

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

**PATENT OWNER PRELIMINARY RESPONSE
UNDER 37 C.F.R. § 42.207(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 <i>et al.</i> , “Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold,” <i>MedChemComm</i> (August 2014) (“Jansen 2014”)
2004	Sikkandhar <i>et al.</i> , “Theranostic Probes for Targeting Tumor Microenvironment: An Overview,” <i>International Journal of Molecular Sciences</i> (May 2017) (“Sikkandhar”)
2005	<i>Intentionally Left Blank</i>
2006	Isherwood <i>et al.</i> , “Live Cell <i>in Vitro</i> and <i>in Vivo</i> Imaging Applications: Accelerating Drug Discovery,” <i>Pharmaceutics</i> (April 2011) (“Isherwood”)
2007	<i>Intentionally Left Blank</i>
2008	Loktev <i>et al.</i> , “Development of Fibroblast Activation Protein–Targeted Radiotracers with Improved Tumor Retention,” <i>The Journal of Nuclear Medicine</i> (October 2019) (“Loktev”)
2009	Nishida <i>et al.</i> , “Angiogenesis in cancer,” <i>Vascular Health and Risk Management</i> (September 2006) (“Nishida”)
2010	Seaman <i>et al.</i> , “Molecular imaging agents: impact on diagnosis and therapeutics in oncology,” <i>Expert Reviews in Molecular Medicine</i> (July 2010) (“Seaman”)
2011	Slania <i>et al.</i> , “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”)

Exhibit No.	Description
2012	Xu <i>et al.</i> , “Albumin Binder–Conjugated Fibroblast Activation Protein Inhibitor Radiopharmaceuticals for Cancer Therapy,” <i>The Journal of Nuclear Medicine</i> (June 2022) (“Xu”)
2013	Zboralski <i>et al.</i> , “Fibroblast activation protein targeted radiotherapy induces an immunogenic tumor microenvironment and enhances the efficacy of PD-1 immune checkpoint inhibition,” <i>European Journal of Nuclear Medicine and Molecular Imaging</i> (July 2023) (“Zboralski”)
2014	<i>Intentionally Left Blank</i>
2015	U.S. Patent No. 11,938,201 (“the ’201 patent”)
2016	VanBrocklin <i>et al.</i> “ $^{16}\beta$ -([^{18}F]Fluoro)estrogens: Systematic Investigation of a New Series of Fluorine-18-Labeled Estrogens as Potential Imaging Agents for Estrogen-Receptor-Positive Breast Tumors,” <i>Journal of Medicinal Chemistry</i> (May 1993) (“VanBrocklin 1993”)
2017	VanBrocklin <i>et al.</i> “Anilinodialkoxyquinazolines: Screening Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors for Potential Tumor Imaging Probes,” <i>Journal of Medicinal Chemistry</i> (October 2005) (“VanBrocklin 2005”)

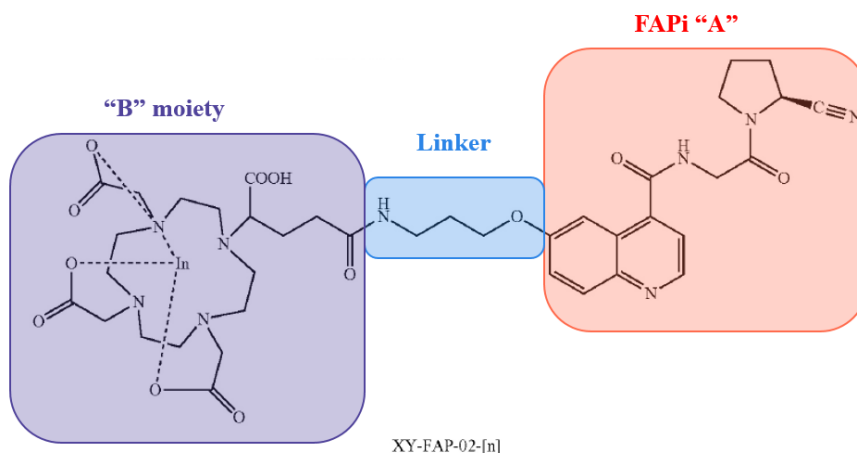
I. INTRODUCTION

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, 1:54-61, 7:46-53, 35:47-52.

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, *e.g.*, for *in vitro*, *ex vivo*, or *in vivo* applications. 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, 2:1-5. An example of such a radiotracer is shown below:



EX1001, col. 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 ignores that the prior art as a whole would have presented a person of ordinary skill in the art ("POSA") with various, *better-performing*, choices of FAP-targeting moiety (A) 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.

Compounding the problem for Ground 1, GE—without basis—chooses US-633’s “B-L-A” radiotracers as a starting point, but US-633 discloses that its “B-A” radiotracers (*lacking* the linker “L”) outperformed the “B-L-A” radiotracers. GE provides no reason or evidence grounded in the prior art to select the *worse*-performing B-L-A radiotracers over US-633’s *better*-performing B-A radiotracers. As Patent Owner the Johns Hopkins University’s (“JHU”) expert Dr. Henry VanBrocklin (EX2001, ¶¶4-13) explains, selecting the better-performing “B-A” radiotracers would not have led to the claimed invention, revealing the hindsight GE used to develop its arguments. Rather than follow the path a POSA would have taken, GE used the claims as a roadmap.

Second, GE incorrectly seeks to import *in vivo* functionality into the claims where none is required. This error also infects GE’s unpatentability analyses and provides further basis for denying institution. For example, GE treats the claimed compounds as though they were functionally-defined, and as though the function were limited to *in vivo* uses. But GE’s claim interpretation and consequent analyses are unfounded because the claims are solely defined by the *structure* of the claimed compounds, not by their *function*. Despite the import of proper claim construction

to GE's arguments and the requirements of 37 C.F.R. § 42.204(b)(4) to explain how "the construed claims is unpatentable," GE does not undertake any claim construction analysis under *Phillips* to support its interpretation of the claims. *Phillips v. AWH Corp.* 415 F.3d 1303 (Fed. Cir. 2005). Contrary to GE's unsupported position, the claims' plain language, the specification, and prosecution history establish that compounds of the challenged claims are defined by their *structure*, with the claims reciting a "low molecular weight compound" of "Formula (I): B-L-A."

GE improperly seeks to impose upon the claims a requirement that they "must be stable under physiological conditions" and "must exhibit satisfactory bioavailability." *See, e.g.,* EX1003, ¶275; Pet., 115. In doing so, GE improperly seeks to import into the claims a requirement that the compounds are useful *in vivo*. But, importing such a limitation into the claims is improper under *Phillips*. Indeed, the specification makes it clear that the claimed compounds can be used *ex vivo* or *in vitro*. GE thus fails to explain why the challenged patent must describe and enable compounds specifically for *in vivo* use. GE's improper importation of *in vivo* functionality into the claims leads to it applying inapt analyses and case law to allege lack of enablement and written description in Grounds 3 and 4. Rather, the challenged claims are structural claims, and are sufficiently described and enabled by the specification.

Indeed, GE should be held to its multiple 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 numerous deficiencies in GE’s Petition warrant denial and PGR should not be instituted.

II. THE ’233 PATENT

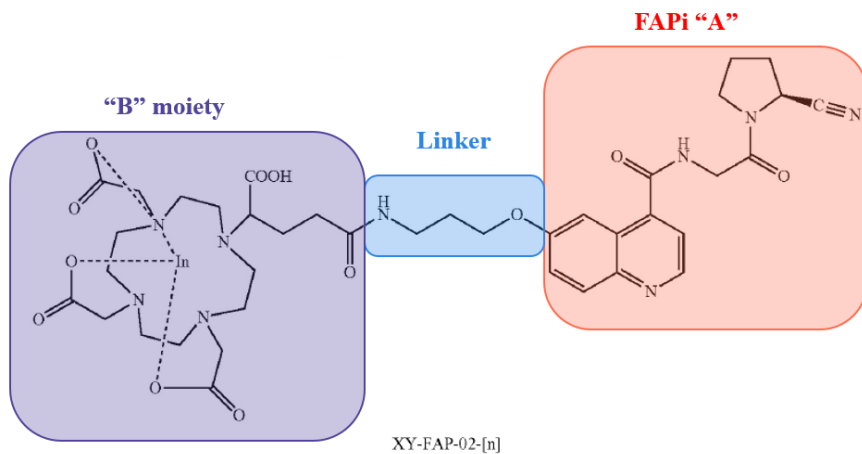
The invention of the ’233 patent is directed to novel low molecular weight imaging and radiotherapeutic agents (collectively, radiotracers) targeting fibroblast activation protein- α (FAP). EX1001, Abstract; EX2001, ¶14. FAP is also referred to as seprase or FAP- α and is a transmembrane protein expressed on the stroma of cells, *i.e.*, the supportive framework of an organs or tissues. EX1001, Abstract, 1:25-43; EX1016, 259-260; EX2001, ¶14. 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, 1:25-43; EX1022, 124; EX1024, 456; EX1023, 288; EX1041, 2; EX2001, ¶14. 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, 1:25-43; EX1016, 260; EX1007, 491; EX2001, ¶14. In contrast, FAP has been found to be typically undetectable or low in healthy cell tissues. EX1001, Abstract, 1:25-43; EX2001, ¶14.

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, ¶¶4-13), before October 23, 2017, FAP molecular imaging had been plagued with challenges. EX2001, ¶15. 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, ¶15. 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, ¶15. 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, ¶15. In fact, the only attempt to develop a low molecular weight FAP imaging agent before the '233 patent ended in a failure. EX1008, 2089-2090; EX2001, ¶15. 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, ¶15.

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, ¶15. 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, 1:50-61; EX2001, ¶15.

Against that background, the inventors of the '233 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, ¶16. The '233 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, 2:1-5. An exemplary '233 patent radiotracer is shown below:



EX1001, col. 57-58 (annotated); EX2001, ¶16.

The '233 patent's low molecular weight B-L-A radiotracers have “ideal properties for nuclear imaging of FAP- α .” EX1001, 1:59-61; EX2001, ¶17. 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, 1:54-58; EX2001, ¶17.

The '233 patent demonstrates that its radiotracers, for example, have high selectivity and affinity for cell lines expressing FAP. *See, e.g.*, EX1001, 5:40-42 ("FIG. 3A, FIG. 3B, and FIG. 3C show the assessment of the *in vitro* binding ability and specificity of XY-FAP-01 and [¹¹¹In]-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"), 60:53-55 ("Taken together, these results support the specificity of XY-FAP-01 and 111 In-XY-FAP-02 [*sic*] in the engagement of FAP *in vitro*"); EX2001, ¶17. The '233 patent's radiotracers, moreover, exhibit "favorable biodistribution and retained uptake in the FAP-positive xenograft at various imaging time points." EX2011, Abstract, 8; EX2001, ¶17.

Further, the '233 patent states that its low molecular weight B-L-A radiotracers can have multiple applications *in vivo*, *ex vivo*, and *in vitro*. EX2001, ¶18. The radiotracers, for instance, can be used for "*in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α."

EX1001, 7:46-54, 35:47-52; EX2001, ¶18. More specifically, the claimed compounds “allow[] the specific imaging of FAP- α expressing tumors,” which can then be used in the diagnosis of cancer. EX1001, 8:6-9; EX2001, ¶18. The patent’s novel B-L-A radiotracers also can be employed for “treating a fibroblast-activation protein- α (FAP- α)-related disease or disorder,” such as “a proliferative disease, including [many different types of cancer].” EX1001, 4:44-61; EX2001, ¶18. The claimed radiotracers of the ’233 patent, therefore, can be used to diagnose and treat a variety of diseases or disorders in humans. EX2001, ¶18.

In addition to *in vivo* uses, the ’233 patent’s radiotracers are suitable for *ex vivo* uses, as well as for “*in vitro* applications[] such as *in vitro* diagnostic and research applications.” EX1001, 7:46-53, 35:47-52; EX2001, ¶19. One *ex vivo* use for the claimed radiotracers includes collecting data on the biodistribution of other therapeutic agents *ex vivo*. EX2008, 1424, 1427; EX2001, ¶19. Such studies permit evaluating potential drug candidates as imaging agents, and also providing valuable information target protein expression within tissues, including FAP expression. EX2008, 1424, 1427; EX2011, 6; EX2001, ¶19.

