UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ITM ISOTOPE TECHNOLOGIES MUNICH SE,
Petitioner

v.

THE JOHNS HOPKINS UNIVERSITY,
Patent Owner

Case PGR2025-00012
U.S. Patent No. 11,938,201

DECLARATION OF DR. HENRY VANBROCKLIN IN SUPPORT OF PATENT OWNER DISCRETIONARY DENIAL BRIEF

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JHU EX2001
ITM v. JHU
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LIST OF EXHIBITS CONSIDERED

Exhibit No.	Description
1001	U.S. Patent No. 11,938,201 to Yang et al., issued March 26, 2024, with Sept. 24, 2024, Certificate of Correction ("'201 patent")
1002	Declaration of Dr. Stephen F. Martin
1003	*Curriculum Vitae* of Dr. Stephen F. Martin
1004	Prosecution History for U.S. Patent No. 11,938,201 (downloaded from USPTO Patent Center)
1005	U.S. Patent Publication No. 2011/0064657 to Pomper et al., published March 17, 2011 ("US '657")
1006	U.S. Patent Publication No. 2012/0009121 to Pomper et al., published Jan. 12, 2012 ("Pomper")
1007	U.S. Patent No. 9,346,814 to Jansen et al., issued May 24, 2016 ("Jansen I")
1008	Petra Dvořáková at al., *Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein*, 60 JOURNAL OF MEDICINAL CHEMISTRY 8385-8394 (2017), available at https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b00767 (last accessed Dec. 19, 2024) ("Dvořáková")
1009	U.S. Patent Publication No. 2010/0098633 to Zimmerman et al., published April 22, 2010 ("Zimmerman")
1010	Keon Jansen et al., *Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold*, 2013(4) ACS MEDICINAL CHEMISTRY, 491-96 (2013) ("Jansen II")
1011	*Product Information: ATTO 488*., ATTO-TEC GMBH (2024) available at https://www.atto-tec.com/fileadmin/user_upload/Katalog_Flyer_Support/ATTO_488.pdf (last accessed Dec. 18, 2024)

Exhibit No.	Description
1015	Ronnie C. Mease et al., *N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L- cysteine, [18F]DCFBC: A new Imaging probe for prostate cancer*, 14 CLIN CANCER RES 3036-43 (2008)
1016	Suzanne E. Lapi et al., *Assessment of an 18F-Labeled Phosphoramidate Peptidomimetic as a New Prostate-Specific Membrane Antigen–Targeted Imaging Agent for Prostate*, 50 J NUCL MED 2042-48 (2009)
1017	Ronny Rüger et al., *In Vivo Near-Infrared Fluorescence Imaging Of FAP-Expressing Tumors With Activatable FAP-Targeted, Single-Chain Fv-Immunoliposomes*, 186 JOURNAL OF CONTROLLED RELEASE 1-10 (2014)
1018	Zhi-Yi Chen et al., *Advance of Molecular Imaging Technology and Targeted Imaging Agent in Imaging and Therapy*, BIOMED RESEARCH INT'L 819324 (2014)
1021	Anne Hellebust et al., *Advances in molecular imaging: Targeted Optical Contrast Agents For Cancer Diagnostics*, 7 NANOMEDICINE 429-45 (2012)
1022	Sumith A. Kularatne et al., *Prostate-Specific Membrane Antigen Targeted Imaging and Therapy of Prostate Cancer Using a PSMA Inhibitor as a Homing Ligand*, 6 MOLECULAR PHARMACEUTICS 780-89 (2009)
1023	Yonghwang Ha, *Recent Conjugation Strategies of Small Organic Fluorophores and Ligands for Cancer-Specific Bioimaging*, 248 CHEMICO-BIOLOGICAL INTERACTIONS 36-51 (2016)
2003	*Curriculum Vitae* of Dr. Henry VanBrocklin
2018	WO 2010/108125 A2 to Pomper *et al.*

I, Dr. Henry VanBrocklin, hereby declare as follows.

I. INTRODUCTION

1. I have been retained as an expert witness on behalf of Patent Owner The Johns Hopkins University ("JHU") for the above-captioned post-grant review (PGR). I am being compensated for my time in connection with this PGR at my standard consulting rate, which is $350.00 per hour.

2. I understand that this Declaration accompanies JHU's Discretionary Denial Brief in response to the Petition for Post-Grant Review of U.S. Patent No. 11,938,201 ("the '201 patent" (EX1001)), issued on March 26, 2024, and 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. I refer to this date throughout this Declaration.

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 timelines discussed herein. In formulating my opinions, I have relied upon my experience, education, and knowledge in the relevant art.

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 most recently as President of the Molecular Imaging Center of Excellence from 2008-2010, and the Society of Radiopharmaceutical Sciences, wherein I served as president from 2015-2017, and currently serve as Historian. I am currently the Editor-in-Chief for the academic journal *Molecular Imaging.*

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), and imaging in drug development.

6. My *curriculum vitae* is submitted herewith as Exhibit 2003.

7. In 1984, I obtained a B.S. in Chemistry from Rensselaer Polytechnic Institute, from where I graduated *cum laude.* Subsequently, I obtained an M.S. in Nuclear Chemistry from Rensselaer Polytechnic Institute in 1986, followed by an

M.A. in Nuclear Chemistry from Washington University in St. Louis in 1988, after which I completed my Ph.D. in Radiopharmaceutical Chemistry, also from Washington University in St. Louis, in 1990. During my Ph.D., I studied the synthesis and biological evaluation of fluorine-18 labeled estrogens and progestins as positron emission tomography imaging agents for detection of breast cancer.

