

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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GE HEALTHCARE LTD.,  
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,  
Patent Owner

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

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**PATENT OWNER RESPONSE  
UNDER 37 C.F.R. § 42.220**

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**PATENT OWNER'S EXHIBIT LIST**

| <b>Exhibit No.</b> | <b>Description</b>                                                                                                                                                                          |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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”)                     |

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| 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        | 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>                                                                                                                                                                                                                                                                |
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| 2016        | VanBrocklin <i>et al.</i> “16β-([ <sup>18</sup> 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”)                                                   |
| 2018        | Errata to Declaration of Dr. Brian Zeglis (EX1003)                                                                                                                                                                                                                                             |
| 2019        | 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) (“Zeglis 2013 II”)                         |

| Exhibit No. | Description                                                                                                                                                                                                                        |
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| 2020        | 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”)                          |
| 2021        | Pages 7 and 8 of U.S. Patent Application Publication No. 2010/0098633 A1 (EX1004) (annotated by Dr. Brian Zeglis)                                                                                                                  |
| 2022        | Pages 12–14 of U.S. Patent Application Publication No. 2010/0098633 A1 (EX1004) (annotated by Dr. Brian Zeglis)                                                                                                                    |
| 2023        | Transcript of the Deposition of Dr. Brian Zeglis, March 11, 2026                                                                                                                                                                   |
| 2024        | Sugiura <i>et al.</i> , “Radiolabeling Strategies for Tumor-Targeting Proteinaceous Drugs,” <i>Molecules</i> 19: 2135–2165 (2014) (“Sugiura”)                                                                                      |
| 2025        | 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”)                            |
| 2026        | 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”)           |
| 2027        | Hall, H.K., “Correlation of the Base Strengths of Amines,” <i>Journal of the American Chemical Society</i> , 79(20): 5441–5444 (October 20, 1957) (“Hall”)                                                                         |
| 2028        | 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”)             |
| 2030        | 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”) |

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| 2032        | Aertgeerts <i>et al.</i> , “Structural and Kinetic Analysis of the Substrate Specificity of Human Fibroblast Activation Protein $\alpha$ ,” <i>The Journal of Biological Chemistry</i> , 280(20): 19441–19444 (May 20, 2005) (“Aertgeerts”)                                |
| 2033        | 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”)        |
| 2034        | Däpp <i>et al.</i> , “PEGylation, increasing specific activity and multiple dosing as strategies to improve the risk-benefit profile of targeted radionuclide therapy with $^{177}\text{Lu}$ -DOTA-bombesin analogues,” <i>EJNMMI Research</i> , 2 (June 9, 2012) (“Däpp”) |
| 2035        | 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”)                                      |
| 2036        | 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”)                                                                          |
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| 2038        | Keane <i>et al.</i> , “Neuropeptide Y, B-type natriuretic peptide, substance P and peptide YY are novel substrates of fibroblast activation protein- $\alpha$ ,” <i>FEBS Journal</i> , 278: 1316–1332 (2011) (“Keane”)                                                     |

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| 2039        | 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”)                             |
| 2040        | 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”)                                           |
| 2041        | 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”) |
| 2042        | 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”)                              |
| 2043        | Rablen, P., “Typical Electron-Withdrawing Groups Are ortho, meta-Directors Rather than meta-Directors in Electrophilic Aromatic Substitution,” <i>The Journal of Organic Chemistry</i> , 90(17): 6090–6093 (2025) (“Rablen”)                   |
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| 2045        | 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: 2207–2219 (2020) (“Bvumbi”)                           |
| 2046        | Xu <i>et al.</i> , “Discovery of potent and selective phenylalanine based dipeptidyl peptidase IV inhibitors,” <i>Bioorganic &amp; Medicinal Chemistry Letters</i> , 15(10): 2533–2536 (2005) (“Xu”)                                           |

| Exhibit<br>No. | Description                                                                                                                                                                                                                                                                             |
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| 2047           | Calcaterra <i>et al.</i> , “Classics in Chemical Neuroscience: Diazepam (Valium),” <i>ACS Chemical Neuroscience</i> , 5(4): 253–260 (2014) (“Calcaterra”)                                                                                                                               |
| 2048           | Kim <i>et al.</i> , “A New Class of SN2 Reactions Catalyzed by Protic Solvents: Facile Fluorination for Isotopic Labeling of Diagnostic Molecules,” <i>Journal of the American Chemical Society</i> , 128(50): 16394–16397 (2006) (“Kim”)                                               |
| 2049           | Westaway <i>et al.</i> , “Determining the Transition-State Structure for Different SN2 Reactions Using Experimental Nucleophile Carbon and Secondary alpha-Deuterium Kinetic Isotope Effects and Theory,” <i>Journal of Physical Chemistry A</i> , 112: 10264–10273 (2008) (“Westaway”) |
| 2050           | Basha <i>et al.</i> , “Therapeutic potential of pyrrole and pyrrolidine analogs: an update,” <i>Molecular Diversity</i> , 26(5): 2915–2937 (2022) (“Basha”)                                                                                                                             |
| 2051           | Wilbur, D., “Radiohalogenation of Proteins: An Overview of Radionuclides, Labeling Methods, and Reagents for Conjugate Labeling,” <i>Bioconjugate Chemistry</i> , 3(6): 433–470 (1992) (“Wilbur”)                                                                                       |
| 2052           | Glaser <i>et al.</i> , “Radiosynthesis and Biodistribution of Cyclic RGD Peptides Conjugated with Novel [ <sup>18</sup> F]Fluorinated Aldehyde-Containing Prosthetic Groups,” <i>Bioconjugate Chemistry</i> , 19: 951–957 (2008) (“Glaser”)                                             |
| 2053           | Hsieh <i>et al.</i> , “Direct Solid-Phase Synthesis of Octreotide Conjugates: Precursors for Use as Tumor-Targeted Radiopharmaceuticals,” <i>Bioorganic &amp; Medicinal Chemistry</i> , 7(9): 1797–1803 (1999) (“Hsieh”)                                                                |
| 2054           | Haider <i>et al.</i> , “Emerging Pharmaceutical Applications of Piperidine Pyrrolidine and its Derivatives,” <i>World Journal of Pharmaceutical Research</i> , 3(7): 987–1024 (2014) (“Haider”)                                                                                         |

| Exhibit<br>No. | Description                                                                                                                                                                                                                            |
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| 2055           | Pichon <i>et al.</i> , “Synthesis of 2,5-Disubstituted Pyrrolidines,” <i>Tetrahedron: Asymmetry</i> , 7(4): 927–964 (1996) (“Pichon”)                                                                                                  |
| 2056           | Dukat <i>et al.</i> , “Pyrrolidine-modified and 6-substituted analogs of nicotine: a structure-affinity investigation,” <i>European Journal of Medicinal Chemistry</i> , 31: 875–888 (1996) (“Dukat”)                                  |
| 2057           | Zeglis <i>et al.</i> “Optimization of a Pretargeted Strategy for the PET Imaging of Colorectal Carcinoma via the Modulation of Radioligand Pharmacokinetics,” <i>Molecular Pharmaceutics</i> , 12: 3575–3587 (2015) (“Zeglis 2015 II”) |

## **I. INTRODUCTION**

GE Healthcare Ltd. (“GE”) has not met—and cannot meet—its burden to establish that any of claims 1-4 (“the Challenged Claims”) of U.S. Patent No. 12,115,233 (“the ’233 patent”) are unpatentable by a preponderance of the evidence on the more developed record discussed herein.

As the Board rightly recognized, the claims “recite a compound, not a result.” Paper 8, 34. GE’s Petition nonetheless depends on rewriting the claims to impose unclaimed functional requirements, reconstructing the prior art with hindsight, and misapplying enablement and written description standards. When evaluated against the claims as written, the specification, and the state of the art, GE’s theories fail.

The ’233 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, 1:25-43; EX1008, 2089-90; EX2029, ¶51. 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. EX2029, ¶51. Against that backdrop, the inventors developed a novel class of small-molecule radiotracers defined by a modular B-L-A structure, in which a quinolinyl-based

FAP-targeting moiety (A) is covalently linked via a linker (L) to an imaging or radiolabeling group (B). EX1001, 2:1-5.

GE's obviousness challenges (Grounds 1 and 2) rest on impermissible hindsight. EX2029, ¶¶16-23; EX2001, ¶¶22-25. 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.

GE's challenges under 35 U.S.C. §112 also fail. EX2029, ¶¶24-26; EX2001, ¶26. GE improperly analyzes written description and enablement as if the claims

required *in vivo* diagnostic or therapeutic performance. They do not. When evaluated as written, the specification's extensive structural disclosure—including defined chemical formulae, representative species, and incorporation of well-known Bs and Ls—demonstrates possession of the invention, confirming the Board's preliminary finding of written description support. Paper 8, 34. And as developed herein, the record establishes that POSAs would have been able to make and use the claimed compounds across their full scope using only routine work and not undue experimentation.

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 1-4.

## **II. THE '233 PATENT**

The '233 patent is directed to novel radiotracers targeting fibroblast activation protein- $\alpha$  (FAP) that can be used for *in vitro*, *ex vivo*, and *in vivo* applications. EX1001, Abstract; EX2001, ¶14. The patent describes low-molecular-weight FAP-targeting radiotracers having a B-L-A structure. EX1001, 2:1-5; EX2001, ¶16. 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, 1:59-61, 5:40-42, 7:46-54; EX2011, Abstract; EX2001, ¶¶17-18.

As shown below, the '233 patent discloses innovative, highly selective FAP-targeting radiotracers that overcome prior FAP-imaging failures. EX2001, ¶20.

### 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).

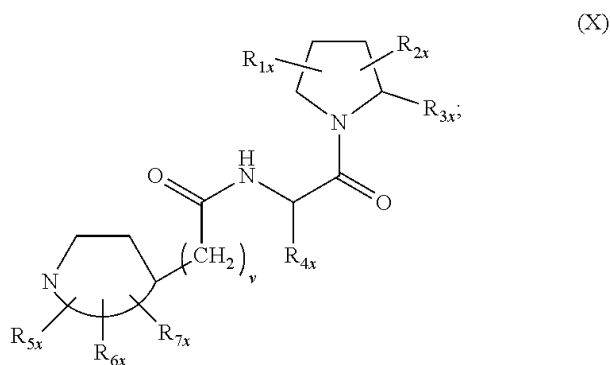
#### A. The Claimed “B-L-A” Compounds Are Not Defined Functionally.

GE’s §112-based Grounds 3 and 4 improperly introduce *in vivo* functionality into the claims, which are purely structural. GE’s expert, Dr. Brian Zeglis, repeatedly frames his discussion of the claimed compounds as requiring that they be “viable optical imaging agents or radiolabeled imaging or therapeutic agents” based on importing the patent specification’s disclosures regarding *in vivo* utility of the disclosed compounds. EX1003, ¶273. Dr. Zeglis improperly demands that the claimed compounds achieve attributes relevant only for *in vivo* performance, such as “stability *in vivo*,” “pharmacokinetic profile,” “bioavailability, stability “in plasma,” etc. EX1003, ¶277; EX2029, ¶¶41, 43; EX2001, ¶¶44-46.

But it is improper to “import[] limitations from the specification into the claims.” *Phillips*, 415 F.3d at 1303, 1323; *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1571 (Fed. Cir. 1988) (stating that “particular embodiments and examples appearing in the specification will not generally be read into the claims.”).

The claims are plainly structural. Independent claim 1 recites “a low molecular weight compound of Formula (I): B-L-A,” wherein:

A is a targeting moiety for FAP- $\alpha$ , 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, 64:6-55; EX2029 ¶41.

Claim 2 depends from claim 1 and narrows the  $R_{1x}$  and  $R_{2x}$  groups of A. EX1001, 64:56-58; EX2029, ¶41. Claim 3 depends from claim 2 and narrows the  $R_{3x}$  group of A. EX1001, 64:59; EX2029, ¶41. And claim 4 depends from claim 3 and narrows B to an optical or radiolabeled functional group comprising a chelating agent. EX1001, 64:60-61; EX2029, ¶41.

The only functional language present in the claims specifically defines B and L. EX1001, 64:48-53; EX2029, ¶¶41-44; EX2001, ¶¶44-46. 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, 64:6-55; EX2029, ¶¶1-15, 41-44.

The specification likewise defines the recited B-L-A compounds in structural terms, consistent with the claims' plain language. *See, e.g.*, EX1001, 2:4-12, 4:30-51, 7:45-65, 8:14-24, 11:22-30, 12:40-50, 15:40-44; EX2029, ¶42. 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, 169-171; EX2029, ¶42.

The Board, therefore, rightly preliminarily rejected any interpretation of the claims as being functional, finding "[t]he claims recite a compound, not a result."

Paper 8, 34. The Board thus should maintain its preliminary finding that the claims are not functional. And any analysis of the claims by GE and Zeglis in Grounds 3 and 4 that depends on the claims being functional is not applicable. Pet., 34; EX1003, ¶74.

**B. “low molecular weight”**

Each claim requires that the compound of formula B-L-A is of “low molecular weight.” EX1001, 64:6-61. 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 ’233 patent, during prosecution. Paper 7, 19-22; EX2029, ¶45; EX2001, ¶¶47-48. The Board disagreed. Paper 8, 10. 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.*, 12.

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

**IV. GE’S PETITION FAILS TO ESTABLISH THAT THE CHALLENGED CLAIMS ARE UNPATENTABLE.**

**A. Grounds I and II: The Challenged Claims Would Not Have Been 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.

- 1. Ground I: The claims would not have been obvious over US-633, Jansen, and Meletta because GE and Zeglis rely on selectively picking and choosing from a crowded field.**
  - a. POSAs designing FAP-targeting radiotracers would have been faced with numerous paths that 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. EX2001, ¶15; EX2029, ¶¶46-51; EX2001, ¶¶14-15. Non-specific binding by FAP-targeting agents “limit[ed] the fabrication of FAP targeted imaging probe[s].” EX2029, ¶51; EX2004, 11. Studies also consistently described FAP as being structurally similar to other family members, underscoring the difficulty in designing selective FAP-targeted radiotracers. EX2032, Abstract; EX2029, ¶51; EX2001, ¶15.

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.a.ii. EX2029, ¶¶51-52. Indeed, as 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.” EX2023, 43:2-7; *see also id.*, 61:11-19, 68:8-14, 69:2-70:2, 78:20-79:3; EX2029, ¶52.

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. EX2029, ¶¶51-52; EX2001, ¶15. Zeglis, however, ignores the foregoing in favor of jumping straight to small-molecule radiotracers using hindsight. *Id.*

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

Zeglis contends that POSAs would have homed in on small-molecule FAP radiotracers. EX1003 ¶40; EX2029, ¶53. The contemporaneous state of the art, however, demonstrates the opposite. EX2029, ¶¶53-57. 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. EX1004; EX1008; EX1035; EX2029, ¶53. Indeed, Zeglis even conceded that he is “not aware of any other references that disclose small molecule FAP-imaging agents before 2017.” EX2023, 162:15-22; EX2029, ¶53.

None of those references, moreover, would have led POSAs to small-molecule FAP radiotracers because none of those references disclosed a successful FAP radiotracer. EX2029, ¶54.

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; EX2029, ¶54. Yet, US-633 did not investigate the FAP-selectivity of its radiotracers. EX2029, ¶54.

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; EX2029, ¶¶54-55. 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). EX1035, Abstract; EX2029, ¶55.

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;

EX2029, ¶¶55-56. 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; EX2029, ¶55. 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; EX2029, ¶55.

But Meletta’s subsequent work would have suggested to POSAs that small-molecule FAP radiotracers lacked viability. EX2029, ¶¶56-57. 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; EX2029, ¶56. ***But radioiodinated MIP-1232 failed to selectively accumulate in FAP-expressing tissue.*** EX1008, 2089-2090; EX2029, ¶56. Indeed, Meletta stated, “Binding of [<sup>123</sup>I-MIP-1232] to endarterectomized tissue was similar in plaques and normal arteries, ***hampering its use for atherosclerosis imaging.***” EX1008, Abstract<sup>1</sup>; EX2029, ¶56.

Thus, the prior art did not reflect that small-molecule FAP radiotracers would have provided a fruitful avenue for FAP-imaging. EX2029, ¶57.

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<sup>1</sup> Emphasis added throughout except where otherwise indicated.