The claimed radiotracers can also be used *in vitro*. One exemplary use is for prediction of tumor responses to potential therapeutic agents. EX2001, ¶19. The claimed radiotracers, for instance, can be used in determining whether tumor cells have changed their molecular phenotype, *e.g.*, through changes in gene expression

or changes in enzymatic activity, in response to treatment. EX2010, 9; EX2001,

¶19. The claimed radiotracers, moreover, can be used to monitor other cellular processes in response to radiotracer treatment. EX2006, 144; EX2009, 213;

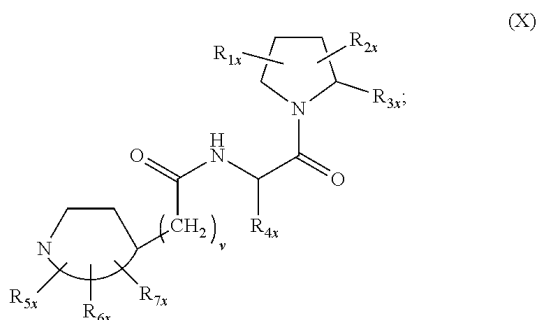
EX2001, ¶19. For instance, they can monitor angiogenesis, which is the process of forming new blood and lymphatic vessels that contributes to the progression of malignant tumors. EX2006, 144; EX2009, 213; EX2001, ¶19.

The '233 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, ¶20.

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

Independent claim 1 of the '233 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:

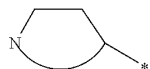
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

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 H;

v is 0; and



represents a quinolinyl ring having a point of attachment to a remainder of the FAP binding moiety at the 4-position of the 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, 64:6-55, Certificate of Correction; EX2001, ¶44. Claim 2 depends from claim 1 and further narrows the R_{1x} and R_{2x} groups of A to being each independently selected from the group consisting of H and F. EX1001, 64:56-58; EX2001, ¶44. Claim 3 depends from claim 2 and further narrows the R_{3x} group of A to —CN. EX1001, 64:59; EX2001, ¶44. And claim 4 depends from claim 3 and further narrows B to an optical or radiolabeled functional group comprising a chelating agent. EX1001, 64:60-61; EX2001, ¶44.

As can be seen from the elements of the challenged claims, 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. EX1001, 64:6-55, Certificate of Correction; EX2001, ¶¶45-46. 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.” EX1001, 64:6-55, Certificate of Correction; EX2001, ¶¶45-46.

A. The Claimed “B-L-A” Compounds Are Not Defined Functionally.

While GE alleges that “the claims generally employ objective language that requires no special construction,” it nevertheless seeks to import functional limitations into the claims where none are recited in order to advance GE’s erroneous position that the claims lack written description and enablement. Indeed, GE’s §112 arguments and relied-upon case law in the Petition’s Grounds 3 and 4 are predicated on GE’s position that the claimed compounds must have achieve some level of *in vivo* functionality. Pet., 18; EX1003, ¶¶251, 248, 275, 279; EX2001, ¶¶89-91. But GE’s arguments are merely a thinly veiled attempt to import *in vitro* function into the claimed compounds when none is recited in the claims. EX2001, ¶46.

This can be seen throughout the declaration of GE’s expert, Dr. Brian Zeglis, who repeatedly frames his discussion of the claimed compounds as requiring that the compounds be “viable optical imaging agents or radiolabeled imaging or therapeutic agents.” *See, e.g.*, EX1003, ¶273. In fact, Dr. Zeglis demands that the claimed compounds achieve the following attributes:

- “**Stability *in vivo***. A radiopharmaceutical or optical imaging agent must remain **intact in the body** for a long enough time to accumulate in its biological target. Even a compound with very high selectivity and affinity **will not be effective *in vivo*** if it is metabolized rapidly or the

radionuclide dissociates or decays before binding the target.” EX1003,

¶59;¹ EX2001, ¶¶104, 107.

- “**Pharmacokinetic Profile.** As I explained above (¶ 51), a general principle of radiopharmaceutical design is that the physical half-life of the radionuclide should match the **pharmacological half-life** of the radiopharmaceutical precursor to ensure that there is sufficient **distribution in the target tissue** that can be imaged before the compound is cleared or the radionuclide decays.” EX1003, ¶59; EX2001, ¶104.
- “**Bioavailability.** Bioavailability refers to the relative amount of an administered radiopharmaceutical or optical imaging agent that enters **systemic circulation *in vivo*** in an unchanged state and is largely dictated by the compound’s pharmacokinetic profile.” EX1003, ¶59; EX2001, ¶104.
- “The compounds must **be stable under physiological conditions.**” EX1003, ¶275; EX2001, ¶104.

¹ Emphasis added throughout, unless otherwise specified.

- “The compound must exhibit **satisfactory bioavailability.**” EX1003, ¶275; EX2001, ¶104.
- “These experiments are generally straightforward to perform, but they require synthesizing and purifying each compound and then subjecting it to an array of binding studies, **stability studies (e.g., in plasma), and animal testing for bioavailability and toxicity.**” EX1003, ¶277; EX2001, ¶104.

But, here, the claims are plainly structural. 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*, 415 F.3d at 1323 (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

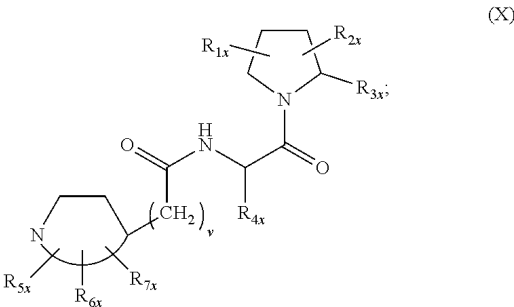
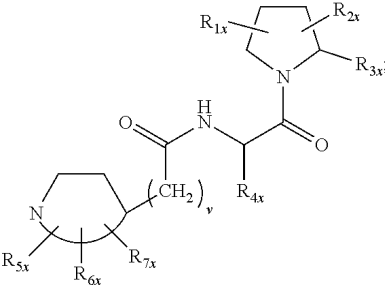
read into the claims.”); *Boehringer Ingelheim Animal Health USA Inc. v. Kansas State Univ. Research Found.*, PGR2022-00021, Paper 11 at 5-6 (P.T.A.B. Feb. 24, 2023) (Director Vidal finding that “the Board was correct to focus on whether the claims themselves were enabled and to find inapposite Petitioner’s arguments as to whether functional language—appearing only in the specification—was enabled.”).

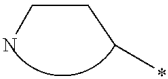
GE also cites no case law to support its position that functionality should be imported from the specification to claims that are plainly structural. That notwithstanding, GE also ignores that the specification also states that the claimed compounds can have *in vitro* and *ex vivo* utility that does not require *in vivo* functionality. *See* §II; EX2001, ¶¶17-20.

The Board also properly preliminarily decided that the claimed compounds should be treated as purely structural claims in a related proceeding, PGR2025-00012. That proceeding involved the ’233 patent’s parent patent (U.S. Patent No. 11,938,201 (“the ’201 patent”)), which likewise claims compounds having the formula B-L-A without any functional requirement for the compounds as a whole. There, 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).

Table 1 below demonstrates the similarity between the two sets of claims that should lead to the same conclusion here that the Challenged Claims are not functional.

Table 1. Comparison of '233 and '201 patent claim 1

Claim 1 of the '233 Patent	Claim 1 of the '201 Patent
1. A low molecular weight compound of Formula (I): B-L-A (I) wherein: A is a targeting moiety for FAP-α, wherein A has the structure of:  (X) 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;	1. A low molecular weight compound of Formula (I): B-L-A (I) 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;

Claim 1 of the '233 Patent	Claim 1 of the '201 Patent
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 H; v is 0; and  represents a quinolinyl ring having a point of attachment to a remainder of the FAP binding moiety at the 4-position of the 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)	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

Claim 1 of the '233 Patent	Claim 1 of the '201 Patent
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, 64:6-55; EX2001, ¶45.)	adapted to form a chemical bond with B and A; or a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof. (EX2015, Certificate of Correction; EX2001, ¶45.)

B. “low molecular weight”

Each of the Challenged Claims of the '233 patent requires that the compound of formula B-L-A is of “low molecular weight.” EX1001, 64:6-61. JHU also provides a construction for “low molecular weight,” to the extent the Board finds it necessary to reach a decision on institution.

GE has submitted that the '233 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., 21. This interpretation is flawed, however, because it ignores that Dr. Martin Pomper, one of the inventors of the '233 patent, defined the term “low molecular weight” during prosecution of the '201 patent, which is the parent of the '233 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.” EX1031, 385; EX2001, ¶¶47-48. 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. 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. Celco 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 his explanation, elaboration, and qualification regarding the scope of the invention he sought to capture with the term “low molecular weight.” EX1031, 329; EX2001, ¶¶47-48.

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], elaborate[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, ¶¶47-48. 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.”).

Thus, even though the B moieties of VivoTag-680, AlexaFluor790, and IRDye 700DX identified in the specification would be excluded by a range of “about 50 Daltons to about 1,500 Daltons,” those B moieties are *not* identified as preferred embodiments in the ’233 patent.² Their exclusion, moreover, cannot outweigh the definitional language provided in the prosecution history. *N. Am. Container, Inc. v. 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.

² 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.

IV. GROUNDS 1 & 2: GE FAILS TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE 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 numerous choices that 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, ¶¶38, 105, 124; EX2001, ¶¶49-50. 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 A moiety of US-633’s compounds with a “new, more selective

small molecule FAP inhibitor as the targeting moiety.” EX1003, ¶¶167; EX2001, ¶49. Dr. Zeglis then lands on Jansen’s Compound 60 as the “new, more selective” FAPi a POSA would have allegedly selected. EX1003, ¶¶167-168; EX2001, ¶49.

But Zeglis’s analysis relying on linker-*containing* radiotracers is fundamentally flawed because he overlooks the fact that US-633 provides both linker-containing radiotracers (B-L-A) *and* linker-less radiotracers (B-A), and a POSA would have favored the linker-*less* radiotracers based on the disclosures of US-633. EX1004, Abstract; EX2001, ¶¶50-58; *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, ¶¶59-62; *see* §§IV.A.1(b)-(c). A POSA following Dr. Zeglis’s path, therefore, would have had to select the *worse*-performing linker-*containing* radiotracers from US-633 over the better-performing linker-*less* radiotracers. EX2001, ¶¶63-69; *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, ¶¶63-75; *see* §§IV.A.1(b)-(c).

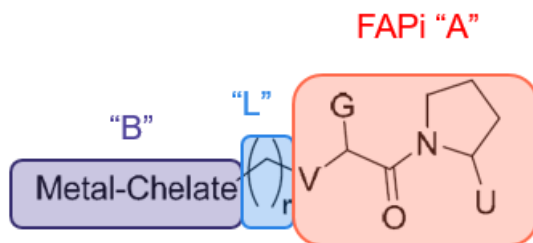
In selecting Jansen’s Compound 60, moreover, Dr. Zeglis ignores other prior art publications from which a POSA would have selected several other better-performing FAPis over Compound 60. EX2001, ¶¶76-86; *see* §§IV.A.2-IV.A.3.,

In view of the above, Dr. Zeligis has improperly “selectively culled from the prior art to fit the parameters of the patented invention.” *ATD Corp.*, 159 F.3d at 546.

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

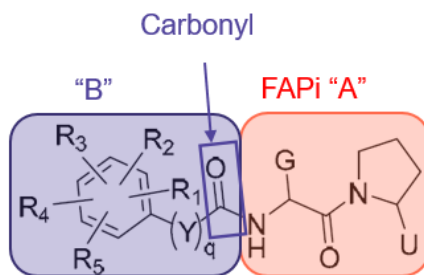
As discussed, Dr. Zeligis alleges that a POSA would have purportedly developed a FAP-targeting radiotracer having “a modular three-component design,” *i.e.*, B-L-A design, based on the radiotracers of US-633. EX1003, ¶¶38, 105, 167; EX2001, ¶¶49-50. In doing so, Dr. Zeligis incorrectly treats all of US-633’s radiotracers as having a modular three-component design. EX1003, ¶¶38, 105, 167; EX2001, ¶¶49-58.

In fact, US-633 discloses two sets of radiotracers: radiotracers that have linkers (linker-containing) and radiotracers that lack linkers (linker-less). EX1004, Abstract; EX2001, ¶¶50-52. It is only US’633’s linker-containing radiotracers that have the modular B-L-A design, as shown by the annotation of a Formula I radiotracer from US-633::



Formula I
US-633, Abstract.

