

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GE HEALTHCARE LTD.,
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner

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

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

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Johns Hopkins University EX2047
GE Healthcare v. Johns Hopkins
IPR2026-00069

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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 January 30, 2026 (EX2001), in support of Patent Owner The Johns Hopkins University's ("Patent Owner") Preliminary Response for the above-captioned *inter partes* review (IPR) 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 IPR at my standard consulting rate, which is \$350.00 per hour.

3. I understand that this Declaration accompanies the Patent Owner Response (POR) filed in this IPR involving U.S. Patent No. 11,938,201 ("the '201 patent") (EX1001), which resulted from U.S. Patent Application No. 18/354,282 ("the '282 application"), filed on July 18, 2023. I understand that the '201 patent ultimately claims priority to U.S. Provisional Patent Application No. 62/575,607, filed on October 23, 2017.

4. In preparing this Declaration, I have reviewed the '201 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”) prior to October 23, 2017.

II. MY BACKGROUND AND QUALIFICATIONS

5. My background and qualifications were provided in ¶¶4-14 of my first declaration, EX2001, and my CV provided as EX2002. My statements in my first declaration regarding my background and qualifications remain unchanged.

III. SUMMARY OF OPINIONS

6. 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 1–3 of the ’201 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.

7. 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 1–3 of the ’201 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* Section VII; *see also* EX2001, ¶¶20-24. When the prior

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

art is 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.

8. 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. EX2035, Abstract, 780, FIG. 1; EX2033, Abstract, 1202; EX2032, Abstract, 1639–40, FIGs. 1-2; EX2031, Abstract, 6214-17, FIGs. 1 and 4; EX2036, Abstract, 8–9, FIGs. 12; EX2037, Abstract, 58, FIG. 3; EX2038, Abstract, 49193, 495, FIG. 1; EX2039, 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, 2888–90; EX2035, Abstract,

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

780, FIG. 1; EX2033, Abstract, 1202; EX2032, Abstract, 163940, FIGs. 1–2; EX2031, Abstract, 6214–17, FIGs. 1 and 4; EX2036, Abstract, 89, FIGs. 1–2; EX2037, Abstract, 58, FIG. 3; EX2038, Abstract, 49193, 495, FIG. 1; EX2039, 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.

9. 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 can be measured using the term half maximal inhibitory concentration (IC_{50}) or dissociation constant (K_d). EX1004, ¶185; *see also* EX2046, Abstract. Lower IC_{50} and K_d numbers signify better binding to the target and signify a more potent targeting moiety. EX1004, ¶185; *see also* EX2046, 953-55.

⁴ Selectivity is calculated as a ratio of the affinity (IC_{50}) 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, ¶45; EX2001, ¶¶23-24. 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.

10. 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, 491–92; EX1044, ¶4.

necessary for imaging), each associated with different chemical and biological tradeoffs. Section VII.B. *infra*. 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.

11. 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, ¶22. 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* Section VII *infra*; *see also* EX2001, ¶22.

12. 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.

13. 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 1–3 of the '201 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* Section VIII; *see also* EX2001, ¶24. 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, ¶182. 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.

IV. LIST OF DOCUMENTS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 11,938,201 (“the '201 patent”)
1002	File History of U.S. Patent No. 11,938,201

Exhibit No.	Description
1003	Declaration of Dr. Brian Zeglis
1004	U.S. Patent Application Publication No. 2010/0098633
1005	U.S. Patent Application Publication No. 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”)
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) (“Jansen 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)

Exhibit No.	Description
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)
1017	Sarko et al., “Bifunctional Chelators in the Design and Application of Radiopharmaceuticals for Oncological Diseases,” Current Medicinal Chem., 19:2667-2688 (2012)
1018	Fichna et al., “Synthesis of Target-Specific Radiolabeled Peptides for Diagnostic Imaging,” Bioconjugate Chem., 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,” Semin. Nucl. Med., 47(5):474-492 (August 2017)
1020	Saha et al., “Synthesis of PET Radiopharmaceuticals,” Chapter 8,161-168, in Basics of PET Imaging (Saha, editor), Springer Int. Publ. (2010)
1021	Kettenbach et al., “ ¹⁸ F-Labeling Using Click Cycloadditions,” BioMed Research International, 2014:1-16 (2014)
1022	Liu et al., “Fibroblast activation protein, A potential therapeutic target in cancer,” Cancer Biology & Ther., 13(3):123-129 (2012)
1023	DiMagno et al., “Advanced Fibroblast Activation Protein-Ligand Developments, FAP Imaging Agents: A Review of the Structural Requirements,” PET Clin., 18:287-294 (2023)

Exhibit No.	Description
1024	Hamson et al., “Understanding fibroblast activation protein (FAP): Substrates, activities, expression and targeting for cancer therapy,” Proteomics Clin. Appl., 8:454-463 (2014)
1025	O'Brien et al., “Seprase: An overview of an important matrix serine protease,” Biochimica et Biophysica Acta, 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,” BMC Cell Biology, 15(16): 1-14 (2014)
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)
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)

Exhibit No.	Description
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)
1037	Karakatsanis et al., “Dosage optimization in positron emission tomography: state-of-the-art methods and future prospects,” Am. J. Nucl. Med. Mol. Imaging, 5(5):527-547 (2015)
1038	LeBeau et al., “Targeting the cancer stroma with a fibroblast activation protein-activated promelittin protoxin,” Mol. Cancer Ther. 8(5):1378-1386 (2009)
1039	Nelson et al., “Good practices for ⁶⁸ Ga radiopharmaceutical production,” EJNMMI Radiopharmacy and Chem., 7(1):1-26 (2022)
1040	Meyer et al., “Exploring Structural Parameters for Pretargeting Radioligand Optimization,” J. Med. Chem., 60:8201-8217 (2017)
1041	Gorrell, “Dipeptidyl peptidase IV and related enzymes in cell biology and liver disorders,” Clinical Science, 108:1-16 (2005)
1042	Kiesewetter et al., “Automated radiochemical synthesis of [¹⁸ F]FBEM: A thiol reactive synthon for radiofluorination of peptides and proteins,” Appl. Radiation and Isotopes, 69(2): 410-414 (2011)
1043	Chansaenpak et al., “[¹⁸ F]NHC-BF ₃ adducts as water stable radio-prosthetic groups for PET imaging,” Chem. Commun., 51(62):12439-12442 (2015)
1044	U.S. Patent Application Publication No. 2014/0357650 to Jansen et al.

Exhibit No.	Description
1045	Ji et al., “Tumor fibroblast specific activation of a hybrid ferritin nanocage-based optical probe for tumor microenvironment imaging,” <i>Small J.</i> , 9(14):2427-2431 (2013)
1046	Wilson et al., “Chapter 1, Dipeptidyl Peptidases: Substrates and Therapeutic Targeting in Human Health and Disease,” Royal Society of Chemistry, (2012)
1047	Tsai et al., “Substituted 4- carboxymethylpyroglutamic Acid Diamides as Potent and Selective Inhibitors of Fibroblast Activation Protein,” <i>J. Med. Chem.</i> 53(18):6572-6583 (2010)
1048	International Application Publication PCT/US2010/108125 published as WO 2010/108125 A2 to Pomper et al.
1051	Harris et al., “Impact of 2-Deoxy-2[F-18]Fluoro-D-Glucose Positron Emission Tomography on the Management of Patients with Advanced Melanoma,” <i>Mol. Imaging Biol.</i> , 7(4):304-308 (2005)
1052	Zhou et al., “Radiolabeled Cyclic RGD Peptides as Radiotracers for Imaging Tumors and Thrombosis by SPECT,” <i>Theranostics</i> , 1:58-82 (2011)
2002	<i>Curriculum vitae</i> of Dr. Henry VanBrocklin
2003	Jansen et al., “Selective inhibitors of fibroblast activation protein (FAP) with a xanthine scaffold,” <i>MedChemComm</i> (August 2014) (“Jansen 2014”)
2004	Sikkandhar et al., “Theranostic Probes for Targeting Tumor Microenvironment: An Overview,” <i>International Journal of Molecular Sciences</i> (May 2017) (“Sikkandhar”)
2011	Slania et al., “Imaging of Fibroblast Activation Protein in Cancer Xenografts Using Novel (4-Quinolinoyl)-glycyl-2 cyanopyrrolidine-Based Small Molecules,” <i>Journal of Medicinal Chemistry</i> (April 2021) (“Slania”)

