

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GE HEALTHCARE LTD.,
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner

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

**PATENT OWNER RESPONSE
UNDER 37 C.F.R. § 42.120**

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<i>In re O'Farrell</i> , 853 F.2d 894 (Fed. Cir. 1988)	46
<i>ITM Isotope Techs. Munich SE v. The Johns Hopkins Univ.</i> , PGR2025-00012, Paper 12 (P.T.A.B. July 16, 2025)	6
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007)	44, 48
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005)	3, 6
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Regulations

37 C.F.R. § 42.100(b)3

PATENT OWNER'S UPDATED 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”)
2005-2010	<i>Intentionally Left Blank</i>
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”)
2012-2017	<i>Intentionally Left Blank</i>
2018	Bvumbi, M., “Activity of Riminophenazines against Mycobacterium tuberculosis: A Review of Studies that Might be Contenders for Use as Antituberculosis Agents,” <i>ChemMedChem</i> 15(23):2207-2219 (December 2020) (“Bvumbi”)
2019	Xu <i>et al.</i> , “Discovery of potent and selective phenylalanine based dipeptidyl peptidase IV inhibitors,” <i>Bioorganic & Medicinal Chemistry Letters</i> , 15:2533-2536 (May 2005) (“Xu 2005”)
2020	Calcaterra <i>et al.</i> , “Classics in Chemical Neuroscience: Diazepam (Valium),” <i>ACS Chemical Neuroscience</i> , 5:253-260 (February 2014) (“Calcaterra”)

Exhibit No.	Description
2021	Lever, A.B.P., “Lewis Structures and the Octet Rule,” <i>Journal of Chemical Education</i> , 49(12):819-821 (December 1972) (“Lever”)
2022	Errata to Declaration of Dr. Brian Dr. Zeglis (EX1003) (submitted as Exhibit 2018 in PGR2025-00059)
2023	Dr. Zeglis <i>et al.</i> , “Radiopharmaceuticals for Imaging in Oncology with Special Emphasis on Positron Emitting Agents,” Chapter 3 of <i>Nuclear Oncology: Pathophysiology and Clinical Applications</i> , H.W. Strauss <i>et al.</i> , eds. (2013) (“Dr. Zeglis 2013 II”)
2024	Poplawski <i>et al.</i> , “Identification of Selective and Potent Inhibitors of Fibroblast Activation Protein and Prolyl Oligopeptidase,” <i>J Med Chem.</i> 56(9): 3467–3477 (May 9, 2013) (“Poplawski”) (submitted as Exhibit 2020 in PGR2025-00059)
2025	Pages 7 and 8 of U.S. Patent Application Publication No. 2010/0098633 A1 (EX1004) (annotated by Dr. Brian Dr. Zeglis) (submitted as Exhibit 2021 in PGR2025-00059)
2026	Pages 12–14 of U.S. Patent Application Publication No. 2010/0098633 A1 (EX1004) (annotated by Dr. Brian Dr. Zeglis) (submitted as Exhibit 2022 in PGR2025-00059)
2027	Transcript of the Deposition of Dr. Brian Dr. Zeglis, March 11, 2026
2028	Sugiura <i>et al.</i> , “Radiolabeling Strategies for Tumor-Targeting Proteinaceous Drugs,” <i>Molecules</i> 19: 2135–2165 (2014) (“Sugiura”)
2029	Testa <i>et al.</i> , “The influence of lipophilicity on the pharmacokinetic behavior of drugs: Concepts and examples,” <i>Perspectives in Drug Discovery and Design</i> , 19: 179–211 (2000) (“Testa”)
2030	Siwowska <i>et al.</i> , “Preclinical Comparison of Albumin-Binding Radiofolates: Impact of Linker Entities on the in Vitro and in Vivo Properties,” <i>Molecular Pharmaceutics</i> , 14(2): 523–532 (2017) (“Siwowska”)

Exhibit No.	Description
2031	Fischer <i>et al.</i> , “Radioimmunotherapy of Fibroblast Activation Protein Positive Tumors by Rapidly Internalizing Antibodies,” <i>Clinical Cancer Research</i> , 18(22): 6208–6218 (November 15, 2012) (“Fischer”)
2032	Scott <i>et al.</i> , “A Phase I Dose-Escalation Study of Sibrotuzumab in Patients with Advanced or Metastatic Fibroblast Activation Protein-positive Cancer,” <i>Clinical Cancer Research</i> , 9: 1639–1647 (May 2003) (“Scott”)
2033	Welt <i>et al.</i> , “Antibody Targeting in Metastatic Colon Cancer: A Phase I Study of Monoclonal Antibody F19 Against a Cell-Surface Protein of Reactive Tumor Stromal Fibroblasts,” <i>Journal of Clinical Oncology</i> , 12(6): 1193–1203 (June 1994) (“Welt”)
2034	Aertgeerts <i>et al.</i> , “Structural and Kinetic Analysis of the Substrate Specificity of Human Fibroblast Activation Protein α ,” <i>The Journal of Biological Chemistry</i> , 280(20): 19441–19444 (May 20, 2005) (“Aertgeerts”)
2035	Laverman <i>et al.</i> , “Immuno-PET and Immuno-SPECT of Rheumatoid Arthritis with Radiolabeled Anti-Fibroblast Activation Protein Antibody Correlates with Severity of Arthritis,” <i>The Journal of Nuclear Medicine</i> , 56(5): 778–783 (May 2015) (“Laverman”)
2036	Rüger <i>et al.</i> , “ <i>In vivo</i> near-infrared fluorescence imaging of FAP-expressing tumors with activatable FAP-targeted, single-chain Fv-immunoliposomes,” <i>Journal of Controlled Release</i> , 184: 1–10 (2014) (“Rüger”)
2037	LeBeau <i>et al.</i> , “Targeting the cancer stroma with a fibroblast activation protein-activated promelittin protoxin,” <i>Molecular Cancer Therapy</i> , 8(5): 1378–1386 (May 2009) (“LeBeau”)
2038	Huang <i>et al.</i> , “Evaluation of the tumor targeting of a FAP α -based doxorubicin prodrug,” <i>Journal of Drug Targeting</i> , 19(7): 487–496 (2011) (“Huang”)

Exhibit No.	Description
2039	Keane <i>et al.</i> , “Neuropeptide Y, B-type natriuretic peptide, substance P and peptide YY are novel substrates of fibroblast activation protein- α ,” <i>FEBS Journal</i> , 278: 1316–1332 (2011) (“Keane”)
2040	Reiner <i>et al.</i> , “Harnessing the Bioorthogonal Inverse Electron Demand Diels-Alder Cycloaddition for Pretargeted PET Imaging,” <i>Journal of Visualized Experiments</i> , 96 (February 2015) (“Zeglis 2015”)
2041	Adumeau <i>et al.</i> , “Site-Specifically Labeled Immunoconjugates for Molecular Imaging—Part 1: Cysteine Residues and Glycans,” <i>Molecular Imaging Biology</i> , 18: 1–17 (2016) (“Zeglis 2016”)
2042	Zeglis <i>et al.</i> , “Chemoenzymatic Strategy for the Synthesis of Site-Specifically Labeled Immunoconjugates for Multimodal PET and Optical Imaging,” <i>Bioconjugate Chemistry</i> , 25(12): 2123–2128 (November 24, 2014) (“Zeglis 2014”)
2043	Penner <i>et al.</i> , “Radiolabeled Absorption, Distribution, Metabolism, and Excretion Studies in Drug Development: Why, When, and How?” <i>Chemical Research in Toxicology</i> , 25: 513–531 (2012) (“Penner”)
2044	Jensen, “The Origins of the Ortho-, Meta-, and Para- Prefixes in Chemical Nomenclature.” <i>Journal of Chemical Education</i> , 83(3): 1-2 (2006).
2045	International Patent Appl. No. PCT/US2022/023374, published as WO 2022/212958 (“WO ’958”)
2046	Xu <i>et al.</i> , “Albumin Binder–Conjugated Fibroblast Activation Protein Inhibitor Radiopharmaceuticals for Cancer Therapy,” <i>The Journal of Nuclear Medicine</i> , 63(6):952-958 (June 2022) (“Xu”)
2047	Declaration of Dr. Henry VanBrocklin in Support of Patent Owner Response

I. INTRODUCTION

GE Healthcare Ltd. (“GE”) has not met—and cannot meet—its burden to establish that any of claims 1-3 (“the Challenged Claims”) of U.S. Patent No. 11,938,201 (“the ’201 patent”) are unpatentable by a preponderance of the evidence on the more developed record discussed herein.

The ’201 patent addresses a long-recognized problem in the field: failure to develop reliable small-molecule FAP radiotracers due to selectivity challenges arising from FAP’s structural homology with related peptidases. EX1001, 1:29-48; EX1008, 2089-90; EX2047, ¶¶6-13, 36; EX2001, ¶¶15-19. As newly presented here, the art viewed small-molecule FAP radiotracers as unpredictable, and instead pursued alternative, large-molecule strategies, such as FAP-targeting antibodies and peptides. EX2047, ¶¶31-37. Against that backdrop, the inventors developed a novel class of small-molecule radiotracers defined by a modular B-L-A structure, in which a quinolinylnyl-based FAP-targeting moiety (A) is covalently linked via a linker (L) to an imaging or radiolabeling group (B). EX1001, 2:8-12.

GE’s obviousness challenges (Grounds 1 and 2) rest on impermissible hindsight. EX2047, ¶¶6-13, 56, 69-76; EX2001, ¶¶20-24; EX2027, ¶¶6-13. GE selectively elevates one compound from a crowded FAP-inhibitor (“FAPi”) landscape, ignores more selective and better-performing alternatives that fall outside the claimed A-moiety, and then retrofits its chosen compound into the

claimed B-L-A architecture. As newly presented herein, that approach does not reflect how a person of ordinary skill in the art (“POSA”) would have proceeded from the art and disregards the lack of direction toward linker-containing architectures. The record herein further shows that the art provided no reasonable expectation that appending bulky reporter and linker moieties to quinolinyl FAPis would have successfully preserved selectivity.

The developed record also confirms that the claimed B-L-A architecture produces unexpected, orders-of-magnitude improvements in FAP-selectivity relative to the corresponding targeting moieties alone—results that the prior art neither taught nor predicted. Those unexpected results arise from the claimed architecture itself and supply powerful confirmation of nonobviousness.

For these reasons, GE has failed to establish unpatentability of any claim under any asserted Ground. The Board should enter judgment confirming the patentability of claims 1-3.

II. THE ’201 PATENT

The ’201 patent is directed to novel radiotracers targeting fibroblast activation protein- α (FAP) that can be used for *in vitro*, *ex vivo*, and *in vivo* applications. EX1001, Abstract; EX2001, ¶¶15-19. The patent describes low-molecular-weight FAP-targeting radiotracers having a B-L-A structure. EX1001, 2:8-12; EX2001, ¶17. These radiotracers exhibit unexpectedly high

selectivity and affinity for FAP-expressing cells, favorable biodistribution, and retained tumor uptake, making them suitable for imaging, diagnostic, and therapeutic applications. EX1001, 1:62-67, 5:39-41, 7:46-54; EX2011, Abstract; EX2001, ¶¶16-18.

As shown below, the '201 patent discloses innovative, highly selective FAP-targeting radiotracers that overcome prior FAP-imaging failures. EX2001, ¶19.

III. CLAIM CONSTRUCTION

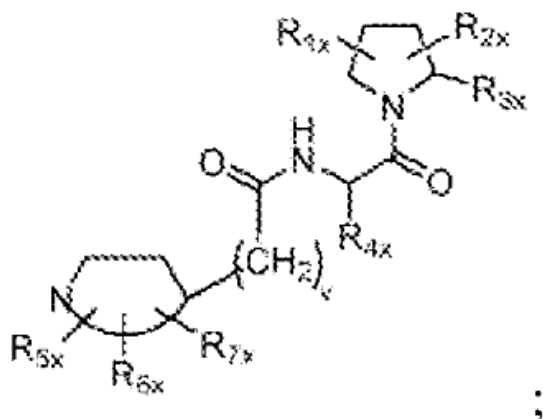
Claim terms must be given their “ordinary and customary meaning ... as understood by one of ordinary skill in the art” in view of the specification and prosecution history. 37 C.F.R. §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc).