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

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

10. Over the course of my career, I have received a variety of prizes and awards. At Lawrence Berkeley National Lab, I received the Lawrence Berkeley National Laboratory Outstanding Performance Award four separate times. At

UCSF, I was awarded the MSBI Outstanding Teacher Award three times (2019, 2021, 2023). I received the Society of Nuclear Medicine President's Distinguished Service Award twice (2006, 2010). I was selected as a Research Distinguished Investigator of the Academy for Radiology & Biomedical Imaging (2018). I have also been elected Fellow to both the Society of Nuclear Medicine and Molecular Imaging (2019) and the Society of Radiopharmaceutical Sciences (2021). I received the Michael J. Welch award (2020) and the prestigious Paul C. Abersold award (2023) from the Society of Nuclear Medicine and Molecular Imaging.

11. 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. I also translate radiopharmaceuticals for human research studies, working closely with clinical colleagues to navigate the regulatory pathway, FDA, radiation safety committee, and IRB, to fulfill the requirements to safely administer the radiopharmaceuticals to human subjects and patients.

12. My research has led to over 150 peer-reviewed research publications, 7 book chapters, and 10 filed patent applications, of which the vast majority relate directly to radiotherapeutics or imaging. 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}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}F]F-AraG, in Healthy Volunteers," *Molecular Imaging* **2022**; "Evaluation of ^{134}Ce/^{134}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).

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

14. In addition to my 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, the US Department of Energy, 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.

15. In addition to my educational training and my professional and research experience, I have kept abreast of the fields of molecular imaging, radiopharmaceutical chemistry, positron emission tomography, single photon emission computed tomography, optical imaging, oncologic imaging agents, proteases, steroids, prostate specific membrane antigen (PSMA), and imaging in drug development 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" yearly since 2011.

III. LEGAL BASIS FOR MY ANALYSIS

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

A. Claim Construction

17. I understand that in a PGR, patent claim terms are given their ordinary and customary meaning as understood by a POSA at the time of the invention, in

view of the patent's specification and its prosecution history—unless the patent explicitly defines the claim term. I also understand that when a patent explicitly defines a claim term in the specification, the patent's definition controls.

18. 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

19. 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

[1] Dr. Martin assessed obviousness before October 23, 2017.

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.

20. 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.

21. 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. I also understand

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

C. Enablement

22. I understand that an enabling disclosure in the patent specification must allow a POSA to make and use the full scope of the claimed invention without undue experimentation as of the filing date (here, I assess the ’201 patent’s disclosure at least as of July 18, 2023). I understand that the following factors can be used to determine whether undue experimentation would have been needed (the so-called *Wands* factors): (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of

experimentation needed to make or use the invention based on the content of the disclosure.

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

D. Written Description

24. I understand that the written description provided by a patent specification must convey clearly to a POSA that the applicant was in possession of the claimed invention as of the patent's filing date (here, I assess the '201 patent's disclosure at least as of July 18, 2023). And I understand that this involves an objective inquiry into the specification from the perspective of a POSA. Further, I understand that possession does not mean physical possession and does not require making or testing the invention.

25. I further understand that this written description requirement must be applied in the context of the particular invention and the state of the knowledge in the art. In addition, I understand that a patent specification is written for a POSA and that such a hypothetical person presumably has all of the knowledge of the

state of the art as of the patent's filing date, in addition to the knowledge provided by the patent specification itself.

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

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

28. I further understand that a sufficient description of a genus requires the disclosure of either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus.

Additionally, I understand that an adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials.

E. Indefiniteness

29. I understand that the written description provided by a patent specification must inform the POSA, with a reasonable degree of certainty, the metes and bounds of the claimed subject material.

IV. SUMMARY OF OPINIONS

30. As an expert, I have been asked to opine from the perspective of a POSA on whether the Examiner considered the same or substantially the same art and arguments as now presented by Dr. Martin. Dr. Martin relies on Jansen I (EX1007), Jansen II (EX1010), Zimmerman (EX1009), and Pomper (EX1006) for Ground I, and Dvořáková (EX1008) and Pomper (EX1006) for Ground II, to contend that claims 1-3 would have been obvious to a person of ordinary skill in the art ("POSA"). EX1002, ¶¶16-17. A POSA reviewing the prosecution history of the '201 patent and its priority application would conclude that the Examiner considered Jansen I, Jansen II, Zimmerman, Dvořáková, and Pomper during prosecution. Specifically, the Examiner based her rejections on Jansen I, Jansen II, Zimmerman, and Dvořáková—a fact that Dr. Martin does not dispute. The

following table summarizes the references used by the Examiner during prosecution of the ’201 patent and by Dr. Martin in his declaration:

Reference	Used in Dr. Martin's Declaration	Use in Prosecution
U.S. Patent No. 9,346,814 (Jansen I, EX1007)	Ground I	Cited in Information Disclosure Statement (IDS) on 7/18/2023, applied in an obviousness rejection on 9/26/2023
Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold (Jansen II, EX1010)	Ground I	Cited in IDS on 7/18/2023, applied in an obviousness rejection on 9/26/2023
U.S. Patent Publication No. 2010/0098633 (Zimmerman, EX1009)	Ground I	Applied in an obviousness rejection on 10/30/2023
Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein (Dvořáková, EX1008)	Ground II	Cited in IDS on 7/18/2023, applied in a lack of novelty rejection on 9/26/2023
U.S. Patent Publication No. 2012/0009121 (Pomper, EX1006)	Grounds I and II	Cited in IDS on 7/18/2023, incorporated by reference to '201 patent, cumulative to Zimmerman

31. I also note that WO 2010/108125 (EX2018), which I understand is the Patent Cooperation Treaty (PCT) version of Pomper and contains identical disclosure to Pomper, was submitted to the Examiner in an Information Disclosure Statement (IDS) on 8/8/23, EX1004, 274, and the Examiner signed the Information Disclosure Statement on 9/2/23, which I understand indicates that the Examiner had considered the reference. EX1004, 1171 (signed IDS). Pomper is also incorporated by reference in its entirety in the '201 patent specification, EX1001, 17:45-54, which I understand indicates that the Examiner considered Pomper, because I understand that the Examiner is presumed to have read the '201 patent specification. I also conclude that the disclosure of Pomper is cumulative to the disclosure of Zimmerman because Zimmerman, like Pomper, discloses low molecular weight agents for imaging and radiotherapy. EX1009, ¶2; EX1005, ¶3. Specifically, Zimmerman is directed to "small molecule inhibitors of seprase that can be used as **therapeutic agents** through inhibition of seprase's enzymatic activity, or as **radiopharmaceuticals** that bind to seprase and **therefore enable imaging of tissues that express seprase or for delivering radiotherapy to tumor tissues** that express seprase." EX1009, ¶2.[2] Thus, I conclude that the Examiner previously considered each of Jansen I, Jansen II, Zimmerman,

[2] Emphasis added throughout unless otherwise indicated.