Exhibit No.	Description
2018	Bvumbi, M., “Activity of Riminophenazines against Mycobacterium tuberculosis: A Review of Studies that Might be Contenders for Use as Antituberculosis Agents,” <i>ChemMedChem</i> 15(23):2207-2219 (December 2020) (“Bvumbi”)
2019	Xu et al., “Discovery of potent and selective phenylalanine based dipeptidyl peptidase IV inhibitors,” <i>Bioorganic & Medicinal Chemistry Letters</i> , 15:2533-2536 (May 2005) (“Xu 2005”)
2020	Calcaterra et al., “Classics in Chemical Neuroscience: Diazepam (Valium),” <i>ACS Chemical Neuroscience</i> , 5:253-260 (February 2014) (“Calcaterra”)
2021	Lever, A.B.P., “Lewis Structures and the Octet Rule,” <i>Journal of Chemical Education</i> , 49(12):819-821 (December 1972) (“Lever”)
2022	Errata to Declaration of Dr. Brian Zeglis (EX1003) (submitted as Exhibit 2018 in PGR2025-00059)
2023	Zeglis <i>et al.</i> , “Radiopharmaceuticals for Imaging in Oncology with Special Emphasis on Positron Emitting Agents,” Chapter 3 of <i>Nuclear Oncology: Pathophysiology and Clinical Applications</i> , H.W. Strauss <i>et al.</i> , eds. (2013) (“Zeglis 2013 II”)
2024	Poplawski <i>et al.</i> , “Identification of Selective and Potent Inhibitors of Fibroblast Activation Protein and Prolyl Oligopeptidase,” <i>J Med Chem.</i> 56(9): 3467–3477 (May 9, 2013) (“Poplawski”) (submitted as Exhibit 2020 in PGR2025-00059)
2025	Pages 7 and 8 of U.S. Patent Application Publication No. 2010/0098633 A1 (EX1004) (annotated by Dr. Brian Zeglis) (submitted as Exhibit 2021 in PGR2025-00059)
2026	Pages 12–14 of U.S. Patent Application Publication No. 2010/0098633 A1 (EX1004) (annotated by Dr. Brian Zeglis) (submitted as Exhibit 2022 in PGR2025-00059)
2027	Transcript of the Deposition of Dr. Brian Zeglis, March 11, 2026

Exhibit No.	Description
2028	Sugiura <i>et al.</i> , “Radiolabeling Strategies for Tumor-Targeting Proteinaceous Drugs,” <i>Molecules</i> 19: 2135–2165 (2014) (“Sugiura”)
2029	Testa <i>et al.</i> , “The influence of lipophilicity on the pharmacokinetic behavior of drugs: Concepts and examples,” <i>Perspectives in Drug Discovery and Design</i> , 19: 179–211 (2000) (“Testa”)
2030	Siwowska <i>et al.</i> , “Preclinical Comparison of Albumin-Binding Radiofolates: Impact of Linker Entities on the in Vitro and in Vivo Properties,” <i>Molecular Pharmaceutics</i> , 14(2): 523–532 (2017) (“Siwowska”)
2031	Fischer <i>et al.</i> , “Radioimmunotherapy of Fibroblast Activation Protein Positive Tumors by Rapidly Internalizing Antibodies,” <i>Clinical Cancer Research</i> , 18(22): 6208–6218 (November 15, 2012) (“Fischer”)
2032	Scott <i>et al.</i> , “A Phase I Dose-Escalation Study of Sibrotuzumab in Patients with Advanced or Metastatic Fibroblast Activation Protein-positive Cancer,” <i>Clinical Cancer Research</i> , 9: 1639–1647 (May 2003) (“Scott”)
2033	Welt <i>et al.</i> , “Antibody Targeting in Metastatic Colon Cancer: A Phase I Study of Monoclonal Antibody F19 Against a Cell-Surface Protein of Reactive Tumor Stromal Fibroblasts,” <i>Journal of Clinical Oncology</i> , 12(6): 1193–1203 (June 1994) (“Welt”)
2034	Aertgeerts <i>et al.</i> , “Structural and Kinetic Analysis of the Substrate Specificity of Human Fibroblast Activation Protein α ,” <i>The Journal of Biological Chemistry</i> , 280(20): 19441–19444 (May 20, 2005) (“Aertgeerts”)
2035	Laverman <i>et al.</i> , “Immuno-PET and Immuno-SPECT of Rheumatoid Arthritis with Radiolabeled Anti-Fibroblast Activation Protein Antibody Correlates with Severity of Arthritis,” <i>The Journal of Nuclear Medicine</i> , 56(5): 778–783 (May 2015) (“Laverman”)

Exhibit No.	Description
2036	Rüger <i>et al.</i> , “ <i>In vivo</i> near-infrared fluorescence imaging of FAP-expressing tumors with activatable FAP-targeted, single-chain Fv-immunoliposomes,” <i>Journal of Controlled Release</i> , 184: 1–10 (2014) (“Rüger”)
2037	LeBeau <i>et al.</i> , “Targeting the cancer stroma with a fibroblast activation protein-activated promelittin protoxin,” <i>Molecular Cancer Therapy</i> , 8(5): 1378–1386 (May 2009) (“LeBeau”)
2038	Huang <i>et al.</i> , “Evaluation of the tumor targeting of a FAP α -based doxorubicin prodrug,” <i>Journal of Drug Targeting</i> , 19(7): 487–496 (2011) (“Huang”)
2039	Keane <i>et al.</i> , “Neuropeptide Y, B-type natriuretic peptide, substance P and peptide YY are novel substrates of fibroblast activation protein- α ,” <i>FEBS Journal</i> , 278: 1316–1332 (2011) (“Keane”)
2040	Reiner <i>et al.</i> , “Harnessing the Bioorthogonal Inverse Electron Demand Diels-Alder Cycloaddition for Pretargeted PET Imaging,” <i>Journal of Visualized Experiments</i> , 96 (February 2015) (“Zeglis 2015”)
2041	Adumeau <i>et al.</i> , “Site-Specifically Labeled Immunoconjugates for Molecular Imaging—Part 1: Cysteine Residues and Glycans,” <i>Molecular Imaging Biology</i> , 18: 1–17 (2016) (“Zeglis 2016”)
2042	Zeglis <i>et al.</i> , “Chemoenzymatic Strategy for the Synthesis of Site-Specifically Labeled Immunoconjugates for Multimodal PET and Optical Imaging,” <i>Bioconjugate Chemistry</i> , 25(12): 2123–2128 (November 24, 2014) (“Zeglis 2014”)
2043	Penner <i>et al.</i> , “Radiolabeled Absorption, Distribution, Metabolism, and Excretion Studies in Drug Development: Why, When, and How?” <i>Chemical Research in Toxicology</i> , 25: 513–531 (2012) (“Penner”)

Exhibit No.	Description
2044	Jensen, “The Origins of the Ortho-, Meta-, and Para- Prefixes in Chemical Nomenclature.” <i>Journal of Chemical Education</i> , 83(3): 1-2 (2006)
2045	International Patent Appl. No. PCT/US2022/023374, published as WO 2022/212958 (“WO ’958”)
2046	Xu <i>et al.</i> , “Albumin Binder–Conjugated Fibroblast Activation Protein Inhibitor Radiopharmaceuticals for Cancer Therapy,” <i>The Journal of Nuclear Medicine</i> , 63(6):952-958 (June 2022) (“Xu”)

V. LEGAL BASIS FOR MY ANALYSIS

14. 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

15. I understand that in an IPR, 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.

16. I understand that claims 1 and 3 are the independent claims in the

'201 patent, and that claim 2 is a dependent claim depending directly from claim 1.

I understand that a dependent claim contains all limitations of the claim from which it depends. Thus, I understand that claim 2 contains all the limitations of claim 1.

B. Obviousness

17. 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).¹ I understand that obviousness must be assessed from the viewpoint of a POSA at the time of the invention. 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.

18. 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.

19. 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.

20. 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.

VI. CLAIM CONSTRUCTION

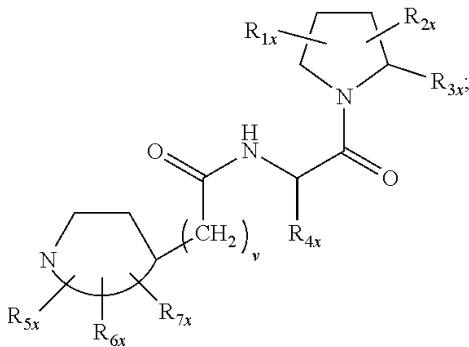
21. Claim 1 of the '201 patent recites:

A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

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



wherein:

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

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

R_{4x} is H;

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

v is 0;



represents a quinolinyl ring;

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

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

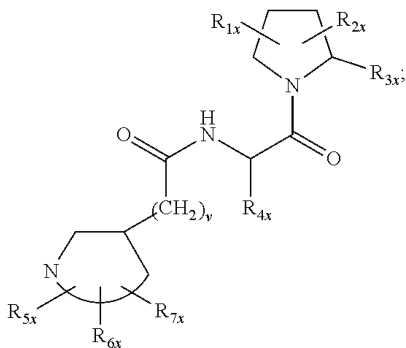
EX1001, 64:46-65:63, Certificate of Correction.

22. Claim 2 depends from claim 1 and further narrows B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy. EX1001, 65:64-67.