**ii. 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. EX2029, ¶¶58-61.

Before testifying for GE, Zeglis himself repeatedly described antibodies as uniquely well-suited imaging vectors. *Id.* 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.” EX2039, Abstract; EX2029, ¶58. In 2016, he emphasized that antibodies exhibit “remarkable selectivity and specificity for cancer biomarkers.” EX2040, Abstract; EX2029, ¶58. And he identified antibodies as “promising platforms for the development of hybrid PET/OI [optical imaging] agents” because of their “high selectivity and affinity.” EX2041; EX2029, ¶58. Consistent with those views, Zeglis admitted that he was not aware of “any examples where a small molecule provided more selectivity for FAP over PREP than an antibody.” EX2023, 67:45-68:2; EX2029, ¶58.

The prior art confirms that antibody-based agents were successfully developed and tested before October 2017. EX2029, ¶59. As Laverman explained, “[b]ecause FAP is expressed in tumor stroma, various anti-FAP antibodies have been studied for radioimmunotargeting of malignancies,” including an <sup>131</sup>I-labeled

murine F19 antibody and an  $^{131}\text{I}$ -labeled sibrotuzumab, a humanized F19 antibody. EX2033, 778; EX2029, ¶59. 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. EX2031, 1198; EX2030, 1645-1646; EX2029, ¶59.

Additional antibody-based agents further demonstrated the maturity of this approach. Laverman reported that  $^{177}\text{Lu}$ -ESC11 and  $^{177}\text{Lu}$ -ESC14 exhibited “excellent targeting in melanoma xenografts.” EX2033, 778; EX2029, ¶60. Fischer showed that ESC11 and ESC14 “bound selectively to both human and mouse FAP, with affinities in the low nanomolar range.” EX2028, Abstract; EX2029, ¶60. Laverman also disclosed that the anti-FAP radiotracer  $^{111}\text{In}$ -28H1 “resulted in excellent image quality,” attributable to low background uptake in off-target tissues. EX2033, 780, 783; EX2029, ¶60.

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. EX2029, ¶61.

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 Zeglis acknowledges that

antibodies in general could serve as “[t]argeting moieties in a radiopharmaceutical” (EX1003 ¶40; EX2023, 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. EX2029, ¶¶61, 64. Yet, he praised antibody-based agents before becoming GE’s expert in this proceeding. *Id.*

**iii. 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. *Id.*, ¶62. 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*.” EX2035, Abstract; EX2029, ¶62. 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. EX2035, Abstract; EX2029, ¶62.

POSAs likewise would have understood peptide-based agents to be an established and well-recognized route for developing radiotracers before

October 2017. EX2029, ¶63. 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.” EX2019, 58; EX2029, ¶63. 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.*, EX2036, Abstract; EX2037, Abstract; EX2038, Abstract, 1328; EX2029, ¶63. POSAs, therefore, would have viewed peptide-based constructs as viable starting points for FAP-targeting radiotracers. EX2029, ¶63-64.

**b. 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 Zeglis took, as discussed below in §IV.A.1.d.i. EX2029, ¶65. To the contrary, the art recognized multiple, materially different strategies for labeling small-molecule radiotracers. *See, e.g.*, EX1014, 31; EX2029, ¶¶65-70. A radionuclide is the radioactive isotope incorporated into a radiotracer that emits detectable radiation and enables imaging of a target. EX1014, 31; EX2029, ¶65. 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; EX2029, ¶65.

POSAs would have recognized, as 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* EX2019, 58; EX1003, ¶59; EX2029, ¶65.

POSAs would have been aware of the following different ways of incorporating a radionuclide into a radiotracer. EX2029, ¶¶65-70. Zeglis immediately jumps to using bulky L and B moieties to add a radionuclide to A, but as discussed below and in §IV.A.1.d.i, 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.*

**i. Direct isotopologous labeling with non-metallic radionuclides**

One well-established option would have been direct isotopologous labeling—particularly with radiohalogens. *Id.*, ¶67. Under this approach, a stable atom within the parent molecule (e.g., <sup>19</sup>F, <sup>127</sup>I, <sup>79</sup>Br, <sup>81</sup>Br) is replaced with its radioactive isotope counterpart (e.g., <sup>18</sup>F, <sup>123</sup>I, <sup>124</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>76</sup>Br). EX1014, 44; EX2029, ¶67. 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, ¶44; EX2029, ¶67.

The principal advantage of isotopologous labeling is that it introduces minimal structural perturbation. EX2029, ¶67. For example,  $^{18}\text{F}$  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; EX2029, ¶67. Consistent with this understanding, Zeglis testified that isotopologue labeling produces a molecule that differs only “in a very small way” from the starting structure. EX2023, 92:15-93:1; EX2029, ¶67.

**ii. Prosthetic-group labeling of non-metallic radionuclides**

POSAs also would have known that non-metallic radionuclides could be introduced indirectly through prosthetic-group labeling. EX2029, ¶68. The radionuclide is first covalently attached to a prosthetic group, which is then conjugated to the radiotracer precursor. EX1014, 44; EX1033, 137-38; EX2029, ¶68. Unlike isotopologous substitution, prosthetic-group labeling adds new structural elements to the molecule. EX1003, ¶44; EX2029, ¶68.

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. EX2029, ¶28. Otherwise, the modification would have risked disrupting the compound’s affinity and/or selectivity for its target—a proposition Zeglis expressly acknowledges. EX1003 ¶59(b); EX2029, ¶68.

**iii. Chelation strategies for metallic radionuclides**

For metallic radionuclides, chelation would have been required. *See, e.g.*, EX1017, 2667; EX2029, ¶69. Radiometals are incorporated by coordinating the radionuclide within a chelator that forms a stable complex with the metal ion. EX1013, Abstract; EX2029, ¶69. 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”); EX2029, ¶69.

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, ¶46; EX2029, ¶69.

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. EX2029, ¶70. 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.a.-IV.A.1.b, 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. EX2029, ¶¶64, 70. 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 claims. *Id.*

As discussed below, GE's and Zeglis's contrary position that POSAs would have immediately focused on a small-molecule approach rests on hindsight reconstruction. Moreover, 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. EX2029, ¶¶64, 70.

**c. 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. *Id.*, ¶71.

**i. Zeglis excludes numerous FAPis disclosed in prior art.**

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, ¶149; EX2029, ¶71. But, the prior art did not disclose Compound 60 in B-L-A form.<sup>2</sup> EX2029, ¶72. And, rather than evaluating the prior art as whole, including the dozens of other FAPis disclosed in different references than Jansen, Zeglis selectively focuses on a single reference, Jansen, and selected a single compound that fits the claims, while disregarding the broad and diverse body of FAPi disclosures that would have confronted POSAs. EX1003, ¶161; EX2029, ¶¶72-79. 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. EX2029, ¶¶72-

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<sup>2</sup> At institution, the Board mistakenly found that Compound 60 “is already in B-L-A form.” Paper 8, 25.

79. 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, ¶161; EX2029, ¶¶72-79. Instead, he simply assumes that POSAs would have “invariably discovered” Compound 60. EX1003, ¶¶167-168; EX2029, ¶72.

That leap, however, is unsupported by the art and fails to identify any reason favoring Compound 60 over the many available alternatives. EX2029, ¶¶86-90. Zeglis has emphasized that FAP-selectivity is “the most important factor” when choosing a FAPi for a radiopharmaceutical. EX1003, ¶55; EX2029, ¶73. 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. EX2029, ¶¶86-90.

Jansen 2013 (EX1007) alone disclosed 36 distinct FAPis. EX1007, Tables 2-3; EX2029, ¶74; EX2001, ¶72, 84. 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; EX2029, ¶74. And the most selective compound in that study—Compound 26—falls outside the scope of the claims because it contains a substituent on the quinolinyl ring that

the claims exclude. EX1007, Tables 2-3; EX1001, 64:6-55, COC; EX2029, ¶74; EX2001, ¶72, 84. Zeglis does not evaluate these alternative compounds or explain why POSAs would have bypassed them in favor of Compound 60. EX2029, ¶74; EX2001, ¶72, 84.

Similarly, US-650 (EX1044) disclosed 43 additional FAPis, many of which matched or exceeded Compound 60's selectivity. EX1044, Table 4; EX2001, ¶74. Compounds 22 (>4500), 23 (2100), 21 (1700), and 11 (677) all outperformed Compound 60 in FAP-selectivity. EX1044, Table 4. 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 (EX2023, 154:8-156:17). EX2029, ¶75; EX2001, ¶74. 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. EX2029, ¶75. 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 claims. EX1044; EX1001, 64:6-55, COC; EX2029, ¶75; EX2001, ¶¶74-75.

The prior art further disclosed FAPis employing entirely different chemical scaffolds. EX2029, ¶76. 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; EX2029, ¶76; EX2001, ¶73. Jansen 2014 characterized several of its compounds as selective FAPis, with reported selectivity over DPP<sup>IV</sup> and PREP. EX2003, Tables 3 and 5; EX2029, ¶76; EX2001, ¶73. Zeglis conceded familiarity with this reference but did not evaluate these compounds or explain why POSAs would have ignored them. EX2023, 129:5-132:6; EX2029, ¶76; EX2001, ¶73.

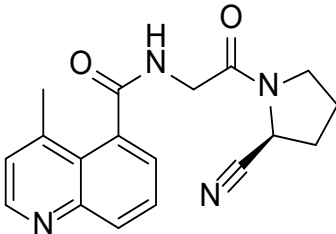
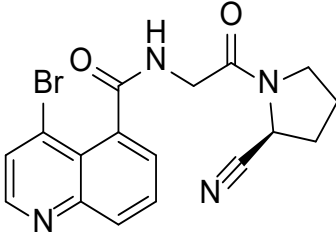
Other groups also disclosed potent and selective FAPis. EX2029, ¶77. Poplawski reported 22 non-quinoliny FAPis and described them as the first compounds to combine low-nanomolar potency with selectivity over both DPPs and PREP. EX2020, 7, Tables 1-4; EX2029, ¶77. Poplawski's Compound 6 exhibited FAP-selectivity on the same order of magnitude as Compound 60, yet Zeglis discounted it based on the absence of published *in vivo* pharmacokinetic (PK) data. EX1003 ¶143; EX2029, ¶77. That rationale is inconsistent with his own deposition testimony that optical radiotracers may also be useful *in vitro*, which would not implicate pharmacokinetics. EX2023, 80:13-15; EX2029, ¶77.

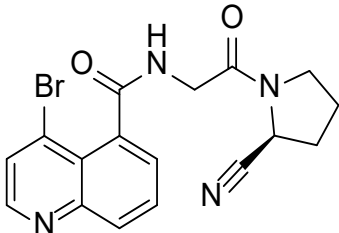
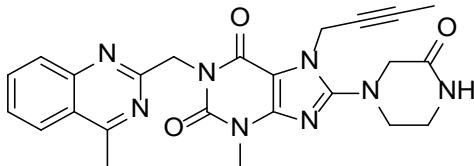
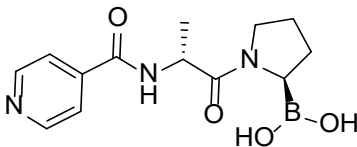
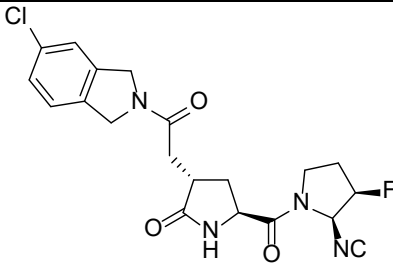
Tsai similarly disclosed 27 FAPis based on a pyroglutamic-acid scaffold, reporting IC<sub>50</sub> values below 100 nM and excellent selectivity over DPPs. EX1047, Abstract, Table 2; EX2029, ¶78. Tsai identified Compounds 18a, 18b, and 19 as uniquely potent and selective FAPis. EX1047, Abstract, Table 2; EX2029, ¶78. Zeglis dismissed the reference based on alleged "poor" PK concerns raised for *one* compound disclosed in Tsai. EX1003 ¶143; EX2029, ¶78. Yet, Tsai also

demonstrated that its Compound 18b had favorable half-life, clearance, and exposure maintaining FAP-selectivity. EX1047, 6578; EX2029, ¶78. Zeglis, however, has offered no explanation for how these disclosures would have informed—or failed to inform—POSAs evaluating the available FAPi landscape. EX2029, ¶78.

As demonstrated below, the most selective compounds disclosed across multiple prior art references fall outside the scope of the claims. EX2029, ¶79.

**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<br>(All compounds below are outside of the claims’ “A” moiety scope)          |
|-----------|---------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| Jansen    | 54                        | 3                                          |  <p><b>(Compound 53)</b></p> |
| US-650    | 43                        | 1                                          |  <p><b>(Compound 22)</b></p> |

| Reference   | Number of FAPis disclosed | Number of FAPis that fall within claimed A | Highest-selectivity FAPi structure<br>(All compounds below are outside of the claims' "A" moiety scope)    |
|-------------|---------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Jansen 2013 | 36                        | 2                                          |  <p>(Compound 26)</p>    |
| Jansen 2014 | 33                        | None                                       |  <p>(Compound 3)</p>     |
| Poplawski   | 22                        | None                                       |  <p>(Compound 6)</p>    |
| Tsai        | 27                        | None                                       |  <p>(Compound 18b)</p> |

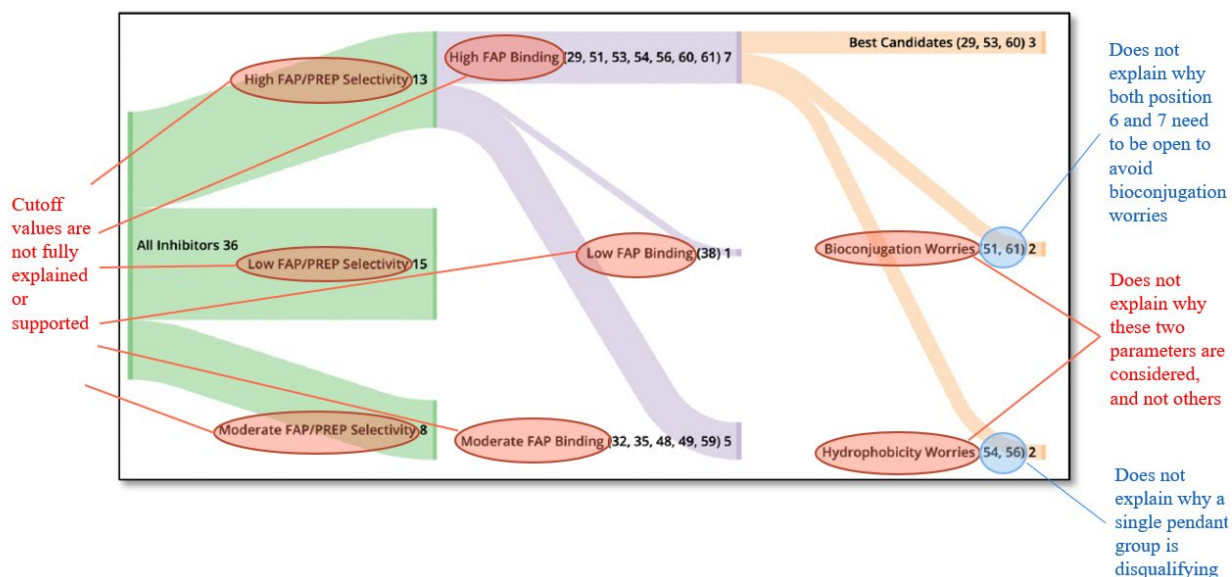
The forgoing demonstrates that Zeglis's theory depends on reconstructing the invention by cherry-picking Compound 60 with knowledge of the claims, rather than on any scientific rationale that would have guided POSAs specifically to that compound. EX2029, ¶79. The absence of any reason or design principle favoring Compound 60 confirms his hindsight-based selection. *Id.*

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

Zeglis has not demonstrated that POSAs would have been led to select Compound 60 from the quinoline-based FAPis disclosed in the prior art. EX2029, ¶80; EX2001, ¶¶78-83. 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, ¶¶149-155; EX2029, ¶80; EX2001, ¶¶78-83. His framework, however, is unsupported by any evidence and does not exemplify how POSAs would have evaluated all the compounds reported in Jansen. EX2029, ¶80. Nor does 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 ¶¶78-79; EX2029, ¶81.

Zeglis also excludes compounds that satisfy his stated selectivity and affinity criteria, yet that fall outside the claims, based on conclusory assertions regarding “hydrophobicity” or “bioconjugation” feasibility, while favoring Compound 60, which does fall within the claims. EX1003, ¶154; EX2029, ¶82-85; EX2001, ¶83. For instance, he alleges that Jansens’s Compounds 51 and 61 would “pose conjugation 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, ¶154; EX2029, ¶¶82-85; EX2001, ¶80. 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, ¶154; EX2029, ¶82; EX2001, ¶80. The figure below provided by Dr. VanBrocklin summarizes the foregoing issues with Zeglis’s framework:



EX2029, ¶80.

