

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 PRELIMINARY RESPONSE**

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Johns Hopkins EX2001
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 have been retained as an expert witness on behalf of Patent Owner The Johns Hopkins University (“Patent Owner”) for the above-captioned *inter partes* review (IPR). I am being compensated for my time in connection with this IPR at my standard consulting rate, which is \$350.00 per hour.

2. I understand that this Declaration accompanies the Patent Owner Preliminary Response (POPR) 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.

3. 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”) in light of general knowledge in the art as of the timeframes discussed herein.

II. MY BACKGROUND AND QUALIFICATIONS

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

5. I have extensive experience in the fields of molecular imaging, radiopharmaceutical chemistry, positron emission tomography, single photon emission computed tomography, oncologic imaging agents, proteases, steroids, prostate-specific membrane antigen (PSMA), imaging in drug development,

radiometal chemistry/labeling, radiopharmaceutical therapy, and theranostics.

6. In 1984, I obtained a B.S. in Chemistry from Rensselaer Polytechnic Institute, from where I graduated *cum laude*. Subsequently, I obtained an M.S. in Nuclear Chemistry from Rensselaer Polytechnic Institute in 1986, followed by an M.A. in Nuclear Chemistry from Washington University in St. Louis in 1988, after which I completed my Ph.D. in Radiopharmaceutical Chemistry, also from Washington University in St. Louis, in 1990. During my Ph.D., I studied the synthesis and biological evaluation of fluorine-18 labeled estrogens and progestins as positron emission tomography imaging agents.

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

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

faculty member at Lawrence Berkeley National Laboratory.

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

10. At UCSF, my research focuses include radioactive imaging agents, radiopharmaceuticals, and the use of such agents for the evaluation and interrogation of a variety of diseases, as well as normal physiologic and metabolic processes. I develop new imaging agents radiolabeled with a variety of isotopes and study their properties *in vitro* and in small animal models. Some examples of this *in vitro* work include a report on the evaluation of labeled estrogens for

imaging breast cancer, and a report on screening tyrosine kinase inhibitors for tumor imaging. I also develop radiopharmaceuticals past the laboratory bench for use in human research studies, working closely with clinical colleagues to navigate the regulatory pathway, FDA, radiation safety committee, and IRB.

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

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

- “CD46-Targeted Theranostics for Positron Emission Tomography and ^{225}Ac -Radiopharmaceutical Therapy of Multiple Myeloma,” *Clinical Cancer Research* 2024;
- “Prostate Specific Membrane Antigen Targeted StarPEG Nanocarrier for Imaging and Therapy of Prostate Cancer,” *Advanced Healthcare Materials* 2024;
- “Actinium-225 targeted alpha-particle therapy for prostate cancer,” *Theranostics* 2024;
- “Quantitative positron emission tomography (PET) imaging preclinical rat studies targeting the L-glutamate Excitatory Amino Acid Transporter 2 (EAAT2) with tracer [^{18}F]RP-115,” *Clinical Cancer Research* 2025;
- and the book chapter “Positron Emission Tomography Radiochemistry,” in *Molecular Imaging: Principles and Practice* (2020).

12. Over my career in the field, I have obtained over \$16 million in grants to study radioligands, radiotherapeutics, or imaging, including from the National Institutes of Health, the U.S. Department of Energy, the U.S. Department of Defense and several foundations, including the Michael J. Fox Foundation, the PolyBio Research Foundation, and the Alzheimer’s Drug Discovery Foundation. At UCSF, I have directly mentored or served as research advisor for at least 15 early-career faculty, 33 postdoctoral fellows, and 51 pre-doctoral students.

13. In addition to my prior duties as Editor-in-Chief of *Molecular Imaging*, I frequently perform peer review for academic journals, including as an Editorial Advisory Board member of *Current Molecular Imaging* (2013-2016), *Assay and Drug Development Technologies* (2012-present), and *Current Medicinal Chemistry* (2010-2018), as well as an Editorial Board member of *Reports in Medical Imaging* (2008-2015), *Letters in Drug Design and Discovery* (2002-2015), and *Nuclear Medicine and Biology* (2001-2012). I also perform peer review on an *ad hoc* basis for a variety of journals, including *Science*, *Proceedings of the National Academy of Science (USA)*, *Frontiers in Nuclear Medicine*, the *Journal of Nuclear Medicine*, the *Journal of Labelled Compounds and Radiopharmaceuticals*, *Molecular Imaging*, and *Molecular Imaging and Biology*. I also have served as a peer-reviewer for grants submitted to the National Institutes of Health (NIH), the US Department of Energy (DOE), the Congressionally Directed Medical Research Programs (US Department of Defense) and the Cancer Prevention and Research Institute of Texas, among other domestic and international organizations.

14. In addition to my educational training and my professional and research experience, I have kept abreast of the fields of molecular imaging, radiopharmaceutical chemistry, positron emission tomography, single photon emission computed tomography, oncologic imaging agents, proteases, steroids, (PSMA), imaging in drug development, radiometal chemistry, radiopharmaceutical

therapy, and theranostics by reading scientific literature, conferring with colleagues in the field, and attending and presenting lectures at scientific conferences. I have spoken at over 100 national or international conferences on topics including radiopharmaceuticals, imaging, biomarkers, PSMA, radiometals, drug design, and radiochemistry, and given over 30 invited lectures on the same. I have also regularly taught undergraduate and graduate courses since 2003, most recently, the course “Imaging Probes for Nuclear and Optical Imaging” every year since 2011.

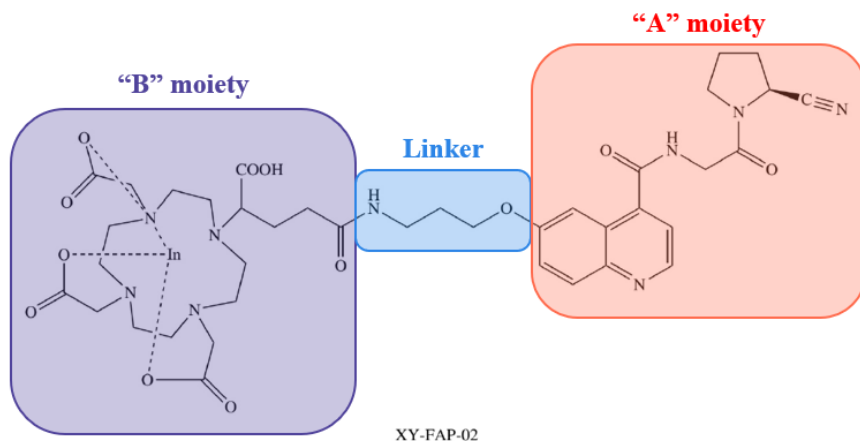
III. THE '201 PATENT

15. The '201 patent relates to innovative low molecular weight imaging and radiotherapeutic agents (collectively, radiotracers) targeting fibroblast activation protein- α (FAP). EX1001, Abstract. FAP, also referred to as seprase or FAP- α , is a transmembrane serine protease that is expressed on the stroma (the supportive framework of an organ or tissue) of cells. EX1001, Abstract, 1:30-48; EX1016, 3-4. FAP is typically undetectable or low in healthy cell tissues, but overexpressed in diseases and disorders associated with activated stroma, such as wound healing, rheumatoid arthritis, osteoarthritis, cirrhosis, and pulmonary fibrosis. EX1001, Abstract, 1:30-48; EX1022, 124; EX1024, 456; EX1023, 288; EX1041, 2. FAP is also overexpressed in cancer cells, where it has been detected in over 90% of cancer stroma examined. EX1001, Abstract, 1:30-48; EX1016, 4; EX1007, 491.

16. As the '201 patent explains, before October 23, 2017, molecular imaging of FAP was plagued with challenges. *See, e.g.*, EX1001, 1:65-67. This was partially due to concerns associated with developing radiotracers that are selective for FAP. FAP shares structural homology with several enzymes in its family (prolyl oligopeptidase (PREP) and dipeptidyl peptidases (DPP) DPP^{IV}, DPP^{II}, and DPP^{IX}), and the structural similarities result in FAP-targeting compounds having off-target activity against the PREP and DPPs peptidases. EX1016, 259; EX1044, ¶4; EX1007, 491. Indeed, the single previous clinical attempt to develop low molecular FAP imaging agents resulted in a failure: the radiotracer failed to “selectively accumulate in the atherosclerotic tissue” when tested for atherosclerotic plaque imaging by *in vitro* autoradiography with human carotid plaques. EX1008, 2089-2090. As a result, it was generally believed that the non-specific binding of FAP due to sharing peptide substrate homology with other peptidases “limit[ed] the fabrication of FAP targeted imaging probe[s].” EX2004, 11. And imaging with more selective agents, such as anti-FAP antibodies, “suffer[ed] from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake.” EX1001, 1:56-60.

17. Against this backdrop, the inventors of the '201 patent developed novel low molecular weight FAP imaging agents that addressed the selectivity and

biodistribution problems seen with other imaging agents. The radiotracers described in the '201 patent have a general formula "B-L-A," where A is "a targeting moiety for FAP- α ," B is an "optical or radiolabeled functional group" suitable for imaging, and L is a linker connecting B and A. EX1001, 2:1-12. An example of a radiotracer of the '201 patent is shown below:



EX1001, cols. 57-58 (annotated).

