

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 PRELIMINARY RESPONSE**

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TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	MY BACKGROUND AND QUALIFICATIONS	2
III.	SUMMARY OF OPINIONS.....	7
IV.	LIST OF DOCUMENTS CONSIDERED	10
V.	PERSON OF ORDINARY SKILL IN THE ART (“POSA”).....	14
VI.	LEGAL BASIS FOR MY ANALYSIS.....	21
	A. Claim Construction	21
	B. Obviousness.....	21
	C. Enablement.....	24
	D. Written Description	24
	E. Indefiniteness.....	26
VII.	CLAIM CONSTRUCTION	27
	A. The Claimed Compounds Are Defined Structurally, Not Functionally.....	27
	1. The Plain Language Of The Claims Is Consistent With The Claimed Compounds Being Defined Structurally, Not Functionally.	27
	2. The ’201 Patent Specification And The Prosecution History Are Consistent With The Claimed Compounds Being Defined Structurally, Not Functionally.....	32
	B. Dr. Martin Incorrectly Construes C(O)Alkyl” And “Aryl” To Have An Unlimited Length	33
	C. A POSA Would Have Understood The Meaning And Scope Of “Low Molecular Weight” And Thus The Claims Of The ’201 Patent Are Definite.....	38
VIII.	CLAIMS 1-3 OF THE ’201 PATENT WOULD NOT HAVE BEEN OBTAINABLE IN VIEW OF JANSEN I AND/OR JANSEN II, TAKEN IN VIEW OF ZIMMERMAN AND POMPER, OR DVOŘÁKOVÁ, TAKEN IN VIEW OF POMPER.....	44
	A. FAP Background And State Of The Art Before October 23, 2017	44

B.	Dr. Martin Does Not Explain How Or Why A POSA Would Have Selected Particular Compounds Or How A POSA Would Have Modified The Selected Compounds	46
1.	Dr. Martin Did Not Explain How A POSA Would Have Selected “A” From Jansen I/Jansen II To Arrive At The Claimed Invention.....	47
2.	Dr. Martin did not explain how a POSA would have selected “B” and “L” from Zimmerman to arrive at the claimed invention.....	53
C.	Claims 1-3 of the ’201 Patent Would Not Have Been Obvious in View of Jansen I and/or Jansen II, Taken in View of Zimmerman and Pomper (Ground I).	60
1.	Dr. Martin Fails to Explain how a POSA would have Combined Zimmerman, Jansen I and/or Jansen II, and Pomper to Arrive at the Claimed Invention.....	60
2.	Dr. Martin Fails To Show That A POSA Would Have Had A Reason To Modify The Jansen I And/Or Jansen II FAPis To Arrive At The Claimed Invention.	62
3.	Dr. Martin Fails to Show that a POSA Would Have Had a Reasonable Expectation of Success in Combining Jansen I and/or Jansen II, Zimmerman, and Pomper.....	67
D.	Claims 1-3 of the ’201 Patent Would Not Have Been Obvious in View of Dvořáková and Pomper.....	68
1.	Dr. Martin Fails to Show a POSA Would Have Been Motivated to Modify Dvořáková with Pomper to Create a Low Molecular Weight Compound.	68
2.	Dr. Martin Fails To Show A Reasonable Expectation Of Success In A Dvořáková/Pomper Combination.	74
E.	Dr. Martin Ignored Unexpectedly Superior Results Achieved with the Claimed Compounds.....	76
IX.	THE ’201 PATENT CLAIMS HAVE SUFFICIENT WRITTEN DESCRIPTION.	78
A.	Dr. Martin’s Written Description Analysis Wrongly Focuses On A Functional Definition Of The Compounds.....	78

B.	Dr. Martin Did Not Show That There Is A Lack Of A Representative Number Of Species Disclosed In The '201 Patent.....	79
X.	THE '201 PATENT CLAIMS ARE ENABLED.....	83
A.	Dr. Martin's Enablement Analysis Wrongly Focuses on a Functional Definition of the Compounds.....	83
B.	Dr. Martin Fails to Show Undue Experimentation Would be Required.	85
1.	Dr. Martin Misrepresented the True Size of the Claimed Genus and the Skill Level of a POSA in Concluding that the Claims are not Enabled.	85
2.	Dr. Martin Underestimated the Predictability of the Invention, and the Level of Guidance Provided by the Specification.....	86
XI.	THE CLAIMED INVENTION IS DEFINITE.	89
A.	A POSA Would Have Understood the Scope of the Term "Low Molecular Weight."	89
XII.	CONCLUSION.....	91

I, 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 (“Patent Owner”) 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 the Patent Owner Preliminary Response to the Petition for Post-Grant Review of U.S. Patent No. 11,938,201 ("the '201 patent") (EX1001), which 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.