23. Claim 3 recites:

A low molecular weight compound consisting essentially of components B-L-A; wherein:

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



wherein:

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

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

R_{4x} is H;

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

v is 0;



represents a quinolinyl ring;

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

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

EX1001, 66:1-67:5, Certificate of Correction.

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

24. The challenged claims recite low molecular weight compounds having the formula “B-L-A.” EX1001, 64:46-67:5, Certificate of Correction. Dr. Zeglis does not offer a specific construction (*i.e.*, interpretation) for the term “B-L-A,” although he agrees the claimed compounds are defined structurally: “All the claims define ‘low molecular weight compounds’ having *a general formula ‘B-L-A.’*” EX1003, ¶162 (emphasis added). Dr. Zeglis further acknowledges that “A” in the claimed “B-L-A” is also “defined using a *chemical formula.*” EX1003, ¶166 (emphasis added). The functional language present in the claims is limited to “B” and “L.”

25. I note that during deposition, Dr. Zeglis “impos[ed] B’s function onto the entire B-L-A compound” (*see e.g.*, EX2027, 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, ¶35.

26. 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, 2:3–30, 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, 14:56–17:42) and an imaging or therapeutic agent “B” that similarly has dozens of well-defined, structural options described in the specification (EX1001, 17:55–30:55).

27. And during prosecution, JHU distinguished the genus of compounds over the prior art on structural grounds: JHU pointed to the claimed B-L-A structure to distinguish from US-650, Jansen 2013, and US-633. EX1002, 359-62. In other words, the specification completely lacks functionally defined limitations when referring to the compounds as a whole. EX2001, ¶35.

28. Nowhere in the claims, specification, or prosecution history are the claimed B-L-A compounds described solely by their ability to perform any particular function. 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* diagnostic” or *in vitro* “research applications” in addition to therapeutic uses. EX1001, 36:1–6.

29. 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”

30. Dr. Zeglis did not offer a construction of the term “low molecular weight,” but stated that “a skilled artisan would understand ‘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, ¶174. As discussed in my previous declaration, I disagree with Dr. Zeglis, and agree with Dr. Pomper, a co-inventor of the ’201 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, 360; EX2001, ¶¶36-37.

VII. CLAIMS 1–3 OF THE ’201 PATENT WOULD NOT HAVE BEEN OBVIOUS OVER US-633, JANSEN, AND MELETTA (GROUND 1)

31. Based on my review of the prior art and my experience in radiopharmaceutical chemistry and molecular imaging, it is my opinion that claims 1–3 of the ’201 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.

32. 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. *See* Section VII.A *infra*. Nothing in the prior art suggested that a POSA would have focused primarily on low molecular weight FAP radiotracer development.

33. 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.

34. 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.

35. 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 1–3 of the ’201 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

36. Before October 23, 2017, the art reported that developing FAP-targeting radiotracers presented significant selectivity challenges. EX1016, 259; EX1044, ¶4; EX1007, 491; EX2001, ¶¶16-17. 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, ¶¶15-16. Non-specific binding arising from this homology “is the limitation for 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. EX2034, 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, ¶16. 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.

37. 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, ¶40; EX2027, 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 (EX2027, 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

38. Dr. Zeglis opined that a POSA would have been motivated to develop small molecule FAP radiotracers (EX1003, ¶43), 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, ¶¶151-81; EX1008, Abstract; EX1035, 2083. Dr. Zeglis, also, is “not aware of any other references that disclose small molecule FAP imaging agents before 2017.” EX2027, 162:15-22.

39. 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. 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 compounds disclosed in US-633, Marquis selected a radiotracer with nanomolar affinity for FAP, Compound 1024, for further studies.

40. 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.

41. 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

⁵ The terms *ortho*, *para*, and *meta* refer to three different sites on a benzene ring. EX2046, 1-2. The iodine was conjugated to the benzene ring of MIP-1231 at three different sites in the three Marquis compounds.

plaque vulnerability and to detect FAP-positive tumors that may respond to FAP-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 high levels of FAP expression than normal arteries. 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, 2089-90. Indeed, Meletta stated, “binding of [¹²³I-MIP-1232] to endarterectomized tissue was similar in plaques and normal arteries, *hampering its use for atherosclerosis imaging*.” EX1008, Abstract (emphasis added).

42. 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

43. 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.” EX2040, Abstract. He likewise wrote, in work contemporaneous with the filing date of the ’201 patent, that antibodies exhibit “remarkable selectivity and specificity for cancer biomarkers,” and described antibodies as “promising platforms for the development of hybrid PET/OI agents” because of their “high selectivity and affinity.” EX2042, 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.” EX2027, 67:7–68:4.

44. 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* EX2035, 778, 781-83; EX2033, 1193, 1196-1202; EX2032, 1639, 1645-46; EX2031, 6206, 6214-17. 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.” EX2035, 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 mAb F19 could serve both diagnostic

and therapeutic purposes. EX2033, 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. EX2032, 1645–46.

45. Two other anti-FAP antibodies, ^{177}Lu -ESC11 and ^{177}Lu -ESC14, labeled with ^{177}Lu , showed “excellent targeting in melanoma xenografts.” EX2035, 778. In addition, Fischer demonstrated that ESC11 and ESC14 “bound selectively to both human and mouse FAP, with affinities in the low nanomolar range.” EX2031, Abstract. Laverman likewise reported that another anti-FAP antibody radiotracer, ^{111}In -28H1, “result[ed] in excellent image quality” due to low background uptake in off-target tissues. EX2035, 780, 783.

46. 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 '201 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, ¶30; *see also* EX2027, 68:6-10.

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

47. 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*.” EX2036, 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. EX2036, Abstract. But Dr. Zeglis did not address this approach in his declaration.

48. 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.” EX2023, 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. EX2037, Abstract; EX2038, Abstract; EX2039, Abstract, 1328.

49. 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

50. 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; *see also* EX1003, ¶49 (“slight modifications to the structure of a targeting moiety can alter its selectivity and affinity for its target”); EX2023, 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, ¶¶38-61.

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

52. 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, ¶34. Dr. Zeglis agrees. EX1003, ¶34. 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; *see also* 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)); EX2027, 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)); EX2001, ¶¶60-61.

53. 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, 137–38. Dr. Zeglis acknowledges that this strategy necessarily introduces additional structural elements into the molecule being labeled. EX1003, ¶¶34, 49(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, ¶49(b).

54. **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, ¶36.

55. 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

56. 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, ¶115. 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

57. 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 thus 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, ¶133), but then immediately jumps to the conclusion that “a skilled artisan would have invariably discovered the compounds characterized in Jansen.” EX1003, ¶134.

58. 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, ¶62. 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, 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”) (emphasis added). Nothing in Jansen suggests that its FAPi could be used diagnostically as radiotracers, as Dr. Zeglis agrees. EX2027, 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.

59. Before 2017, the prior art disclosed numerous small molecule FAP inhibitors, a point Dr. Zeglis readily acknowledged. EX2027, 128:2-6 (as summarized in the table in ¶64 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, ¶45. 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.

60. For example, Jansen 2013 disclosed thirty-six distinct small molecule FAP inhibitors. EX1007, Tables 2-3, EX2001, ¶¶64, 77. 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, ¶¶64, 77. 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 quinolinyl ring, which the claims exclude. EX1001, 64:46-67:5, 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, ¶¶64, 77.

61. A POSA would have also been aware of additional FAPi references published by the Jansen research group that were not cited by Dr. Zeglis. For example, U.S. Patent Application 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,

¶66. 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, ¶66. 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 (EX2027, 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, ¶142 fn.165. 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, 64:46-67:5, 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, ¶¶66-67.

62. 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, ¶65. Jansen 2014 describes those FAPis to be “selective” for FAP: “we managed to decouple DPP^{IV} and FAP potency.” EX2003, Abstract; EX2001, ¶65. 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, ¶65; EX2027, 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”).

63. A POSA also would have been aware of FAPi references published by other research groups. For example, Poplawski discloses twenty-two non-quinolinyl FAP inhibitors incorporating a boronic-acid warhead. EX2024, 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.” EX2024, 7. The selectivity of Poplawski’s Compound 6 (which falls outside of the claimed scope, due to the lack of a quinolinyl 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, ¶109(d). But Dr. Zeglis himself acknowledged that a POSA would not have been limited to FAP radiotracers intended solely for *in vivo* use. EX2027, 80:13-15 (noting that “[o]ptical imaging agents can be useful *in vivo* or *in vitro*”).

64. 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 quinoliny1 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, ¶109(c). This is, again,

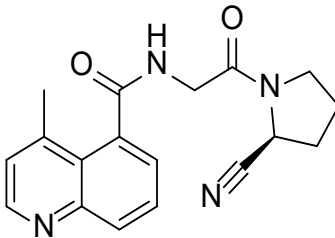
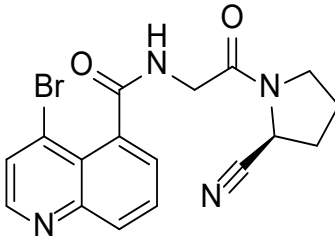
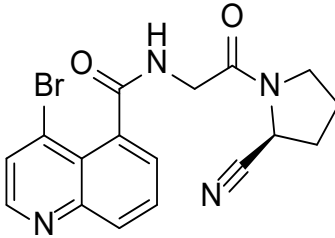
⁶ Jansen refers to Tsai as “Jiaang.” EX1006, 3063, Citation 23.