Even assuming that POSAs would have prioritized compounds in the manner Zeglis alleges, the prior art disclosed over twenty compounds with high selectivity, as defined by Zeglis, five of which outperformed Compound 60. EX2029, ¶¶86-90; EX2001, ¶85. Indeed, US-650 and Jansen 2013 reported multiple FAPis that meet Zeglis’s criteria but also outperform Compound 60.

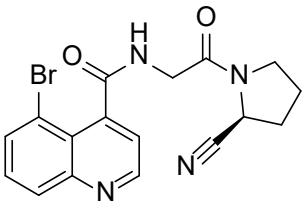
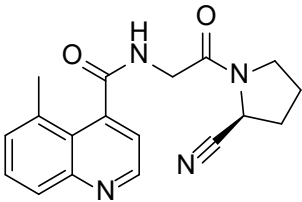
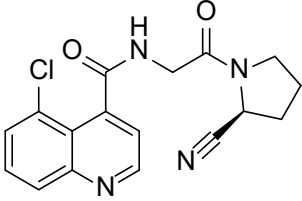
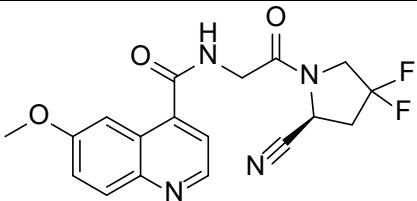
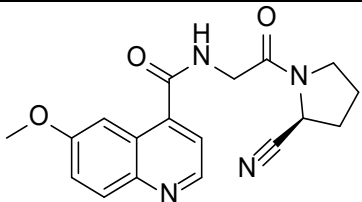
EX1044, Tables 3-4; EX1007, Tables 2-3; EX2029, ¶¶87-90; EX2001, ¶85. Zeglis also acknowledged on cross-examination that several such compounds—Compounds 21, 22, 23, 24, and 11 from US-650—exhibited greater FAP-selectivity than Compound 60. EX2023, 154:21-157:14; EX2029, ¶86.

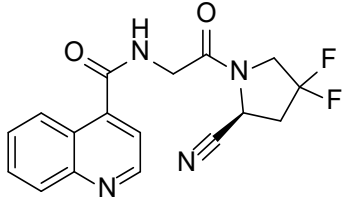
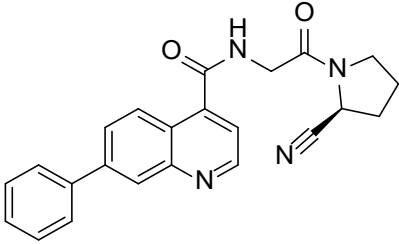
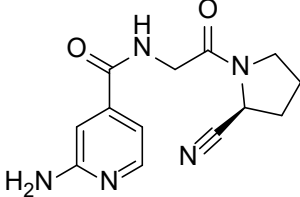
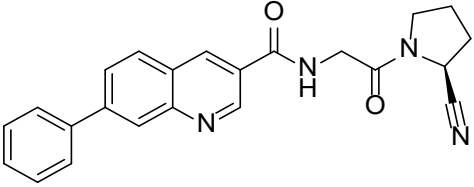
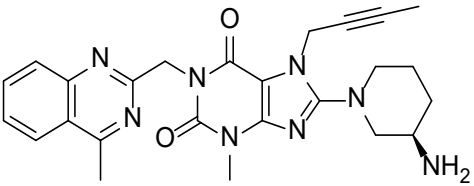
Even Jansen, the reference on which Zeglis principally relies, identifies compounds with substantially higher selectivity, including Compound 53 (selectivity = 2100; Jansen 2013’s Compound 23). EX1004, Table 4; EX2029, ¶87. Zeglis nevertheless discounts those compounds because allegedly “it was not possible 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, ¶157; EX2029, ¶87. 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, ¶160; EX2029, ¶87. The claims, however, are structural and ***do not require*** *in vivo* performance. *See* §III.A.; EX2029, ¶87.

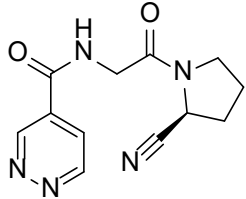
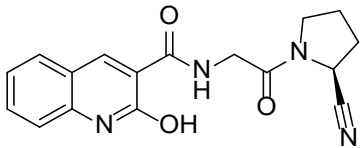
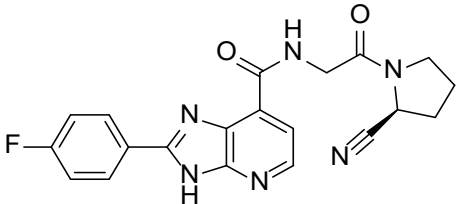
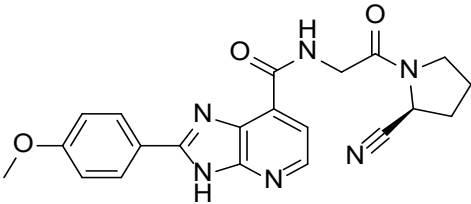
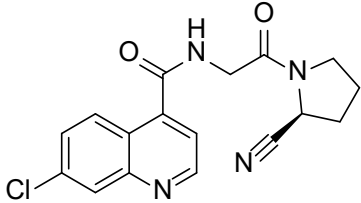
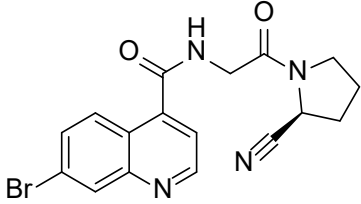
Excluding compounds that exceed his purported selection criteria based on considerations nowhere required by the claims confirms that Zeglis is tailoring his analysis to fit the claims and not conducting a full assessment of the prior art from the perspective of a POSA. EX2029, ¶87.

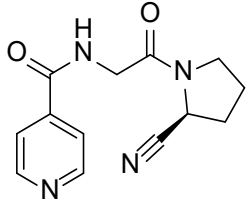
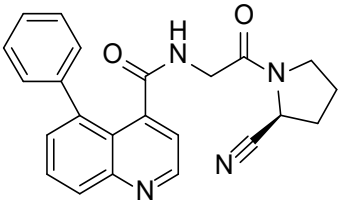
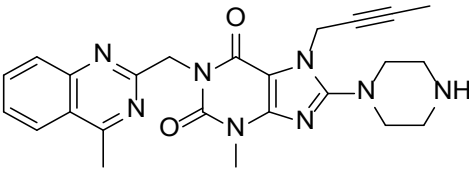
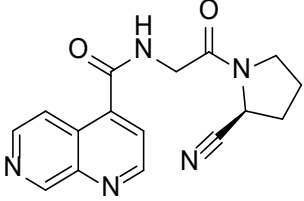
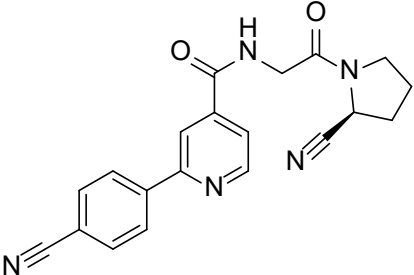
Dr. VanBrocklin's table below summarizes the quinoliny1-based FAPis from Jansen, US-650, Jansen 2013, and Jansen 2014 that satisfy Zeglis's stated thresholds (selectivity >100; affinity <0.1  $\mu$ M). The entries are ordered by selectivity ( $IC_{50}^{PREP}/IC_{50}^{FAP}$ ), which Zeglis identified as the "most important" factor. EX1003, ¶¶55, 151; EX2029, ¶88; EX2001, ¶85. Based on 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. EX2029, ¶89-90; EX2001, ¶85. In other words, the claims guided Zeglis to Compound 60.

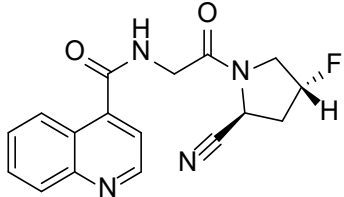
**Top FAPis, ranked by selectivity in Jansen, US-650, Jansen 2013, and Jansen 2014**

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

| Compound Number         | Structure                                                                           | FAP Affinity ( $\mu\text{M}$ ) | FAP Selectivity | Fall within scope of claims? |
|-------------------------|-------------------------------------------------------------------------------------|--------------------------------|-----------------|------------------------------|
| US 650: 1<br>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                            |

| Compound Number               | Structure                                                                           | FAP Affinity ( $\mu\text{M}$ ) | FAP Selectivity | Fall within scope of claims? |
|-------------------------------|-------------------------------------------------------------------------------------|--------------------------------|-----------------|------------------------------|
| Jansen: 38                    |    | 0.164                          | 237.8           | N                            |
| US 650: 38<br>Jansen 2013: 24 |    | 0.16                           | 230             | N                            |
| Jansen: 48                    |   | <0.2                           | >200            | N                            |
| US 650: 28<br>Jansen: 49      |  | <0.2                           | >200            | N                            |
| US 650: 13<br>Jansen 2013: 31 |  | 0.0071                         | 197             | N                            |
| US 650: 12<br>Jansen 2013: 32 |  | 0.0062                         | 193             | N                            |

| Compound Number          | Structure                                                                           | FAP Affinity ( $\mu\text{M}$ ) | FAP Selectivity | Fall within scope of claims? |
|--------------------------|-------------------------------------------------------------------------------------|--------------------------------|-----------------|------------------------------|
| US 650: 4<br>Jansen: 29  |    | 0.063                          | 179             | N                            |
| US 650: 26<br>Jansen: 56 |    | 0.064                          | 135             | N                            |
| Jansen 2014: 13a         |   | 0.74                           | >135            | N                            |
| US 650: 33<br>Jansen: 51 |  | 0.028                          | 120             | N                            |
| US 650: 16<br>Jansen: 35 |  | 0.27                           | 107             | N                            |

| Compound Number | Structure                                                                         | FAP Affinity ( $\mu\text{M}$ ) | FAP Selectivity | Fall within scope of claims? |
|-----------------|-----------------------------------------------------------------------------------|--------------------------------|-----------------|------------------------------|
| 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

EX2029, ¶89; EX2001, ¶85.

Accordingly, the current record does not support selecting Compound 60 from the prior art as a whole on 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. EX2029, ¶¶89-90; EX2001, ¶85.

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.

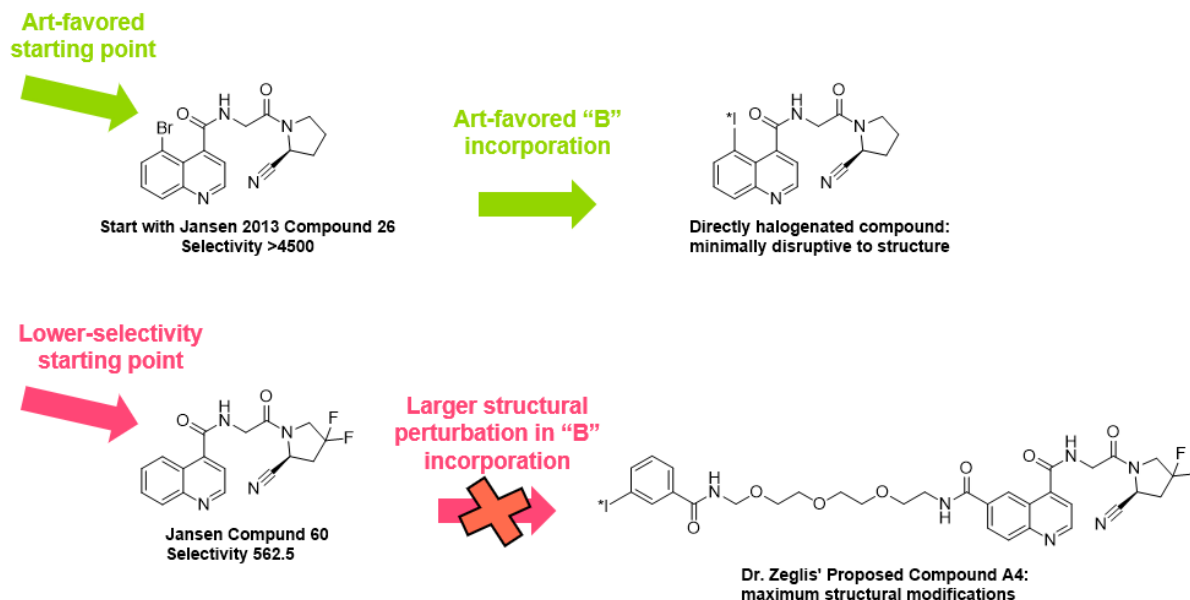
- d. POSAs would not have been directed to the claimed B-L-A architecture, and Compound 60 was not present in the art in B-L-A format.**
  - i. POSAs would have been directed to direct halogenation, not adding bulky B and L moieties.**

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. EX2029, ¶¶91-93.

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; EX2029, ¶91. That structure-activity relationship (“SAR”) was not incidental; it was expressly identified as beneficial and central to performance, with Jansen 2013 stating, “Introducing 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; EX2029, ¶91; EX2001, ¶¶68-69. POSAs purportedly seeking to develop a FAP-targeting radiotracer therefore would have been guided toward those halogen-substituted scaffolds, not away from them. EX2023, ¶91; EX2001, ¶¶68-69.

Consistent with that SAR, the prior art taught that when radiolabeling is desired, the most straightforward and least disruptive strategy is direct isotopologous substitution—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; EX2029, ¶91; EX2001, ¶¶68-69. 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; EX2029, ¶¶91, 96; EX2001, ¶¶68-69. POSAs therefore would have had little reason to abandon direct labeling in favor of constructing a fundamentally different B-L-A architecture. EX2029, ¶¶92.



EX2029, ¶92.

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. EX2029, ¶92. He then asserts that POSAs would have preferred linker-based modification over direct radiohalogenation due to purported “adverse effects.” EX1003, ¶175; EX2029, ¶92. 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. EX2029, ¶92. The more

credible explanation for his choice is he worked backward from the 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. EX2029, ¶¶94-98. Zeglis acknowledges that "slight modifications to the structure of a targeting moiety can alter its selectivity and affinity for its target." EX1003 ¶59; EX2029, ¶96. Yet arriving at the claimed compounds would have required not a slight modification, but adding a large linker-chelator substituent to the FAPi scaffold. EX2029, ¶95. The prior art provided no rationale for making such a disruptive change, particularly where direct radiohalogenation offered a known and conservative alternative. EX2029, ¶¶95-97.

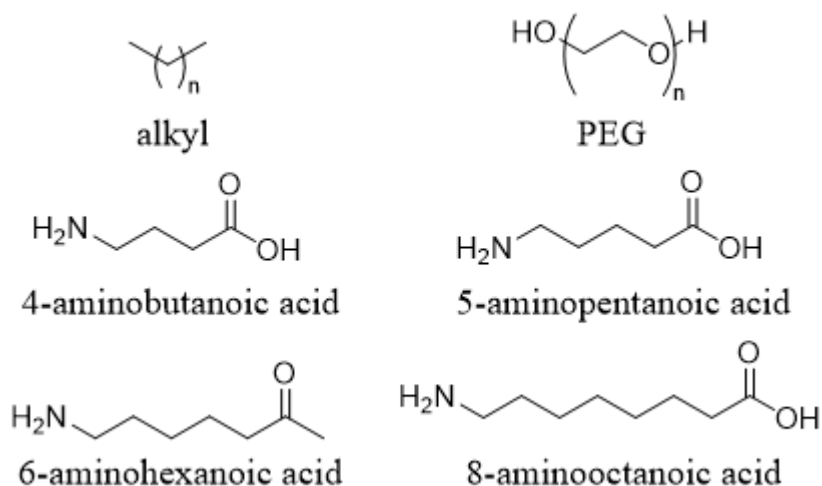
The developmental history of FAP-radiotracers confirms those teachings. *Id.* The earliest small-molecule FAP radiotracers relied on iodine-substituted analogs and direct halogenation strategies, not bulky linker-based architectures. EX1035, Abstract; EX2029, ¶97. That historical record is consistent 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. EX2029, ¶¶94-98.

The prior art as a whole, therefore, would not have directed POSAs toward the claimed B-L-A compounds. EX2029, ¶98.

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

Zeglis's obviousness theory in Ground I hinges on the assertion that POSAs would have selected a three-monomer polyethylene glycol (PEG) linker. EX1003, ¶199; EX2029, ¶99. 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. EX2029, ¶99. Indeed, 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, ¶99; EX2029, ¶¶99-105.