Dvořáková, and Pomper. And Dr. Martin did not identify any errors the Examiner made in her assessment of Jansen I, Jansen II, Zimmerman, Dvořáková, and Pomper.

32. Dr. Martin also did not explain whether or how his arguments regarding the definiteness of the term "low molecular weight" differ from what the Examiner already considered during prosecution. As Dr. Martin notes, the Examiner considered the term "low molecular weight," explaining that "[t]he phrase 'low molecular weight' was further discussed during prosecution." EX1002, ¶186; *see also* ¶183 ("During prosecution of the '201 patent, after Patent Owner added the phrase 'low molecular weight' to the claims in an attempt to overcome the prior art, Patent Owner provided another statement" explaining the meaning of the term). Yet, Dr. Martin does not explain what error, if any, the Examiner made in accepting JHU's meaning of the term "low molecular weight."

33. I have also been asked to opine on the level of skill for a person of ordinary skill in the art ("POSA"). A POSA here would have an advanced degree, typically a Ph.D. or an M.D., **multiple years of both formal training and actual, practical experience** in i) nuclear or optical imaging, or ii) radiotherapeutics (collectively, radiopharmaceuticals), as well as in radiopharmaceutical development, and in using molecular imaging techniques (such as positron emission tomography and single photon emission computed tomography). This

contrasts with Dr. Martin's opinion; his proposed POSA lens does not require the formal training and actual, practical experience I describe above,[3] but rather, with respect to radiopharmaceuticals, radiopharmaceutical development, and molecular imaging, merely requires "**an understanding of** processes employed for synthesis and evaluation of imaging and radiotherapeutic agents" and ability "to evaluate published literature and patents." EX1002, ¶95. Dr. Martin's definition of a POSA does not have a sufficient amount of practical experience and education in the field of i) nuclear or optical imaging, or ii) radiotherapeutics (collectively, radiopharmaceuticals), as well as in radiopharmaceutical development, and in using molecular imaging techniques, impacting his patentability analysis for each of grounds 1-5. As discussed below, **formal training and experience** in radiopharmaceutical development and nuclear imaging or radiotherapeutics would be required to understand and evaluate patentability of the subject matter of the '201 patent claims.

V. THE PETITION RELIES ON THE SAME ART CONSIDERED AND OVERCOME DURING PROSECUTION, AND FAILS TO ESTABLISH MATERIAL ERROR.

A. Dr. Martin cited art that the Examiner already considered during prosecution of the '201 patent.

34. Dr. Martin argues that the claims are unpatentable for obviousness

[3] Dr. Martin's full POSA definition is reproduced in paragraph 52.

over the prior art and indefiniteness. EX1002, ¶¶16-19. However, Dr. Martin does not explain whether or how his arguments differ from what the Examiner already considered during prosecution.

35. As explained below, I have reviewed the prosecution history of the '201 patent, as well as each prior art document Dr. Martin cites, and Dr. Martin does not present any new art compared to the art that the Examiner raised—and found the claimed compounds patentable over—during prosecution. Further, I understand that, if the art or arguments raised by the Examiner and those advanced by Dr. Martin are the same or substantially the same, Dr. Martin must show material error by the Examiner. Dr. Martin does not identify any material error made by the Examiner during prosecution.

1. The Examiner considered Dvořáková, Zimmerman, Jansen I, and Jansen II.

36. Dr. Martin himself noted that Dvořáková, Jansen I, Jansen II, and Zimmerman were considered and discussed by the Examiner during prosecution of the '201 patent. Specifically, Dr. Martin stated: "A non-final rejection ('Office Action'; EX1004 at 1175-84) was issued on September 26, 2023, which included rejections of the only pending claim under 35 U.S.C. § 102(a)(1) as anticipated by Dvořáková and under 35 U.S.C. § 103 as obvious over Jansen I in view of Zimmerman and Jansen II. EX1004 at 1177-82 (Sept. 26, 2023 Office Action)." EX1002, ¶81. I have reviewed the prosecution history of the '201 patent, and I

agree that the Examiner used Dvořáková, Jansen I, Jansen II, and Zimmerman to reject JHU's claims during prosecution. EX1004, 1177-1182. Specifically, the Examiner claimed that "Claim(s) 29 is/are rejected under 35 U.S.C. 102(a)(l) as being anticipated by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393)" and "Claim(s) 29 is/are rejected under 35 U.S.C. 103 as being unpatentable over Jansen et al. (US2014/0357650Al) in view of Zimmerman et al. (US2010/0098633Al) and Jensen et al. [Jansen II] (ACS Med. Chem. Lett. 2013, 14, 491-496)." EX1004, 1177-1182.

2. The Examiner considered Pomper.

37. As I discussed above, I have reviewed the prosecution history of the '201 patent and I understand that patent examiners are charged with determining whether the patent application complies with the patent laws. I also understand that applicants are obligated to submit to the United States Patent and Trademark Office (USPTO) any known information that may be material to patentability, and such information may be provided in the form of an Information Disclosure Statement (IDS). I also understand the Examiner is expected to consider the information submitted and indicate that they have done so.

