in the low micromolar range” and were deemed to be “selective FAP-inhibitors[.]” EX2003, Abstract, 1706; EX2001, ¶65. Yet, Dr. Zeglis does not explain why a POSA would have not considered the FAPis of Jansen 2014 when modifying the compounds of US-633. *Id.*

The table below illustrates the numerous FAPi choices that a POSA would have had in front of them when purportedly deciding how to modify the compounds of US-633:

Overview of Prior Art References that Disclose Selective FAPis

Reference	Number of FAPis disclosed	Number of FAPis that fall within claims	Highest-selectivity FAPi
Jansen	54	6	 (Not within claimed “A” moiety scope)

Reference	Number of FAPis disclosed	Number of FAPis that fall within claims	Highest-selectivity FAPi
US-650	43	1	 (Not within claimed “A” moiety scope)
Jansen 2013	36	2	 (Not within claimed “A” moiety scope)
Jansen 2014	33	None	 (Not within claimed “A” moiety scope)

EX2001, ¶¶67.

In short, Dr. Zeglis ignored or did not explain why POSAs would not have chosen any of the above prior art compounds when evaluating suitability of FAPis for a radiotracer. *Id.*, ¶¶62-67. Notably, the table shows that the FAPi demonstrating the highest FAP selectivity in each reference does not fall within the scope of the claimed “A” moiety, highlighting Dr. Zeglis’s hindsight bias when performing his obviousness analysis, because he ignored the high-selectivity

radiotracers in favor of selecting radiotracers that could lead to the challenged claims. *Id.*

3. Dr. Zeglis’s selection of Compound 60 is driven by hindsight.

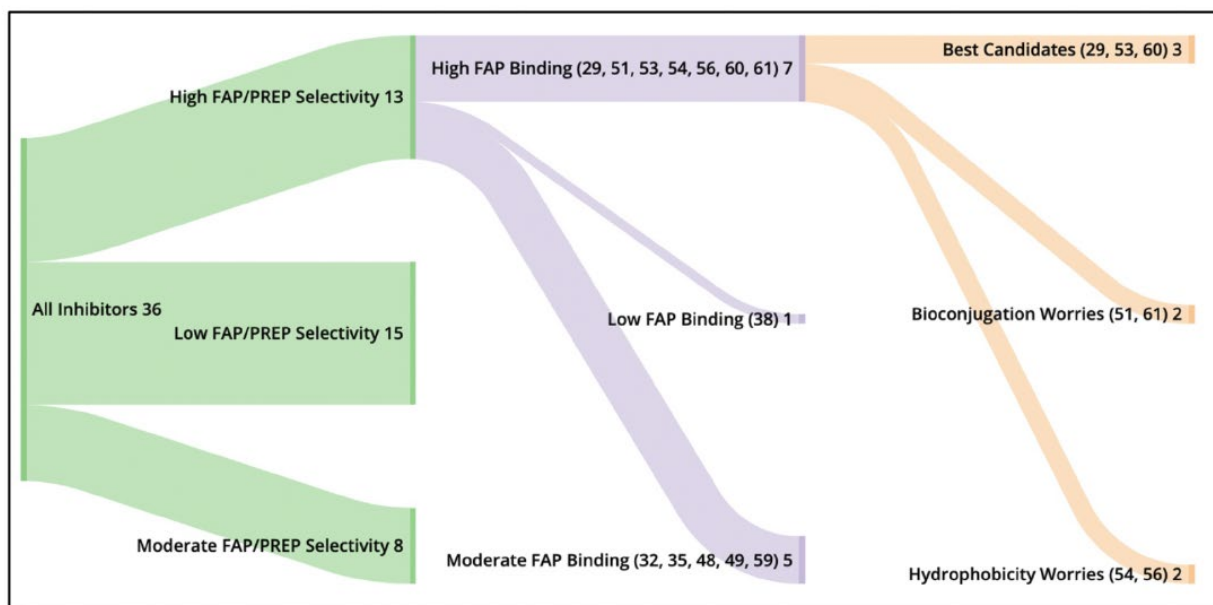
Dr. Zeglis’s selection of Compound 60 from Jansen is unsupported and erroneous in view of his own selection criteria and the art as a whole. EX2001, ¶¶68-79. Indeed, a POSA following Dr. Zeglis’s own Sankey diagram approach would not have invariably arrived at Compound 60. *Id.* As described below, Dr. Zeglis inappropriately eliminates other compounds using his Sankey diagram approach. *See* Section IV.A.3.a.

a. Dr. Zeglis’s classification scheme is arbitrary and lacks independent support.