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

GE states that “[c]laims 1 to 3 use functional language ... to define the ‘B’ and ‘L’ components of the claimed compounds.” Pet., 24. But GE does not explain how that has any impact on the analyses it provides in its Grounds. To the extent the Board finds it necessary to construe “B” and “L” to reach a final decision on patentability of the Challenged Claims, the Board should not import any functionality to the claimed compounds as a whole.

Indeed, the Challenged Claims are plainly structural. Independent claims 1 and 3 each 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:



...

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

EX1001, 64:46-67:5, Certificate of Correction (“COC”); EX2047, ¶21.

Claim 2 depends from claim 1 narrows B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon

emission computed tomography (SPECT) imaging, or radiotherapy. EX1001, 65:64-67; EX2047, ¶22.

The only functional language present in the Challenged Claims specifically defines B and L. EX1001, 65:54-60; EX2047, ¶¶21-28; EX2001, ¶35.

As explained by JHU's expert, Dr. Henry VanBrocklin, POSAs would have understood that, because the "suitab[ility]" for imaging/radiotherapy and "bi-functionalization" claim language defines specifically and only B and L, that language does not also define the claimed genus of low molecular weight compounds of formula B-L-A. EX1001, 64:46-67:5; EX2047, ¶¶24-29.

The specification likewise defines the recited B-L-A compounds in structural terms, consistent with the claims' plain language. *See, e.g.*, EX1001, 2:3-30, 7:46-65, 8:14-24, 11:22-30, 12:40-50, 15:40-44; EX2047, ¶26. And during prosecution, JHU distinguished the genus of compounds over the prior art on structural grounds: JHU pointed to the claimed B-L-A structure to distinguish from US-650, Jansen 2013, and US-633. EX1002, 359-362; EX2047, ¶27.

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.”).

The Board properly preliminarily decided that the claimed compounds should be treated as purely structural claims in a related proceeding, PGR2025-00012, involving the same ’201 patent, as well as in a related proceeding involving a child of the ’201 patent, PGR2025-00059. *ITM Isotope Techs. Munich SE v. The Johns Hopkins Univ.*, PGR2025-00012, Paper 12 at 54 (P.T.A.B. July 16, 2025); *GE Healthcare Ltd. v. The Johns Hopkins Univ.*, PGR2025-00059, Paper 8 at 34 (P.T.A.B. Jan. 14, 2026).

In PGR2025-00012, the Board explained: “The claims recite a compound, not a result. Although the B moiety must be suitable for specific imaging or radiotherapy uses, the claims do not require that the claimed compound has this functionality. This is true of the L linker as well.” *ITM*, Paper 12 at 54.

Thus, to the extent the Board finds it necessary to construe “B” and “L,” the Board should apply its preliminary finding in PGR2025-00012 that the Challenged

Claims are not functional. And any analysis of the claims by GE and Dr. Zeglis that depends on the claims being functional is not applicable.

B. “low molecular weight”

Each claim requires that the compound of formula B-L-A is of “low molecular weight.” EX1001, 64:46-67:5. In its Patent Owner Preliminary Response (“POPR”), JHU argued that this term should be construed as meaning “about 50 Daltons to about 1,500 Daltons” in view of the definition given to the term by Dr. Pomper, a co-inventor of the ’201 patent, during prosecution. POPR, 14-18; EX2047, ¶30; EX2001, ¶¶36-37. The Board in PGR2025-00059 disagreed. PGR2025-00059, Paper 8 at 10. There, the Board also “invite[d] the parties to further address construction of ‘low molecular weight’ ... to the extent needed to clarify this issue at trial.” *Id.* at 12.

JHU disagrees with the Board’s preliminary conclusion and maintains its arguments presented in its POPR here and in PGR2025-00059. Nevertheless, construing this term is not necessary to resolve this proceeding.

IV. GE’S PETITION FAILS TO ESTABLISH IN GROUNDS 1 AND 2 THAT THE CHALLENGED CLAIMS ARE UNPATENTABLE FOR BEING OBVIOUS.

To prevail in its obviousness grounds (Grounds 1 and 2), GE must show that POSAs would have been motivated to combine the asserted art to achieve the claimed invention with a reasonable expectation of success. *In re Magnum Oil*

Tools Int'l, Ltd., 829 F.3d 1364, 1381 (Fed. Cir. 2016). And “[c]are must be taken to avoid hindsight reconstruction by using ‘the patent in suit as a guide ... so as to achieve the result of the claims in suit.’” *Grain Processing Corp. v. Am. Maize- Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988).

Grounds 1 and 2 fail in this account.

A. Ground 1: The Challenged Claims Would Not Have Been Obvious over US-633, Jansen, and Meletta Because GE and Dr. Zeglis Rely on Selectively Picking and Choosing from a Crowded Field.

1. POSAs designing FAP-targeting radiotracers would have been faced with numerous paths that Dr. Zeglis inappropriately discounts.

Before October 2017, POSAs would have understood that FAP-imaging faced significant challenges—most notably, difficulty developing radiotracers selective for FAP over other members of the dipeptidyl peptidase (DPP) family, and the related prolyl oligopeptidase (PREP) with which FAP shares peptide substrate homology. EX2047, ¶¶31-37; EX2001, ¶¶16-18. Non-specific binding by FAP-targeting agents “limit[ed] the fabrication of FAP targeted imaging probe[s].” EX2047, ¶36; EX2004, 11. Studies also consistently described FAP as being structurally similar to other family members, underscoring the difficulty in designing selective FAP-targeted radiotracers. EX2034, Abstract; EX2047, ¶¶36-37; EX2001, ¶16.

The art, moreover, would not have pointed POSAs toward a single solution—much less small-molecule agents—but instead would have emphasized a range of competing strategies for FAP-imaging, as discussed below in §IV.A.1.b. EX2029, ¶¶51-52. Indeed, as Dr. Zeglis admits, the problem facing researchers was not limited to any single modality, but broadly encompassed “molecular imaging, *in vivo* imaging, *in vitro* imaging, optical imaging, PET imaging, ... radiotherapy, [and] SPECT imaging.” EX2027, 43:2-7; *see also* EX2027, 61:11-19, 68:8-14, 69:2-70:2, 78:20-79:3; EX2047, ¶37.

Accordingly, POSAs would have been presented with numerous different design pathways, each with its own tradeoffs and uncertainties, rather than a clear or predictable route toward the claimed invention. EX2047, ¶¶36-37; EX2001, ¶17. Dr. Zeglis, however, ignores the foregoing in favor of jumping straight to small-molecule radiotracers using hindsight. *Id.*

a. The prior art demonstrated that small-molecule FAP-targeting radiotracers would not have been known as a predictable approach.

Dr. Zeglis contends that POSAs would have homed in on small-molecule FAP radiotracers. EX1003 ¶30; EX2047, ¶38. The contemporaneous state of the art, however, demonstrates the opposite. EX2047, ¶¶38-49. By October 2017, the field of small-molecule FAP radiotracers was exceedingly sparse and had not yielded success. *Id.*

By then, only US-633, Marquis, and Meletta disclosed small molecule FAP radiotracers. *See generally* EX1004; EX1008; EX1035; EX2047, ¶¶38-42. Indeed, Dr. Zeglis even conceded that he is “not aware of any other references that disclose small molecule FAP-imaging agents before 2017.” EX2027, 162:15-22; EX2047, ¶38.

None of those references, moreover, would have led POSAs to small-molecule FAP radiotracers because none of those references disclosed a successful FAP radiotracer. EX2047, ¶¶38-42.

US-633 demonstrated that 25 out of 34 agents tested exhibited FAP-affinity in the high nanomolar range or greater, rather than the preferred low nanomolar range. EX1004, Table 2; EX2047, ¶39. Yet, US-633 did not investigate the FAP-selectivity of its radiotracers. *Id.*

From the compounds disclosed in US-633, Marquis selected a single compound (Compound 1024; FAP-affinity of 3 nm) for further study. EX1035, Abstract; EX1004, Table 2; EX2047, ¶¶40-41. Marquis synthesized three radioiodinated analogs of Compound 1024 (B-FAPi) that differed only in the position at which iodine was substituted on the aromatic ring (referred to as *ortho*-, *meta*-, and *para*-substitution (EX2044, 1-2)). EX1035, Abstract; EX2047, ¶40.

Marquis reported that the *para*-substituted analog (MIP-1232) showed better selectivity *in vitro* compared to the *ortho*- and *meta*-substituted analogs and could

inhibit FAP's enzymatic activity in transfected cell lines. EX1035, Abstract; EX2047, ¶¶40-41. Marquis also described MIP-1232 as having high-specificity because it interacted only with FAP-transfected cells, i.e., cells generated to overexpress FAP, and not non-FAP-expressing cells. EX1035, Abstract; EX2047, ¶41. From this, Marquis concluded that “[r]adiolabeled [FAP] inhibitors could be exploited for the diagnosis, staging, prognosis, and potential treatment of solid tumors.” EX1035, Abstract; EX2047, ¶40.

But Meletta's subsequent work would have suggested to POSAs that small-molecule FAP radiotracers lacked viability. EX2047, ¶¶38-42. Using human carotid plaque samples, Meletta tested MIP-1232 based on its reported binding affinity, selectivity, and the theoretical ability to radioiodinate the compound without structural modification. EX1008, 2083; EX2047, ¶41. ***But radioiodinated MIP-1232 failed to selectively accumulate in FAP-expressing tissue.*** EX1008, 2089-2090; EX2047, ¶41. Indeed, Meletta stated, “Binding of [¹²³I-MIP-1232] to endarterectomized tissue was similar in plaques and normal arteries, ***hampering its use for atherosclerosis imaging.***” EX1008, Abstract¹; EX2047, ¶41.

Thus, the prior art did not reflect that small-molecule FAP radiotracers would have provided a fruitful avenue for FAP-imaging. EX2029, ¶42.

¹ Emphasis added throughout except where otherwise indicated.

b. In contrast to small-molecule FAP radiotracers, antibody-based FAP radiotracers had been established as a successful approach by October 2017.

Before October 2017, antibody-based radiotracers represented the more successful and established approach for FAP-imaging. EX2047, ¶¶43-46.

Before testifying for GE, Dr. Zeglis himself repeatedly described antibodies as uniquely well-suited imaging vectors. EX2040, Abstract; EX2047, ¶43. In 2015, he characterized antibodies as “extremely promising vectors for the delivery of radioisotopes to cancer cells for PET imaging,” citing their “exquisite affinity and specificity.” EX2040, Abstract; EX2047, ¶43. In 2016, he emphasized that antibodies exhibit “remarkable selectivity and specificity for cancer biomarkers.” EX2041, Abstract; EX2047, ¶43. And he identified antibodies as “promising platforms for the development of hybrid PET/OI [optical imaging] agents” because of their “high selectivity and affinity.” EX2042; EX2047, ¶43. Consistent with those views, Dr. Zeglis admitted that he was not aware of “any examples where a small molecule provided more selectivity for FAP over PREP than an antibody.” EX2027, 67:7-68:4; EX2047, ¶43.