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; EX2029, ¶102. Example structures of such linkers are shown below:



EX1004, ¶130; EX2029, ¶102.

Nothing in US-633 singles out a three-monomer PEG, or provides a rationale for preferring it over other expressly disclosed alternatives. EX2029, ¶102. Instead, Zeglis's choice appears to be yet another effort to cull the prior art to reach the claims, rather than explain how the art would have led POSAs to that particular selection. EX2029, ¶¶99-102.

Zeglis attempts to justify this selection by asserting that POSAs would have sought approximately 10-20 bond lengths between A and B. EX1003 ¶¶122, 187; EX2029, ¶100. But he provides no support for why POSAs would have selected that design constraint for Compound 60. EX1003, ¶187; EX2029, ¶100. 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. EX2023, 182:4-20; EX2029, ¶100.

Zeglis seeks to further rationalize his selection by asserting that POSAs would have been familiar with PEG-based linkers. EX1003, ¶122; EX2029, ¶101. 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, ¶122 n.129; EX2029, ¶101. 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, Zeglis invokes hydrophobicity<sup>3</sup> 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, ¶154; EX2029, ¶101.

Nor does Zeglis explain why POSAs would have ignored the specific linkers in US-633's exemplary radiotracers. EX2029, ¶102. 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-

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<sup>3</sup> Lipophilicity and hydrophobicity are closely related, both describing a compound's tendency to associate with nonpolar environments. EX2025, 183-184, 197; EX2029, 101. Increased lipophilicity generally corresponds to increased hydrophobicity. EX2029, ¶101.

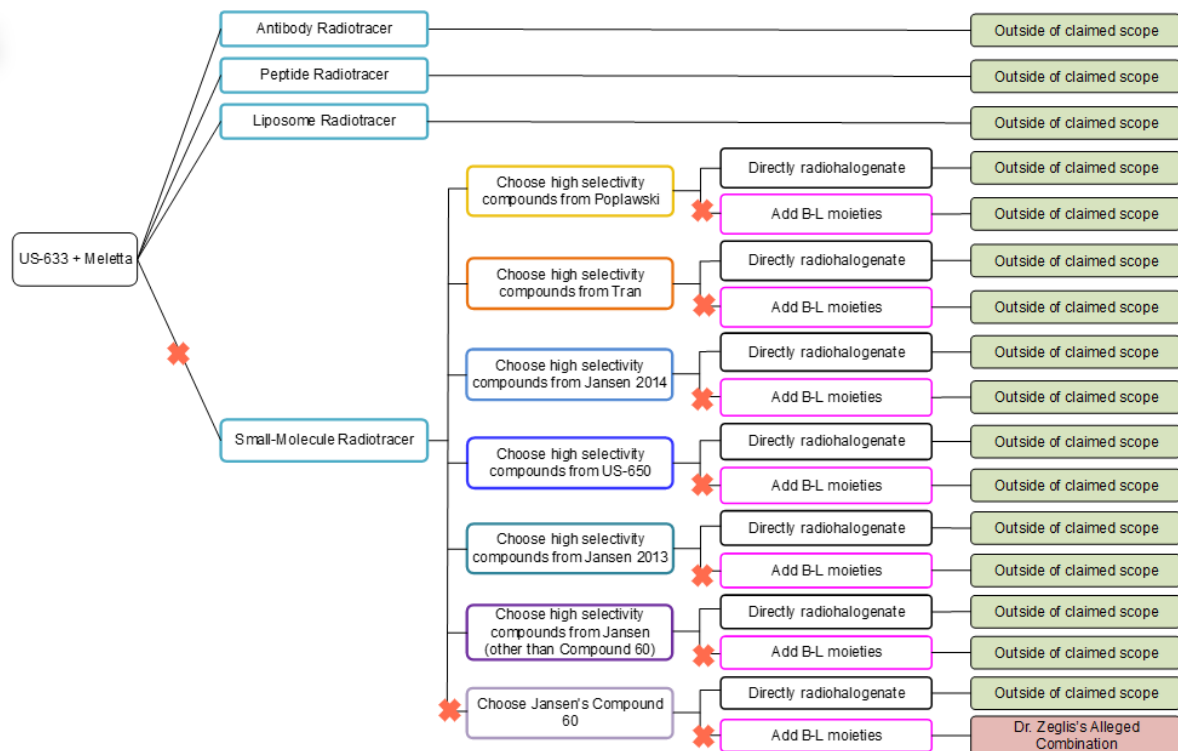
linker portion of these examples with a new targeting moiety (i.e., compound 60).” EX1003, ¶¶235; 238-239 (alleging POSAs would only replace the targeting moiety but keep the rest of the exemplary radiotracer structure, including the L).

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; EX2029, ¶102. And he offers no reason why POSAs would have abandoned those examples over an unexemplified, selectively chosen linker. EX2029, ¶¶102-103.

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, ¶169; EX2029, ¶104. 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. EX2026, Abstract, 823, 830; EX2029, ¶104. Dr. Zeglis did not factor this art into his analysis, further underscoring the absence of a reasoned path to the claimed compounds. EX2029, ¶¶104-105.

\* \* \*

On this record discussed in §§IV.A.1.a-IV.A.1.d, 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 Zeglis's path, POSAs would have had to make a series of nonobvious, scientifically disfavored decisions—not ones grounded in the prior art. EX2029, ¶106. 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 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. 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.

**e. 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. EX2029, ¶¶107-112. As discussed above, the only pre-2017 small-molecule FAP radiotracer evaluated for selectivity *failed* when evaluated *in vitro*. See §IV.A.1.i. 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; EX2029, ¶107. 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. EX2029, ¶107.

The prior art, moreover, consistently taught that even small structural modifications to quinolinyl-based FAPis could profoundly impair both FAP-

affinity and selectivity. *Id.*, ¶¶108-112. 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. *Id.*, ¶108. 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; EX2029, ¶108. This order-of-magnitude loss in selectivity would have signaled to POSAs not having the benefit of the '233 patent specification that even modest substituent changes at the quinoline could destroy the functional properties necessary for a viable FAPi. EX2029, ¶108.

Additional SARs disclosed in Jansen 2013 reinforce this conclusion. *Id.*, ¶109. Jansen 2013 reports that Compound 7 exhibits strong FAP-affinity (0.0103  $\mu$ M) and a selectivity of 83. EX1007, Table 3; EX2029, ¶109. Incorporating additional substituents at the quinolinyl group, however, markedly decreased selectivity. EX1007, Table 3; EX2029, ¶109. These results demonstrate that before the '233 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. EX2029, ¶109.

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, 3; EX2029, ¶110. Jansen 2013 explains that both steric and electronic effects contribute to loss of activity. EX1007, 3; EX2029, ¶110. POSAs would have understood this disclosure as a warning that modifying the quinoline ring was poorly tolerated. EX2029, ¶110. Indeed, a POSA would not have recognized that sites on the quinoliny ring could be modified until after the disclosure provided in the ’233 patent showing that the ring could predictably withstand modification with Bs and Ls. EX1001, 57:61-61:23; EX2029, ¶110.

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.

**2. Ground II: The claims would not have been obvious over US-121 and Jansen because, as in Ground I, Zeglis relies on hindsight.**

Ground 2 fails for the same reason as Ground 1: Zeglis never shows that POSAs would have reached the claimed invention through reasoned

decision-making grounded in the prior art as a whole. EX2029, ¶¶113-114. He instead reasons backward from the claims, rather than from the perspective of POSAs. *Id.*

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, ¶¶207-232; EX2029, ¶¶71-90. And as in Ground 1, he does not meaningfully address the full range of FAPi options available. EX2029, ¶113. He again ignores non-quinolinyl-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 ¶¶207-232; EX2029, ¶113. His selective application of his selection criteria confirms that his analysis is claim-driven, not grounded in the prior art. EX2029, ¶113.

Zeglis’s reliance on US-121, moreover, does not cure those deficiencies. *Id.*, ¶114. US-121 discloses radiotracers for imaging prostate-specific membrane antigen (“PSMA”), not FAP—a point Zeglis concedes. EX1003, ¶210; EX2023, 157:15-158:16; EX2029, ¶114. 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 claims. EX2029, ¶114. 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, ¶227; EX2029, ¶114.

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.

**3. Objective indicia support the nonobviousness of the claims as demonstrated by unexpected results.**

GE has failed to establish a *prima facie* case of obviousness. Objective evidence discussed below, moreover, confirms nonobviousness. EX2029, ¶115.

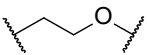
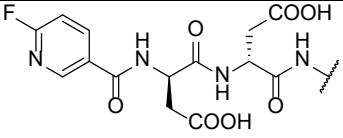
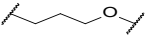
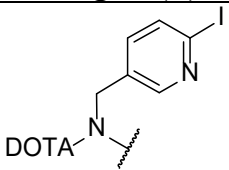
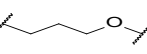
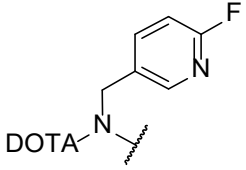
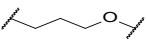
Nonobviousness can be demonstrated by showing evidence of unexpected results compared to the closest prior art. *In re Baxter Travenol Lab 'y*, 952 F.2d 388, 392 (Fed. Cir. 1991). Comparing the claims and prior art “to determine the number of claim limitations in common ..., bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference.” *In re Merchant*, 575 F.2d 865, 867 (C.C.P.A. 1978).

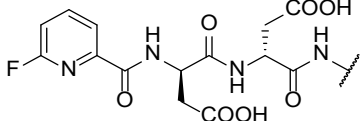
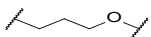
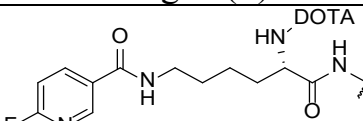
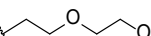
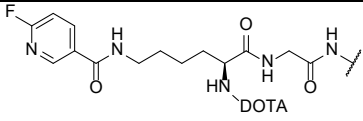
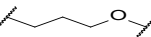
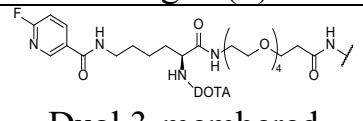
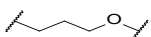
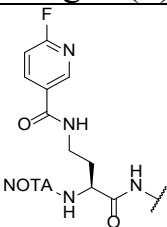
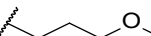
Considering the claimed A as having the most importance due to it being the FAP-targeting moiety, the closest prior art would be Jansen 2013, which discloses the FAP-selectivity of As encompassed by the claims. EX2029, ¶117. Here, the claimed B-L-A compounds exhibit dramatic improvements in selectivity for FAP over PREP ( $SI_{FAP/PREP}$ ) relative to the corresponding A alone. *Id.*, ¶¶116-117.

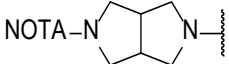
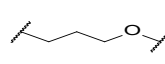
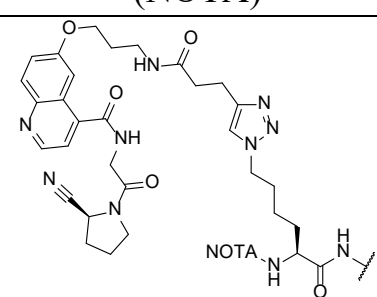
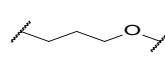
Jansen 2013's Compound 7 exhibited a FAP-selectivity of 86 when tested alone. EX1007, Table 2; EX2029, ¶118. Yet, when conjugated to the claimed Ls

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; EX1002, 174-176; EX2029, ¶118.

The table below summarizes these data, comparing Compound 7 alone to Compound 7 in B-L-A format for selectivity. EX2029, ¶118. Zeglis did not address these data, even though it would have been available from the prosecution the '233 patent family. *Id.*

| B                                                                                                                                                            | L                                                                                   | B-L-A MW (g/mol) | B MW (g/mol) | Selectivity Index/Increase compared to A alone |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------|--------------|------------------------------------------------|
| <br>Halogen (F)                                                            |  | 370              | 19.0         | 4,111<br><b>~48-fold improvement</b>           |
| <br>Prosthetic group with a halogen (F)                                   |  | 734              | 369.3        | 66,084<br><b>~768-fold improvement</b>         |
| <br>Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (I) |  | 983              | 620.4        | 1,418,440<br><b>~16,493-fold improvement</b>   |
| <br>DOTA-                                                                 |  | 876              | 502.4        | 1,052<br><b>~12-fold improvement</b>           |

| B                                                                                                                                                                     | L                                                                                   | B-L-A MW<br>(g/mol) | B MW<br>(g/mol) | Selectivity<br>Index/Increase<br>compared to A<br>alone |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|---------------------|-----------------|---------------------------------------------------------|
| Dual 3-membered<br>chelator (DOTA) /<br>prosthetic group with a<br>halogen (F)                                                                                        |                                                                                     |                     |                 |                                                         |
| <br>Prosthetic group with a<br>halogen (F)                                           |    | 734                 | 369.3           | 5,807<br><b>~68-fold<br/>improvement</b>                |
| <br>Dual 3-membered<br>chelator (DOTA) /<br>prosthetic group with a<br>halogen (F)   |    | 1049                | 652.7           | 779<br><b>~9-fold<br/>improvement</b>                   |
| <br>Dual 3-membered<br>chelator (DOTA) /<br>prosthetic group with a<br>halogen (F) |  | 1073                | 711.4           | 1,693<br><b>~20-fold<br/>improvement</b>                |
| <br>Dual 3-membered<br>chelator (DOTA) /<br>prosthetic group with a<br>halogen (F) |  | 1266                | 888.4           | 407<br><b>~5-fold<br/>improvement</b>                   |
| <br>Dual 3-membered<br>chelator (DOTA) /<br>prosthetic group with a<br>halogen (F) |  | 889                 | 525.3           | 10,694<br><b>~124-fold<br/>improvement</b>              |

| B                                                                                                                                               | L                                                                                 | B-L-A MW<br>(g/mol) | B MW<br>(g/mol) | Selectivity<br>Index/Increase<br>compared to A<br>alone |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------|-----------------|---------------------------------------------------------|
| Dual 2-membered<br>chelator (NOTA) /<br>prosthetic group with a<br>halogen (F)                                                                  |                                                                                   |                     |                 |                                                         |
| <br>2-membered chelator<br>(NOTA)                              |  | 761                 | 397.3           | 11,893<br><br>~134-fold<br>improvement                  |
| <br>Dual 2-membered<br>chelator (NOTA) /<br>second FAPi moiety |  | 1282                | 918.0           | 1,313<br><br>~15-fold<br>improvement                    |

As shown above, the B-L-A compounds exhibited improvements ranging from approximately 5-fold to >16,000-fold over Compound 7. EX1002, 174-176; EX2029, ¶121. 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. EX2029, ¶121. And the increase is attributable to the claimed B-L-A architecture as a whole. *Id.*; *Galderma Lab'ys. 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. EX2029, ¶¶119-120. To the contrary, the art taught that even relatively minor modifications to FAPis frequently degraded selectivity. EX1014, 44; EX1010, 3; EX1003, ¶¶44, 46, 59(b); EX1017, 2669; *see generally* EX1007; EX1044; EX2029, ¶110. Consistent with that teaching, 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 Zeglis identified in his declaration as “paramount.” EX2029, ¶119; EX2023, 151:19-152:1; EX1003, ¶55. That admission at his deposition underscores how unexpected the above results would have been to POSAs at the relevant time. EX2029, ¶119.

If the Board considers art disclosing B-FAPi compounds as the closest prior art, the unexpectedness of Pomper’s observed results is further reinforced by the teachings of Meletta. EX2029, ¶120. 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. EX1002, 174-176; EX1035, Abstract; EX2029, ¶120. 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, 174-176; EX2029, ¶120. 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. EX2029, ¶120.

If selectivity were driven primarily by A, relative performance would track baseline selectivity. *Id.*, ¶122. 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 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; EX2029, ¶121. 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, 1329 (Fed. Cir. 2016).

The unexpectedly high selectivity is not confined to a narrow subset of embodiments, rather it is representative of the full scope of claims 1-4. EX2029, ¶123. The 11 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; EX2029, ¶123. 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. EX2029, ¶123.

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 claims. *Id.*

The claimed compounds, therefore, do not merely preserve the selectivity of known FAPs; they achieve an unexpected enhancement in selectivity that the prior art neither taught nor suggested. *Id.*, ¶124. 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.