18. The low molecular weight B-L-A radiotracers of the '201 patent have "ideal properties for nuclear imaging of FAP- α ." EX1001, 1:65-67. The radiotracers "demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration," and they "can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval." EX1001, 1:60-65. For example, the '201 patent demonstrates high selectivity and affinity of the radiotracers in cell lines expressing FAP. *See, e.g.,* EX1001, 5:39-41 ("FIG. 3A, FIG. 3B, and FIG. 3C show the assessment of

the *in vitro* binding ability and specificity of XY-FAP-01 and [¹¹¹In]-XY-FAP-02”); *see also* EX1001, 7:66-8:3 (“In a particular embodiment, an optical agent conjugated with IRDye-800CW (XY-FAP-01) was synthesized and showed selective uptake *in vitro* on a FAP- α + U87 cell line and *in vivo* on a FAP- α + U87 tumor and clearly detected the tumor”); *see also* EX1001, 61:27-29 (“Taken together, these results support the specificity of XY-FAP-01 and ¹¹¹In-XY-FAP-02 in the engagement of FAP *in vitro*”). Further, the radiotracers exhibit “favorable biodistribution and retained uptake in the FAP-positive xenograft at various imaging time points.” EX2011, Abstract, 8.

19. In sum, the ’201 patent describes novel highly selective radiotracers that can be used in various *in vivo*, *ex vivo*, and *in vitro* as imaging, diagnostic, and therapeutic applications.

IV. SUMMARY OF OPINIONS

20. I have been asked to consider whether, before October 23, 2017, the prior art that Dr. Zeglis cites under Ground 1 (Jansen (EX1006), US-633 (EX1004), and Meletta (EX1008)) would have rendered the challenged claims of the ’201 patent obvious. In view of the state of the art before October 23, 2017, Dr. Zeglis has failed to show that a POSA would have found the challenged claims obvious over the prior art cited in Ground 1.

21. The challenged claims recite low molecular weight compounds having

a “B-L-A” formula, where B is an “optical or radiolabeled functional group,” L is “a linker,” and A is “a targeting moiety for FAP- α ” having a particular structure. EX1001, 64:46-67:5, Certificate of Correction. To arrive at the claimed compounds from the art combination cited by Dr. Zeglis, a POSA would have had to select US-633’s FAP inhibitor (“FAPi”) imaging agents having a linker and replace the FAPi with a very specific compound from Jansen, Compound 60, which the prior art did not disclose as being in a B-L-A structured radiotracer. But such selections could have only been made using the challenged patent’s claims as a roadmap.

22. *First*, Dr. Zeglis treats *all* of US-633’s imaging agents as employing “a modular three-component” B-L-FAPi design. But Dr. Zeglis is incorrect, as US-633 discloses two types of agents, those having a linker-containing (B-L-FAPi) design and those having a linker-less (B-FAPi) design. Those agents having the B-L-FAPi design performed *worse* in terms of affinity for FAP than those having the B-FAPi design, as discussed below in Sections VIII.A.1 and VIII.A.2. For this reason alone, a POSA would not have selected US-633’s B-L-FAPi imaging agents for further modification, and Dr. Zeglis’s choice of those agents is pure hindsight.

23. *Second*, Dr. Zeglis’s choice of Jansen’s Compound 60 as “one of the most promising FAP inhibitors that had been discovered to date” (EX1003, ¶115) is not supported by the published scientific evidence. Indeed, before 2017, the art

described a number of FAPis that outperformed Compound 60 (under Dr. Zeglis's own selection criteria). EX1044, Table 3; EX1007, Tables 2-3. Without explanation, Dr. Zeglis ignores these other, superior FAPis and instead selected Compound 60 apparently because these other compounds fall outside the scope of the claims. In choosing Compound 60 over the other compounds that were superior by Dr. Zeglis's own selection criteria, Dr. Zeglis clearly used the claims as a roadmap in an effort to arrive at the claimed invention, and therefore did not meet his burden to explain why a POSA would have arrived at the claimed compounds.

24. Dr. Zeglis also fails to show obviousness over US-121 (EX1005) and Jansen (EX1006) (Ground 2). For the same reason as in Ground 1, Dr. Zeglis's selection of Jansen's Compound 60 for "A" is made with hindsight. And US-121 does not add anything to aid in the selection of "A" because it is not even related to FAPis, as Dr. Zeglis himself notes. EX1003, ¶182.

V. 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
1003	Declaration of Dr. Brian Zeglis
1004	U.S. Patent Publication 2010/0098633
1005	U.S. Patent Publication 2012/0009121

Exhibit No.	Description
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)
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)

Exhibit No.	Description
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)
1024	Hamson et al., “Understanding fibroblast activation protein (FAP): Substrates, activities, expression and targeting for cancer therapy,” Proteomics Clin. Appl., 8:454-463 (2014)
1024	O'Brien et al., “Seprase: An overview of an important matrix serine protease,” Biochimica et Biophysica Acta, 1784:1130-1145 (2008)

Exhibit No.	Description
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)
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)

Exhibit No.	Description
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 Publication 2014/0357650
1045	Ji et al., “Tumor fibroblast specific activation of a hybrid ferritin nanocage-based optical probe for tumor microenvironment imaging,” Small J., 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)

Exhibit No.	Description
1047	Tsai et al., “Substituted 4- carboxymethylpyroglutamic Acid Diamides as Potent and Selective Inhibitors of Fibroblast Activation Protein,” J. Med. Chem. 53(18):6572-6583 (2010)
1048	International Publication 2010/108125
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,” Mol. Imaging Biol., 7(4):304-308 (2005)
1052	Zhou et al., “Radiolabeled Cyclic RGD Peptides as Radiotracers for Imaging Tumors and Thrombosis by SPECT,” Theranostics, 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”)
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”)

Exhibit No.	Description
2020	Calcaterra et al., “Classics in Chemical Neuroscience: Diazepam (Valium),” ACS Chemical Neuroscience, 5:253-260 (February 2014) (“Calcaterra”)
2021	Lever, A.B.P., “Lewis Structures and the Octet Rule,” Journal of Chemical Education, 49(12):819-821 (December 1972) (“Lever”)

VI. LEGAL BASIS FOR MY ANALYSIS

25. In formulating my opinions set forth in this Declaration, I applied the following legal principles:

A. Claim Construction

26. 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.

27. 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

28. 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.

29. 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-

¹ Dr. Zeglis assessed obviousness before October 23, 2017.

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.

30. 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.

31. 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.

VII. CLAIM CONSTRUCTION

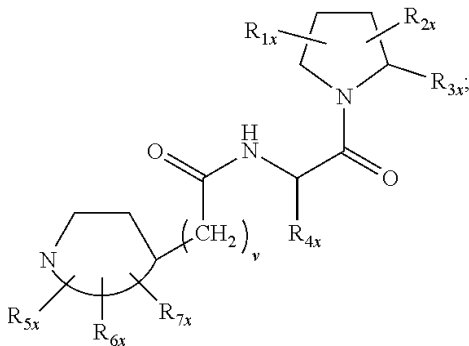
32. Claim 1 of the '201 patent recites:

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:

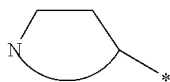
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C₁₋₆alkyl, —O—C₁₋₆alkyl, and —S—C₁₋₆alkyl;

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.

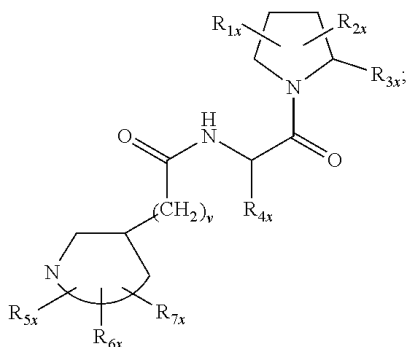
EX1001, 64:46-65:63, Certificate of Correction.

33. 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.

34. 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:

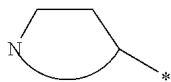
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

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. “B-L-A”

35. 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”. Thus, the claimed compounds are defined structurally.

B. “Low molecular weight”

36. Dr. Zeglis argues 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.” EX1003, ¶174. However, Dr. Pomper, one of the inventors of the ’201 patent, defined the term “low molecular weight” during prosecution of the ’201 patent. Specifically, Dr. Pomper explained that “when used in the scientific references in the chemical arts, [one of ordinary skill in the art would] recognize that low molecular weight compounds

would have a molecular weight of typically from about 50 Daltons to about 1,500 Daltons.” EX1002, 360. A POSA would have understood that Dr. Pomper defined the meaning of the term “low molecular weight” when he made this statement during the prosecution history. And a POSA would have understood Dr. Pomper’s comparison to metabolites to be providing a reference for the type of molecular weight range that Dr. Pomper ascribed to the claimed invention, regardless of whether the compounds are derived from metabolites or not. Dr. Pomper’s comparison is similar to that of a POSA referring to antibodies and polymers as examples of chemical compounds that would fall within the scope of high molecular weight compounds. As such, Dr. Pomper did not need to limit himself to a particular field in chemistry when referencing papers to define the claim term “low molecular weight.”

37. Thus, based on the prosecution history of the ’201 patent, the term “low molecular weight” means compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons.

VIII. DR. ZEGLIS FAILED TO SHOW THAT CLAIMS 1-3 OF THE ’201 PATENT WOULD HAVE BEEN OBVIOUS OVER US-633, JANSEN AND MELETTA (GROUND 1).

38. Dr. Zeglis starts his obviousness analysis by arguing that a POSA would have pursued “a modular three-component design,” such as the claimed “B-L-A” structure, based on his erroneous interpretation that *all* of US-633’s

compounds have such a structure. EX1003, ¶¶28, 71, 90. But, as discussed below, US-633 discloses both linker-containing, B-L-FAPi and linker-less, B-FAPi compounds, with the linker-less compounds generally outperforming the linker-containing ones in terms of FAP affinity. I refer to my discussion in Section VIII.A.