Dr. Zeglis alleges that “a skilled artisan would have viewed compound 60 as one of the most promising FAP inhibitors that had been discovered to date,” and therefore a POSA would have selected it for improving US-633’s radiotracers. EX1003, ¶115; EX2001, ¶68. In selecting Compound 60, Dr. Zeglis claims that a POSA would have first purportedly “rank[ed] the compounds based on their selectivity index and select[ed] those exhibiting the highest selectivity values.” EX1003, ¶118; EX2001, ¶69. Dr. Zeglis states that a POSA then would have allegedly “prioritiz[ed] the compounds based on their affinity for FAP,” and finally would have “assess[ed] the structures of the compounds to identify any concerns

with respect to stability, hydrophobicity, or ease of modification.” EX1003, ¶118;
EX2001, ¶69.

To present his analysis, Dr. Zeglis relies on “a visual representation of [the] classification process using a so-called Sankey diagram” (EX1003, ¶121):



Dr. Zeglis’s Sankey diagram, however, is unsupported. EX2001, ¶70.

Dr. Zeglis uses the following scales for classifying Jansen’s compounds on the basis of selectivity and affinity:

High selectivity	$IC_{50}^{PREP}/IC_{50}^{FAP} > 100$
Moderate selectivity	$10 < IC_{50}^{PREP}/IC_{50}^{FAP} < 100$
Low selectivity	$IC_{50}^{PREP}/IC_{50}^{FAP} < 10$

High affinity	$IC_{50}^{FAP} < 0.1 \mu M$
Moderate affinity	$0.1 \mu M < IC_{50}^{FAP} < 1.0 \mu M$
Low affinity	$IC_{50}^{FAP} > 1.0 \mu M$

EX1003, ¶119; EX2001, ¶71.

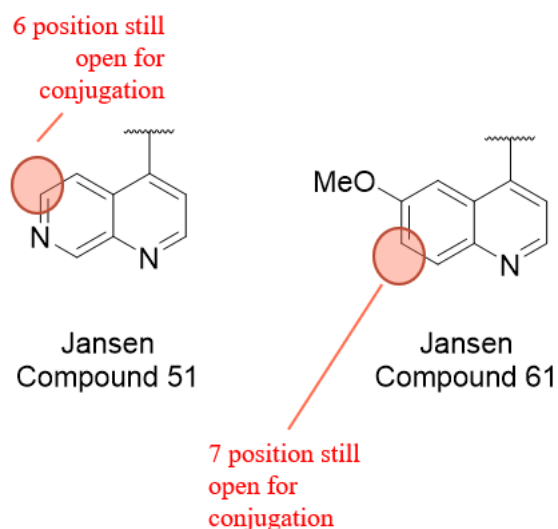
Dr. Zeglis, however, does not explain the basis for those cutoffs in his classification scheme in relation to FAP. EX1003, ¶119-120; EX2001, ¶¶70-71. That alone should render his testimony on this point to have little or no weight. *See* 37 C.F.R. § 42.65(a) (“[e]xpert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”).

Moreover, Dr. Zeglis provides no explanation regarding why a POSA would have further classified Jansen’s compounds based on stability, hydrophobicity, and ease of modification. EX1003, ¶119; EX2001, ¶72. In fact, Jansen provides numerous other parameters that a POSA could have considered, such as kinetic solubility, log D, plasma stability, microsomal stability, cytotoxicity, T_{max} , C_{max} , $T_{1/2}$, AUC, Cl, V_d , and relative bioavailability. *See, e.g.*, EX1006, Tables 7-8; EX2001, ¶72. Contrary to the art, Dr. Zeglis did not account for those factors when choosing or excluding Jansen’s FAPis for consideration. EX2001, ¶72.

When applying classification of Jansen’s compounds based on stability, hydrophobicity, and ease of modification, moreover, Dr. Zeglis is conclusory,

stating without explanation or evidence that two compounds “would pose bioconjugation issues” and that two others would raise “hydrophobicity concerns due to pendant phenyl groups.” EX1003, ¶120; EX2001, ¶¶72-73. Dr. Zeglis also does not explain what is meant by “bioconjugation issues” or the criteria for determining which compounds would be susceptible to such “worries.” EX2001, ¶¶72-73.