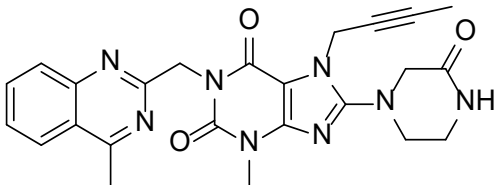
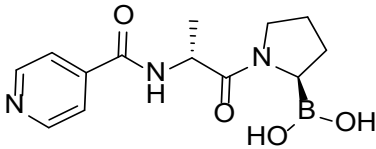
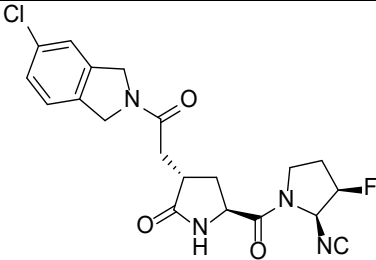
⁷ Lipophilicity and hydrophobicity are closely related concepts, both describing a compound’s tendency to associate with nonpolar environments. EX2029, 183–84, 197. Lipophilicity refers to a compound’s affinity for lipid or fat-like phases, while hydrophobicity describes its tendency to avoid aqueous environments; in practice, increased lipophilicity generally corresponds to increased hydrophobic character in biological systems.

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 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.

65. 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.

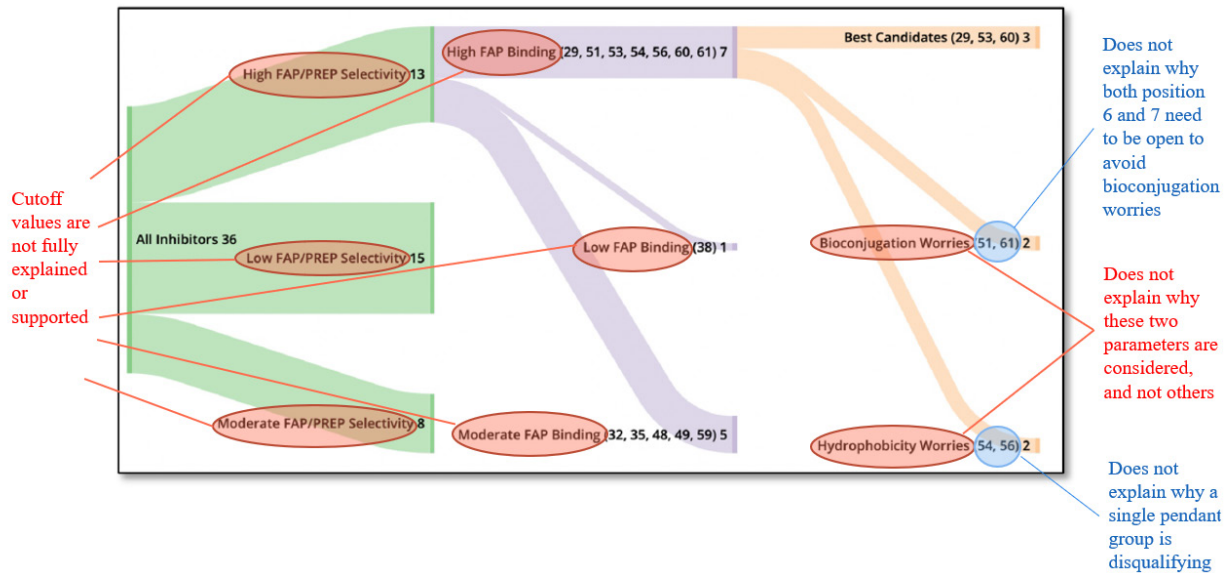
Reference	Number of FAPis disclosed	Number of FAPis that fall within claimed “A” moiety scope	Highest-selectivity FAPi structure
Jansen	54	3	 (Compound 53: Not within claimed “A” moiety scope)
US-650	43	1	 (Compound 22: Not within claimed “A” moiety scope)
Jansen 2013	36	2	

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

This table demonstrates that Dr. Zeglis selects Compound 60 by cherry-picking Compound 60 because it falls within the claimed “A” moiety scope, rather than on any scientific rationale that would have guided POSAs to that compound. And in doing so, he fails to describe any reason or design principle favoring Compound 60.

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

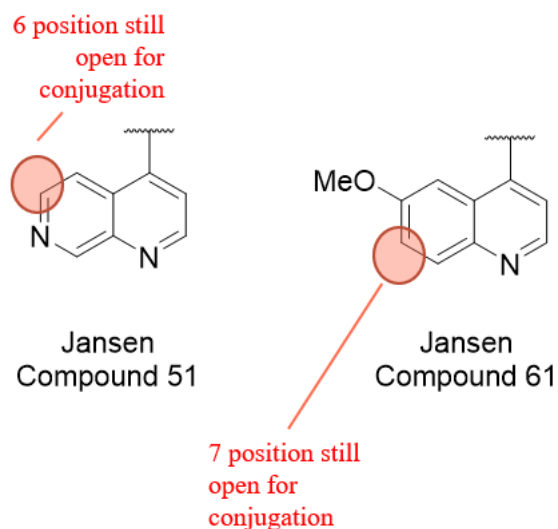
66. To justify selection of Compound 60 as the “A” moiety from the compounds disclosed in Jansen, Dr. Zeglis applied a multi-step classification process that supposedly prioritizes selectivity, then affinity, followed by qualitative assessments of stability, hydrophobicity, and ease of modification, which he illustrates using a Sankey diagram. EX1003, ¶¶116-21. 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, ¶¶68-79.



67. Briefly, Dr. Zeglis does not justify his selectivity and affinity cutoffs. EX2001, ¶71. 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, ¶72.

68. 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, ¶120; EX2001, ¶¶73-76. 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 quinoliny ring would be occupied.” EX1003, ¶¶120–121; EX2001, ¶73. However, both Compounds 51 and 61 have position 6 or

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



EX2001, ¶73. Yet, Dr. Zeglis does not explain why both positions on both compounds need to be open to avoid bioconjugation issues.

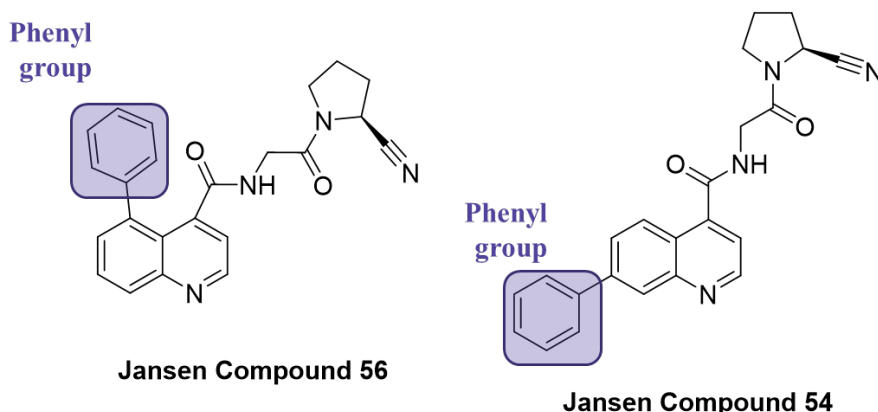
69. But choosing either of the above compounds as a FAPi in a radiotracer would have resulted in compounds outside of the challenged claims because Compound 51 does not have a quinolinyl ring required by the claims (due to the presence of an additional nitrogen in the ring) and Compound 61 has a substituent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

EX2001, ¶74. Thus, Dr. Zeglis discarded Compounds 51 and 61 in favor of Compound 60 in hindsight.

70. 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, ¶121; EX2001, ¶75. 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, ¶120), as illustrated below:



EX2001, ¶75.

71. But Dr. Zeglis fails to show any evidence that a single pendant phenyl ring disqualifies a FAPi from consideration based on pharmacokinetic concerns. EX2001, ¶76. 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. As I described in my first declaration, a POSA would have known that pendant phenyl groups, alone, do not result in unfavorable pharmacokinetic properties. *See, e.g.*, EX2018, 2213-14, FIG. 7 (describing compounds with "pendant phenyl groups" as having "lower lipophilicity ... and excellent *in vivo* efficacy"); EX2019, 2535 (describing a dipeptidyl peptidase IV inhibitor

compound with a substituted “pendant phenyl group” as having “excellent pharmacokinetic properties”); EX2020, 254-56 (describing diazepam variations with “unsubstituted” “pendant phenyl” groups as “essential tools for translational neuroscience”); *see also* EX2001, ¶76. 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.

