

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GE HEALTHCARE LTD.,
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner

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

**DECLARATION OF HENRY F. VANBROCKLIN, PH.D. IN SUPPORT OF
PATENT OWNER RESPONSE**

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Johns Hopkins University EX2029
GE Healthcare v. Johns Hopkins
PGR2025-00059

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I, Henry F. VanBrocklin, Ph.D., hereby declare as follows.

I. INTRODUCTION

1. I am the same Henry VanBrocklin that submitted a declaration dated October 22, 2025 (EX2001), in support of Patent Owner The Johns Hopkins University's ("Patent Owner") Preliminary Response for the above-captioned post-grant review (PGR) proceeding. The opinions I expressed in my first Declaration remain unchanged and I stand by them.

2. I am being compensated for my time in connection with this PGR at my standard consulting rate, which is \$350.00 per hour.

3. I understand that this Declaration accompanies the Patent Owner Response (POR).

4. In preparing this Declaration, I have reviewed U.S. Patent No. 12,115,233 ("the '233 patent") and each of the documents cited herein, in light of general knowledge in the art as of the timeframes discussed herein. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art. In formulating my opinions, I have also considered the viewpoint of a person of ordinary skill in the art ("POSA"), which I defined in my first declaration, prior to October 23, 2017. *See, e.g.*, EX2001, ¶2.

II. MY BACKGROUND AND QUALIFICATIONS

5. I am a Professor in Residence in the Department of Radiology and

Biomedical Imaging at the School of Medicine at the University of California, San Francisco (UCSF). I hold a Ph.D. in Radiopharmaceutical Chemistry from Washington University in St. Louis, where I also obtained an M.A. in Nuclear Chemistry. I also hold an M.S. in Nuclear Chemistry from Rensselaer Polytechnic Institute, where I also obtained a B.S. in Chemistry. I am currently a member of the American Chemical Society, including the divisions of Organic Chemistry, Medicinal Chemistry, and Nuclear Science and Technology. My other active professional memberships include the Society of Nuclear Medicine and Molecular Imaging, wherein I was elected Fellow in 2018 and served as President of the Molecular Imaging Center of Excellence from 2008–2010, and I currently serve as Chair of the Publications Committee; and the Society of Radiopharmaceutical Sciences, wherein I was elected Fellow in 2021 and I served as president from 2015–2017, and currently serve as Historian. I was the Editor-in-Chief for the academic journal *Molecular Imaging* from 2011–2025.

6. I have extensive experience in the fields of molecular imaging, radiopharmaceutical chemistry, positron emission tomography, single photon emission computed tomography, oncologic radiotracers, proteases, steroids, prostate-specific membrane antigen (PSMA), imaging in drug development, radiometal chemistry/labeling, radiopharmaceutical therapy, and theranostics.

7. In 1984, I obtained a B.S. in Chemistry from Rensselaer Polytechnic

Institute, from where I graduated *cum laude*. Subsequently, I obtained an M.S. in Nuclear Chemistry from Rensselaer Polytechnic Institute in 1986, followed by an M.A. in Nuclear Chemistry from Washington University in St. Louis in 1988, after which I completed my Ph.D. in Radiopharmaceutical Chemistry, also from Washington University in St. Louis, in 1990. During my Ph.D., I studied the synthesis and biological evaluation of fluorine-18 labeled estrogens and progestins as positron emission tomography radiotracers.

8. After obtaining my doctoral degree, I studied as a postdoctoral fellow at the University of Illinois, Urbana-Champaign under the prestigious Alexander Hollaender Fellowship, awarded by the U.S. Department of Energy, from 1990–1992. As a postdoctoral fellow, I developed positron-labeled estrogens, progestins, and androgens for tumor imaging for detection of breast and prostate cancer.

9. From 1992–2005, I worked as a Staff Scientist and Radiopharmaceutical Chemistry Group Leader at Lawrence Berkeley National Laboratory in the Department of Functional Imaging. During this time period, I was also an Assistant Adjunct Professor of Radiology at UCSF. In 2005, I was promoted to my current role, Professor in Residence and Director of Radiopharmaceutical Research at UCSF. I concurrently hold the position of joint faculty member at Lawrence Berkeley National Laboratory.

10. Over the course of my career, I have received a variety of prizes and

awards. At Lawrence Berkeley National Lab, I received the Lawrence Berkeley National Laboratory Outstanding Performance Award four separate times. At UCSF, I was awarded the MSBI Outstanding Teacher Award three times (2019, 2021, 2023). I received the Society of Nuclear Medicine President's Distinguished Service Award twice (2006, 2010). I was selected as a Research Distinguished Investigator of the Academy for Radiology & Biomedical Imaging (2018). I have also been elected Fellow to both the Society of Nuclear Medicine and Molecular Imaging (2019) and the Society of Radiopharmaceutical Sciences (2021). I received the Michael J. Welch Award (2020), the Paul C. Abersold award (2023) from the Society of Nuclear Medicine and Molecular Imaging, and the Glenn T. Seaborg Award (2026) in Nuclear Chemistry from the American Chemical Society.

11. At UCSF, my research focuses include radioactive radiotracers, radiopharmaceuticals, and the use of such agents for the evaluation and interrogation of a variety of diseases, as well as normal physiologic and metabolic processes. I develop new radiotracers radiolabeled with a variety of isotopes and study their properties *in vitro* and in small animal models. Some examples of this *in vitro* work include a report on the evaluation of labeled estrogens for imaging breast cancer, and a report on screening tyrosine kinase inhibitors for tumor imaging. I also develop radiopharmaceuticals past the laboratory bench for use in

human research studies, working closely with clinical colleagues to navigate the regulatory pathway, FDA, radiation safety committee, and IRB.

12. My research has led to over 150 peer-reviewed research publications, 7 book chapters, and 11 filed patent applications, of which the vast majority relate directly to radiotherapeutics or imaging. As shown in my CV (EX2002), my publications on these topics include:

- “Structure-activity relationship of ^{18}F -labeled phosphoramidate peptidomimetic PSMA-targeted inhibitor analogues for PET imaging of prostate cancer,” *Journal of Medicinal Chemistry* 2016;
- “An Improved Radiosynthesis of $[^{18}\text{F}]$ O-(2-Fluoroethyl)-O-(p-nitrophenyl)methylphosphonate: A First-in-Class Cholinesterase PET Tracer,” *Journal of Labelled Compounds and Radiopharmaceuticals* 2017;
- “In vivo PET imaging of the activated immune environment in a small animal model of inflammatory arthritis,” *Molecular Imaging* 2017;
- “Biodistribution of a Mitochondrial Metabolic Tracer, $[^{18}\text{F}]$ F-AraG, in Healthy Volunteers,” *Molecular Imaging* 2022;
- “Evaluation of $^{134}\text{Ce}/^{134}\text{La}$ as a PET Imaging Theranostic Pair for ^{225}Ac α -Radiotherapeutics,” *Journal of Nuclear Medicine* 2023;
- “CD46-Targeted Theranostics for Positron Emission Tomography and ^{225}Ac -Radiopharmaceutical Therapy of Multiple Myeloma,” *Clinical Cancer*

Research 2024;

- “Prostate Specific Membrane Antigen Targeted StarPEG Nanocarrier for Imaging and Therapy of Prostate Cancer,” *Advanced Healthcare Materials* 2024;

- “Actinium-225 targeted alpha-particle therapy for prostate cancer,”

Theranostics 2024;

- “Effective treatment of prostate cancer micrometastases using CD46-targeted ²²⁵Ac therapy,” *Clinical Cancer Research* 2025; and
- the book chapter “Positron Emission Tomography Radiochemistry,” in *Molecular Imaging: Principles and Practice* (2020).

13. Over my career in the field, I have obtained over \$100 million in grants to study radioligands, radiotherapeutics, or imaging, including from the National Institutes of Health, the U.S. Department of Energy, the U.S. Department of Defense and several foundations, including the Michael J. Fox Foundation, the PolyBio Research Foundation, and the Alzheimer’s Drug Discovery Foundation. At UCSF, I have directly mentored or served as research advisor for at least 15 early-career faculty, 33 postdoctoral fellows, and 51 pre-doctoral students.

14. In addition to my prior duties as Editor-in-Chief of *Molecular Imaging*, I frequently perform peer review for academic journals, including as an Editorial Advisory Board member of *Current Molecular Imaging* (2013–2016),

Assay and Drug Development Technologies (2012–present), and *Current Medicinal Chemistry* (2010–2018), as well as an Editorial Board member of *Reports in Medical Imaging* (2008–2015), *Letters in Drug Design and Discovery* (2002–2015), and *Nuclear Medicine and Biology* (2001–2012). I also perform peer review on an *ad hoc* basis for a variety of journals, including *Science*, *Proceedings of the National Academy of Science (USA)*, *Frontiers in Nuclear Medicine*, the *Journal of Nuclear Medicine*, the *Journal of Labelled Compounds and Radiopharmaceuticals*, *Cancer Research*, and *Molecular Imaging and Biology*. I also have served as a peer-reviewer for grants submitted to the National Institutes of Health (NIH), the US Department of Energy (DOE), the Congressionally Directed Medical Research Programs (US Department of Defense) and the Cancer Prevention and Research Institute of Texas (CPRIT), among other domestic and international organizations.

15. In addition to my educational training and my professional and research experience, I have kept abreast of the fields of molecular imaging, radiopharmaceutical chemistry, positron emission tomography, single photon emission computed tomography, oncologic imaging agents, proteases, steroids, (PSMA), imaging in drug development, radiometal chemistry, radiopharmaceutical therapy, and theranostics by reading scientific literature, conferring with colleagues in the field, and attending and presenting lectures at scientific conferences. I have

spoken at over 100 national or international conferences on topics including radiopharmaceuticals, imaging, biomarkers, PSMA, radiometals, drug design, and radiochemistry, and given over 30 invited lectures on the same. I have also regularly taught undergraduate and graduate courses since 2003, most recently, the course “Imaging Probes for Nuclear and Optical Imaging” every year since 2011.

III. SUMMARY OF OPINIONS

16. I have been asked to consider whether Dr. Zeglis’s asserted prior art (Ground 1: US-633, Jansen, and Meletta; and Ground 2: US-121 and Jansen) would have rendered claims 1–4 of the ’233 patent obvious to a person of ordinary skill in the art. In my opinion, in view of the state of the art before October 23, 2017, a POSA would not have found the challenged claims obvious over the prior art.

17. Based on my review of US-633, Jansen, and Meletta and my experience in radiopharmaceutical chemistry and molecular imaging, it is my opinion that claims 1–4 of the ’233 patent would not have been obvious to a person of ordinary skill in the art before October 23, 2017¹ over US-633, Jansen, and Meletta (Ground 1). *See* § VII, *see also* EX2001, ¶¶21-24. When the prior art is

¹ Throughout this declaration, I use the phrase “October 2017” as shorthand for the date “October 23, 2017.”

considered as a whole, it does not point a POSA toward the claimed B-L-A compounds or provide a reasonable expectation of success in arriving at such compounds. Instead, the art reflects multiple divergent and competing approaches to FAP imaging, without identifying a clear or directed path leading to the claimed invention.

18. Before 2017, a person of ordinary skill in the art seeking to develop a FAP-targeting imaging agent, or “radiotracer,”² would have been confronted with multiple fundamentally different strategies employing different targeting moieties (also called “pharmacophores”), including antibodies, antibody fragments, peptides, oligonucleotides, and small molecule inhibitors. EX2033, Abstract, 731, FIG. 1; EX2031, Abstract, 1202; EX2030, Abstract, 1639–1640, FIGs. 1–2; EX2028, Abstract, 6214–6217, FIGs. 1 and 4; EX2035, Abstract, 8–9, FIGs. 1–2; EX2036, Abstract, 5–8, FIG. 3; EX2037, Abstract, 491–493, 495, FIG. 1; EX2038, Abstract. The literature repeatedly emphasized antibodies, antibody-derived constructs, fusion proteins, and peptides as viable—and often advantageous—approaches, particularly in view of selectivity concerns and the limited success of early small molecule FAP imaging efforts. EX1008, Abstract, 2888–2890;

² Throughout this declaration, I use the terms “imaging agent” and “radiotracer” interchangeably.

EX2033, Abstract, 731, FIG. 1; EX2031, Abstract, 1202; EX2030, Abstract, 1639–1640, FIGs. 1–2; EX2028, Abstract, 6214–6217, FIGs. 1 and 4; EX2035, Abstract, 8–9, FIGs. 1–2; EX2036, Abstract, 5–8, FIG. 3; EX2037, Abstract, 491–493, 495, FIG. 1; EX2038, Abstract. Nothing in the prior art suggested that a POSA would have focused primarily, let alone exclusively, on developing small molecule, low-molecular-weight FAP radiotracers.

19. Even assuming that a POSA elected to pursue a small molecule FAP radiotracer, the prior art disclosed a broad and structurally diverse universe of FAP-binding pharmacophores (called FAP inhibitors or FAPis) across multiple scaffolds. Many of those FAPis exhibited affinity³ and selectivity⁴—the very two

³ Affinity is a measure of how tightly a given molecule (here, a FAPi) binds to its target protein/enzyme (here, FAP), and is measured using the term half maximal inhibitory concentration, or IC₅₀. EX1004, ¶185. Lower IC₅₀ numbers signify better binding to the target and signify a more potent targeting moiety. EX1004, ¶185.

⁴ Selectivity is calculated as a ratio of the affinity (IC₅₀) of the FAPi for FAP versus PREP or DPP^{IV}. EX1044, Table 3, ¶¶631–633. A higher FAP/PREP or FAP/DPP^{IV} selectivity indices signify reduced off-target binding, potentially

factors Dr. Zeglis characterizes as “paramount” in selecting a pharmacophore for a radiotracer—equal to or better than the compound Dr. Zeglis selected: Jansen’s Compound 60. *See* Section VII.C *infra*; *see also* EX1003, ¶55; EX2001, ¶¶22, 24. The most selective and highest-affinity FAP inhibitors disclosed in the literature, if chosen by a POSA, would have fallen outside the scope of the claimed “A” moiety. *See* Section VII.C *infra*. Although Dr. Zeglis focused his analysis on Jansen’s Compound 60 as the compound a POSA purportedly would have selected for use in a low molecular weight FAP radiotracer, the prior art does not support a POSA’s choice of that compound over the many available alternatives that were equal or superior in performance. Section VII.C.

20. In addition, even after selecting a particular FAP-targeting moiety as the pharmacophore, a POSA would have faced multiple independent choices regarding how to label that moiety for imaging or therapeutic use. The prior art disclosed a range of labeling strategies, including direct halogenation, attachment of metal-binding chelators, and use of prosthetic groups. *See* Section VII.B *infra*. The literature also described numerous metallic and non-metallic radionuclides (a required component of a radiopharmaceutical, as it provides the radioactive signal

resulting in lower side-effects for a drug or higher resolution for an imaging agent. EX2004, 11; EX1007, 491–492; EX1044, ¶4.

necessary for imaging), each associated with different chemical and biological tradeoffs. Section VII.B. These additional layers of design choice further demonstrate that the prior art did not point a POSA toward a single, predictable path leading to the claimed B-L-A compounds.

21. Moreover, the prior art did not direct a POSA to further modify a selected FAP inhibitor by adding both a linker and a bulky reporter moiety, as required by the claimed B-L-A structure. To the contrary, the literature emphasized labeling strategies that minimized structural perturbation—such as direct halogenation—and cautioned that even small structural changes could adversely affect binding affinity and selectivity. *See* Section VII *infra*; *see also* EX2001, ¶23. And in constructing hypothetical B-L-A compounds that Dr. Zeglis said a POSA would have been motivated to do, Dr. Zeglis failed to show that a POSA would have selected the particular linker (“L” in the claimed “B-L-A” compound)—a three-monomer polyethylene glycol (PEG)—from the prior art to add to Compound 60 (“A” in the claimed “B-L-A” compound), thus failing to show that a POSA would have arrived at the claimed “B-L-A” compounds. *See* EX2001, ¶23.

22. Critically, the only pre-2017 small molecule FAP radiotracer specifically evaluated for selectivity—a directly radiohalogenated compound derived from US-633 that deliberately avoided bulky linker-connected groups—failed when evaluated *in vitro*, as it showed no meaningful ability to distinguish

FAP-expressing tissue from normal tissue. EX1008, 2089. In other words, the only small molecule FAP radiotracer in the prior art that was actually tested for selectivity failed outright, leaving the field without a successful precedent and providing no reasonable expectation of success for the claimed B-L-A compounds.

23. Further, based on my review of US-121 and Jansen and my experience in radiopharmaceutical chemistry and molecular imaging, it is my opinion that claims 1–4 of the '233 patent would not have been obvious to a person of ordinary skill in the art as of October 23, 2017 over US-121 and Jansen (Ground 2). *See* §VIII, *see also* EX2001, ¶25. US-121 adds nothing to the selection of the “A” moiety from the myriad choices for FAP-targeting radiotracers discussed above, as it does not concern FAP-targeting compounds at all—a point Dr. Zeglis himself acknowledges. EX1003, ¶233. Further, this combination of references similarly fails to guide a POSA to the claimed invention, and does not provide a POSA with a reasonable expectation of success in doing so, similar to the analysis discussed above for Ground 1.

24. I have also been asked to consider whether a POSA would have found the '233 patent's claimed compounds to be adequately described in the patent (see Ground 3), and if a POSA would have required undue experimentation to practice the claimed invention in light of the teachings in the '233 patent specification (see Ground 4). In my opinion, in view of the teachings in the '233 patent, and in light

of the state of the art as of October 23, 2017, a POSA would have found the challenged claims adequately described and enabled. *See* § IX; *see also* EX2001, ¶26.

25. With respect to written description, Dr. Zeglis’s analysis requires that the claimed compounds possess certain properties that make them useful for *in vivo* diagnostic or therapeutic applications. EX1003, ¶¶59, 273–277; EX2001, ¶¶104–105. But the claims do not contain any such functional requirements—the compounds are claimed by their structure, not their function. A POSA would have recognized that the inventors possessed the full scope of the claimed B-L-A compounds given the disclosure of a multitude modular “B,” “L,” and “A” groups and the guidance of assembling the claimed compounds in the specification. This is particularly true due to the multitude of potential “B” and “L” groups that a POSA would have been aware of in the art—a fact that Dr. Zeglis does not contest. EX1003, ¶¶253–255, 256, 262; *see also* EX2001, ¶102; EX2023, 54:21–55:1. As such, a POSA would have been able to recognize the full claimed genus from the ’233 patent disclosure.

26. With respect to enablement, Dr. Zeglis’s analysis once again is placing a heightened requirement that the claimed compounds must be useful *in vivo*. EX1003, ¶¶59, 273–277. When properly considered for all potential uses, including *in vitro* uses disclosed in the ’233 patent specification, a POSA would

have been fully equipped to make and use the claimed invention without undue experimentation. *See* § X, *see also* EX2001, ¶26. Given the extensive disclosure of modular groups and the guidance provided in the working examples found in the '233 patent, a POSA would have been able to put together such modular compounds using basic organic chemistry and without undue experimentation. Indeed, the patent provides a synthetic route that allows a POSA to make the full scope of the claimed compounds. And Dr. Zeglis provided no evidence that a POSA would not have been able to use the claimed compound *in vitro* without undue experimentation. *In vitro* use, indeed, would have been routine. As such, the claims of the '233 patent are adequately described and enabled.

IV. LIST OF DOCUMENTS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 12,115,233 (“the ’233 patent”)
1002	File History of U.S. Patent No. 12,115,233
1003	Declaration of Dr. Brian Zeglis
1004	U.S. Patent Publication 2010/0098633
1005	U.S. Patent Publication 2012/0009121
1006	Jansen et al., “Extended Structure—Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP),” J. Med. Chem, 57:3053–3074 (2014) (“Jansen”)

Exhibit No.	Description
1007	Jansen et al., “Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold,” ACS Med. Chem. Lett., 4:491–496 (2013)
1008	Meletta et al., “Evaluation of the Radiolabeled Boronic Acid-Based FAP Inhibitor MIP-1232 for Atherosclerotic Plaque Imaging,” Molecules, 20:2081–2099 (2015) (“Meletta”)
1009	Jamous et al., “Synthesis of Peptide Radiopharmaceuticals for the Therapy and Diagnosis of Tumor Diseases,” Molecules, 18:3379–3409 (2013)
1010	Zeglis et al., “A practical guide to the construction of radiometallated bioconjugates for positron emission tomography,” Dalton Trans., 40(23):6168–6195 (2011)
1011	Zeglis et al., “Underscoring the Influence of Inorganic Chemistry on Nuclear Imaging with Radiometals,” Inorg. Chem., 53:1880–1889 (2013)
1012	Wadas et al., “Coordinating Radiometals of Copper, Gallium, Indium, Yttrium, and Zirconium for PET and SPECT Imaging of Disease,” Chem. Rev., 110(5):2858–2902 (2010)
1013	Price et al., “Matching chelators to radiometals for radiopharmaceuticals,” Chem. Soc. Rev., 43:260–290 (2014)
1014	Riondato et al., “Radiopharmaceuticals,” Chapter 4,31-57, in PET-CT and PET-MRI in Neurology (Ciarmiello and Mansi, editors), Springer, Int. Publ., (2016)
1015	Ross, “The Click Chemistry Approach Applied to Fluorine-18,” Current Radiopharmaceuticals, 3:202–223 (2010)
1016	Brennen et al., “Rationale Behind Targeting Fibroblast Activation Protein—Expressing Carcinoma-Associated Fibroblasts as a Novel Chemotherapeutic Strategy,” Mol. Cancer Ther., 11(2):257–266 (2012)

Exhibit No.	Description
1017	Sarko et al., “Bifunctional Chelators in the Design and Application of Radiopharmaceuticals for Oncological Diseases,” <i>Current Medicinal Chem.</i> , 19:2667–2688 (2012)
1018	Fichna et al., “Synthesis of Target-Specific Radiolabeled Peptides for Diagnostic Imaging,” <i>Bioconjugate Chem.</i> , 14:3–17 (2003)
1019	Schirrmacher et al., “Small Prosthetic Groups in ¹⁹ F-Radiochemistry: Useful Auxiliaries for the Design of ¹⁹ F-PET Tracers,” <i>Semin. Nucl. Med.</i> , 47(5):474–492 (August 2017)
1020	Saha et al., “Synthesis of PET Radiopharmaceuticals,” Chapter 8, 161–168, in <i>Basics of PET Imaging</i> (Saha, editor), Springer Int. Publ., (2010)
1021	Kettenbach et al., “ ¹⁸ F-Labeling Using Click Cycloadditions,” <i>BioMed Research International</i> , 2014:1–16 (2014)
1022	Liu et al., “Fibroblast activation protein, A potential therapeutic target in cancer,” <i>Cancer Biology & Ther.</i> , 13(3):123–129 (2012)
1023	DiMagno et al., “Advanced Fibroblast Activation Protein-Ligand Developments, FAP Imaging Agents: A Review of the Structural Requirements,” <i>PET Clin.</i> , 18:287–294 (2023)
1024	Hamson et al., “Understanding fibroblast activation protein (FAP): Substrates, activities, expression and targeting for cancer therapy,” <i>Proteomics Clin. Appl.</i> , 8:454–463 (2014)
1025	O’Brien et al., “Seprase: An overview of an important matrix serine protease,” <i>Biochimica et Biophysica Acta</i> , 1784:1130–1145 (2008)
1026	Jia et al., “FAP-a (Fibroblast activation protein-a) is involved in the control of human breast cancer cell line growth and motility via the FAK pathway,” <i>BMC Cell Biology</i> , 15(16): 1–14 (2014)

Exhibit No.	Description
1027	Agdeppa et al., “A Review of Imaging Agent Development,” The American Association of Pharmaceutical Scientists (AAPS) J., 11(2):286–299 (2009)
1028	Mankoff et al., “Tumor Receptor Imaging,” J. Nucl. Med., 49:149S–163S (2008)
1029	Ryabtsova et al., “Acylated Gly-(2- cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity,” Bioorganic & Medicinal Chemistry Letters, 22(10):3412–3417 (2012)
1030	Eder et al., “ ⁶⁸ Ga-Complex Lipophilicity and the Targeting Property of a Urea-Based PSMA Inhibitor for PET Imaging,” Bioconjugate Chem., 23:688–697 (2012)
1031	File History of U.S. Patent No. 11,938,201
1032	Fani et al., “Radiolabeled Peptides: Valuable Tools for the Detection and Treatment of Cancer,” Theranostics, 2(5):481–501 (2012)
1033	Mach et al., “Challenges for Developing PET Tracers: Isotopes, Chemistry, and Regulatory Aspects,” 5(2): 131–153 (2010)
1034	Meyer et al., “Click Chemistry and Radiochemistry: The First 10 Years,” Bioconjugate Chem., 27:2791–2807 (2016)
1035	Marquis et al., “Abstract #4467: Targeting tumor microenvironment with radiolabeled inhibitors of seprase (FAP\#945;),” Cancer Chem., 69:4467 (2009)
1036	Maurer et al., “Current use of PSMA-PET in prostate cancer management,” Nature Reviews: Urology, 13:226–235 (2016)
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2022	Pages 12–14 of U.S. Patent Application Publication No. 2010/0098633 A1 (EX1004) (annotated by Dr. Brian Zeglis)
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V. LEGAL BASIS FOR MY ANALYSIS

27. As I explained in my first Declaration, in formulating my opinions set forth in this Declaration, I applied the following legal principles:

A. Claim Construction

28. I understand that in a PGR, patent claim terms are given their ordinary and customary meaning as understood by a POSA at the time of the invention, in view of the patent’s specification and its prosecution history—unless the patentee has acted as his own lexicographer. I understand that a patentee may act as his own lexicographer when providing definitions in the specification or prosecution

history. For example, an inventor may clearly set forth a definition of the claim term in either the specification or prosecution history that is different from the term's ordinary meaning.