38. I also note that WO 2010/108125, which is the PCT version of Pomper and contains identical disclosure to Pomper, was submitted to the Examiner in an Information Disclosure Statement (IDS) on 8/8/23, EX1004, 274,

and the Examiner signed the IDS on 9/2/23, which I understand indicates that the Examiner had considered the reference. EX1004, 1171 (signed IDS).

39. I also understand that if a reference is incorporated by reference in its entirety[4] in the patent specification, the Examiner is presumed to have considered the reference. In my review of the '201 patent, I note that the patent incorporates Pomper by reference in its entirety: "Suitable linkers are disclosed in . . . U.S. Patent Application Publication No. US2012/0009121 A1, for 'PSMA-Targeting Compounds and Uses Thereof,' published Jan. 12, 2012, to Pomper et al, . . . which is incorporated by reference in its entirety." EX1001, 17:45-54.

40. Thus, the Examiner considered Pomper.

3. The relied-upon teachings of Pomper are cumulative to Zimmerman.

41. The teachings that Dr. Martin relies on in Pomper are entirely cumulative to Zimmerman, which Dr. Martin agrees was cited and considered by the Examiner during prosecution. Specifically, Dr. Martin states that "the Office recognized that Zimmerman discloses 'radiopharmaceuticals useful in diagnostic

[4]I understand that incorporating published prior art documents by reference into the patent specification allows for the information incorporated as such to become as much a part of the specification as if the text were repeated in the specification, and should be treated as part of the text of the specification.

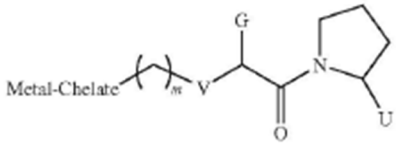
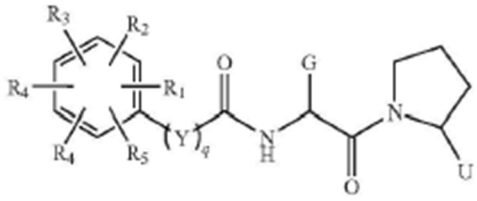
imaging and therapeutic treatment of disease comprising: [Formulas I and II]' *Id.* at 1180-81." EX1002, ¶84. Dr. Martin cites Pomper for teaching the benefits of low molecular compounds, describing that "low molecular weight inhibitors may have better access to tumors than larger antibodies and that low molecular weight agents had shown promise in pre-clinical imaging studies." EX1002, ¶113. However, Zimmerman *also* teaches the benefits of low molecular weight radiopharmaceuticals, EX1009, ¶¶2, 7, FIGs. 7-9, as Dr. Martin readily admits: "Zimmerman is directed to '**[s]mall molecule inhibitors** of seprase [FAP-α] [] **for use as therapeutic medicines or as radiopharmaceuticals** useful in diagnostic imaging and in the therapeutic treatment of diseases characterized by overexpression of seprase [FAP-α]." EX1002, ¶118. A POSA would have understood that the term "small molecule" also refers to compounds of "low molecular weight." Additionally, Dr. Martin argues that Pomper "discloses suitable linkers that can be used to link the PSMA inhibiting moiety and the optical or radiolabeled moiety." EX1002, ¶125. However, Dr. Martin does not explain what Pomper's linkers offer beyond what Zimmerman's linkers already disclose. Thus, without additional information on what Dr. Martin relies on using Pomper's linkers, a POSA would conclude that Pomper is cumulative to Zimmerman in its disclosure of linkers.

42. Dr. Martin relies on the same teachings of Pomper that Zimmerman

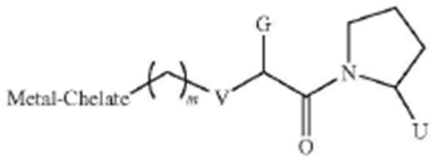
discloses. Moreover, the Examiner relied on Zimmerman during prosecution of the '201 patent for the same teachings that Dr. Martin relies on Pomper now. The table below compares the disclosures of Pomper that Dr. Martin relies on in his declaration and the equivalent disclosure of Zimmerman and the Examiner's statements on Zimmerman during prosecution.

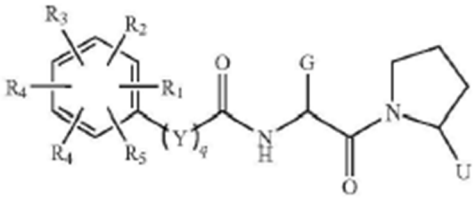
Dr. Martin's Arguments Based on Pomper	**Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination**
"Pomper describes new imaging and therapeutic compounds for targeting cancer and cancer angiogenesis." EX1002, ¶125; EX1006, Abstract, ¶12.	"This invention relates in general to small molecule inhibitors of seprase that can be used as **therapeutic agents** through inhibition of seprase's enzymatic activity, or as **radiopharmaceuticals** that bind to seprase and **therefore enable imaging of tissues that express seprase or for delivering radiotherapy to tumor tissues** that express seprase." EX1009, ¶2.

Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	"Seprase is expressed in epithelial **cancers** and has been implicated in extracellular matrix remodeling, tumor growth, and metastasis." EX1009, ¶3. "The expression of seprase on **tumors** makes it an attractive target to exploit for **noninvasive imaging as well as targeted radiotherapy**." EX1009, ¶5. "The complexes or compounds, may be used in accordance with the methods also described herein, by those skilled in the art, e.g., by specialists in nuclear medicine, **for diagnostic imaging of tissue** which expresses seprase, and therapeutic treatment of diseases which

Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	are characterized by overexpression of seprase." EX1009, ¶136. Formula I:  Formula II:  "Zimmerman et al. (US2010/0098633Al) discloses radiopharmaceuticals useful in **diagnostic imaging and therapeutic treatment of disease** comprising

Dr. Martin's Arguments Based on Pomper	**Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination**
	[Formulas I and II] wherein U is -$B(OH)_2$, -CN, etc.; G is H, alkyl, etc.; V is a bond, etc.; the metal is a metallic moiety include [sic] a radionuclide for PET, SPECT; chelate is a chelating moiety that coordinates with the radionuclide; Y is -CH_2-, etc.; and R_1-R_5 may comprise radiohalogen, etc. (p1-2, [0008-0028]; p3, [0048-0049]; p6, [0087-0099]; p9, [0111-0117]; p13,)" EX1004, 1180-1181.
"These compounds include a PSMA inhibitor used to treat cancer that is linked with a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping." EX1002, ¶125; EX1006, ¶¶31-34, 279.	"Small molecule inhibitors of seprase are provided for use as therapeutic medicines or as radiopharmaceuticals useful in **diagnostic imaging and in the therapeutic treatment** of diseases characterized by overexpression of

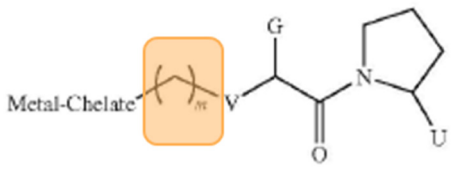
Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	seprase. The radiopharmaceuticals include complexes or compounds that contain a functionalized proline moiety which is capable of **selectively inhibiting** seprase, and **a radionuclide** adapted for **radioimaging and/or radiotherapy**." EX1009, ¶7. "In one aspect, a complex of Formula I, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided:  where . . . [**m**]**etal represents a**

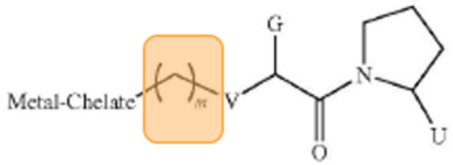
Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	metallic moiety including a radionuclide[.]" EX1009, ¶¶8–19. "In another aspect, a compound of general Formula II, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided:  where . . . R_1, R_2 , R_3, R_4 and R_5 are independently hydrogen, halogen, cyano, carboxyl, alkyl, alkylamino, alkoxy, or substituted or unsubstituted amino; with the proviso that at least

Dr. Martin's Arguments Based on Pomper	**Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination**
	one of R_1, R_2 , R_3, R_4 and R_5 is a halogen ***(*including radiohalogen**)." EX1009, ¶¶21–28. "Zimmerman et al. teaches of radiohalogenation of **FAP inhibitors** for the advantage of **diagnostic imaging and therapeutic treatment of diseases**." EX1004, 1181.
"These imaging agents 'offer better contrast between target tissues and non-target tissues,' 'greater cellular retention,' and 'low molecular weight.'" EX1002, ¶125; EX1006, ¶12.	"The expression of distinct proteins on the surface of tumor cells offers the opportunity to diagnose and characterize disease by probing the phenotypic identity and biochemical composition and activity of the tumor. Radioactive molecules that **selectively bind to specific tumor cell surface**

Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	proteins allow for the use of noninvasive imaging techniques, such as molecular imaging or nuclear medicine, for detecting the presence and quantity of tumor associated proteins . . . . [T]herapy may be realized through the use of radiopharmaceuticals that are not only capable of imaging disease, but also are capable of delivering a therapeutic radionuclide to the diseased tissue. **The expression of seprase on tumors makes it an attractive target to exploit for noninvasive imaging as well as targeted radiotherapy.** Furthermore, since seprase has both dipeptidyl peptidase and endopeptidase

Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	activity, and DPP-IV exhibits only dipeptidyl peptidase activity, **selective seprase inhibitors would be useful to reduce unwanted side effects**." EX1009, ¶¶5–6. "**Small molecule inhibitors** of seprase are provided for use as therapeutic medicines or as **radiopharmaceuticals** useful in **diagnostic imaging** and in the therapeutic treatment of diseases characterized by overexpression of seprase." EX1009, ¶7. Zimmerman contains explicit reference to selectivity and references the compounds as "**small molecule**,"

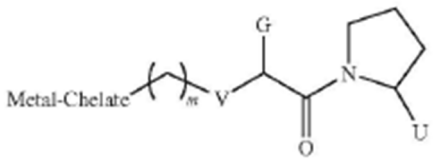
Dr. Martin's Arguments Based on Pomper	**Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination**
	EX1009, ¶2, including several times on page 1, which the Examiner cites. EX1004, 1181.
"Pomper also discloses suitable linkers that can be used to link the PSMA inhibiting moiety and the optical or radiolabeled moiety." EX1002, ¶125; EX1006, ¶12.	"In one aspect, a complex of Formula I, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided where . . . m is an integer ranging from 0 to 6[.] EX1009, ¶¶8–19. Formula I:  (linker annotation added) "Zimmerman et al.

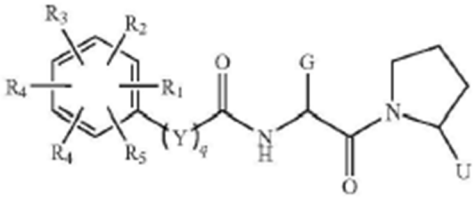
Dr. Martin's Arguments Based on Pomper	**Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination**
	(US2010/0098633Al) discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease comprising [Formulas I and II]." EX1004, 1180. Formula I:  (linker annotation added)
"Pomper also teaches the benefits of low molecular weight compounds. Pomper discusses how 'antibodies may have less access to tumor[s] than low molecular weight agents, which can be manipulated pharmacologically.'"	"This invention relates in general to **small molecule inhibitors of seprase that can be used as therapeutic agents** through inhibition of seprase's enzymatic activity, or as radiopharmaceuticals that bind to