Dr. Zeglis also eliminates Jansen’s Compounds 51 and 61, which do not fall within the scope of the claimed “A” moiety, without sufficient justification. EX2001, ¶¶73-74. Indeed, by Dr. Zeglis’s own admissions, those compounds have high selectivity and affinity. EX1003, ¶120; EX2001, ¶73. Dr. Zeglis eliminates Compounds 51 and 61, however, because those compounds “would pose conjugation issues because of their 7 and 6 position substitutions, respectively, on the quinoliny ring would be occupied.” EX1003, ¶120; EX2001, ¶73. But in fact, occupying only *one* of the two 7 and 6 position sites would still have allowed for conjugation, as shown below:

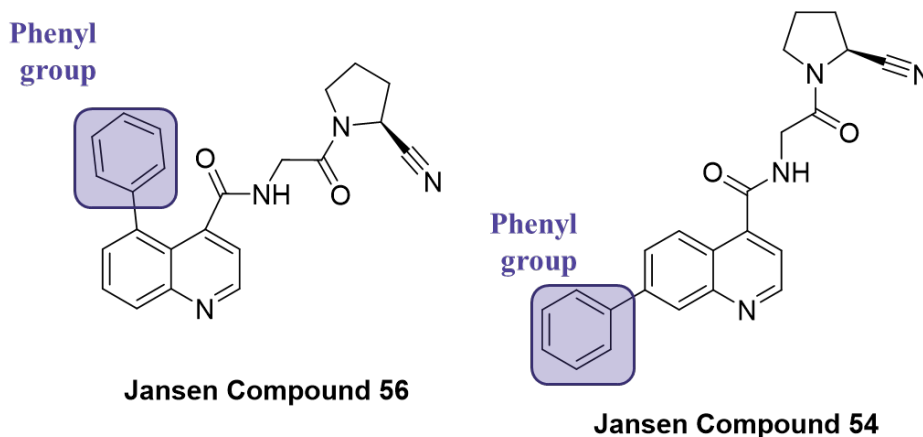


EX2001, ¶73.

Notably, choosing either of the above compounds to replace the FAPi in US-633's radiotracers would have resulted in compounds outside the scope of the claimed compounds because (1) Compound 51 does not have a quinolinyl ring required by the claims; and (2) Compound 61 has a substituent on the quinolinyl ring (MeO-), which is excluded by the claims. EX1002, 508-509; EX2001, ¶74. Dr. Zeglis, therefore, discarded Jansen's Compounds 51 and 61 in favor of Compound 60 in hindsight. EX2001, ¶74.

Additionally, Dr. Zeglis does not provide the basis for his threshold for determining when hydrophobicity might pose a concern. EX1003, ¶120; EX2001, ¶¶75-76. To that end, Dr. Zeglis eliminates Jansen's Compounds 54 and 56, which also have high affinity and selectivity according to Dr. Zeglis's criteria and which do not fall within the scope of the claimed "A" moiety, due to unsubstantiated

“hydrophobicity worries” because of the presence of a phenyl ring in those compounds, as depicted below. EX1003, ¶120; EX2001, ¶¶75-76.



EX2001, ¶75.

Dr. Zeglis, however, fails to establish with any evidence that a single pendant phenyl ring would have disqualified a FAPi from consideration based on PK concerns. EX2001, ¶¶75-76; EX2018, 2213-2214; EX2019, 2535; EX2020, 254-256. Dr. Zeglis, therefore, inappropriately discounts Compounds 54 and 56, which notably both contain substituents that are excluded from the claimed compounds. EX2001, ¶¶75-76; EX2018, 2213-2214; EX2019, 2535; EX2020, 254-256.