29. I understand that claim 1 is the independent claim in the '233 patent, and that claims 2–4 are dependent claims depending directly or indirectly from claim 1. I understand that a dependent claim contains all limitations (*i.e.*, elements) of the claim from which it depends. Thus, I understand that claims 2–4 contain all the limitations of claim 1.

B. Obviousness

30. I understand that an obviousness analysis involves comparing a claim to the prior art to determine whether the claimed subject matter would have been obvious to a POSA in view of the prior art and general knowledge in the prior art (here, before October 23, 2017). I understand that obviousness must be assessed from the viewpoint of a POSA at the time of the invention (here, before October 23, 2017). I further understand that to establish obviousness, a party must perform the following factual inquiries: (a) determining the scope and content of the prior art; (b) ascertaining the differences between the claimed invention and the prior art; and (c) resolving the level of skill in the art. I understand that, in determining the scope and content of the prior art and ascertaining the differences between the claimed invention, a patent challenger must specify where each

element of the claim is found in the prior art.

31. I understand that one way of establishing obviousness is by establishing that a POSA would have had both (i) a reason to modify or combine the teachings of the prior art to achieve the claimed invention and (ii) a reasonable expectation of success in doing so. I understand that the reason to combine prior-art references can come from a variety of sources, not just the prior art itself or the specific problem the patentee was trying to solve. And I understand that the references themselves need not provide a specific hint or suggestion of the alteration needed to arrive at the claimed invention; the analysis may include recourse to logic, judgment, and common sense available to a person of ordinary skill that does not need to be explicit in any reference. I also understand that one cannot use the claims themselves as a roadmap to establish obviousness.

32. I understand that a “reasonable expectation of success” is assessed in view of the prior art and general knowledge in the art from the viewpoint of a POSA before the relevant date (October 23, 2017), and it does not require an absolute certainty of success. Furthermore, I understand that determining whether the prior art would have suggested to those of ordinary skill in the art to carry out the claimed invention with a reasonable expectation of success must be done after determining that the claimed elements are present in the prior art.

33. I also understand that, before reaching a conclusion that the claimed

invention would have been obvious, one must consider any objective evidence of non-obviousness if it is available. The objective evidence of non-obviousness can include evidence of commercial success attributable to the claimed invention, evidence of industry praise for the claimed invention, evidence of a long-felt need that was solved by the claimed subject matter, evidence that others copied the claimed subject matter, or evidence that the claimed subject matter achieved an unexpected, superior result relative to the closest prior art. I understand that such evidence must have a nexus, or causal relationship, to the claimed subject matter beyond what was available in the prior art and must be commensurate in scope with the patent claim(s) at issue.

C. Enablement

34. I understand that an enabling disclosure in the patent specification must allow a POSA to make and use the full scope of the claimed invention without undue experimentation as of the filing date (October 23, 2017). I understand that the following factors can be used to determine whether undue experimentation would have been needed (the so-called *Wands* factors): (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the

invention based on the content of the disclosure.

35. I understand that the determination that “undue experimentation” would have been needed to make and use the claimed invention is a conclusion reached by weighing the above-noted factual considerations. I understand that whether some experimentation is necessary does not necessarily make such experimentation undue and that even a considerable amount of experimentation is not undue, if it is merely routine.

D. Written Description

36. I understand that the written description provided by a patent specification must convey clearly to a POSA that the applicant was in possession of the claimed invention as of the patent’s filing date. And I understand that this involves an objective inquiry into the specification from the perspective of a POSA. Further, I understand that possession does not mean physical possession and does not require making or testing the invention.

37. I further understand that this written description requirement must be applied in the context of the particular invention and the state of the knowledge in the art. In addition, I understand that a patent specification is written for a POSA and that such a hypothetical person presumably has all of the knowledge of the state of the art as of the patent’s filing date, in addition to the knowledge provided by the patent specification itself.

38. I understand that there is sufficient written description support when a POSA can visualize or recognize the identity of the full scope of the claimed subject matter and that the claimed subject matter need not be provided verbatim in a specification because a skilled artisan comes to the patent with knowledge in the art, and it is therefore unnecessary to spell out every detail of the invention in the specification for a skilled artisan to conclude that there is written description support.

39. I understand that assessing whether there is written description support for a genus claim in the chemical arts involves consideration of a number of factors, including (i) the nature and scope of the claims; (ii) existing knowledge in the particular field and extent and content of the prior art; (iii) maturity of the science of technology and scientific and technologic knowledge already in existence; (iv) predictability of the aspect at issue; and (v) scope of the invention at issue.

40. I further understand that 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. Additionally, I understand that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or

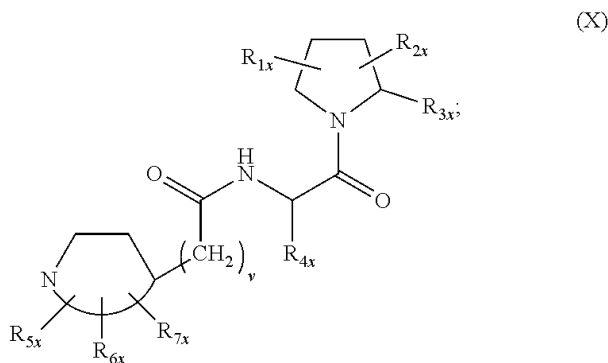
other properties, of species falling within the genus sufficient to distinguish the genus from other materials.

VI. CLAIM CONSTRUCTION

A. The term “B-L-A” is defined structurally

41. The challenged claims recite low molecular weight compounds having the formula “B-L-A.” EX1001, 64:6–8, Certificate of Correction. 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- α , wherein A has the structure of:



...

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

EX1001, 64:6-55. Claim 2 depends from claim 1 and narrows the R_{1x} and R_{2x}

groups of A. EX1001, 64:56-58. Claim 3 depends from claim 2 and narrows the R_{3x} group of A. EX1001, 64:59. 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. Dr. Zeglis does not offer a specific construction (*i.e.*, interpretation) for the term “low molecular weight,” although he implicitly acknowledges that the claimed compounds are defined structurally: “Claim 1 defines ‘low molecular weight compounds’ having *the formula ‘B-L-A.’*” EX1003, ¶74 (emphasis added). Dr. Zeglis further acknowledges that “A” in the claimed “B-L-A” is also “defined by reference to a chemical structure,” and that the functional language present in the claims is limited to “B” and “L”: “[t]he first two components of these compounds, ‘B’ and ‘L,’ are defined with very general language that identifies the purpose or function of each moiety in the compound.” EX1003, ¶74. I note that during deposition, Dr. Zeglis “impos[ed] B’s function onto the entire B-L-A compound” (*see e.g.*, EX2023, 177:15–22, 174:6–10, 174:16–19, 187:7–9, 179:5–9), but this interpretation is inconsistent with the plain language of the claims, which recites a *compound with a particular formula*. EX2001, ¶¶44-46.

42. The specification likewise defines the recited “compound of Formula (I): B-L-A” in structural terms, consistent with the plain language of the claims. EX1001, 8:14–19. The specification describes the claimed invention in the context

of three modular, structural components: an “A” moiety that is defined by a structural formula (EX1001, 10:14:11–29), a linking “L” moiety, of which dozens of structural examples are disclosed (EX1001, 14:55–17:4) and an imaging or therapeutic agent “B” that similarly has dozens of well-defined, structural options described in the specification (EX1001, 18:35–30:55). 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. In other words, the specification completely lacks functionally defined limitations when referring to the compounds as a whole. EX2001, ¶¶44-46.

43. Nowhere in the claims, specification, or prosecution history are the claimed B-L-A compounds described solely by their ability to perform a particular function, much less an *in vivo* function, contrary to Dr. Zeglis’s assertion that the compounds be “viable optical imaging agents or radiolabeled imaging or therapeutic agents.” EX1003, ¶273. And the specification does not describe these compounds solely by their ability to perform a particular function. Indeed, the specification highlights the varied uses of such compounds, including “*in vitro* diagnostics” or “research applications” in addition to diagnostic or therapeutic uses. EX1001, 35:46–52.

44. As such, given the plain language of the claims, the specification, and

the prosecution history, a POSA would have understood the challenged claims to recite structurally defined, not functionally defined compounds.

B. The term “low molecular weight” should be construed to mean “about 50 Daltons to about 1,500 Daltons”

45. Dr. Zeglis did not offer a construction of the term “low molecular weight,” but stated that “a skilled artisan would have understood ‘low molecular weight’ compounds to be radiopharmaceuticals that do not include a large protein like an antibody as the targeting moiety” and have a molecular weight of “from a few hundred to a few thousand Daltons.” EX1003, ¶83. As discussed in my previous declaration, I disagree with Dr. Zeglis, and agree with Dr. Pomper, a co-inventor of the ’233 patent, who stated during prosecution of the patent that “low molecular weight” means compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. EX1002, 169; EX2001, ¶¶47–48.

VII. CLAIMS 1–4 OF THE ’233 PATENT WOULD NOT HAVE BEEN OBVIOUS OVER US-633, JANSEN, AND MELETTA (GROUND 1)

46. Based on my review of the prior art and my experience in radiopharmaceutical chemistry and molecular imaging, it is my opinion that claims 1–4 of the ’233 patent would not have been obvious to a person of ordinary skill in the art over US-633, Jansen, and Meletta before October 23, 2017. Considered as a whole, the prior art neither points a POSA toward the claimed B-L-A compounds nor provides a reasonable expectation of success in arriving at them, instead the

prior art reflects multiple divergent approaches to FAP imaging without a clear or directed path to the claimed invention.

47. Before 2017, a POSA seeking to develop a FAP-targeting radiotracer would have faced fundamentally different strategies employing distinct targeting moieties (“A” in the claimed compounds), including antibodies, antibody fragments, peptides, oligonucleotides, and small molecule inhibitors. *See* Section VII.A *infra*. The literature repeatedly emphasized antibodies, antibody-derived constructs, fusion proteins, and peptides as viable—and often advantageous—approaches, particularly given affinity and selectivity concerns and the limited success of small molecule FAP radiotracers. Section VII.A. Nothing in the prior art suggested that a POSA would have focused primarily on low molecular weight FAP radiotracer development.

48. Further, before 2017, a POSA would also have faced multiple independent labeling choices (“B” and “L” in the claimed compounds), including direct halogenation, attachment of metal-binding chelators, or use of prosthetic groups, and using a wide range of metallic and non-metallic radionuclides (an essential component of any radiopharmaceutical). *See* Section VII.B *infra*. The literature emphasized minimizing structural perturbation and cautioned that even small changes could adversely affect affinity and selectivity. *See, e.g.*, EX1008, 2083; EX1010, 3. Consistent with these teachings, US-633 showed that small

molecule FAP radiotracers lacking bulky chelators and linkers exhibited better affinity and selectivity for FAP. *See* EX1004, Table 2. Critically, the only pre-2017 small molecule FAP radiotracer evaluated for selectivity—a directly radiohalogenated compound (first described in US-633)—failed *in vitro* because it was not able to distinguish FAP-expressing tissue from normal tissue. EX1008, 2089. Thus, the prior art provided no successful precedent and no reasonable expectation of success for the small molecule B-L-A radiotracers.

49. Even assuming a POSA would have elected to pursue a small molecule FAP radiotracer, the prior art disclosed a broad and structurally diverse universe of small molecule FAP targeting agents across different chemical scaffolds, many of which exhibited equal or superior affinity and selectivity compared to Jansen’s Compound 60—the compound that Dr. Zeglis selected as the “A” moiety for his obviousness analysis. *See* Section VII.C *infra*. In fact, the most selective and highest-affinity FAP inhibitors known in the art before 2017 would have fallen outside the scope of the claimed “A” moiety. Section VII.C. Thus, although Dr. Zeglis focused on Compound 60, the prior art does not support selecting that compound over numerous disclosed alternatives for use in small molecule FAP radiotracers that were equal or superior in performance.

50. As I explain in detail below, the prior art before October 23, 2017, reflects a field marked by divergent strategies and unresolved technical tradeoffs,

not one pointing toward the claimed “B-L-A” FAP radiotracers. Rather than guiding POSAs to the claimed compounds, the art would have required them to navigate multiple independent layers of choice—pharmacophore, chemical scaffold, and radiolabeling strategy—without any teaching that would have led them to select and successfully combine the particular elements recited in claims 1–4 of the ’233 patent. This lack of direction and predictability precludes a finding of obviousness.

A. Before 2017, a POSA would have faced multiple paths for making FAP-targeting radiotracers

51. Before October 23, 2017, the art reported that developing FAP-targeting radiotracers presented significant selectivity challenges. EX1016, 259; EX1044, ¶4; EX1007, 491; EX2001, ¶¶14-15. FAP belongs to the dipeptidyl peptidase family and shares substrate homology and structural features with related enzymes, including DPP^{IV}, DPP^{II}, and prolyl oligopeptidase. EX1016, 259; EX1044, ¶4; EX1007, 491; EX2001, ¶15. Non-specific binding arising from this homology “limited the fabrication of FAP-targeted imaging probes,” reflecting the difficulty of achieving selective FAP imaging. EX2004, 11. Structural and biochemical studies likewise described FAP as having a “DPPIV-like fold” and structural similarities with other family members, underscoring the challenge of designing selective imaging probes. EX2032, Abstract. As a result of these reported limitations, the literature emphasized—and a POSA would have had to

select from—multiple distinct FAP-targeting strategies, rather than converging on small molecule agents alone. *See* Section VII.B *infra*; *see also* EX2001, ¶15. These strategies included imaging FAP with, among others:

- Full length anti-FAP antibodies and antibody fragments;
- Antibody derived constructs, such as immunoconjugates;
- Peptide based targeting agents, including FAP activated peptides; and
- Small molecule FAP targeting compounds.

52. While not exhaustive, this list reflects the potential principal approaches explored, reported, or proposed in the field as of 2017. Dr. Zeglis agrees that antibodies, antibody fragments, peptides, and oligonucleotides were all recognized and routinely used classes of targeting vectors for radiotracers. EX1003, ¶50; EX2023, 68:8–14 (acknowledging that “[t]here are other vectors that are used in radiopharmaceuticals that are not immunoglobulins or full-length antibodies,” including peptides and oligonucleotides), 61:11–19 (describing antibodies as providing high affinity and selectivity for their targets), 69:2–70:2, 78:20–79:3. Thus, faced with a problem of developing FAP-targeting “molecular imaging, *in vivo* imaging, *in vitro* imaging, optical imaging, PET imaging, ... radiotherapy, SPECT imaging, all of these molecular imaging and therapy areas,” as Dr. Zeglis defined it (EX2023, 43:2–7), a POSA would have been faced with many different options.

1. The field of small molecule FAP radiotracers was sparse before 2017 and had not yielded successful radiotracers

53. Dr. Zeglis opined that a POSA would have been motivated to develop small molecule FAP radiotracers (EX1003, ¶40), but before October 23, 2017, the knowledge of small molecule FAP radiotracers was exceedingly limited. In fact, only three sources—US-633, Meletta, and Marquis—disclosed such radiotracers. EX1004, ¶¶151–181; EX1008, Abstract; EX1035, 2083. Dr. Zeglis, also, is “not aware of any other references that disclose small molecule FAP imaging agents before 2017.” EX2023, 162:15–22.

54. Notably, none of those references would have suggested to a POSA that small molecule FAP radiotracers would have been successful. US-633 was the first and only pre-2017 reference that reported *in vitro* affinity values of a number of different small molecule FAP-targeting radiotracers. EX1004, Table 2; EX2001, ¶¶16-17. Most of the radiotracers (25 out of 34) demonstrated FAP affinities in the high nanomolar range or greater (*i.e.*, did not bind to FAP sufficiently tight), rather than the preferred low nanomolar range. EX1004, Table 2. US-633 did not investigate the FAP-selectivity of its radiotracers. From those, Marquis selected a radiotracer with nanomolar affinity for FAP, Compound 1024, for further studies.

55. Marquis, in 2009, selected Compound 1024 (referred to as “MIP”) due to its “potential to be radiolabeled with either ¹²³I or ¹³¹I for radiodiagnostic or radiotherapeutic use, respectively.” EX1035, Abstract. Marquis studied the *ortho*-

(MIP-1231), *para*- (MIP-1232), and *meta*-substituted (MIP-1233)⁵ iodine analogs of Compound 1024, and identified the *para*-iodine substituted analog as “display[ing] better selectivity.” EX1035, Abstract. Marquis then evaluated MIP-1232, radiolabeled with ¹²³I, in FAP-transfected human embryonic kidney cells, and showed that the compound “inhibit[ed] the seprase enzymatic activity of the stable seprase expressing cells.” EX1035, Abstract. Marquis also described the high selectivity of MIP-1232, reporting that this inhibition occurred without “specific binding to a non-expressing clone.” EX1035, Abstract. In other words, MIP-1232 did not bind to cloned cells that did not express FAP (but were otherwise identical to the targeted cells). EX1035, Abstract. Marquis thus concluded that “[r]adiolabeled seprase inhibitors could be exploited for the diagnosis, staging, prognosis, and potential treatment of solid tumors.” EX1035, Abstract.

56. Following the teachings of Marquis, Meletta, in 2015, selected *para*-MIP-1232 to “assess the potential of FAP as an imaging target for the staging of plaque vulnerability and to detect FAP-positive tumors that may respond to FAP-

⁵ The terms *ortho*, *para*, and *meta* refer to three different sites on a benzene ring. EX2043, Abstract, FIGs. 1–2. The iodine was conjugated to the benzene ring of MIP-1231 at three different sites in the three Marquis compounds.

targeted therapy.” EX1008, 2083. Meletta explained its selection based on MIP-1232’s “high binding affinity to FAP and the selectivity profile,” and, notably, “the possibility to radioiodinate MIP-1232 without altering its structure.” EX1008, 2083. Taking Marquis’s experiments (which involved analyzing MIP-1232’s binding to FAP-expressing cells versus non-FAP-expressing cells) a step further, Meletta’s experiments were directed towards analyzing, *in vitro*, MIP-1232’s binding to carotid plaques with higher levels of FAP expression than other carotid plaques. EX1008, 2089. MIP-1232 failed, as the compound did not “selectively accumulate in the atherosclerotic tissue” when evaluated by *in vitro* autoradiography using human carotid plaques. EX1008, 2089–2090.

57. Thus, as of October 23, 2017, the prior art did not indicate that small molecule FAP radiotracers were promising.

2. In contrast to small molecule efforts, antibody-based pharmacophores were the proven FAP imaging approach

58. In contrast, the pre-2017 research in the FAP-imaging field focused far more heavily on antibody-based strategies for FAP imaging than on small molecule approaches. In work unrelated to these proceedings, Dr. Zeglis himself described antibodies as “extremely promising vectors for the delivery of radioisotopes to cancer cells for PET imaging,” emphasizing that they exhibit “exquisite affinity and specificity.” EX2039, Abstract. He likewise wrote, in work contemporaneous with the filing date of the ’233 patent, that antibodies exhibit

“remarkable selectivity and specificity for cancer biomarkers” (EX2040, Abstract), and described antibodies as “promising platforms for the development of hybrid PET/OI agents” because of their “high selectivity and affinity.” EX2040, Abstract. Dr. Zeglis also agreed 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.

59. The pre-2017 literature reflects Dr. Zeglis’s contemporaneous views on antibody-based imaging and, consistent with those views, disclosed a range of FAP radiotracers built on antibody platforms before October 23, 2017. *See* EX2033, 778, 781–783; EX2031, 1193, 1196–1202; EX2030, 1639, 1645–1646; EX2028, 6206, 6214–6217. As Laverman explained, “[b]ecause FAP is expressed in tumor stroma, various anti-FAP antibodies have been studied for radioimmunotargeting of malignancies,” including “¹³¹I-labeled murine F19 and ¹³¹I-labeled sibrotuzumab, a humanized version of the F19 antibody.” EX2033, 778. When tested in patients, sibrotuzumab showed “no toxicity ... and achieve[d] consistent targeting to metastatic lesions in patients with colorectal carcinoma,” leading POSAs to believe that humanized mAbF19 could serve both diagnostic and therapeutic purposes. EX2031, 1198. Sibrotuzumab also “showed rapid and selective uptake in sites of tumor” and a “relatively short half-life”—an advantage for radioimmunotherapy because it limits bone-marrow toxicity. EX2030, 1645–

1646.

60. Two other anti-FAP antibodies, ESC11 and ESC14, labeled with ¹⁷⁷Lu, showed “excellent targeting in melanoma xenografts.” EX2033, 778. In addition, Fischer demonstrated that ESC11 and ESC14 “bound selectively to both human and mouse FAP, with affinities in the low nanomolar range.” EX2028, Abstract. Laverman likewise reported that another anti-FAP antibody radiotracer, ¹¹¹In-28H1, “resulted in excellent image quality” due to low background uptake in off-target tissues. EX2033, 780, 783.

61. Collectively, these findings would have reinforced for a POSA that antibody-based radiotracers represented a reliable and effective strategy for FAP imaging, particularly in light of the shortcomings observed with small molecule approaches. In offering his opinion on the obviousness of the small molecule radiotracers claimed in the '233 patent, however, Dr. Zeglis did not consider the substantial body of prior art relating to FAP radiotracers based on anti-FAP antibodies. Nor did he explain how that body of knowledge would have informed a POSA's approach to designing FAP-radiotracers before 2017, despite acknowledging that antibodies can serve as “[t]argeting moieties in a radiopharmaceutical.” EX1003, ¶40; EX2023, 68:6–10.

3. Beyond antibodies, peptide- and protein-based pharmacophore strategies were more mature than small molecule approaches

62. In addition to antibody-based FAP imaging approaches, POSAs would have been also aware of other antibody-derived strategies for FAP radiotracers that extended beyond full-length antibodies. For example, Rüger described liposomes incorporating “single-chain Fv fragments directed against FAP (scFv/FAP),” which showed “specific interaction and binding with FAP-expressing cells *in vitro*.” EX2035, Abstract. Rüger further demonstrated *in vivo* selectivity, reporting that “anti-FAP-IL accumulated selectively in FAP-expressing xenograft models *in vivo*” and could serve as “a suitable *in vivo* diagnostic tool” for disorders characterized by high FAP expression. EX2035, Abstract. But Dr. Zeglis did not address this approach in his declaration.

63. POSAs also would have been aware of peptide-based strategies as another established route for developing radiotracers before 2017. As Dr. Zeglis himself explained, peptides “hold a significant position in the field of radiotracer development,” and receptors that bind peptide ligands and are overproduced in tumors “represent promising candidates for imaging.” EX2019, 58. Because FAP binds peptide ligands and is overexpressed in tumors, the literature disclosed multiple peptide-based approaches—ranging from FAP-activated peptide protoxins and FAP-specific dipeptides to naturally occurring FAP substrates—leading

POSAs to view peptide-based constructs as viable starting points for FAP-targeting radiotracers. EX2036, Abstract; EX2037, Abstract; EX2038, Abstract, 1328.