39. Dr. Zeglis then argues that a POSA would have been motivated to improve on “the *entire class* of radiotracers described in US-633” by replacing US-633’s FAPi with a “new, more selective small molecule FAP inhibitor as the targeting moiety” because the targeting moieties in US-633 were purportedly not sufficiently selective. EX1003, ¶133 (emphasis added). But as I explain below, replacing FAPi in the B-FAPi compounds (without a linker) would not have resulted in the claimed compounds; instead, to arrive at the claimed invention, a POSA would have had to select the compounds *with* a linker (B-L-FAPi), which were worse-performing than the linker-less B-FAPi radiotracers of US-633. *See infra* Section VIII.A.2; EX1004, Table 2, p. 34. Dr. Zeglis fails to show that a POSA would have had a reason to do so.

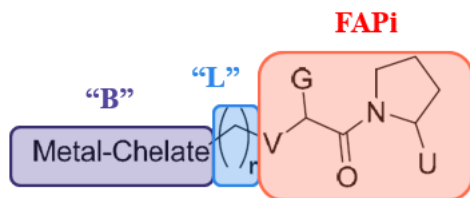
40. Also, according to Dr. Zeglis, a POSA would have identified Jansen’s Compound 60 as “the most promising candidate” for the “new, more selective” FAPi to include in US-633’s radiotracers. EX1003, ¶¶134-135. Yet, as discussed in Section VIII.B. below, in arriving at his selection of Jansen’s Compound 60,

Dr. Zeglis ignores several other references disclosing multiple better-performing FAPis and even wrongly applies his own selection criteria to select Compound 60. In doing so, Dr. Zeglis arrives at the claimed compounds only by using the claims as the roadmap.

A. Dr. Zeglis's Proposed Modifications of US-633's B-L-FAPi Radiotracers is Guided by Hindsight.

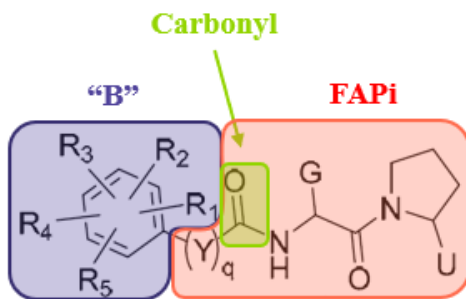
1. US-633 discloses two different classes of radiotracers: linker-containing and linker-less; Dr. Zeglis wrongly treats them as having the same B-L-FAPi design.

41. Dr. Zeglis argues that a POSA would have arrived at the claimed compounds by improving “the entire class of radiotracers described in US-633,” but Dr. Zeglis incorrectly treats all US-633's radiotracers as having “a modular three-component [B-L-FAPi] design.” EX1003, ¶¶28, 71, 90, 133. Contrary to Dr. Zeglis's view, a POSA would have understood that US-633 discloses two types of radiotracers: those having a linker-containing (B-L-FAPi) design and those having a linker-less (B-FAPi) design. And it is only the compounds with a linker that employ the modular B-L-FAPi design, as demonstrated by annotation of Formula I:



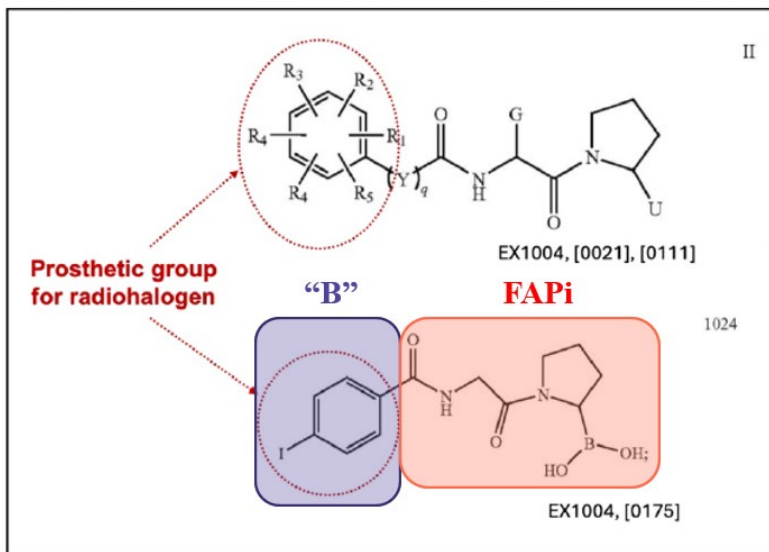
EX1004, Abstract (annotated).

42. The vast majority of compounds of Formula II, which contain radiohalogens directly conjugated to the aryl part of the inhibitor, in fact do *not* employ the modular B-L-FAPi design, contrary to Dr. Zeglis's argument. Compounds of Formula II have the generic formula below. Here, the substituent (Y)_q is depicted as a potential linker, and in twenty-two total exemplified compounds of Formula II, twenty have q equal to 0, and the carbonyl is directly conjugated to the radioprosthetic "B" group. EX1004, ¶¶171-175, 178-180 (Compounds 1023-1033, 1039-48):

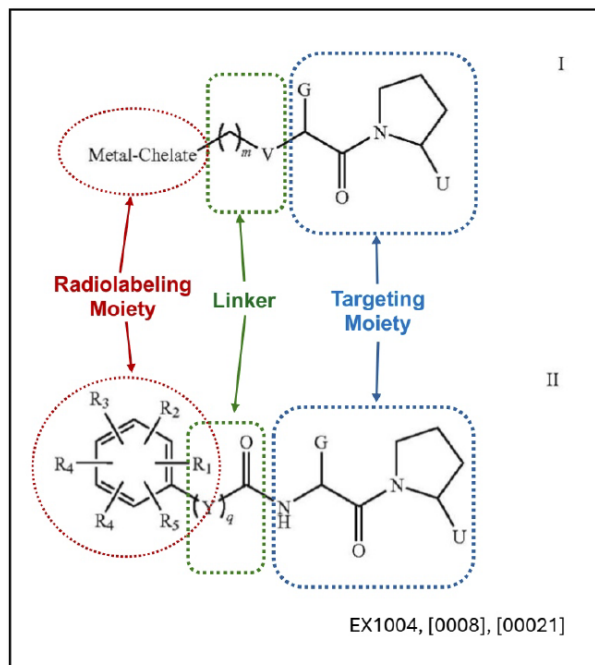


EX1004, Abstract (annotated).

43. Dr. Zeglis himself points to linker-less Compound 1024 as an example of a compound of Formula II.



EX1003, ¶156 (annotations added). In this example, the iodine-containing radioprosthetic group is “B,” and no linker component is present: the B moiety is directly conjugated to the FAPi. Yet, Dr. Zeglis argues that the carbonyl group of Formula II is a linker “L,” as indicated by his green annotation in the figure below:

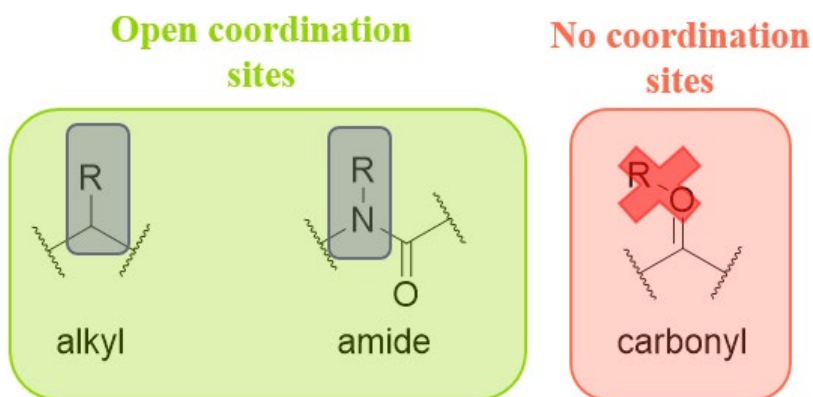


EX1003, ¶71.

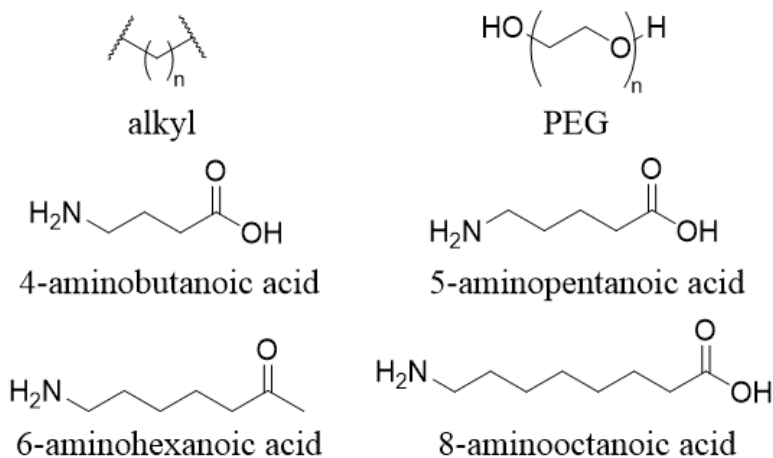
44. Dr. Zeglis is incorrect. *First*, as Dr. Zeglis admits, a linker must “spatially separate the radiolabeling moiety from the targeting moiety.” EX1003, ¶35. However, a one-carbon long carbonyl group that Dr. Zeglis points to as the linker cannot be said to spatially separate A from B, as the figure above illustrates.