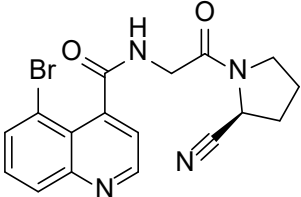
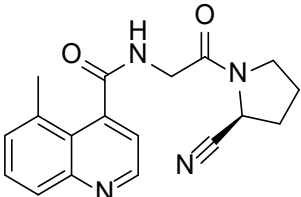
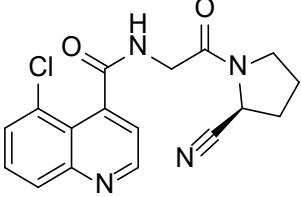
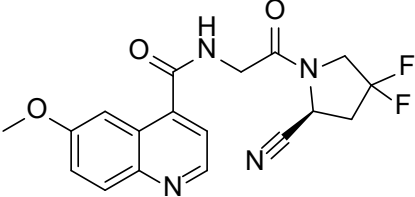
72. But even applying Dr. Zeglis’s own criteria to the quinoline-based compounds, the literature discloses over twenty compounds with a high selectivity, defined by Dr. Zeglis as > 100 (EX1003, ¶119), such that a POSA would *not* have been led uniquely—or even preferentially—to Compound 60 absent hindsight 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. *See* Section VII.C.1, *infra*. Dr. Zeglis agrees that these compounds have higher selectivity for FAP over PREP than Compound 60. *See* EX2027, 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

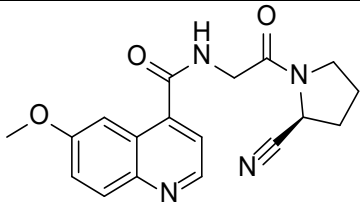
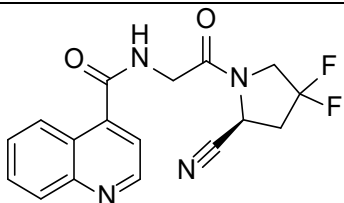
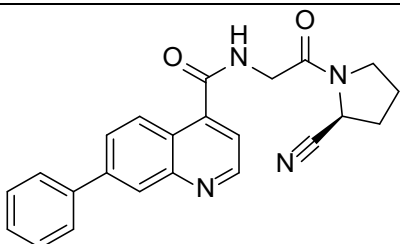
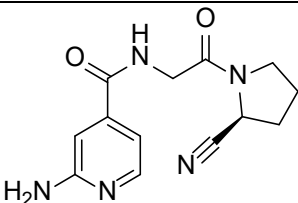
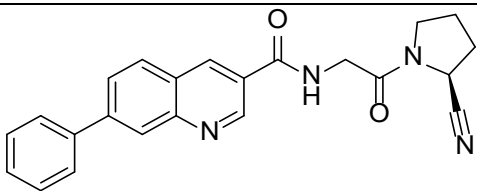
that Compound 53 of Jansen is “more selective than Compound 60”).

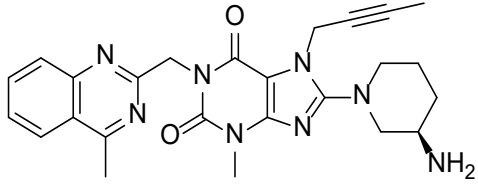
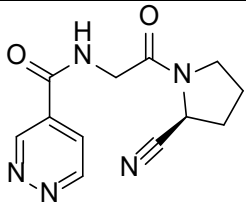
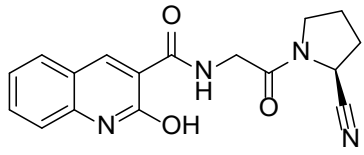
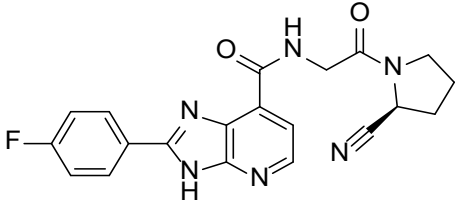
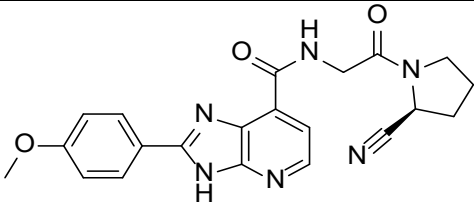
73. Even Jansen reports multiple compounds with higher selectivity than Compound 60. For instance, Compounds 53 and 61 have a selectivity of 2100 and 970, respectively. EX1006, Tables 4, 5. Yet Dr. Zeglis discounts Compound 53 because “it was not possible to compare the *in vitro* [microsomal] stability, PK, bioavailability and *in vivo* characteristics” of this compound to Compound 60. EX1003, ¶123; 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, ¶126. 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.*, EX2043, 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.

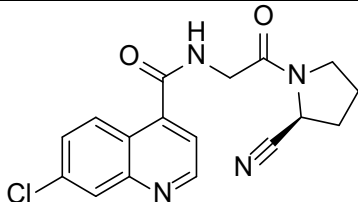
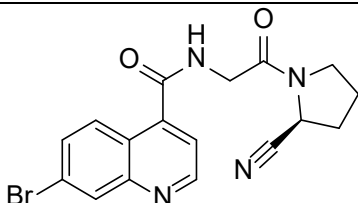
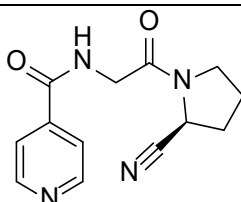
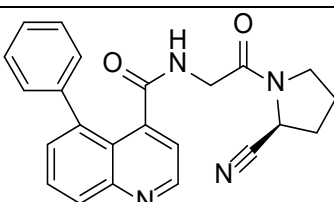
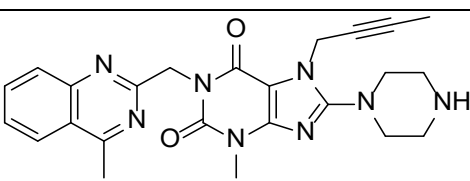
74. A tabulated set of FAPis across the quinolinyl-based references, Jansen, US-650, Jansen 2013, and Jansen 2014 that meet Dr. Zeglis’s criteria (selectivity >100) is shown below, ranked in the order of selectivity (calculated by dividing $IC_{50}^{PREP}/IC_{50}^{FAP}$) that Dr. Zeglis characterized as the “most important” characteristic. EX1003, ¶¶45, 117.

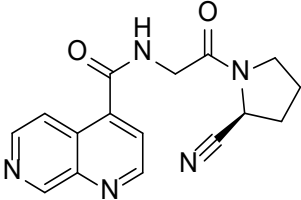
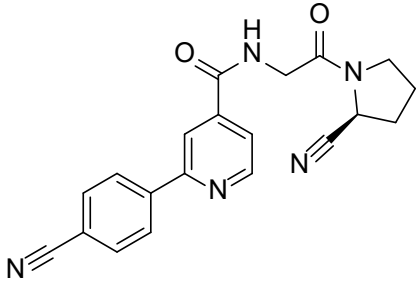
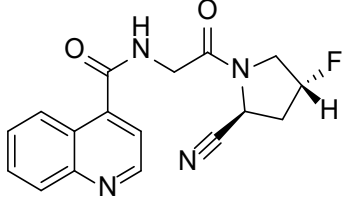
**Top prior-art FAPis, ranked by selectivity in Jansen, US-650, Jansen 2013,
and Jansen 2014.**

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

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claimed "A" structure ?
US 650: 11 Jansen 2013: 30		0.0092	677	N
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

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claimed "A" structure ?
Jansen 2014: 3		0.37	>270	N
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

Compound Number	Structure	FAP Affinity (μM)	FAP Selectivity	Fall within scope of claimed "A" structure ?
US 650: 13 Jansen 2013: 31		0.0071	197	N
US 650: 12 Jansen 2013: 32		0.0062	193	N
US 650: 4 Jansen: 29		0.063	179	N
US 650: 26 Jansen: 56		0.064	135	N
Jansen 2014: 13a		0.74	>135	N

Compound Number	Structure	FAP Affinity (μ M)	FAP Selectivity	Fall within scope of claimed “A” structure ?
US 650: 33 Jansen: 51		0.028	120	N
US 650: 16 Jansen: 35		0.27	107	N
Jansen: 59		1	>100	Y

75. 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, ¶¶77–78.