The prior art confirms that antibody-based agents were successfully developed and tested before October 2017. EX2047, ¶44. As Laverman explained, “[b]ecause FAP is expressed in tumor stroma, various anti-FAP antibodies have been studied for radioimmunotargeting of malignancies,” including an ¹³¹I-labeled

murine F19 antibody and an ¹³¹I-labeled sibrotuzumab, a humanized F19 antibody. EX2035, 778; EX2047, ¶44. Clinical testing of sibrotuzumab showed “no toxicity” and “consistent targeting to metastatic lesions in patients with colorectal carcinoma,” confirming viability of anti-FAP antibodies for diagnostic and potentially therapeutic use. EX2033, 1198; EX2032, 1645-1646; EX2047, ¶44.

Additional antibody-based agents further demonstrated the maturity of this approach. Laverman reported that ¹⁷⁷Lu-ESC11 and ¹⁷⁷Lu-ESC14 exhibited “excellent targeting in melanoma xenografts.” EX2035, 778; EX2047, ¶45. Fischer showed that ESC11 and ESC14 “bound selectively to both human and mouse FAP, with affinities in the low nanomolar range.” EX2031, Abstract; EX2047, ¶45. Laverman also disclosed that the anti-FAP radiotracer ¹¹¹In-28H1 “result[ed] in excellent image quality,” attributable to low background uptake in off-target tissues. EX2035, 780, 783; EX2047, ¶45.

Taken together, the prior art would have bolstered a POSA’s view that antibody-based radiotracers represented a proven, effective, and predictable strategy for FAP-imaging, in contrast to the failure of small-molecule radiotracers. EX2047, ¶46.

It is, therefore, telling that GE’s obviousness case focuses narrowly on small-molecule approaches while simultaneously ignoring the successful antibody-based FAP-imaging literature. Indeed, although Dr. Zeglis acknowledges

that antibodies in general could serve as “[t]argeting moieties in a radiopharmaceutical” (EX1003 ¶30; EX2027, 68:6-10), he did not meaningfully address how the well-established antibody-based FAP-imaging art would have informed a POSA’s approach when developing a FAP radiotracer. EX2047, ¶¶43-46. Yet, he praised antibody-based agents before becoming GE’s expert in this proceeding. *Id.*

c. Peptide- and protein-based FAP-targeting strategies were more developed than small-molecule agents before October 2017.

The prior art also demonstrates that peptide- and protein-based FAP-targeting agents represented a more successful strategy for FAP-imaging. EX2047, ¶47. Indeed, beyond full-length antibodies, the art described multiple antibody-derived pharmacophores that achieved specific binding to FAP. *Id.*

Rüger reported constructs incorporating single-chain anti-FAP antibody “Fv” fragments (scFv’FAP), which exhibited “specific interaction and binding with FAP-expressing cells *in vitro*.” EX2036, Abstract; EX2047, ¶47. Rüger further demonstrated *in vivo* selectivity, observing that the constructs accumulated selectively in FAP-expressing xenografts and concluding that such constructs could serve as “a suitable *in vivo* diagnostic tool” for disorders causing elevated FAP expression. EX2036, Abstract; EX2047, ¶47.

POSAs likewise would have understood peptide-based agents to be an established and well-recognized route for developing radiotracers before October 2017. EX2047, ¶48. Dr. Zeglis acknowledged prior to this proceeding that peptides “hold a significant position in the field of radiotracer development,” and receptors that bind peptide ligands and are overexpressed in tumors “represent promising candidates for imaging.” EX2023, 58; EX2047, ¶48. And because FAP binds peptide ligands, the art disclosed numerous peptide-based strategies directed to FAP, including peptide protoxins, dipeptides, and naturally occurring substrates. *See, e.g.*, EX2037, Abstract; EX2038, Abstract; EX2039, Abstract, 1328; EX2047, ¶48. POSAs, therefore, would have viewed peptide-based constructs as viable starting points for FAP-targeting radiotracers. EX2047, ¶¶47-49.

2. POSAs would also have been presented with multiple radiolabeling choices.

POSAs would have understood from the prior art that radiotracer design did not involve a single approach to radionuclide incorporation, in contrast to the hindsight approach Dr. Zeglis took, as discussed below in §IV.A.4.a. EX2047, ¶50. To the contrary, the art recognized multiple, materially different strategies for labeling small-molecule radiotracers. *See, e.g.*, EX1014, 31; EX2047, ¶¶50-55. A radionuclide is the radioactive isotope incorporated into a radiotracer that emits detectable radiation and enables imaging of a target. EX1014, 31; EX2047, ¶50. Radionuclides may be incorporated by covalent attachment or stable coordination

through a chelator, and no approach was universally preferred across molecular scaffolds or targets. EX1014, 31; EX2047, ¶50.

POSAs would have recognized, as Dr. Zeglis stated before this proceeding, that successful labeling strategies for small-molecule radiotracers generally sought to “disturb[] the activity of the parent molecule as little as possible,” because even minor structural changes can significantly alter affinity, selectivity, solubility, or biodistribution. EX1010, 3; *see also* EX2023, 58; EX1003, ¶49; EX2047, ¶50.

POSAs would have been aware of the following different ways of incorporating a radionuclide into a radiotracer. EX2047, ¶¶51-55. Dr. Zeglis immediately jumps to using bulky L and B moieties to add a radionuclide to A, but as discussed below and in §IV.A.4.a, POSAs would not have made such a choice based on general radiotracer design principles and the risk of adding L and B negatively affecting FAPi-selectivity and affinity. *Id.*

a. Direct isotopologous labeling with non-metallic radionuclides

One well-established option would have been direct isotopologous labeling—particularly with radiohalogens. EX2047, ¶52. Under this approach, a stable atom within the parent molecule (e.g., ¹⁹F, ¹²⁷I, ⁷⁹Br, ⁸¹Br) is replaced with its radioactive isotope counterpart (e.g., ¹⁸F, ¹²³I, ¹²⁴I, ¹²⁵I, ¹³¹I, ⁷⁶Br). EX1014, 44; EX2047, ¶52. These non-metallic radionuclides are “ordinarily attached to a

radiopharmaceutical via a covalent bond,” and may be “incorporated directly into the targeting moiety structure.” EX1003, ¶34; EX2047, ¶52.

The principal advantage of isotopologous labeling is that it introduces minimal structural perturbation. EX2047, ¶52. For example, ^{18}F is particularly attractive for *in vivo* imaging because its incorporation causes only “minimal perturbation” to the parent molecule while offering a favorable half-life. EX1014, 44; EX2047, ¶52. Additionally, radioiodination was frequently described as “the most versatile radiolabeling strategy” prior to October 23, 2017. EX2028, Abstract. Consistent with this understanding, Dr. Zeglis testified that isotopologue labeling produces a molecule that differs only “in a very small way” from the starting structure. EX2027, 92:15-93:1; EX2047, ¶52.

b. Prosthetic-group labeling of non-metallic radionuclides

POSAs also would have known that non-metallic radionuclides could be introduced indirectly through prosthetic-group labeling. EX2047, ¶53. The radionuclide is first covalently attached to a prosthetic group, which is then conjugated to the radiotracer precursor. EX1014, 44; EX1033, 137-38; EX2047, ¶53. Unlike isotopologous substitution, prosthetic-group labeling adds new structural elements to the molecule. EX1003, ¶34; EX2047, ¶53.

POSAs would have understood that this approach required the prosthetic group and its attachment point to be positioned sufficiently distant from the portion

of a compound that interacts with the target. EX2047, ¶53. Otherwise, the modification would have risked disrupting the compound's affinity and/or selectivity for its target—a proposition Dr. Zeglis expressly acknowledges. EX1003 ¶49(b); EX2029, ¶68.

c. Chelation strategies for metallic radionuclides

For metallic radionuclides, chelation would have been required. *See, e.g.*, EX1017, 2667; EX2047, ¶54. Radiometals are incorporated by coordinating the radionuclide within a chelator that forms a stable complex with the metal ion. EX1013, Abstract; EX2047, ¶54. Like prosthetic-group labeling, chelation necessarily would have introduced substantial structural modifications to the parent molecule, implicating the possibility of interfering with target recognition. EX1017, 2669 (warning that “the conjugated chelator should not interfere with the binding affinity of the peptide”); EX2047, ¶54.

Dr. Zeglis likewise agrees that chelation strategies add bulk, charge, and rigidity, frequently requiring linkers and altering key physicochemical and biological properties such as solubility, blood residence time, and biodistribution. EX1003, ¶36; EX2047, ¶55.

The prior art thus confirms that POSAs would have faced multiple distinct radiolabeling strategies, each of which would have necessitated considering factors such as the chemical nature of the targeting moiety, its sensitivity to structural

modification, and the identity of the radionuclide. EX2047, ¶¶54-55. These variables would have added a substantial additional layer of design complexity, compounding the already significant choices among different classes of FAP radiotracers. *Id.*

* * *

In view of §§IV.A.1-IV.A.2, the prior art did not provide a single, predictable path, but instead required case-specific judgments with uncertain outcomes, offering no reasonable expectation as to how a small-molecule radiotracer selective for FAP could be achieved. EX2047, ¶¶36-37, 50. Nor did the art provide any reasoned basis to converge on small-molecule FAP radiotracers—much less the specific B-L-A structure recited in the Challenged Claims. *Id.*

As discussed below, GE's and Dr. Zeglis's contrary position that POSAs would have immediately focused on a small-molecule approach rests on hindsight reconstruction. Moreover, Dr. Zeglis used hindsight to selectively elevate one FAPi (Jansen's Compound 60) from among many disclosed alternatives while disregarding the broader landscape of competing approaches and contemporaneous failures that counseled against small-molecule FAP-imaging altogether. EX2047, ¶¶38-42.

3. The variety of FAPis described in the prior art would have further increased the complexity of design decisions POSAs faced.

Had POSAs pursued a small-molecule FAP radiotracer—a premise unsupported by the prior art—POSAs would still have faced an additional and substantial design challenge: selecting a FAP-targeting compound from among the many structurally and functionally distinct FAPis disclosed in the literature.

EX2047, ¶56.

a. Dr. Zeglis excludes numerous FAPis disclosed in prior art.

Dr. Zeglis asserts that POSAs would have regarded Jansen’s Compound 60 as “one of the most promising FAP inhibitors that had been discovered to date” and therefore would have selected it as the targeting moiety. EX1003, ¶115; EX2047, ¶56. But, the prior art did not disclose Compound 60 in B-L-A form.² EX2047, ¶58. And, rather than evaluating the prior art as whole, including the dozens of other FAPis disclosed in different references than Jansen, Dr. Zeglis selectively focuses on a single reference, Jansen, and selected a single compound that fits the Challenged Claims, while disregarding the broad and diverse body of

² At institution in the related PGR2025-00059 proceeding, the Board mistakenly found that Compound 60 “is already in B-L-A form.” PGR2025-00059, Paper 8 at 25.

FAPi disclosures that would have confronted POSAs. EX1003, ¶127; EX2047, ¶¶56-65. Obviousness, however, cannot be established by using the claims as a roadmap to pick and choose among prior-art disclosures absent a reason that would have led POSAs to make specific selections. *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The prior art disclosed dozens of FAPis spanning multiple chemical scaffolds, selectivity profiles, and structure-activity relationships. EX2047, ¶¶56-65. Dr. Zeglis does not articulate any reason that would have led POSAs to set aside this broader art and instead single out Jansen and its Compound 60 as the preferred choice. EX1003, ¶127; EX2047, ¶¶56-79. Instead, he simply assumes that POSAs would have “invariably discovered” Compound 60. EX1003, ¶¶133-143; EX2047, ¶57.

That leap, however, is unsupported by the art and fails to identify any reason favoring Compound 60 over the many available alternatives. EX2047, ¶¶66-79. Dr. Zeglis has emphasized that FAP-selectivity is “the most important factor” when choosing a FAPi for a radiopharmaceutical. EX1003, ¶45; EX2047, ¶59. Yet, even if selectivity were the most important factor, the prior art provided no reason to favor Compound 60 over others, as numerous FAPis exhibited selectivity profiles substantially better than Compound 60, undercutting any contention that

Compound 60 would have stood out to POSAs as the obvious selection. EX2047, ¶¶60-76.