64. In sum, although Dr. Zeglis acknowledged that radiopharmaceuticals have employed diverse targeting vectors, his obviousness analysis focused narrowly on small molecule FAP inhibitors. That focus overlooks the pre-October 2017 art, in which the only tested small molecule FAP radiotracer failed *in vitro*, while antibody-based approaches had already demonstrated selective targeting and clinical promise. Rather than accounting for this contrast, Dr. Zeglis bypassed the more successful antibody- and peptide-based literature and assembled a small-molecule pathway that tracks the claims, not the prior art as a POSA would have understood it.

B. Radiotracer design also would have presented POSAs with multiple labeling choices

65. Before 2017, POSAs would have known that radiotracer design offered multiple routes for incorporating radionuclides, and that no single approach was universally preferred. A radionuclide is a radioactive isotope incorporated into a radiotracer that emits radiation detectable by imaging instruments; the presence of the radionuclide is what enables imaging of a given biological target. *See, e.g.*, EX1014, 31. Radionuclides may be incorporated either by covalent attachment or by stable coordination through a chelator, and no approach was universally preferred across molecular scaffolds or targets. EX1014, 31. Importantly, and Dr.

Zeglis agrees with me, the best labeling strategy for small molecule radiotracers involves “disturbing the activity of the parent molecule as little as possible.” EX1010, 3; EX1003, ¶59 (“slight modifications to the structure of a targeting moiety can alter its selectivity and affinity for its target”); *see also* EX2019, 58 (for “many small molecules ... modest changes in the molecular structure ... can have dramatic effects on the solubility [and] binding properties ... of the agent”); EX2001, ¶¶49-69.

66. Below is a summary of different approaches for incorporating a radionuclide into a radiotracer.

67. Isotopologous (Direct) Labeling with Non-Metallic Radionuclides

One recognized option available to POSAs before 2017 was direct, isotopologous labeling, particularly using radiohalogens. Isotopologue labeling involves substituting stable atoms (e.g., ^{19}F , ^{127}I , ^{79}Br , ^{81}Br) in a molecule with radioactive isotopes (e.g., ^{18}F , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{76}Br). These so-called “non-metallic” radionuclides are “ordinarily attached to a radiopharmaceutical via a covalent bond,” and the radiohalogen “can be incorporated directly into the targeting moiety structure.” EX1003, ¶44. Dr. Zeglis agrees. EX1003, ¶44. The benefit of direct halogenation as a labeling strategy is that radiohalogens such as ^{18}F introduced minimal structural disruption. As Riondato explains, ^{18}F ’s “exceptional employment for *in vivo* imaging is primarily due to the minimal perturbation

caused by its incorporation ... combined with [its] advantageous physical half-life.” EX1014, 44; EX1010, 3 (“In small molecule tracers, the radionuclide most often replaces an isotopologue (e.g. [^{11}C]-acetate or [^{15}O]- H_2O) or is incorporated into the basic structure of a molecule with either the intent of strategically altering the behavior of the parent molecule (e.g. [^{18}F]-FDG) or, more likely, disturbing the activity of the parent molecule as little as possible (e.g. [^{18}F]-FDHT or [^{18}F]-FES)); EX2023, 92:15–93:1 (Dr. Zeglis noting that isotopologue labeling “generates a new molecule that, in a very *small* way, has a different molecular structure” and is “[i]dentical in all ways [to the starting structure] except for the number of neutrons in the atom that you replaced” (emphasis added)); *see also* EX2001, ¶¶68-69.

68. **Prosthetic-Group Labeling of Non-Metallic Radionuclides.** POSAs also knew that non-metallic radionuclides could be introduced indirectly through prosthetic groups. Under this approach, the prosthetic group is first covalently attached to the radiohalogen, and the radiolabeled prosthetic group is then attached to the radiopharmaceutical precursor. *See, e.g.,* EX1014, 44; EX1033, 137–138. Dr. Zeglis acknowledges that this strategy necessarily introduces additional structural elements into the molecule being labeled. EX1003, ¶¶44, 59(b). As a result, prosthetic-group labeling must be carefully designed. In particular, the prosthetic group and its point of attachment must be positioned sufficiently far

from the structural motif of the targeting moiety that interacts with the target.

Otherwise, the modification risks disrupting binding affinity or selectivity—a proposition with which Dr. Zeglis agrees. EX1003, ¶59(b).

69. **Chelation Strategies for Metallic Radionuclides.** For metallic radionuclides, POSAs understood that chelation was required. *See, e.g.*, EX1017, 2667 (describing radiometal-chelator systems for radiopharmaceutical application). Radiometals are incorporated by stably coordinating the radionuclide within a chelator moiety, which forms a stable coordination complex with the radiometal. EX1013, Abstract. This strategy, like prosthetic-group labeling, necessarily introduces significant structural changes to the parent molecule and therefore must be executed carefully to avoid interfering with target binding. *See, e.g.*, EX1017, 2669 (cautioning that “the conjugated chelator should not interfere with the binding affinity of the peptide”). Dr. Zeglis agrees that chelation strategies introduce additional bulk, charge, and rigidity into the molecule, often requiring the use of linkers and altering physicochemical and biological properties, including solubility, residence time in blood, and biodistribution. EX1003, ¶46.

70. Taken together, before 2017, POSAs would have been confronted with multiple radiolabeling strategies, including direct isotopologous labeling, prosthetic-group attachment, and chelator-based approaches turning on factors such as the choice of pharmacophore, the sensitivity of the pharmacophore to

structural changes, and the identity of the radionuclide. These radiolabeling decisions added a substantial additional layer of design choice, compounding the already significant selection among different classes of targeting vectors, including antibodies, peptides, and small molecules.

C. The wide range of FAP-targeting small molecules disclosed in the prior art would have further compounded the design choices confronting a POSA

71. Even if a POSA—contrary to what the prior art supports—had elected to pursue small molecule FAP radiotracers, the POSA would then have faced the additional task of selecting a FAP-targeting compound from among numerous alternatives disclosed in the art. Dr. Zeglis suggests that “a skilled artisan would have viewed compound 60 as one of the most promising FAP inhibitors that had been discovered to date” and therefore would have selected it to improve the radiotherapeutic or imaging compounds of US-633. EX1003, ¶149. That selection, however, reflects hindsight. In reaching it, Dr. Zeglis ignored other highly selective FAP inhibitors disclosed in the prior art and instead focused on a compound from Jansen that could be retrofitted to the challenged claims. Moreover, using Dr. Zeglis’s own selection criteria, a POSA would not have been led to Compound 60 in light of the other FAP inhibitors disclosed in the literature.

1. Numerous FAP inhibitors were disclosed in the prior art, most of which Dr. Zeglis did not consider

72. Before 2017, the prior art disclosed a wide array of FAP inhibitors

across multiple structural scaffolds, most of which Dr. Zeglis did not consider.

Critically, Dr. Zeglis did not articulate a technical basis for why a POSA would have set aside the broader body of small molecule FAP-inhibitor literature—including disclosures of both quinolinyll and non-quinolinyll scaffolds—and focused instead on Jansen’s quinolinyll compounds when seeking to improve on Meletta’s failed radiotracer. Dr. Zeglis argues that, “a skilled artisan would have recognized that the entire class of radiotracers described in US-633 could be improved by using a new, more selective small molecule FAP inhibitor as the targeting moiety (EX1003, ¶167), but then immediately jumps to the conclusion that “a skilled artisan would have invariably discovered the compounds characterized in Jansen.” EX1003, ¶168. But Dr. Zeglis does not explain why, after reviewing US-633 and Meletta, a POSA would have prioritized Jansen over the many other available FAP-inhibitor references, including additional publications from Jansen’s own research group. EX2001, ¶70. From a technical perspective, the prior art offers no principle or trend that would have singled out Jansen’s compounds—or Compound 60 in particular—over the numerous alternative FAP inhibitors disclosed at the time. In fact, the trend in the art pointed away from spotlighting Jansen’s Compound 60, as other disclosed FAP inhibitors would have appeared more attractive to a POSA based on reported selectivity and affinity profiles. *Additionally, I note that Compound 60 was not in “B-L-A” form.*

EX1006, Abstract, p. 3053 (noting the “ongoing evaluation [of FAP] as a *drug target*” and that “FAP inhibition is investigated as a therapeutic option for [multiple disease states involving remodeling of the extracellular matrix], with most attention...devoted to oncology applications”). Nothing in Jansen suggests that its FAPi could be used diagnostically as radiotracers, as Dr. Zeglis agrees. EX2023, 159:1-5 (agreeing that Jansen does not “relate to radiopharmaceuticals” because “[i]t relates to pharmacophores that inhibit FAP”). Indeed, the words “diagnosis,” “imaging,” “radiotracer,” or “radiopharmaceutical” do not appear in Jansen at all. As such, Jansen does not disclose any compounds in “B-L-A” form.

73. Before 2017, the prior art disclosed numerous small molecule FAP inhibitors, a point Dr. Zeglis readily acknowledged. EX2023, 128:2–6 (as summarized in the table in ¶88 below). As Dr. Zeglis himself has emphasized, selectivity for FAP is “the most important factor” when choosing a pharmacophore for use in a radiopharmaceutical. EX1003, ¶55. Yet many of the FAP inhibitors disclosed in the literature exhibited selectivity for FAP that was comparable to—or greater than—that of Compound 60, undermining any suggestion that Compound 60 would have stood out to a POSA as the preferred or inevitable choice.

74. For example, Jansen 2013 disclosed thirty-six distinct small molecule FAP inhibitors. EX1007, Tables 2–3, EX2001, ¶72, 84. Many of the FAP

inhibitors reported in Jansen 2013 exhibited the same or even greater selectivity (the higher the number, the better) for FAP over PREP than Jansen's Compound 60 (with a selectivity of 562), such as Compound 26 (with a selectivity > 4500), Compound 25 (with a selectivity of 1700), and Compound 30 (with a selectivity of 677). EX2001, ¶¶72, 84. Notably, the most selective FAP inhibitor disclosed in that study—Compound 26—does not fall within the scope of the claimed “A” moiety due to the presence of the bromine on the quinoliny ring, which the claims exclude. EX1001, 64:5–55, Certificate of Correction. Dr. Zeglis's obviousness analysis does not reflect any evaluation of these alternative Jansen 2013 compounds for potential use in a small molecule FAP radiotracer, nor does he provide a technical rationale for why a POSA would have discounted those compounds in favor of Compound 60. EX2001, ¶¶72, 84.

75. A POSA would have also been aware of additional FAPi references published by the Jansen research group that were not cited by Meletta. For example, U.S. Patent Publication No. 2014/0357650 (“US-650”), in which Jansen is the first-named inventor, discloses forty-three compounds, many of which either outperformed, or performed similarly to, Jansen's Compound 60 with respect to their selectivity for FAP over PREP. EX1044, Table 4; EX2001, ¶¶74. For instance, Compound 22 has a selectivity >4500, Compound 23 has a selectivity of 2100, Compound 21 has a selectivity of 1700, and Compound 11 has a selectivity of 677

(compared with a selectivity of 562 for Compound 60). EX1044, Table 4, EX2001,

¶74. Although Dr. Zeglis acknowledges US-650 in his declaration, and although Dr. Zeglis agrees that Compounds 11, 21, 22, and 24 of US-650 are more selective for FAP over PREP than Compound 60 (EX2023, 154:8–156:17), he does not explain how the data disclosed in US-650 would have informed a POSA's technical evaluation of which FAP inhibitors to select when designing a small molecule FAP radiotracer. EX1003, ¶¶178 fn.187, 288 fn.300. Here, again, the most selective FAPi disclosed in US-650 (Compound 22, with a FAP selectivity > 4500) does not fall within the scope of the claimed "A" moiety because it contains a substituent on the quinoline ring, which is excluded by the claims. EX1044, Table 4; EX1001, 64:5–55, Certificate of Correction. However, Dr. Zeglis fails once again to explain why a POSA would have discarded all these potential "A" moieties in favor of Jansen's Compound 60. EX2001, ¶¶74-75.

76. Another reference, Jansen 2014, disclosed thirty-three distinct FAP inhibitors having xanthine scaffolds (which is different from the quinoline-based scaffold employed in the compounds of Jansen, Jansen 2013, and US-650). EX2001, ¶73. Jansen 2014 describes those FAPis to be "selective" for FAP: "we managed to decouple DPP^{IV} and FAP potency." EX2003, Abstract; EX2001, ¶73. Jansen 2014 notes that Compounds 13f, 13g, and 14a were "selective FAP inhibitors" that were more selective for FAP over DPP^{IV}. EX2003, 1706, Table 3,

Table 5. Compounds 3 and 13a were more selective for FAP over PREP, with selectivities of >270 and >135, respectively. EX2003, Table 3. But Dr. Zeglis does not evaluate the suitability of Jansen 2014's xanthine-based compounds, nor does he explain why a POSA would not have considered Jansen 2014 altogether. EX2001, ¶73; EX2023 129:5–132:6 (agreeing that he has “seen this exhibit before” but that he has not previously “carefully examin[ed]” Table 4 and that “[Compounds] 13k, 13l, 13m, and 13n do inhibit FAP at some concentration”).

77. A POSA also would have been aware of FAPi references published by other research groups. For example, Poplawski discloses twenty-two non-quinoliny FAP inhibitors incorporating a boronic-acid warhead. EX2020, Tables 1–4. Poplawski characterized the compounds as “the first FAP inhibitor ... that combines low-nanomolar potency with selectivity against both the DPPs and PREP.” EX2020, 7. The selectivity of Poplawski's Compound 6 (which falls outside of the claimed scope, due to the lack of a quinoliny ring) for FAP over PREP is 360, the same order of magnitude as Jansen's Compound 60. However, Dr. Zeglis discards Poplawski's Compound 6, indicating that “no *in vivo* PK data have so far been published for 6.” EX1003, ¶143. But Dr. Zeglis himself acknowledged that a POSA would not have been limited to FAP radiotracers intended solely for *in vivo* use. EX2023, 80:13–15 (noting that “[o]ptical imaging agents can be useful *in vivo* or *in vitro*”).

78. Another reference, Tsai,⁶ discloses twenty-seven FAPis based on a pyroglutamic-acid scaffold and having “IC₅₀ < 100 nM and excellent selectivity over DPP-IV, DPP-II, DPP8, and DPP9.” EX1047, Abstract, Table 2. In particular, Tsai notes that its Compounds 18a, 18b, and 19 (which fall outside of the claimed scope of “A” due to their lack of a quinolinyll ring) are “the only known potent and selective FAP inhibitors.” EX1047, Abstract. However, Dr. Zeglis discounted Tsai as a whole based on Jansen’s observation that *one* compound in Tsai exhibited “poor pharmacokinetic (PK) behavior in mice.” EX1003 ¶143. This is, again, despite Dr. Zeglis’s agreement that a POSA would not have limited its development for *in vivo* uses. And even if a POSA had limited the inquiry to *in vivo* radiotracers—which claims do not require—Tsai’s Compound 18b nonetheless exhibited “a longer half-life, lower total body clearance, and favorable

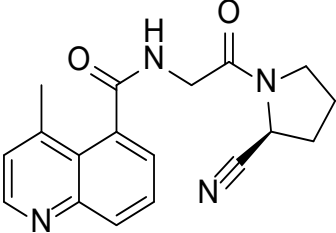
⁶ Jansen refers to Tsai as “Jiaang.” EX1006, 3063, Citation 23.⁷

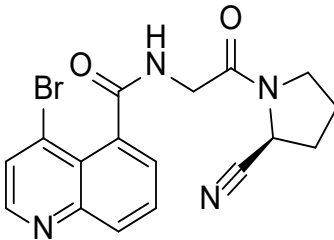
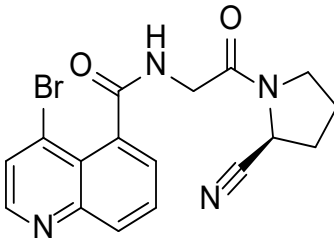
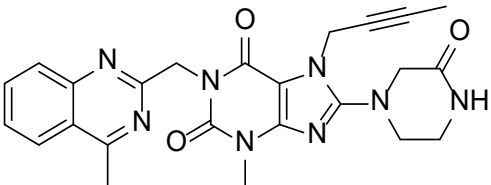
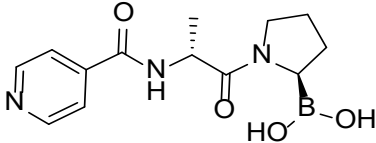
Lipophilicity and hydrophobicity are closely related concepts, both describing a compound’s tendency to associate with nonpolar environments. EX2025, 183–184, 197. Lipophilicity refers to a compound’s affinity for lipid or fat-like phases, while hydrophobicity describes its tendency to avoid aqueous environments; in practice, increased lipophilicity generally corresponds to increased hydrophobic character in biological systems.

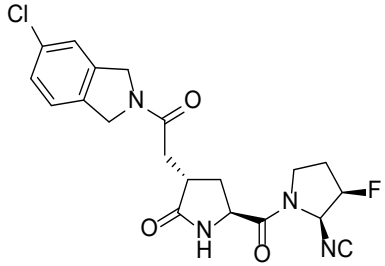
drug exposure (AUC)” following intravenous administration, while maintaining FAP selectivity over the DPP family of enzymes, indicating potential suitability for *in vivo* evaluation. EX1047, 6578. Dr. Zeglis did not explain how Tsai’s compounds would have factored into a POSA’s evaluation of the small-molecule pharmacophore landscape.

79. In sum, the table below illustrates the choices that a POSA would have had, and that Dr. Zeglis did not account for in his analysis, when evaluating the suitability of FAPis for use in a radiotracer. Notably, the table below shows that highly selective compounds in each reference do not fall within the scope of “A” in the challenged claims, as discussed above.

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

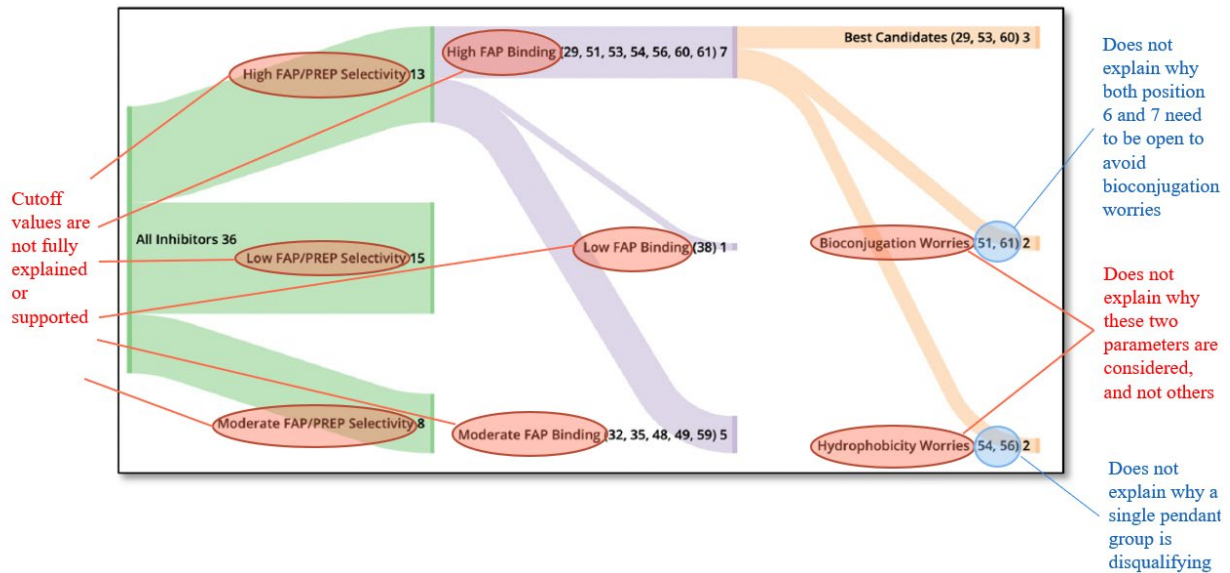
Reference	Number of FAPis disclosed	Number of FAPis that fall within claimed “A” moiety scope	Highest-selectivity FAPi structure
Jansen	54	3	 (Compound 53: Not within claimed “A” moiety scope)

Reference	Number of FAPis disclosed	Number of FAPis that fall within claimed "A" moiety scope	Highest-selectivity FAPi structure
US-650	43	1	 (Compound 22: Not within claimed "A" moiety scope)
Jansen 2013	36	2	 (Compound 26: Not within claimed "A" moiety scope)
Jansen 2014	33	None	 (Compound 3: Not within claimed "A" moiety scope)
Poplawski	22	None	 (Compound 6: Not within claimed "A" moiety scope)

Reference	Number of FAPis disclosed	Number of FAPis that fall within claimed “A” moiety scope	Highest-selectivity FAPi structure
Tsai	27	None	 (Compound 18b: Not within claimed “A” moiety scope)

2. Applying Dr. Zeglis’s own classification framework, a POSA would not have been led to Compound 60 given the availability of other quinoline-based FAP inhibitors with comparable or superior properties

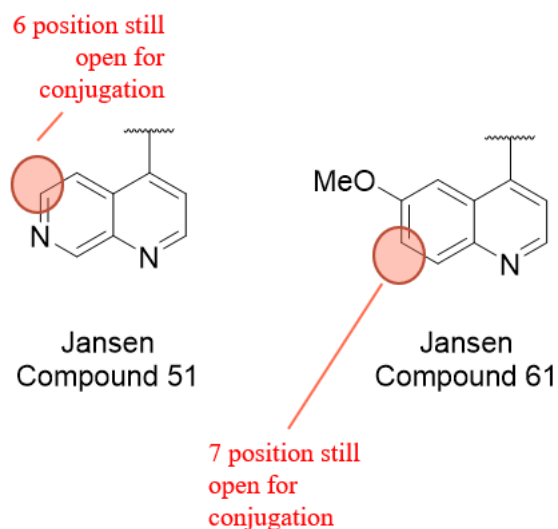
80. To justify selection of Compound 60 as the “A” moiety from the compounds disclosed in Jansen, Dr. Zeglis applied a multi-step classification process that supposedly prioritizes selectivity, then affinity, followed by qualitative assessments of stability, hydrophobicity, and ease of modification, which he illustrates using a Sankey diagram. EX1003, ¶¶149–155. However, that framework is unsupported by evidence and does not reflect how a POSA would have evaluated the full Jansen dataset, as I explained in my first declaration, and summarize in the annotated figure below. EX2001, ¶¶78–83.



81. Briefly, Dr. Zeglis does not justify his selectivity and affinity cutoffs. EX2001, ¶78. He also does not explain how these two criteria would have been evaluated in conjunction with the other parameters disclosed in Jansen, including solubility, stability, cytotoxicity, and pharmacokinetics. EX2001, ¶79.

82. He further excludes compounds with both high selectivity and affinity based on conclusory “hydrophobicity” or “bioconjugation” concerns without evidentiary support, while discarding compounds that fall outside the claim scope in favor of Compound 60. EX1003, ¶154; EX2001, ¶¶79–82. In particular, Dr. Zeglis eliminates Jansen’s Compounds 51 and 61, which, by Dr. Zeglis’s own statements, have high selectivity and affinity, because these compounds purportedly “would pose bioconjugation issues because of their 7 and 6 position substitutions, respectively, on the quinolinyl ring would be occupied.” EX1003, ¶¶154–155; EX2001, ¶80. However, both Compounds 51 and 61 have position 6 or

7 available for conjugation, as explained in my first declaration and shown below:



EX2001, ¶80. Yet, Dr. Zeglis does not explain why both positions on both compounds need to be open to avoid bioconjugation issues.