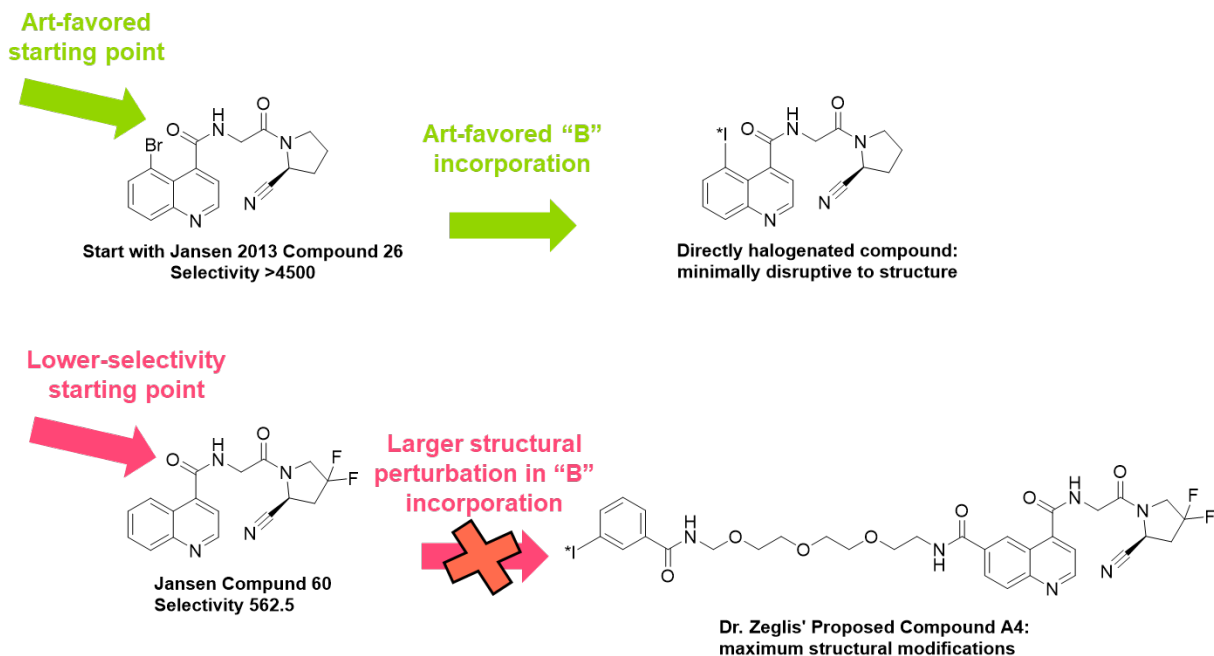
76. Thus, selecting Compound 60 from this set cannot be explained by the technical record and would only have been made with knowledge of the claim limitations, not from the perspective of a POSA evaluating the prior art as it existed before 2017.

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

77. 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, ¶¶60–61. 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 or halogen exchange as the most straightforward and least disruptive route to a radiotracer. EX1014, 44; EX1010, 3; *see also* EX2001, ¶¶60–61.

78. 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, ¶139. 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.



79. 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 or halogen exchange 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

80. 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; EX2027, 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 (EX2027, 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.

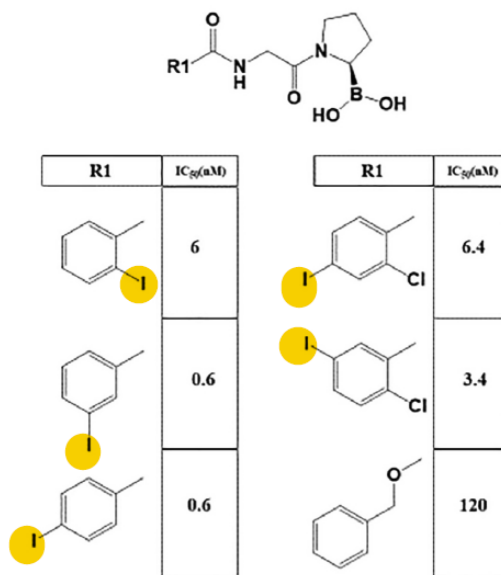
1. A POSA would not have been motivated to make “B-L-FAPi” based on general radiotracer principles

81. 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.

82. 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. EX2028, 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, ¶49(b); *see also* EX2023, 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, ¶139.

83. 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.



84. 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

85. 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, ¶165. He derives that selection from selecting PEG from US-633's laundry list of linkers and US-633's broad genus of linkers. EX1003, ¶149. 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, ¶149.

86. 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, ¶¶88, 151. 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, ¶151; EX2027, 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).

87. 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, ¶88. In support, he cites a reference noting that long PEG increases the lipophilicity of radiopharmaceuticals. EX1003, ¶88 fn.110 (“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, ¶120.

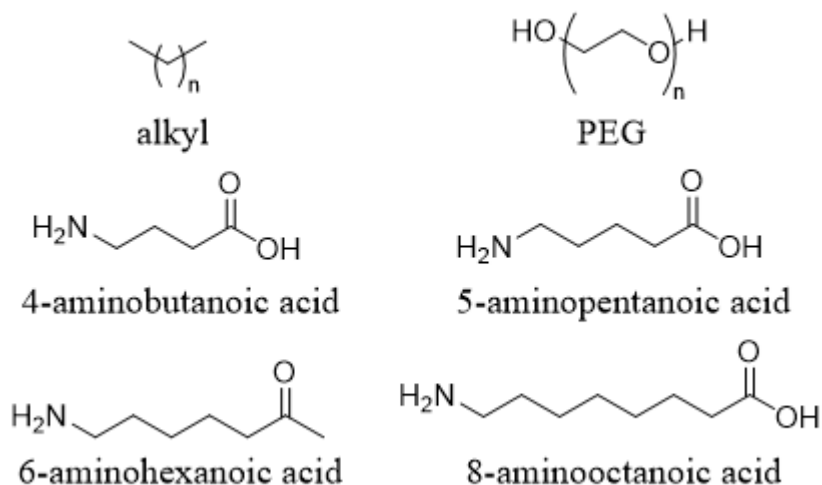
88. Furthermore, Dr. Zeglis does not explain why a POSA would not have selected any of the other linkers disclosed in US-633. Indeed, US-633 discloses many potential linkers such as “a simple alkyl chain as shown, a PEG $(\text{CH}_2\text{CH}_2\text{O})_n$, a polyethylene amine $((\text{CH}_2\text{CH}_2\text{NH})_n)$, or the like. Terminal aminoalkanoic acids (such as β -alanine, 4-aminobutanoic acid, 5-aminopentanoic

⁷ Lipophilicity and hydrophobicity are closely related concepts, both describing a compound’s tendency to associate with nonpolar environments. EX2029, 183–84, 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.

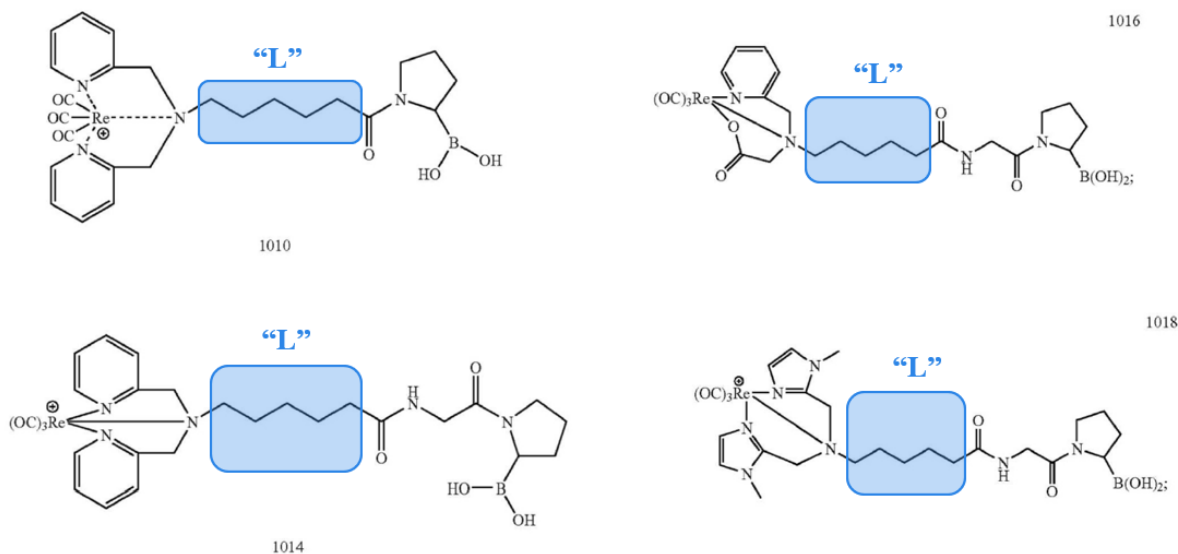
acid, 6-aminohexanoic acid and the 8-aminooctanoic acid) or amino-PEG-acids

($\text{NH}_2-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2-\text{COOH}$, e.g. 2-(2-(3-aminopropoxy)ethoxy)acetic acid).”

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.

89. 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, ¶207; *see also* EX1003, ¶210 (“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, ¶211 (“[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.