45. *Second*, Dr. Zeglis argues that “[l]inkers can be selected or designed to influence the biochemical and pharmacokinetic characteristics of the radiopharmaceutical. For example, a radiopharmaceutical chemist can introduce hydrophobic character into a radiopharmaceutical by incorporating one or more benzyl groups into the linker moiety.” EX1003, ¶36. But a carbonyl group cannot serve the purpose of allowing a chemist to control the characteristics of a compound, because it cannot be modified: there is no way to remove the carbonyl,

and there is no way to add a different group to replace the carbonyl. Doing so would violate the “octet rule,” which limits the number of bonds that an oxygen can form to two, both of which are taken up by the carbon-oxygen double bond. EX2021, 819. Similarly, the carbon atom of a carbonyl cannot have more than four bonds, all of which are taken up by either the double bond to oxygen (2 bonds) or single bonds to the two fragments to be linked (2 total bonds). *Id.* As the figure below shows, a carbonyl has no open coordination (bond-forming) sites, and thus would not allow a POSA to “introduce hydrophobic character” or any other group that would “influence the biochemical and pharmacokinetic characteristics of the compound.” This stands in direct contrast with the linker groups delineated by US-633, such as alkyl or amide linkers, which do allow for modification of the physical properties of the compound.

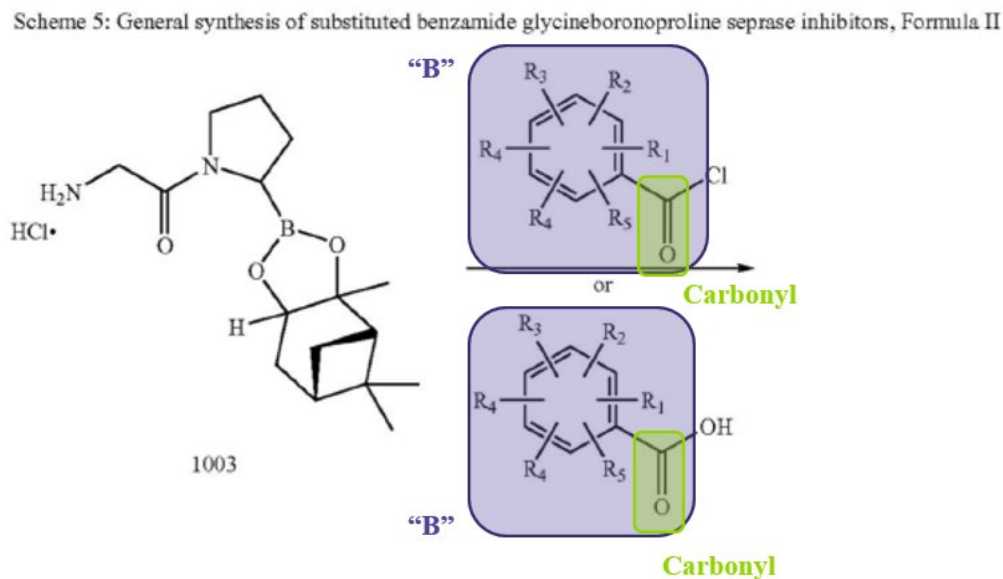


46. *Third*, a carbonyl is not listed among the myriad potential linkers in US-633.² Instead, according to US-633, “[t]he tether [i.e., linker] may comprise a simple alkyl chain as shown, a PEG (CH₂CH₂O)_n, a polyethylene amine ((CH₂CH₂NH)_n), or the like. Terminal aminoalkanoic acids (such as (β-alanine, 4-aminobutanoic acid, 5-aminopentanoic acid, 6-aminohexanoic acid and the 8-aminooctanoic acid) or amino-PEG-acids (NH₂–(CH₂CH₂O)_n–CH₂–COOH, e.g. 2-(2-(3-aminopropoxy)ethoxy)acetic acid) may be utilized as tethers, according to some embodiments.” EX1004, ¶130. Example structures of such linkers are shown below, in which $n \geq 1$:



² Nor is a carbonyl listed as a potential linker in the '201 patent. *See, e.g.*, EX1001, 17:45-54.

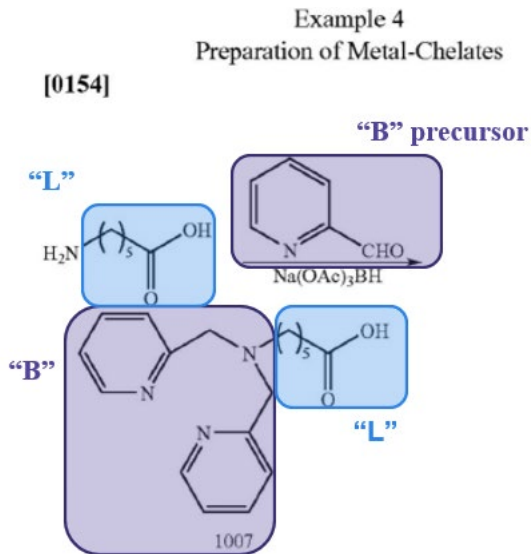
47. *Fourth*, Dr. Zeglis, in discussing the modular design of B-L-FAPi compounds, describes that linkers can be “selected or designed” to influence the properties of the compound. EX1003, ¶36. However, a carbonyl group cannot be “selected” or “designed” since the “B” moiety is directly conjugated to the FAPi, there is no potential for other selections in between the two groups. As shown below, the carbonyl component is integrated into the “B” component, meaning that a POSA would understand that such a moiety would not allow for the selection of other linking groups, or “designed” differently:



EX1004, ¶134, Scheme 5 (annotated).

48. As can be seen above, the carbonyl is already integrated into the “B” moiety prior to conjugation with the FAPi. This stands in direct contrast to the syntheses described for the linker-containing compounds. For example, in the

synthesis described in Example 4, the alkyl linker is added to the “B” moiety before further conjugation to the FAPi through a modular design, as described below. This design facilitates the synthesis of the “B-L” portion of the radiotracer, as well as the easy swapping out of different “L” moieties as desired.



EX1004, ¶154 (annotated).

49. Furthermore, each time the word “tether” appears in US-633, it is in reference *only* to the compounds of Formula I, and *not* in reference to the compounds of Formula II. Examples of this language include:

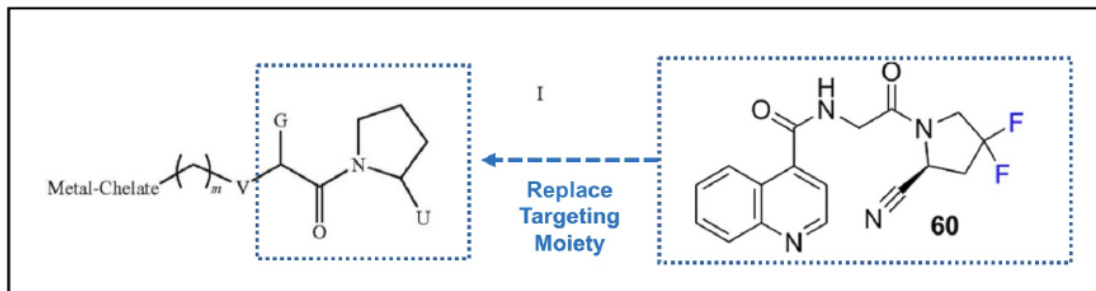
- “The distance between the Metal-Chelate moiety and the pyrrolidine moiety of the complex *represented by Formula I can be varied by altering the tether and/or expanding the length of the tether* between them...”; EX1004, ¶101(emphasis added);

- “Scheme 3 [describing the synthesis of a *compound of Formula I*] can be utilized to synthesize functionalized proline-M⁺(CO)₃ complexes to explore the effect of more significant variations of the distance of the metal chelator from the proline moiety by incorporating a tether into these structures”; EX1004, ¶130;
- “The above reaction scheme [Scheme 4, describing the synthesis of a *compound of Formula I*] is applicable to any modification of the tether”; EX1004, ¶133.

50. As such, a POSA would have understood that US-633 describes two classes of compound, those having the linker-containing (B-L-FAPi) design and those having the linker-less (B-FAPi) design.

2. A POSA would not have used US-633’s linker-containing (B-L-FAPi) radiotracer for further modification given the affinity data in US-633.

51. Dr. Zeglis argues that “in Formula I of US-633, the skilled artisan would have replaced the boronic acid pyrrolidine structure within Formula I with compound 60” (EX1003, ¶146), but Dr. Zeglis does not explain why a POSA would have specifically chosen such linker-containing radiotracers, given their inferior performance, as explained further below. Dr. Zeglis’s proposed modification is shown in the figure below:



EX1003, ¶146.