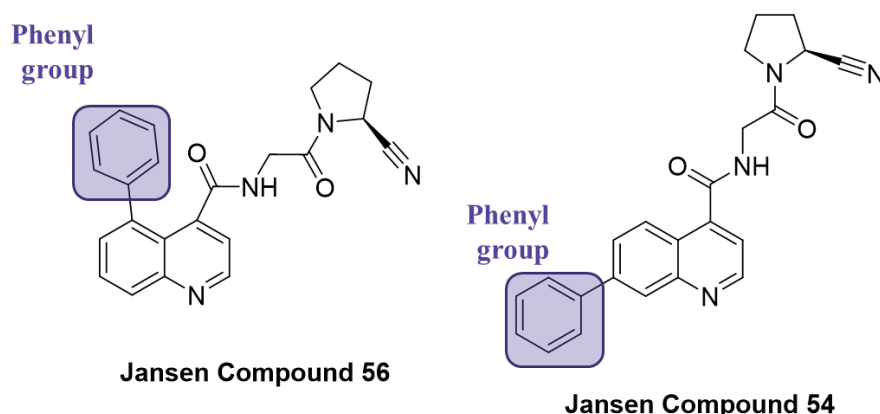
83. But choosing either of the above compounds as a FAPi in a radiotracer would have resulted in compounds outside of the challenged claims because Compound 51 does not have a quinolinyl ring required by the claims (due to the presence of an additional nitrogen in the ring) and Compound 61 has a substituent on the quinolinyl ring (MeO-) that is not allowed by the claims.

EX2001, ¶81. Thus, Dr. Zeglis discarded Compounds 51 and 61 in favor of Compound 60 in hindsight.

84. Additionally, Dr. Zeglis does not explain the threshold for determining when hydrophobicity might pose a concern, or the reason why pharmacokinetic parameters need to be considered at all considering that the

claimed compounds need not be used *in vivo*. EX1003, ¶155; EX2001, ¶82. Dr.

Zeglis eliminates Compounds 54 and 56, which also have sufficient affinity and selectivity according to Dr. Zeglis's criteria, due to unsubstantiated "hydrophobicity concerns" because of the presence of a phenyl ring on the quinolinyl ring (EX1003, ¶154), as illustrated below:



85. But Dr. Zeglis fails to show any evidence that a single pendant phenyl ring disqualifies a FAPi from consideration based on pharmacokinetic concerns. EX2001, ¶83. And indeed, a POSA would not have eliminated well performing compounds, such as Jansen's Compound 56 or 54, solely because of a pendant phenyl ring. A POSA would have known that pendant phenyl groups, alone, do not result in unfavorable pharmacokinetic properties. *See, e.g.*, EX2045, 2213–2214, FIG. 7 (describing compounds with "pendant phenyl groups" as having "lower lipophilicity ... and excellent *in vivo* efficacy"); EX2046, 2535 (describing a dipeptidyl peptidase IV inhibitor compound with a substituted "pendant phenyl group" as having "excellent pharmacokinetic properties"); EX2047, 254–256

(describing diazepam variations with “unsubstituted” “pendant phenyl” groups as “essential tools for translational neuroscience”). Instead, Dr. Zeglis discards Compounds 54 and 56 because they both contain substituents that are excluded from the claimed compounds. Thus, once again, Dr. Zeglis discarded Compounds 54 and 56 in favor of Compound 60 in hindsight.

86. But even applying Dr. Zeglis’s own criteria to the quinoline-based compounds, the literature discloses over twenty compounds with a high selectivity, defined by Dr. Zeglis as > 100 (EX1003, ¶153), such that a POSA would *not* have been led uniquely—or even preferentially—to Compound 60 absent hindsight driven by the claim limitations. US-650 and Jansen 2013 both disclose five FAPis that not only meet Dr. Zeglis’s selectivity and affinity criteria but outperform Compound 60, as I discussed above. Section VII.C.1. Dr. Zeglis agrees that these compounds have higher selectivity for FAP over PREP than Compound 60. *See* EX2023, 154:21–157:14 (agreeing that “Compound 21 [of US-650] is more selective than Compound 60,” agreeing that “Compound 22 [of US-650 is] more selective for FAP over PREP versus Compound 60,” agreeing that Compound 24 of US-650 is “more selective for FAP over PREP versus Compound 60,” agreeing that Compound 11 of US-650 “is more selective than Compound 60,” and agreeing that Compound 53 of Jansen is “more selective than Compound 60”).

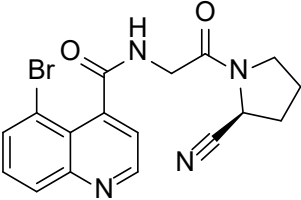
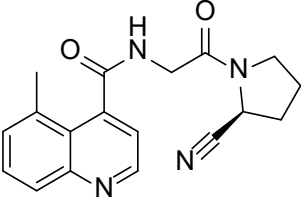
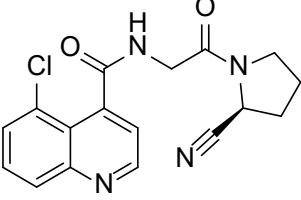
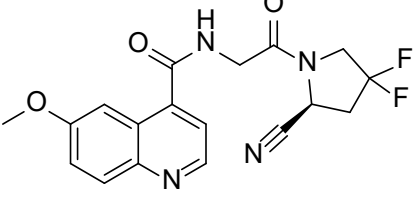
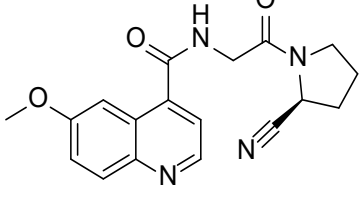
87. Even Jansen reports multiple compounds with higher selectivity than

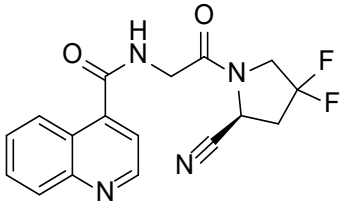
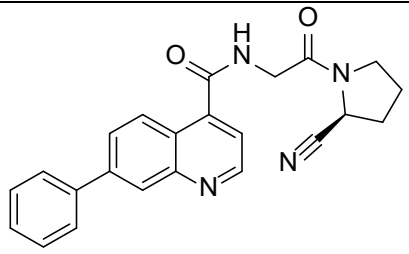
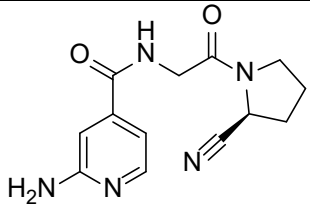
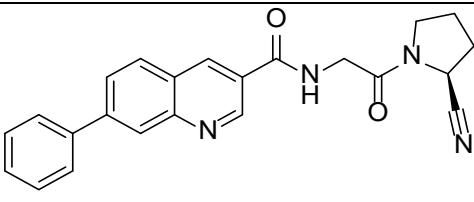
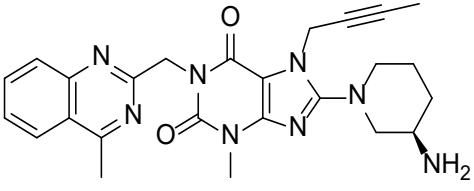
Compound 60. For instance, Compounds 53 and 61 have a selectivity of 2100 and 970, respectively. Yet Dr. Zeglis discounts Compound 53 because “it was not possible to compare the *in vitro* [microsomal] stability, PK, bioavailability and *in vivo* characteristics” of this compound to Compound 60. EX1003, ¶157; EX1006, Table 7. Dr. Zeglis also discards Compound 61 due to “the longer and more pronounced *in vivo* FAP inhibition results observed for compound 60 relative to compounds 5 and 61.” EX1003, ¶160. But, as discussed above, the claims do not require any particular *in vivo* use, and thus, do not require any particular surrogate markers of *in vivo* characteristics, such as microsomal stability. *See, e.g.*, EX2042, 525–526 (noting that a compound’s metabolism is often assessed using “*in vitro* profiles in liver microsomes”). As such, Dr. Zeglis’s failure to properly consider these selective small molecule FAP inhibitors for incorporation into a FAP radiotracer is based on hindsight.

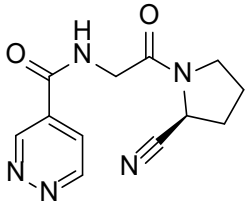
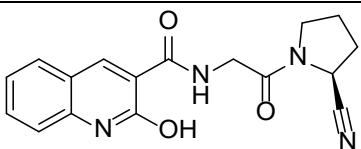
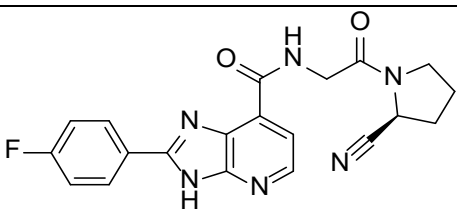
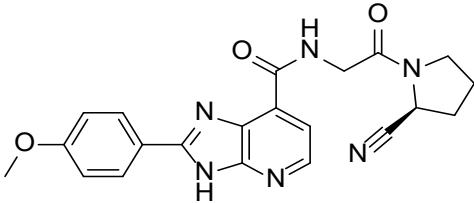
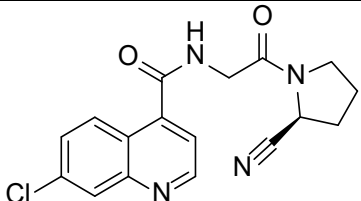
88. A tabulated set of FAPis across the quinolinyl-based references, Jansen, US-650, Jansen 2013, and Jansen 2014 that meet Dr. Zeglis’s criteria (selectivity >100) is shown below, ranked in the order of selectivity (calculated by dividing $IC_{50}^{PREP}/IC_{50}^{FAP}$) that Dr. Zeglis characterized as the “most important” characteristic. EX1003, ¶¶55, 151.

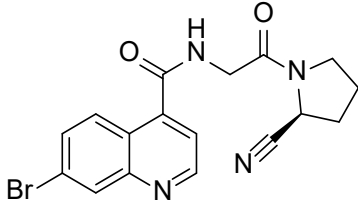
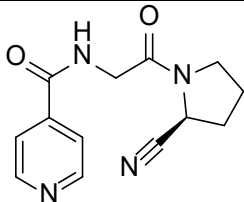
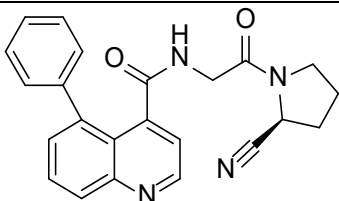
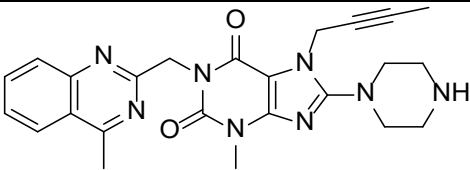
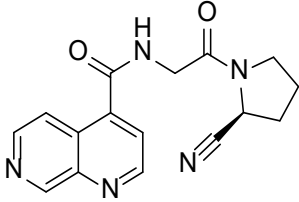
Top prior-art FAPis, ranked by selectivity in Jansen, US-650, Jansen 2013,

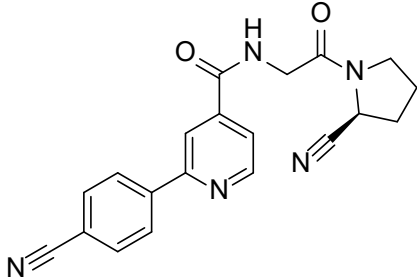
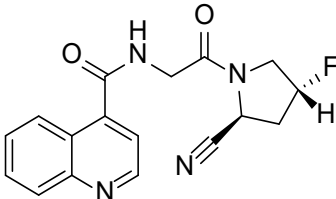
and Jansen 2014.

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

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claimed "A" structure ?
US 650: 1 Jansen: 60		0.0032	562	Y
US 650: 25		0.07	280	N
Jansen: 32		0.138	244.2	N
Jansen: 54		0.070	277.1	N
Jansen 2014: 3		0.37	>270	N

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claimed "A" structure ?
Jansen: 38		0.164	237.8	N
US 650: 38 Jansen 2013: 24		0.16	230	N
Jansen: 48		<0.2	>200	N
US 650: 28 Jansen: 49		<0.2	>200	N
US 650: 13 Jansen 2013: 31		0.0071	197	N

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claimed "A" structure ?
US 650: 12 Jansen 2013: 32		0.0062	193	N
US 650: 4 Jansen: 29		0.063	179	N
US 650: 26 Jansen: 56		0.064	135	N
Jansen 2014: 13a		0.74	>135	N
US 650: 33 Jansen: 51		0.028	120	N

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claimed "A" structure ?
US 650: 16 Jansen: 35		0.27	107	N
Jansen: 59		1	>100	Y

89. Applying Dr. Zeglis's own selectivity and affinity criteria, the data summarized in the table above show that, among the twenty-two highest-performing compounds disclosed across Jansen, US-650, and Jansen 2013, only two—Compound 60 and Compound 59 in Jansen—fall within the scope of the claimed "A" moiety. Notably, Compound 60 is not the strongest candidate within that group; five other compounds (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)

exhibit superior selectivity and affinity for FAP. *See* EX2001, ¶85.

90. Thus, selecting Compound 60 from this set cannot be explained by the technical record and would only have been made with knowledge of the claim limitations, not from the perspective of a POSA evaluating the prior art as it existed before 2017.

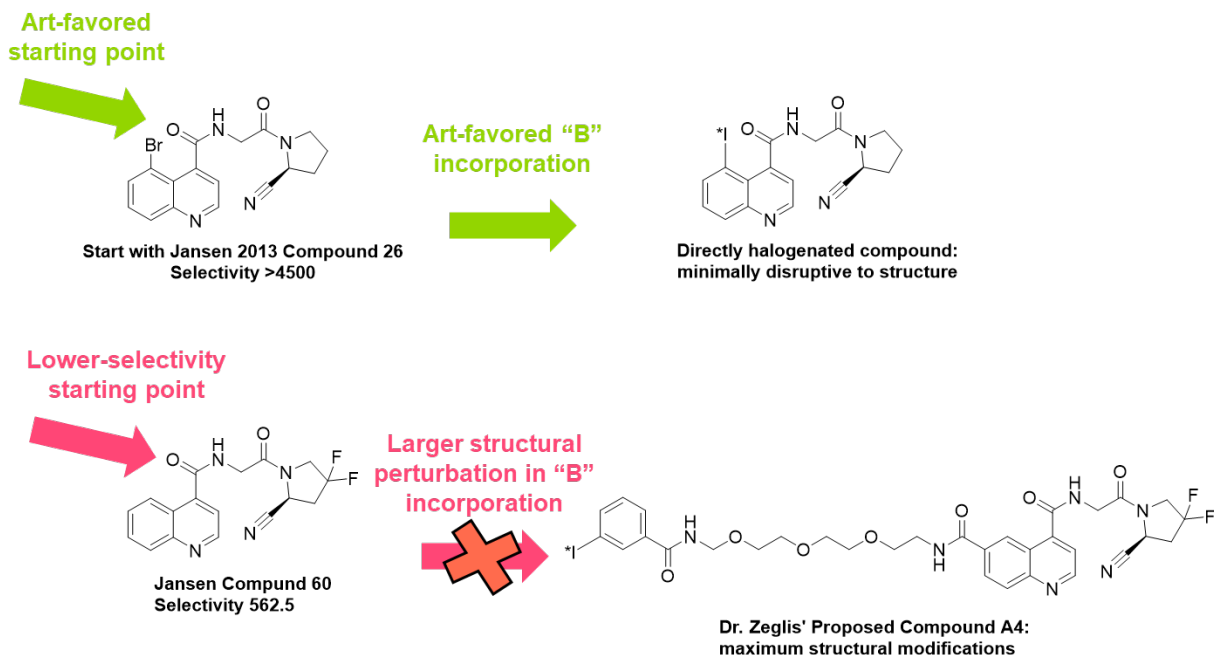
3. Dr. Zeglis’s selection of compound 60 is driven by the claims’ B-L-A architecture, not by the prior art

91. Dr. Zeglis’s selection of Compound 60 is not the result of following the technical teachings of the prior art, but rather reflects a claim-driven choice necessitated by the requirement to arrive at the claimed B-L-A compounds. As demonstrated by Jansen 2013, the most selective quinolinyl-based FAP inhibitors—Compounds 25 and 26—achieved their superior affinity and selectivity precisely through halogen substitution at the quinolinyl ring, a modification that the prior art recognized as beneficial, yet was lacking from Compound 60. EX1007, 493–494 (“[i]ntroducing a chlorine or bromine substituent at the 5-position of the quinoline ring” results in the “selectivity with respect to PREP of these inhibitors [to] sharply increase[] ... rendering them *the most favorable* affinity/selectivity profile of all FAP inhibitors we had identified so far” (emphasis added)); *see also* EX2001, ¶¶68-69. Starting from those compounds, a POSA would have had little reason to remove the halogen and introduce a bulky L-B assembly; instead, the prior art would have pointed toward direct isotopologous

substitution as the most straightforward and least disruptive route to a radiotracer.

EX1014, 44; EX1010, 3; *see also* EX2001, ¶¶68-69.

92. Dr. Zeglis avoids that conclusion by selecting Compound 60, which lacks the halogen substitution that drove favorable SAR in Jansen 2013. He then argues—contrary to the disclosed SAR for quinolinyll compounds—that a POSA would have viewed linker-based modification as preferable to direct radiohalogenation due to purported “adverse effects” of halogen substitution. EX1003, ¶175. That argument is inconsistent with the data in Jansen 2013 showing that halogenation of the quinolinyll ring, going from Compound 7 to Compound 25 or 26, enhanced selectivity. *See* Section VII.D *infra*. Indeed, the prior art described direct radiohalogenation as a versatile and well-established approach, particularly where the parent compound already contained a halogen shown to support binding and selectivity. EX1014, 44; EX1010, 3. The more plausible explanation for Dr. Zeglis’s approach is that beginning with the most selective compounds in the art would have undermined any argument that a POSA would have abandoned direct halogenation in favor of a B-L-A structure with a naked quinolinyll ring.



93. Thus, Dr. Zeglis selected Compound 60 not because it would have stood out to a POSA based on the prior art, but because it is one of the few compounds that can be retrofitted into the claimed B-L-A framework. By working backward from the claim requirements and discounting the most favorable SAR in the art, Dr. Zeglis substitutes hindsight for technical reasoning. Nothing in the prior art suggests that a POSA, starting from the most selective known FAP inhibitors, would have removed beneficial halogen substitutions and replaced them with linkers and chelators, rather than pursuing direct isotopologous labeling consistent with established radiotracer design principles.

D. A POSA would not have added "B" and "L" to Compound 60 in an effort to make a FAP radiotracer

94. Even assuming that a POSA would have been motivated to develop a small molecule FAP radiotracer, which Dr. Zeglis does not show, the claimed

B-L-A compounds would not have been obvious. When choosing to develop a small molecule FAP radiotracer, a POSA would have had several options, including either (i) appending a bulky chelating moiety or a prosthetic group—thereby materially altering the molecule and risking the FAPi’s selectivity and affinity in forming a B-L-A structure—or (ii) directly attaching a radiohalogen to form a radiotracer without materially altering its structure. *See, e.g.*, EX1013, 260; EX1014, 44. Dr. Zeglis agrees that a POSA would have been faced with these choices. *See, e.g.*, EX1003, ¶¶41–44; EX2023, 90:21–92:8, 94:2–97:3. Critically, the direct halogenation approach, which Dr. Zeglis agrees avoids bulky linkers and chelators and introduces minimal changes to the molecular structure of a FAPi (EX2023, 92:15–93:1, 98:1–99:5), would have led a POSA to compounds outside the scope of the claims, underscoring that the claimed B-L-A architecture would not have been an obvious design choice. Further, in constructing hypothetical B-L-A compounds that Dr. Zeglis said a POSA would have been motivated to do (which I do not agree), Dr. Zeglis failed to show that a POSA would have selected the particular linker (a three-monomer polyethylene glycol (PEG)) from the prior art, thus failing to show that a POSA would have arrived at the claimed B-L-A compounds.

1. A POSA would not have been motivated to make “B-L-FAPi” based on general radiotracer principles

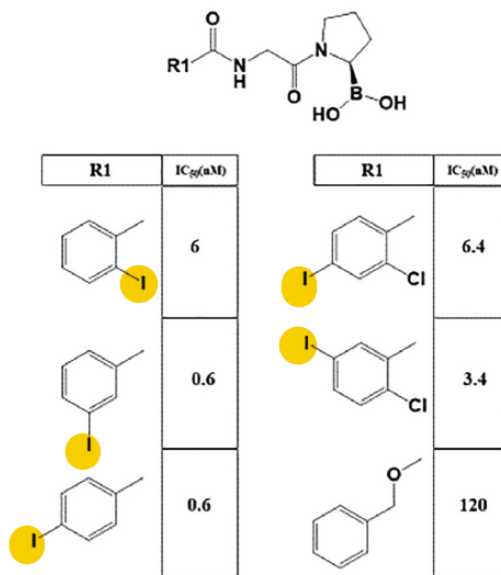
95. To arrive at the claimed invention (“B-L-A” with “A” being

Compound 60, as per Dr. Zeglis), a POSA would have had to modify a small molecule FAPi by considerably changing its structure—adding a bulky B-L substituent. Dr. Zeglis failed to show that the art would have directed a POSA towards making FAPi-based radiotracers by adding the bulky B-L substituent (as the claims require) instead of directly radiohalogenating FAPis.

96. Specifically, a POSA would have known that radioiodination, a type of direct halogenation, was frequently described as “the most versatile radiolabeling strategy” prior to October 23, 2017. EX2024, Abstract. This is because before 2017 it was known that even small changes to inhibiting moieties could dramatically alter their behavior, as Dr. Zeglis concedes: “slight modifications to the structure of a targeting moiety can alter its selectivity and affinity for its target.” EX1003, ¶59; *see also* EX2019, 58 (for “many small molecules ... modest changes in the molecular structure ... can have dramatic effects on the solubility [and] binding properties ... of the agent”). Yet Dr. Zeglis argues that a POSA would have done the exact opposite of making a slight modification when developing a FAP-targeting radiotracer (*i.e.*, added a “B-L” to alter the FAP’s structure). EX1003, ¶175.

97. Indeed, consistent with the notion that direct halogenation of a targeting moiety would have been a versatile radiolabeling strategy, the first small molecule FAP radiotracers were based on a series of iodine-substituted benzamido-

glycine-boronoproline analogs, as shown below. EX1035, Abstract.



98. Thus, the prior art as a whole touted the benefits of direct halogenation, and thus, if anything, would have motivated a POSA to develop a B-FAPi radiotracer, not a B-L-FAPi radiotracer, as the claims require.

2. Dr. Zeglis does not show how a POSA would have selected the particular linker from the prior art in his obviousness analysis

99. Dr. Zeglis's position is that, in constructing a B-L-A compound, a POSA would have selected a specific linker—namely, a three-monomer polyethylene glycol (PEG) linker. EX1003, ¶199. He derives that selection from selecting PEG from US-633's laundry list of linkers and US-633's broad genus of linkers. EX1003, ¶185. Those disclosures, however, encompass a wide range of possible linkers, and Dr. Zeglis does not explain why a POSA would have selected this particular PEG linker instead of the many other disclosed options. In doing so,

Dr. Zeglis again attempts to retrofit the prior art to arrive at compounds that fall within the claimed scope, rather than explaining how the prior art itself would have guided a POSA to that specific choice. A PEG linker of any length is neither highlighted nor specifically described anywhere in US-633, yet Dr. Zeglis plucks this linker out of the broadly disclosed genus to use in his hypothetical compounds. EX1003, ¶ 99.

100. To justify selecting a three-monomer PEG linker from US-633's broad and generic disclosure, Dr. Zeglis asserts that a POSA would have sought to create approximately 10–20 bond lengths between the targeting and reporter moieties, and that a three-monomer PEG would have provided that separation. EX1003, ¶¶122, 187. He provides no support for why a POSA would have targeted that bond-length range with Jansen's Compound 60, cites no authority for it, and elsewhere acknowledges that shorter linkers are also suitable. EX1003, ¶187; EX2023, 182:4–20 (noting that linkers shorter than 10 bonds would “not necessarily” have meant that the reporter moiety would have interfered with the targeting moiety's ability to bind to its target).