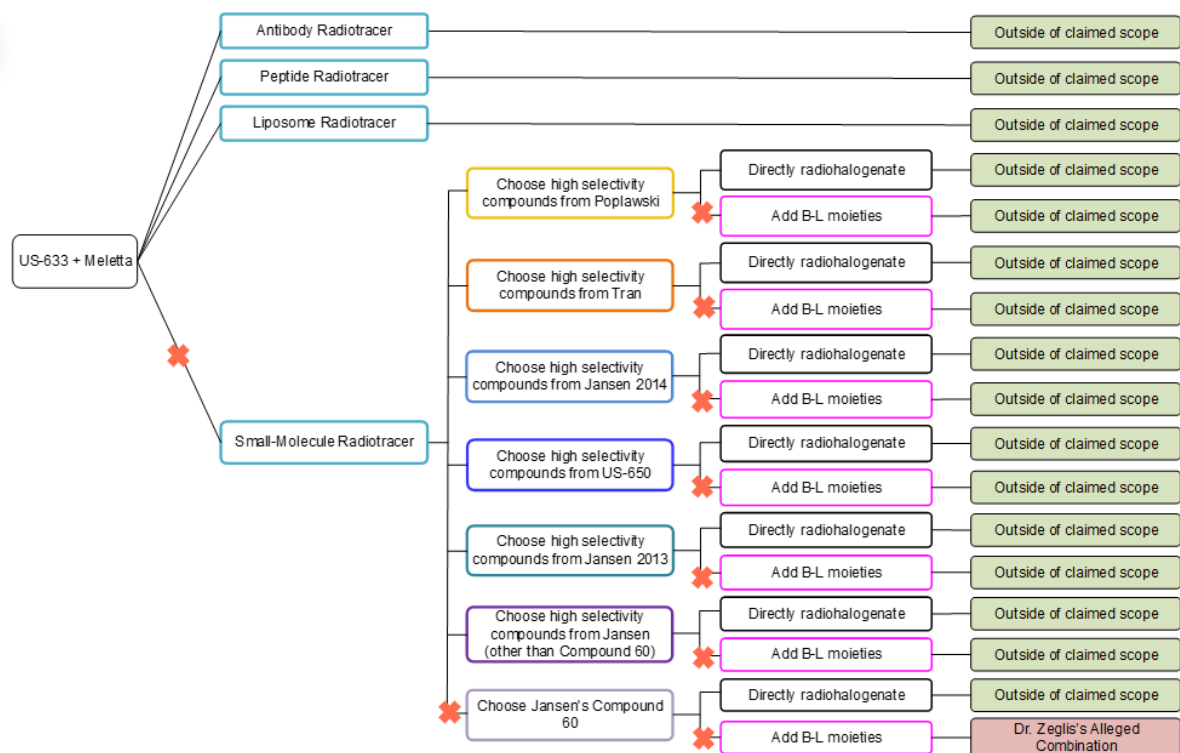
90. Dr. Zeglis proposes that FAP radiotracers, including those that contain PEG-based linkers, could be used *in vivo*. See, e.g., EX1003, ¶135. But a skilled artisan would have known that the use of PEG-based linkers in imaging and therapeutic agents came with its own set of drawbacks. For example, 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. EX2030, 523, 530. 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.” EX2030, 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.

91. In sum, Dr. Zeglis did not show that the compounds made with his choice of linkers would have rendered the '201 claims obvious.

* * *

92. 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.

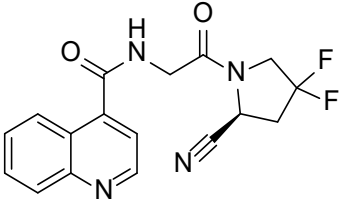
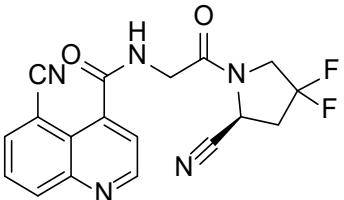


E. Even if a POSA had a reason to combine Jansen's Compound 60 with "B" and "L," a POSA would not have had a reasonable expectation of success in doing so.

93. 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, 2089-90. 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.

94. 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. EX1006, Table 5. A comparison of these compounds is provided in the table below.

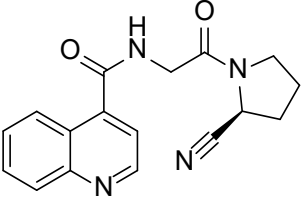
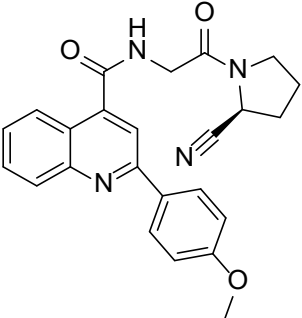
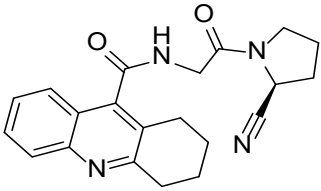
Jansen Compound Number	Structure	FAP Affinity (μM)	Selectivity Index
60		0.0032	562
63		7.2	2.3

95. 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

96. Jansen 2013 expressly reports that “substituents in the 2- and 3-position of the quinoline ring, as in compounds 19–24, hav[e] 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 '201 patent that a POSA would have understood this quinolinyl ring to be able to tolerate modification in certain sites on the ring. EX1001, 57:61-61:62.

97. 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.

98. That understanding reflected the view in the art until the '201 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 1–3 OF THE '201 PATENT WOULD NOT HAVE BEEN OBVIOUS OVER US-121 AND JANSEN (GROUND 2)

99. 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, ¶¶179–204; *see also* EX2027, 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, ¶199.

100. 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-quinolinylyl 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 quinolinylyl-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, ¶¶80–83.

101. 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, ¶182; EX2027, 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

102. 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.

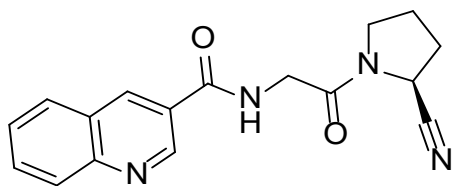
A. Unexpected results demonstrate that the Claimed Compounds would not have been obvious

103. 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.

1. The claimed “B-L-A compounds” demonstrate unexpected results

104. 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’s $SI_{FAP/PREP}$ of 86, reaching values in the hundreds of thousands and, in one such “B-L-A” compound, exceeding one million.



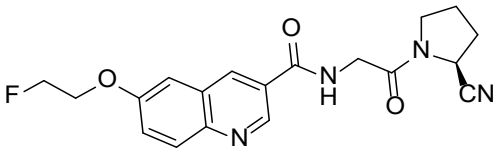
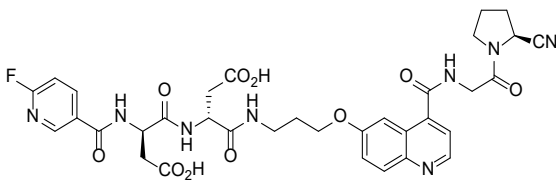
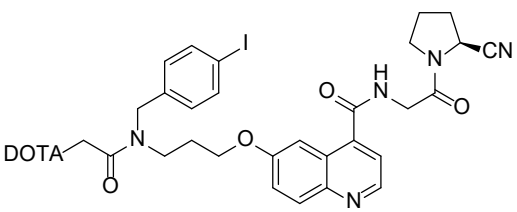
Compound 7. EX1007 (Jansen 2013), Scheme 1, Table 2.

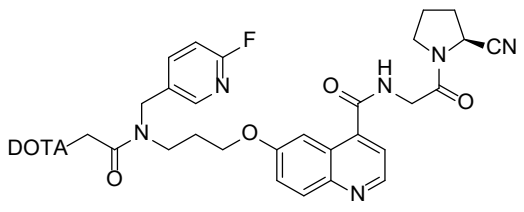
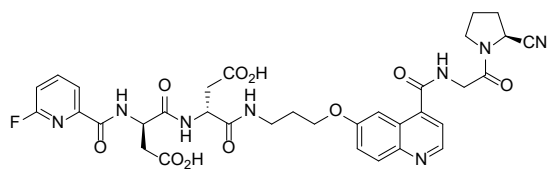
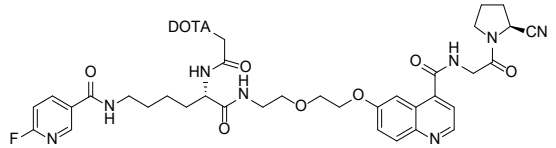
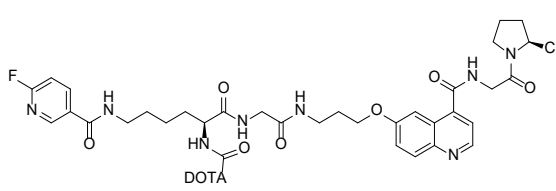
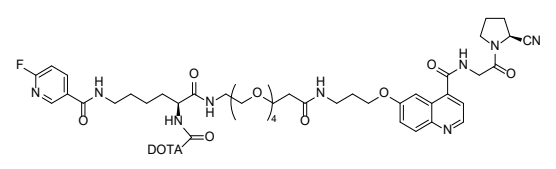
105. This unexpected increase in selectivity of the Claimed Compounds is evidenced by the data disclosed in International Patent Appl. No. PCT/US2022/023374, published as WO 2022/212958 (“WO ’958”). WO ’958 provides compounds representative of the scope of the claimed “B-L-A” structure. These compounds contain an “A” moiety (i.e., a quinoliny-based FAPi); a “B” moiety (i.e., an optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging, or radiotherapy) and a linker having bi-functionalization adapted to form a chemical bond with B and A. EX2045, Table 3;