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 a 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.

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

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

10. Over the course of my career, I have received a variety of prizes and awards. At Lawrence Berkeley National Lab, I received the Lawrence Berkeley National Laboratory Outstanding Performance Award four separate times. At UCSF, I was awarded the MSBI Outstanding Teacher Award three times (2019, 2021, 2023). I received the Society of Nuclear Medicine President's Distinguished Service Award twice (2006, 2010). I was selected as a Research Distinguished Investigator of the Academy for Radiology & Biomedical Imaging (2018). I have also been elected Fellow to both the Society of Nuclear Medicine and Molecular Imaging (2019) and the Society of Radiopharmaceutical Sciences (2021). I received the Michael J. Welch award (2020) 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. As shown in my CV (EX2003), my publications on these topics include: “Structure-activity relationship of ^{18}F -labeled phosphoramidate peptidomimetic PSMA-targeted inhibitor analogues for PET imaging of prostate cancer,” *Journal of Medicinal Chemistry* **2016**; “An Improved Radiosynthesis of $[^{18}\text{F}]$ O-(2-Fluoroethyl)-O-(p-nitrophenyl)methylphosphonate: A First-in-Class Cholinesterase PET Tracer,” *Journal of Labelled Compounds and Radiopharmaceuticals* **2017**; “In vivo PET imaging of the activated immune environment in a small animal model of inflammatory arthritis,” *Molecular Imaging* **2017**; “Biodistribution of a Mitochondrial Metabolic Tracer, $[^{18}\text{F}]$ F-AraG, in Healthy Volunteers,” *Molecular Imaging* **2022**; “Evaluation of $^{134}\text{Ce}/^{134}\text{La}$ as a PET Imaging Theranostic Pair for ^{225}Ac α -Radiotherapeutics,” *Journal of Nuclear Medicine* **2023**; “CD46-Targeted Theranostics for Positron Emission Tomography and ^{225}Ac -Radiopharmaceutical Therapy of Multiple Myeloma,” *Clinical Cancer Research* **2024**; “Prostate Specific Membrane Antigen Targeted StarPEG Nanocarrier for Imaging and Therapy of Prostate Cancer,” *Advanced Healthcare Materials* **2024**; “Actinium-225 targeted alpha-particle therapy for prostate cancer,” *Theranostics* **2024**; “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, oncologic imaging agents, proteases, steroids, (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. SUMMARY OF OPINIONS

16. I have been asked to consider whether, before October 23, 2017, the prior art that Dr. Martin cites under Ground I (Jansen I (EX1007), Jansen II

(EX1010), and Zimmerman (EX1009)) or Ground II (Dvořáková (EX1008) and Pomper (EX1006)) would have rendered the challenged claims of the '201 patent obvious. In view of the state of the art before October 23, 2017, Dr. Martin failed to show that a POSA would have found the challenged claims obvious over the prior art. First, because Dr. Martin evaluated the claims and the art from an incorrect perspective, he incorrectly concluded that the challenged claims would have been obvious to a 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 that the level of skill in the art is a prism or lens (i.e., "POSA lens") through which the prior art and the claimed invention must be viewed. As discussed below, Zimmerman, Jansen I, and Jansen II disclose a panoply of possible FAPi compounds that could be used as a starting point (based on their affinity and selectivity) to be modified. Dr. Martin does not mention or address most of the disclosed compounds. Nor does Dr. Martin explain **how** or **why** a POSA would have selected a particular compound or compounds for further modification. Second, again due to the incorrect application of a POSA lens, Dr. Martin fails to show why a POSA would have had a reason to modify the prior art compounds to arrive at the claimed invention. Specifically, Dr. Martin does not address why a POSA would have had a reason to modify Jansen I or Jansen II compounds to

remove substituents on the quinolinyl moiety—substituents that were shown to dramatically increase selectivity of the compounds—before attaching it to Zimmerman’s linker (Ground I), or to remove multiple FAPi agents, a polymeric backbone, and biotin units from Dvořáková’s iBody (Ground II), when the art clearly taught that polymeric agents with multiple FAPis and biotin units such as those in Dvořáková performed better. I refer to Section VIII below.