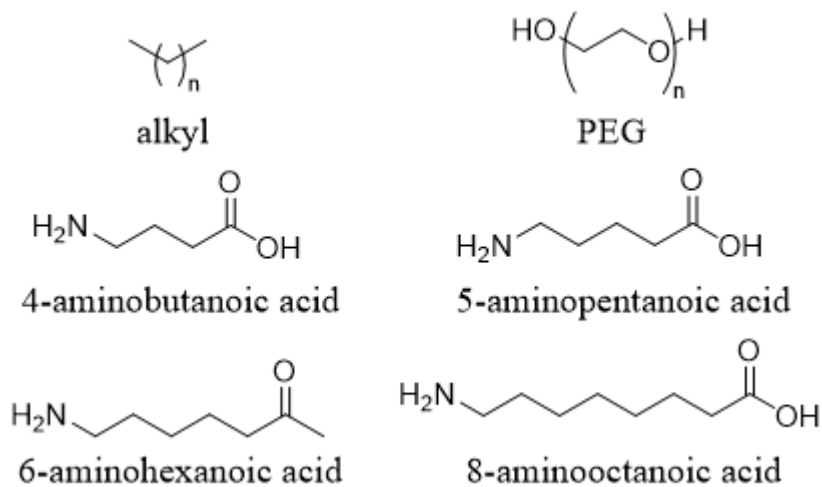
101. Dr. Zeglis further attempts to justify his “PEG-based” linker selection by arguing that a POSA would have been familiar with PEG-based linkers before 2017. EX1003, ¶122. In support, he cites a reference noting that long PEG increases the lipophilicity of radiopharmaceuticals. EX1003, ¶122 n.129 (“long

poly(ethylene glycol) (PEG) or hydrocarbon chains ... increase the lipophilicity [of radiopharmaceuticals]”); EX1018, 5. But Dr. Zeglis does not explain why that general familiarity or property would have led a POSA to select a PEG linker here, particularly where he elsewhere invokes similar considerations (e.g., hydrophobicity⁷) to exclude certain compounds from Jansen in order to arrive at Compound 60. EX1003, ¶154.

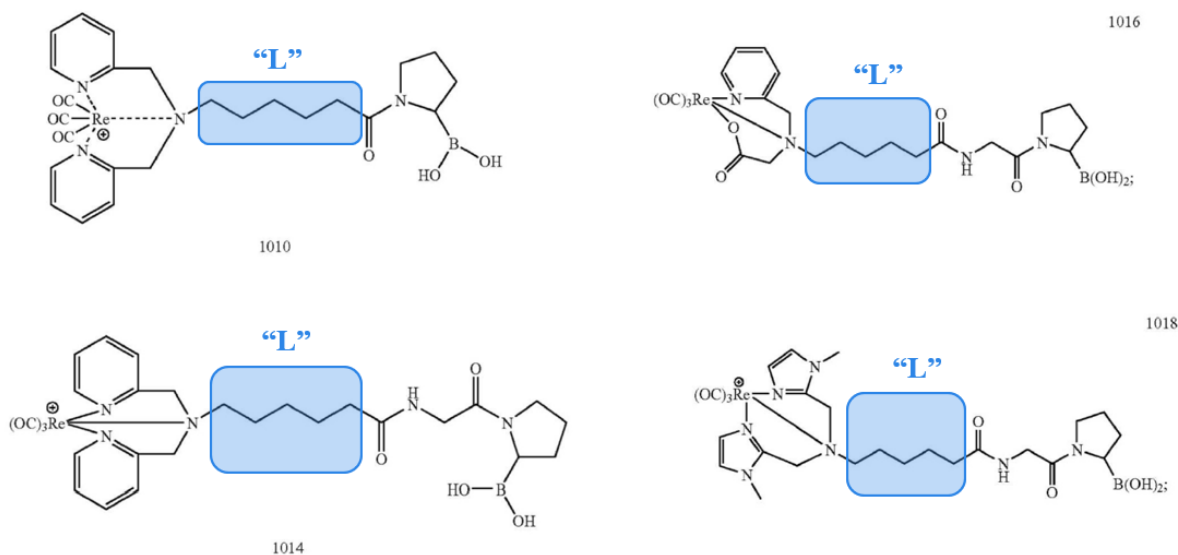
102. Furthermore, Dr. Zeglis does not explain why a POSA would not have selected any of the other linkers disclosed in US-633. Indeed, US-633 discloses many potential linkers such as “a simple alkyl chain as shown, a PEG $(\text{CH}_2\text{CH}_2\text{O})_n$, a polyethylene amine $((\text{CH}_2\text{CH}_2\text{NH})_n)$, or the like. Terminal aminoalkanoic acids (such as β -alanine, 4-aminobutanoic acid, 5-aminopentanoic acid, 6-aminohexanoic acid and the 8-aminooctanoic acid) or amino-PEG-acids $(\text{NH}_2-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2-\text{COOH}$, e.g. 2-(2-(3-aminopropoxy)ethoxy)acetic acid).”

⁷ Lipophilicity and hydrophobicity are closely related concepts, both describing a compound’s tendency to associate with nonpolar environments. EX2025, 183–184, 197. Lipophilicity refers to a compound’s affinity for lipid or fat-like phases, while hydrophobicity describes its tendency to avoid aqueous environments; in practice, increased lipophilicity generally corresponds to increased hydrophobic character in biological systems.

EX1004, ¶130. Example structures of such linkers are shown below:



Moreover, the linkers in US-633's compounds contain alkyl chains. Importantly, *none* of US-633's compounds contain a PEG-based linker. Annotated examples of such compounds are provided below:



EX1003, ¶¶157, 160, 162.

103. Dr. Zeglis himself notes in Ground 2 that it is important for a POSA

“to avoid ‘recreating the wheel’ by starting with one or more of the examples of radiotracers in US-121 and using the chelator-linker portion of these examples with a new targeting moiety (i.e., compound 60).” EX1003, ¶235; *see also* EX1003, ¶238 (“starting with compound SRV27 that is shown on page 40 of US-121, and replacing [only] the *targeting moiety* with Compound 60, yields a radiotracer I designated Compound B1”) (emphasis added); EX1003, ¶239 (“[o]ther examples of compounds that would result from replacing the *targeting moiety* of compounds in US-121 with compound 60 include Examples B2, B3 and B4” (emphasis added)). But Dr. Zeglis does not explain why, in Ground 1, he decides to “recreat[e] the wheel” by replacing *both* the targeting moiety and linker, rather than starting with one or more of the examples of radiotracers in US-633 and simply replacing the targeting moiety only.

104. Dr. Zeglis proposes that FAP radiotracers, including those that contain PEG-based linkers, could be used *in vivo*. *See, e.g.*, EX1003, ¶169. But, a skilled artisan would have known that the use of PEG-based linkers in imaging and therapeutic agents came with its own set of drawbacks. For example, researchers developing radionuclide therapies compared PEG-11 with six-carbon long alkane linkers, and found that, the compound containing the PEG linker “resulted in reduced tumor uptake and increased retention of activity in the kidneys,” thereby “compromis[ing] the beneficial tissue distribution” seen with the compound

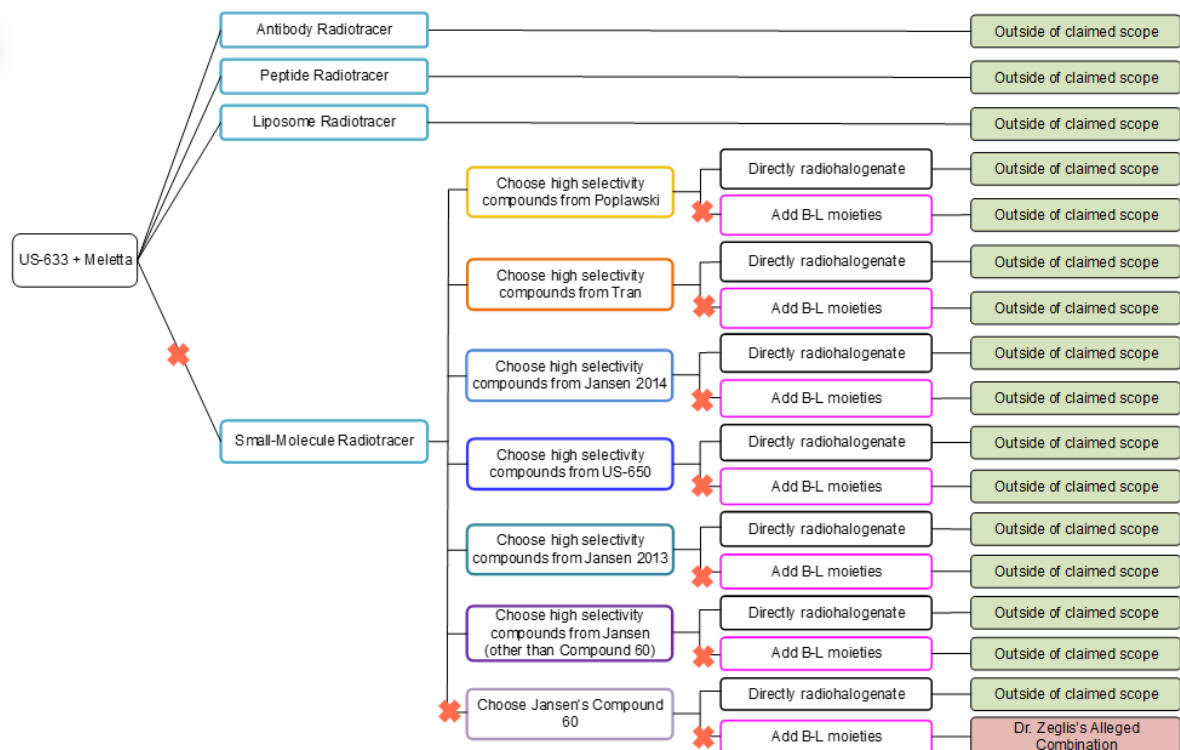
containing the alkane linker. EX2026, 823, 830. Thus, the authors concluded that a “PEG spacer compromised the beneficial effects of the lead compound,” while “the design with a short alkane spacer appeared to be promising.” EX2026, Abstract. In the face of at least one example showing that a PEG linker was detrimental, Dr. Zeglis failed to show that a POSA would have selected this linker over others.

105. In sum, Dr. Zeglis did not show that the compounds made with his choice of linkers would have rendered the '233 claims obvious.

* * *

106. In sum, a POSA seeking to develop a low molecular weight FAP radiotracer before 2017 would have confronted multiple, independent layers of choice, including selection of the overall molecular platform and pharmacophore (e.g., antibody-, peptide-, immunoliposome-, or small molecule), the choice of a particular FAP-targeting pharmacophore within any selected molecular platform, and the selection of an appropriate radiolabeling strategy (such as direct radiohalogenation versus incorporation of a B-L construct, including those with prosthetic groups). As illustrated in the diagram below, only one narrow combination of pharmacophore and labeling decisions would have led to the claimed invention. And, as explained above, following that path would have required a POSA to make a series of non-obvious and technically disfavored

choices, rather than choices suggested or favored by the prior art.

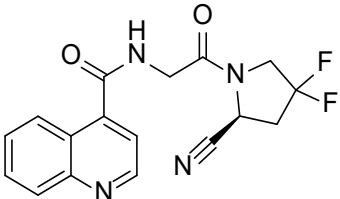
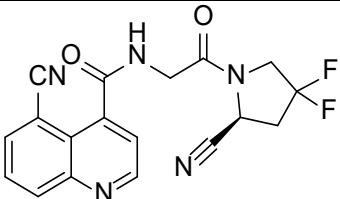


E. Even if a POSA had a reason to combine Jansen’s Compound 60 with “B” and “L,” a POSA would not have had a reasonable expectation of success in doing so

107. Even though I do not agree that a POSA would have been motivated to combine US-633 with Jansen in view of Meletta, even assuming such a motivation for the sake of argument, the prior art would not have provided a reasonable expectation of success in arriving at the claimed compounds. As discussed above, the only pre-2017 small-molecule FAP radiotracer evaluated for selectivity—Meletta—failed when evaluated in vitro. Meletta reported that its radiolabeled FAP inhibitor did not selectively accumulate in FAP-expressing tissue

and showed no meaningful ability to distinguish FAP-positive tissue from normal tissue. EX1008, 2089–2090. Thus, the prior art affirmatively demonstrated that low molecular weight FAP radiotracers lacked sufficient selectivity, and a POSA would not have derived any reasonable expectation of success for small-molecule FAP radiotracers from Meletta or the surrounding art.

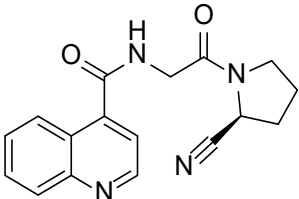
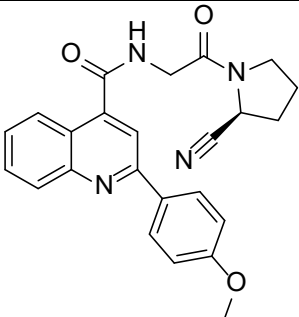
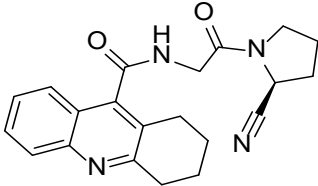
108. Further, the pre-2017 literature taught that even very small structural modifications to quinoliny-based FAP inhibitors could profoundly impair affinity and, more importantly, selectivity for FAP. Indeed, Jansen shows that adding certain substituents to the quinoline, such as a cyano group, completely destroy the selectivity of Compound 60. The selectivity of Jansen's Compound 63, for example, decreased from 562.5 to 2.3 when the cyano group is added to the quinoline, meaning that a POSA would not have had a reasonable expectation of success in adding a large substituent to the quinoline ring, in light of Jansen's SAR. Jansen, Table 5. A comparison of these compounds is provided in the table below.

Jansen Compound Number	Structure	FAP Affinity (μM)	Selectivity Index
60		0.0032	562
63		7.2	2.3

109. Jansen 2013 further illustrates this sensitivity of substitutions at the quinoline, showing that attachment of substituents on the quinolinyl group can negatively—and sometimes dramatically—affect compound selectivity.

Compound 7 exhibits a FAP affinity of 0.0103 μM and a selectivity of 83.

EX1007, Table 3. Incorporation of an anisole group (approximately 108 Da) or a cyclohexyl group (approximately 56 Da), as in Compounds 22 and 23, similarly degrades FAP selectivity, reducing the selectivity index from 83 (Compound 7) to 0.1 and 24, respectively. EX1007, Table 3. A comparison of these compounds is provided in the table below.

Jansen 2013 Compound Number	Structure	FAP Affinity (μ M)	Selectivity Index
7		0.0103	83
22		>10	>0.1
23		0.77	24

110. Jansen 2013 expressly reports that “substituents in the 2- and 3-position of the quinoline ring, as in compounds 19–24, have a clearly negative effect” on FAP potency. EX1007, 493. Jansen further explains that “both steric (19, 22, and 23) and electronic (20, 21, and 24 ...) factors seem to be contributive” to this loss of activity. EX1007, 493. A POSA would have understood these disclosures as a warning that modifying the quinoline ring was poorly tolerated. It was only until after the disclosure of working examples from the ’233 patent that a POSA would have understood this quinolinyl ring to be able to tolerate modification in certain sites on the ring. EX1001, 57:61-61:23.

111. Before 2017, a POSA would have understood these data to demonstrate that quinolinyl-based FAP inhibitors could be highly intolerant of structural modification, and therefore possibly poorly suited for conjugation strategies that require appending additional groups, depending on the site of conjugation. This concern would have been especially acute given that prospective “B” and “L” moieties are substantially larger than a single methyl substituent.

112. That understanding reflected the view in the art until the ’233 patent demonstrated for the first time that small molecule FAPis could nonetheless be used to make low molecular weight FAP radiotracers. Accordingly, prior to October 23, 2017, a POSA would not have had a reasonable expectation of success in arriving at the claimed B-L-A compounds.

VIII. CLAIMS 1–4 OF THE ’233 PATENT WOULD NOT HAVE BEEN OBVIOUS OVER US-121 AND JANSEN (GROUND 2)

113. As with Ground 1, Dr. Zeglis does not demonstrate that a POSA would have arrived at the claimed invention, because his analysis of both the selection of the “A” moiety and the use of a modular B-L-A design is guided by hindsight. In Ground 2, Dr. Zeglis relies on US-121—which discloses B-L-A-type radiotracers for imaging an unrelated protein (PSMA)—together with Jansen, the same reference he relied upon in Ground 1. EX1003, ¶¶207–232; *see also* EX2023, 158:11–16 (noting that US-121 “relates to PSMA-targeting compounds and the uses thereof”). Dr. Zeglis argues that a POSA would have combined these

references because “a skilled artisan would have considered the radiotracer designs illustrated in US-121 when evaluating how to create other low molecular weight radiotracers for tumor imaging based on small molecule targeting moieties.”

EX1003, ¶227. But as in Ground 1, Dr. Zeglis does not consider whether a POSA would have pursued an alternative to a small molecule FAP inhibitor, such as antibodies or peptides. *See* Sections VII.B.2–3. Nor does Dr. Zeglis consider the broader non-quinoliny1 based FAPis when evaluating which FAP-targeting moiety a POSA would have selected for incorporation into a radiotracer. Additionally, Dr. Zeglis does not account for the broader quinoliny1-based FAPi literature—including Jansen 2013, Jansen 2014, and US-650—when evaluating which FAP-targeting moiety a POSA would have selected for incorporation into a radiotracer. *See* Section VII.C. Nor does he explain, under his own stated criteria, why a POSA would have selected Compound 60 in light of numerous disclosed FAP inhibitors that outperform it. *See* Section VII.C; *see also* EX2001, ¶¶87-88.

114. US-121 adds nothing to the selection of the “A” moiety, as it does not concern FAP-targeting compounds at all—a point Dr. Zeglis himself acknowledges. EX1003, ¶210; EX2023, 157:15–158:16. And, without a disclosure of the “A” moiety, it also cannot aid a POSA in determining whether to directly halogenate or add a “B-L” to the A moiety. Thus, Dr. Zeglis’s assertion that a POSA would have broadly considered US-121 when designing other radiotracers

is based on hindsight.

IX. OBJECTIVE EVIDENCE DEMONSTRATES THAT THE CLAIMS WOULD NOT HAVE BEEN OBVIOUS

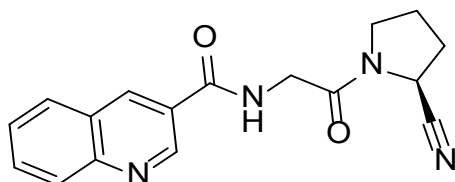
115. Dr. Zeglis failed to show that a POSA would have had a motivation to combine or a reasonable expectation of success in arriving at the claimed invention. In addition to this failure, objective indicia of non-obviousness, such as unexpected results, further confirm that the claimed compounds would not have been obvious to a person of ordinary skill in the art.

A. Unexpected results demonstrate that the Claimed Compounds would not have been obvious

116. Specifically, the claimed B–L–A compounds exhibit a selectivity index, $SI_{FAP/PREP}$, that is orders of magnitude greater than the demonstrated selectivity of the corresponding “A” compounds alone—an outcome that would have been unexpected to a person of ordinary skill in the art before 2017.

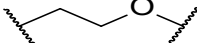
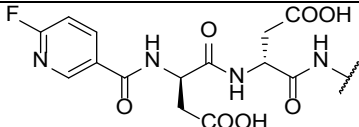
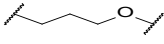
117. Considering the claimed “A” as having the most importance due to it being the FAP-targeting moiety, the closest prior art would be Jansen 2013, which discloses the FAP-selectivity of “A”s encompassed by the claims. Here, the claimed “B-L-A” compounds exhibit dramatic, orders-of-magnitude improvements in selectivity for FAP over PREP ($SI_{FAP/PREP}$) relative to the corresponding “A” alone. Specifically, when Jansen 2013 Compound 7, pictured below, was conjugated to a linker (“L”) and reporter moiety (“B”), the resulting claimed “B–

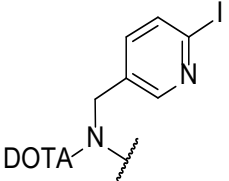
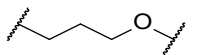
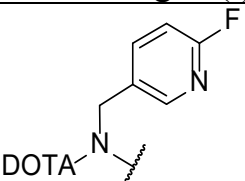
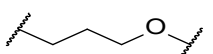
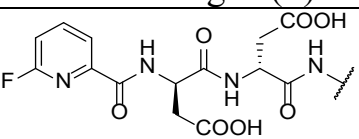
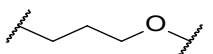
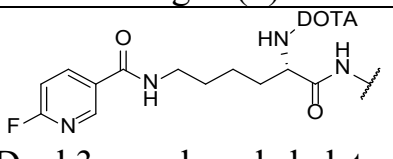
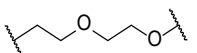
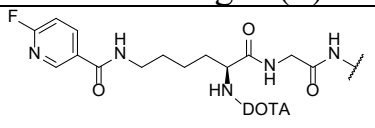
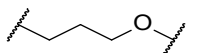
L–A” compounds exhibited increased selectivity by several orders of magnitude compared to Compound 7, reaching values in the hundreds of thousands and, in one such “B-L-A” compound, exceeding one million. EX1002, 174–176 (Pomper Declaration, ¶42).

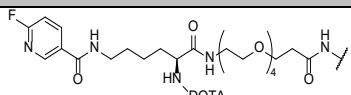
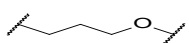
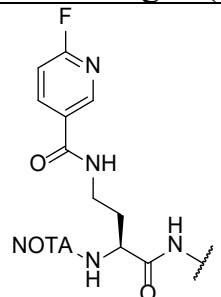
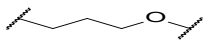
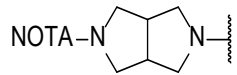
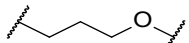
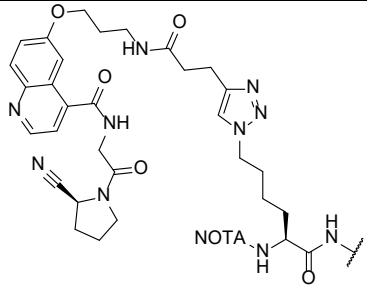
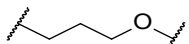


Compound 7. EX1007 (Jansen 2013), Scheme 1, Table 2.

118. The table below summarizes these data and compares them to the selectivity of Jansen 2013 Compound 7, which had a $SI_{FAP/PREP}$ of 86. Dr. Zeglis does not discuss or address these data in his declaration, even though it would have been available to him from the prosecution history of the '233 patent family.

“B” Moiety	“L” Moiety Structure	B-L-A MW (g/mol)	B MW (g/mol)	Selectivity Index/Increase compared to A alone
 Halogen (F)		370	19.0	4,111 ~48-fold improvement
 Prosthetic group with a halogen (F)		734	369.3	66,084 ~768-fold improvement

“B” Moiety	“L” Moiety Structure	B-L-A MW (g/mol)	B MW (g/mol)	Selectivity Index/Increase compared to A alone
 Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (I)		983	620.4	1,418,440 ~16,493-fold improvement
 Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (F)		876	502.4	1,052 ~12-fold improvement
 Prosthetic group with a halogen (F)		734	369.3	5,807 ~68-fold improvement
 Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (F)		1049	652.7	779 ~9-fold improvement
 Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (F)		1073	711.4	1,693 ~20-fold improvement

“B” Moiety	“L” Moiety Structure	B-L-A MW (g/mol)	B MW (g/mol)	Selectivity Index/Increase compared to A alone
 Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (F)		1266	888.4	407 ~5-fold improvement
 Dual 2-membered chelator (NOTA) / prosthetic group with a halogen (F)		889	525.3	10,694 ~124-fold improvement
 2-membered chelator (NOTA)		761	397.3	11,893 ~134-fold improvement
 Dual 2-membered chelator (NOTA) / second FAPi moiety		1282	918.0	1,313 ~15-fold improvement

119. This dramatic increase in selectivity is not at all predictable from the starting selectivity of the “A” compounds, and reflects a qualitative and

unexpected shift in properties, attributable to the claimed “B-L-A” structure as a whole. The prior art would not have led a POSA to expect that attaching a linker and reporter group to a small molecule FAP inhibitor would have so profoundly enhanced selectivity. To the contrary, the art taught that even minor substitutions on known FAP inhibitors often degrade affinity and selectivity. *See, e.g.*, EX1014, 44; EX1010, 3; EX1003 ¶¶44, 46, 59(b); EX1017, 2669; EX1007, 493; EX1044. Indeed, Dr. Zeglis himself 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.” EX2023, 151:19–152:1.