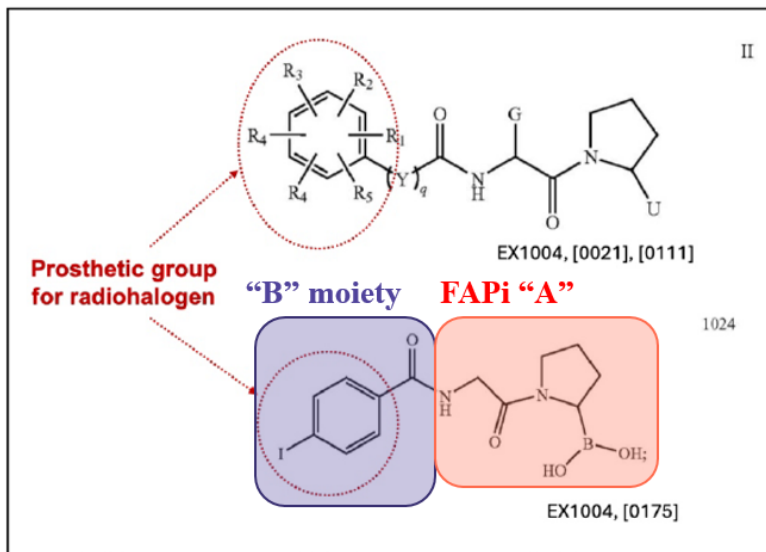
EX1004, Abstract; EX2001, ¶50. And US-633 discloses linker-less compounds, with radiohalogens directly conjugated to the aryl group of the FAPi and only a B-A design, as illustrated below with the generic Formula II formula from US-633:



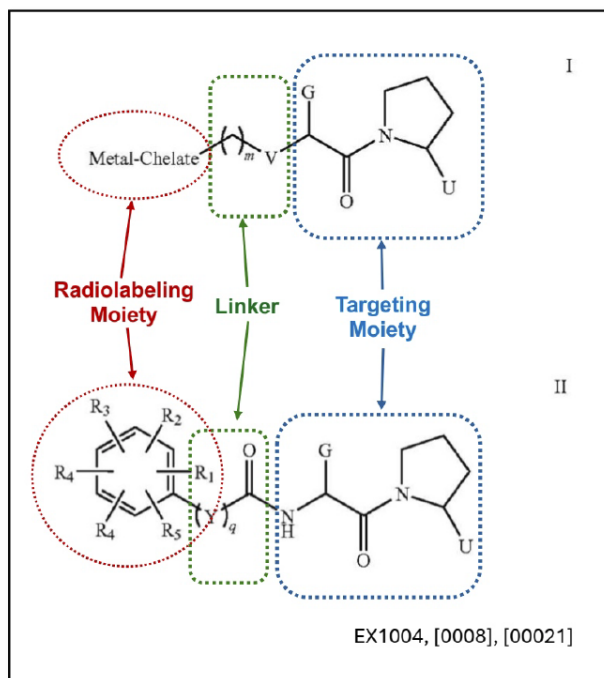
Formula II
US-633, Abstract.

EX1004, Abstract; EX2001, ¶51. For the Formula II compounds shown above, the substituent (Y)_q is depicted as a potential linker. EX2001, ¶51. 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).

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, ¶117 (annotated); EX2001, ¶52. In Dr. Zeligs's relied-upon example shown above, the iodine-containing radioprosthetic group corresponds to the B moiety. EX2001, ¶52. No linker component is present because the B moiety is directly conjugated to the corresponding A moiety. *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, ¶105):



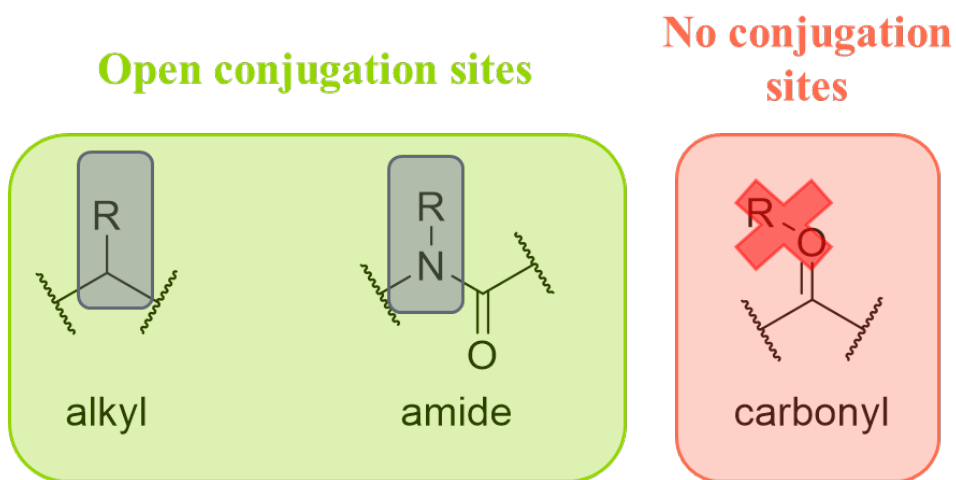
EX1003, ¶105; EX2001, ¶52. But, as Dr. VanBrocklin explains, Dr. Zeglis is incorrect; the carbonyl group in Compound 1024, and in other similar carbonyl containing compounds of US-633, is not a linker. EX2001, ¶¶53-58.

First, as Dr. Zeglis admits, a linker should “spatially separate the reporter moiety from the targeting moiety.” EX1003, ¶45; EX2001, ¶53. But, a POSA would have known that the carbonyl group is one-carbon long. EX2001, ¶53. 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 compound.

For example, a radiopharmaceutical chemist can introduce hydrophobic character into a radiopharmaceutical by incorporating one or more benzyl groups into the linker moiety” EX1003, ¶46; EX2001, ¶53. A POSA would have understood that a carbonyl group, however, could not have served that purpose of controlling the characteristics of a compound, as a carbonyl group cannot be modified. EX2001, ¶53. Indeed, the carbonyl cannot be removed because it is integrated into the B moiety. *Id.* And one cannot add a different group to replace the carbonyl. *Id.*

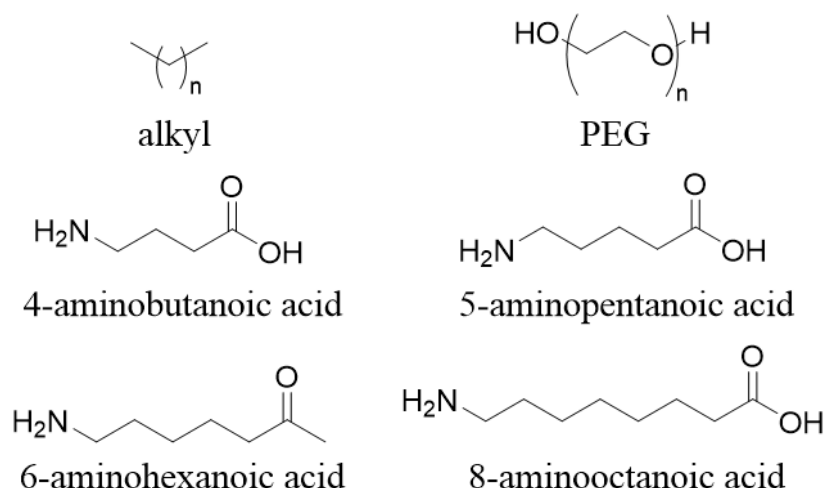
As shown in the figure below provided by Dr. VanBrocklin, the carbonyl group has no open sites for conjugation, which would have prevented a POSA from “introduc[ing] hydrophobic character” or any other substituent group that would “influence the biochemical and pharmacokinetic characteristics of the compound,” as Dr. Zeglis states linkers would allow. *Id.*



Id. The foregoing nature of the carbonyl group stands in direct contrast with 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. *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.³ 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, ¶54. Exemplary structures of the above linkers disclosed in US-633 are shown below.

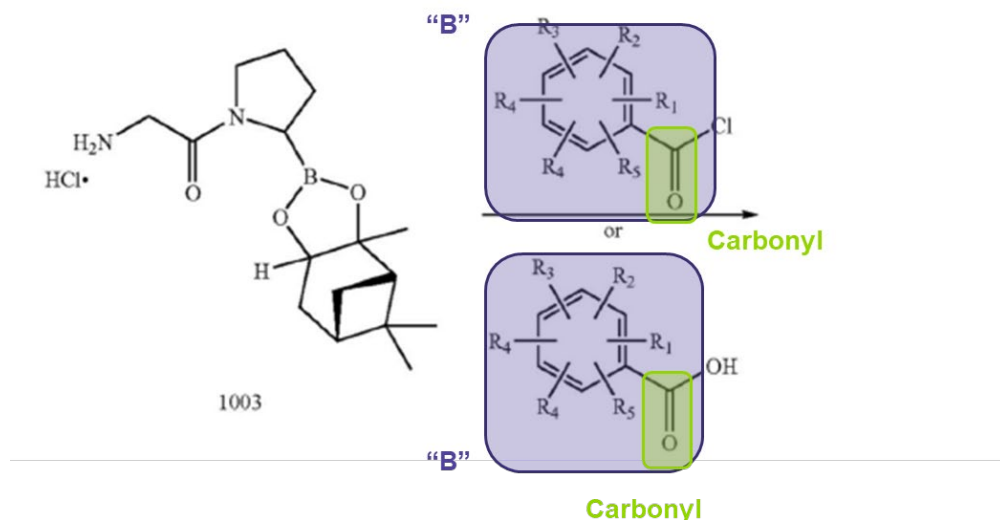
³ Nor is a carbonyl listed as a potential linker in the '233 patent. EX2001, ¶54, fn.



EX1004, ¶130; EX2001, ¶54.

Fourth, as discussed above, Dr. Zeglis states that linkers can be “selected or designed” to influence the properties of a compound. EX1003, ¶46; EX2001, ¶55. 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 A moiety. EX2001, ¶55. 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:

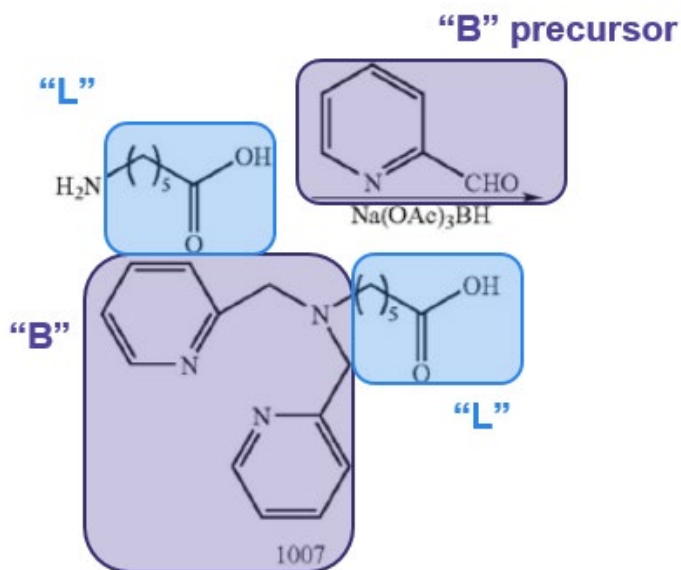
Scheme 5: General synthesis of substituted benzamide glycineboronoproline seprase inhibitors, Formula II



EX1004, ¶133; EX2001, ¶55. 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, *i.e.*, A moiety. EX2001, ¶¶55-56. 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 A. As an example, Example 3 of US-633 involves adding an alkyl linker to B before conjugating the B-L structure to A, as illustrated below:

Example 4
Preparation of Metal-Chelates

[0154]



EX1004, ¶154; EX2001, ¶56.

US-633 also never discusses its “tethers,” *i.e.*, linkers, in the context of the Formula II compounds. EX1004, ¶¶101, 130, 133; EX2001, ¶57. 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, ¶57. Examples of such disclosures including 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, ¶57.

Accordingly, a POSA viewing US-633’s disclosures would have understood that US-633 discloses two classes of radiotracers: those having the B-L-A design (linker-containing) and those having the B-A design (linker-less). And, therefore, not all of US-633’s radiotracers employ a modular B-L-A design that is required by each of the Challenged Claims. EX2001, ¶58.