Jansen 2013 (EX1007) alone disclosed 36 distinct FAPis. EX1007, Tables 2-3; EX2047, ¶60; EX2001, ¶¶64, 77. Many of these compounds exhibited equal or greater FAP-selectivity compared to Compound 60 (selectivity of 562), including Compounds 26 (>4500), 25 (1700), and 30 (677). EX1007, Tables 2-3; EX2047, ¶60. And the most selective compound in that study—Compound 26—falls outside the scope of the Challenged Claims because it contains a substituent on the quinolinyl ring that the claims exclude. EX1007, Tables 2-3; EX1001, 64:46-67:5, COC; EX2047, ¶60; EX2001, ¶¶64, 77. Dr. Zeglis does not evaluate these alternative compounds or explain why POSAs would have bypassed them in favor of Compound 60. EX2047, ¶60; EX2001, ¶¶64, 77.

Similarly, US-650 (EX1044) disclosed 43 additional FAPis, many of which matched or exceeded Compound 60's selectivity. EX1044, Table 4; EX2001, ¶66; EX2047, ¶61. Compounds 22 (>4500), 23 (2100), 21 (1700), and 11 (677) all outperformed Compound 60 in FAP-selectivity. EX1044, Table 4; EX2047, ¶61. Dr. Zeglis acknowledged that he considered US-650 and admitted as his deposition that several of US-650's compounds are more selective than Compound 60 (EX2027, 154:8-156:17). EX2047, ¶61; EX2001, ¶66.

Yet, he again provides no rationale as to how US-650 would have guided a POSA's analysis or why POSAs would have rejected US-650's compounds in favor of Compound 60. EX2047, ¶61. And as with Jansen 2013, the most selective compound in US-650 (Compound 22) falls outside the claims' A moiety because it contains a quinoline ring-substituent that is excluded by the Challenged Claims. EX1044, Table 4; EX1001, 64:46-67:5, COC; EX2047, ¶61; EX2001, ¶¶66-67.

The prior art further disclosed FAPis employing entirely different chemical scaffolds. EX2047, ¶64. Jansen 2014 (EX2003) disclosed 33 xanthine-based FAPis (not covered by the claims' requirement for a quinoline-based scaffold) and reported successful decoupling of FAP-potency from related proteases. EX2003, Abstract; EX2047, ¶64; EX2001, ¶65. Jansen 2014 characterized several of its compounds as selective FAPis, with reported selectivity over DPP^{IV} and PREP. EX2003, Tables 3 and 5; EX2047, ¶62; EX2001, ¶65. Dr. Zeglis conceded familiarity with this reference but did not evaluate these compounds or explain why POSAs would have ignored them. EX2027, 129:5-132:6; EX2047, ¶62; EX2001, ¶65.

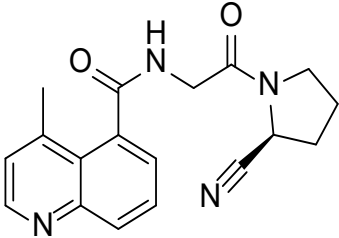
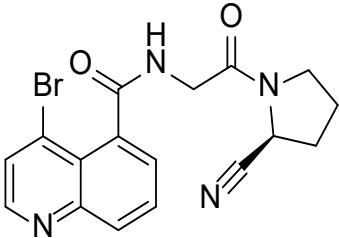
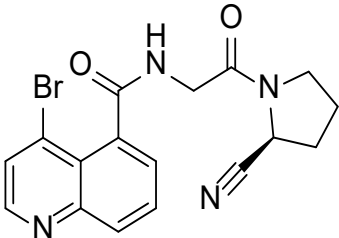
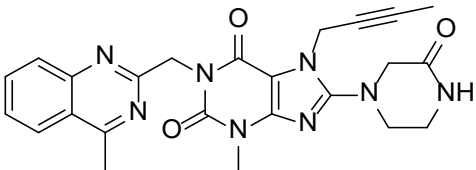
Other groups also disclosed potent and selective FAPis. EX2047, ¶63. Poplawski reported 22 non-quinolinyll FAPis and described them as the first compounds to combine low-nanomolar potency with selectivity over both DPPs and PREP. EX2024, 7, Tables 1-4; EX2047, ¶63. Poplawski's Compound 6

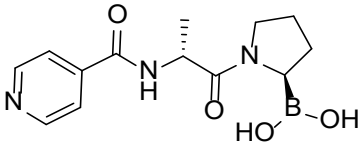
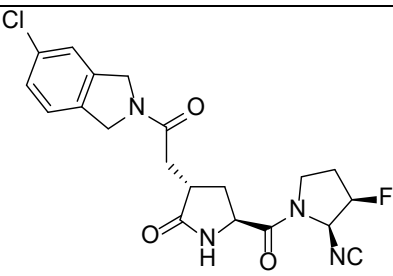
exhibited FAP-selectivity on the same order of magnitude as Compound 60, yet Dr. Zeglis discounted it based on the absence of published *in vivo* pharmacokinetic (PK) data. EX1003 ¶109(c); EX2047, ¶63. That rationale is inconsistent with his own deposition testimony that optical radiotracers may also be useful *in vitro*, which would not implicate pharmacokinetics. EX2027, 80:13-15; EX2047, ¶63.

Tsai similarly disclosed 27 FAPis based on a pyroglutamic-acid scaffold, reporting IC₅₀ values below 100 nM and excellent selectivity over DPPs. EX1047, Abstract, Table 2; EX2047, ¶64. Tsai identified Compounds 18a, 18b, and 19 as uniquely potent and selective FAPis. EX1047, Abstract, Table 2; EX2047, ¶64. Dr. Zeglis dismissed the reference based on alleged “poor” PK concerns raised for *one* compound disclosed in Tsai. EX1003 ¶109; EX2047, ¶64. Yet, Tsai also demonstrated that its Compound 18b had favorable half-life, clearance, and exposure maintaining FAP-selectivity. EX1047, 6578; EX2047, ¶64. Dr. Zeglis, however, has offered no explanation for how these disclosures would have informed—or failed to inform—POSAs evaluating the available FAPi landscape. EX2047, ¶64.

As demonstrated below, the most selective compounds disclosed across multiple prior art references fall outside the scope of the Challenged Claims. EX2047, ¶65.

Overview of prior art references that disclose selective FAPis and the highest-selectivity FAPi for each reference

Reference	Number of FAPis disclosed	Number of FAPis that fall within claimed A	Highest-selectivity FAPi structure (All compounds below are outside of the claims' "A" moiety scope)
Jansen	54	3	 <p>(Compound 53)</p>
US-650	43	1	 <p>(Compound 22)</p>
Jansen 2013	36	2	 <p>(Compound 26)</p>
Jansen 2014	33	None	 <p>(Compound 3)</p>

Reference	Number of FAPis disclosed	Number of FAPis that fall within claimed A	Highest-selectivity FAPi structure (All compounds below are outside of the claims' "A" moiety scope)
Poplawski	22	None	 <p>(Compound 6)</p>
Tsai	27	None	 <p>(Compound 18b)</p>

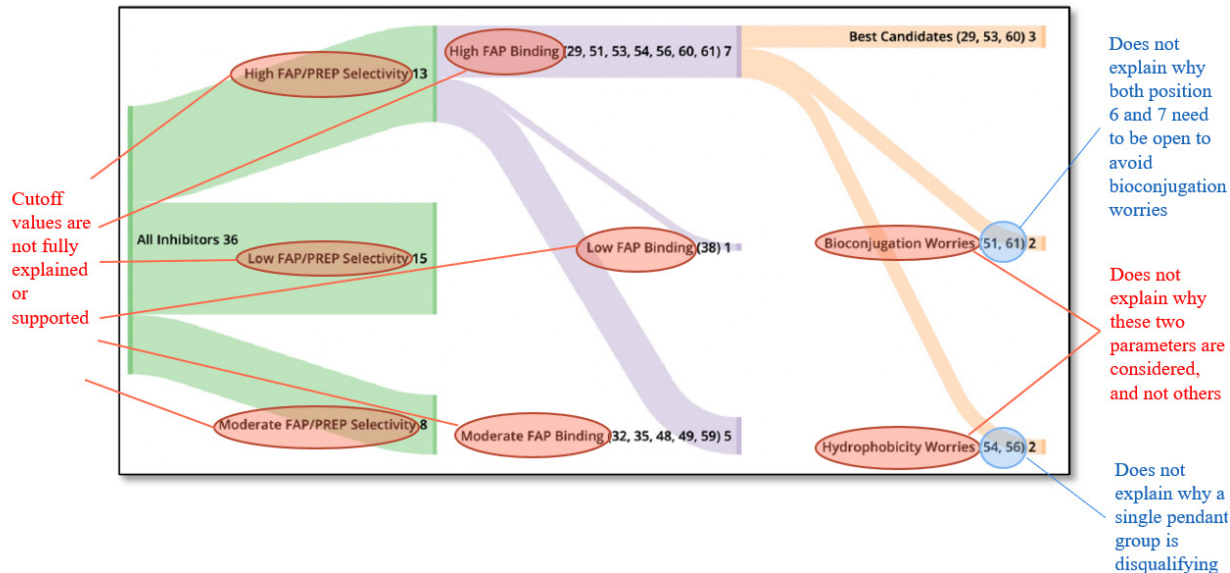
The forgoing demonstrates that Dr. Zeglis's theory depends on reconstructing the invention by cherry-picking Compound 60 with knowledge of the Challenged Claims, rather than on any scientific rationale that would have guided POSAs specifically to that compound. EX2047, ¶65. The absence of any reason or design principle favoring Compound 60 confirms his hindsight-based selection. *Id.*

b. Using Dr. Zeglis's classification criteria, POSAs would not have selected Compound 60 when other quinoline-based FAPis had comparable or superior properties.

Dr. Zeglis has not demonstrated that POSAs would have been led to select Compound 60 from the quinoline-based FAPis disclosed in the prior art. EX2047, ¶66; EX2001, ¶¶71-76. Dr. Zeglis proposes a multi-step prioritization scheme that places FAP-selectivity first, followed by affinity, and then relies on qualitative assessments of stability, hydrophobicity, and ease of modification. EX1003, ¶¶116-121; EX2047, ¶66; EX2001, ¶¶71-76. His framework, however, is unsupported by any evidence and does not exemplify how POSAs would have evaluated all the compounds reported in Jansen. EX2047, ¶66. Nor does Dr. Zeglis explain how those two criteria would have been evaluated by POSAs together with the other parameters disclosed in Jansen, including solubility, stability, cytotoxicity, and PK. EX2001 ¶¶71-72; EX2047, ¶67.

Dr. Zeglis also excludes compounds that satisfy his stated selectivity and affinity criteria, yet that fall outside the Challenged Claims, based on conclusory assertions regarding “hydrophobicity” or “bioconjugation” feasibility, while favoring Compound 60, which does fall within the claims. EX1003, ¶120; EX2047, ¶¶68-71; EX2001, ¶¶73-76. For instance, he alleges that Jansens's Compounds 51 and 61 would “pose bioconjugation issues because of their 7 and 6 position substitutions, respectively, on the quinolinyl ring would be occupied” and

that Compounds 54 and 56 “raised hydrophobicity concerns due to pendant phenyl groups.” EX1003, ¶¶120-121; EX2047, ¶¶68-71; EX2001, ¶¶73-76. But he does not explain why the 6 and 7 positions on Compounds 51 and 61 need to be open to avoid conjugation issues, nor does he point to any evidence, or even explain through his own argument, how adding a single pendant phenyl group would impact hydrophobicity. EX1003, ¶¶120-121; EX2047, ¶¶73-76; EX2001, ¶76. As Dr. Van Brocklin explains, pendant phenyl groups, alone, do not result in unfavorable pharmacokinetic properties. EX2047, ¶71; EX2018, 2213–2214, FIG. 7; EX2019, 2535; EX2020, 254–256; EX2001, ¶76. The figure below provided by Dr. VanBrocklin summarizes the foregoing issues with Dr. Zeglis’s framework:



EX2047, ¶66.