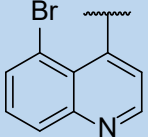
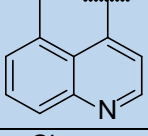
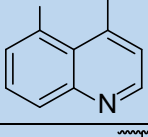
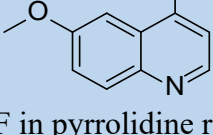
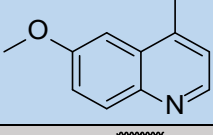
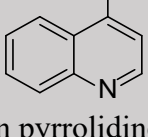
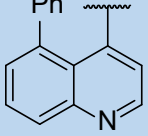
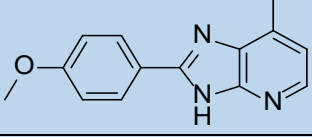
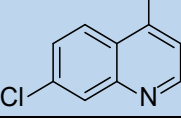
In sum, Dr. Zeglis makes unfounded, conclusory, or arbitrary choices in performing his Sankey analysis—that fortuitously eliminates four compounds (Compounds 51, 54, 56, and 61) that do not fall within the scope of the claimed “A” moiety—to land on Jansen’s Compound 60 as his final choice. *Id.*, ¶¶68-76.

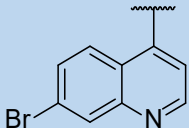
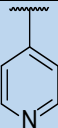
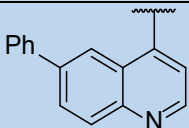
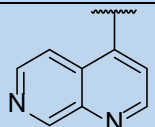
b. A POSA, following Dr. Zeglis' classification scheme, would not have arrived at Compound 60 due to the numerous other superior compounds.

As discussed in §IV.A.2., copious other FAPis were known in the art before October 2017. But, when creating his classification scheme, Dr. Zeglis looked solely to Jansen's compounds. EX1003, ¶¶119-121; EX2001, ¶¶63, 77. A POSA, however, would not have looked solely to Jansen when identifying suitable FAP inhibitors. EX2001, ¶¶63-66, 77. Instead, a POSA would have looked to the prior art as a whole, which includes publications such as US-650 and Jansen 2013. *Id.* Dr. Zeglis was aware of those publications, yet did not include them in his flawed Sankey analysis. This renders GE's Ground 1 flawed for at least this additional reason. *Impax*, 893 F.3d at 1380 (stating that "in an obviousness analysis, prior art should be viewed as a whole").

US-650 and Jansen 2013 both disclose FAPis that not only meet Dr. Zeglis's selectivity and affinity criteria, but outperform Compound 60. EX2001, ¶77. Dr. VanBrocklin provides a tabulated set of FAPis disclosed in Jansen, US-650, and Jansen 2013 that meet Dr. Zeglis's arbitrary selectivity and affinity criteria (selectivity >100 and affinity <0.1 µM), which are shown in the table below. EX2001, ¶77. The various FAPis are ranked in the order of selectivity (calculated by dividing $IC_{50}^{PREP}/IC_{50}^{FAP}$) that Dr. Zeglis has stated is the "most important" characteristic. EX1003, ¶¶45, 117; EX2001, ¶77.

FAP Selectivity and Affinity Across Jansen, US-650, & Jansen 2013

Compound Number	Structure	FAP Selectivity	FAP Affinity (μM)	Fall within scope of claims?
US-650: 22, Jansen 2013: 26		>4500	0.011	N
US-650: 23, Jansen: 54		2100	0.0043	N
US-650: 21, Jansen 2013: 25		1700	0.0099	N
US-650: 24, Jansen: 61	 (F, F in pyrrolidine ring)	970	0.0085	N
US-650: 11, Jansen 2013: 30		677	0.0092	N
US-650: 1, Jansen: 60	 (F, F in pyrrolidine ring)	562	0.0032	Y
US-650: 25, Jansen: 56		280	0.07	N
US-650: 28		>200	<0.2	N
US-650: 13, Jansen 2013: 31		197	0.0071	N

Compound Number	Structure	FAP Selectivity	FAP Affinity (μM)	Fall within scope of claims?
US-650: 12, Jansen 2013: 32		193	0.0062	N
US-650: 4, Jansen: 29		179	0.063	N
US-650: 26, Jansen: 54		135	0.064	N
US-650: 33, Jansen: 51		120	0.028	N

The table above demonstrates that, under Dr. Zeglis’s own criteria, five other compounds (all ignored by Dr. Zeglis) would have been known to a POSA as outperforming Jansen’s Compound 60 in terms of selectivity and affinity. EX2001, ¶78. And none of those five compounds fall within the scope of the claimed “A” moiety. *Id.* In fact, except for Jansen’s Compound 60, none of the remaining seven compounds in the list of 13 above fall within the scope of the claimed “A” moiety. *Id.* In view of this, Dr. Zeglis fails to establish why a POSA would have selected Compound 60 for modifying the compounds of US-633 in light of all the other FAPis known in the art, except for the fact that only Compound 60 falls within the scope of the claimed “A” moiety. *Id.*