- 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

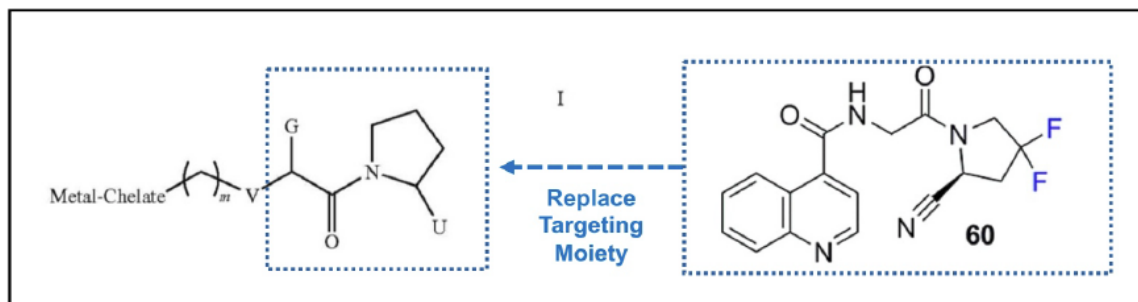
targeting moiety in the FAP-targeting radiotracers described in US-633 with compound 60 from Jansen” to arrive at the claimed modular B-L-A radiotracers. EX1003, ¶182; EX2001, ¶59.

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 A. EX1003, ¶182; EX2001, ¶¶59-62. 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 A. EX1003, ¶182; EX2001, ¶63-67. Given the worse performance of US-633’s linker-containing radiotracers, a POSA would not have had a reason to pursue either path.⁴

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:

⁴ 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, ¶182; EX2001, ¶59.

Dr. Zeglis has not shown that a POSA would have selected one of US-633's compounds *with* linkers for further modification in view of US-633's disclosures. EX2001, ¶¶60-62. 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, ¶55. Yet, US-633 discloses that radiotracers comprising a boronic acid pyrrolidine targeting moiety *and a linker* 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, ¶¶59-62.

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

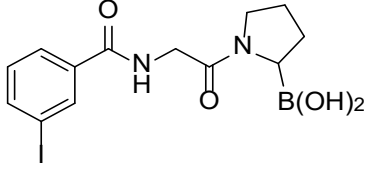
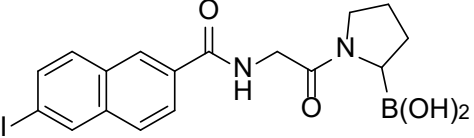
Contains Linkers
No Linkers

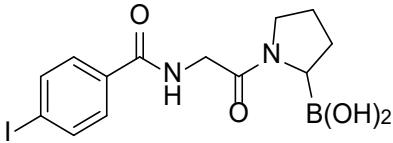
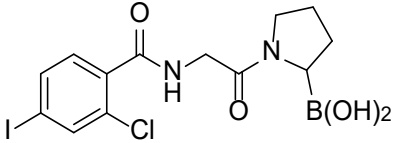
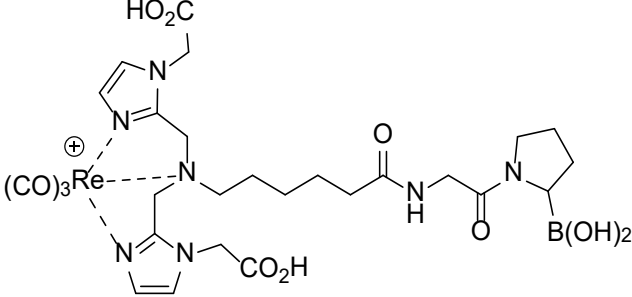
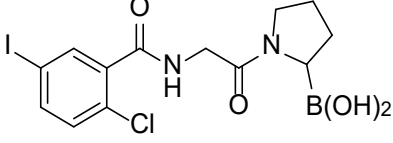
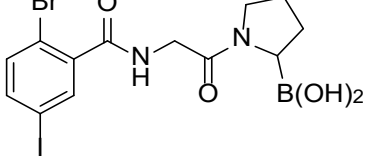
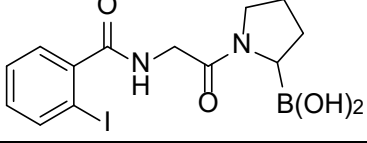
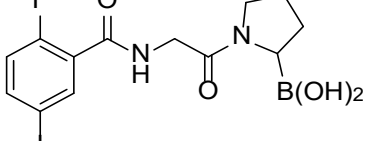
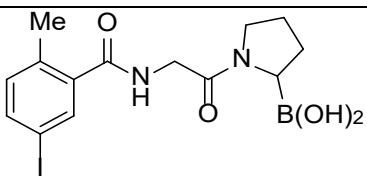
EX1004, Table 2, p. 34 (annotated); EX2001, ¶60.

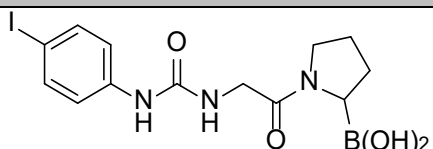
As shown in the annotated version of Table 2 from US-633, above, the linker-less radiotracers overall had the best FAP affinity. EX1004, Table 2, p. 34 (annotated); EX2001, ¶¶60-61. For instance, linker-less radiotracers 1025 and 1030 displayed the best FAP affinity—an IC₅₀ of 2 nM. EX1004, Table 2, p. 34 (annotated); EX2001, ¶61. Table 2 of US-633 also discloses that ten 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, ¶61.

The structures of those eleven radiotracers with the highest FAP affinity are shown in Table 2, below. EX1004, Table 2, p. 34 (annotated); EX2001, ¶61. 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 IC₅₀ values, with the lower IC₅₀ values meaning better affinity:

Table 2: 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, ¶¶61.

Consequently, only two of the B-L-A radiotracers in US-633 had high FAP affinity, whereas the remainder of the top performers were linker-less radiotracers (nine linker-less radiotracers). EX2001, ¶¶61-62. And given that, Dr. Zeglis's claim that a POSA would have moved forward with modifying a linker-containing radiotracer is driven by the hindsight desire to arrive at the claimed B-L-A formula, rather than 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.

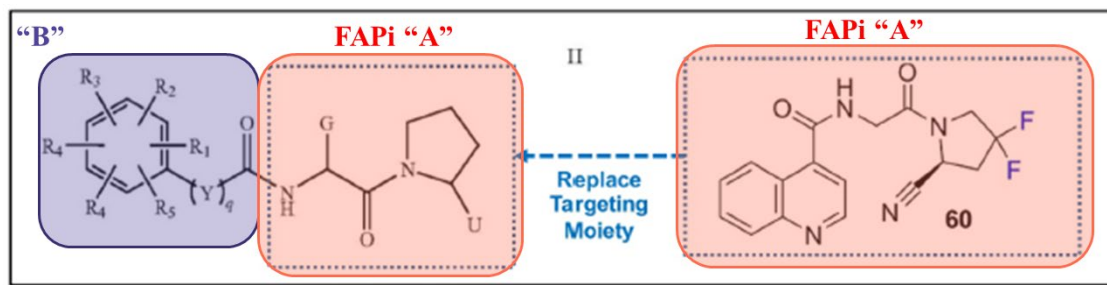
In addition to erroneously arguing that a POSA would have chosen US-633's linker-containing compound for modification with Jansen's Compound 60, Dr. Zeglis alleges that a POSA would have also selected US-633's linker-less compounds to arrive at the claimed compounds. EX1003, ¶194; EX2001, ¶¶63-64. But to do so, a POSA would have had to make the additional modification of adding a linker. *See* §IV.A.1(a); EX2001, ¶¶50-58.

In advancing this argument, Dr. Zeglis, however, does not state that his proposed modification would require adding a linker between the corresponding B

and A moieties of US-633's linker-less radiotracers. EX1003, ¶194; EX2001, ¶63.

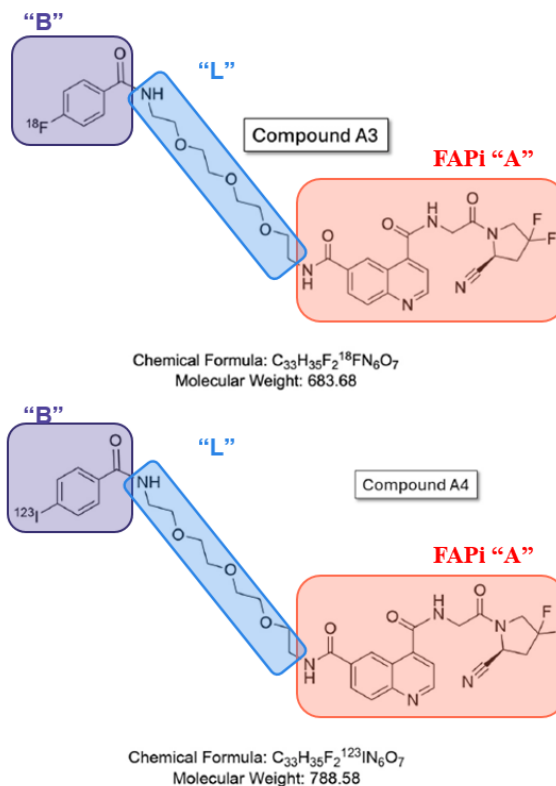
Indeed, reproduced below is an annotated version of the figure provided by Dr.

Zeglis that depicts his proposed modification:



EX1003, ¶194 (purple and red annotations added); EX2001, ¶63. As discussed in §IV.A.1(a), the B moiety in the radiotracer depicted above is directly conjugated to the A 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, ¶64. 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, ¶197; EX2001, ¶¶64-65. Dr. Zeglis's hypothetical Compounds A3 and A4 are reproduced below, annotated by Dr. VanBrocklin:

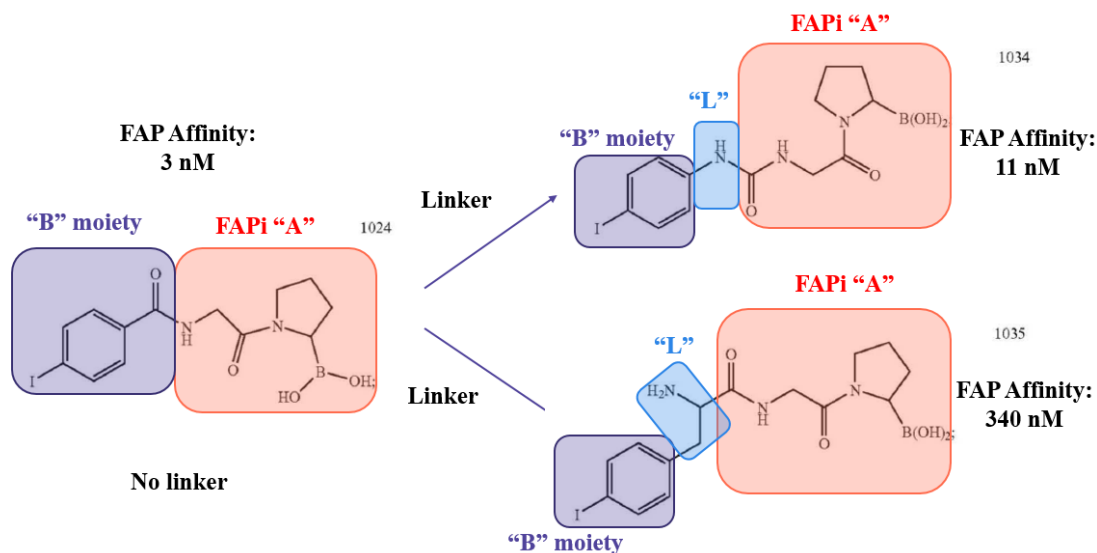


EX2001, ¶64.