52. Dr. Zeglis has not shown that a POSA would have selected US-633's linker-containing radiotracers for further modification in view of the teachings of US-633, which discourage the use of such radiotracers. Indeed, US-633 demonstrates that linker-containing radiotracers perform worse in terms of affinity³ for FAP—a characteristic that Dr. Zeglis deemed “paramount” for making a radiotracer (EX1003, ¶45)—than those without linkers. EX1004, Table 2, p. 34. An annotated version of Table 2 from US-633 is presented below, with the top 11-performing compounds indicated in the blue boxes, illustrating the inferior performance on average, of linker-containing compounds compared to those

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

without a linker:

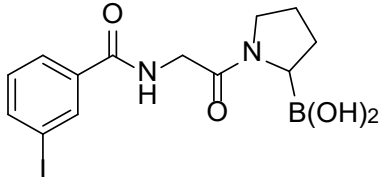
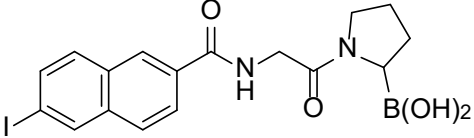
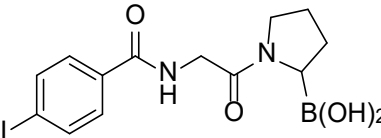
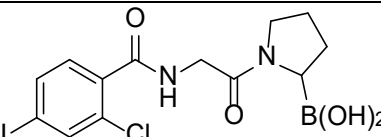
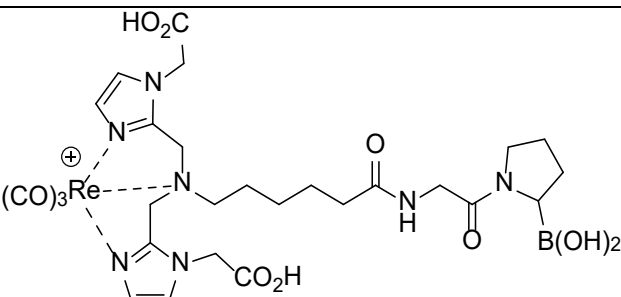
TABLE 2		
<u>Summary of in vitro data against seprase</u>		
Compound No.	FAP (IC ₅₀ nM)	
1010	2,540	Contain Linkers
1014	21	
1016	3,533	
1018	20	
1020	4	
1022	236	
1023	7	No Linkers
1024	3	
1025	2	
1026	3	
1027	5	
1028	5	
1029	8	
1030	2	
1031	262	
1032	11	
1033	500	
1034	11	Contain Linkers
1035	340	
1036	37	
1039	511	
1040	35	No Linkers
1041	692	
1042	785	
1043	115	
1044	23,680	
1045	1,437	
1046	970	
1048	7,414	
1049	953	Contain Linkers
1050	1152	
1051	67	
1060	41,300	Contain Linkers
1061	24,540	

EX1004, Table 2, p. 34 (annotated).

53. The best affinity, an IC₅₀ of 2 nM, was displayed by compounds 1025 and 1030 (compounds without a linker). EX1004, Table 2, p. 34 (annotated). Moreover, nine of the top eleven highest affinities are displayed by the compounds without a linker, rather than the compounds with a linker. EX1004, Table 2, p. 34.

The table below summarizes the top eleven highest-affinity compounds in US-633 (a POSA would have easily ranked these compounds by simply reviewing the data presented in Table 2 of US-633, and comparing the IC₅₀ values, with the lower IC₅₀ values meaning better affinity):⁴

Tabulated highest affinity compounds of US-633.

US-633 Compound No.	IC ₅₀ (nM)	Formula	Structure
1025	2	II (linker-less)	
1030	2	II (linker-less)	
1024	3	II (linker-less)	
1026	3	II (linker-less)	
1020	4	I (linker-containing)	

⁴ This top 11 ranking provides a representative number of the best-performing compounds.

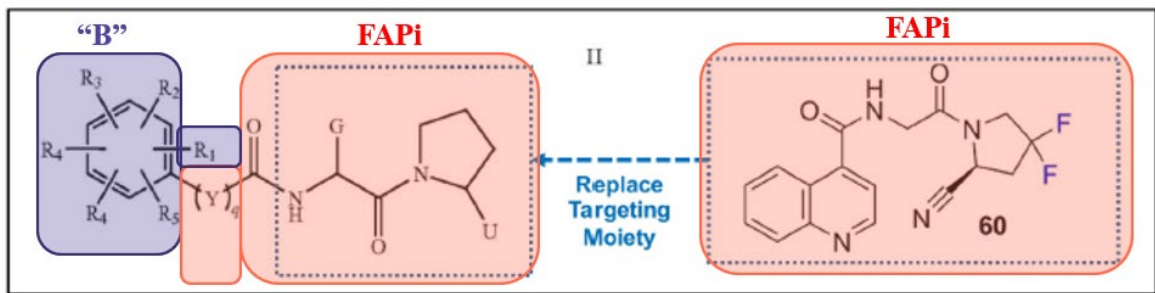
US-633 Compound No.	IC ₅₀ (nM)	Formula	Structure
1027	5	II (linker-less)	
1028	5	II (linker-less)	
1023	7	II (linker-less)	
1029	8	II (linker-less)	
1032	11	II (linker-less)	
1034	11	II (linker-containing)	

54. Of the eleven best-performing compounds, only two were based on the modular “B-L-FAPi” design. Thus, Dr. Zeglis’s choice of such a design was driven by the claimed “B-L-A” formula, rather than US-633’s teachings.

3. A POSA would not have modified US-633’s linker-less radiotracers to include a linker; Dr. Zeglis proposed this modification in hindsight.

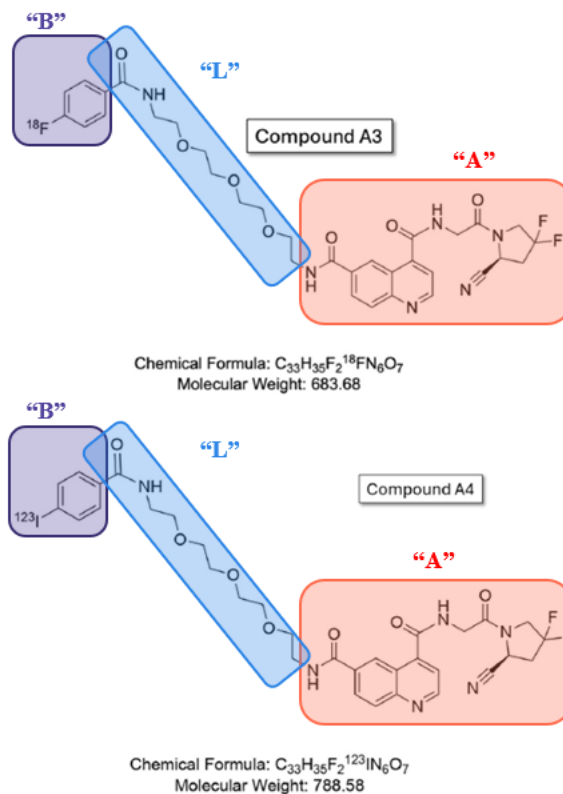
55. Dr. Zeglis also argues that a POSA would have also “replace[d] the

boronic acid pyrrolidine targeting moiety in the FAP-targeting radiotracers described in US-633 with compound 60” (EX1003, ¶146), but here, a POSA would have had to make an additional modification: to add a linker between the “B” moiety and the FAPi. Dr. Zeglis does not mention that he also proposes adding a linker between these two radiotracer moieties, instead only depicting the replacement of the FAPi with Compound 60, as shown below:



EX1003, ¶146 (purple and red annotations added).

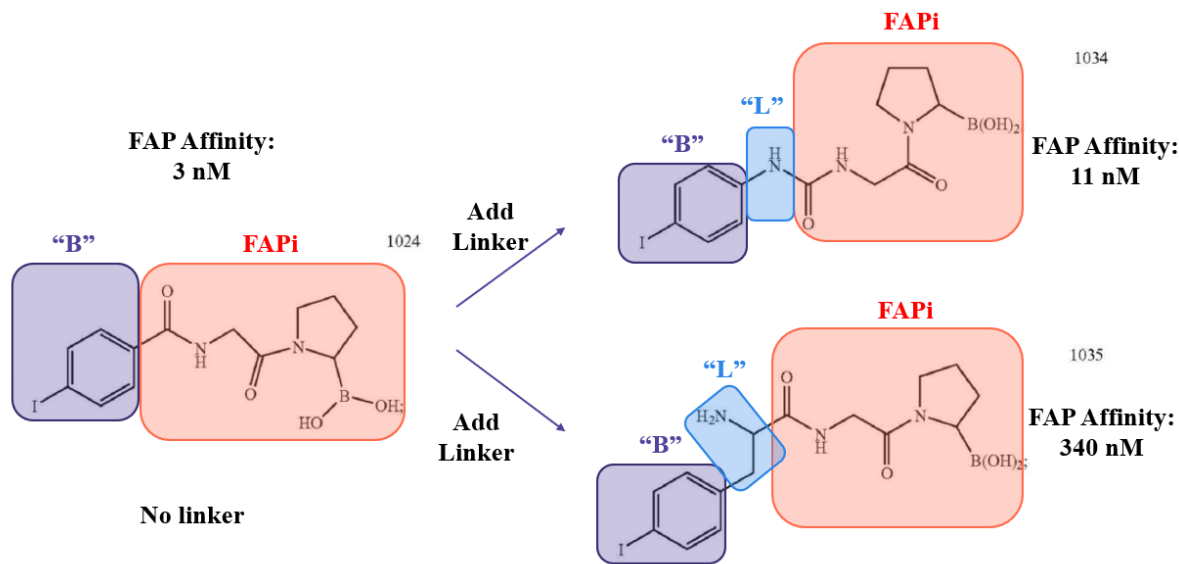
56. However, it is evident that Dr. Zeglis agrees that a linker would have had to be added, in addition to replacing the FAPi, in order to arrive at the claimed compounds from Formula II, as he proposes that a POSA would have arrived at the following two compounds A3 and A4:



EX1003, ¶161 (annotations added).