120. As another point of comparison, the selectivity exhibited by the claimed compounds is vastly superior to that of Meletta’s radiotracer, and cannot be explained by the baseline properties of the underlying “A” moiety. Meletta’s MIP-1232 displays a selectivity index of just 32, making it between ~12-fold to greater than ~44,000-fold less selective than the exemplified claimed compounds. EX1002, 174–176 (Pomper Declaration, ¶42); *see also* EX1035, Abstract. Critically, this dramatic disparity does not track with the starting selectivity of the corresponding “A” moiety in the claimed and tested compounds (Table above), which has a selectivity index of approximately 86—only about 2.7-fold greater than Meletta’s compound. EX1007, Table 2; EX1035, Abstract; EX1002, 174–176 (Pomper Declaration, ¶42). Thus, the orders-of-magnitude improvement observed

in the claimed compounds cannot be attributed to the inherent selectivity of the “A” moiety alone, but instead reflects an unexpected and non-linear enhancement arising from the claimed “B–L–A” design. The orders-of-magnitude improvement observed here thus strongly supports non-obviousness.

121. There is a direct nexus between the unexpected selectivity gains observed here and the limitations recited in the claims. As I explained, and Dr. Zeglis agrees, the claims require a specific “B–L–A” structural architecture comprising a quinolinyl “A” moiety covalently linked, through a linker “L,” to a reporter or labeling group “B.” It is precisely this claimed structure that gives rise to the dramatic increases in FAP/PREP selectivity. In contrast, the corresponding quinolinyl compound disclosed in Jansen 2013 lacks the claimed “B–L–A” configuration and exhibits selectivity values that are approximately 5-fold to more than 16,000-fold lower than those of the claimed compounds. The improved selectivity seen with the claimed compounds is a difference in kind, not merely a difference in degree, because incorporation of the “A” moiety into the claimed “B–L–A” compounds suppresses off-target binding and produces a qualitatively different selectivity profile than that of the prior art.

122. Likewise, Meletta’s radiotracer does not include the claimed quinolinyl “A” moiety, nor does it have the claimed “B–L–A” architecture, and is approximately 44,000-fold less selective than the most selective claimed example,

and still roughly 12-fold less selective than the least selective claimed embodiment. These comparisons demonstrate that the observed orders-of-magnitude improvement in selectivity does not arise from the baseline properties of the underlying pharmacophore, but instead results from the claimed “B–L–A” structure as a whole, thereby establishing a clear and direct nexus (connection) between the claimed invention and the unexpected results.

123. The unexpectedly high selectivity observed for the claimed compounds is representative of, and expected across, the full scope of claims 1–4 of the '233 patent. The exemplified compounds span a wide, representative range of molecular and structural diversity across the claimed genus of compounds. The eleven examples cover molecular weights from approximately 370 g/mol to over 1,280 g/mol, encompassing an order of magnitude difference in molecular weights. They also vary substantially in reporter functionality—including halogens, prosthetic groups, chelators, and dyes—as well as steric bulk and functional group composition. The “B” moiety alone ranges from extremely small (e.g., 19 g/mol for a halogen such as fluorine) to quite large (e.g., 1,066.2 g/mol for a dye). Despite this diversity across the dimensions of claim scope, each exemplified species exhibited excellent FAP selectivity, with PREP/FAP selectivity indices ranging from 407 to 1,418,440. *See supra* ¶118. These consistent results across structurally diverse embodiments confirm that the unexpected selectivity is a

property of the claimed “B–L–A” architecture itself and is reasonably expected to extend across the full scope of the challenged claims.

124. In sum, the claimed compounds do not merely preserve the selectivity of known FAP inhibitors, but instead achieve an unexpected and extraordinary improvement in FAP selectivity that the prior art neither taught nor suggested. This orders-of-magnitude enhancement in selectivity is directly tied to the claimed “B–L–A” structure and is precisely the type of unexpected result that strongly supports non-obviousness under §103.

X. THE ’233 PATENT CLAIMS HAVE SUFFICIENT WRITTEN DESCRIPTION (GROUND 3)

A. The claimed invention recites a compound, not a result

125. As discussed above in Section VI.A, and as I described in my previous declaration, given the plain language of the claims, a POSA would have understood the challenged claims to recite structurally defined, not functionally defined compounds. EX2001, ¶46. Although the “*B*” moiety must be suitable for specific uses, the claims do not require that the claimed “B-L-A” compounds have this functionality. Similarly, “L” must have the capability to form a chemical bond between “B” and “A,” but the claims do not require that the claimed compounds have this function—and indeed, such a function would be nonsensical.

126. Dr. Zeglis repeatedly demands a function of the claimed compounds, despite no functional requirements being present. For example, he describes that

the compounds need to be “viable [as] optical imaging agents or radiolabeled imaging or therapeutic agents.” EX1003, ¶273. Further, he argues in his section on written description that the claimed compounds need to be “useful as optical imaging agents, or as diagnostic or therapeutic radiopharmaceuticals.” EX1003, ¶248; *see also* EX2001, ¶¶89–90. In doing so, Dr. Zeglis does not analyze whether the claimed compounds *themselves* are described—which, as I understand it, is the correct analysis—but rather whether the specification describes using the claimed compounds *in vivo*.

127. And even putting aside the fact that Dr. Zeglis conducts an incorrect analysis by requiring a specific activity of the claimed compounds, the specification describes other applications for the claimed compounds (besides *in vivo* applications), as I explained in detail in my first declaration. EX2001, ¶91, ¶18–19. For example, the ’233 patent discusses *in vitro* diagnostic applications such as biodistribution analysis, *in vitro* analysis of tumor responses, or other research applications. EX2001, ¶¶91-93, 18–19.

128. As such, Dr. Zeglis reached his conclusion regarding lack of written description by improperly requiring that the claimed compounds must function *in vivo*.

B. The specification contains adequate disclosure to support description of the claimed invention

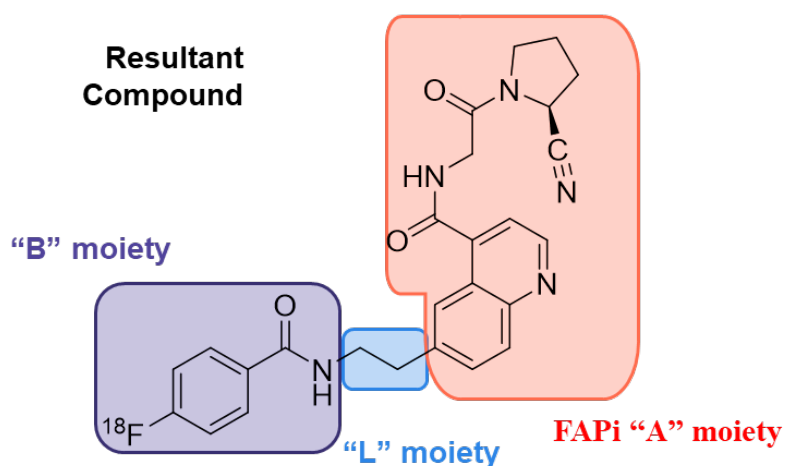
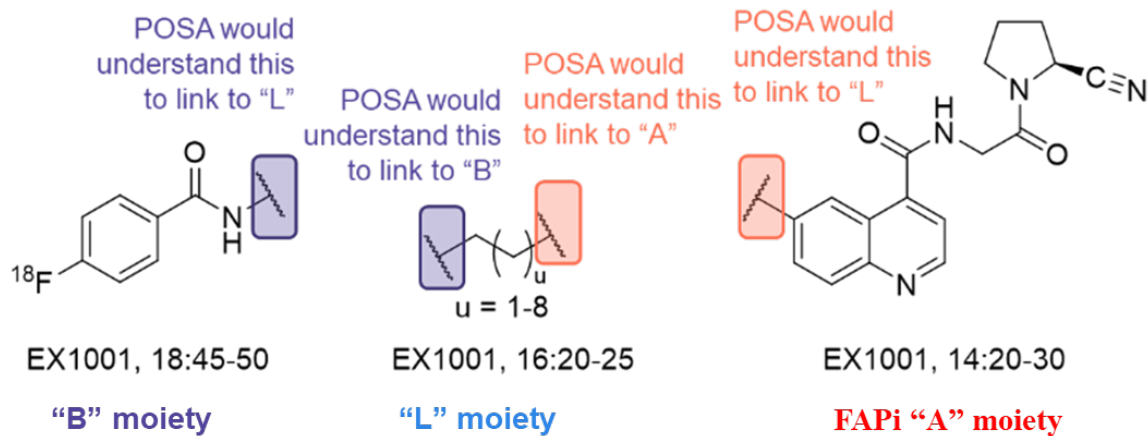
129. As I explained in detail in my previous declaration, the specification

of the '233 patent describes many “B-L-A” compounds because extensive guidance is given as to the structures that performed the recited “B” and “L” functions. EX2001, ¶94. Briefly, the claimed invention is a combination of known “B” and “L” moieties, along with the structurally defined “A” formula. In the '233 patent specification, there are dozens of exemplary “A,” “L,” and “B” moieties that a POSA would have used when making the claimed compounds. EX1001, 12:50-32:45; *see also* EX2001, ¶¶94–96; EX1003, ¶251 (Dr. Zeglis describing that the '233 patent lists an “incredible diversity” of options for “B” and “L” components). The '233 patent also incorporates by reference a multitude of references to provide even more examples of such suitable moieties that a POSA would have been able to incorporate into “B-L-A” radiotracers. EX1001, 8:25-32,17:46–54; EX2001, ¶97. As 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.

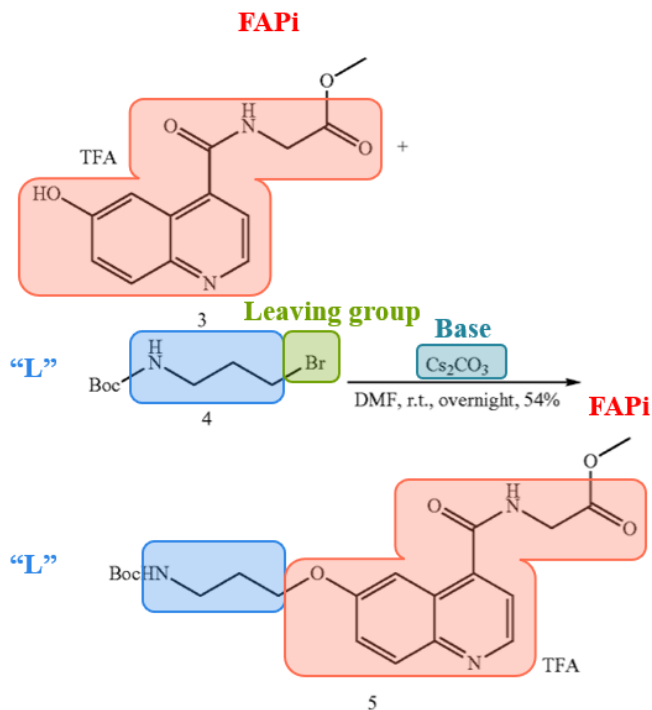
130. Further, the potential “B-L-A” moieties that a POSA would have used are bolstered by what was known in the art as of the critical date of the '233 patent. Indeed, Dr. Zeglis himself admits that a POSA would have had at their disposal many well-known options, including an “extensive survey of known chelators,” “many more options for prosthetic groups,” and a “number of well-known” groups used for ¹⁸F-based radiopharmaceuticals. EX1003, ¶¶254–255, 256, 262; *see also*

EX2001, ¶102; EX2023, 54:21–55:1 (“many common prosthetic groups and many common chelators were not described in the ’233 patent”). And in Dr. Zeglis’s declaration, Dr. Zeglis argues that the ’233 patent specification provides “limited guidance” about chelator chelator-radionuclide choices. EX1003, ¶254. However, I understand that the patent specification need not re-describe these known elements.

131. A POSA with experience in developing and evaluating radiotracers would have known how to combine these known “A,” “B,” and “L” moieties as disclosed in the ’233 patent specification. Specifically, as described in my previous declaration, a POSA would have understood that the labeled attachment points of each “B” and “L” group are where each of these compounds attach to one another. EX2001, ¶100. As an example, I have taken three disclosed “B,” “L,” and “A” moieties from the ’233 patent and annotated them, in color, the way a POSA would have understood.

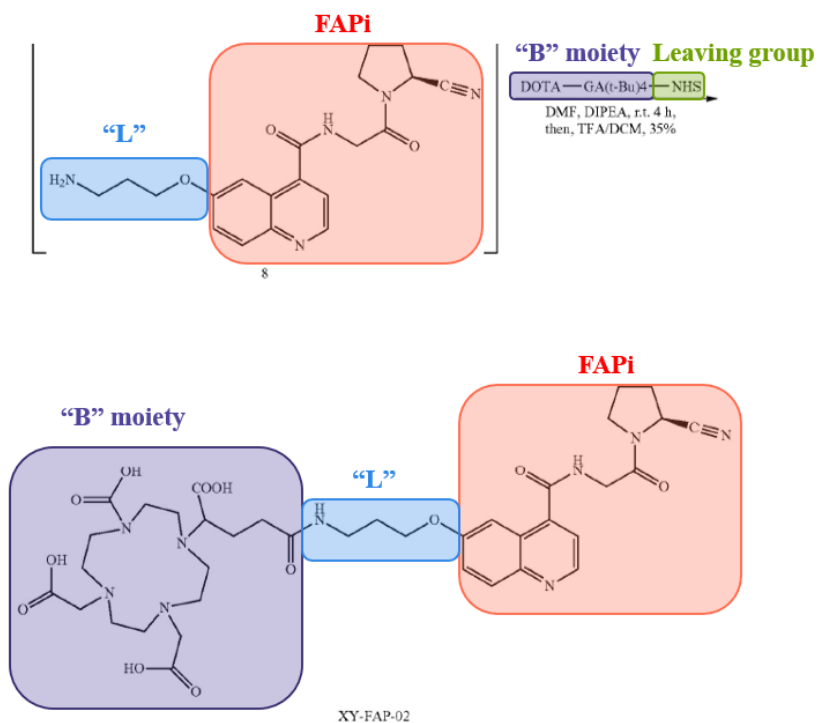


The '233 patent describes forming A-L intermediates. For instance, the '233 patent teaches the following base-promoted S_N2 reaction in one of its working examples. EX1001, 51:22–48. This type of reaction is a standard organic chemistry reaction. See EX1033, 136; *see also* EX2048, Abstract; EX2049, Abstract.



A POSA would have readily understood that linker 4 above could be swapped out for any other linker that has a suitable leaving group to form a variety of A-L moieties. In the example above, the leaving group is a Br⁻ anion, but the leaving group could be a variety of leaving groups, as is known in the art, such as other halogens, amines, tosylates, or triflate. *See, e.g.*, EX1050, 169; EX1033, 136. A POSA would have been aware of these options when deciding how to incorporate a linker into the claimed invention. As such a POSA would have understood this disclosure to not only describe a single A-L species, but also a broad genus of A-L species using standard chemistry procedures. To attach “B” to A-L, the ’233 patent teaches conjugation of a terminal amine to DOTA (as shown below) and to an IR dye, Li-COR-800, by way of N-hydroxysuccinimide (NHS)-based chemistry,

wherein a terminal amine forms a new amide bond with the “B” moiety, displacing NHS as a leaving group.



EX1001, cols. 55–56 (annotated).

A POSA would have readily understood that a wide variety of “B” moieties could be conjugated using NHS-based (or other activated ester) chemistry, as was readily known in the art. *See, e.g.*, EX1017, 2683 (stating that “[e]lectrophiles, such as ... N-hydroxysuccinimide (NHS) esters ... are typical groups for conjugation that have been developed to modify biomolecules with the appropriate [bifunctional chelating agent]”). Dr. Zeglis himself has used some of these NHS reactions in his own work. EX2057, 5 (describing the purchase of “[a]mine-reactive AlexaFluor

680 (AF680-NHS) ... from ThermoFisher Scientific”). A POSA would also have understood that, apart from NHS-based chemistry, there were a variety of other choices of functional groups that could be used to conjugate “B” moieties onto the primary amine linker of the A-L compound, such as chemistries in which the primary amine acts as a nucleophile in the presence of a “B” group with an accessible electrophile (such as an aldehyde). Examples of these well-known types of chemistries are reviewed in, e.g., Wilbur, and are exemplified in, e.g., Glaser. EX2051, Tables 3-9; EX2052, Abstract, Scheme 1. Other conjugation chemistries that could have been used in this way include Fmoc chemistry and so-called “click” chemistry, all of which was well-known in the art. *See, e.g.*, EX1003, ¶63 (Dr. Zeglis conceding that “click” chemistry was known in the art); EX2053, Abstract. In sum, a POSA would have known of many types of chemistry reactions suitable for making the claimed invention from the modular “B,” “L,” and “A” moieties, and that such disclosures of various linkers and “B” moieties used in the examples are illustrative, rather than limiting.

132. Further, POSAs would have had at their disposal a wide variety of pyrrolidine building blocks to choose from. Indeed, a search on the chemical supply site Fisher Scientific for the term “pyrrolidine” yields over 6,000 results, including hundreds of examples of alkyl-substituted groups, halogenated groups,

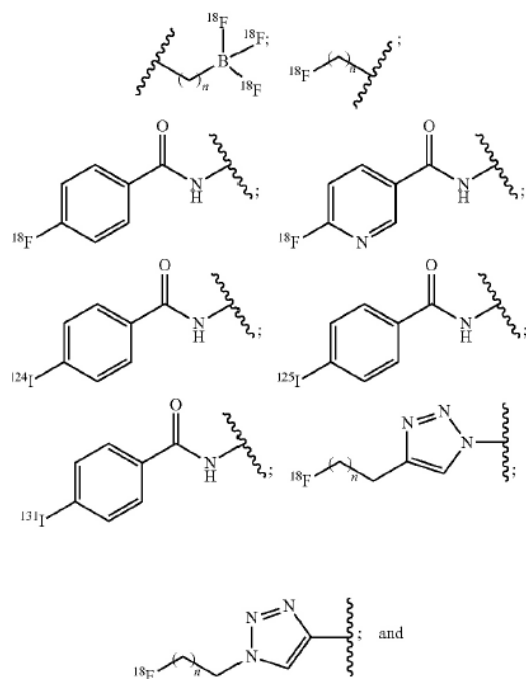
heteroaryl groups, and similar modifications.⁸ A POSA would have been able to readily incorporate a desired pyrrolidine group into the FAPi synthesis step above. Further, a POSA would have immediately that one pyrrolidine derivative could have been substituted for another without altering the overall synthetic scheme, as it involves standard and well-known chemical synthetic methods. *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. As such, a POSA would have understood the '233 patent disclosure to describe a wide range of FAPis that fall within the claimed "A" scope, particularly in view of the high level of skill in the field. As such, a POSA would have understood the individual disclosures of "B" and "L" moieties to disclose "B-L-A" compounds incorporating any of the moieties. In doing so, a POSA would have understood the specification to provide sufficient species representative of the claimed genus, and thus likewise would have readily understood the inventors of

⁸ These results would have not have significantly changed from 2017 until now, as substituted pyrrolidine groups have been used in synthetic organic chemistry for a long time. *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.

the '233 patent to have possession of the claimed subject matter.

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

133. Dr. Zeglis also argues that the '233 patent provides “no examples of B-L-A compounds with a radiolabeled prosthetic group,” in his written description analysis. EX1003, ¶252. This characterization is inaccurate. The '233 patent does describe B-L-A compounds with a radiolabeled prosthetic group as a POSA would have understood it. EX1001, 18:35–70. In fact, Dr. Zeglis agrees that that the specification discloses “six different chemical formulae” (“B” moieties) that provide radiolabeled prosthetic groups and “*ten* examples based on those formulae.” EX1003, ¶253 (emphasis added). Each of those radiolabeled prosthetic “B” groups, is illustrated in the '233 patent specification with the “L” attachment point demarcated in the structures with a squiggly line, as shown below. EX1001, 18:35–70; EX2001, ¶¶99-101.



EX1001, 18:35–70.

134. Dr. Zeglis does not explain why this disclosure, when combined with the rest of the '233 patent specification's disclosures, is not sufficiently representative of "B-L-A" compounds with a radiolabeled prosthetic group. A POSA would have read those disclosures and understood that the labeled attachment points are where each of the radiolabeled prosthetic groups could be attached an "L" moiety. Similarly, the '233 patent specification marks the intended attachment points of the "L" and "A" moieties to each other. As described above in Section X.B and below in Section XI.A, a POSA would have understood how to combine the various "B," "L," and "A" disclosures to yield a radiotracer of the claimed compounds, and this applies to the "B" radiolabeled prosthetic group "B" moieties as well. EX2001, ¶¶99-101. As such, a POSA would have understood

from the individual disclosures of radiolabeled prosthetic “B” moieties that the ’233 patent discloses “B-L-A” compounds incorporating such moieties.

D. Given the specification’s disclosure of the modular nature of the “B-L-A” examples and its disclosure of how to put these modular components together, the specification’s disclosure is sufficient to describe the full scope of the “B-L-A” radiotracers

135. As described above, the disclosure of the ’233 patent describes a wide variety of “B” and “L” moieties that a POSA would have known how to put together in order to arrive at the claimed compounds. In addition, the ’233 patent also describes how to put together these moieties in the form of two working examples. A POSA would have understood these working examples as giving instructions for how to put together these moieties. Indeed, as Dr. Zeglis himself admits—and I agree—the claimed compounds are modular, containing “three primary components:” “(a) a *targeting moiety* ... (b) a *reporter moiety* ... and (c) a *linker*[.]” EX1003, ¶37; EX2001, ¶93. Dr. Zeglis further emphasizes, as I also agree with this, that this design “allows one to replace individual components when designing, synthesizing and evaluating a new radiopharmaceutical or optical imaging agent.” EX1003, ¶38; EX2001, ¶93. This admission signifies that Dr. Zeglis knows that a POSA would have been able to easily swap out these “modular” components with one another, increasing the ability of a POSA to incorporate the enumerated “B” and “L” moieties that are described in “incredible diversity” in the ’233 patent.

XI. THE '233 PATENT CLAIMS ARE ENABLED (GROUND 4)

136. I understand that a patent specification must teach a POSA how to make and use the full scope of the claimed invention without undue experimentation to show enablement. I further understand that some experimentation is permissible and does not preclude enablement, such as routine experimentation.

137. In my opinion, the '233 patent claims are enabled because the '233 patent teaches a POSA how to make and use the claimed low-molecular-weight B-L-A compounds. These claims do not require any function, yet Dr. Zeglis bases his enablement analysis on the theory that the claims must meet *in vivo* performance criteria, such as biodistribution, pharmacokinetics, and clinical efficacy. EX1003, ¶¶59, 273–277; EX2001, ¶¶104–105. Because the '233 patent provides a modular and easily reproducible synthetic scheme, a POSA would have been able to make the full scope of the claimed compounds using routine chemistry. And that '233 patent teaches a POSA how to use the claimed compounds by disclosing the *in vitro* applications of these compounds. And any additional effort to confirm the utility (such as the selectivity of a given compound) would have involved routine experimentation—a proposition with which Dr. Zeglis agrees. As such, the claimed invention is enabled by the '233 patent specification.

A. A POSA would have been able to make the claimed compounds without undue experimentation

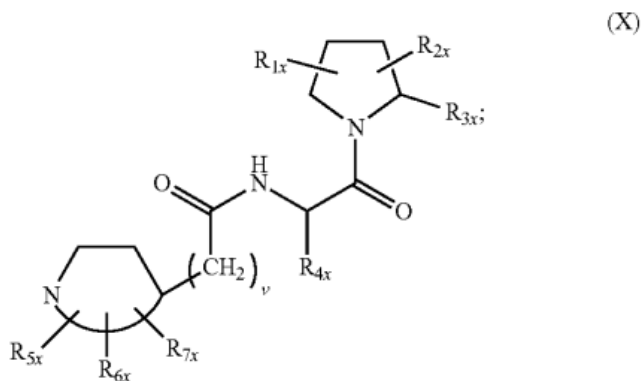
138. As described below, a POSA would have been able to make the claimed compounds without undue experimentation. The '233 patent provides sufficient enabling disclosure to allow a POSA to put together modular “A,” “L,” and “B” moieties. And the scope of the claimed “A” moiety would not have contributed to undue experimentation for a POSA trying to make the full scope of the claimed invention.