**B. Ground III: The Claims Have Written Description Support in View of the Patent Specification’s Extensive Disclosure.**

The Board rightly found that the claims “recite a compound, not a result.” Paper 8, 34. GE’s analysis—requiring that the claimed compounds possess *in vivo* diagnostic or therapeutic utility—is, therefore, not applicable. *Id.*; EX2029, ¶¶125-128. Indeed, “[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); *Phillips*, 415 F.3d at 1323 (it is improper to “import[] limitations from the specification into the claims”). Nothing in the record thus warrants disturbing the Board’s preliminary finding that GE “fails to demonstrate that the claims lack written description.” Paper 8, 34.

**1. GE’s reliance on cases involving functionally defined genera is misplaced.**

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

*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 court found no written description because the specification did not provide “any indication as to *which* of th[e] undisclosed [compounds] would be effective.” *Id.*

*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 met the claims functional requirements. *Id.* at 1300.

In contrast to *Idenix* and *AbbVie*, the current record shows that the claims here define the claimed compounds by their *structure*, not by their ability to achieve any particular function, such as being effective for *in vivo* diagnostic or therapeutic use as GE alleges. *See* §III. As discussed below, the patent adequately describes the claimed invention through structure and physical properties of A, B, and L and the claimed B-L-A structure, from which that POSAs would be able to recognize the members of the claimed genus. *See* §IV.C.2.b.; EX2029, ¶¶129-134. The specification, moreover, discloses actual examples of the claimed compounds and numerous examples of As, Bs, and Ls that POSAs would have employed when

making the claimed compounds. EX1001, cols. 8-32; EX2029, ¶135. Thus, as discussed below in §IV.C.2.c, the specification provides sufficient representative species. EX2029, ¶¶125-135.

**2. The claimed compounds are adequately described in view of apposite case law.**

An “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). And “a sufficient description of a genus ... requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can ‘visualize or recognize’ the members of the genus.” *Id.* Here, the specification does just that. EX2029, ¶¶129-135.

**a. The patent need not re-describe known elements to have sufficient written description support.**

Where claims recite a novel combination of otherwise known elements, the patent specification need not re-describe these known elements and “add unnecessary bulk to the specification.” *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1368 (Fed. Cir. 2006). That is the case here with the claimed compounds.

Thus, cases such as *Falko-Gunter* and *Capon v. Eshhar* are appropriately applicable here.

In *Falko-Gunter*, the claims at issue involved novel poxvirus vaccines made from known DNA elements. *Id.* at 1360-61. Falkner argued that the Inglis’s priority applications did not describe ““essential regions”” of any poxviruses sufficient to provide written description. *Id.* at 1361-62, 1367. The court rejected that argument because the claimed DNA elements were known and “recit[ing] known DNA structures ... would serve no goal of the written description requirement.” *Id.* Thus, where POSAs would understand from the specification what DNA elements to use and would know their structure from knowledge in the art, the specification did not need to redescribe those elements. *Id.* at 1367-68.

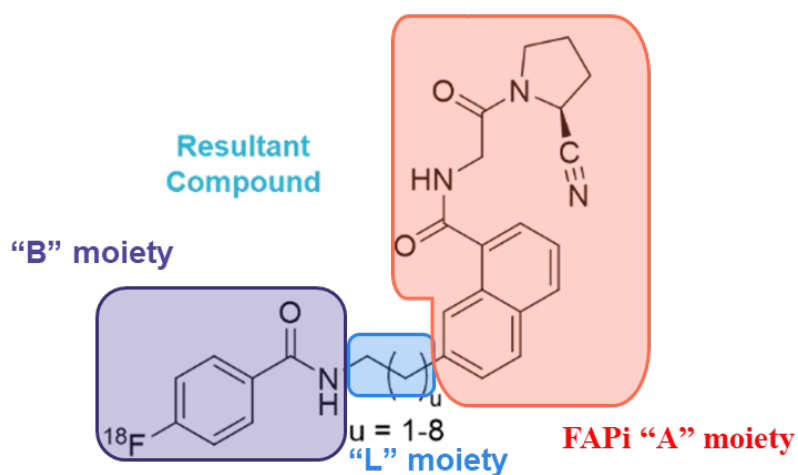
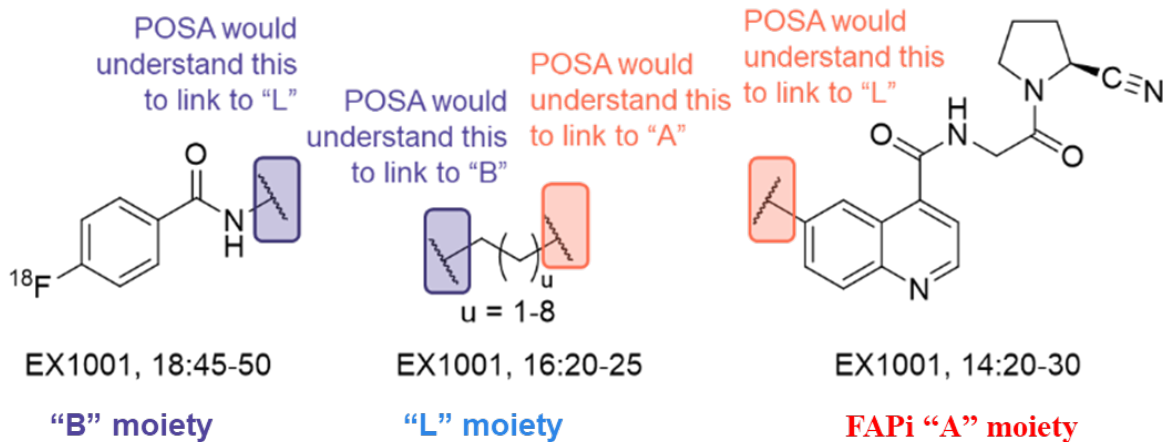
In *Capon*, the claims recited known DNA segments linked by known methods to create “a novel combination of the DNA segments to achieve a novel result.” *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005). The court held that the specification need not recite those known elements. *Id.*

Here, as with *Falko-Gunter* and *Capon*, the specification makes clear that the invention is a novel combination of known As, Bs, and Ls, and then provides dozens of columns of exemplary As, Bs, and Ls that POSAs would have used when making the claimed compounds. EX1001, cols. 8-32; EX2029, ¶129. The

specification also incorporates by reference additional As, Bs, and Ls that could be used. EX1001, 17:45-54; EX2029, ¶129.

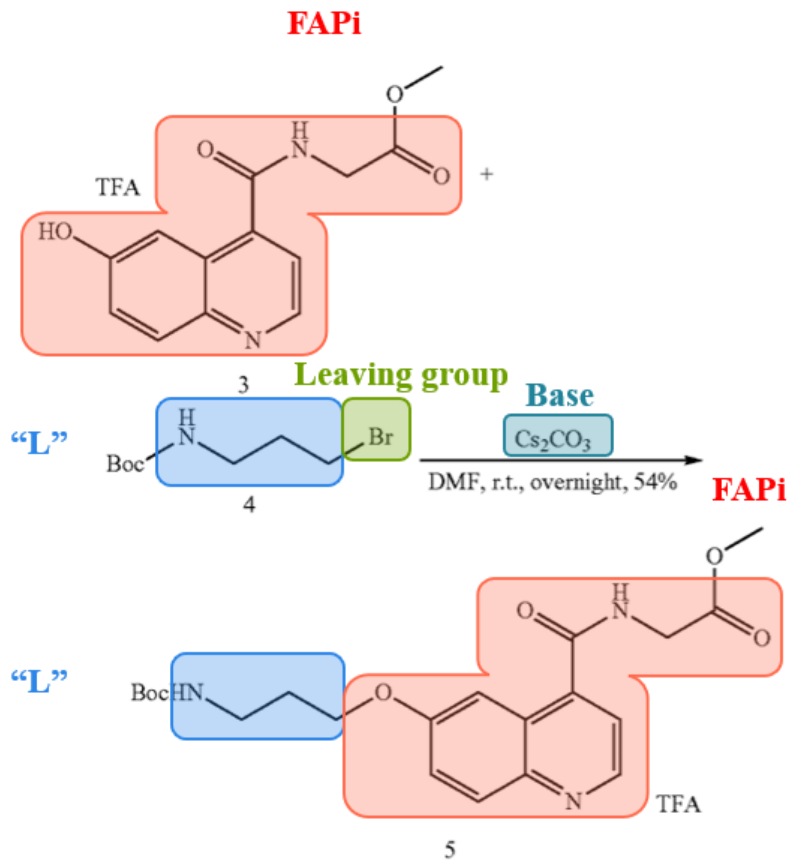
POSAs who had extensive practical experience in developing and evaluating radiotracers would thus have readily ascertained from the specification that it discloses how to combine As, Bs, and Ls to make the recited novel B-L-A compounds—and would thus likewise have readily understood that the inventors possessed the full scope of the recited subject matter. EX2029, ¶¶130-131; *see also* §IV.C.1.

Indeed, as Dr. VanBrocklin explains, the patent provides a blueprint for assembling Bs, Ls, and As that POSAs would have easily understood, depicted below from annotated excerpts of the specification:



EX2029, ¶131.

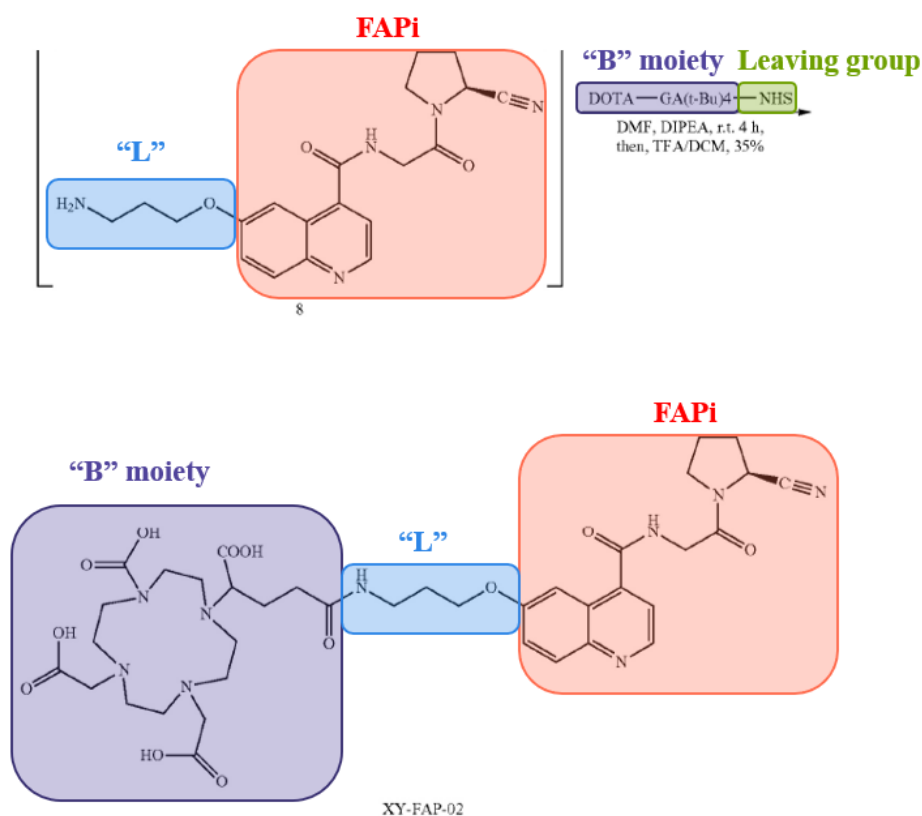
The specification describes forming A-L intermediates using conventional coupling reactions, including a base-promoted S<sub>N</sub>2 reaction—one of the most routine transformations in organic chemistry known well before October 2017. EX1054, Abstract, Tables 1-2; EX2049, Abstract, 1; EX2029, ¶131. As shown from the patent excerpted below and annotated, L bears a leaving group that reacts with A to form the desired A-L intermediate. EX1001, 51:22-48; EX2029, ¶131.



EX1001, 51:22-48; EX2029, ¶131.

POSAs would have readily understood that the specific linker used in the example is illustrative, not limiting. EX2029, ¶131. Any linker bearing a suitable leaving group could have been substituted to generate a wide variety of A-L intermediates. *Id.* As was well-known, suitable leaving groups included halides, tosylates, protonated amines, and similar functionalities. EX1050, 169; EX1033, 136; EX2039, 5; EX2029, ¶131. The patent thus describes assembling not just a single A-L species, but a genus of A-L intermediates formed using standard chemistry. EX2029, ¶131.

The patent then teaches conjugating B to terminal functional groups on L using standard bioconjugation techniques, such as N-hydroxysuccinimide (NHS)-based chemistry. EX1001, 53:45-55:50; EX2029, ¶131; EX2051, Tables 3-9; EX2052, Abstract, Scheme 1. In this reaction, the terminal amine of the A-L intermediate forms an amide bond with B, displacing NHS as a leaving group, as shown below.



EX1001, 53:45-55:50; EX2029, ¶131.

POSAs would have immediately recognized that NHS chemistry would have been broadly applicable to a wide range of reporter groups and chelators. EX2029, ¶131. POSAs would have also understood that NHS chemistry would not have

been the only viable approach. EX2029, ¶131. Alternative, well-known conjugation strategies—such as aldehyde-amine coupling, Fmoc-based coupling, and so-called “click” chemistry—were all available and routinely used at the time. Hsieh, Abstract; EX1003, ¶63; EX2029, ¶131.

And the patent discloses a straightforward, modular synthetic strategy for assembling A. EX1001, 52:15-35; EX2029, ¶132. The specification shows the pyrrolidine ring of A is introduced as a discrete building block through a conventional peptide-coupling reaction using standard reagents. EX1001, 52:15-35; EX2029, ¶132. Because the pyrrolidine is incorporated as a single modular unit, POSAs would have immediately understood that one pyrrolidine derivative identified in the specification for use in the claimed B-L-A compounds could have been substituted for another without altering the overall synthetic scheme. EX2029, ¶132. By October 2017, chemical suppliers also offered thousands of pyrrolidine derivatives, including alkyl-substituted, halogenated, heteroaryl-substituted, and otherwise modified variants such that a POSA could have easily obtained or made any of the ~30,000 As that GE and Zeglis identify as making up the claimed genus. *See, e.g.*, EX2054, Abstract, 998-1000, FIGs. 1-26; EX2055, Abstract, Table 1, FIGs. 1-6; EX2056, Abstract, 876, Table 5; EX2050, Abstract, FIGs. 1-24; EX2044, 34, FIGs. 1, 4-5, 7; Pet., 112; EX1003, ¶94; EX2029, ¶132. Modification of such commercially available pyrrolidine groups to

make additional pyrrolidine compounds, moreover, would have involved standard, well-known synthetic methods. EX2029, ¶132; EX2054, Abstract, 998-1000, FIGs. 1-26; EX2055, Abstract, Table 1, FIGs. 1-6; EX2056, Abstract, 876, Table 5.

The foregoing is sufficient to supply written description for the claimed compounds. *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 729-30 (Fed. Cir. 2014) (finding written description where the specification provided the structure of the invention and the method of creating it). Thus, there is no need for the specification to provide any disclosure beyond that which it already provides. *Falko-Gunter*, 448 F.3d at 1367-68; *Capon*, 418 F.3d at 1358.

For the individual Bs and Ls—those that are suitable for imaging/radiotherapy and have bi-functionalization, respectively—the specification indisputably does “disclose a variety of species” of such Bs and Ls across several columns of the specification. EX1001, cols. 16-30; EX2029, ¶129. The specification also provides two examples that GE and Zeglis incorrectly decry as not being sufficient (*see* §IV.B.2.c.). EX1001, 51:5-61:62; Pet., 114; EX1003, ¶248; EX2029, ¶135. The specification here is thus in sharp contrast to the specifications at-issue in GE’s cited cases. *Cf. Ariad*, 598 F.3d at 1350 (relying on the specification’s failure to disclose “a variety of species that accomplish the result” for lack of written description).

GE and Zeglis improperly burden the inventors with describing known prior art concepts and fail to consider the disclosures in the specification and existing knowledge in the field of suitable As, Bs, and Ls. Indeed, Zeglis admitted when cross-examined that he faulted the specification because “many common prosthetic groups and many common chelators were not described.” EX2023, 54:21-55:1. This is improper. *Falko-Gunter*, 448 F.3d at 1367-68; *Capon*, 418 F.3d at 1358.