Dr. Martin's Arguments Based on Pomper	**Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination**
EX1002, ¶126; EX1006, ¶8.	seprase and therefore **enable imaging of tissues that express seprase or for delivering radiotherapy to tumor tissues that express seprase**." EX1009, ¶2. "**Small molecule inhibitors** of seprase are provided for use as therapeutic medicines or as **radiopharmaceuticals useful in diagnostic imaging and in the therapeutic treatment of diseases** characterized by overexpression of seprase." EX1009, ¶7. Zimmerman contains explicit reference to selectivity and references the compounds as "**small molecule**,"

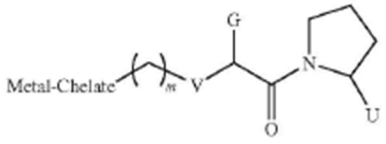
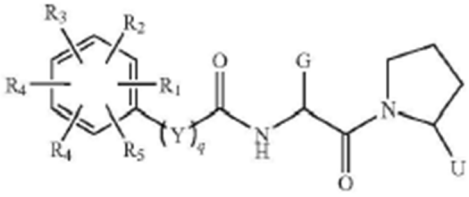
Dr. Martin's Arguments Based on Pomper	**Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination**
	EX1009, ¶2, including several times on page 1, which the Examiner cites. EX1004, 1181.
"Pomper also discusses how low molecular weight inhibitors have 'shown promise in preclinical imaging studies.'" EX1002, ¶126 (citing EX1015 and EX1016); EX1006, ¶242.	"This invention relates in general to small molecule inhibitors of seprase that can be used as therapeutic agents through inhibition of seprase's enzymatic activity, or as radiopharmaceuticals that bind to seprase and therefore **enable imaging of tissues that express seprase or for delivering radiotherapy to tumor tissues that express seprase**." EX1009, ¶2. "Small molecule inhibitors of seprase are provided for use as therapeutic

Dr. Martin's Arguments Based on Pomper	**Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination**
	medicines or as **radiopharmaceuticals useful in diagnostic imaging and in the therapeutic treatment of diseases** characterized by overexpression of seprase." EX1009, ¶7. Zimmerman contains explicit reference to selectivity and references the compounds as "**small molecule**," EX1009, ¶2, including several times on page 1, which the Examiner cites. EX1004, 1181.
"Zimmerman and Pomper disclose radiolabeled functional groups suitable for PET imaging, SPECT imaging, or radiotherapy." EX1002, ¶129.	"In one aspect, a complex of Formula I, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided:

Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	 where . . . [**m**]**etal represents a metallic moiety including a radionuclide**[.]" EX1009, ¶¶8–19. "'Radionuclide' refers to molecule that is capable of generating a detectable image that can be detected either by the naked eye or using an appropriate instrument, **e.g. positron emission tomography (PET) and single photon emission computed tomography (SPECT)**." EX1009, ¶49.

Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	In another aspect, a compound of general Formula II, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided:  where . . . R_1, R_2 , R_3, R_4 and R_5 are independently hydrogen, halogen, cyano, carboxyl, alkyl, alkylamino, alkoxy, or substituted or unsubstituted amino; with the proviso that at least one of R_1, R_2 , R_3, R_4 and R_5 is a halogen ***(*****including radiohalogen**).” EX1009, ¶¶21–28.

Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	"'**Radiohalogen**,' as used herein, refers to those **radionuclides** that are also halogens (i.e. F, Br, I, or At)." EX1009, ¶49. "Zimmerman et al. (US2010/0098633Al) discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease comprising [Formulas I and II] wherein U is -$B(OH)_2$, -CN, etc.; G is H, alkyl, etc.; Vis a bond, etc.; the metal is a metallic moiety include [sic] a radionuclide for **PET, SPECT**; chelate is a chelating moiety that coordinates with the

Dr. Martin's Arguments Based on Pomper	Same Art (Zimmerman) and Arguments (Examiner's Statements) Made During Examination
	radionuclide; Y is-CH_2-, etc.; and R_1-R_5 may comprise radiohalogen, etc." EX1004, 1180-1181.  

43. In sum, Dr. Martin relies on Pomper for the same teachings that are disclosed in Zimmerman—low molecular weight imaging and radiotherapeutic agents, linkers, and radiolabeled functional groups suitable for use in such agents. And Dr. Martin's reliance on Pomper does not provide anything beyond what the Examiner already raised and considered.

B. Dr. Martin did not identify any Examiner error during prosecution of the ’201 patent.

44. I understand that when the same or substantially the same art is used to challenge patentability in a PGR that was applied during prosecution, it is necessary to show error in a manner material to patentability by the Examiner. I reviewed Dr. Martin’s declaration, and I did not see any discussion of any error made by the Examiner, let alone any discussion as to why such an error was material to patentability. Further, I reviewed the prosecution history, and conclude a POSA would find no error in the Examiner’s analysis of the claims in light of the cited references.

45. Dr. Martin states the following: “[A] POSA would have been motivated with a reasonable expectation of success to combine the teachings of Jansen I and/or Jansen II with Zimmerman and Pomper to arrive at the subject matter of claim 1[,]” and “a POSA would have been motivated with a reasonable expectation of success to combine the teachings of Dvořáková and Pomper to arrive at the subject matter of claim 1.” EX1002, ¶¶130, 157. But a POSA would not read those statements as an identification of a material error by the Examiner, even though the Examiner did not expressly reject the claims over Pomper during prosecution. Moreover, as discussed above, JHU cited the PCT version of Pomper in an IDS, and the Examiner signed the IDS, which indicates that Pomper was before the Examiner. EX1004, 1171 (signed IDS). And, Pomper is cumulative to

Zimmerman, and the Examiner relied on Zimmerman for the same teachings that Dr. Martin relies on Pomper now, as I explained above in § V.A.3. Thus, a POSA would not consider the Examiner's failure to cite Pomper in an obviousness rejection a material error, as even if the Examiner raised Pomper in a rejection, there would have been no material difference in the examination of the '201 patent, because it is cumulative to Zimmerman.