1. A skilled artisan guided by the specification would have understood how to combine modular “B,” “L,” and “A” moieties

139. The disclosure of the '233 patent fully equips a POSA to make the claimed “B-L-A” compounds based on its modular design using the “B,” “L,” and “A” components, which are chemically linked to form a “B-L-A” radiotracer. First, Dr. Zeglis fails to account for the instructions that a POSA was given in assembling these components together, both in the body of the specification and in the examples themselves. Second, Dr. Zeglis fails to consider the level of skill that a POSA would have had in constructing “B-L-A” compounds. When both of these aspects are properly considered, it is clear that a POSA would have been able to make the claimed invention without undue experimentation. Indeed, Dr. Zeglis himself conceded that assembling the claimed invention would have involved “conventional chemical synthesis techniques well-known to skilled artisans” and

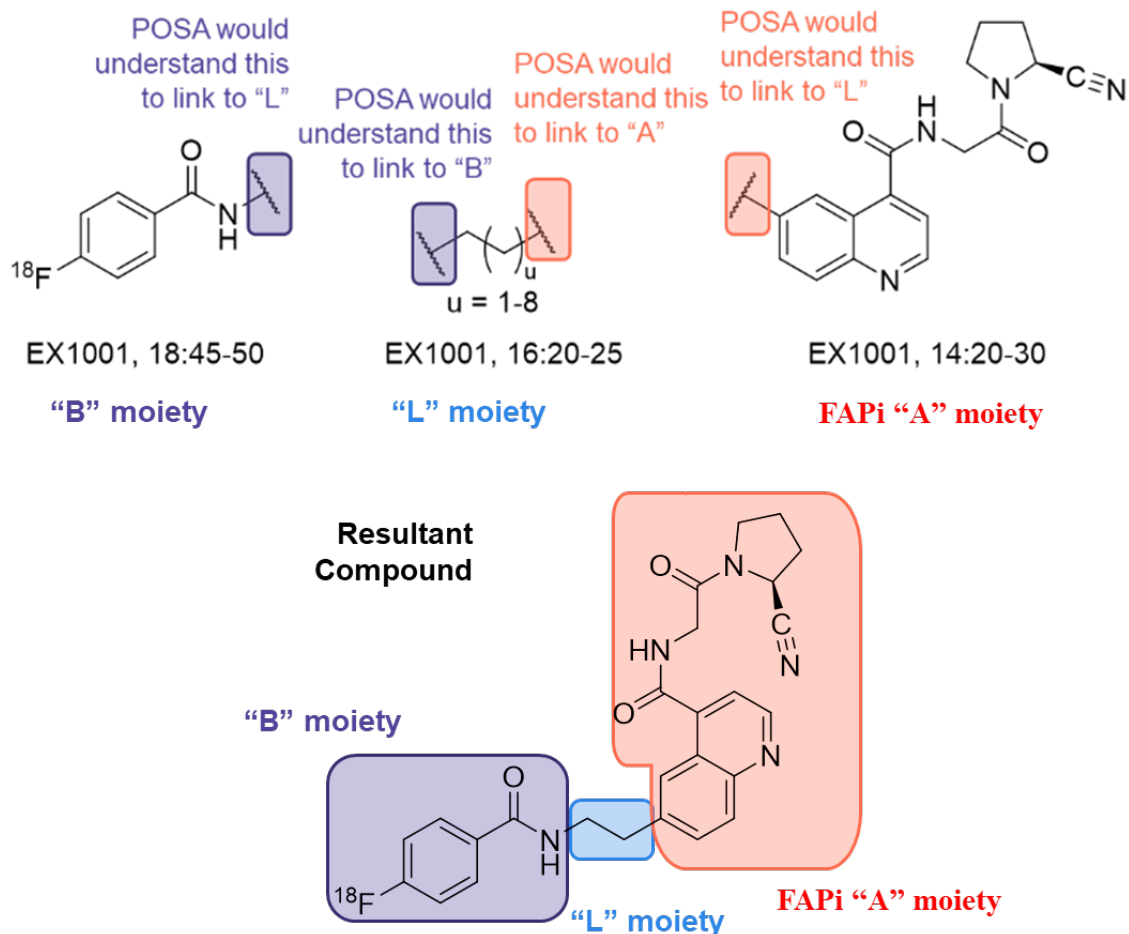
that it would have been “straightforward” for a POSA to select appropriate B and L moieties and synthesize the resulting compounds. EX1003, ¶¶121, 172. As such, Dr. Zeglis cannot argue that assembling the compounds would have required undue experimentation.

140. As discussed above in the written description section, the '233 patent discloses a myriad “B,” “L,” and “A” moieties. Section X.B *supra*; EX1001, 18-20, 20:17, 55-65; 21:20, 9-11; 24:25, 19-25; *see also* EX2001, ¶¶94-96, EX1003, ¶251. And the claims explicitly identify “A” by structure, as depicted below:



EX1001, 2:9-24.

Moreover, a POSA would have understood how to put together individual moieties as part of the claimed compounds based on the blueprint presented by the '233 patent, as depicted in the scheme below.

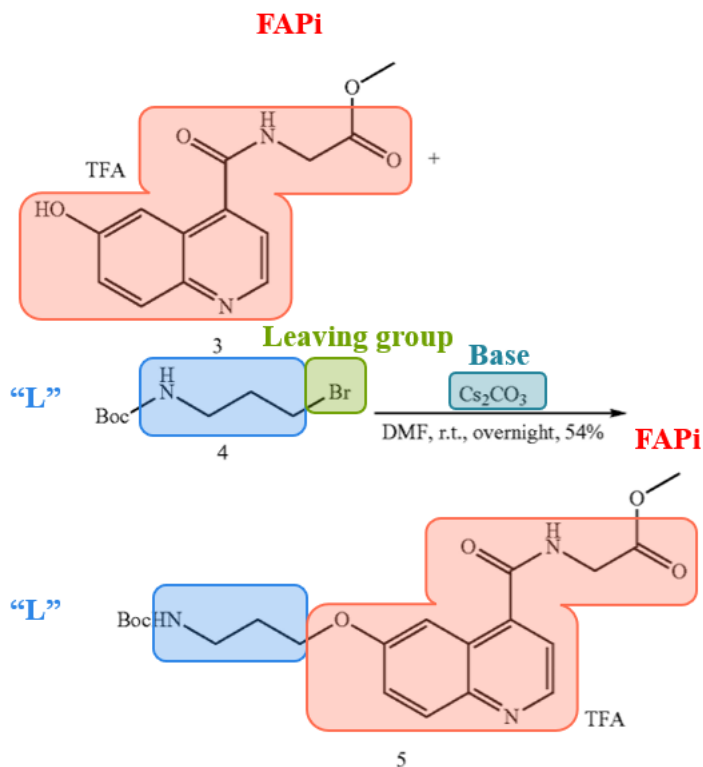


141. Indeed, the '233 patent also provides extensive direction as to where and how "L" and "B" should be conjugated to "A," to preserve FAP-binding. EX1001, 2:7–24 (describing beneficial conjugation sites as "any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle" of "A"), 10:16–30 (same), 3:45–51 (disclosing that carbons 5 through 8 of the quinolinyl ring as sites for conjugating "L"); cols. 16–32 (depicting how to conjugate "L" and "B"). Given this guidance, not only would a POSA have known what modular elements to combine to form a compound, a

POSA would also have known how to put these modular elements together.

142. In particular, for adding a linker “L” to the FAPi moiety, a POSA would have readily been able to apply the teachings of the ’233 patent to form a wide variety of A-L compounds. The ’233 patent provides guidance as to where the linker should be attached: “a point of attachment of the FAP- α binding ligand to a linker, e.g., “L,” or a reporter moiety, such as an optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging or radiotherapy ... can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyll ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.” EX1001, 12:43–50. As such, a POSA already would have been guided by the specification as to a linker location.

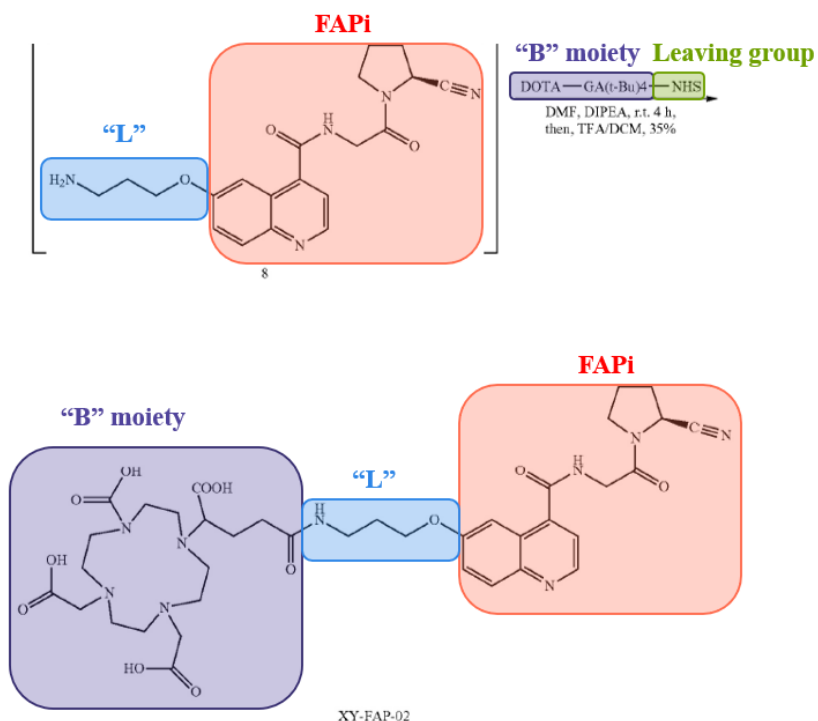
143. The ’233 patent also provides guidance for *how* to attach the linker to “A.” For instance, the ’233 patent teaches the following base-promoted S_N2 reaction in one of its working examples. EX1001, 51:22–48. This type of reaction is a standard organic chemistry reaction. *See* EX1033, 136; *see also* EX2048, Abstract; EX2049, Abstract.



144. A POSA would have readily understood that linker 4 above could be swapped out for any other linker that has a suitable leaving group to form a variety of A-L moieties. In the example above, the leaving group is a Br⁻ anion, but the leaving group could be a variety of leaving groups, as is known in the art, such as other halogens, amines, tosylates, or triflate. *See, e.g.*, EX1050, 169; EX1033, 136. A POSA would have been aware of these options when deciding how to incorporate a linker into the claimed invention. As such a POSA would have understood this disclosure to not only enable a single A-L species, but also a broad genus of A-L species using standard chemistry procedures.

145. To attach “B” to A-L, the '233 patent teaches conjugation of a terminal amine to DOTA (as shown below) and to an IR dye, Li-COR-800, by way

of N-hydroxysuccinimide (NHS)-based chemistry, wherein a terminal amine forms a new amide bond with the “B” moiety, displacing NHS as a leaving group.



EX1001, cols. 55–56 (annotated).

146. A POSA would have readily understood that a wide variety of “B” moieties could be conjugated using NHS-based (or other activated ester) chemistry, as was readily known in the art. *See, e.g.*, EX1017, 2683 (stating that “[e]lectrophiles, such as ... N-hydroxysuccinimide (NHS) esters ... are typical groups for conjugation that have been developed to modify biomolecules with the appropriate [bifunctional chelating agent]”). Dr. Zeglis himself has used some of these NHS reactions in his own work. EX2057, 5 (describing the purchase of

“[a]mine-reactive AlexaFluor 680 (AF680-NHS) ... from ThermoFisher Scientific”).

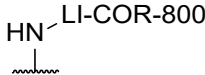
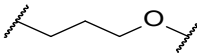
147. A POSA would also have understood that, apart from NHS-based chemistry, there were a variety of other choices of functional groups that could be used to conjugate “B” moieties onto the primary amine linker of the A-L compound, such as chemistries in which the primary amine acts as a nucleophile in the presence of a “B” group with an accessible electrophile (such as an aldehyde). Examples of these well-known types of chemistries are reviewed in, e.g., Wilbur and are exemplified in, e.g., Glaser. EX2051, Tables 3-9; EX2052, Abstract, Scheme 1. Other conjugation chemistries that could have been used in this way include Fmoc chemistry and so-called “click” chemistry, all of which was well-known in the art. *See, e.g.*, EX1003, ¶63 (Dr. Zeglis conceding that “click” chemistry was known in the art); EX2053, Abstract. In sum, a POSA would have known of many types of chemistry reactions suitable for making the claimed invention from the modular “B,” “L,” and “A” moieties, and that such disclosures of various linkers and “B” moieties used in the examples are illustrative, rather than limiting.

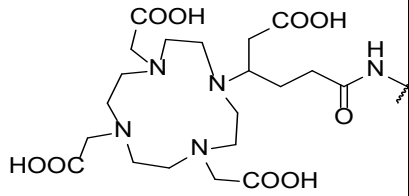
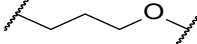
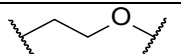
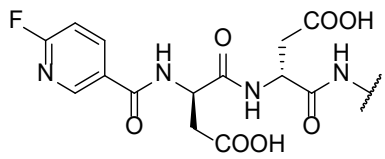
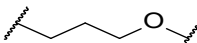
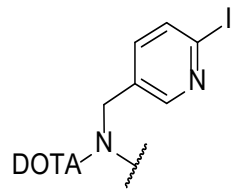
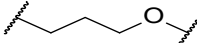
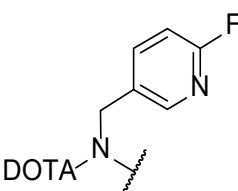
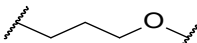
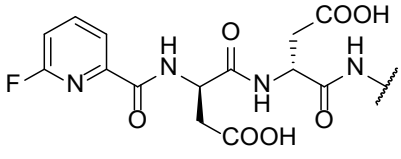
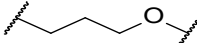
148. Additionally, as previously discussed, the level of skill here is high. While some experimentation may have been required to optimize these reaction conditions, such experimentation would have been well within the routine actions

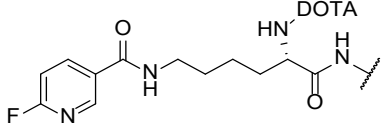
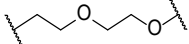
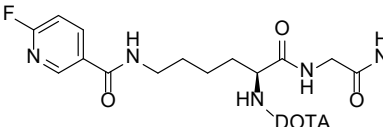
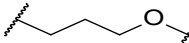
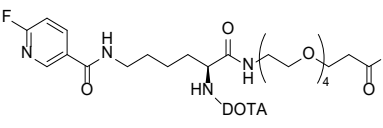
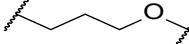
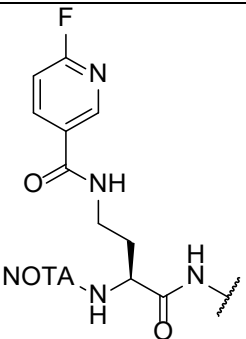
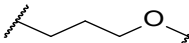
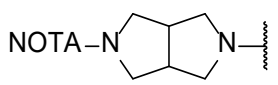
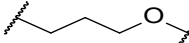
of one of skill in the art, especially given the high level of skill in this context.

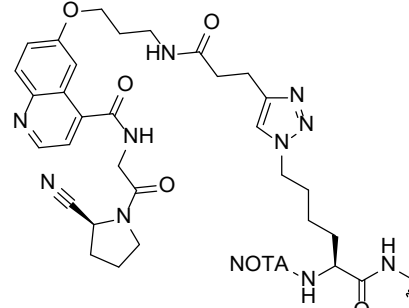
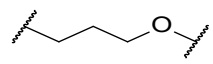
Thus, a POSA would have understood that the dozens of exemplary “A” and “B” moieties would have adequately enabled the entire scope of the claims.

149. Furthermore, the additional working examples disclosed during the prosecution of the '233 patent provide additional enabling disclosure. Specifically, Dr. Pomper disclosed an additional 11 species that fall within the scope of the claims which have a diverse set of “B” and “L” moieties. EX1002, 174–176. And the overall “B-L-A” structures themselves also display diversity in their molecular weights, spanning from 370 g/mol to 1282 g/mol, almost the entire span of the “low molecular compounds” as defined by Dr. Pomper during prosecution. EX1002, 69; *see also* Section IX, *supra*. These compounds are tabulated below. And there is no indication that anything beyond the patent’s disclosure and ordinary skill a POSA would have had in 2017 would have been needed to make these compounds.

Citation	“B” Moiety Structure	“L” Moiety Structure	B-L-A MW (g/mol)	B Function	B MW (g/mol)
EX1001, 50:35-54:50			1365.4	IR dye (LI-COR-800)	1066.2

Citation	“B” Moiety Structure	“L” Moiety Structure	B-L-A MW (g/mol)	B Function	B MW (g/mol)
EX1001, 53:54- 56:38			839.9	4- membered chelator (DOTA- GA)	488.5
EX1002, 174 (Pomper Decl., ¶42)			370	Radiohalo gen (F)	19.0
EX1002, 174 (Pomper Decl., ¶42)			734	Radiohalo gen (F)	369.3
EX1002, 174 (Pomper Decl., ¶42)			983	Dual 3- membered chelator (DOTA) / radiohalog en (I)	620.4
EX1002, 174 (Pomper Decl., ¶42)			876	Dual 3- membered chelator (DOTA) / radiohalog en (F)	502.4
EX1002, 175 (Pomper Decl., ¶42)			734	Radiohalo gen (F)	369.3

Citation	“B” Moiety Structure	“L” Moiety Structure	B-L-A MW (g/mol)	B Function	B MW (g/mol)
EX1002, 175 (Pomper Decl., ¶42)			1049	Dual 3-membered chelator (DOTA) / radiohalogen (F)	652.7
EX1002, 175 (Pomper Decl., ¶42)			1073	Dual 3-membered chelator (DOTA) / radiohalogen (F)	711.4
EX1002, 175 (Pomper Decl., ¶42)			1266	Dual 3-membered chelator (DOTA) / radiohalogen (F)	888.4
EX1002, 175 (Pomper Decl., ¶42)			889	Dual 2-membered chelator (NOTA) / radiohalogen (F)	525.3
EX1002, 176 (Pomper Decl., ¶42)			761	2-membered chelator (NOTA)	397.3

Citation	“B” Moiety Structure	“L” Moiety Structure	B-L-A MW (g/mol)	B Function	B MW (g/mol)
EX1002, 176 (Pomper Decl., ¶42)			1282	Dual 2-membered chelator (NOTA) / second FAPi moiety	918.0

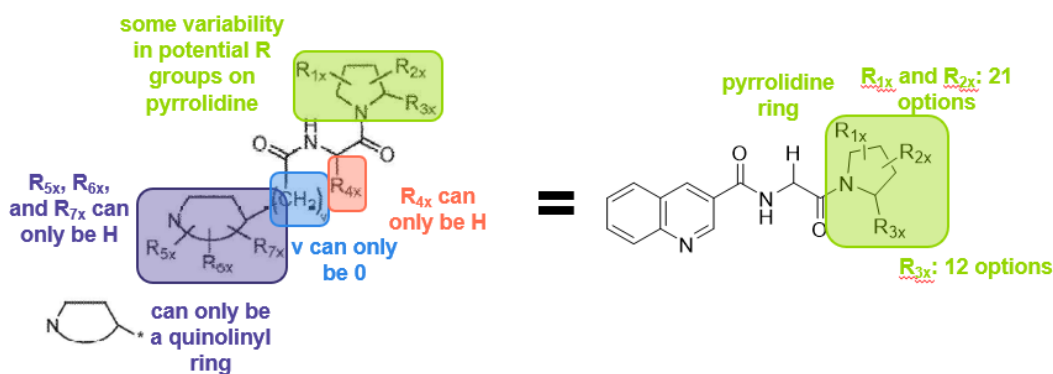
150. Based on the data shown above, it is clear that Dr. Pomper, using the disclosures of the '233 patent, was able to make a broad set of compounds within scope of the claimed invention as of the filing date. And there is no indication that anything beyond the patent's disclosure and ordinary skill a POSA would have had in 2017 would have been needed to make these compounds. As such, the '233 patent's specification was adequate to enable such compounds. The table above illustrates that the disclosure in the specification enables compounds across significant variation in “B” group structure, molecular weight, function, sterics, and functional groups. And each of those species had excellent FAP-selectivity ranging from 407-11,893. Dr. Zeglis's failure to account for this additional enabling disclosure further harms his argument for lack of enablement.

151. In sum, the straightforward disclosures in the '233 patent and its prosecution history, coupled with POSA's high skill in the art, would have allowed

a POSA to make the claimed compounds across the entire scope of the claims using this straightforward, modular method disclosed.

2. The scope of the claimed “A” moiety would not have resulted in undue experimentation in making the claimed compounds

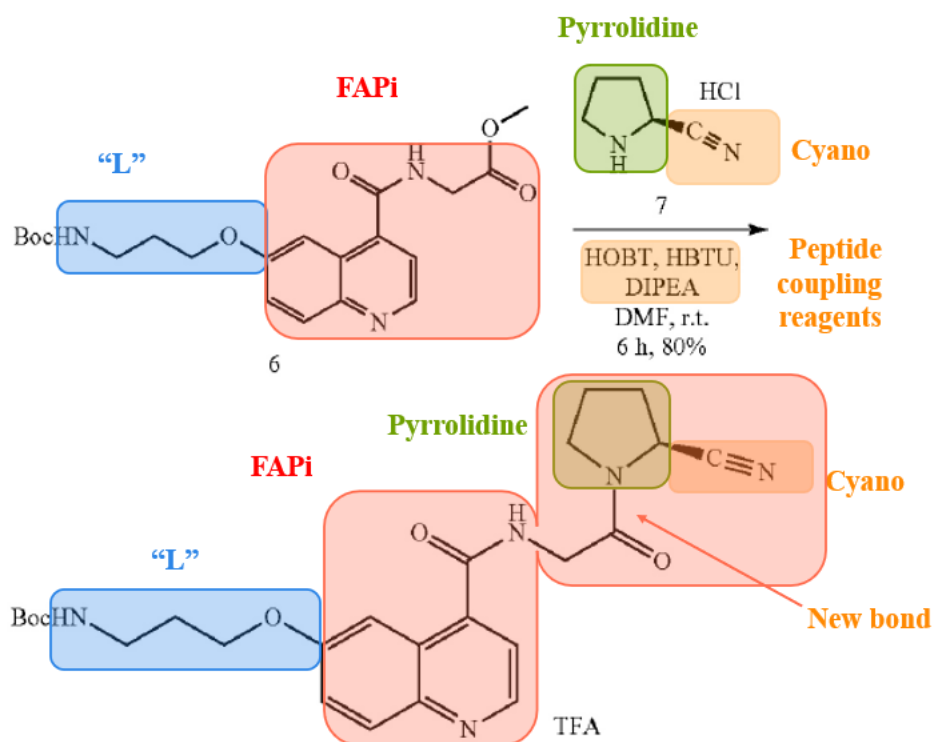
152. The scope of the claims does not result in an unduly burdensome synthetic task. Dr. Zeglis states that the claimed “A” moiety contains significant breadth, arguing that there are “~30,000 FAP-targeting moieties that meet the parameters of the A component of the claims.” EX1003, ¶288. But the scope of this claimed “A” moiety is not particularly broad. Specifically, the diversity is only limited to a single ring group in the “A” structure – the pyrrolidine-based FAPi targeting ring. There is no potential for variation anywhere else other than in the ring, as shown below:



153. Moreover, just as the “B-L-A” compounds are added together as individual “B,” “L,” and “A” components when forming a full radiotracer, so too is the pyrrolidine ring when putting together the “A” moiety. The '233 patent

discloses a straightforward, modular synthetic method for making the “A” moiety.

Because “A” is introduced as a discrete building block, a POSA would have immediately understood that one pyrrolidine derivative could have been substituted for another without altering the overall synthetic scheme, shown below:



EX1001, 52:15–35.

154. In this reaction, a pyrrolidine with a cyano (CN) group is conjugated to the rest of the FAPI and linker using a base (DIPEA) and peptide coupling reagents HOBT and HBTU. This peptide coupling reaction is used to form a new amide bond, which is a bond between a carbonyl of the FAPI-L structure and the N of the pyrrolidine. As can be seen here, the cyanopyrrolidine moiety is added to the

rest of the “A” group as a single component, meaning that it can be easily swapped out with other pyrrolidine moieties with a standard peptide-coupling reaction. As long as the NH on the pyrrolidine is present and available to be deprotonated, which is the case for most pyrrolidine rings due to their typical pKa of approximately 11 (EX2027, Table 1), a POSA would have known that this type of reaction would have been easily achievable for any given pyrrolidine.