Zeglis also alleged that the specification provides “limited guidance” about chelator choices and chelator-radionuclide pairs. EX1003, ¶254; EX2029, ¶130. Yet, Zeglis rightly acknowledges that POSAs would have had at their disposal many well-known options. EX1003, ¶254; EX2029, ¶130. These examples included dozens of prosthetic groups, chelators, and metal-chelator pairs (EX1003, ¶¶254-256, 262) that need not be re-described and included as “unnecessary bulk [in] the specification.” *Falko-Gunter*, 448 F.3d at 1368; EX2029, ¶130.

**b. The specification adequately discloses the claimed invention through the structure and properties of A, B, and L and the B-L-A structure, such that POSAs could recognize the claimed genus.**

The specification and claims make clear that the invention is a genus of novel compounds having the common B-L-A structure. EX1001, 64:5-61; EX2029, ¶135. Zeglis, moreover, acknowledges that the claimed compounds have a common modular structure containing “three primary components:” “(a) a

*targeting moiety* [A] ... (b) a *reporter moiety* [B] ... and (c) a *linker* [L.]”

EX1003, ¶37; EX2029, ¶135.

The patent further provides the “structure” of the claimed As, provides exemplary As, and incorporates by reference publications disclosing numerous other As falling within the claims. EX1001, 8:25-33; EX2029, ¶129. The structure of A, therefore, is adequately described. *Ariad*, 598 F.3d at 1350 (“[A]dequate written description requires a precise definition, such as by structure ... of species falling within the genus sufficient to distinguish the genus from other materials.”).

For the recited B and L, the specification and claims make clear the “other properties” they should possess, *i.e.*, suitable for imaging/radiotherapy and having bifunctionalization, respectively. EX1001, 64:5-55; EX2029, ¶129; *Ariad*, 598 F.3d at 1350 (“[A]dequate written description requires a precise definition, such as by ... other properties[] of species falling within the genus sufficient to distinguish the genus from other materials.”). The specification then provides *dozens* of columns of exemplary Bs and Ls that can be used in making the claimed compounds. EX1001, cols. 8-32; EX2029, ¶129. The specification also incorporates by reference publications that provide even further examples of such Bs and Ls that can be used in the claimed invention. EX1001, 8:25-32, 17:46-55; EX2029, ¶129. Indeed, GE admits the specification contains these extensive disclosures, stating that the 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. As discussed above in §IV.B.2.a., in addition to disclosure in the specification, POSAs also would have been aware of other Bs that were known in the art, such that the specification need not repeat them unnecessarily. EX2029, ¶130.

The specification also discloses how to assemble the various Bs, Ls, and As in a common manner to yield the full B-L-A compound. §IV.C.1; EX2029, ¶¶131-132. Indeed, the patent discloses where to attach B to L and L to A using routine chemistry that would have been well known to POSAs before October 2017. §§IV.B.2.a, IV.C.1.; EX2029, ¶135.

POSAs, therefore, would have been able to recognize the various species making up the claimed genus and how they are combined because the specification (1) discloses and incorporates by reference the various structures of the species encompassed by A; (2) discloses and incorporates by reference the types of Bs and Ls that could be used in the claimed compounds, which also would have been known to POSAs from the art (§IV.B.2.a); and (3) discloses the routine and well-known chemistry for forming B-L-A compounds. EX2029, ¶¶129-135.

The patent’s disclosures thus “demonstrate that the inventors possessed the claimed invention,” FAP-radiotracers having the B-L-A structure and the various types of Bs, Ls, and As that can be combined to yield those compounds. *Alcon*

*Research Ltd. v. Barr Lab 'ys, Inc.*, 745 F.3d 1180, 1191 (Fed. Cir. 2014). “That is all the written description requirement demands.” *Id.*; *Ariad*, 598 F.3d at 1350; *GlaxoSmithKline*, 744 F.3d at 729-30.

**c. The patent discloses sufficient representative species of the claimed compounds.**

Faced with the patent’s extensive disclosure as to A, B, and L and how they can be combined to form B-L-A compounds, such that POSAs could recognize species of the claimed genus (§IV.B.2.c.), GE and Zeglis demand that the specification must provide a sufficient number of representative species of the combined B-L-A compounds that meet the unclaimed *in vivo* utility that it wrongly seeks to import into the claims. Pet., 107; EX1003, ¶275; EX2029, ¶¶125-128; EX2001, ¶¶81-93.

But, as discussed above in §III and the Board rightly found at institution, the claims are not functional. Paper 8, 34. And “[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). GE’s and Zeglis’s attempt to import *in vivo* functionality into the claims for their written description analysis should be rejected.

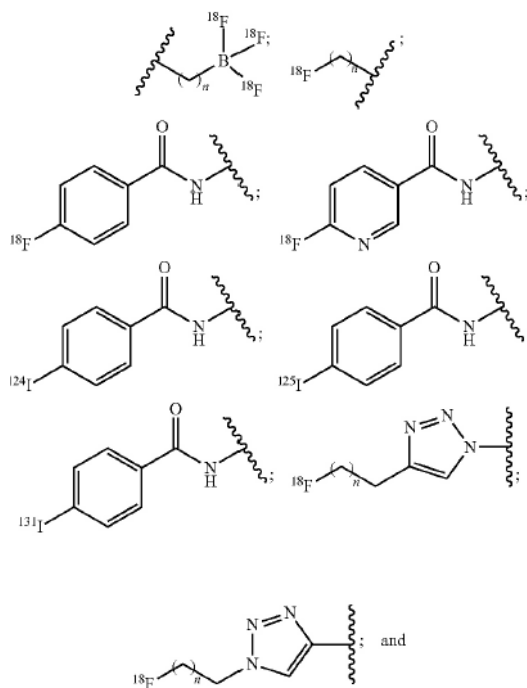
When the claims are viewed properly as structural, the two working examples in the specification represent the common modular structure containing

“three primary components:” “(a) a *targeting moiety* ... (b) a *reporter moiety* ... and (c) a *linker*” that Zeglis acknowledges. EX1003, ¶37; EX2029, ¶135. And the specification provides an extensive description on how to identify and combine A, B, and L into the novel B-L-A combination. EX1001, col. 8-20; §IV.B.2.a; EX2029, ¶135. Thus, the specification provides sufficient species representative of the claimed genus because the examples in the specification typify the fully combined B-L-A compound made using common chemistry that the specification discloses can be applied to various combinations of Bs, Ls, and As making up the full scope of B-L-A compounds. EX2029, ¶135; §IV.B.2.a.

**d. The patent adequately describes B-L-A compounds comprising a radiolabeled prosthetic group.**

GE and Zeglis also allege that the patent provides “no examples of B-L-A compounds with a radiolabeled prosthetic group,” when contending that there is a lack of representative species in the specification. EX1003, ¶252; Pet., 123; EX2029, ¶133. But adequate written description does not require examples of every conceivable embodiment. *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003) (“[O]ur case law makes clear, however, ‘an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention.’”); *Falko-Gunter*, 448 F.3d at 1366 (a “specification do[es] not [have to] contain examples explicitly covering the full scope of the claim language”).

The patent, nevertheless, does provide B-L-A compounds with a radiolabeled prosthetic group. EX1001, 18:35-70; EX2029, ¶133. In fact, Zeglis states that the specification discloses “six different chemical formulae” that provide radiolabeled prosthetic groups and “*ten* examples based on those formulae.” EX1003, ¶253; EX2029, ¶133. Each of those radiolabeled prosthetic groups, moreover, is illustrated in the specification with the L attachment point demarcated in the structures with a squiggly line, as shown below. EX1001, 18:35-70; EX2029, ¶133.



EX1001, 18:35-70.

Zeglis does not explain why this disclosure, when combined with the rest of the specification, is not sufficiently representative of B-L-A compounds with a

radiolabeled prosthetic group. EX2029, ¶134. POSAs would have read those disclosures and understood that the labeled attachment points are where each of the radiolabeled prosthetic groups could be attached to an L. *Id.* Similarly, the patent marks the intended attachment points of L and A to each other. *Id.*

As shown in §IV.B.2.a., Dr. VanBrocklin illustrated how POSAs would have known from the patent how to combine the various disclosures of radiolabeled prosthetic group Bs with Ls and As to yield a B-L-A compound comprising a radiolabeled prosthetic group. EX2029, ¶134. Consequently, POSAs would have understood from the individual disclosures of radiolabeled prosthetic Bs that the patent discloses compounds incorporating such groups. *Id.*

The Board thus should continue to reject GE's assertions of lack of written description based on any alleged lack of representative species in the specification.

**3. GE's reliance on *Fujikawa* is misplaced: the case is inapposite.**

GE erroneously relies on *Fujikawa v. Wattanasin*, 93 F.3d 1559 (Fed. Cir. 1996). 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 and whether the written description of the junior party's patent application provided support for a

subgenus of compounds having specific R-groups that the senior party sought to add to the count. 93 F.3d at 1569-1571.

The court found that the junior party's specification did not support the subgenus because the specification did not provide sufficient "blazemarks" that would have led POSAs to including a specific R-group in the claimed subgenus of compounds. *Id.* In so finding, the court 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.*

The findings in *Fujikawa*, however, are not relevant here because the claims do not require POSAs to be directed to a specific subgenus of B-L-A compounds. Rather, here, the specification (1) is replete with multiple types of As, Bs, and Ls that POSAs would have understood could be combined to yield ***the full genus of claimed compounds***; and (2) discloses two exemplary compounds that sufficiently represent the ***common modular structure of the claimed genus*** that is encompassed by the claims. §IV.C.2.c. This conveys possession of the claimed subject matter. *GlaxoSmithKline*, 744 F.3d at 730 ("Describing a complex of dutasteride and solvent molecules is an identification of 'structural features commonly possessed by members of the genus that distinguish them from others,' allowing one of skill in the art to 'visualize or recognize the identity of the members of the genus.'").

POSAs, therefore, would not be left with having to be directed to whether a specific B, L, or A is to be included in a specific subgenus, but rather the specification directs POSAs to the full scope of Bs, Ls, and As that can be combined to yield 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 to a genus that has the specific B-L-A structure.

**C. Ground IV: The Claims Are Enabled Because Undue Experimentation Would Not Be Required to Make and Use the Claimed Compounds.**

Enablement requires that a patent teach POSAs how to make and use the full scope of the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). “The key word is undue, ***not*** experimentation,” and enablement is not precluded by the necessity for some experimentation such as routine screening. *Id.* at 737 (quotations omitted). Moreover, “the specification must enable the full scope of the invention as defined by its claims.” *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023). In other words, the enablement inquiry is measured against the claims as written. *Id.*; *CFMT, Inc. v. Yieldup Int’l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003) (finding that the patent did not need to enable a specific level of contaminant removal where none was recited in the claims)

A specification, furthermore, does not have to “describe with particularity how to make and use every single embodiment within a claimed class,” rather “it

may suffice to give an example (or a few examples) if the specification also discloses ‘some general quality ... running through’ the class that gives it ‘a peculiar fitness for the particular purpose.’” *Amgen*, 598 U.S. at 610-11.

GE’s enablement challenge departs from that framework. Rather than assessing whether the patent teaches POSAs how to make and use the claimed B-L-A compounds that have no recited function, GE collapses the analysis into an outcome-driven inquiry: measuring enablement against unclaimed *in vivo* performance criteria—such as biodistribution, pharmacokinetics, and clinical efficacy. Pet., 107-108; EX1003, ¶¶59, 273-277; EX2001, ¶¶104-105; EX2029, ¶¶136-138. That approach is legally flawed. The claims are structural; they do not require *in vivo* diagnostic or therapeutic performance. §III; EX2029, ¶41-44. Enablement may not be predicated on functionality that the claims do not demand because “the specification must [only] enable the full scope of the invention as defined by its claims.” *Amgen*, 598 U.S. at 610-11. When the inquiry is conducted under the proper legal standard, GE’s challenge fails.

As set forth below, the patent provides a modular, reproducible synthetic route that enables POSAs to **make** the full scope of the claimed compounds using routine chemistry. See §IV.D.1; EX2029, ¶¶136-138. The patent also enables how to **use** those compounds, *e.g.*, in the *in vitro* applications disclosed in the specification, which GE did not address in its Petition. §IV.D.2.; EX2029, ¶164.

And “[t]he enablement requirement is met if the description enables any mode of making and using the claimed invention.” *CFMT*, 349 F.3d at 1338 (quotations omitted). Any additional effort to confirm operability across the structurally constrained claim scope when guided by the patent would have merely involved routine work and optimization, not undue experimentation. §§IV.C.1-IV.C.3; EX2029, ¶171.

As *Amgen* confirms, the time required to exhaust a claimed genus, standing alone, does not defeat enablement where the specification provides sufficient guidance to do so through routine, non-inventive experimentation. *Amgen*, 598 U.S. at 615. In other words, “enablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim.” *Id.* Nor does the Board’s preliminary observation that experimentation may be “substantial” alter that conclusion, where—by the Board’s own assessment—the experimentation would nonetheless be routine given the high level of skill in the art, and where the specification and the art would have provided sufficient guidance. Paper 8, 39; EX2029, ¶¶173-196.

Rather, as demonstrated below, the Board’s preliminary observation that experimentation may be “substantial” warrants reconsideration. Paper 8, 39.

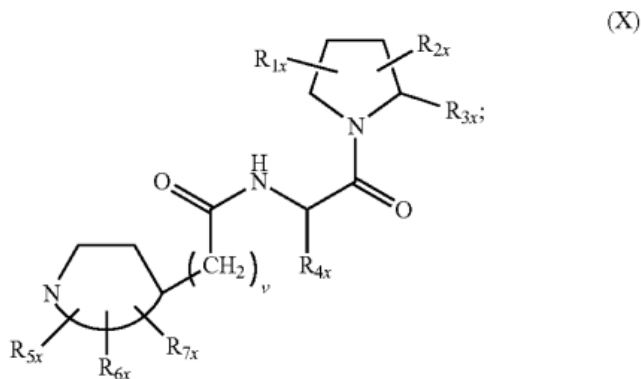
**1. The patent enables POSAs to make the claimed B-L-A compounds without undue experimentation.**

The enablement analysis begins with whether the specification teaches POSAs how to make the claimed invention. *Wands*, 858 F.2d at 736-37. Here, the answer is unequivocally yes. EX2029, ¶138.

**a. The patent discloses a well-established, modular synthetic method for assembling the claimed B-L-A compounds.**

The claims are directed to compounds having a common structural architecture: A chemically linked via L to B. EX1001, 64:5-61; EX2029, ¶139. And the specification provides detailed guidance for selecting each component and for how those components are combined to make the claimed B-L-A compounds. §IV.B.2.a; EX2029, ¶139.

First, the claims explicitly identify A by its structure, as depicted below.



EX1001, 64:6-47, COC; EX2001, ¶¶94-96; EX2029, ¶140.

Second, the specification discloses numerous exemplary Bs and Ls across multiple columns. EX1001, 18-20, 20:17, 55-65, 21:20, 9-11, 24:25, 19-25; *see*

*also* EX2001, ¶¶94-96, EX1003, ¶251. And, third, the specification further incorporates by reference multiple prior-art publications that disclose additional suitable As, Bs, and Ls, reinforcing the scope of enabling disclosure. EX1001, 20, 17:46-54; EX2001, ¶97.

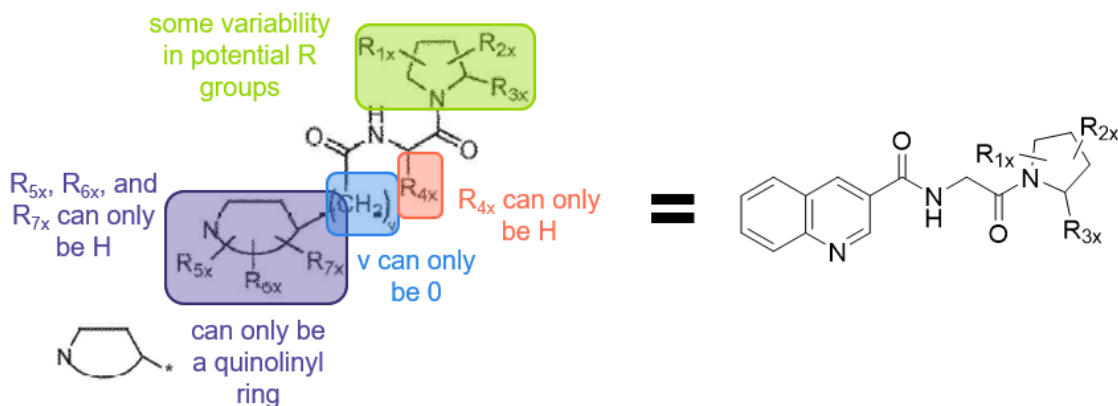
The patent, moreover, provides direction as to where and how L and B should be conjugated to A to preserve FAP-binding functionality, which would not have been predicted from the prior art's disclosures that structural modifications to quinolinyl-based FAPs could profoundly impair both FAP affinity and selectivity. *See* §§IV.A.1.d-IV.A.1.e, IV.A.3; EX2029, ¶¶140-144. The specification depicts that L should be conjugated to A using "any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle" of A. EX1001, 2:7-24, 10:16-30; EX2029, ¶141. The specification further directs POSAs to carbons 5 through 8 of the quinolinyl ring of A as sites for conjugating L. EX1001, 3:45-51; EX2029, ¶141. And the specification provides direction on how to conjugate L and B. EX1001, cols. 16-32; EX2029, ¶141-145.