To arrive at the compounds Dr. Zeglis proposed above, a POSA would have had to not only replace US-633's A with Compound 60, but also add a linker (depicted in blue) between the B (the radioprosthetic group) and the A (Compound 60). EX1003, ¶197; EX2001, ¶65. 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

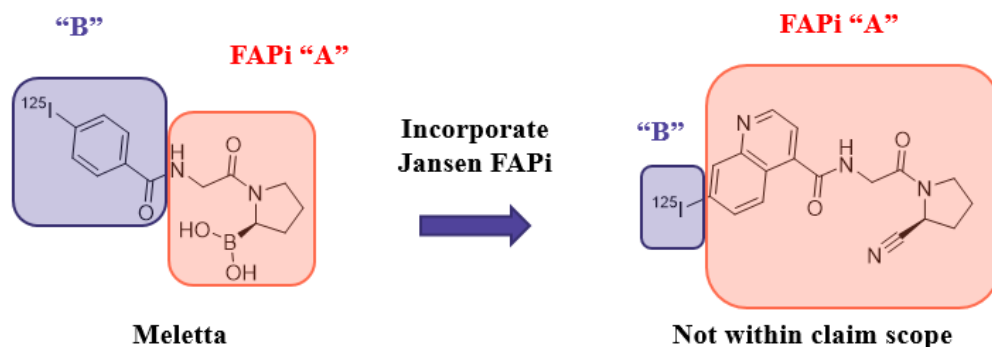
compounds in terms of FAP affinity. EX1004, Table 2; EX2001, ¶65.⁵ Indeed, US-633 discloses that adding a linker to the linker-less compounds of US-633 reduces FAP affinity, as the figure below shows:

⁵ 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 Prod. 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.’”).



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, ¶65.

What is more, as Dr. VanBrocklin explains, were a POSA to “replace[] the boronic acid pyrrolidine targeting moiety in [linker-less radiotracers] of US- 633 [] with compound 60,” as Dr. Zeglis suggested (EX1003, ¶194), 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, ¶¶66-67. This is illustrated below:



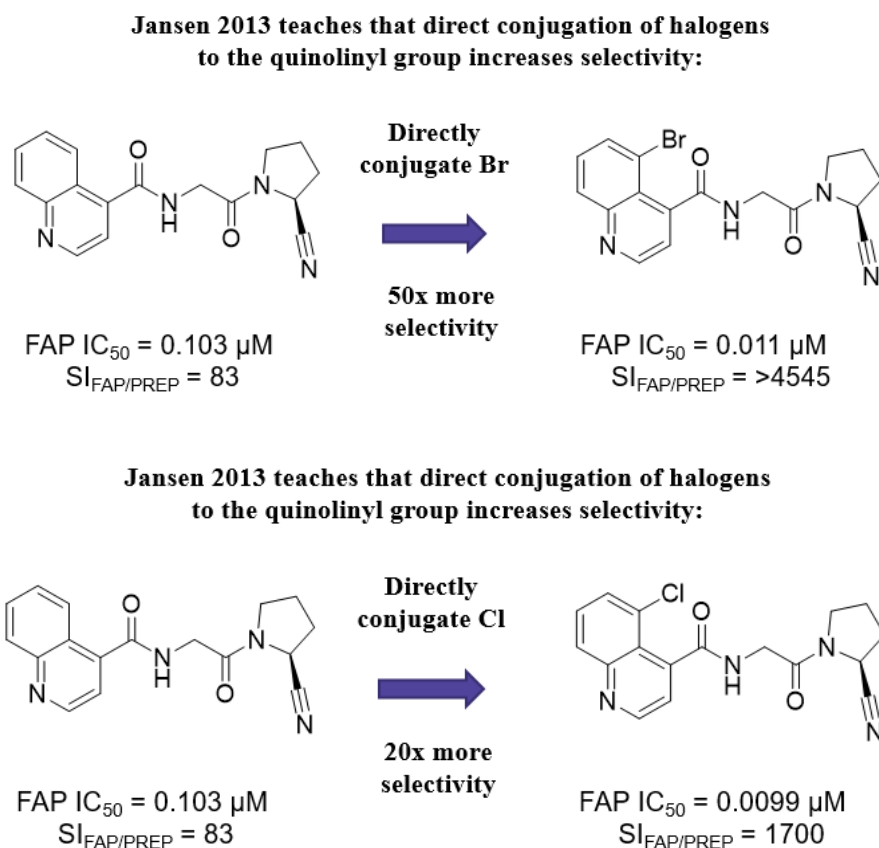
EX2001, ¶66. The above compound has a formula B-A, not B-L-A, as required by the claims. *Id.*

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 pursue 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, ¶175; EX2001,

¶68. 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. 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:



EX2003, Tables 2-3; EX2001, ¶68.

Thus, as Dr. VanBrocklin explains, a POSA would not have viewed use of 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, ¶175; EX2001,

¶69. But direct halogenation would have resulted in a compound outside the claim scope. EX2001, ¶¶66-67. In view of that outcome, Dr. Zeglis 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 a B-L-A compound. EX2001, ¶¶66-69. Indeed, Dr. Zeglis does not explain why a POSA would have ignored the known SAR data in the art for quinolinyl-based FAPis. EX2001, ¶69.

In sum, given the art as a whole, a POSA would not have selected a linker to add a radiohalogen to Jansen's FAPis. EX2001, ¶¶63-69. 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 to modify US-633's compounds. Pet., 65; EX1003, ¶175; EX2001, ¶70. 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 FAPi. EX1003, ¶55; EX2001, ¶¶70-86. Dr. Zeglis's cherry-picking of the art demonstrates his hindsight reconstruction of the art to arrive at the challenged

claims. *Impax Lab 'ys 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”). Indeed, a flaw that arises in Dr. Zeglis’s analysis is his overlooking of other references in the art that disclosed known FAPis, including references cited in the Meletta reference on which he bases his proposed obviousness combination. EX2001, ¶71. 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, ¶71. Based on *in vitro* studies that found Meletta’s compound to not selectively accumulate in target tissue, which, according to Dr. Zeglis, would have led a POSA looking for “new, more selective FAP inhibitors, ... [to] invariably discovered the compounds characterized in Jansen.” EX1008, 2089; EX1003, ¶168; EX2001, ¶¶70-71. 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 FAPis, *including other references from Jansen’s research group*, for a suitable FAPi to use in modifying Meletta’s [¹²⁵I]MIP-1232. EX2001, ¶¶70-71.

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, ¶¶70-71. 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, ¶71.

Skipping over Jansen 2013, Dr. Zeglis jumps straight to Jansen with no explanation. EX2001, ¶71. 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, ¶¶178, fn. 188, 189, 190, 291. C-3); and (2) Jansen 2013 is considered in context with Jansen and other publications disclosing FAPis. EX2001, ¶71.

Jansen 2013 investigated the FAP and PREP affinities (and, therefore, the FAP selectivity) of 36 FAPi compounds. EX1007, Tables 2-3; EX2001, ¶72. 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. But Dr. Zeglis's obviousness analysis does not indicate that he evaluated Jansen 2013's compounds for modifying US-633's compounds, nor does he state why rejected the

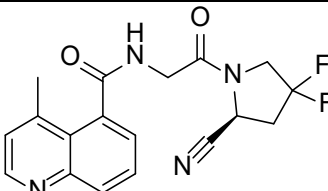
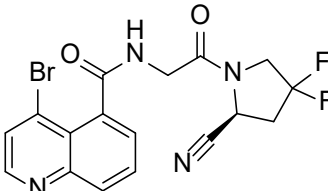
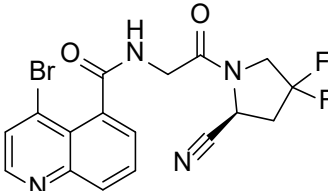
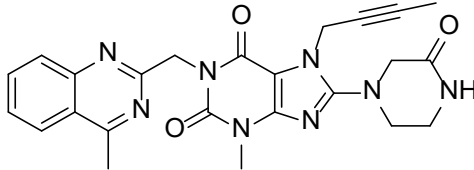
compounds of Jansen 2013, some of which were more selective than Compound 60, in favor of Jansen's Compound 60. EX2001, ¶72.

Dr. Zeglis also indicates that he considered US-650 (EX1044), also by Jansen. EX1003, ¶178, C-6; EX2001, ¶74. But, Dr. Zeglis's obviousness analysis does not indicate that evaluated the compounds of US-650 for modifying US-633's compounds, nor does he state why rejected the compounds of US-650 in favor of Jansen's Compound 60. EX2001, ¶74. In fact, US-650 discloses 43 FAPi compounds, many of which are highly selective for FAP and outperformed Jansen's Compound 60. EX1044, Table 4; EX2001, ¶74.

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, ¶73. A POSA would have been aware of these 33 FAPis with xanthine scaffolds. 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, ¶73. 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.*

Table 3 below illustrates the choices that a POSA would have had in front of them when purportedly deciding how to modify the compounds of US-633:

Table 3: 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)
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, ¶75.

Dr. Zeglis ignored or did not explain why POSAs would not have chosen any of the above compounds when evaluating suitability of FAPis for a radiotracer. *Id.*, ¶¶70-75. Notably, the table shows that the FAPi demonstrating the highest FAP selectivity in each reference does not fall within the scope of the challenged claims, demonstrating 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.

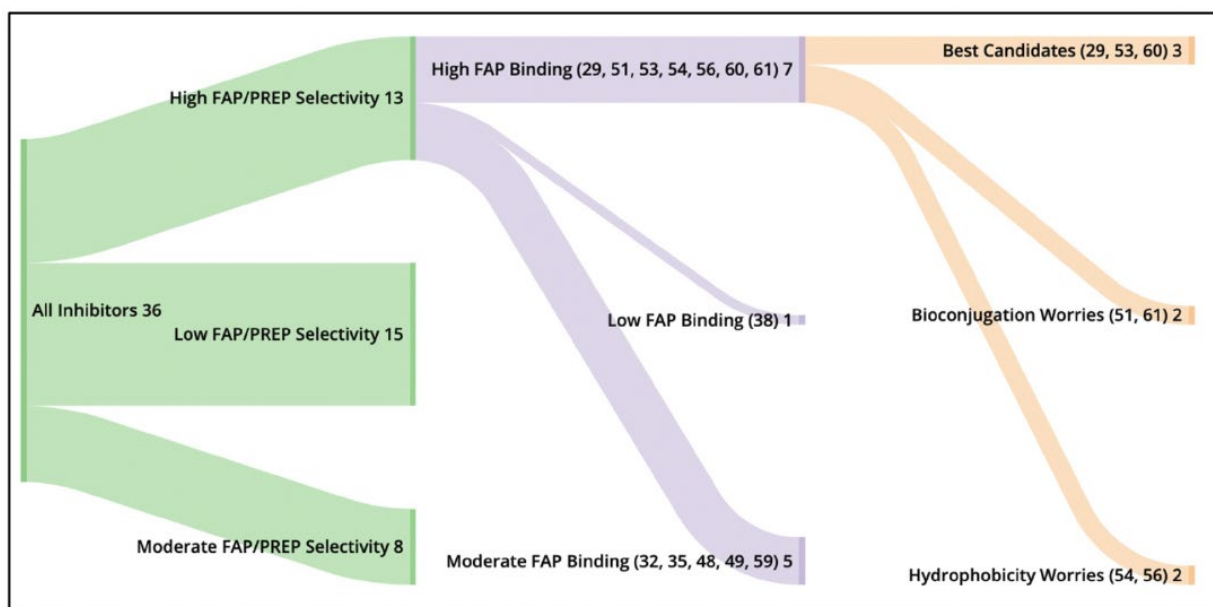
Dr. Zeglis's selection of Compound 60 from Jansen is unsupported and erroneous in view of his own selection criteria and the art as a whole. EX2001, ¶¶76-86. Indeed, a POSA following Dr. Zeglis's own Sankey diagram approach would not have arrived only at Compound 60. *Id.*

a. Dr. Zeglis's classification scheme 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, ¶149; EX2001, ¶76. 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, ¶152; EX2001, ¶76. Dr. Zeglis states that a POSA then would have allegedly would have “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, ¶152; EX2001, ¶76.

To present his analysis, Dr. Zeglis relies on “a visual representation of [the] classification process using a so-called Sankey diagram” (EX1003, ¶155):



Dr. Zeglis’s Sankey diagram, however, is unsupported. 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, ¶153; EX2001, ¶78.

Dr. Zeglis, however, does not explain the bases for those cutoffs in his classification scheme in relation to FAP. EX1003, ¶153-154; EX2001, ¶¶77-78.