17. I have also been asked to consider whether a POSA would have found the subject matter of claims 1-3 of the ’201 patent (i.e., the claimed invention) to require undue experimentation to make and use in light of the teachings in the ’201 specification (Ground III), and whether a POSA would have found the claimed invention to be adequately described in the patent (Ground IV). In view of the state of the art at least as of July 18, 2023, and in light of the teachings in the ’201 patent, a POSA would not have found the challenged claims to lack written description support or enablement at least as of July 18, 2023. First, regarding written description, because Dr. Martin’s POSA lens does not include sufficient practical experience and training in the field of the ’201 patent, he incorrectly concludes that a POSA would not have been able to determine from the ’201 patent specification, including its incorporated references, suitable “B” and “L” moieties for use in practicing the claimed invention. Second, regarding enablement, Dr. Martin fails to establish why a POSA would have been unable to

make and use the claimed invention, given the high level of disclosure provided by the '201 patent specification and the post-filing reports describing objective evidence of others practicing the claimed invention. When viewed through the proper POSA lens, it is clear that the claims are described and enabled by the '201 patent. I refer to my analysis in Sections X and XI below.

18. Further, I have been asked whether a POSA would have understood the metes and bounds of the claimed compounds of the '201 patent (Ground V) at least as of July 18, 2023. The claims of the '201 patent are not indefinite, and a POSA would have understood the scope of the claimed compounds. Specifically, as discussed in Section XII, a POSA, viewed through the proper lens of having sufficient practical experience and education in the field, would have readily understood the term “low molecular weight” according to its plain and ordinary meaning. And this meaning is supported by the patent specification as well as in the prosecution history of the '201 patent.

IV. LIST OF DOCUMENTS 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	<i>Curriculum Vitae</i> of Dr. Stephen F. Martin

Exhibit No.	Description
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 et al., <i>Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein</i> , 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., <i>Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold</i> , 2013(4) ACS MEDICINAL CHEMISTRY, 491-96 (2013) (“Jansen II”)
1011	<i>Product Information: ATTO 488.</i> , ATTO-TEC GMBH (2024) available at https://www.attotec.com/fileadmin/user_upload/Katalog_Flyer_Support/ATTO_488.pdf (last accessed Dec. 18, 2024)
1015	Ronnie C. Mease et al., <i>N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L- cysteine, [18F]DCFBC: A new Imaging probe for prostate cancer</i> , 14 CLIN CANCER RES 3036-43 (2008)

Exhibit No.	Description
1016	Suzanne E. Lapi et al., <i>Assessment of an 18F-Labeled Phosphoramidate Peptidomimetic as a New Prostate-Specific Membrane Antigen–Targeted Imaging Agent for Prostate</i> , 50 J NUCL MED 2042-48 (2009)
1017	Ronny Rüger et al., <i>In Vivo Near-Infrared Fluorescence Imaging Of FAP-Expressing Tumors With Activatable FAP-Targeted, Single-Chain Fv-Immunoliposomes</i> , 186 JOURNAL OF CONTROLLED RELEASE 1-10 (2014)
1018	Zhi-Yi Chen et al., <i>Advance of Molecular Imaging Technology and Targeted Imaging Agent in Imaging and Therapy</i> , BIOMED RESEARCH INT’L 819324 (2014)
1021	Anne Hellebust et al., <i>Advances in molecular imaging: Targeted Optical Contrast Agents For Cancer Diagnostics</i> , 7 NANOMEDICINE 429-45 (2012)
1022	Sumith A. Kularatne et al., <i>Prostate-Specific Membrane Antigen Targeted Imaging and Therapy of Prostate Cancer Using a PSMA Inhibitor as a Homing Ligand</i> , 6 MOLECULAR PHARMACEUTICS 780-89 (2009)
1023	Yonghwang Ha, <i>Recent Conjugation Strategies of Small Organic Fluorophores and Ligands for Cancer-Specific Bioimaging</i> , 248 CHEMICO-BIOLOGICAL INTERACTIONS 36-51 (2016)
2003	<i>Curriculum Vitae</i> of Dr. Henry VanBrocklin
2004	Krippendorff <i>et al.</i> , “Mechanism-Based Inhibition: Deriving K_i and k_{inact} Directly from Time-Dependent IC_{50} Values,” <i>Society for Biomolecular Sciences</i> (Mar. 2009) (“Krippendorff”)
2005	Šácha <i>et al.</i> , “iBodies: Modular Synthetic Antibody Mimetics Based on Hydrophilic Polymers Decorated with Functional Moieties,” <i>Wiley-VCH Verlag GmbH & Co.</i> (Jan. 2016) (“Šácha”)