46. Dr. Martin also argued that "the evidence of unexpected results presented during prosecution should be given little or no weight, and is certainly insufficient to overcome the strength of the prior art's teachings." EX1002, ¶¶133-135. But Dr. Martin did not provide *any* explanation as to why such evidence was "certainly insufficient," and thus a POSA would not agree with Dr. Martin.

C. The Examiner considered definiteness of the phrase "low molecular weight" and did not show material error in the Examiner's analysis.

47. Dr. Martin admits that the Examiner considered the phrase "low molecular weight" during prosecution: "The phrase 'low molecular weight' was further discussed during prosecution." EX1002, ¶186. Dr. Martin also states that the term "low molecular weight" was one of the chief reasons for the '201 patent's allowance: "The Examiner issued a Notice of Allowance on January 10, 2024 ('Notice of Allowance'; EX1004 at 1303-09), which indicated that the claims were allowed in light of the addition of the phrase 'low molecular weight' and the

purportedly unexpected results provided in the Office Action Response, Pomper Declaration, and Supplemental Amendment. EX1004 at 1308 (Notice of Allowance).” EX1002, ¶92. These statements indicate that the definiteness of the term “low molecular weight” was considered during the prosecution of the ’201 patent.

48. Additionally, Dr. Pomper provided a discussion of this key phrase “low molecular weight” in a declaration. EX1004, 1196-98, 1213-1215. In prosecution, Dr. Pomper also pointed to support in the specification for the claimed “low molecular weight” compounds and how they differed from “polymers” having “high relative molecule mass,” a topic which was also discussed during an Examiner’s interview. EX1004, 1214, 1237. Specifically, in the Applicant-Initiated Interview Summary, the Examiner indicated that a topic of the interview was “low molecular weight compounds wherein low molecular weight is defined as compounds under ~ 1500Da.” EX1004, 1237 (Interview Summary).

49. Dr. Martin’s declaration does not provide any discussion of any error made by the Examiner, let alone any discussion as to why such an error was material to patentability, regarding the definiteness of the term “low molecular weight.” Beyond stating that “there is no clear definition of the phrase ‘low molecular weight’ in the claims of the ’201 patent[,]” Dr. Martin does not identify a material error by the Examiner. EX1002, ¶187.

VI. DR. MARTIN ANALYZED THE CLAIMS THROUGH THE WRONG POSA LENS

50. As an expert, I have offered opinions throughout this declaration from the perspective of a person of ordinary skill in the art ("POSA"). I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art, who thinks along conventional wisdom in the art, and is a person of ordinary creativity. I also understand the level of a POSA is a prism or lens through which the Board views the prior art and the claimed invention.

51. I understand that the following factors are pertinent to the determination of the level of ordinary skill: (1) educational level and any specialties of the inventor(s), (2) types of problems encountered in the art, (3) prior art solutions to those problems, (4) rapidity with which innovations are made, (5) sophistication of the technology, (6) educational level of active workers in the field, and (7) nature of any testing described in the patent (and skills required of those doing such testing).

52. I understand that Dr. Martin provided the following definition for a POSA:

> [A] POSA would comprise a person possessing a Bachelor's degree in organic chemistry or a related field such as medicinal chemistry and two to five years of experience employing organic chemistry as a tool for the development of molecules with targeted biological activity. A POSA could also include individuals with a Master's degree or a

> Ph.D. in chemistry or a related field with comparatively less experience. A POSA would have an understanding of processes employed for synthesis and evaluation of imaging and radiotherapeutic agents that selectively target a specific protein and would be able to evaluate published literature and patents to ascertain those features of a molecule that contribute to its affinity and selectivity for a particular drug target.

EX1002, ¶95.

53. I disagree with Dr. Martin's assessment of the level of skill of a POSA. The patentability of the challenged claims should be assessed through a prism of a POSA having **actual formal training and experience** in i) nuclear or optical imaging, or ii) radiotherapeutics (collectively, radiopharmaceuticals), as well as in radiopharmaceutical development, and in using molecular imaging techniques, and not through someone who is an organic or medicinal chemist with merely "**an understanding** of processes employed for synthesis and evaluation of imaging and radiotherapeutic agents" and ability "to evaluate published literature and patents." EX1002, ¶95. I explain the basis for my conclusion below.

54. The '201 specification and its cited references are informative to factors (2), (3), and (7) I listed in paragraph 51, above. Regarding factor (2), the types of problems encountered in the art, the '201 patent contains significant description regarding nuclear imaging and radiotherapy, and the '201 patent cites numerous references relating to imaging and radiotherapy. EX1001, 62:20-64:38.

For example, more than 10 references cited plainly relate to targeted imaging or radiopharmaceuticals in their title. EX1001, 62:20-64:38 (containing more than 10 references mentioning PET, SPECT, or other imaging techniques in their titles). The patent also identifies the problem in the field as a lack of low-molecular weight ligands "with ideal properties for **nuclear imaging** of FAP-α." EX1001, 1:65-67. And the background of the invention discusses FAP-α being "a potential **imaging and radiotherapeutic target** for cancer and inflammation diseases." EX1001, 1:46-48.

55. With respect to factor (7), the nature of any testing described in the patent, the patent describes performing imaging quality testing. EX1001, FIGs. 6-8. For example, Figure 6 of the '201 patent shows serial NIRF (near-infrared fluorescence imaging) data of a FAP-targeting compound, XY-FAP-01 in mice bearing tumor xenografts, directly relating to fluorescence imaging data acquisition and evaluation. Figure 7 of the '201 patent shows SPECT (single-photon emission computed tomography) of [^{111}In]-XY-FAP-02 in mice bearing tumor xenografts, while Figure 8 shows three-dimensional images of the same, again directly relating to the acquisition and evaluation of imaging data (in this case, nuclear imaging data). To perform those types of tests, a POSA would have needed to have actual experience designing, performing, analyzing, and interpreting imaging data.