That alone should render his testimony on this point to little or no weight. 37

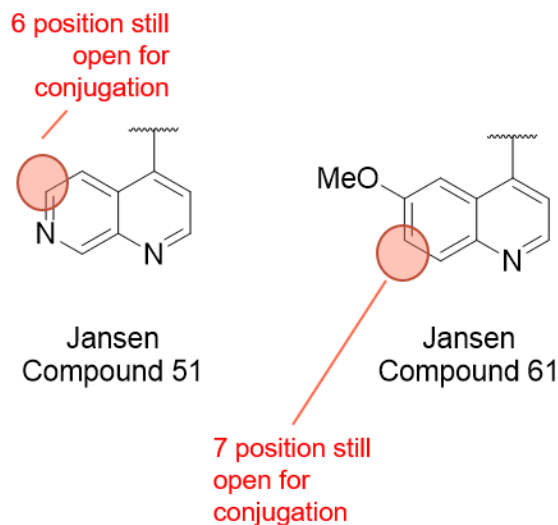
C.F.R. § 42.65(a) (“[e]xpert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”).

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, ¶153; EX2001, ¶79. 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.*, EX1007, Tables 7-8;

EX2001, ¶79. Contrary to the art, Dr. Zeglis did not account for those factors when choosing or excluding Jansen's FAPis for consideration. EX2001, ¶79.

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 conjugation issues" and that two others would raise "hydrophobicity concerns due to pendant phenyl groups." EX1003, ¶154; EX2001, ¶80-83. Dr. Zeglis also does not explain what is meant by "bioconjugation worries" or the criteria for determining which compounds would be susceptible to such "worries." EX2001, ¶80-83.

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, ¶¶80-81. Indeed, by Dr. Zeglis's own admissions, those compounds have high selectivity and affinity. EX1003, ¶¶154-155; EX2001, ¶80. 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 quinolinyl ring would be occupied." EX1003, ¶154; EX2001, ¶80. But in fact, occupying one of the two 7 and 6 position sites would still have allowed for conjugation, as shown below:

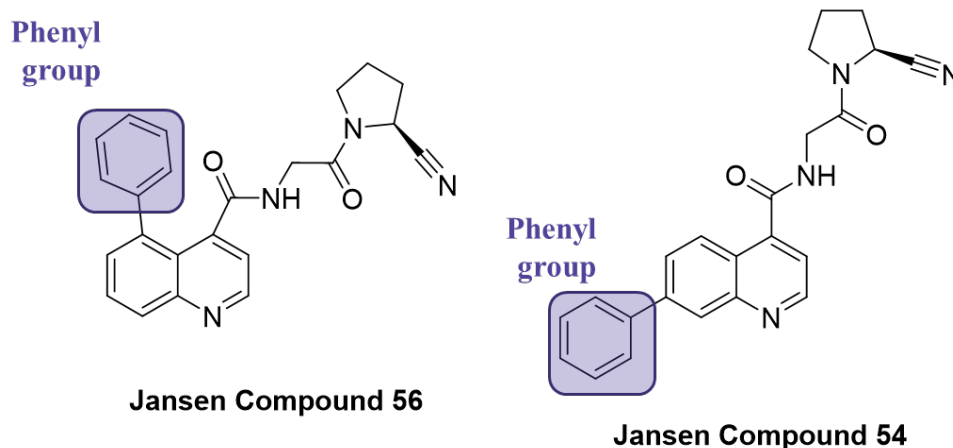


EX2001, ¶¶80-81.

Moreover, choosing either of the above compounds to replace the A moiety 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. EX1001, 64:5-55, Certificate of Correction; EX2001, ¶81. Dr. Zeglis, therefore, discarded Jansen's Compounds 51 and 61 in favor of Compound 60 in hindsight. *Id.*

Additionally, Dr. Zeglis does not provide the basis for his threshold for determining when hydrophobicity might pose a concern. EX1003, ¶154; EX2001, ¶¶82-83. 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, ¶154; EX2001, ¶¶82-83.



EX2001, ¶82.

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, ¶83. Dr. Zeglis, therefore, inappropriately discounts Compounds 54 and 56, which notably both contain substituents that are excluded from the claimed compounds. *Id.*, ¶¶78-83.

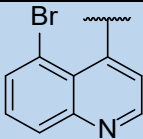
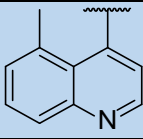
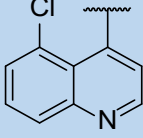
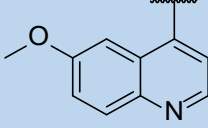
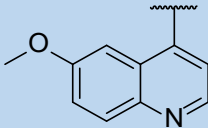
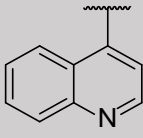
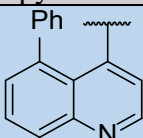
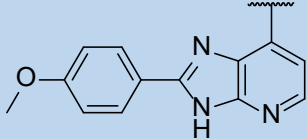
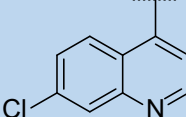
In sum, Dr. Zeglis makes unfounded, conclusory, or arbitrary choices in performing his Sankey analysis—that fortuitously eliminates four compounds (Compounds 51, 54, 56, and 61) that do not fall within the scope of the claimed “A” moiety—to land on Jansen’s Compound 60 as his final choice. *Id.*, ¶¶78-83.

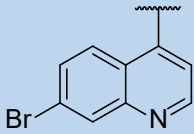
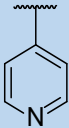
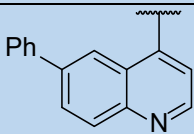
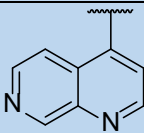
b. A POSA, following Dr. Zeglis' classification scheme, would not have arrived at Compound 60 due to the numerous other superior compounds.

As discussed in §IV.A.2., numerous 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, ¶¶153-155; EX2001, ¶¶71, 84. A POSA, however, would not have looked solely to Jansen when identifying suitable FAP inhibitors. EX2001, ¶¶71-75, 84. 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 I 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' selectivity and affinity criteria, but outperform Compound 60. EX2001, ¶84. Dr. VanBrocklin provides a tabulated set of FAPis disclosed in Jansen, US-650, and Jansen 2013 that meet Dr. Zeglis' arbitrary selectivity and affinity criteria (selectivity >100 and affinity <0.1 µM), which are shown in Table 4 below. EX2001, ¶84. 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, ¶¶55, 151; EX2001, ¶84.

Table 4. FAP Selectivity and Affinity Across Jansen, US-650, & Jansen 2013

Compound Number	Structure	FAP Selectivity	FAP Affinity	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	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, ¶85. 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 I. 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 has failed to establish that a POSA would have focused on the singular Jansen reference that is a sliver of the FAPi art that would have been available by October 2017. EX2001, ¶¶21-22, 70-75. 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.*, ¶¶24, 76-86. One, therefore, is only left with the reason being that Compound 60 falls within the scope of the claimed moiety, while the other compounds do not. *Id.* Dr. Zeglis also 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 conjugating a B to the FAPi and to avoid using a linker. *Id.*, ¶¶23, 50-67.

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 and Fails to Establish That a POSA Would Have Had a Reasonable Expectation of Success in Combining the Art.

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, ¶87. But as discussed for Ground 1, Dr. Zelig'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, ¶¶70-87. Dr. Zeglis's opinions are, therefore, guided by hindsight and do not establish that a POSA would have arrived at the Challenged Claims. EX2001, ¶88.

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

C. GE Fails to Address Known Objective Indicia of Nonobviousness.

The Petition is facially defective. GE's Grounds 1 and 2 are each based on challenging the Challenged Claims as obvious. But GE fails to make a case of obviousness as a matter of law because it does not address known objective indicia of nonobviousness, namely unexpected results of the claimed compounds.

All four *Graham* factors must be considered in an obviousness analysis. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1075 (Fed. Cir. 2012); *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Ignoring objective indicia in presenting an argument for unpatentability based on obviousness is, therefore, a fatal failure of proof. *Graham*, 383 U.S. at 17-18; *Stratoflex Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)(explaining that objective indicia of nonobviousness “must always when present be considered en route to a determination of obviousness”). Indeed, objective indicia of nonobviousness are “often ... the most probative and cogent evidence in the record.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016) (quoting *Stratoflex*, 713 F.2d at 1538).

Accordingly, objective indicia of nonobviousness must be addressed in a petition if they are developed and the petitioner is aware of them. *See Nike, Inc. v. Adidas AG*, 812 F.3d 1326, 1335 (Fed. Cir. 2016) (“Importantly, we have repeatedly emphasized that an obviousness inquiry requires examination of all four

Graham factors and that an obviousness determination can be made only after consideration of each factor.”) (citing, *inter alia*, *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012)).

The Board has “cautioned petitioners in prior proceedings that petitions may be denied if they do not address known evidence of secondary considerations.” *Stryker Corp. v. KFX Med. LLC*, IPR2019-00817, Paper 10 at 28 (P.T.A.B. Sept. 16, 2019); *see also Robert Bosch Tool Corp. v. SD3 LLC*, IPR2016-01751, Paper 15 (P.T.A.B. Mar. 22, 2017) (denying institution for failure to address objective indicia presented during an ITC proceeding); *Coalition for Affordable Drugs V LLC v. Hoffman-LaRoche, Inc.*, IPR2015-01792, Paper 14 (P.T.A.B. Mar. 11, 2016) (denying institution for failure to address objective indicia considered by Examiner during original prosecution); *Merial Ltd. v. Virbac*, IPR2014-01279, Paper 13 (P.T.A.B. Jan. 22, 2015) (denying institution for failure to address objective indicia considered by Examiner during original prosecution and noting “Merial was aware of the unexpected results showing which the Examiner found persuasive.... Merial should have addressed unexpected results in the first instance”); *Omron Oilfield & Marine, Inc. v. MD/TOTCO*, IPR2013-00265, Paper 11 (P.T.A.B. Oct. 31, 2013) (denying institution for failure to address objective indicia successfully argued in a reexamination).

Here, GE's failure to address the known evidence of the unexpected results of the claimed compounds that were submitted during prosecution of the '233 patent is fatal to its Petition. This objective indicium of nonobviousness undermines GE's *prima facie* case and represents another flaw in its Petition.

V. GROUND 3: GE FAILS TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CLAIMS LACK WRITTEN DESCRIPTION.

GE's written description arguments are erroneously predicated on the claimed compounds having to meet "the diagnostic or therapeutic utility identified in the specification." Pet., 107; EX2001, ¶¶89-92. But the Challenged Claims recite no such function for the claimed compounds. *See* §III.A. It is thus improper for GE to import functions from specification into the claims. *Schwing*, 305 F.3d at 1324; *Phillips*, 415 F.3d at 1323; *Constant*, 848 F.2d at 1571; *Boehringer*, Paper 11 at 5-6. Indeed, "[w]hether a claimed invention would 'work,' or whether it is operable, goes more directly to the utility requirement or the enablement requirement, not the written description requirement." *Allergan USA, Inc. v. MSN Lab'ys Pvt. Ltd.*, 111 F.4th 1358, 1376 (Fed. Cir. 2024). An invention, furthermore, "need only be useful to some extent and in certain applications." *Id.* GE's written description arguments, therefore, wrongly focus on whether the '233 patent describes claim scope that is *not* actually required by the claims.

Rather, as explained in §III.A., the claimed compounds are defined structurally, *i.e.*, having formula B-L-A. It is only the specific "B" and "L"

moieties that must be selected for use in the recited compounds based on their individual functional characteristics—*i.e.*, suitability for imaging/radiotherapy and bi-functionalization, respectively. The Board similarly preliminarily found that the '233 patent's parent's claims, which recite similar B-L-A compounds, “recite a compound, not a result,” and were adequately described. *ITM*, Paper 12 at 54; *see* §III.A. GE's reliance on cases involving claims reciting functionally defined genera, *i.e.*, *Idenix* and *AbbVie* (Pet., 120, 125, 127), therefore, is misplaced.

But even if GE's attempt to import functionality into the claims is credited, the Challenged Claims are sufficiently described when taking into account the *in vitro* and *ex vivo* utility for the claimed compounds disclosed in the '233 patent specification.