Exhibit No.	Description
2006	Meletta <i>et al.</i> , “Evaluation of the Radiolabeled Boronic Acid-Based FAP Inhibitor MIP-1232 for Atherosclerotic Plaque Imaging,” <i>Molecules</i> (Jan. 2015) (“Meletta”)
2007	Dvořáková <i>et al.</i> , “Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein: Supporting Information,” <i>Journal of Medicinal Chemistry</i> (Sept. 2017) (“Dvořáková SI”) Accessed Apr. 26, 2025 at: https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b00767
2008	Tassa <i>et al.</i> , “Binding Affinity and Kinetic Analysis of Targeted Small Molecule-Modified Nanoparticles,” <i>American Chemical Society</i> (Dec. 2009) (“Tassa”)
2009	Tweedle, “Adventures in multivalency, the Harry S. Fischer memorial lecture CMR 2005; Evian, France,” <i>Wiley InterScience</i> (Feb. 2006) (“Tweedle”)
2010	Carlucci <i>et al.</i> , “Preclinical Evaluation of a Novel ¹¹¹ In-Labeled Bombesin Homodimer for Improved Imaging of GRPR-Positive Prostate Cancer,” <i>Molecular Pharmaceutics</i> (Apr. 2013) (“Carlucci”)
2011	Sikkandhar <i>et al.</i> , “Theranostic Probes for Targeting Tumor Microenvironment: An Overview,” <i>International Journal of Molecular Sciences</i> (May 2017) (“Sikkandhar”)
2012	Brennen <i>et al.</i> , “Rationale Behind Targeting Fibroblast Activation Protein–Expressing Carcinoma-Associated Fibroblasts as a Novel Chemotherapeutic Strategy,” <i>American Association for Cancer Research</i> (Feb. 2012) (“Brennen”)
2013	McLuckey & Stephenson, “Ion/Ion Chemistry Of High-Mass Multiply Charged Ions,” <i>Mass Spectrometry Reviews</i> (Dec. 1998) (“McLuckey”)
2018	WO 2010/108125 A2 to Pomper <i>et al.</i>

V. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

19. 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 prior art and the claimed invention are viewed.

20. 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 patent (and skills required of those doing such testing).

21. 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.

22. I disagree with Dr. Martin's assessment of the level of skill of a POSA. In my opinion, the patentability of the challenged claims should be assessed through a lens of a POSA who has **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;¹ his proposed POSA lens does not require the formal training and actual, practical experience I describe above, 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

¹ Dr. Martin's full POSA definition is reproduced in paragraph 21.

(emphasis added). I explain the basis for my conclusion below.

23. The '201 specification and its cited references are informative to factors 2, 3, and 7 that I listed in paragraph 20, above. With regard to factor (2), the types of problems encountered in the art, the '201 patent explicitly states that “[i]maging and radiotherapeutics agents targeting fibroblast-activation protein- α (FAP- α) and their use in imaging and treating FAP- α related diseases and disorders are disclosed.” EX1001, Abstract. The '201 patent also contains significant description regarding nuclear imaging and radiotherapy from the research lab to the clinic, 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 radiopharmaceutical development, targeted imaging or radiotherapeutics in their title. EX1001, 62:20-64:38 (containing more than 10 references mentioning PET, SPECT, or other imaging techniques in their titles); EX1001, 62:20-64:38. 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 ,” and discusses various key functional groups for these purposes. EX1001, 1:46-48, 1:65-67 (emphasis added). 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, 1:65-67 (emphasis added).

24. Regarding factor (7), the nature of testing described in the patent (and

the skill required for such testing), the patent describes performing imaging quality testing. EX1001, FIGs. 6-8. 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). In my opinion, to perform those types of tests, a POSA would have needed to have actual experience designing, performing, analyzing, and interpreting imaging and radiotherapeutic data.

25. Additionally, references that Dr. Martin relies upon for his obviousness analysis (Zimmerman, Pomper, and Dvořáková) relate to radiopharmaceutical development, 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”) (all emphasis added). In short, formal training and/or experience in radiopharmaceutical development, nuclear imaging or radiotherapeutics, and in using molecular imaging techniques would be required to understand not only the subject matter of the ’201 patent.