Finally, POSAs would have understood that the chemistry required to assemble the claimed compounds would have been routine once armed with the patent's disclosures on how to specifically assemble B, L, and A. §IV.B.2.a; EX2029, ¶¶141, 143-149. Indeed, as discussed in §IV.B.2.a, the patent provides a blueprint for assembling B, L, and A that POSAs would have easily understood.

EX2029, ¶140. The patent, therefore, discloses a straightforward, modular synthetic method for assembling the claimed compounds. EX2029, ¶¶150-151.

**b. The scope of the claims would not have made it undue to make the claimed compounds.**

Nor does the scope of the claims render synthesis unduly burdensome. EX2029, ¶152. The variability in the claimed A is structurally constrained to defined substitutions on the pyrrolidine-ring of A, as shown below.



*Id.*

And, as discussed in §IV.B.2.a., the patent discloses a straightforward, modular synthetic strategy for assembling A that would have allowed POSAs to substitute for each other any of the ~30,000 As that GE and Zeglis identify as making up the claimed genus. EX1001, 52:15-35; EX2029, ¶¶140-141, 153-156.

Similarly, while the claims encompass multiple possible Bs and Ls, the patent provides explicit attachment guidance and reaction schemes, as discussed in §IV.B.2.a, that would have enabled POSAs to assemble the full range of claimed

B-L-A compounds without resorting to inventive skill or trial-and-error experimentation. EX2029, ¶¶143-147. POSAs, therefore, would have readily known that the specific Bs and Ls disclosed in the specification are illustrative rather than limiting and that structurally analogous linkers, leaving groups, and reporter moieties to those disclosed in the patent could have been substituted without altering the overall synthetic approach. *Id.*

Zeglis confirms this point. He acknowledges that assembling the claimed compounds would have involved “conventional chemical synthesis techniques well-known to skilled artisans” and that it would have been “straightforward” for POSAs to select appropriate Bs and Ls and synthesize the resulting compounds. EX1003, ¶¶121, 172; EX2029, ¶¶139, 156. Such admissions are fatal to any suggestion that undue experimentation would have been required merely to make the claimed invention. EX2029, ¶¶139, 156; *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1338-39 (Fed. Cir. 2013) (“[E]xtensive experimentation does not necessarily render the experiments unduly extensive where the experiments involve repetition of known or commonly used techniques.”).

In short, the patent provides more than sufficient guidance—through structural definitions, exemplary components, explicit reaction schemes, and incorporated prior art—to enable POSAs to make the full scope of B-L-A compounds using routine methods. EX2029, ¶¶139, 156.

**2. The patent enables POSAs to use the claimed compounds in *in vitro* applications without undue experimentation.**

The enablement inquiry next turns to whether the patent teaches POSAs how to use the claimed compounds. *Wands*, 858 F.2d at 736-37. It does. EX2029, ¶157.

Notably—and in contrast to GE’s and Zeglis’s arguments—the claims do not recite any requirement that the claimed B-L-A compounds achieve a particular diagnostic or therapeutic outcome, nor do they impose any requirement of *in vivo* efficacy, biodistribution, or pharmacokinetic performance. *See* §III; EX2001, ¶91; EX2029, ¶157. Instead, the patent discloses the compounds can be used in *in vitro* applications that simply require the claimed compounds to bind FAP when mixed with cells in “a culture dish or tube.” EX1001, 37:22-25; EX2029, ¶165.

Ultimately, the claims are structural, and enablement must be assessed against that backdrop and the utilities disclosed in the specification. *Amgen*, 598 U.S. at 610-11 (“[T]he specification must enable the full scope of the invention as defined by its claims.”); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 957 (Fed. Cir. 1983) (“That claims are interpreted in light of the specification does not mean that everything expressed in the specification must be read into all the claims.”).

Consistent with those principles, the patent expressly teaches that the claimed compounds may be used in *in vitro* contexts, including for detection, visualization, and analysis of FAP-expressing cells and tissues. EX2029, ¶157. The specification describes how the disclosed compounds can bind FAP and generate

detectable optical or radiolabel signals, enabling their use in laboratory-based assays, tissue analyses, and other non-*in vivo* applications. EX1001, 37:22-25; EX2029, ¶¶165, 169. Zeglis himself conceded at deposition that the claimed compounds could be used *in vitro*, in line with the patent’s disclosures. EX2023, 80:14-15 (“[o]ptical imaging agents can be useful in vivo or in vitro”).

Enabling just *in vitro* uses is sufficient to satisfy the “use” prong of §112(a), as they are practical uses for the claimed compounds, for example, in *in vitro* diagnostic and research applications (EX1001, 7:46-53, 35:47-52). *Raytheon*, 724 F.2d at 957; *Fujikawa*, 93 F.3d at 1563 (“[A] patent may not be granted to an invention unless substantial or practical utility for the invention has been discovered and disclosed.”); EX2029, ¶157.

**a. POSAs could have used the claimed compounds in *in vitro* applications without undue experimentation.**

The patent discloses how to deploy the claimed compounds *in vitro* using routine techniques well within the skill in the art when equipped with the specifications’ guidance, such as mixing the claimed compounds with cells in “a culture dish or tube” and then imaging the sample. EX1001, 37:22-25; EX2029, ¶165. GE and Dr. Zeglis did not address such uses, instead demanding *in vivo* utility. EX2029, ¶¶165-166.

Indeed, *in vitro* applications do not implicate aspects of *in vivo* applications that Zeglis focuses on, such as absorption, stability, and biodistribution of the

claimed compounds in the subject. EX2042, 512; EX1003, ¶¶277, 275, 59; EX2001, ¶108; EX2029, ¶¶166-168. While *in vitro* applications can involve the selectivity of the claimed compounds, compounds that are not highly selective can still have utility. EX2029, ¶168. For example, a diseased tissue sample, such as a biopsy, can be easily imaged *in vitro* with FAPi-based radiotracers having a range of selectivity not meeting Zeglis’s standards because there would be no concern that “the compound will bind to FAP on ... sites associated with healthy tissue” and lead to inappropriate radiotherapy, contrary to Zeglis’s arguments directed to *in vivo* uses. EX1003, ¶¶59, 275; EX2029, ¶¶167-168.

Rather than address the *in vitro* utility disclosed in the patent, GE and Zeglis focus their arguments on alleged uncertainty surrounding *in vivo* performance—such as how a compound might behave in a living organism, how long it might circulate, or whether it might achieve a desired imaging contrast in a clinical setting. Pet., 139-140; EX1003, ¶¶277, 275, 59; EX2001, ¶106; EX2029, ¶¶168-169. Those considerations are beside the point here.

The claims do not require *in vivo* administration or performance, and any alleged challenges associated with obtaining compounds for *in vivo* use cannot render the claims non-enabled. *Amgen*, 598 U.S. at 610-611. Enablement does not demand that POSAs be taught how to perfect or optimize an invention for unclaimed uses. *CFMT*, 349 F.3d at 1338; *Alcon*, 745 F.3d at 1189.

Any further experimentation to improve or tailor the claimed compounds beyond the properties needed for using them in *in vitro* applications (or even for *in vivo* use) represents **optimizing** the compounds to reach unclaimed uses. EX2029, ¶¶170-172. It would **not constitute undue experimentation**. *Id.*; *Alcon*, 745 F.3d at 1189. Indeed, Zeglis acknowledges that POSAs would have known that certain Ls and Bs would pose operability issues (albeit from his incorrect lens of requiring *in vivo* activity). EX1003, ¶¶280-286; EX2029, ¶171. But “if some of the claimed combinations [may be] inoperative, the claims are not necessarily invalid” for lack of enablement when POSAs can readily recognize them. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984); EX1003, ¶¶280-286; EX2029, ¶171.

Zeglis then identifies various cases for which POSAs purportedly “would have believed [they] would need to be tested to determine if the compound could be suitable in imaging or therapeutic uses” and “as FAP-targeting radiopharmaceuticals.” EX1003, ¶¶279-302; EX2001, ¶¶105-108; EX2029, ¶171. But again, Zeglis’s allegations regarding a need to test for “suitab[ility] in imaging or therapeutic uses” and “as FAP-targeting radiopharmaceuticals” are based on improperly imparting an *in vivo* utility requirement. EX1003, ¶¶279-302; EX2029, ¶171. Zeglis, thus, treats “utility” in his enablement analysis as requiring that essentially every B-L-A compound satisfy a detailed suite of pharmacological

performance metrics. EX1003, ¶¶279-302; EX2029, ¶171. Rather, when viewed in the proper context of the claimed compounds only having to achieve some amount of *in vitro* utility, determining what combinations of Bs, Ls, and As could be used only amounts to ***optimizing*** the claimed compounds for *in vitro* use, ***not trial-and-error testing***. EX2001, ¶106; EX2029, ¶171.

Ultimately, the law has long recognized that where, as is the case here, “the experiments involve repetition of known or commonly used techniques” to adjust variables, improve performance, or select among known alternatives there is no undue experimentation under §112(a). *Cephalon*, 707 F.3d at 1338-39; *Wands*, 858 F.2d at 736-37 (“Enablement is not precluded by the necessity for some experimentation such as routine screening.”); *Atlas Powder*, 750 F.2d at 1576-77 (claims enabled despite broad scope and presence of some inoperative embodiments); *Alcon*, 745 F.3d at 1189 (finding that optimizing stability of a claimed formulation did not rise to the level of undue experimentation).

Accordingly, the patent enables POSAs to use the claimed B-L-A compounds for *in vitro* applications without undue experimentation.

**b. The scope of the claims would not have required undue experimentation to use the claimed compounds in *in vitro* applications.**

As for the claims’ scope, the specification discloses the structure of As that target FAP, providing POSAs direction as to what FAPis would function in *in vitro*

contexts, where only direct incubation is needed. EX1001, 37:22-25; EX2029, ¶158. As discussed, the only varied structure within A is the pyrrolidine ring. §IV.C.1.b.; EX2029, ¶158. POSAs would have immediately understood that one pyrrolidine derivative could have been easily substituted for another falling within the claim scope based on the routine chemistry required and the SAR of the claimed FAPis in the prior art and incorporated by reference. *See* EX2054, Abstract, 998-1000, FIGs. 1-26; EX2055, Abstract, Table 1, FIGs. 1-6; EX2056, Abstract, 876, Table 5; EX2050, Abstract, FIGs. 1-24; EX2044, 34, FIGs. 1, 4-5, 7; EX2029, ¶158. GE and Zeglis, moreover, acknowledge the narrow nature of A, stating that it encompasses only ~30,000 compounds, far from being some large, unbounded claim scope given the routine chemistry employed here.<sup>4</sup> EX2029,

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<sup>4</sup> At institution the Board stated that the breadth of R<sub>3x</sub> in A rendered A's scope "voluminous." Paper 8, 39. Neither GE nor Zeglis have made such an assertion or sought to construe the scope of the R<sub>3x</sub> substituent in the Petition. In fact, GE and Zeglis have only alleged that R<sub>3x</sub> in claim 1 has 12 possible options. Pet., 109 (citing EX1003, ¶¶91-92). This proceeding should be limited to the bases for the Petition's Grounds. *Koninklijke Philips N.V. v. Google LLC*, 948 F.3d 1330, 1336 (Fed. Cir. 2020) (stating that the Board should not depart from Grounds advanced in the petition).

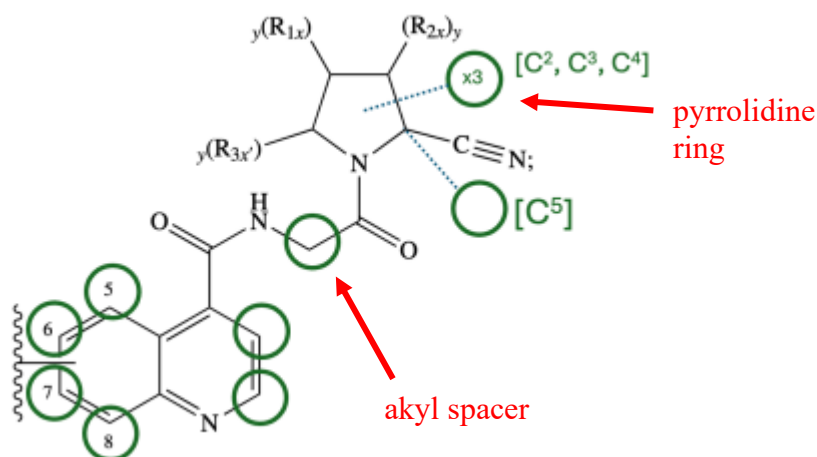
¶158. The patent also incorporates by reference publications disclosing numerous other FAPis falling within the scope of the claims that POSAs would have understood would similarly function in *in vitro* applications by the nature of their FAP-selectivity. EX1001, 8:25-33; EX2029, ¶156. And the patent and the prior art disclose numerous well-known linkers, chelators, dyes, and prosthetic groups, including many that GE and Zeglis identify as viable selections. Pet., 125-127; EX1003, ¶¶252-266; EX2029, ¶¶142-147, 159.

The '223 patent also provides direction on how and where to conjugate A with L and B, so as to not disrupt FAP-selectivity. §IV.C.1; EX2029, ¶159. The prior art, moreover, would have provided direction to a POSA through the SAR studies of Jansen 2013 and US-650 that disclosed where FAPis encompassed by A could be conjugated without disrupting FAP-selectivity. EX1007, Tables 2-3; EX2029, ¶159. Indeed, Zeglis acknowledges that SAR studies with Jansen's various FAPis provided information on where conjugating at certain locations (such as, in certain cases, the 5 position on the quinolinyl ring of A) or how changing A's substituents affected FAP-selectivity. EX1003, ¶¶178-179; EX2029, ¶159. Those same SAR studies from Jansen 2013 and US-650 are incorporated by reference into the patent. EX1001, 7:14-15, 8:26-29; EX2029, ¶159.

GE and Zeglis attempt to balloon the breadth of the claims with their combinatorial math by alleging that A has 11 possible points of attachment for L

and B. Pet., 111; EX1003, ¶93; EX2029, ¶160. But as discussed, the specification directs a POSA to attaching L and B to “any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle” of A. EX1001, 2:7-24, 10:16-30; *see also id.*, 3:45-51 (disclosing that carbons 5 through 8 of the quinoliny ring of the A as sites for conjugating L); EX2029, ¶160. Consistent with that express guidance, and with known SARs for FAPis in the prior art, POSAs would have understood that conjugation sites are constrained to positions expected to preserve FAP-binding, rather than every theoretically possible site on A. EX2029, ¶160.

GE and Zeglis attempt to dismiss this disclosure as being limited to only certain embodiments of the patent. Pet., 111; EX1003, ¶93; EX2029, ¶161. But based on the direction provided in the patent and known SARs for FAPis falling within the scope of A provided in the prior art, POSAs would not have been directed to conjugating A at the other places GE and Zeglis identify, i.e., the three locations on the pyrrolidine ring or the alkyl spacer between the carbonyl group and secondary amine close to the pyrrolidine ring, shown below with red arrows added to the figure provided by GE and Zeglis. EX2029, ¶161.



Pet., 111 (annotations in red added); EX1003, ¶93.

POSAs would have understood such conjugations would have likely rendered the resulting B-L-A unable to bind to FAP. EX2029, ¶162. And when POSAs can readily recognize inoperable embodiments, the claims remain enabled. *Atlas Powder*, 750 F.2d at 1577. In fact, POSAs would have understood from SAR studies that perturbations of the pyrrolidine ring of the claimed FAPis with bulky Ls and Bs would have been detrimental to FAP-selectivity. Indeed, the art disclosed that even minor modifications to the pyrrolidine, such as swapping out the cyano group for a hydrogen, boronic acid, or alkyl chloride, had a significant detrimental impact on FAP-selectivity. EX1006, Table 6; EX2029, ¶162. Likewise, POSAs would have understood that attaching bulky Ls and Bs close to the pyrrolidine ring via the alkyl spacer would also have led to detrimental effects on FAP-selectivity. EX2029, ¶162.