A. GE's Reliance on Cases Involving Functionally Defined Genera is Misplaced.

As discussed in §III.A., GE wrongly imports a requirement for *in vivo* diagnostic or therapeutic utility into claims that recite a compound by its structure, not the compound's function. GE thus inappropriately conflates what the claim *requires* (as ascertained via claim construction), *i.e.*, compounds with a B-L-A structure, and must be adequately described, with what it simply *covers*, compounds that can have various utilities. *In re Entresto*, 125 F.4th 1090, 1097-98 (Fed. Cir. 2025). In other words, the claimed compounds can encompass compounds that happen to have *in vivo* diagnostic or therapeutic utility, but the

Challenged Claims are not limited to such compounds. GE’s assertions based on the idea that the specification must provide some “indication which [B-L-A compounds] have the characteristics necessary for diagnostic or therapeutic utility” are, therefore, wrong and not what the claims require. Pet., 127-128; *Entresto*, 125 F.4th at 1097-98.

The cases that GE cites for its written description arguments, moreover, involve claims reciting functionally defined genera. Pet., 120, 125, 127 (citing *Idenix* and *AbbVie*). The specifications in those cases also lacked sufficient representative examples of structures that could achieve the expressly claimed functionality in view of the scope of the claimed genera. *Id.* They are thus inapposite, as discussed below.

Idenix Pharms. LLC v. Gilead Scis. Inc., 941 F.3d 1149, 1163-64 (Fed. Cir. 2019) involved methods of treating using a genus of compounds that were “effective in treating HCV,” There, the Federal Circuit found no written description because the specification did not provide “any indication as to *which* of th[e] undisclosed [compounds] would be effective.” *Id.*

Likewise, *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285 (Fed. Cir. 2014) involved claims reciting “a genus using functional language to define a desired result,” namely, antibodies that “bind[] to human IL–12 and dissociate[] from human IL–12.” *Id.* at 1292, 1299. Yet, the specification

described only “one type” of antibody that fell under the scope of the claims. *Id* at 1300.

In contrast to *Idenix* and *AbbVie*, the claims here define the claimed compounds by their *structure*, not by their ability to achieve any particular function or level of functionality, such as being effective for *in vivo* diagnostic or therapeutic use as GE alleges. *See* §III.A. The ’233 specification, moreover, discloses actual examples of the claimed compounds and numerous examples of A, B, and L moieties that a POSA would have considered when making the claimed compounds. EX1001, cols. 8-30; EX2001, ¶¶93-103. Thus, as discussed below in §V.B.2., the ’233 patent specification provides a sufficient number of representative species. EX2001, ¶¶93-103.

In sum, the cases GE cites for its written description arguments involve functionally defined genera and with those cases’ holdings turning on those specific facts. That is not the case here.

B. The Claimed Compounds Are Adequately Described in View of Apposite Case Law.

The Federal Circuit has stated that “adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*,

598 F.3d 1336, 1350 (Fed. Cir. 2010). Here, the '233 patent specification does just that.

1. The '233 patent specification adequately discloses the claimed invention through structure and physical properties of the claimed compounds and the A, B, and L moieties.

Here, the specification and claims make clear that the invention is a genus of novel compounds having the common structure B-L-A. EX1001, 64:5-62, Certificate of Correction; EX2001, ¶¶89-92. Dr. Zeglis, moreover, acknowledges that the claimed compounds have a common modular structure containing “three primary components:” “(a) a *targeting moiety* ... (b) a *reporter moiety* ... and (c) a *linker*[.]” EX1003, ¶37; EX2001, ¶93.

The '233 patent specification also provides the “structure” of the claimed A moieties, provides exemplary FAPi moieties, and incorporates by reference publications disclosing numerous other FAPis falling within the claims. EX1001, ¶8:25-33; EX2001, ¶93. The claimed A moiety, therefore, is adequately described. *Ariad*, 598 F.3d at 1350.

As for the claimed B and L moieties, the specification and claims make clear their “physical properties,” *i.e.*, suitable for imaging/radiotherapy and have bifunctionalization, respectively. EX1001, 64:5-55, Certificate of Correction; EX2001, ¶91. The specification then provides *dozens* of columns of exemplary B and L moieties that can be used in the claimed invention. EX1001, cols. 8-30;

EX2001, ¶¶94-96. The specification also incorporates by reference publications that provide even further examples of such moieties. EX1001, 17:46-55; EX2001, ¶97. Indeed, GE admits the specification contains these extensive disclosures, stating that the '233 patent provides “many possible choices for chelators and prosthetic groups via its formulae and laundry lists” and such groups were “well-known.” Pet., 125-127.

In addition to disclosure in the specification, a POSA also would have been aware of other “B” moieties that were known in the art, but not necessarily recited in the specification. Dr. Zeglis argues that the '233 patent specification provides “limited guidance” about chelator choices and chelator-radionuclide pairs, but then admits that a POSA would have had at their disposal many well-known options. EX1003, ¶254; EX2001, ¶102. These examples included dozens of prosthetic groups, chelators, and metal-chelator pairs. EX1003, ¶¶254-256, 262; EX2001, ¶102. As such, given the breadth of existing knowledge in the art regarding suitable “B” moieties, the specification did not have to include moieties known in the art to sufficiently describe the claimed invention. EX2001, ¶103.

A POSA thus would have readily understood that the inventors were in possession of the claimed compounds.

2. The '233 patent specification discloses sufficient representative species of the claimed compounds.

Faced with the '233 patent specification's extensive disclosure as to A, B, and L moieties, GE and Dr. Zeglis instead demand that the specification must provide a sufficient number of representative species of the combined B-L-A compounds to meet the unclaimed *in vivo* utility that it wrongly seeks to import into the claims. Pet., 107; EX1003, ¶275; EX2001, ¶90. To that end, GE states that the specification does not sufficiently "guide skilled artisans in the selection of B, L and A components, and equally important, how to arrange them, to yield compounds with the diagnostic or therapeutic utilities identified in the specification." Pet., 107. But, as discussed above in §III.A., the Challenged Claims are not functional. And GE ignores the *in vitro* and *ex vivo* utility of the claimed compounds. See §II; EX2001, ¶¶17-19.

When viewed properly as structural claims, the two working examples in the '233 patent specification sufficiently represent the common modular structure containing "three primary components:" "(a) a **targeting moiety** ... (b) a **reporter moiety** ... and (c) a **linker**" that Dr. Zeglis acknowledges. EX1003, ¶37; EX2001, ¶93. And the specification provides an extensive description on how to identify and combine the claimed A, B, and L moieties into the novel B-L-A combination. EX1001, columns 8-20; EX2001, ¶93-103. Thus, the specification provides sufficient species representative of the claimed genus. EX2001, ¶¶93-101.

But, even if the utility of the claimed compounds is taken into account for analyzing written description (which it should not be),⁶ GE and Dr. Zeglis have not established that a POSA would not have understood the '233 patent to provide sufficient representative species that indicate that inventors were in possession of the Challenged Claims. EX2001, ¶¶93-103. Indeed, as stated, the specification provides an extensive description on how to identify and combine the claimed A, B, and L moieties into the novel B-L-A combination. EX1001, columns 8-20; EX2001, ¶¶93-101. GE and Dr. Zeglis, moreover, have not demonstrated that a POSA would have been able to identify the full scope of A, B, and L moieties, and in turn B-L-A compounds, that could be used to yield compounds that were useful in *in vitro* and *ex vivo* applications based on the different A, B, and L species identified in the specification. EX2001, ¶98.

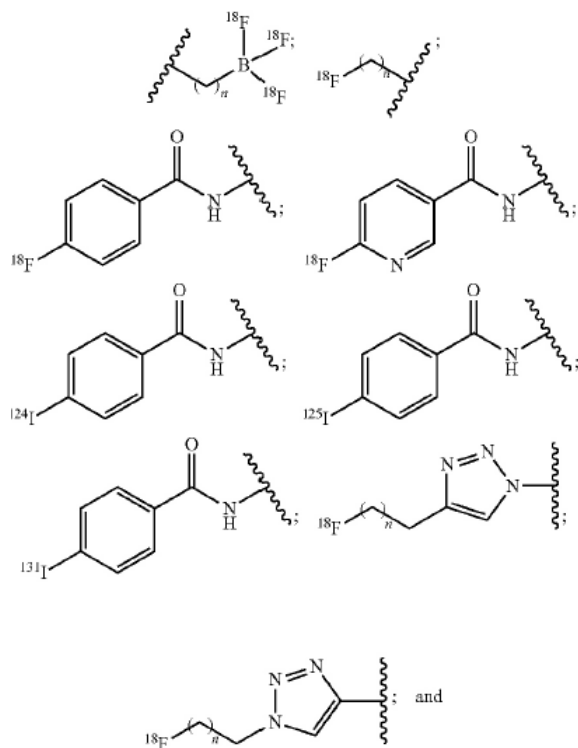
3. The '233 patent specification adequately describes B-L-A compounds comprising a radiolabeled prosthetic group.

GE and Dr. Zeglis also allege that the '233 patent provides “no examples of B-L-A compounds with a radiolabeled prosthetic group,” in claiming there is a lack of representative species in the specification. EX1003, ¶252; Pet., 123;

⁶ *Allergan*, 111 F.4th at 1376 (“Whether a claimed invention would ‘work,’ or whether it is operable, goes more directly to the utility requirement or the enablement requirement, not the written description requirement.”).

EX2001, ¶99. But examples of every conceivable embodiment are not required to have adequate written description. *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (stating that “our case law makes clear, however, ‘[a]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention’”); *see also Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (“A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language.”).

The '233 patent, nevertheless, does provide B-L-A compounds with a radiolabeled prosthetic group. EX1001, 18:35-70; EX2001, ¶99. In fact, Dr. Zeglis states that the specification discloses “six different chemical formulae” that provide radiolabeled prosthetic groups and “*ten* examples based on those formulae.” EX1003, ¶253; EX2001, ¶99. Each of those radiolabeled prosthetic groups, moreover, is illustrated in the '233 patent specification with the “L” attachment point demarcated in the structures with a squiggly line, as shown below. EX1001, 18:35-70; EX2001, ¶99.

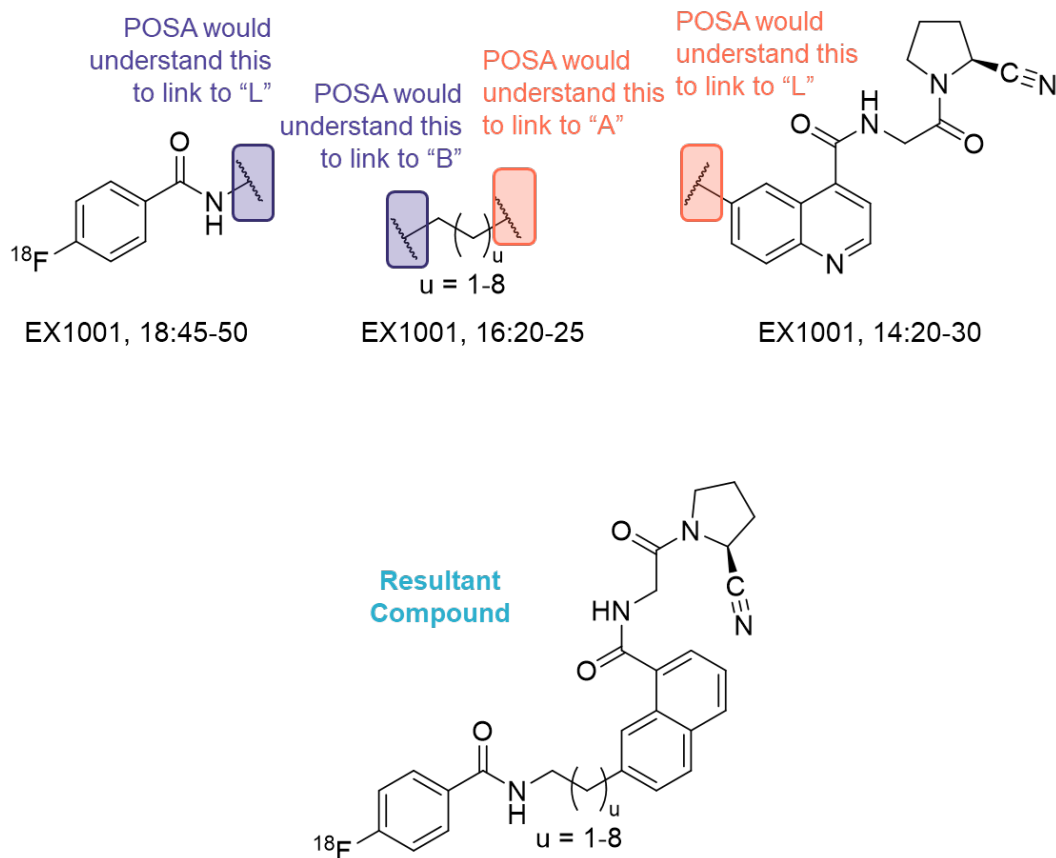


EX1001, 18:35-70.