26. Furthermore, the types of problems encountered in the relevant art (factor (2)), and the prior art’s solutions to the problems (factor (3)), require formal training and experience in nuclear imaging or radiotherapeutics because 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, for example, perform mammalian imaging (EX1001, 61:1-62:67, FIGs. 6-8) to determine selectivity and specificity of the agents, and to combat problems such as off-target binding to other proteins/enzymes, drug pharmacokinetics, cellular uptake of the agents, etc. EX1001, 1:49-67, 59:36-67, 61:4-28. Dr. Martin did not explain how a POSA would have obtained such skills merely through “understanding of processes employed” or “evaluat[ing] published literature” (EX1002, ¶95). Notably, 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. 5-8, and mammal imaging data of its imaging agent iBody, EX1009, FIG. 4. Zimmerman analyzes affinity, EX1009, Table 2, and biodistribution of its imaging agents, EX1009, ¶¶188-193. And Pomper discusses selectivity and affinity, EX1005, ¶¶313, 375, imaging data, EX1005, FIGs. 3-6, and uptake, EX1005, ¶307, of its imaging compounds. The existence of these problems in both FAP-targeting and PSMA-targeting compounds speaks to the widespread nature of these problems in the field as a whole. Thus, common problems encountered relate to fields in which practical experience with radiopharmaceuticals, as well as in radiopharmaceutical development, and in using molecular imaging techniques, such as positron emission tomography, single photon emission computed tomography and other imaging techniques. The solutions to these problems are also instructive to the level of a POSA. *See, e.g.*, EX1005, ¶282 ("In certain embodiments, the invention provides **compounds comprising one or more radioisotope suitable for use in radiation therapy**"); EX1008, 3-4 ("Finally, **anti-FAP iBody 1 was used to visualize FAP-transfected tumor cells in frozen tissue sections of glioma tumor xenografts** (Figure 4d)."); EX1009, ¶¶29-30 ("In another aspect, a **method of imaging tissue** of a mammal which expresses seprase is provided which includes administering to the mammal an effective amount of a **radiolabeled compound or**

complex that selectively inhibits seprase or binds to the enzymatic domain of seprase”) (all emphasis added).

27. Finally, factor (1), the educational level and any specialties of the inventor(s), also points to a POSA that would have had formal training and experience with radiopharmaceutical development, nuclear imaging or radiotherapeutics, and in using molecular imaging techniques. I understand that Dr. Pomper, the primary investigator and one of the inventors 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 (emphasis added).

28. 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** 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 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 pharmaceutical formulator.

VI. LEGAL BASIS FOR MY ANALYSIS

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

A. Claim Construction

30. 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.

31. 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

32. 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).² 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.

33. 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

² Dr. Martin assessed obviousness before October 23, 2017.

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.

34. 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

35. 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. 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.

36. 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

37. I understand that the written description provided by a patent specification must convey clearly to a POSA that the applicant was in possession

of the claimed invention as of the patent's filing date. And I understand that this involves an objective inquiry into the specification from the perspective of a POSA. Further, I understand that possession does not mean physical possession and does not require making or testing the invention.

38. 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.

39. 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.

40. 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.

41. 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

42. 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.

VII. CLAIM CONSTRUCTION

A. The Claimed Compounds Are Defined Structurally, Not Functionally.

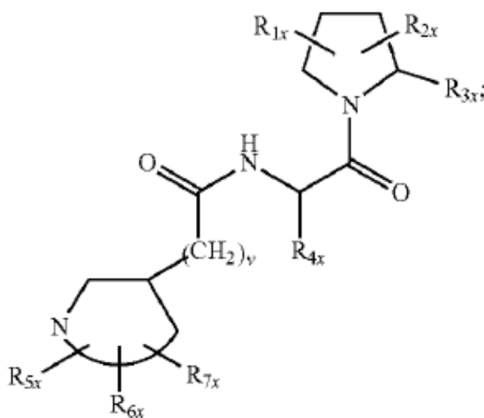
1. The Plain Language Of The Claims Is Consistent With The Claimed Compounds Being Defined Structurally, Not Functionally.

43. Dr. Martin incorrectly construed the claimed compounds as being functionally defined. Specifically, Dr. Martin argued that the claimed compounds must “perform the claimed functions.” EX1002, ¶167 (“The ’201 patent does not even describe why or how the two disclosed examples—XY-FAP-01 and XY-FAP-02—perform the claimed functions, or why other compounds do not.”). In reviewing Dr. Martin’s declaration, I note that Dr. Martin did not expressly construe how the claimed compounds are defined, applying instead “the plain and ordinary meaning of the words in the claim.”³ EX1002, ¶97.