Even assuming that POSAs would have prioritized compounds in the manner Dr. Zeglis alleges, the prior art disclosed over twenty compounds with

high selectivity, as defined by Dr. Zeglis, five of which outperformed Compound 60. EX2047, ¶¶72-76; EX2001, ¶78. Indeed, US-650 and Jansen 2013 reported multiple FAPis that meet Dr. Zeglis’s criteria but also outperform Compound 60. EX1044, Tables 3-4; EX1007, Tables 2-3; EX2047, ¶72; EX2001, ¶78. Dr. Zeglis also acknowledged on cross-examination that several such compounds—Compounds 21, 22, 23, 24, and 11 from US-650—exhibited greater FAP-selectivity than Compound 60. EX2027, 154:21-157:14; EX2047, ¶72.

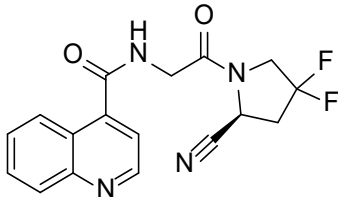
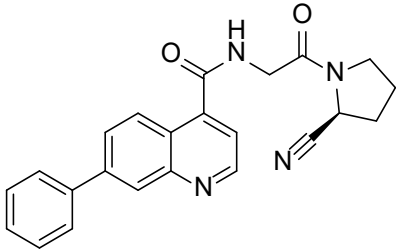
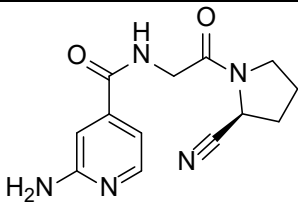
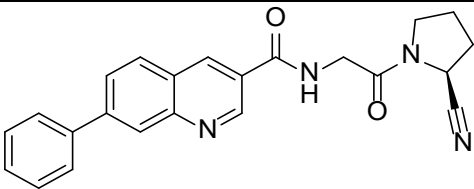
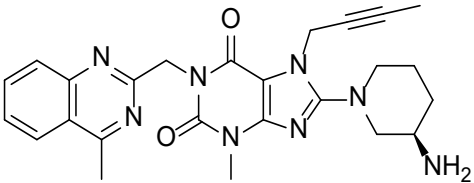
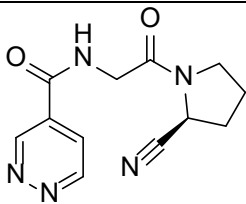
Even Jansen, the reference on which Dr. Zeglis principally relies, identifies compounds with substantially higher selectivity, including Compound 53 (selectivity = 2100; Jansen 2013’s Compound 23). EX1004, Table 4; EX2047, ¶73. Dr. Zeglis nevertheless discounts those compounds because allegedly “it was not possible to compare the *in vitro* [microsomal] stability, PK, bioavailability and *in vivo* characteristics,” all markers of *in vivo* performance, of those compounds to Compound 60. EX1003, ¶123; EX2047, ¶73. He, likewise, gives short shrift to Jansen’s Compound 61 (selectivity = 970) because of “the longer and more pronounced *in vivo* FAP inhibition results observed for compound 60 relative to compounds 5 and 61.” EX1003, ¶126; EX2047, ¶73. The Challenged Claims, however, are structural and ***do not require*** *in vivo* performance, and thus, do not require any particular surrogate markers of *in vivo* characteristics. *See* §III.A.; EX2047, ¶73; EX2043, 525–526.

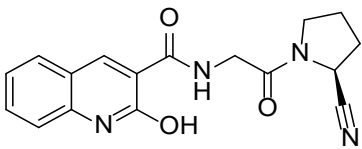
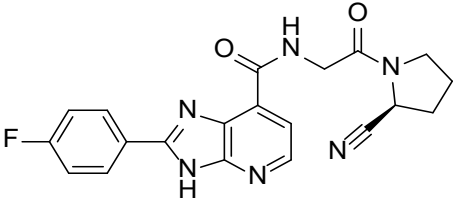
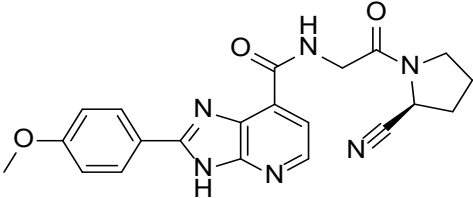
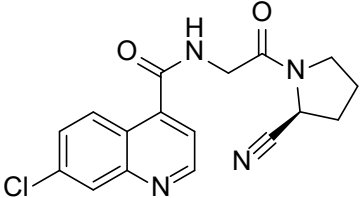
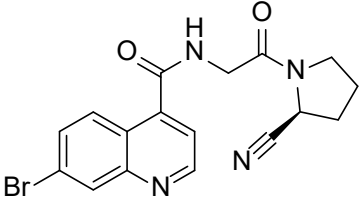
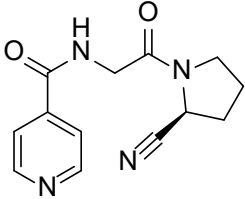
Excluding compounds that exceed his purported selection criteria based on considerations nowhere required by the Challenged Claims confirms that Dr. Zeglis is tailoring his analysis to fit the claims and not conducting a full assessment of the prior art from the perspective of a POSA. EX2047, ¶¶73-74.

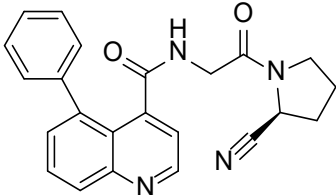
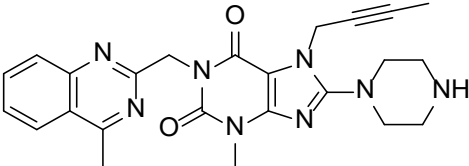
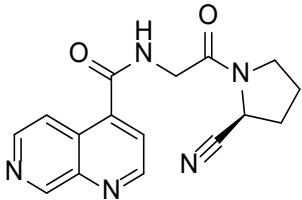
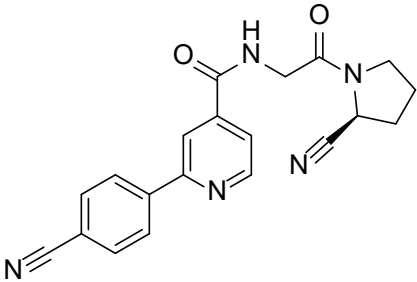
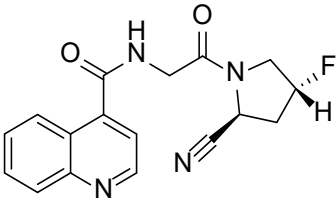
Dr. VanBrocklin's table below summarizes the quinoliny-based FAPs from Jansen, US-650, Jansen 2013, and Jansen 2014 that satisfy Dr. Zeglis's stated thresholds (selectivity >100; affinity <0.1 μ M). The entries are ordered by selectivity ($IC_{50}^{PREP}/IC_{50}^{FAP}$), which Dr. Zeglis identified as the "most important" factor. EX1003, ¶¶45, 117; EX2047, ¶74; EX2001, ¶77. Based on Dr. Zeglis's selectivity and affinity standards, the results below demonstrate that, out of the top thirteen highest-performing compounds, only Compounds 59 and 60 are encompassed by the claimed A. EX2047, ¶¶74-76; EX2001, ¶78. In other words, the Challenged Claims guided Dr. Zeglis to Compound 60.

**Top FAPis, ranked by selectivity in Jansen, US-650, Jansen 2013, and Jansen
2014**

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claims?
US 650: 22 Jansen 2013: 26 Jansen: 5		0.011	>4500	N
US 650: 23 Jansen: 53		0.0043	2100	N
US 650: 21 Jansen 2013: 25		0.0099	1700	N
US 650: 24 Jansen: 61		0.0085	970	N
US 650: 11 Jansen 2013: 30		0.0092	677	N

Compound Number	Structure	FAP Affinity (μ M)	FAP Selectivity	Fall within scope of claims?
US 650: 1 Jansen: 60		0.0032	562	Y
US 650: 25		0.07	280	N
Jansen: 32		0.138	244.2	N
Jansen: 54		0.070	277.1	N
Jansen 2014: 3		0.37	>270	N
Jansen: 38		0.164	237.8	N

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claims?
US 650: 38 Jansen 2013: 24		0.16	230	N
Jansen: 48		<0.2	>200	N
US 650: 28 Jansen: 49		<0.2	>200	N
US 650: 13 Jansen 2013: 31		0.0071	197	N
US 650: 12 Jansen 2013: 32		0.0062	193	N
US 650: 4 Jansen: 29		0.063	179	N

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claims?
US 650: 26 Jansen: 56		0.064	135	N
Jansen 2014: 13a		0.74	>135	N
US 650: 33 Jansen: 51		0.028	120	N
US 650: 16 Jansen: 35		0.27	107	N
Jansen: 59		1	>100	Y

The above further shows that Compound 60 is **not** the strongest candidate within this group. Five other compounds each have superior FAP-selectivity and affinity over Compound 60:

- Compound 22 of US-650 / Compound 26 of Jansen 2013;
- Compound 23 of US-650 / Compound 53 of Jansen;
- Compound 21 of US-650 / Compound 25 of Jansen 2013;
- Compound 24 of US-650 / Compound 61 of Jansen; and
- Compound 11 of US-650 / Compound 30 of Jansen 2013

EX2047, ¶75; EX2001, ¶77.

Accordingly, the current record does not support selecting Compound 60 from the prior art as a whole on Dr. Zeglis's own selection grounds, and he does not explain why POSAs would have selected Compound 60 from this crowded field. Rather, his choice of Compound 60 would have been made only with knowledge of the claim limitations, not from the vantage point of POSAs assessing the prior art as it stood before 2017. EX2047, ¶¶75-76; EX2001, ¶78.

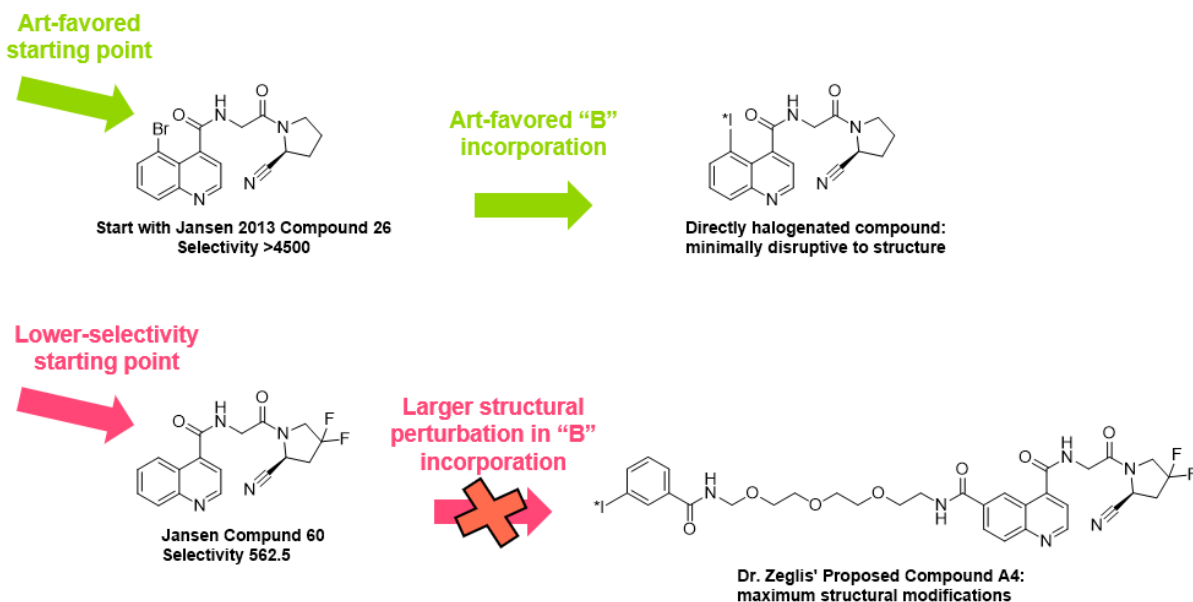
This is impermissible, as “[c]are must be taken to avoid hindsight reconstruction by using ‘the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.’” *Grain Processing*, 840 F.2d at 907.