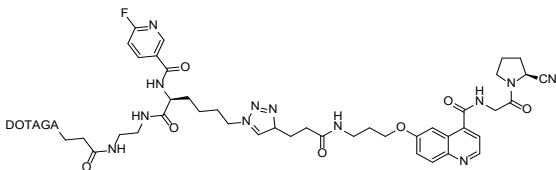
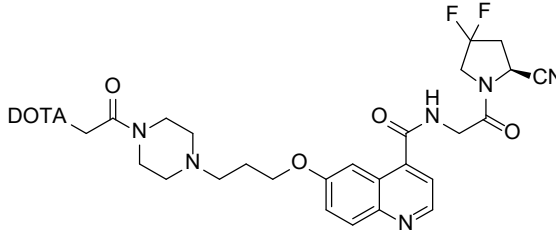
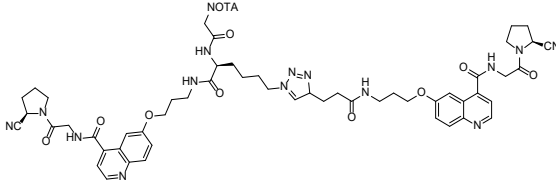
EX1001, 64:46-65:63, Certificate of Correction. The PREP IC₅₀ and FAP IC₅₀, i.e., the affinity for PREP and FAP, are also provided in WO '958. EX2045, Table 3.

As noted above, FAP-selectivity is determined by dividing a compound's PREP IC₅₀ by its FAP IC₅₀ (PREP IC₅₀/FAP IC₅₀). *See* Section VII.C.2. From these values, the FAP selectivity of the compounds can be calculated. *See* Section III, fn.

4.

WO '958 Cpd. No.	WO '958 Compound Structure	MW (g/mol)	PREP IC ₅₀ (nM)	FAP IC ₅₀ (nM)	SI Increase Compared to A Alone
7		370.38	1410	0.343	4,111 ~48-fold improvement
14		734.7	86,570	1.31	66,084 ~768-fold improvement
11		983.86	2 x 10 ⁶	1.41	1,418,440 ~16,493-fold improvement

WO '958 Cpd. No.	WO '958 Compound Structure	MW (g/mol)	PREP IC ₅₀ (nM)	FAP IC ₅₀ (nM)	SI Increase Compared to A Alone
12		876.94	21,950	2.09	10,052 ~117-fold improvement
13		734.70	6910	1.19	5,807 ~68-fold improvement
15		1049.13	1090	1.40	779 ~9-fold improvement
16		1076.15	1710	1.01	1,693 ~20-fold improvement
17		1266.39	240	0.59	407 ~5-fold improvement

WO '958 Cpd. No.	WO '958 Compound Structure	MW (g/mol)	PREP IC ₅₀ (nM)	FAP IC ₅₀ (nM)	SI Increase Compared to A Alone
23		1282.4 3	630	0.48	1,313 ~15-fold improvement
1		872.93	796	0.75	1,061 ~12-fold improvement
22		1257.3 5	510	0.35	1,457 ~17-fold improvement

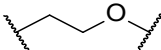
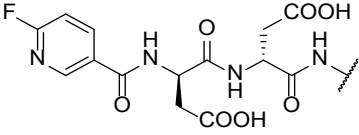
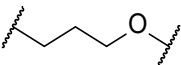
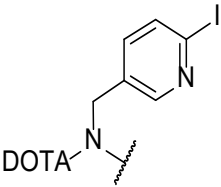
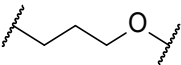
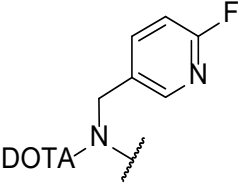
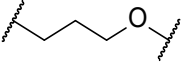
EX2045, Table 3.

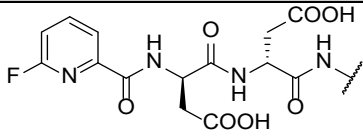
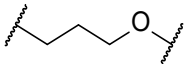
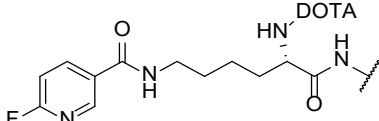
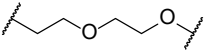
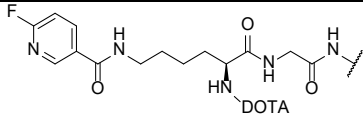
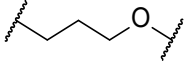
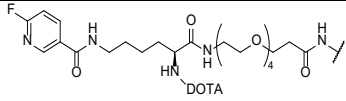
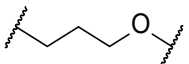
106. The above B-L-A compounds exhibited improvements ranging from approximately 5-fold to >16,000-fold over Jansen 2013's Compound 7. EX2045, Table 3.

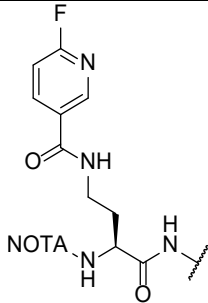
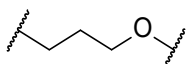
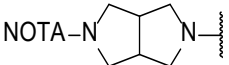
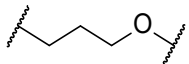
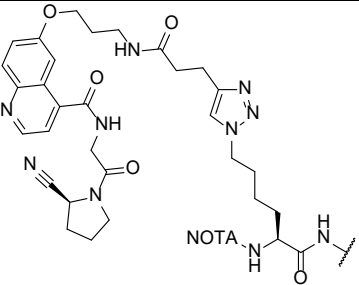
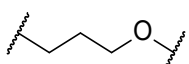
107. This dramatic increase in selectivity is not at all predictable from the starting selectivity of the "A" compounds, and reflects a qualitative and

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.

108. The data discussed above in WO '958 was also present in the declaration that Dr. Pomper submitted during the prosecution of the '201 patent. EX1002, 365-67. The table below summarizes the data presented in Dr. Pomper's declaration and compares them to the selectivity of Jansen 2013 Compound 7, which had a $SI_{FAP/REP}$ of 86. Dr. Zeglis does not discuss or address these data in his declaration, even though he cited the prosecution history of the '201 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
 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

“B” Moiety	“L” Moiety Structure	B-L-A MW (g/mol)	B MW (g/mol)	Selectivity Index Increase compared to A alone
 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
 Dual 3-membered chelator (DOTA) / prosthetic group with a halogen (F)		1266	888.4	407 ~5-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 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

109. Compounds 7, 14, 11, 12, 13, 15, 16, 17, and 23 of WO '958,

respectively, correspond to the compounds from Dr. Pomper's declaration listed as Nos. 1-8 and 11, respectively, in the table above. EX2045, Table 3; EX1002, 365-67. Dr. Pomper's declaration also provides the selectivity data for Compounds 29 and 33 of WO '958 (Compounds 9 and 10 in Dr. Pomper's declaration) that was not reported in WO '958, similarly confirming the unexpected orders-of-magnitude improvement in FAP-selectivity for Jansen 2013's Compound 7 when put into "B-L-A" form. EX2045, Table 3; EX1002, 365-67.

2. When compared to "B-FAPi" compounds, the claimed "B-L-A" compounds demonstrate unexpected results

110. As another point of comparison, the selectivity exhibited by the claimed compounds is vastly superior to that of Meletta's B-FAPi 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, 357–68 (Pomper Declaration, ¶42); *see also* EX1035, Abstract. Critically, this dramatic disparity does not track with the starting selectivity of the corresponding "A" moiety (Jansen 2013's Compound 7) in the claimed and tested compounds (Tables 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, 365–67 (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.

111. 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.

112. 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.

3. The unexpected results are representative of, and are commensurate with, the full scope of the claims

113. The unexpectedly high selectivity observed for the claimed compounds described above in WO '958 and in Dr. Pomper's declaration is representative of, and are commensurate with, the full scope of claims 1–3 of the '201 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.

* * *

114. 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. CONCLUSION

115. In signing this declaration, I recognize that the declaration will be filed as evidence in an *inter partes* review before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required, I will appear for cross-examination within the United States during the time allotted.

116. 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 15th day of June 2026, in San Francisco, CA.



Henry F. VanBrocklin, Ph.D.