44. I disagree with Dr. Martin that a POSA would have interpreted the claimed compounds to be defined functionally. First, looking at the plain language of the claims, a POSA would have understood the claimed compounds being defined structurally. The claims state that the “low molecular weight compound”

³ I understand that “plain and ordinary meaning” refers to the understanding a term would have to a POSA, unless the specification or prosecution history reveals the inventor intended a different, special meaning.

must have “Formula (I): B-L-A.” EX1001, Certificate of Correction, 1-2. The claims further state that the “A” moiety “has the *structure* of:”



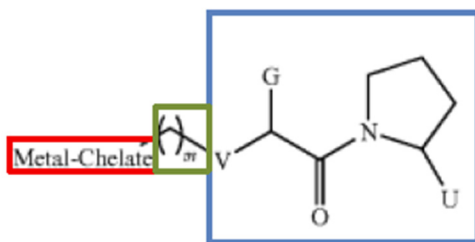
EX1001, Certificate of Correction, 1-2.

45. A POSA would have also understood that the various R group substituents in the structure for A are also defined structurally: the claims recite, e.g., “H, OH, halogen, C₁₋₆alkyl,” etc., which all have a known chemical structure associated with them. EX1001, Certificate of Correction, 1-2.

46. The only functional language that appears in the claims is with regard to the “B” and “L” subgroups: “B” as “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” as a “linker having bi-functionalization adapted to form a chemical bond with B and A.” EX1001, Certificate of Correction, 1-2. Dr. Martin agrees that it is the

“B” and “L” subgroups that are functionally defined: “The claims of the ’201 patent contain two functional limitations: (1) B is ‘any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computer tomography (SPECT) imaging or radiotherapy[’]; and (2) L is “a linker having bifunctionalization adapted to form a chemical bond with B and A.” EX1002, ¶160.

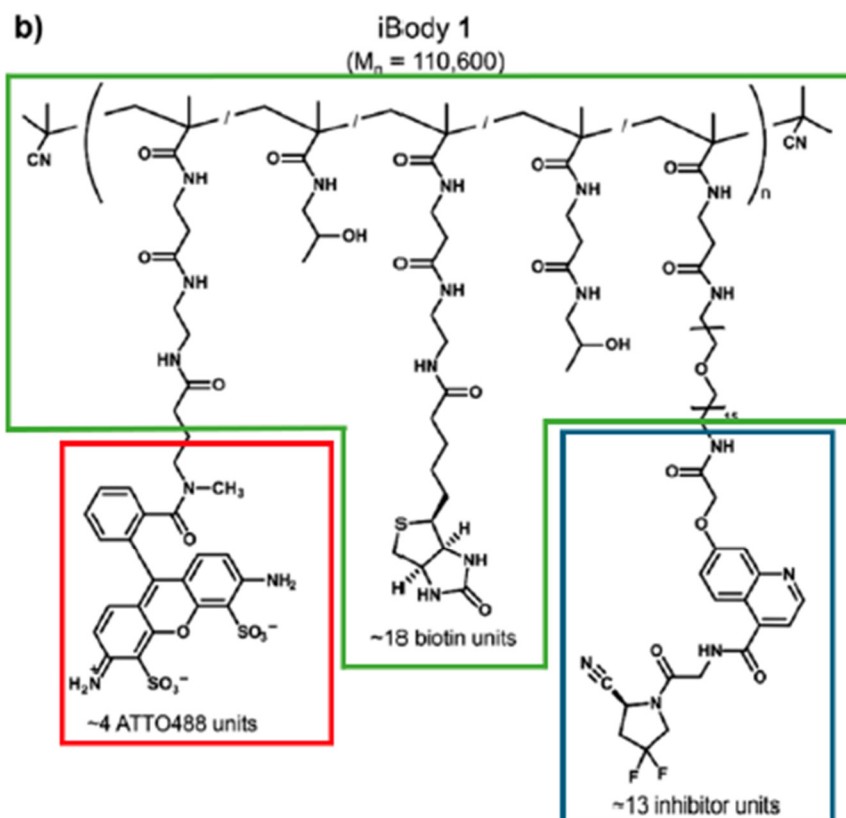
47. Further, in evaluating the art, Dr. Martin repeatedly assigns function to only B and L. In obviousness Ground I, Dr. Martin annotates a formula from Zimmerman’s claim 1 as follows:



EX1002, p. 69.