This demonstrates the hindsight-based approach that GE and Dr. Zeglis have taken in the Petition’s Ground 1. This is sufficient to find that GE has failed to

demonstrate that it is more likely than not that the Challenged Claims are unpatentable over US-633, Jansen, and Meletta. *ATD Corp.*, 159 F.3d at 546 (a “[d]etermination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention”); *Impax*, 893 F.3d at 1380 (stating that “in an obviousness analysis, prior art should be viewed as a whole”).

* * *

In sum, for Ground 1, Dr. Zeglis begins his obviousness analysis by first selecting the poorer performing linker-containing FAPi radiotracer structure. Yet, Dr. Zeglis fails to establish why a POSA would have incorporated a linker into US-633’s compounds when combining the disclosures of Jansen, when the art as a whole would have directed a POSA to directly conjugate a B moiety to the FAPi and to avoid using a linker. *Id.*, ¶¶41-61. Dr. Zeglis then fails to establish why, after making that first poor choice, a POSA would have then focused on the singular Jansen reference that is a sliver of the multiple pieces of FAPi art that would have been available by October 2017. EX2001, ¶¶63-66, 77. Indeed, other FAPis outperformed Dr. Zeglis’s Compound 60, and Dr. Zeglis does not address those compounds or why a POSA would have rejected those in favor of Compound 60. *Id.*, ¶¶77-79. One, therefore, is only left with the reason being that a linker-containing FAPi radiotracer containing Compound 60 falls within the scope

of the claims, while other better performing compound and a linker-less structure do not. *Id.*

Accordingly, Dr. Zeglis fails to show how a POSA would have arrived at the claimed compounds in view of US-633, Jansen, and Meletta. *ATD Corp.*, 159 F.3d at 546; *Impax*, 893 F.3d at 1380.

B. Ground 2: GE Fails to Establish That the Challenged Claims Would Have Been Obvious Over US-121 and Jansen Because GE Uses Impermissible Hindsight.

As in Ground 1 of the Petition, GE fails to consider the prior art as a whole and uses impermissible hindsight to combine US-121 and Jansen to arrive at the compounds of the Challenged Claims.

In Ground 2, GE again relies on Dr. Zeglis's opinion that a POSA would have selected Jansen's Compound 60 to arrive at making the claimed B-L-A compounds. EX2001, ¶¶80-81. But as discussed for Ground 1, Dr. Zeglis fails to explain why a POSA would have started by using US-121's linker-containing radiotracers for FAP imaging in light of the fact that US-633 demonstrates that linker-less FAP radiotracers outperform linker-containing FAP radiotracers. EX2001, ¶82. And Dr. Zeglis's selection of Jansen's Compound 60 ignores the prior art as a whole by failing to factor Jansen 2013, US-650, and Jansen 2014 in his analysis. *See* §§IV.A.2.-IV.A.3.; EX2001, ¶¶80-82. Dr. Zeglis's opinions are,

therefore, guided by hindsight and do not establish that a POSA would have arrived at the Challenged Claims. EX2001, ¶83.

This provides sufficient basis to reject Ground 2. *ATD Corp.*, 159 F.3d at 546.

V. CONCLUSION

The Petition fails to show that GE is reasonably likely to prevail in establishing that any of the Challenged Claims are unpatentable and, therefore, the Director should deny institution.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: January 30, 2026

1101 K Street, NW
10th Floor
Washington, DC 20005
(202) 371-2600

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

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Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: January 30, 2026

1101 K Street, NW
10th Floor
Washington, DC 20005
(202) 371-2600

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Jeffrey P. Kushan (Lead Counsel)
Lauren Katzeff (Back-up Counsel)
Amit Bhatla (Back-up Counsel)
SIDLEY AUSTIN LLP
jkushan@sidley.com
lkatzeff@sidley.com
abhatla@sidley.com

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

Eldora L. Ellison, Ph.D.
Registration No. 39,967
Lead Attorney for Patent Owner

Date: January 30, 2026

1101 K Street, NW
10th Floor
Washington, DC 20005
(202) 371-2600