4. **POSAs would not have been directed to the claimed B-L-A architecture, and Compound 60 was not present in the art in B-L-A format.**
 - a. **POSAs would have been directed to direct halogenation, not adding bulky B and L moieties.**

Dr. Zeglis's path to putting Compound 60, which was not present in the art in B-L-A form, into the claimed B-L-A architecture reflects his working backward to arrive at the claimed compounds—rather than by any scientific reason found in the art. EX2047, ¶¶77-79.

As Jansen 2013 makes clear, the most selective quinolinyl-based FAPis in the art achieved their performance precisely because of halogen substitution on the quinolinyl ring, which Compound 60 lacks. EX1007, 493-494; EX2047, ¶77. That structure-activity relationship (“SAR”) was not incidental; it was expressly identified as beneficial and central to performance, with Jansen 2013 stating, “[i]ntroducing a chlorine or bromine substituent at the 5-position of the quinoline ring” results in the “selectivity with respect to PREP of these inhibitors [to] sharply increase[] ... rendering them *the most favorable* affinity/selectivity profile of all FAP-inhibitors we had identified so far.” EX1007, 493-494; EX2047, ¶77; EX2001, ¶¶60-61. POSAs purportedly seeking to develop a FAP-targeting radiotracer therefore would have been guided toward those halogen-substituted scaffolds, not away from them. EX2027, ¶91; EX2001, ¶¶60-61.

Consistent with that SAR, the prior art taught that when radiolabeling is desired, the most straightforward and least disruptive strategy is direct isotopologous substitution or halogen exchange—i.e., replacing an existing halogen with a radiohalogen—rather than removing a known beneficial substituent and introducing a bulky linker-chelator assembly. EX1014, 44; EX1010, 3; EX2047, ¶¶77; EX2001, ¶¶60-61. The prior art described direct radiohalogenation as a versatile and well-established approach, particularly where the parent compound already contained a proven binding- and selectivity-supporting halogen. EX1014, 44; EX1010, 3; EX2047, ¶¶77-79, 80, 81-84; EX2001, ¶¶60-61. POSAs therefore would have had little reason to abandon direct labeling in favor of constructing a fundamentally different B-L-A architecture. EX2047, ¶¶77-79.



EX2047, ¶78.

Dr. Zeglis avoids that POSAs would have been directed to direct labeling, and in doing so, bypasses the most selective halogen-substituted compounds disclosed in the art, instead selecting Compound 60 that notably lacks the halogen substituent Jansen 2013 identified as key to performance. EX2047, ¶¶78-79. He then asserts that POSAs would have preferred linker-based modification over direct radiohalogenation due to purported “adverse effects.” EX1003, ¶139; EX2047, ¶¶78-79. But beginning with the most selective compounds in the art would have foreclosed using linker-based modification altogether, because it would have required POSAs to discard an expressly beneficial radiohalogen and replace it with a bulky modification known to risk impairing binding. EX2047, ¶¶78-79. The more credible explanation for his choice is he worked backward from the Challenged Claims rather than forward from the art’s teachings. *Id.*

General radiotracer design principles reinforce this conclusion. The art repeatedly cautioned that even modest structural changes to small-molecule targeting moieties can dramatically alter affinity, selectivity, and PK. EX2047, ¶¶80-84. Dr. Zeglis acknowledges that “slight modifications to the structure of a targeting moiety can alter its selectivity and affinity for its target.” EX1003 ¶49(b); EX2047, ¶82. Yet arriving at the claimed compounds would have required not a slight modification, but adding a large linker-chelator substituent to the FAPi scaffold. EX2047, ¶¶82-84. The prior art provided no rationale for making such a

disruptive change, particularly where direct radiohalogenation offered a known and conservative alternative. EX2047, ¶¶82-84.

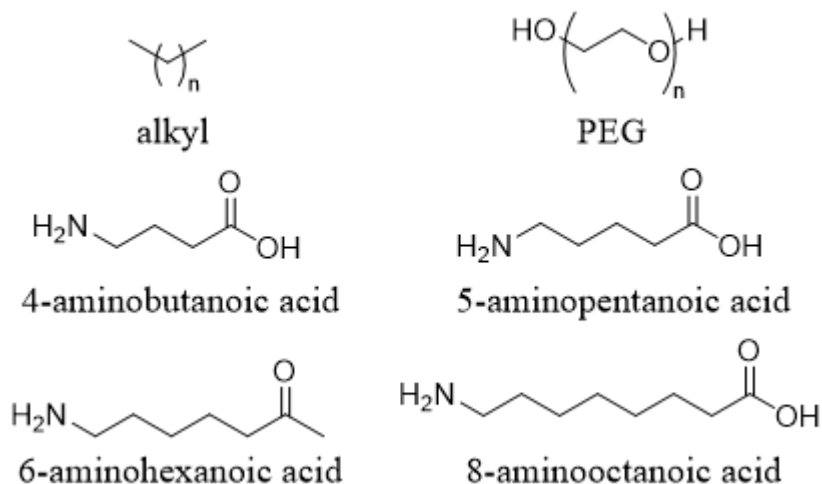
The developmental history of FAP-radiotracers confirms those teachings. *Id.* The earliest small-molecule FAP radiotracers relied on iodine-substituted analogs and direct halogenation strategies, not bulky linker-based architectures. EX1035, Abstract; EX2047, ¶83. That historical record is consistent with the SAR and radiochemistry principles described above and underscores that POSAs would have sought to preserve, not replace, features aiding FAP-selectivity, e.g., performance-enhancing radiohalogens. EX2047, ¶¶82-84.

The prior art as a whole, therefore, would not have directed POSAs toward the claimed B-L-A compounds. EX2047, ¶84.

b. Dr. Zeglis fails to show that POSAs would have chosen the specific linkers he selects from prior art.

Dr. Zeglis's obviousness theory in Ground 1 hinges on the assertion that POSAs would have selected a three-monomer polyethylene glycol (PEG) linker. EX1003, ¶165; EX2047, ¶¶85-86. That assertion, however, is based on selecting PEG from US-633's laundry list of linkers, even though none of its examples utilize PEG linkers. EX2047, ¶85. Indeed, Dr. Zeglis plucks his proposed linker out of this list to use in his hypothetical compounds when US-633 does not specifically direct POSAs to using it, nor would have the art. EX1003, ¶149; EX2047, ¶¶85-91.

The US-633 disclosures on which he relies for L describe a broad genus of possible linkers, such as simple alkyl chains, PEGs of non-specific length, polyethylene amines, and multiple aminoalkanoic acids. EX1004, ¶130; EX2047, ¶88. Example structures of such linkers are shown below:



EX1004, ¶130; EX2047, ¶88.

Nothing in US-633 singles out a three-monomer PEG, or provides a rationale for preferring it over other expressly disclosed alternatives. EX2047, ¶86-87, 89-90. Instead, Dr. Zeglis's choice appears to be yet another effort to cull the prior art to reach the Challenged Claims, rather than explain how the art would have led POSAs to that particular selection. EX2047, ¶¶89-91.

Dr. Zeglis attempts to justify this selection by asserting that POSAs would have sought approximately 10-20 bond lengths between A and B. EX1003 ¶¶88, 151; EX2047, ¶86. But he provides no support for why POSAs would have

selected that design constraint for Compound 60. EX1003, ¶151; EX2047, ¶86.

And when cross-examined he conceded that linkers shorter than 10 bonds would “not necessarily” mean that the reporter moiety would interfere with A’s binding ability. EX2027, 182:4-20; EX2047, ¶86.

Dr. Zeglis seeks to further rationalize his selection by asserting that POSAs would have been familiar with PEG-based linkers. EX1003, ¶88; EX2047, ¶87. For support, he references literature indicating that extended PEG chains enhance the lipophilicity (i.e., affinity of a compound for lipids or fat-like phases) of radiopharmaceuticals. EX1003, ¶88 fn.110; EX2047, ¶87. Supposed general familiarity with PEG-based linkers by POSAs, or the observation that long PEG chains can increase lipophilicity, nevertheless, does not explain why POSAs would have selected a PEG linker. In fact, Dr. Zeglis invokes hydrophobicity³ as a reason to *exclude* certain compounds when selecting Compound 60 thus suggesting that his selection of PEG is inconsistent with his selection of Compound 60. EX1003, ¶120; EX2047, ¶87.

³ Lipophilicity and hydrophobicity are closely related, both describing a compound’s tendency to associate with nonpolar environments. EX2029, 183-184, 197; EX2047, ¶87. Increased lipophilicity generally corresponds to increased hydrophobicity. EX2047, ¶87.

Nor does Dr. Zeglis explain why POSAs would have ignored the specific linkers in US-633's exemplary radiotracers. EX2047, ¶88. Indeed, in Ground 2, he emphasizes the importance of "avoid[ing] 'recreating the wheel' by starting with one or more of the examples of radiotracers in US-121 and using the chelator-linker portion of these examples with a new targeting moiety (i.e., compound 60)." EX1003, ¶¶207; 210-211 (alleging POSAs would only replace the targeting moiety but keep the rest of the exemplary radiotracer structure, including the L).

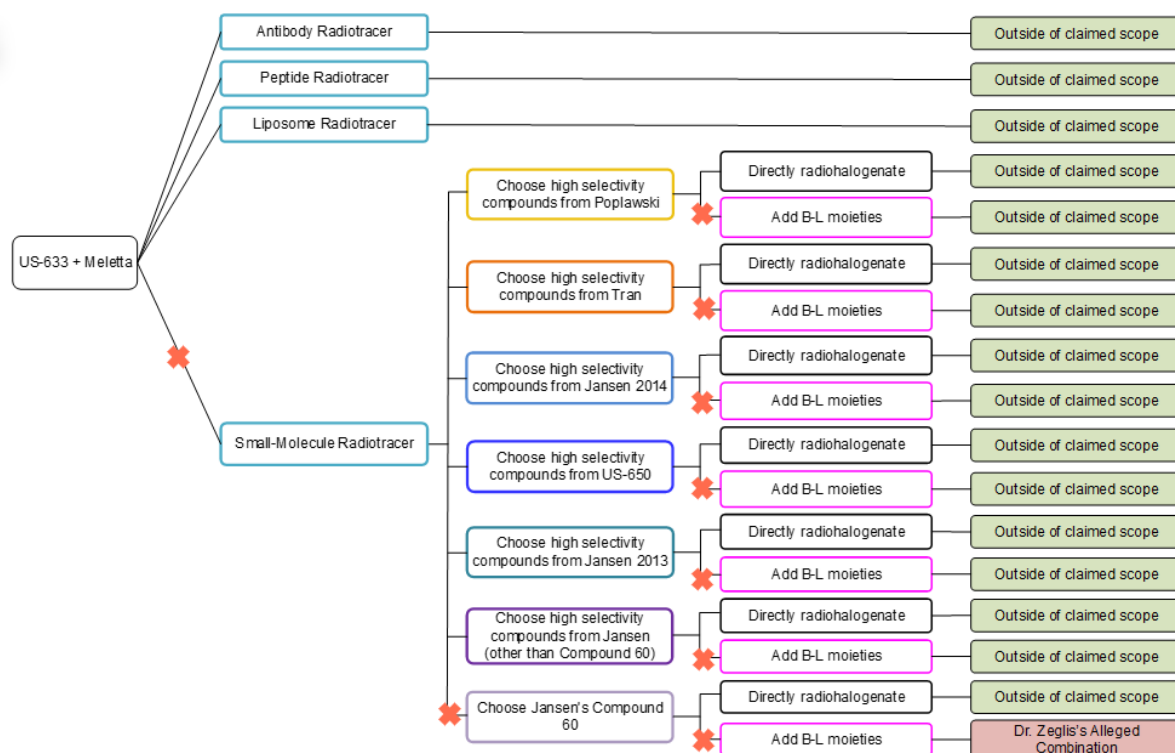
But he does not explain *why*, in Ground 1, he decides to "recreat[e] the wheel" by not starting with the specific radiotracer structures in US-633. EX2029, ¶103. Indeed, *none* of US-633's exemplified radiotracers use a PEG linker. EX1004, 17-28; EX2047, ¶89. And he offers no reason why POSAs would have abandoned those examples over an unexemplified, selectively chosen linker. EX2047, ¶¶89-90.