48. According to Dr. Martin, it is “the linker, ” that “meets the parameters of the claimed linker, L.” EX1002, ¶121. The same is true for the “Metal-Chelate” moiety, which Dr. Martin only evaluates as a “B” subgroup satisfying the function “any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy,” rather than

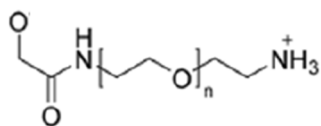
for the compound as a whole. EX1002, ¶¶123-124, 117. Dr. Martin performs similar analysis with Dvořáková's iBody compound in obviousness Ground II, separately assigning the linking function and imaging/therapeutic function to the groups annotated in green and red, respectively, EX1002, ¶¶149, 152:



EX1002, p. 84.

49. Indeed, when discussing the imaging capabilities of Dvořáková, Dr. Martin analyzes the ATTO488 group itself, rather than the compound as a whole: “A POSA would interpret the optical functional group as any molecule that absorbs and emits light, and thus would have recognized ATTO488 as an ‘optical or radiolabeled functional group suitable for optical imaging, positron-emission

tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy,’ as recited in claim 1 Accordingly, Dvořáková discloses the B moiety as recited in claim 1.” EX1002, ¶149. Similarly, Dr. Martin analyzes the linker moiety separately from the compound as a whole: “The structure of Compounds 1-4 of Dvořáková, shown above, includes:



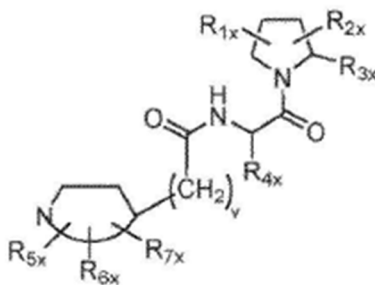
. . . . Therefore, this linker falls within the broad scope of L as recited in claim 1.” EX1002, ¶¶151-152. Despite clearly assigning the claimed functions to B and L, respectively, Dr. Martin concludes, without any explanation or support, that it is the *claimed compounds* that must “perform the claimed functions.” EX1002, ¶167.

50. In fact, assigning the second function cited in the claims—“having bi-functionalization adapted to form a chemical bond with B and A”—to the compounds as a whole yields a nonsensical result. Yet, Dr. Martin has done exactly that. The compound of Formula I already contains B and A, and a POSA would have understood that the compound cannot be “adapted to form a chemical bond with B and A” because those moieties are already part of the compound. Dr. Martin does not attempt to explain how this would be possible. Using the plain and ordinary meaning, a POSA, regardless of whether Dr. Martin’s or my POSA lens applies, would have understood that the “bi-functionalization” modifies “L” and

“B” only, rather than the whole compound.

2. The '201 Patent Specification And The Prosecution History Are Consistent With The Claimed Compounds Being Defined Structurally, Not Functionally.

51. The '201 patent specification is consistent with the claimed compounds being defined structurally, not functionally. The '201 patent describes the claimed compound repeatedly throughout the specification as having the “B-L-A” structure. EX1001, 2:3-12, 4:30-51, 7:46-65, 8:14-24, 11:22-30, 12:40-50, 15:40-44. The “A” moiety is also clearly defined structurally in the specification, with the following structural formula:



EX1001, Certificate of Correction, 1-2.

52. And each of the R substituents are likewise defined structurally, with clearly defined groups listed for each substituent: “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 O.”

EX1001, Certificate of Correction, 1-2. And during the prosecution history of the '201 patent, one of the inventors, Dr. Pomper, defined the invention in structural terms over the cited prior art, citing the structural feature of "low molecular weight." EX1004, 1196-97 (Pomper Declaration).

53. In sum, given the plain language of the claims, the specification, and the prosecution history, a POSA would have understood the challenged claims to recite structurally-defined, not functionally-defined compounds. And Dr. Martin fails to identify any portion of the '201 patent that defines the claimed invention functionally, rather than structurally.