56. Factors (2) and (3) are also relevant when reviewing the references

that Dr. Martin relies upon for his obviousness analysis (Zimmerman, Pomper, and Dvořáková), which all relate to imaging and radiotherapeutics, as do many of the other references Dr. Martin cites in his Declaration, including, *e.g.*, EX1001 (the '201 patent); EX1017 ("In vivo **near-infrared fluorescence imaging** of FAP-expressing tumors with activatable FAP-targeted, single-chain Fv-immunoliposomes"); EX1018 ("Advance of **Molecular Imaging Technology and Targeted Imaging Agent** in Imaging and Therapy"); EX1011 (a catalogue on ATTO 488, a fluorescent label); EX1023 ("Recent conjugation strategies of small organic fluorophores and ligands for **cancer-specific bioimaging**"); EX1022 ("Prostate-Specific Membrane Antigen **Targeted Imaging and Therapy of Prostate Cancer** Using a PSMA Inhibitor as a Homing Ligand"); and EX1021 "Advances in molecular imaging: **targeted optical contrast agents** for cancer diagnostics"). In short, formal training and experience in radiopharmaceutical development and nuclear imaging or radiotherapeutics would be required to understand and evaluate patentability of the subject matter of the '201 patent claims.

57. Furthermore, factors (2) and (3), the types of problems encountered in the relevant art, and the prior art's solutions to the problems, require formal training and experience in radiotherapeutic development and nuclear imaging or radiotherapeutics. In designing and evaluating the performance of FAPi-based

imaging or radiotherapeutic agents, such as those claimed in the challenged claims, a POSA would have had to perform mammalian imaging, EX1001, 61:4-28, FIGs. 6-8, to determine selectivity and specificity of the agents, and to combat problems such as off-target binding to other enzymes, drug pharmacokinetics, cellular uptake of the agents, etc. EX1001, 1:49-67, 59:36-67, 61:4-28. Those types of problems are addressed in Dr. Martin's cited art: Dvořáková discusses selectivity and affinity, EX1008, FIG. 2, compound internalization and uptake, EX1009, FIGs. 6-9, and mammalian imaging data with its imaging agent iBody, EX1009, FIG. 4. Zimmerman, likewise, analyzes affinity, EX1009, Table 2, and biodistribution of its imaging agents, EX1009, ¶¶188-193. And Pomper discusses selectivity and affinity, EX1006, ¶¶240, 277, imaging data, EX1006, FIGs. 1-3, and uptake, EX1006, ¶187, of its imaging compounds. Thus, common problems encountered in the field required practical experience with imaging, radiotherapy, radiopharmaceuticals, or nuclear chemistry.

58. Factor (1), the educational level and any specialties of the inventor(s), also points to a POSA having formal training and experience in radiopharmaceutical development and nuclear imaging or radiotherapeutics. Dr. Pomper, the principal investigator and an inventor listed on the '201 patent, underwent a "postgraduate medical training at Johns Hopkins that included a medical internship, residencies in **diagnostic radiology and nuclear medicine**,

and a fellowship in **neuroradiology**" with B.Sc., Ph.D., and M.D. degrees. EX1004, 1195-1196.

59. I, therefore, conclude that a POSA for the '201 patent would have an advanced degree, typically a Ph.D. and/or an M.D., and also have **multiple years of both formal training and actual, practical experience** of i) nuclear or optical imaging, or ii) radiotherapeutics (collectively, radiopharmaceuticals), as well as in radiopharmaceutical development, and in using molecular imaging techniques (such as positron emission tomography and single photon emission computed tomography). This training and experience would involve developing and evaluating agents for biomedical imaging or radiopharmaceuticals, and using molecular imaging techniques. A POSA may also have worked as part of a multi-disciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others in the team, to solve a given problem. For example, such a team may include a clinician, an oncologist, a manufacturing specialist, a medical physicist, a molecular biologist, and/or a pharmaceutical formulator.

VII. DR. MARTIN LACKS SUFFICIENT RELEVANT EXPERIENCE IN THE FIELD.

60. As I explained in § VI above, a POSA here would have had actual formal training and experience in radiotherapeutic development and nuclear imaging or radiotherapeutics. Yet nothing in Dr. Martin's *curriculum vitae* (CV) or

discussion of his "Qualifications" indicates that he has *any* formal experience or training in radiopharmaceutical development and nuclear imaging or radiotherapeutics. As Dr. Martin himself acknowledges, Dr. Martin's research "involved the synthesis of biologically active natural products." EX1002, ¶6. According to his CV, Dr. Martin published 13 books, six of which are editions, from 1994 to 2015, of "*Experimental Organic Chemistry: A Miniscale & Microscale Approach*." EX1003, 2. This book and the remainder of his book publications are all on the topic of organic chemistry or the interpretation of experimental organic chemistry data, which do not relate to radiotherapeutics or imaging, and do not indicate practical experience with these topics. EX1003, 2. Dr. Martin's publications, the most recent of which are titled "Loss of Sigma-2 Receptor/TMEM97 Is Associated with Neuropathic Injury-Induced Depression-Like Behaviors in Female Mice" (2024), "Structure-Affinity Relationships of Novel σ_2R/TMEM97 Ligands" (2024), and "Validation of σ_2R /TMEM97 as a neuropathic pain target: Specificity, human expression and mechanism of action" (2023), are medicinal chemistry papers that do not encompass the fields of radiotherapeutics, imaging, or related fields. EX1003, 3. Dr. Martin's publication record and career path, as reflected on his CV and in his Declaration, show that he does not have formal training and experience in nuclear or optical imaging or radiotherapeutics (collectively, radiopharmaceuticals), nor in radiopharmaceutical

development, or in using molecular imaging techniques.

CONCLUSION

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

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 28th day of April 2025, in San Francisco.

Henry F. VanBrocklin, Ph.D.