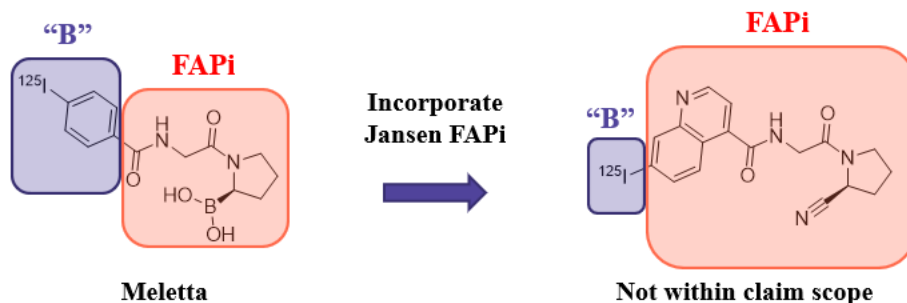
57. As the figure above illustrates, to arrive at Dr. Zeglis's hypothetical compound A3 or A4, one would need to add a linker (depicted in blue) between the B (the radioprosthesis group) and Compound 60. Ironically, to justify the addition of a linker here, Dr. Zeglis uses the rationale behind *linker-containing* radiotracers: to “introduce a sufficient distance ... between the radionuclide-prosthetic group and the compound 60 component of the radiotracer.” EX1003, ¶160, fn.171. But as I explained above, Dr. Zeglis fails to show that a POSA would have done that, because linker-containing radiotracers were generally outperformed by the linker-less compounds, as discussed above in Section

VIII.A.1. Furthermore, US-633 teaches that adding a linker to the linker-less compounds of Formula II reduces affinity, as the figure below shows:



When comparing linker-less Compound 1024, with a FAP affinity of 3 nM, to Compounds 1034 and 1035 with linkers, FAP affinity is reduced to 11 nM and 340 nM, respectively, with an unknown effect on selectivity. EX1004, Table 2.

58. Notably, were a POSA to “replace the boronic acid pyrrolidine targeting moiety in the FAP-targeting radiotracers described in US-633 with compound 60,” as Dr. Zeglis suggested (EX1003, ¶146), a POSA would not have arrived at the claimed compounds. This is illustrated below, using US-633’s Compound 1024 having Formula II (the failed compound of Meletta that, according to Dr. Zeglis, would have motivated a POSA to improve upon selectivity of US-633’s compounds (EX1003, ¶¶100-101)) as an example:



59. As the figure illustrates, the above compound does not have a formula "B-L-A" as required by the challenged claims (it has a formula B-FAPi and lacks a linker).

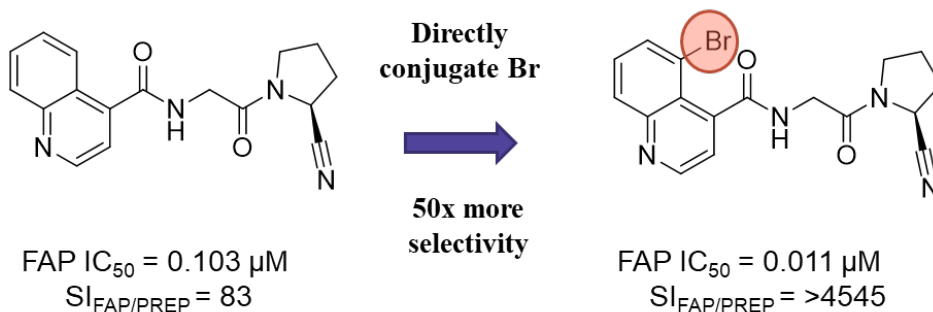
4. Known structure-activity relationship (SAR) for quinolinyl-based FAPis would not have led a POSA to linker-containing compounds.

60. In arguing that a POSA would have pursued linker-containing compounds of US-633, Dr. Zeglis also ignores known structure-activity relationship (SAR) data for quinolinyl-based FAPis that were present in the prior art. Dr. Zeglis argues that a POSA "would have viewed use of a linker in a radiotracer based on compound 60"—the only way to arrive at the claimed invention from the cited references—"to be preferable to direct attachment of a radiohalogen to the quinolinyl ring of compound 60" because of observed "adverse effects on selectivity/affinity" from halogen attachment to C⁵ position of the quinolinyl ring of Compound 60. EX1003, ¶139. But the opposite was actually true. The SAR for quinolinyl-based FAPi showed that halogens, such as Br and Cl,

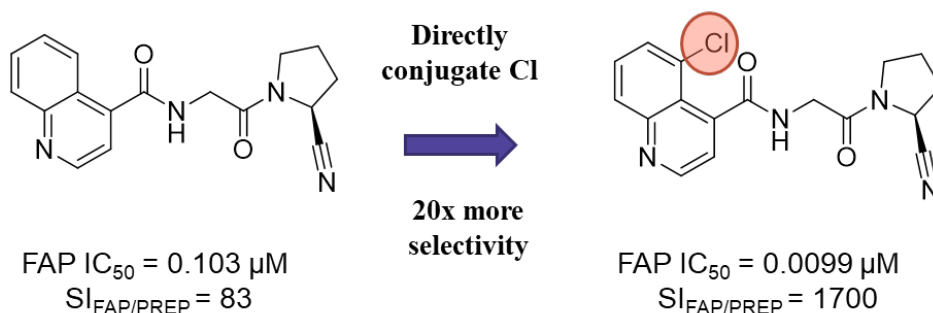
had a *beneficial*, not “adverse”, effects on FAP selectivity.⁵ According to Jansen 2013, “[i]ntroducing a chlorine or bromine substituent at the 5-position of the quinoline ring” results in the “selectivity with respect to PREP of these inhibitors [to] sharply increase[] ... rendering them *the most favorable* affinity/selectivity profile of all FAP inhibitors we had identified so far.” EX1007, 493-494 (emphasis added). This is illustrated in the figure below, which demonstrates that adding a bromine or chlorine increases selectivity by 50x and 20x, respectively.

⁵ 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 resulting in lower side-effects for a drug or higher resolution for an imaging agent. EX2004, 11; EX1007, 491-492; EX1044, ¶4.

**Jansen 2013 teaches that direct conjugation of halogens
to the quinolinyl group increases selectivity:**



**Jansen 2013 teaches that direct conjugation of halogens
to the quinolinyl group increases selectivity:**



61. In view of the available SAR, a POSA would not have viewed use of a linker in a FAPI-based radiotracer to be “preferable to direct attachment of a radiohalogen to the quinolinyl ring,” contrary to Dr. Zeglis’s argument (EX1003, ¶139), because direct halogenation of the quinolinyl ring actually had beneficial effects on a FAPI’s selectivity and affinity, as explained above. Moreover, Dr. Zeglis failed to explain why a POSA would have ignored *all* known SAR related to halogenation, or how a POSA would have evaluated the *positive* effect of such halogenation in making FAPI-based radiotracers. Instead, using claims as the roadmap, Dr. Zeglis wrongly concluded that a POSA would have viewed use of a

linker “be preferable to direct attachment of a radiohalogen to the quinolinyl ring of compound 60.” EX1003, ¶139. And Dr. Zeglis fails to explain why a POSA would have ignored this known SAR data in the art, for quinolinyl-based FAPis, to arrive at the claimed compound.

B. Dr. Zeglis Did Not Explain Why a POSA Would Have Had a Reason to Combine US-633 and Meletta with Jansen.

62. Dr. Zeglis fails to explain why a POSA would have ignored all available FAPi art and instead would have combined US-633 and Meletta with Jansen. Dr. Zeglis argues that in looking for “new, more selective” FAPis to incorporate into a “B-L-A” compound after Meletta’s [¹²⁵I]MIP-1232 failure, “a skilled artisan would have invariably discovered the compounds characterized in Jansen.” EX1003, ¶134. But Dr. Zeglis does not explain why a POSA would have looked to Jansen in particular, out of all of the other available FAPi references, including other references from Jansen’s research group. This is particularly notable because Dr. Zeglis ignores other FAPis disclosed in other prior art references with higher selectivity than Compound 60 of Jansen, even though Dr. Zeglis calls selectivity “ultimately the most important factor” when evaluating FAPis for use in radiotracers. EX1003, ¶45, fn. 50.

63. For example, the reference Meletta describes one of US-633’s linker-less compounds as a “target for atherosclerosis imaging” because of its “high binding affinity to FAP,” its favorable selectivity profile (“MIP-1232 was 32-fold

more potent in inhibiting FAP than PREP”), and “the possibility to radioiodinate MIP-1232 without altering its structure.” EX1008, 2083. After describing the shortcomings of [¹²⁵I]MIP-1232, Meletta states: “[t]o overcome limitations in specificity, novel lead structures and the use of antibodies and fusion proteins was proposed to minimize off-target effects.” EX1008, 2090. The three references that Meletta cites at the end of this sentence are Jansen 2013, a reference pertaining to an anti-FAP antibody, and Jansen (in that order). EX1008, 2090, fn.24, fn.34, fn.44. However, Dr. Zeglis does not explain why a POSA would have looked to Jansen in particular and would not have considered Jansen 2013’s FAPis, some of which were more selective than Compound 60, even though Dr. Zeglis was aware of Jansen 2013 (EX1007 in Dr. Zeglis’s declaration), and even though Jansen 2013 is considered in context with Jansen and other publications disclosing FAPis. EX1003, ¶¶142, fn. 166, 167.

64. Jansen 2013 describes the FAP and PREP affinities (and, therefore, the FAP selectivity) of thirty-six FAPis. EX1007, Tables 2-3. Notably, of those thirty-six, the most selective FAPi does not fall within the scope of the claimed “A,” as I explain below in Section VIII.C.2. Further, as discussed in Section VIII.C.2 below, many of these Jansen 2013 FAPis showed better selectivity than Compound 60 of Jansen. But Dr. Zeglis did not explain why a POSA would have combined Jansen with US-633 and Meletta, and not Jansen 2013. Dr. Zeglis’s

obviousness analysis does not even indicate he evaluated Jansen 2013's compounds for potential modification in view of US-633, nor does he explain why a POSA would not have selected any of the compounds disclosed in Jansen 2013 for modification.