155. Further, POSAs would have had at their disposal a wide variety of pyrrolidine building blocks to choose from. Indeed, a search on the chemical supply site Fisher Scientific for the term “pyrrolidine” yields over 6,000 results, including hundreds of examples of alkyl-substituted groups, halogenated groups, heteroaryl groups, and similar modifications.⁹ A POSA would have been able to readily incorporate a desired pyrrolidine group into the FAPi synthesis step above. Further, a POSA would have known how to make additional modifications to these pyrrolidine groups as desired, as it involves standard and well-known chemical

⁹ These results would have not have significantly changed from 2017 until now, as substituted pyrrolidine groups have been used in synthetic organic chemistry for a long time. *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.

synthetic methods. *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. As such, a POSA would have been enabled to make a wide range of FAPis that fall within the claimed “A” scope, particularly in view of the high level of skill in the field. This is true even though both working examples employ the same FAPi (A moiety). Indeed, the specification contemplates variation in the pyrrolidine ring—exemplary “A” moieties explicitly suggest modifications in the five-membered ring. EX1001, 12:55–14:15. A POSA would have understood from the ’233 patent specification that one pyrrolidine derivative could have been substituted for another.

156. Further, the ’233 specification provides additional enabling disclosure for use of the “A” moiety in the claimed invention. Specifically, US-650 is specifically incorporated by reference into the ’233 patent specification, and would have provide a POSA with additional enabling disclosure for the breadth of the “A” moiety, as shown below:

Representative targeting moieties for FAP- α are disclosed in U.S. Patent Application Publication No. US2014/0357650 for Novel FAP Inhibitors to Jansen et al., published Dec. 4, 2014; U.S. Pat. No. 9,346,814 for Novel FAP Inhibitors to Jansen et al., issued May 24, 2016; and International PCT Patent Publication No. WO 2013/107820 for Novel FAP Inhibitors to Jansen et al., published Jul. 25, 2013, each of which are incorporate by reference in their entirety.

EX1001, 8:25–32. A POSA would have been able to readily incorporate the additional “A” moiety disclosures into the claimed invention. As such, the claimed “A” moiety scope does not result in undue experimentation being necessary to make the full scope of the claimed invention. Indeed, Dr. Zeglis confirms that this type of chemistry involves “conventional chemical synthesis techniques well-known to skilled artisans” and that it would have been “straightforward” for POSAs to select appropriate “B”s and “L”s and synthesize the resulting compounds. EX1003, ¶¶121, 172. As such, Dr. Zeglis himself acknowledges that these types of syntheses would have been well within the skill of a POSA.

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

157. Dr. Zeglis’s enablement analysis is centered around the experimentation necessary to determine what “B-L-A” compounds could be *used* as imaging or therapeutic agents *in vivo*. EX1003, ¶274. Dr. Zeglis, while agreeing that a POSA “would have expected that many compounds could be designed ... that yield a structure that makes them a viable diagnostic or imaging candidate,” nevertheless argues that many other “B-L-A” compounds would have led a POSA to “doubt that it could be a viable FAP-targeting radiopharmaceutical or optical imaging candidate” EX1003, ¶276. But, as discussed above, the claimed invention does not require any *in vivo* functionality. Section VI, *infra*; *see also* EX2001, ¶91.

Indeed, the '233 patent expressly teaches that the claimed compounds may be used in *in vitro* contexts, including the detection, visualization, and analysis of FAP-expressing cells and tissues. EX1001, 35:46-52. However, Dr. Zeglis fails to consider that making and using the claimed compounds across the claimed scope, for either *in vitro* utility, would not have been undue. Dr. Zeglis even describes that it is “typical” to answer questions that arise from the chemical structure of a compound, describing the “typical” experiments required to answer these questions. EX1003, ¶277 (emphasis added). If performing these experiments are typical (i.e., routine), as Dr. Zeglis states, then the evaluation of these compounds cannot be considered undue experimentation.

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

158. As for the scope of the Challenged Claims, the specification discloses the structure of “A” moieties that target FAP, providing a POSA direction as to what FAPi-based radiotracers would have functioned in *in vitro* contexts, where only direct incubation is needed. EX1001, 37:22–25. This guidance informs a POSA how to make and use the full scope of the claimed compounds as intended. And as discussed above, the only structure within the claimed “A” moiety that allows variation is the pyrrolidine ring. Section XI.A.2. A POSA would have immediately understood that one pyrrolidine derivative, identified by the

specification for use in the “B-L-A” compounds, 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 into the ’233 patent specification. Section XI.A.2. Indeed, Dr. Zeglis acknowledges the narrow nature of the claimed “A” moiety, stating that it encompasses only ~30,000 compounds. EX1003, ¶91. The ’233 patent also incorporates by reference publications disclosing numerous other FAPis falling within the scope of the claimed “A” moiety that a POSA would have understood would have similarly functioned in *in vitro* applications by the nature of their selectivity for FAP. EX1001, 8:25–33. And the ’233 patent and the prior art disclose numerous well-known linkers, chelators, dyes, and prosthetic groups, including many that Dr. Zeglis identifies as viable selections, for use in the claimed compounds, as discussed above. Section X.

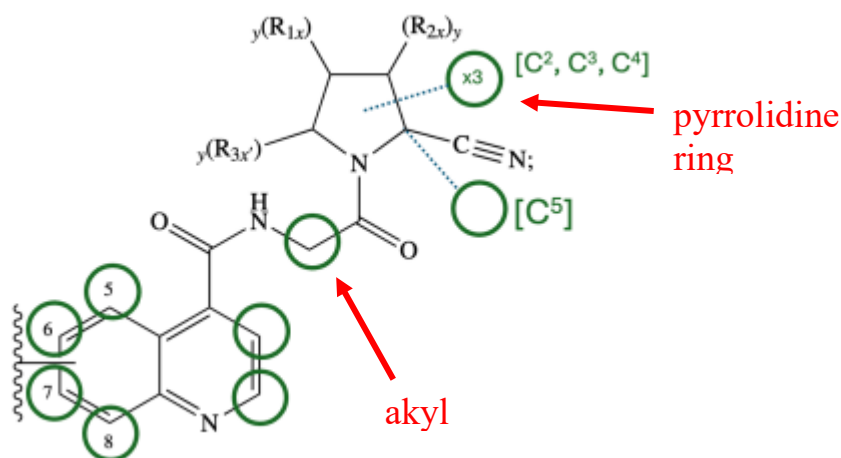
159. Additionally, as discussed above, the ’223 patent specification also provides direction on how and where to conjugate “A” with “L” and position “B” so as to not disrupt selectivity for FAP. The prior art, moreover, would have provided direction to a POSA through the SAR studies of Jansen 2013 that disclosed where the FAPis encompassed by the claimed “A” moiety could be conjugated without disrupting FAP selectivity. EX1007, Tables 2 and 3; EX1006, Table 6. Indeed, Dr. Zeglis acknowledges that SAR studies with Jansen’s various

FAPis provided information on where conjugating FAPis at certain locations (such as, in certain cases, the 5 position on the quinolinyl ring of the “A”) or how changing “A”’s substituents affected FAP-selectivity. EX1003, ¶¶178; EX1007, Tables 2 and 3; EX1044, Table 4. Those same SAR studies from Jansen 2013 and US-650 are incorporated by reference into the ’233 patent. EX1001, 7:14–15, 8:26–29.

160. Dr. Zeglis attempts to expand the breadth of the claimed invention by alleging that the claimed “A” moiety has 11 possible points of attachment for “L” and “B.” EX1003, ¶¶91, 93, 176–177. But as discussed above, the ’233 patent 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* EX1001, 3:45–51 (disclosing that carbons 5 through 8 of the quinolinyl ring of the “A” as sites for conjugating “L”). Consistent with that express guidance, and with known SARs for FAPis in the prior art, a POSA would have understood that conjugation sites are constrained to positions expected to preserve FAP binding, as taught by the ’233 patent. Thus, a POSA would have known to conjugate the “A” moiety with a linker on the quinolinyl ring, consistent with the teachings of the ’233 patent and the SAR that was known prior to 2017. And a POSA would have known to avoid conjugation where it might be harmful for binding, sites such as the pyrrolidine

ring. EX1006, Table 6. As such, the scope of the claimed “A” group is more limited than the scope that Dr. Zeglis articulates.

161. Dr. Zeglis attempts to dismiss this disclosure as being limited to only certain embodiments of the '233 patent. EX1003, ¶93. But based on the direction provided in the '233 patent specification and known SARs for FAPis falling within the scope of “A” provided in the prior art, a POSA would not have been directed to conjugate “A” at the other places Dr. Zeglis identify on the “A” moiety, *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 on the figure provided Dr. Zeglis.



EX1003, 93 (annotations in red added).

162. A POSA would have understood such conjugations would have likely rendered the resulting “B-L-A” unable to bind to FAP, based on the SAR discussed above from Jansen 2013 and US-650. In fact, a POSA would have understood from

SAR studies that perturbations of the pyrrolidine ring of the claimed FAPis with bulky linkers (“L”) and radiotracers (“B”) 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. Likewise, a POSA would have understood that attaching bulky linkers (“L”) and radiotracers (“B”) close to the pyrrolidine ring via the alkyl spacer would also have led to detrimental effects on FAP-selectivity. EX1006, Table 2.

163. Dr. Zeglis, moreover, acknowledged at his deposition that a POSA would have wanted to conjugate “B” far enough from the “A” moiety in order to minimize the risk of interference between the “A” moiety and “B” moiety. EX2023, 181:15–28. In other words, a POSA would not have wanted to risk rendering the “A” moiety 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” (emphasis added)). And here, it was known in the art that the pyrrolidine ring of the claimed “A” moiety was crucial for its FAP-targeting activity. EX1006, Table 6.

164. Accordingly, a POSA would have understood based on the ’233

patent specification and the art that there would be at most six possible sites for conjugation of “L” and “B” to “A,” thus reducing the alleged claim scope put forth. Because bioavailability, *in vivo* stability, and biodistribution concerns are not relevant to *in vitro* use, it would not have required undue experimentation for a POSA to select “B” and “L” moieties 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.”

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

165. The ’233 patent discloses how to use the claimed compounds in *in vitro* settings using routine techniques well within the skill of the art, such as mixing the claimed compounds “and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube” and then imaging the sample. EX1001, 37:22-25. However, as described above, Dr. Zeglis did not address that the specification discloses such uses, instead requiring that the claimed compounds demonstrate *in vivo* utility.

166. Dr. Zeglis argued that each compound must be subjected to an “array of binding studies, **stability studies (e.g., in plasma), and animal testing for bioavailability and toxicity.**” EX1003, ¶277 (emphasis added). In particular, Dr. Zeglis’s testing would involve determining whether the synthesized compound:

- “enter[s] **systemic circulation *in vivo*** in an unchanged state” (EX1003, ¶59)

(emphasis added));

- “exhibit[s] **satisfactory bioavailability**” (EX1003, ¶275 (emphasis added));
- “remain[s] **intact in the body** for a long enough time to accumulate in its biological target” (EX1003, ¶59 (emphasis added));
- “sufficient[ly] distribut[es] **in the target tissue** that can be imaged before the compound is cleared or the radionuclide decays” (EX1003, ¶59 (emphasis added)); and
- is “**stable under physiological conditions**” (EX1003, ¶275 (emphasis added)).

167. However, Dr. Zeglis does not explain why he is imposing these *in vivo* requirements on the claimed compounds. In fact, Dr. Zeglis himself conceded at deposition that the claimed compounds could be used in *in vitro* contexts. EX2023, 80:14-15 (“[o]ptical imaging agents can be useful *in vivo* or *in vitro*”). Yet Dr. Zeglis never explains whether a POSA would have needed to expend the same “incredible amount of labor and resources” (EX1003, ¶273) to use the claimed compounds *in vitro* as he suggests is needed for *in vivo* use. EX2001, ¶106. And indeed, he cannot make such an argument, because the testing required for *in vitro* applications would have been far less laborious than for *in vivo* applications.

168. *In vivo* experiments of a compound typically require oral or parenteral

administration to a subject (e.g., a rodent or a human), implicating biological processes such as absorption, metabolism, and biodistribution in the subject. *See* EX2042, 512. Because other receptors exist in the body other than the target, selectivity of the compound plays a role in *in vivo* applications of the compound, a point with which Dr. Zeglis readily agrees (EX1003, ¶55). But *in vitro* applications do not necessarily require such a rigid requirement for selectivity – even compounds that are *not* highly selective for their target can nevertheless be useful. EX2001, ¶108. For example, a diseased tissue sample, such as a biopsy, can be easily imaged *in vitro* with a FAPi radiotracer that does not meet Dr. Zeglis’s selectivity standards because there would have been no concern that “the compound will bind to FAP on ... sites associated with healthy tissue” and lead to inappropriate radiotherapy, contrary to Dr. Zeglis’s arguments directed to *in vivo* uses. EX1003, ¶287; *see also* EX2001, ¶108. If other, off-target enzymes are not present on the excised tissue, selectivity may not be an issue *in vitro* at all. EX2001, ¶108.

169. Moreover, the other experiments that Dr. Zeglis argues that a POSA would have performed would *not* have actually be required for testing the claimed compounds for *in vitro* uses. For instance, bioavailability bears no relevance to the compound’s behavior in “a culture dish or tube,” which is cited as one of the potential utilities of the claimed compounds. EX1001, 37:22-25; EX2001, ¶106.

Clearance from the body also does not play a role when a small sample of tissue is removed from the body and imaged in a “controlled environment” such as a “culture dish or tube” as taught by the ’233 patent. EX1001, 37:22-25; EX2001, ¶106.

170. Furthermore, even if a POSA were to test the claimed compounds for *in vivo* uses, any experimentation required for such tests would not have been undue. Dr. Zeglis agrees: “These experiments are generally straightforward to perform.” EX1003, ¶277. And although they require making and testing each compound, it would have been well within the POSA’s skill to do so by following the teachings in the specification and the art. For example, these studies were performed in one of the references that Dr. Zeglis cites for obviousness, US-121. EX1005, ¶¶285-287, FIGs. 20-22. Indeed, types of experiments that one would have performed to prepare for *in vivo* use were also performed in additional references that Dr. Zeglis cites, including Meletta (EX1008, Abstract, 2084-2086, 2088, FIGs. 2-3) and Jansen (EX1006, Tables 7-8). Evidence of these techniques throughout the relevant literature serves to underscore that this is not the sort of experimentation that a POSA would have considered undue.

171. Dr. Zeglis only identifies potential cases wherein a POSA “would have believed would have needed to be tested to determine if the compound could be suitable in imaging or therapeutic uses” and “as FAP-targeting

radiopharmaceuticals.” EX1003, ¶¶279-302; *see also* EX2001, ¶¶105-108. But again, Dr. Zeglis’s concerns regarding any alleged need to test for “suitab[ility] in imaging or therapeutic uses” are based on improperly requiring that the claimed compounds be used *in vivo*. EX1003, ¶¶279-302. Dr. Zeglis appears to treat “utility” in his enablement analysis as requiring that every claimed “B-L-A” compound satisfy various pharmacological performance metrics. EX1003, ¶¶279-302. When viewed in the proper context of the claimed compounds only having to achieve some amount of *in vitro* utility, determining what combinations of “B,” “L,” and “A” moieties could be used for *in vitro* use does **not** require trial-and-error testing. For example, Jansen, US-633, and US-121 describe synthesis and testing (*in vitro* binding studies, stability studies, and imaging) of FAP radiotracers. The presence of this testing throughout the relevant literature speaks to how routine it is in the field. In addition, US-121 and US-633 are both incorporated by reference into the ’233 patent specification. As such, not only do these references demonstrate the routine nature of such testing, the ’233 patent also explicitly teaches these methods. As such, Dr. Zeglis fails to establish that this amount of experimentation would have been undue and, indeed, admits that the exact testing he proposes for each compound is described in his cited reference Jansen. EX1003, ¶278. Any further experimentation to improve or tailor the claimed compounds beyond the properties needed for *in vitro* applications (or even

for *in vivo* use) represents optimizing the compounds to reach such uses, not undue experimentation. Indeed, Dr. Zeglis acknowledges that that POSAs would have known that certain Ls and Bs would have posed operability issues. EX1003, ¶¶280-286. But a POSA would have been able to readily recognize these potentially operative embodiments, as Dr. Zeglis does in his declaration. *Id.*

172. Accordingly, the '233 patent enables a POSA to use the claimed B-L-A compounds for disclosed *in vitro* applications without undue experimentation.

C. The *Wands* Factors confirm that the Challenged Claims are enabled

1. The quantity of experimentation would have been limited and routine

173. As shown in Section XI.A above, the specification teaches how to synthesize the claimed compounds using conventional chemistry, and as shown in Section XI.B above, it teaches how to use those compounds for disclosed *in vitro* applications.

174. At most, a POSA would have had to engage in ordinary selection among known “B” and “L” moieties or routine assay implementation—work that does not approach undue experimentation. Section XI.B. Here, any time required to traverse the structurally constrained B-L-A genus reflects routine confirmation and selection guided by the specification’s modular teachings—not undue

experimentation.

175. This factor weighs in favor of enablement.

2. The amount of guidance presented in the '233 patent specification supports enablement

176. The '233 patent provides extensive guidance, including structural definitions of the A moiety, numerous exemplary B and L moieties, explicit conjugation strategies, reaction schemes, and incorporated prior-art references. *See* Sections X and XI.A; *see also* EX2001, ¶¶94-101. That guidance enables a POSA to practice the full scope of the claims without guesswork or invention.

177. This factor weighs in favor of enablement. Sections X and XI.A.

3. The working examples in the '233 patent specification weigh in favor of enablement

178. The specification includes working examples demonstrating synthesis of representative B-L-A compounds and their interaction with FAP. EX1001, 50:35–61:23. This synthetic scheme is a generalizable approach that POSAs can apply across the claim scope without undue experimentation.

179. This factor weighs in favor of enablement.

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

180. The challenged claims are directed to chemical compounds. EX1001, 64:5–61, Certificate of Correction. They do not require clinical administration or achievement of any particular therapeutic or diagnostic outcome. EX1001, 34:63–

35:3, 35:47–52; EX2001, 104-105. And as discussed in Section XI.B, they can be predictably implemented in *in vitro* uses that fall squarely within the capabilities of a POSA. EX1001, 64:5–61, Certificate of Correction, 34:63–35:3, 35:47–52; EX2001, ¶¶105-108.

181. This factor weighs in favor of enablement.

5. The state of the prior art supports enablement

182. At the relevant priority date, the underlying chemistry and assay techniques were well developed. *See* Sections X, XI.A, and XI.B. Bioconjugation methods, linker chemistry, reporter moieties, and FAP-binding scaffolds were all familiar tools in the art. *See* Sections X, XI.A, and XI.B. The specification builds on—and expressly incorporates—this established knowledge to provide direction on how to assemble the claimed compounds, further reducing any need for experimentation.

183. This factor weighs in favor of enablement. Sections X, XI.A, and XI.B.

6. Relative skill of those in the art would have been high

184. A POSA in this field would have possessed substantial training and experience in organic and medicinal chemistry and molecular imaging techniques. Such artisans would have been well equipped to synthesize the claimed compounds and employ them in routine *in vitro* assays without difficulty, and Dr. Zeglis does

not dispute this point. EX1003, ¶¶121, 172.

185. This factor weighs in favor of enablement.

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

186. Predictability in the art favors enablement for the uses actually disclosed. As I explained, only predictability for making the compounds and using them for *in vitro* applications is what is relevant here. *See* Section XI.B. And in that context, B-L-A's behavior would have been substantially more predictable and well understood.

187. Indeed, both the '233 patent specification and the art provided sufficient direction for a POSA to choose an A moiety that would have bound FAP and assemble it into a B-L-A structure so as to maintain activity. *See* Sections X and XI.A. In fact, as discussed, Dr. Pomper's declaration providing multiple B-L-A compounds demonstrating variation in reporter function (e.g., radiohalogens, chelators, dyes), steric bulk, and functional group composition each had excellent FAP-selectivity when tested *in vitro*. Section IX.

188. Dr. Zeglis's allegations of unpredictability also relate to *in vivo* performance. Dr. Zeglis alleges that it would have been unpredictable which compounds would have functioned as "viable diagnostic or imaging candidates." EX1003, ¶276. I also understand that Dr. Pomper stated in his declaration during

prosecution that “the art of developing a medical imaging agent is highly unpredictable.” EX1002, 172 (Pomper Declaration, ¶31). Here, Dr. Pomper was discussing unpredictability on *in vivo* functionality of FAP-targeting radiotracers. In discussing unpredictability, Dr. Pomper referred to “biodistribution,” an *in vivo* constraint, as something to take into consideration. EX1002, 172 (Pomper Declaration, ¶31). Both Zeglis and Pomper, therefore, have based their discussions of unpredictability on *in vivo* functionality. The claimed compounds, however, can be used *in vitro* without undue experimentation, as I explained above.

189. Dr. Zeglis also points to Meletta’s failure as evidence of the necessity for more selective FAPi radiotracers in *in vitro* applications (EX1003, ¶¶137–187), but the claimed invention solved Meletta’s issues. Indeed, as discussed, the specification discloses a genus of A moieties selective for FAP, which when conjugated to B and L as guided by the specification retain FAP selectivity—and which in fact, have unexpectedly improved selectivity compared to their unconjugated forms. *See* Section IX. This is evidenced by the 11 compounds having wide variety in B and L structures that Dr. Pomper made per the direction of the ’233 patent specification and that had FAP-selectivity that was orders of magnitude higher than their unconjugated forms. *See* Section IX. Accordingly, the ’233 patent provides sufficient direction to negate any alleged unpredictability in the art regarding the use of the claimed compounds.

190. This factor weighs in favor of enablement.

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

191. As discussed in Section XI.A.2, the scope of the “A” moiety would not have led to undue experimentation. The ’233 patent discloses a straightforward, modular synthetic scheme for assembling the A moiety by easily swapping in one pyrrolidine derivative for another. EX1001, 52:15–35. And the specification describes exemplary A moieties and explicitly teaches that substitutions on the five-membered ring that are within the scope of the invention. EX1001, 12:55–14:15. A POSA would have understood these teachings as affirmatively providing guidance for using the full scope of pyrrolidine-based variants without undue experimentation.

192. While the B and L moieties are not structurally constrained, as discussed, a POSA would have understood how to conjugate B and L to A in view of the specification’s guidance and known FAPi SARs. *See* Sections X and XI.A. And Dr. Pomper’s declaration exemplifies that various types of B and L moieties could be employed without negatively affecting the A moiety’s FAP-selectivity. *See* Section IX.

193. To the extent the number of compounds falling within the scope of the Challenged Claims is considered, given the straightforward and routine nature of

making the claimed compounds and the predictability of their use in *in vitro* applications, it would not have been undue to make and use compounds across the full scope of the Challenged Claims.

194. This factor weighs in favor of enablement.

* * *

195. Considering the *Wands* factors as a whole, Dr. Zeglis has not shown that practicing the challenged claims would have required undue experimentation. To the contrary, the factors confirm that the Challenged Claims of the '233 patent is enabled.

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

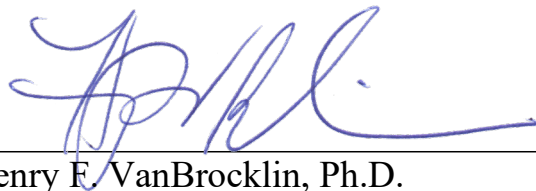
196. Dr. Zeglis argues that claim 2 encompasses 528 A moieties and claims 3 and 4 encompass 44 A moieties. EX1003, ¶94. These claims significantly narrow the scope of the claimed A moiety compared to claim 1. Due to this narrowed claim scope for “A,” the dependent claims have even less of a concern of unpredictability in binding FAP with respect to the “A” moiety.

XII. CONCLUSION

197. In signing this declaration, I recognize that the declaration will be filed as evidence in a post-grant review before the Patent Trial and Appeal Board of the United States Patent and Trademark Office.

198. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on this 8th day of April 2026, in San Francisco, CA.



Henry F. VanBrocklin, Ph.D.