Dr. Zeglis bases his obviousness theory on the premise that POSAs would design FAP-radiotracers containing PEG-based linkers for *in vivo* use. *See, e.g.*, EX1003, ¶135; EX2047, ¶¶90-91. But the art taught that PEG-based linkers can be disadvantageous *in vivo*. For example, one such study showed that PEG-linked compounds exhibited reduced tumor uptake and increased kidney retention compared to compounds with short, alkane linkers. EX2030, Abstract, 823, 830;

EX2047, ¶¶90-91. Dr. Zeglis did not factor this art into his analysis, further underscoring the absence of a reasoned path to the claimed compounds. EX2047, ¶¶90-92.

* * *

On this record discussed in §§IV.A.1-IV.A.3, POSAs seeking to develop a FAP-targeting radiotracer would have faced multiple independent, sequential design choices that would not have led a POSA to the claimed invention, as shown below with red Xs indicating paths that a POSA would have understood were not favored in the art. *Id.*



And in following Dr. Zeglis's path, POSAs would have had to make a series of nonobvious, scientifically disfavored decisions—not ones grounded in the prior

art. EX2047, ¶92. That cannot supply the rational underpinning or reasonable expectation of success required for obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Indeed, 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.” *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998).

GE has thus failed to carry its burden to show that the Challenged Claims would have been obvious in Ground 1. *Magnum Oil*, 829 F.3d at 1381.

5. The prior art would not have provided POSAs a reasonable expectation of success in arriving at the claimed compounds.

Even if POSAs would have been motivated to combine Jansen’s Compound 60 with B and L—which POSAs would not be—the prior art did not provide a reasonable expectation of success in doing so. EX2047, ¶¶93-98. As discussed above, the only pre-2017 small-molecule FAP radiotracer evaluated for selectivity *failed* when evaluated *in vitro*. See §IV.A.1.a. Meletta reported that its radiolabeled FAPi did not selectively accumulate in FAP-expressing tissue and lacked a meaningful ability to distinguish FAP-positive tissue from normal tissue. EX1008, 2089-2090; EX2047, ¶93. Thus, the prior art affirmatively demonstrated that small-molecule FAP radiotracers known before October 2017 lacked sufficient selectivity, and POSAs would not have derived any reasonable expectation of

success for small-molecule FAP radiotracers from Meletta or the prior art.

EX2047, ¶93.

The prior art, moreover, consistently taught that even small structural modifications to quinolinyl-based FAPis could profoundly impair both FAP-affinity and selectivity. EX2047, ¶¶94-97. Those teachings would not have given POSAs a reasonable expectation that large substituents could have been appended at or near the quinoline core. *Id.*

Jansen expressly demonstrated the sensitivity of the quinoline ring to substitution. EX2047, ¶96. Jansen reports SARs in which adding a cyano substituent to Compound 60's quinoline (yielding Compound 63) dramatically reduced selectivity (~562 to 2.3). EX1006, Table 5; EX2047, ¶96. This order-of-magnitude loss in selectivity would have signaled to POSAs not having the benefit of the '201 patent specification that even modest substituent changes at the quinoline could destroy the functional properties necessary for a viable FAPi. EX2047, ¶96.

Additional SARs disclosed in Jansen 2013 reinforce this conclusion. EX2047, ¶97. Jansen 2013 reports that Compound 7 exhibits strong FAP-affinity (0.0103 μM) and a selectivity of 83. EX1007, Table 3; EX2047, ¶¶95-97. Incorporating additional substituents at the quinolinyl group, however, markedly decreased selectivity. EX1007, Table 3; EX2047, ¶¶95-97. These results

demonstrate that before the '201 patent, POSAs would have reasonably expected that adding substituents significantly smaller than the claimed B and L moieties would have been expected to compromise FAP-selectivity. EX2047, ¶¶95-97.

Jansen 2013 underscores this point by expressly concluding that “substituents in the 2- and 3-position of the quinoline ring as in compounds 19-24, have a clearly negative effect” on FAP-potency. EX1007, 493; EX2047, ¶¶95-96. Jansen 2013 explains that both steric and electronic effects contribute to loss of activity. EX1007, 493; EX2047, ¶¶95-96. POSAs would have understood this disclosure as a warning that modifying the quinoline ring was poorly tolerated. EX2047, ¶¶95-96. Indeed, a POSA would not have recognized that sites on the quinoliny ring could be modified until after the disclosure provided in the '201 patent showing that the ring could predictably withstand modification with Bs and Ls. EX1001, 57:61-61:62; EX2047, ¶¶95-96.

Obviousness fails where the prior art does not provide a reasonable expectation of success and the art provides only a general path with no clear direction towards the claimed invention. *See, e.g., In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988); *In re Fine*, 837 F.2d at 1075. POSAs therefore, would not have arrived at the claimed compounds with a reasonable expectation of success. EX2029, ¶¶107-112.

B. Ground 2: The Challenged Claims Would Not Have Been Obvious over US-121 and Jansen Because, as in Ground 1, Dr. Zeglis Relies on Hindsight.

Ground 2 fails for the same reason as Ground 1: Dr. Zeglis never shows that POSAs would have reached the claimed invention through reasoned decision-making grounded in the prior art as a whole. EX2047, ¶¶99-101. He instead reasons backward from the Challenged Claims, rather than from the perspective of POSAs. *Id.*

Dr. Zeglis does not explain why POSAs would have selected a small-molecule radiotracer for FAP-imaging, as opposed to other established modalities such as antibodies, antibody fragments, or peptides. EX1003, ¶¶179-204; EX2047, ¶¶36-49. And as in Ground 1, he does not meaningfully address the full range of FAPi options available. EX2047, ¶¶99-100. He again ignores non-quinolinylnyl-based inhibitors. *Id.* He also does not explain why POSAs would have selected Compound 60 over other disclosed FAPis that showed superior performance, other than its resemblance to the claimed invention. EX1003 ¶¶179-204; EX2047, ¶¶99-100. His selective application of his selection criteria confirms that his analysis is claim-driven, not grounded in the prior art. EX2047, ¶¶99-100.

Dr. Zeglis's reliance on US-121, moreover, does not cure those deficiencies. EX2047, ¶101. US-121 discloses radiotracers for imaging prostate-specific membrane antigen ("PSMA"), not FAP—a point Dr. Zeglis concedes. EX1003,

¶182; EX2027, 157:15-158:16; EX2047, ¶101. Because US-121 does not address FAP-targeting, it provides no guidance or motivation for selecting a FAP-targeting moiety, let alone the specific quinolinyl-based structure recited in the Challenged Claims. EX2047, ¶101. Dr. Zeglis’s assertion that POSAs would have broadly “considered” US-121 when designing other radiotracers thus is a generic, outcome-driven rationale untethered to the art. EX1003, ¶199; EX2047, ¶101.

Absent a reasoned, art-based rationale, Ground 2 fails. *ATD*, 159 F.3d at 546; *In re Fine*, 837 F.2d at 1075; *KSR*, 550 U.S. at 418.

C. Objective Indicia Support the Nonobviousness of the Challenged Claims as Demonstrated by Unexpected Results.

GE has failed to establish a *prima facie* case of obviousness. Objective evidence discussed below, moreover, confirms nonobviousness. EX2047, ¶¶102-103.

Nonobviousness can be demonstrated by showing evidence of unexpected results compared to the closest prior art. *In re Baxter Travenol Lab ’ys*, 952 F.2d 388, 392 (Fed. Cir. 1991). Comparing the claims and prior art “to determine the number of claim limitations in common ..., bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference.” *In re Merchant*, 575 F.2d 865, 868 (C.C.P.A. 1978).

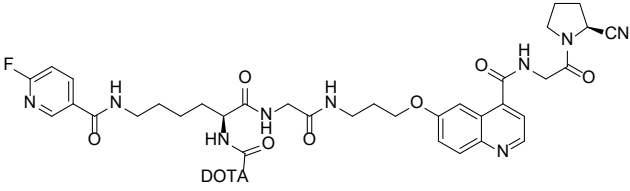
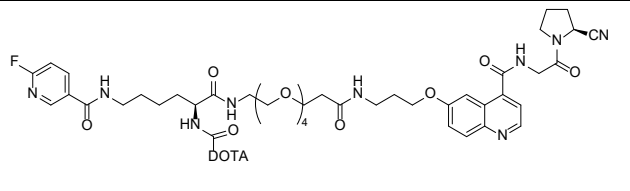
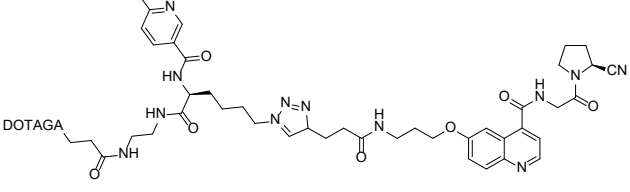
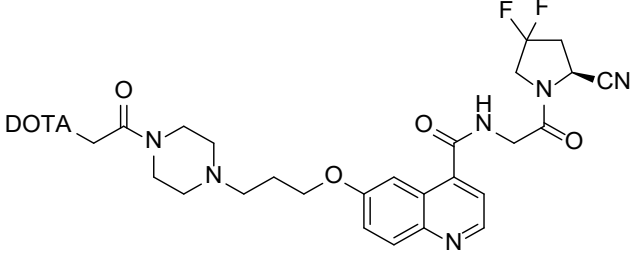
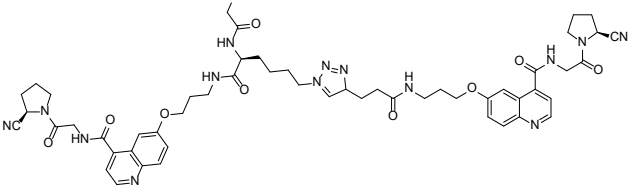
Considering the claimed A as having the most importance due to it being the FAP-targeting moiety, the closest prior art would be Jansen 2013, which discloses

the FAP-selectivity of As encompassed by the Challenged Claims. EX2047, ¶¶103-104. Here, the claimed B-L-A compounds exhibit dramatic improvements in selectivity for FAP over PREP ($SI_{FAP/PREP}$) relative to the corresponding A alone. EX2047, ¶¶103-104.

Jansen 2013's Compound 7 exhibited a FAP-selectivity of 86 when tested alone. EX1007, Table 2; EX2047, ¶¶104-105. Yet, a PCT application filed by JHU disclosing work of Dr. Pomper's group shows that when conjugated to the claimed Ls and Bs, the resulting B-L-A compounds achieved selectivity indices ranging from 407 to 1,418,440, with multiple exemplified species exceeding 10,000. EX1007, Table 2; EX2045, Table 3; EX2047, ¶¶104-107.