Dr. Zeglis does not explain why this disclosure, when combined with the rest of the '233 patent specification's disclosures, is not sufficiently representative of B-L-A compounds with a radiolabeled prosthetic group. EX2001, ¶100. A POSA would have read those disclosures and understood that the labeled attachment points are where each of the radiolabeled prosthetic groups could be attached an L moiety. *Id.* Similarly, the '233 patent specification marks the intended attachment points of the L and A moieties to each other. *Id.*

Dr. VanBrocklin provides the examples below to demonstrate how a POSA would have known to combine the various disclosures of radiolabeled prosthetic

group B moieties with L and A moieties to yield a B-L-A compound comprising a radiolabeled prosthetic group:



Id.

Consequently, a POSA would have understood from the individual disclosures of radiolabeled prosthetic B groups that the '233 patent discloses B-L-A compounds incorporating such groups. *Id.*, ¶101.

In view of the above, GE's assertions of lack of written description based on there allegedly being a lack of representative species provided by the '233 patent specification, therefore, should be rejected.

C. GE's Reliance on *Fujikawa* Is Misplaced Because the Case Is Inapposite.

GE erroneously relies on *Fujikawa v. Wattanasin*, 93 F.3d 1559 (Fed. Cir. 1996). The facts of *Fujikawa* are distinguishable, and that case is inapposite.

GE points to *Fujikawa* for the proposition that “[l]isting possible options of components that *may* be combined to yield the hypothetical B-L-A compounds does not demonstrate possession of the claimed genera of B-L-A compounds.” Pet., 124. *Fujikawa* involved an appeal from an interference proceeding and whether the written description of the junior party’s patent application provided support for a subgenus of compounds having specific R-groups. 93 F.3d, 1569-1571.

The Federal Circuit found that the junior party’s specification did not support the subgenus because the specification did not provide sufficient “blazemarks” that would have led a POSA to the subgenus’s R-groups. *Id.* In so finding, the Federal Circuit stated that “just because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety.” *Id.*, 1571.

The above finding in *Fujikawa*, however, is not relevant here. Rather, here, the ’233 patent specification (1) is replete with multiple types of A, B, and L moieties that a POSA would have understood could be combined to yield the claimed compounds and (2) discloses two exemplary compounds that are

sufficiently representative of the common modular structure of the claimed subgenus of B-L-A compounds that are encompassed by the Challenged Claims. *See* §V.B.2. As such, a POSA is not left with having to be directed to a specific R-group, but rather to compounds having the claimed B-L-A structure. In other words, *Fujikawa* is inapposite as the claims here are not directed to an unidentified subgenus, but rather a genus that is sufficiently supported.

VI. GROUND 4: GE FAILS TO SHOW THAT IT IS MORE LIKELY THAN NOT THAT THE CHALLENGED CLAIMS LACK ENABLEMENT BECAUSE GE IMPROPERLY SEEKS TO IMPORT A REQUIREMENT FOR *IN VIVO* UTILITY INTO THE CLAIMS.

As with written description, GE hinges its enablement analysis on improperly seeking to import *in vivo* functionality into the claims where none is required. *See* §§III.A and V.A. By failing to analyze the Challenged Claims under the proper rubric, GE has failed to meet its burden to show that it is more likely than not that the Challenged Claims are unpatentable for lacking enablement.

GE erroneously relies on the Dr. Zeglis's opinion that the Challenged Claims lack enablement because Dr. Zeglis's opinions are based on his incorrect requirement that the claimed compound must be "viable optical imaging agents or radiolabeled imaging or therapeutic agents" *in vivo*. Pet., 135; EX1003, 273; EX2001, ¶104. Indeed, Dr. Zeglis opines that "undue experimentation would be required to make and use the full scope of the claimed compounds" because a POSA "would need to expend an incredible amount of labor and resources to

identify which of the 10^{27} to 10^{36} (and more) possible [claimed] B-L-A compounds ... actually possess the attributes that make them viable optical imaging agents or radiolabeled imaging or therapeutic agents.” EX1003, ¶273. And Dr. Zeglis predicates what he considers renders the claimed compounds “viable” agents based on them having *in vivo* (*i.e.*, in the body) use, repeatedly framing his discussion of the claimed compounds as such:

- “**Stability *in vivo***. A radiopharmaceutical or optical imaging agent must remain **intact in the body** for a long enough time to accumulate in its biological target. Even a compound with very high selectivity and affinity **will not be effective *in vivo*** if it is metabolized rapidly or the radionuclide dissociates or decays before binding the target.” EX1003, ¶59; EX2001, ¶104.
- “**Pharmacokinetic Profile**. As I explained above (¶ 51), a general principle of radiopharmaceutical design is that the physical half-life of the radionuclide should match the **pharmacological half-life** of the radiopharmaceutical precursor to ensure that there is sufficient **distribution in the target tissue** that can be imaged before the compound is cleared or the radionuclide decays.” EX1003, ¶59; EX2001, ¶104.

- “**Bioavailability.** Bioavailability refers to the relative amount of an administered radiopharmaceutical or optical imaging agent that enters **systemic circulation *in vivo*** in an unchanged state and is largely dictated by the compound’s pharmacokinetic profile.” EX1003, ¶59; EX2001, ¶104.
- “The compounds must **be stable under physiological conditions.**” EX1003, ¶275; EX2001, ¶104.
- “The compound must exhibit **satisfactory bioavailability.**” EX1003, ¶275; EX2001, ¶104.
- “These experiments are generally straightforward to perform, but they require synthesizing and purifying each compound and then subjecting it to an array of binding studies, **stability studies (e.g., in plasma), and animal testing for bioavailability and toxicity.**” EX1003, ¶277; EX2001, ¶104.

As shown above, Dr. Zeglis repeatedly demands *in vivo* utility of the claimed compounds, yet he never explains why the patent must enable a POSA to make and use the claimed compounds *in vivo*. EX2001, ¶105. The Challenged Claims recite no such requirement (*see* §III.A.), nor is there a requirement that they must meet such a utility. *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958 (Fed.

Cir. 1983) (“When a properly claimed invention meets at least one stated objective, utility under § 101 is clearly shown.”)

Indeed, as discussed in §II, the ’233 patent does not limit the compounds disclosed therein to such a use. EX2001, ¶¶105-106. Rather, the ’233 patent is broadly directed to imaging and radiotherapeutic agents that have utility in, *e.g.*, “*in vitro* applications[] such as *in vitro* diagnostic and research applications.” EX1001, 7:46-53; 35:47-52; EX2001, ¶105. For example, the ’233 patent provides that the disclosed compounds can be used “*in vitro* or *ex vivo* by introducing, and preferably mixing, the compound and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube.” EX1001, 37:22-25. The ’233 patent further states that the disclosed compounds can be used in “a method for imaging one or more cells, organs or tissues” and that “the method can be practiced *in vitro* or *ex vivo*.” EX1001, 35:4-9, 37:22-25; EX2001, ¶105.

As discussed in §II above, FAPi radiotracers can have a wide variety of *in vitro* and *ex vivo* utilities. These utilities include *in vitro* stability testing and *in vitro* pharmacokinetic and toxicity evaluation. EX1006, 3064; EX2008, 4, 7; EX2001, ¶105. Imaging agents, such as FAPi radiotracers, can also be used to collect data on the biodistribution of other radiotracers *ex vivo*. EX2008, 4, 7; EX2001, ¶105. These radiotracers can also be used to predict tumor responses to potential therapeutic agents, and can be used to evaluate the accumulation of FAPis

in the body “*in vitro* by radiography.” EX2006, 144; EX2010, 9; EX1008, 2083; EX2008, Abstract, 1421; EX2012, Abstract, 954; EX2001, ¶105.

Dr. Zeglis restricts his enablement analysis, however, to requiring utility of the claimed compounds for *in vivo* use, which is incongruous with the full description in the patent. EX1003, ¶273, 291; EX2001, ¶106. And by failing to acknowledge the *in vitro* uses of the claimed compounds, Dr. Zeglis also fails to establish that a POSA would not have been able to make and use the claimed compounds in such applications. EX2001, ¶¶106-109. Consequently, Dr. Zeglis ultimately fails to show lack of enablement because a POSA would not need to expand the same “incredible amount of labor and resources” to make and use the claimed compounds *in vitro* compared to Dr. Zeglis’s demand for *in vivo* use. *Id.*

A POSA, for instance, would not have needed to identify compounds with “satisfactory bioavailability” to be able to employ the claimed compounds *in vitro*. *Id.* Indeed, the amount of a given compound “in systemic circulation *in vivo*”—the defining feature of bioavailability, as per Dr. Zeglis’s admission (EX1003, ¶59)—has no bearing on a compound’s behavior in “a culture dish or tube,” as the patent describes an *in vitro* use (EX1001, 37:22-25). EX2001, ¶106. Nor does Dr. Zeglis explain why a POSA would not have been able to just “mix” the claimed compounds with target cells when conducting *in vitro* research applications, as the patent describes (EX1001, 37:22-25). EX2001, ¶106.

Rather, Dr. Zeglis merely assesses the amount of experimentation that would have been required to determine whether “[c]ompounds with a highly hydrophobic character ... exhibit unacceptable bioavailability”—*i.e.*, an *in vivo* use. EX1003, ¶280; EX2001, ¶106. Likewise, a POSA would not have had to identify compounds that “remain intact in the body for a long enough time to accumulate in its biological target” in order to “imag[e] one or more cells,” another of Dr. Zeglis’s unnecessary requirements placed on the claimed compounds. EX1003, ¶59; EX2001, ¶107. Cells can be imaged *in vitro* and *not* in the body, as described in the patent. EX1001, 35:4-9, 37:22-26; EX2001, ¶107. And the claimed compounds do not need to “remain intact in the body” when used as imaging agents outside of the body. EX2001, ¶107.

Similarly, Dr. Zeglis does not explain why a POSA would have had to identify compounds with “sufficient distribution in the target tissue” so that the tissue can be imaged “before the compound is cleared” from the body when imaging tissue *in vitro*. EX1003, ¶59; EX2001, ¶107. Indeed, a small sample of tissue can be removed from the body and imaged in “controlled environment” without any of the clearance concerns Dr. Zeglis espouses. EX1001, 37:22-25; EX2001, ¶107.

Further to the above, Dr. Zeglis alleges that “the compounds would have to be produced and tested to assess whether the choice of linker position adversely

affected the FAP selectivity of the compound.” EX1003, ¶291; EX2001, ¶108.

While *in vitro* applications can involve the selectivity of the claimed compounds being important, compounds that are not highly selective can still have utility.

EX2001, ¶108. For example, a diseased tissue sample, such as a biopsy, can be easily imaged *ex vivo* with a poorlyselective FAPi-based imaging agent because there would be no concern that “the compound will bind to FAP on ... sites associated with healthy tissue,” contrary to Dr. Zeglis’s argument. EX2001, ¶108.

Nevertheless, Dr. Zeglis admits that a POSA would have known how to test the claimed compounds for selectivity: “Jansen illustrates the experimentation that a skilled artisan would have had to undertake to meaningfully assess the affinity and selectivity of candidate FAP-targeting compounds.” EX1003, ¶288; EX2001, ¶108. Dr. Zeglis never argues that selectivity-determining experiments, like those in Jansen, would have been anything other than routine to a POSA, and thus undue. EX1003, ¶288; EX2001, ¶108.

Consequently, no “incredible amount of labor and resources” would be needed for such routine *in vitro* and *ex vivo* applications, like those discussed. EX2001, ¶¶104-109. GE and Dr. Zeglis cannot credibly argue otherwise. *Id.*

And because GE and Dr. Zeglis do not assess the enablement of the Challenged Claims under the correct lens, they have failed to meet their burden that making and using the full scope of the Challenged Claims claims would

require engaging in undue experimentation. Accordingly, GE fails to establish that it is more likely than not that the Challenged Claims are unpatentable for lacking enablement.

VII. CONCLUSION

The Petition fails to show that it is more likely than not that any of the Challenged Claims is unpatentable and, therefore, the Board 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: October 22, 2025

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: October 22, 2025

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: October 22, 2025

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