Zeglis, moreover, acknowledged at his deposition that POSAs would have wanted to conjugate B far enough from A in order to minimize the risk of interference between A and B. EX2023, 181:15-28 (acknowledging that one of the values of using a linker is to “to prevent the reporter moiety from interfering with the targeting moiety's ability to bind its target”). In other words, POSAs would not have wanted to risk rendering A inoperable. EX2023, 110:7-16 (“[I]t is desirable to have several possible sites on the targeting moiety that can serve as a point of attachment for the linker and radiolabeling moiety that are *far enough away* from the structural motif of the targeting moiety that interacts with the target on the targeted cells.”); EX2029, ¶163. And here, it was known in the art that the pyrrolidine ring of A was crucial for its FAP-targeting activity. EX1006, Table 6; EX2029, ¶163. Again, when POSAs can readily recognize inoperable embodiments, the claims remain enabled. *Atlas Powder*, 750 F.2d at 1577.

Accordingly, POSAs would have understood based on the specification and the art that there would be at most six possible sites for conjugating L and B to A, thus reducing the alleged claim scope GE and Zeglis put forth. EX2029, ¶164. Because the claimed compounds would not be plagued by bioavailability, *in vivo* stability, and biodistribution concerns, as GE and Zeglis improperly allege, it moreover would not have required undue experimentation for POSAs to select Bs

and Ls across the scope of the claims for use with A to make B-L-A compounds for *in vitro* use and to determine where to conjugate B and L. *Id.*

Finally, the specification discloses the general quality running through the class of claimed compounds that gives them the peculiar fitness for *in vitro* use: the disclosed B-L-A structure, with A being a specific group of FAPis where the only variation is in the pyrrolidine ring. That “general quality” in view of the direction provided in the patent provides enablement. *Amgen*, 598 U.S. at 610-11.

**c. The patent’s working examples and Pomper’s declaration further confirm enablement.**

Enablement is further reinforced by additional working examples disclosed during prosecution of the parent ’201 patent, as discussed in §IV.A.3. There, Pomper described at least 11 additional species that fall squarely within the scope of the claims and exhibit substantial diversity in both B and L. EX1002, 174-176; EX2029, ¶149. While Pomper prepared these compounds after the filing of the ’201 patent, they were made from the patent’s disclosures and illustrate enablement the patent as of the ’201 and ’233 patents’ earliest effective filing date of October 2017. *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1375 (Fed. Cir. 2017) (stating the post-filing art can be used to demonstrate “if the claims were enabled as of the priority date”); EX2029, ¶149. And there is no indication that anything beyond the patent’s disclosure and a POSA’s ordinary skill in 2017 would have been needed. *Id.*

As discussed, those 11 examples span a wide range of molecular weights and demonstrate variation in reporter function (e.g., radiohalogens, chelators, dyes), steric bulk, and functional group composition. §IV.A.3; EX2029, ¶150. And each of those species had excellent FAP-selectivity ranging from 407-11,893. §IV.A.3.; EX1002, 174-176; EX2029, ¶150.

Zeglis's failure to account for these examples further undermines his enablement critique. EX2029, ¶150.

**3. The *Wands* Factors confirm that the claims are enabled.**

The *Wands* Factors confirm what the foregoing analysis already demonstrates: POSAs could make and use the claimed B-L-A compounds without undue experimentation. *Wands*, 858 F.2d at 737. GE's and Zeglis's contrary position depends on importing unclaimed *in vivo* performance requirements into their analysis. Once that legal error is set aside, each *Wands* factor favors enablement.

**a. The quantity of experimentation would have been limited.**

As shown in §IV.B.2.a, the specification teaches how to synthesize the claimed compounds using conventional chemistry. EX2029, ¶173. POSAs armed with the specification and knowledge in the art would have been directed on where to conjugate B and L to A. §IV.C.1. The specification, moreover, teaches how to use those compounds for *in vitro* applications. See §IV.C.2.

At most, POSAs would have had to engage in ordinary selection among known Bs, Ls, and As disclosed by the patent and incorporated by reference—work that does not approach undue experimentation. EX2029, ¶174; *Cephalon*, 707 F.3d at 1338-39. Even on the Board’s preliminary view that substantial experimentation could be required given the claims’ breadth, the Board expressly recognized that, in light of the high level of skill in the art, such experimentation would have been routine. Paper 8, 39.

But, the fact that it may take time to evaluate multiple embodiments within a claimed genus does not itself render the claims non-enabled. The Supreme Court made this clear in *Amgen*: “[E]nablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim.” 598 U.S. at 610-11. Rather, the question is whether the disclosure provides sufficient guidance such that POSAs can identify workable embodiments through routine experimentation. *Id.* Indeed, “the focus ‘is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine.’” *Cephalon*, 707 F.3d at 1338-39. Here, any time required to traverse the claimed B-L-A genus reflects routine selection guided by the specification’s teachings—not undue experimentation. EX2029, ¶174-175.

This factor weighs in favor of enablement. *Id.*

**b. The amount of guidance presented in the patent supports enablement.**

The patent provides extensive guidance, including structural definitions of A, numerous exemplary Bs and Ls, explicit conjugation strategies, reaction schemes, and incorporated prior-art references. §§IV.C.1-IV.C.2. That guidance enables POSAs to practice the full scope of the claims without undue experimentation. EX2001, ¶¶94-101; EX2029, ¶¶176-177.

This factor weighs in favor of enablement. EX2029, ¶177.

**c. The working examples in the patent support enablement.**

The specification includes working examples demonstrating synthesis of representative B-L-A compounds and their interaction with FAP. EX1001, 50:35-61:23; EX2029, ¶178. Consistent with settled law, the specification need not disclose every species within the claimed genus where, as here, it teaches a generalizable approach that POSAs can apply across the claim scope using routine techniques. EX2029, ¶¶178-179; *Cordis Corp.*, 339 F.3d at 1365; *Falko-Gunter*, 448 F.3d at 1366.

This factor weighs in favor of enablement. EX2029, ¶179.

**d. The nature of the invention is directed to B-L-A compounds having utility *in vitro*.**

The claims are directed to chemical compounds. EX1001, 64:5-61, COC; EX2029, ¶180. They do not require achievement of any therapeutic or diagnostic

outcome. EX1001, 64:5-61, COC; 34:63-35:3, 35:47-52; EX2001, 104-105; EX2029, ¶180. And as discussed in §IV.D.2, they can be predictably implemented *in vitro*. EX2001, ¶¶105-108; EX2029, ¶¶180-181.

This factor weighs in favor of enablement. EX2029, ¶181.

**e. The state of the prior art supports enablement.**

At the relevant priority date, the underlying chemistry and assay techniques were well developed. §IV.D.1; EX2029, ¶182. Bioconjugation methods, linker chemistry, reporters, and FAP-binding scaffolds were all familiar tools in the art. §IV.D.1; EX2029, ¶182. The specification builds on—and expressly incorporates—this established knowledge to provide direction on how to assemble the claimed compounds, reducing any need for undue experimentation. §IV.D.1; EX2029, ¶¶182-183.

This factor weighs in favor of enablement. EX2029, ¶183.

**f. GE and Zeglis do not dispute the high level of skill in the art.**

POSAs in this field would have possessed substantial training and experience in organic and medicinal chemistry and molecular imaging. EX2001, ¶29. Such artisans would have been well equipped to synthesize the claimed compounds and employ *in vitro* without difficulty, and GE and Zeglis have not disputed this point. Pet., 16; EX1003, ¶¶121, 172; EX2029, ¶¶184-185.

This factor weighs in favor of enablement. EX2029, ¶185.

**g. Predictability of the art in using the claimed compounds *in vitro*, in view of the guidance in the specification, supports enablement.**

While *in vivo* performance can involve biological variability, the relevant inquiry concerns predictability for making the compounds and using them *in vitro*—contexts in which outcomes would have been substantially more predictable and well understood. EX2029, ¶186.

Both the specification and the art provided sufficient direction for POSAs to choose an A that would have bound FAP and assemble it into a B-L-A structure so as to maintain activity. §§IV.D.1-IV.C.2; EX2029, ¶187. In fact, as discussed, Pomper’s declaration provides multiple B-L-A compounds demonstrating variation in reporter function (e.g., radiohalogens, chelators, dyes), steric bulk, and functional group composition that each had excellent FAP-selectivity when tested *in vitro*. See §IV.D.2.a; EX2029, ¶187.

GE and Zeglis’s allegations of unpredictability also relate to *in vivo* performance. §§III, IV.C.1, IV.C.2; EX2029, ¶188. GE and Zeglis allege that it would have been unpredictable which compounds would function as “viable diagnostic or imaging candidates.” Pet., 137-139; EX1003, ¶276; EX2029, ¶188. And GE points to Pomper’s statement in his declaration that ““the art of developing a medical imaging agent is highly unpredictable.”” Pet., 136 (emphasis removed) (quoting EX1002, 172); EX2029, ¶188. But in discussing unpredictability, Pomper

referred to “biodistribution,” an *in vivo* constraint. EX1002, 172 (¶31); EX2029, ¶188. Both Zeglis and Pomper, therefore, have based their discussions of unpredictability on *in vivo* functionality. EX2029, ¶188. The claims, however, need only meet *in vitro* utility, which GE and Zeglis have not addressed, not the compounds’ possible *in vivo* uses. *Raytheon*, 724 F.2d at 957. Zeglis agreed with this point on cross-examination. EX2023, 80:9-15.

To the extent GE and Zeglis point to Meletta’s failure as evidence of the necessity for more selective FAPis in *in vitro* applications, the claimed invention solved Meletta’s issues. EX2029, ¶189. As discussed, the specification discloses a genus of As selective for FAP, which when conjugated to B and L, as guided by the specification, retain unexpectedly improved FAP-selectivity. §IV.D.2.a; EX2029, ¶189. Accordingly, the patent provides sufficient direction to negate any alleged unpredictability in the art regarding *in vitro* use of the claimed compounds. EX2029, ¶189.

This factor weighs in favor of enablement. EX2029, ¶190.

**h. The breadth of the claims does not weigh against a finding of enablement given the *in vitro* utility of the claimed compounds.**

Although the claims encompass a genus of B-L-A compounds, that breadth is cabined by explicit structural constraints and guidance in the specification.

Traversing the claim scope would have required only routine experimentation, not undue experimentation, as discussed in §§IV.D.1-IV.C.2; EX2029, ¶191.

As discussed in §IV.D.1.b, the scope of A would not have led to undue experimentation. EX2029, ¶191. The patent discloses a straightforward, modular synthetic strategy for assembling A by easily swapping in one pyrrolidine derivative for another. EX1001, 52:15-35; EX2029, ¶191. The specification describes exemplary As and explicitly teaches that substitutions on the pyrrolidine ring that are within the scope of the invention. EX1001, 12:55-14:15; EX2029, ¶191. POSAs would have understood those teachings as affirmatively providing guidance for using the full scope of pyrrolidine-based variants without undue experimentation. §§IV.D.1-IV.C.2; EX2029, ¶191.

While B and L are not structurally constrained, as discussed, POSAs would have understood how to conjugate B and L to A in view of the specification's guidance and known FAPi SARs. §IV.D.2; EX2029, ¶192. Pomper's declaration's data exemplify that various types of Bs and Ls could be employed without negatively affecting A's FAP-selectivity. *See* §IV.C.2.a; EX2029, ¶192.

To the extent the number of compounds falling within the scope of the claims is considered, given the straightforward and routine nature of making the claimed compounds with the specification in hand and the predictability of their use *in vitro*, it would not have been undue to make and use compounds across the

full scope of the claims. EX2029, ¶193. The amount of time required to exhaust a claimed genus, standing alone, moreover, does not defeat enablement where the specification provides sufficient guidance to do so through routine experimentation. *Amgen*, 598 U.S. at 615 (“[W]e agree with Amgen that enablement is not measured against the cumulative time and effort it takes to make every embodiment within a claim”).

In light of the foregoing, the Board’s preliminary observation that experimentation may be “substantial” warrants reconsideration. Paper 8, 39; EX2029, ¶195.

This factor weighs in favor of enablement. EX2029, ¶195.

\* \* \*

Considering the Wands factors as a whole—and in light of the proper claim-focused inquiry—GE has not shown that practicing the claims would have required undue experimentation. To the contrary, weighing the *Wands* factors confirms that the ’233 patent satisfies the enablement requirement. §§IV.D.3.a-IV.C.3.h; EX2029, ¶¶194-195.

#### **4. *Alcon* confirms enablement of the claims.**

Federal Circuit precedent independently confirms that GE’s enablement challenge fails as a matter of law. In *Alcon*, the court addressed an enablement challenge closely analogous to GE’s theory here: claims directed to a broad genus,

where practicing the full scope required selecting among numerous options and adjusting variables to achieve preferred performance characteristics. 745 F.3d at 1188-90.

In *Alcon*, the claims recited a method of enhancing the chemical stability of a composition comprising a prostaglandin by adding a chemically stabilizing amount of polyethoxylated castor oil (“PECO”) to the composition. *Id.* at 1184. The defendant argued that the claims were not enabled because the specification allegedly did not teach which embodiments across the claimed ranges would achieve optimal results. *Id.* at 1188-90.

The court squarely rejected that premise, explaining that enablement does not require a specification to identify which embodiments are best, nor does it require the patentee to eliminate the need for routine experimentation to select among workable options within the claimed scope. *Id.* Instead, enablement is satisfied where the disclosure teaches POSAs how to make and use the claimed compositions, and any remaining work consists of routine screening, adjustment, or optimization. *Id.*

In reaching its decision, the court found that the claims merely required adding a PECO to the composition to provide some increase chemical stability, but not at any particular level or magnitude. *Id.* at 1189. It further found that the patent disclosed numerous prostaglandins and PECOs that could be used in the claimed

invention. *Id.* And it found the three working examples using only one prostaglandin and two PECO's were sufficient, even in view of the broad claim scope, because they detailed step-by-step how to prepare claimed compositions from commercially available ingredients. *Id.*

The court further emphasized that the presence of broad ranges for the composition's components and numerous possible embodiments does not itself render claims non-enabled. *Id.* Rather, the proper question is whether POSAs, armed with the disclosure and the knowledge in the art, could practice the claimed invention without undue experimentation. *Id.* at 1188. And under the case's facts, the court concluded the experimentation was guided, predictable, and within the ordinary skill of the art, making it not undue. *Id.* at 1189-90.

That reasoning applies with full force here. As §§IV.C.1-IV.C.2 explain, the patent teaches POSAs how to make the claimed B-L-A compounds using a modular, reproducible synthetic strategy and how to use those compounds *in vitro*. EX2029, ¶¶151-153, 172. GE's criticism—that additional experimentation would be required to identify compounds with preferred *in vivo* characteristics, when the patent's disclosed *in vitro* applications only need to be met—mirrors the unsuccessful argument rejected in *Alcon*. 745 F.3d at 1188-90. Any such efforts concern refinement and preference, not whether the claimed invention can be made

and used at all across its scope. The same reasoning applies to any argument that the claimed compounds need to be optimized for *in vitro* applications. *Id.*

As in *Alcon*, the challenged claims here do not require achievement of any particular level of performance. EX1001, 64:5-62; EX2029, ¶137. They do not demand a specific imaging contrast, biodistribution profile, pharmacokinetic behavior, or therapeutic effect. EX1001, 64:5-62; EX2029, ¶137. Where claims are satisfied once POSAs can make the claimed compositions and use them for at least one disclosed utility, the fact that some embodiments may perform better than others—or that additional work could improve performance—does not render the claims non-enabled. *Alcon*, 745 F.3d at 1189.

GE's enablement theory thus fails for the same reason rejected in *Alcon*. *Id.* at 1189-90.

**5. The scope of A in claims 2-4 also supports enablement.**

GE and Zeglis allege that claim 2 encompasses 528 As and claims 3 and 4 encompass 44 As. Pet., 112; EX1003, ¶94; EX2029, ¶196. To the extent the Board's enablement concerns are focused on A's scope, these claims significantly narrow the scope of A compared to claim 1 and thus mitigate any purported concerns about variations in A leading to unpredictability. EX2029, ¶196.

The Board should confirm enablement for claims 2-4.

**V. CONCLUSION**

The Board should maintain the Challenged Claims.

Respectfully submitted,

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