The table below shows B-L-A compounds disclosed in International Patent Appl. No. PCT/US2022/023374, published as WO 2022/212958 ("WO '958"; EX2045), that are encompassed by the Challenged Claims along with their PREP IC_{50} and FAP IC_{50} , i.e., the affinity for PREP and FAP, respectively. EX2045, Table 3; EX2047, ¶105. FAP-selectivity is determined by dividing a compound's PREP IC_{50} by its FAP IC_{50} ($PREP\ IC_{50}/FAP\ IC_{50}$). EX2047, ¶105.

WO '958 Cpd. No.	WO '958 Compound Structure	PREP IC ₅₀ (nM)	FAP IC ₅₀ (nM)	Selectivity Index Increase compared to A alone
7		1410	0.343	4,111 ~48-fold improvement
14		86,570	1.31	66,084 ~768-fold improvement
11		2 x 10 ⁶	1.41	1,418,440 ~16,493-fold improvement
12		21,950	2.09	10,052 ~117-fold improvement
13		6910	1.19	5,807 ~68-fold improvement
15		1090	1.40	779 ~9-fold improvement

WO '958 Cpd. No.	WO '958 Compound Structure	PREP IC ₅₀ (nM)	FAP IC ₅₀ (nM)	Selectivity Index Increase compared to A alone
16		1710	1.01	1,693 ~20-fold improvement
17		240	0.59	407 ~5-fold improvement
23		630	0.48	1,313 ~15-fold improvement
1		796	0.75	1,061 ~12-fold improvement
22		510	0.35	1,457 ~17-fold improvement

EX2045, Table 3; EX2047, ¶105.

As shown above, the B-L-A compounds exhibited improvements ranging from approximately 5-fold to >16,000-fold over Jansen 2013's Compound 7.

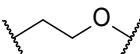
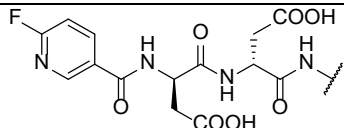
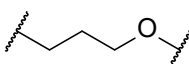
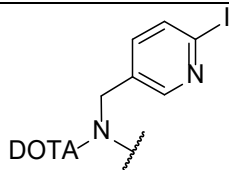
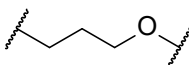
EX2045, Table 3; EX2047, ¶106. Such results reflect a difference in kind with respect to the selectivity of A because the increase in selectivity is more than just a slight improvement. EX2047, ¶¶106-107. And the increase is attributable to the claimed B-L-A architecture as a whole. *Id.*; *Galderma Lab's. L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (“Unexpected results that are probative of nonobviousness are those that are ‘different in kind and not merely in degree from the results of the prior art.’”).

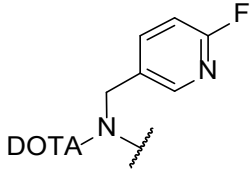
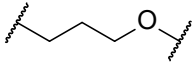
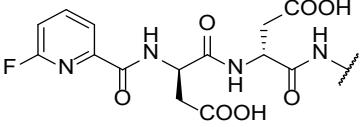
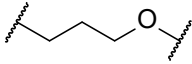
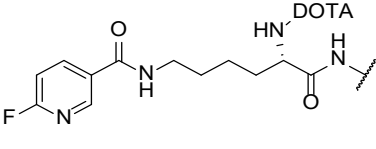
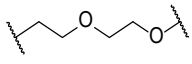
Nothing in the prior art would have led POSAs to expect that appending Ls and Bs to a FAPi would have so profoundly enhanced selectivity. EX2047, ¶¶106-107. To the contrary, the art taught that even relatively minor modifications to FAPis frequently degraded selectivity. EX1014, 44; EX1010, 3; EX1003, ¶¶34, 36, 49(b); EX1017, 2669; *see generally* EX1007; EX1044; EX2047, ¶94. Consistent with that teaching, Dr. Zeglis admitted that he was not “aware of any examples in which adding a radionuclide to a small molecule increased its selectivity for its intended target,” the factor that Dr. Zeglis identified in his declaration as “paramount.” EX2047, ¶107; EX2027, 151:19-152:1; EX1003, ¶45. That admission at his deposition underscores how unexpected the above results would have been to POSAs at the relevant time. EX2047, ¶107.

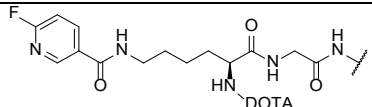
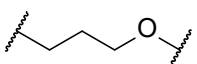
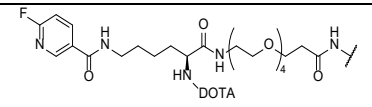
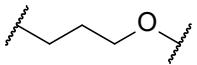
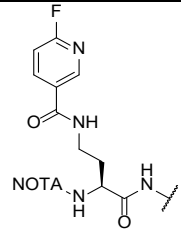
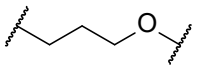
GE and Dr. Zeglis should have been well aware of the data in WO '958 because it also appears in a Rule 1.132 declaration submitted by Dr. Pomper during

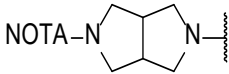
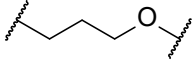
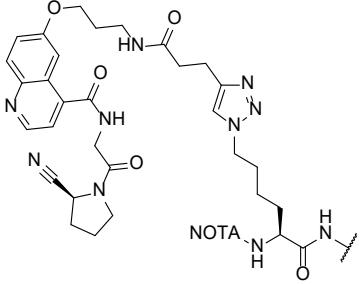
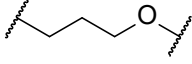
prosecution of the application that issued as the '201 patent that was used to demonstrate unexpected results of the claimed compounds. EX1002, 365-367; EX2047, ¶¶108-109. Yet, GE and Dr. Zeglis chose not to address the publicly available data in WO '958 or data from the intrinsic record of the '201 patent in its Petition.

The table below summarizes the data presented in Dr. Pomper's Rule 1.132 declaration, which matches the data for compounds of the Challenged Claims provided in WO '958. EX1002, 365-367; EX2047, ¶108.

No.	B	L	B-L-A MW (g/mol)	B MW (g/mol)	Selectivity Index Increase compared to A alone
1	 Halogen (F)		370	19.0	4,111 ~48-fold improvement
2	 Prosthetic group with a halogen (F)		734	369.3	66,084 ~768-fold improvement
3	 DOTA		983	620.4	1,418,440 ~16,493-fold improvement

No.	B	L	B-L-A MW (g/mol)	B MW (g/mol)	Selectivity Index Increase compared to A alone
	Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (I)				
4	 Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (F)		876	502.4	10,052 ~117-fold improvement
5	 Prosthetic group with a halogen (F)		734	369.3	5,807 ~68-fold improvement
6	 Dual 3-membered chelator (DOTA) /		1049	652.7	779 ~9-fold improvement

No.	B	L	B-L-A MW (g/mol)	B MW (g/mol)	Selectivity Index Increase compared to A alone
	prosthetic group with a halogen (F)				
7	 <p>Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (F)</p>		1073	711.4	1,693 ~20-fold improvement
8	 <p>Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (F)</p>		1266	888.4	407 ~5-fold improvement
9	 <p>Dual 2-membered chelator (NOTA) /</p>		889	525.3	10,694 ~124-fold improvement

No.	B	L	B-L-A MW (g/mol)	B MW (g/mol)	Selectivity Index Increase compared to A alone
	prosthetic group with a halogen (F)				
10	 2-membered chelator (NOTA)		761	397.3	11,893 ~134-fold improvement
11	 Dual 2-membered chelator (NOTA) / second FAPi moiety		1282	918.0	1,313 ~15-fold improvement

Compounds 7, 14, 11, 12, 13, 15, 16, 17, and 23 of WO '958, respectively, correspond to the compounds from Dr. Pomper's declaration listed as Nos. 1-8 and 11, respectively, in the table above. EX2045, Table 3; EX1002, 365-367; EX2047, ¶109. Dr. Pomper's declaration also provides selectivity data for Compounds 29 and 33 of WO '958 (Pomper declaration Compounds 9 and 10) that was not reported in WO '958, similarly confirming the unexpected orders-of-magnitude

improvement in FAP-selectivity for Jansen 2013's Compound 7 when put into B-L-A form. EX2045, Table 3; EX1002, 365-367; EX2047, ¶109.

If the Board considers art disclosing B-FAPi compounds as the closest prior art, the unexpectedness of Dr. Pomper's observed results presented in WO '958 and in his declaration is further reinforced by the teachings of Meletta. EX2047, ¶110. Indeed, the claimed compounds also exhibit vastly superior selectivity relative to Meletta, which cannot be explained by the baseline properties of the FAPi. Meletta's MIP-1232 has a selectivity of 32, making it ~12-fold to >44,000-fold less selective than the exemplified claimed compounds. EX2045, Table 3; EX1002, 365-367; EX1035, Abstract; EX2047, ¶110. That disparity does not track with the starting selectivity of Compound 7, which has a selectivity of ~86—only about 2.7-fold greater than Meletta's compound. EX1007, Table 2; EX1035, Abstract; EX1002, 365-367; EX2047, ¶110. Thus, the orders-of-magnitude improvement cannot be attributed to the A alone, but instead reflects an unexpected, non-linear enhancement arising from the claimed B-L-A design. EX2047, ¶110.

If selectivity were driven primarily by A, relative performance would track baseline selectivity. EX2047, ¶¶110-112. It does not. *Id.* Instead, the data show that the dramatic improvements arise only upon forming the novel B-L-A structure embodied by the Challenged Claims, confirming both unexpected results and a

nexus to the claims. *Id.* Indeed, the claims require the B-L-A architecture that produces dramatic increases in FAP-selectivity. By contrast, Compound 7 outside of the claimed B-L-A configuration exhibits selectivity values ~5-fold to >16,000-fold lower than those of the claimed compounds. EX1011, Table 2; EX2047, ¶111. And a showing “that the specific [compounds] are embodiments of the claimed invention and that the proffered objective evidence relates to these [compounds]—is sufficient to establish the presumption of nexus for the objective considerations at issue.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330 (Fed. Cir. 2016).

The unexpectedly high selectivity of the compounds outlined above in Dr. Pomper’s declaration and WO ’958 is also not confined to a narrow subset of embodiments, rather it is representative of the full scope of claims 1-3. EX2047, ¶113. The 13 exemplified compounds span a wide range of molecular weights—from approximately 370 g/mol to over 1,280 g/mol—and encompass substantial structural diversity. EX1007, Table 2; EX2047, ¶113. The B alone ranges from extremely small substituents (e.g., halogens with molecular weights as low as 19 g/mol) to large dyes exceeding 1,000 g/mol, and includes prosthetic groups and chelators of varying steric bulk and functionality. EX2047, ¶113.

Despite this diversity, every exemplified species exhibited excellent FAP-selectivity. *Id.* These consistent results across structurally varied embodiments

demonstrate that the unexpected selectivity is a property of the B-L-A architecture itself and would reasonably be expected to extend across the full scope of the Challenged Claims. *Id.*

The claimed compounds, therefore, do not merely preserve the selectivity of known FAPis; they achieve an unexpected enhancement in selectivity that the prior art neither taught nor suggested. EX2047, ¶114. This objective evidence is directly tied to the novel B-L-A structure of the claimed invention and therefore should carry weight in the obviousness analysis. *WBIP*, 829 F.3d at 1328-29 (“[T]he strength of each of the *Graham* factors must be weighed in every case and must be weighted *en route* to the final determination of obviousness or non-obviousness.”). And when properly considered, the unexpected results here compel the conclusion that GE has failed to establish obviousness.

V. CONCLUSION

The Board should maintain the Challenged Claims.

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: June 15, 2026

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

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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: June 15, 2026

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

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

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX PLLC

/Eldora L. Ellison/

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

Date: June 15, 2026

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