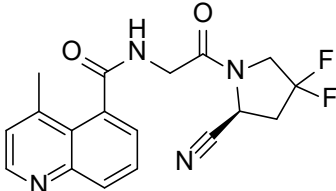
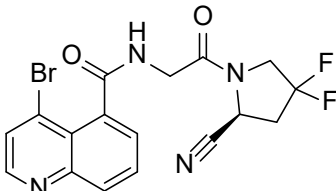
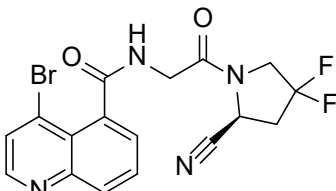
65. Another reference, Jansen 2014, disclosed 33 non-quinolinyl based FAP inhibitors (having xanthine scaffolds), all of which Dr. Zeglis also ignored. Jansen 2014 describes that those FAPis "displayed affinities in the low micromolar range." EX2003, Abstract, 1706. The xanthine compounds were also deemed to be "selective" for FAP: "we managed to decouple DPP^{IV} and FAP potency." EX2003, Abstract. 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.

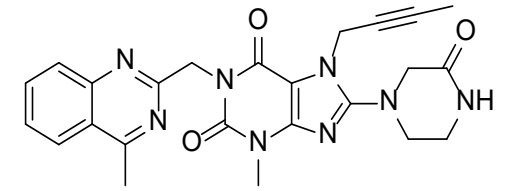
66. Dr. Zeglis also fails to explain why a POSA would not have considered U.S. Patent Publication No. 2014/0357650 ("US-650"), in which Jansen is the first-named inventor, even though Dr. Zeglis was aware of US-650. EX1003, ¶142, fn.165. US-650 discloses forty-three compounds, many of which are highly selective for FAP and outperformed Jansen's Compound 60. EX1044, Table 4. Here, again, the most selective FAPi does not fall within the scope of the claimed "A" moiety. EX1044, Table 4. 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.

67. The table below illustrates the choices that a POSA would have had, and that Dr. Zeglis ignored, when evaluating suitability of FAPis for radiotracers. Notably, the table below shows that the most selective compound for each reference does not fall within the scope of the challenged claims.

Overview of prior art references that disclose selective FAPis.

Reference	Number of FAPis disclosed	Number of FAPis that fall within claims	Highest-selectivity FAPi
Jansen	54	6	 (Not within claimed "A" moiety scope)
US-650	43	1	 (Not within claimed "A" moiety scope)
Jansen 2013	36	2	 (Not within claimed "A" moiety scope)

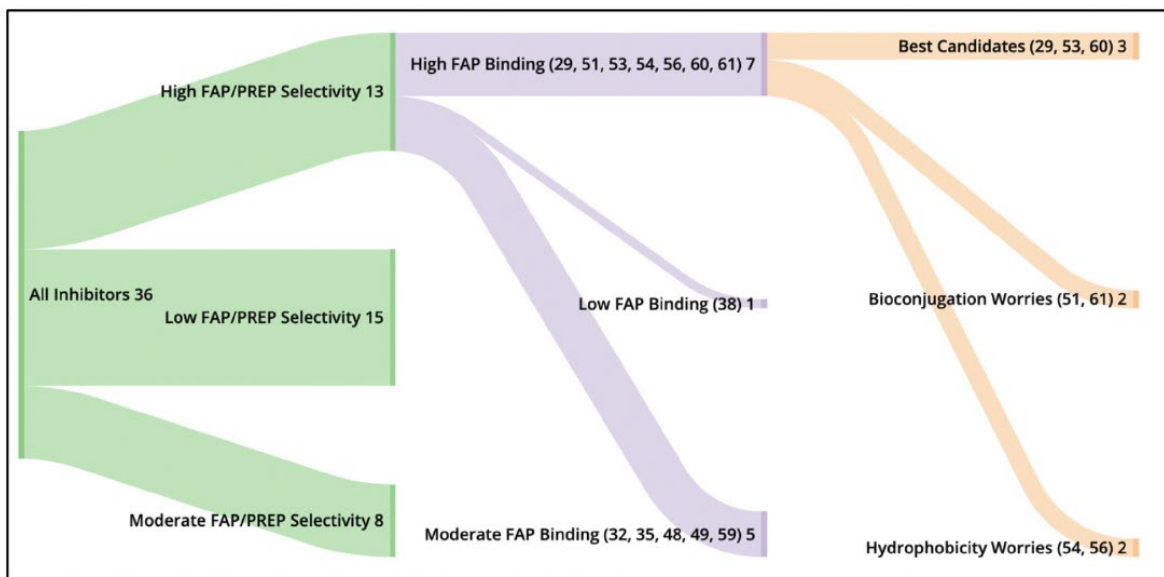
Reference	Number of FAPis disclosed	Number of FAPis that fall within claims	Highest-selectivity FAPi
			scope)
Jansen 2014	33	None	 (Not within claimed “A” moiety scope)

C. Dr. Zeglis’s Choice of Compound 60 is Guided by Hindsight.

68. Dr. Zeglis argues that “a skilled artisan would have viewed compound 60 as one of the most promising FAP inhibitors that had been discovered to date,” and therefore a POSA would have selected it for improving US-633’s radiotherapeutic or imaging compounds. EX1003, ¶115. This selection is guided by hindsight because Dr. Zeglis ignored other high-selectivity FAPis known in the art in favor of selecting compounds that could lead to the challenged claims.

69. To select Compound 60, Dr. Zeglis argues that a POSA first would have “rank[ed] [FAPi] compounds based on their selectivity index and select[ed] those exhibiting the highest selectivity values.” EX1003, ¶118. Only after that, a POSA would have “prioritiz[ed] the compounds based on their affinity for FAP,” and finally would have “assess[ed] the structures of the compounds to identify any concerns with respect to stability, hydrophobicity, or ease of modification.”

EX1003, ¶118. To present his analysis, Dr. Zeglis prepared “a visual representation of [the] classification process using a so-called Sankey diagram”:



EX1003, ¶121.

70. But Dr. Zeglis’s Sankey diagram, beyond high selectivity and high affinity, is unsupported by evidence, as discussed in Section VIII.C.1 below. Moreover, a POSA following Dr. Zeglis’s own Sankey diagram approach would not have arrived exclusively at Compound 60 in light of the other FAPis disclosed in the literature, as disclosed in Section VIII.C.2 below.

1. Dr. Zeglis’s classification scheme is unsupported.

71. Dr. Zeglis uses the following classification scheme for categorizing Jansen’s compounds on the basis of selectivity and affinity:

High selectivity	$IC_{50}^{PREP}/IC_{50}^{FAP} > 100$
Moderate selectivity	$10 < IC_{50}^{PREP}/IC_{50}^{FAP} < 100$
Low selectivity	$IC_{50}^{PREP}/IC_{50}^{FAP} < 10$

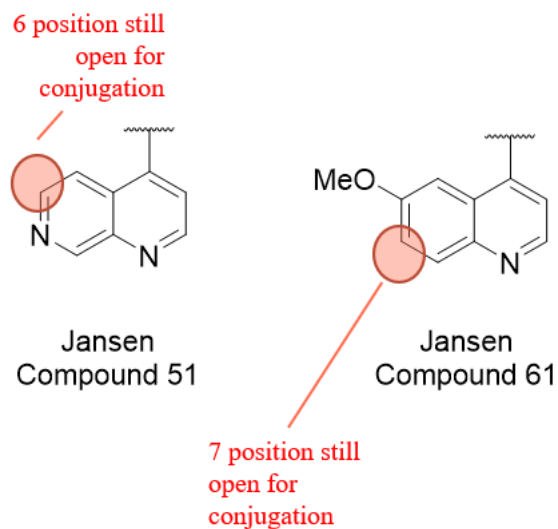
High affinity	$IC_{50}^{FAP} < 0.1 \mu M$
Moderate affinity	$0.1 \mu M < IC_{50}^{FAP} < 1.0 \mu M$
Low affinity	$IC_{50}^{FAP} > 1.0 \mu M$

EX1003, ¶119. Dr. Zeglis does not explain the basis for all the cutoff values in his classification scheme. EX1003, ¶¶119-120.

72. Moreover, Dr. Zeglis does not explain why a POSA would have further classified the compounds based on stability, hydrophobicity, and ease of modification. EX1003, ¶119. Jansen discloses myriad other parameters that a POSA could have looked at, such as kinetic solubility, log D, plasma stability, microsomal stability, cytotoxicity, T_{max} , C_{max} , $T_{1/2}$, AUC, Cl, V_d , and relative bioavailability. *See, e.g.*, EX1006, Tables 7-8. But Dr. Zeglis fails to show how any of these considerations justify the exclusion of any Jansen FAPi but Compound 60. Dr. Zeglis only states, in a conclusory fashion, that Jansen's Compounds 54 and 56 would raise "hydrophobicity concerns due to pendant phenyl groups." EX1003, ¶120. Here, again, Dr. Zeglis fails to point to any evidence, or even explain through his own argument, how the addition of a single

pendant phenyl group would impact the above pharmacokinetic considerations.

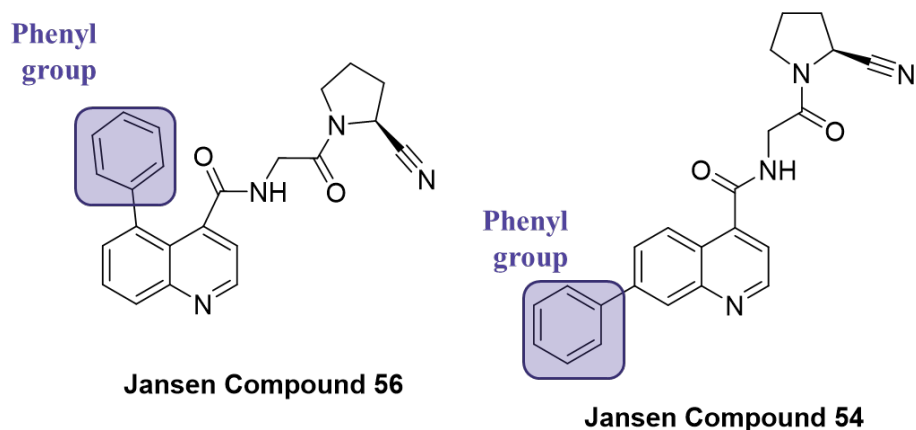
73. Dr. Zeglis also does not explain what is meant by “bioconjugation issues” (EX1003, ¶120) or the criteria for determining which compounds would be susceptible to such worries. Dr. Zeglis eliminates Jansen’s Compounds 51 and 61, which, by Dr. Zeglis’s own admissions, have high selectivity and affinity, because these compounds purportedly “would pose bioconjugation issues because of their 7 and 6 position substitutions, respectively, on the quinolinyl ring would be occupied.” EX1003, ¶120. Contrary to Dr. Zeglis’s argument, both Compounds 51 and 61 have position 6 or 7 available for conjugation, as shown below:



74. But choosing either of the above compounds as a replacement in US-633’s radiotracers would have resulted in compounds outside of the challenged claims because Compound 51 does not have a quinolinyl ring required by the claims and Compound 61 has a substituent on the quinolinyl ring (MeO-) that is

not allowed by the claims. Thus, Dr. Zeglis discarded Compounds 51 and 61 in favor of Compound 60 in hindsight.

75. Additionally, Dr. Zeglis does not explain the threshold for determining when hydrophobicity might pose a concern. EX1003, ¶120. 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:



76. But Dr. Zeglis fails to show any evidence that a single pendant phenyl ring disqualifies a FAPi from consideration based on pharmacokinetic concerns. And indeed, a POSA would not have eliminated well performing compounds, such as Jansen’s Compound 56 or 54, solely because of a pendant phenyl ring. A POSA would have known that pendant phenyl groups, alone, do not result in unfavorable pharmacokinetic properties. *See, e.g.*, EX2018, 2213-2214, Figure 7 (describing compounds with “pendant phenyl groups” as having “lower lipophilicity ... and

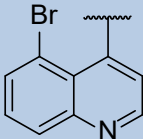
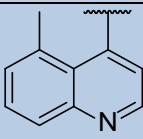
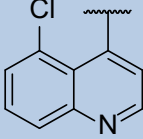
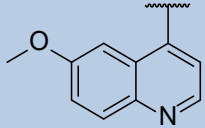
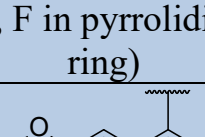
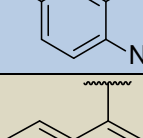
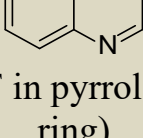
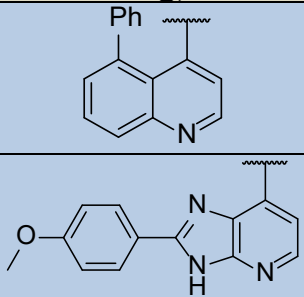
excellent *in vivo* efficacy”); EX2019, 2535 (describing a dipeptidyl peptidase IV inhibitor compound with a substituted “pendant phenyl group” as having “excellent pharmacokinetic properties”); EX2020, 254-256 (describing diazepam variations with “unsubstituted” “pendant phenyl” groups as “essential tools for translational neuroscience”). Instead, Dr. Zeglis discards Compounds 54 and 56 because they both contain substituents that are excluded from the claimed compounds. Thus, once again, Dr. Zeglis discarded Compounds 54 and 56 in favor of Compound 60 in hindsight.

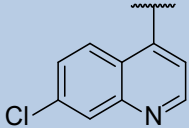
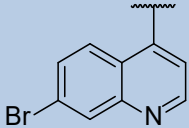
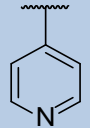
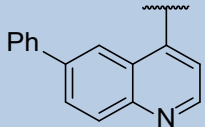
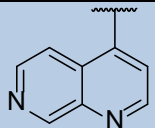
2. A POSA, following Dr. Zeglis’s classification scheme, would not have arrived at Compound 60 due to other potential suitable compounds.

77. Dr. Zeglis, when creating his classification scheme, looks solely to Jansen’s compounds. EX1003, ¶¶119-121. Dr. Zeglis does not, however, explain why a POSA would have looked solely to Jansen and not, *e.g.*, to US-650 and Jansen 2013, which Dr. Zeglis was aware of, as I explained in Section VIII.B. above. US-650 and Jansen 2013 both disclose many FAPis that not only meet Dr. Zeglis’s selectivity and affinity criteria but outperform Compound 60. A tabulated set of FAPis across Jansen, US-650, and Jansen 2013 that meet Dr. Zeglis’s criteria (selectivity >100 and affinity <0.1 μ M) 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.

High FAP selectivity and affinity compounds in Jansen, US-650, and Jansen 2013.

Compound Number	Structure	FAP Selectivity	FAP Affinity (μM)	Fall within scope of claims?
US-650: 22, Jansen 2013: 26		>4500	0.011	N
US-650: 23, Jansen: 54		2100	0.0043	N
US-650: 21, Jansen 2013: 25		1700	0.0099	N
US-650: 24, Jansen: 61	 (F, F in pyrrolidine ring)	970	0.0085	N
US-650: 11, Jansen 2013: 30		677	0.0092	N
US-650: 1, Jansen: 60	 (F, F in pyrrolidine ring)	562	0.0032	Y
US-650: 25, Jansen: 56		280	0.07	N
US-650: 28		>200	<0.2	N

Compound Number	Structure	FAP Selectivity	FAP Affinity (μM)	Fall within scope of claims?
US-650: 13, Jansen 2013: 31		197	0.0071	N
US-650: 12, Jansen 2013: 32		193	0.0062	N
US-650: 4, Jansen: 29		179	0.063	N
US-650: 26, Jansen: 54		135	0.064	N
US-650: 33, Jansen: 51		120	0.028	N

78. Using Dr. Zeglis's own criteria, the above table demonstrates that out of the 13 best compounds from Jansen, US-650, and Jansen 2013, only *one* FAPi falls within the scope of the claimed "A" moiety, Compound 60. And this single compound is not even the best option of these 13 compounds: it is outperformed in terms of selectivity and affinity by five other compounds. Thus, Dr. Zeglis's choice of Compound 60 from the thirteen compounds could have been done only in hindsight.

79. In summary, Dr. Zeglis fails to consider the art as a whole and to explain why a POSA would have selected one prior art FAPi compound that happens to fall within the scope of the claimed "A" moiety, in light of the dozens

of other FAPis known at the time, many of which outperformed his own selection.

Dr. Zeglis also fails to establish why a POSA would have incorporated a linker when combining the disclosures of Jansen and US-633, when known SAR would have discouraged the use of the linker, pointing instead toward a direct radiohalogenation of the quinoliny ring. As such, Dr. Zeglis fails to show how a POSA would have arrived at the claimed B-L-A compounds.

IX. CLAIMS 1-3 OF THE '201 PATENT WOULD NOT HAVE BEEN OBVIOUS OVER US-121 AND JANSEN (GROUND 2).

80. As in Ground 1, Dr. Zeglis fails to show that a POSA would have arrived at the claimed invention because his analysis of the selection of “A” and using the modular B-L-A design in FAPi-based radiotracers is guided by hindsight. Dr. Zeglis’s Ground 2 is based on two references, US-121 (which described B-L-A-type radiotracers for imaging a different protein, PSMA) and Jansen (which is the same Jansen as in Ground 1). According to Dr. Zeglis, a POSA would have combined US-121 and Jansen 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. But as in Ground 1, Dr. Zeglis fails to consider the disclosures of Jansen 2013, Jansen 2014, and US-650 when determining which FAPi moiety to incorporate into a radiotracer of US-121. *See* Section VIII.B.

81. And as in Ground 1, Dr. Zeglis fails to show, based on his own

criteria, that a POSA would have selected Compound 60, in light of the many FAPis that outperform this compound. *See* Section VIII.C. US-121 does not add anything to the “A” selection, as US-121 is not related to FAP-targeting compounds, as Dr. Zeglis himself admits. EX1003, ¶182.

82. Moreover, and Dr. Zeglis cannot deny this, a POSA would have been familiar with US-633 and its affinity data showing that linker-less FAP radiotracers outperform linker-containing FAP radiotracers (described in detail above in Section VIII.A). But Dr. Zeglis does not explain why a POSA would have ignored that data in combining US-121 (which does not provide *any* affinity or selectivity data) and Jansen. Once again, US-121 does not rescue Dr. Zeglis’s incorrect argument that a POSA would have used linker-containing radiotracers for FAP imaging, especially in light of the fact that US-121 is not related to FAP. EX1003, ¶182.

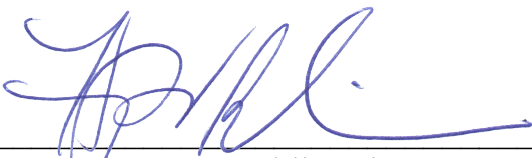
83. As such, as in Ground 1, Dr. Zeglis’s analysis in Ground 2 is guided by hindsight, and Dr. Zeglis fails to show that a POSA would have arrived at the claimed compounds using US-121 and Jansen.

X. CONCLUSION

84. 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.

85. 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 30th day of JANUARY 2026, in San Francisco, CA.



Henry F. VanBrocklin, Ph.D.