B. Dr. Martin Incorrectly Construes C(O)Alkyl" And "Aryl" To Have An Unlimited Length

54. Dr. Martin construes the terms "C(O)alkyl" and "C(O)aryl" for substituent R_{3x} of the A moiety as having an unlimited length. EX1002, ¶¶106-111. Specifically, he argues that because "no range of the number of carbon atoms is provided" for C(O)alkyl substituent of R_{3x}, a POSA would have understood this term to mean "an acyl group comprising an alkyl group of any length." EX1002, ¶110. Dr. Martin applies the same reasoning to the aryl group: "without a number of carbon atoms or rings designated, the —C(O)aryl-, —C=C—C(O)aryl, and —C=C—S(O)₂aryl groups likewise would have been understood by a POSA as not limited to any particular length, size or substitution." EX1002, ¶111. I disagree

with Dr. Martin's argument that a POSA would have viewed the terms "aryl" and "alkyl" used in the above contexts as unlimited (under either POSA definition). A POSA would have understood the terms "C(O)alkyl" and "C(O)aryl" for substituent R_{3x} to have a limit.

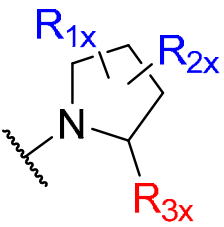
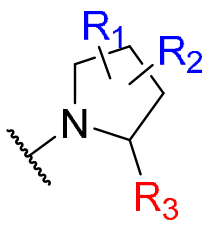
55. I understand that incorporating published prior art references by reference into the patent specification allows for the information incorporated as such to become as much a part of the specification as if the text were repeated in the specification, and should be treated as part of the text of the specification. I note that in discussing "representative targeting moieties for FAP- α "—i.e., the claimed "A" moiety—the '201 patent specification incorporates "by reference in their entirety" U.S. Pat. App. Pub. No. 2014/0357650, U.S. Pat. No. 9,346,814 ("Jansen I"), and International PCT Pat. Pub. No. WO 2013/107820 (collectively "the Jansen FAP- α documents"). EX1001, 8:25-32. Therefore, a POSA would have considered the disclosure of the Jansen FAP- α documents in understanding the scope of the claimed A moiety (and therefore, the R_{3x} substituent on the A moiety).

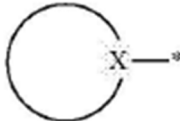
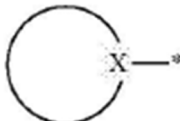
56. The Jansen FAP- α documents state that "[w]hen describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise." EX1007, 22:13-15. They further state that "alkyl groups of this invention comprise from 1 to 6 carbon atoms" and that "'aryl' . . . is generic for a 5- or 6-membered aromatic monocycle

optionally comprising 1 or 2 heteroatoms selected from O, N and S; said aryl further being optionally substituted with from 1 to 3 substituents.” EX1007, 22:16-43. Thus, a POSA would have clearly defined, easily-accessible limits to the length and size of the “aryl” and “alkyl” terms in R_{3x}.

57. Furthermore, the R_{3x} substituent, as well as the entire pyrrolidyl ring (the first row in the table below), in the claimed A is identical to that of the R₃ substituent in the Jansen FAP- α documents, as demonstrated in Table 1 below. EX1001, Certificate of Correction, 1-2; EX1007, 6:25-7:22, 98:45-99:35.

Table 1: Comparison of the claimed A moiety in the '201 patent and the Jansen FAP- α documents' structure corresponding to the “A” moiety.

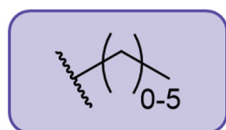
The claimed A moiety	The Jansen FAP- α documents' structure corresponding to the claimed A moiety
<p><u>Pyrrolidyl ring</u></p>  <p>R_{1x} and R_{2x} = H, OH, halogen, C₁₋₆alkyl, OC₁₋₆alkyl or SC₁₋₆alkyl R_{3x} = H, CN, B(OH)₂, C(O)alkyl, C(O)aryl, C=CC(O)aryl, C=CS(O)₂aryl, CO₂H, SO₃H, SO₂NH₂, PO₃H₂, or 5-tetrazoyl</p>	<p><u>Pyrrolidyl ring</u></p>  <p>R₁ and R₂ = H, OH, halo, C₁₋₆alkyl, OC₁₋₆alkyl or SC₁₋₆alkyl R₃ = H, CN, B(OH)₂, C(O)alkyl, C(O)aryl, C=CC(O)aryl, C=CS(O)₂aryl, CO₂H, SO₃H, SO₂NH₂, PO₃H₂, or 5-tetrazoyl</p>
<u>Connection between rings</u>	<u>Connection between rings</u>

The claimed A moiety	The Jansen FAP- α documents' structure corresponding to the claimed A moiety
$R_{4x} = H$ $v = 0$	$R_4 = H, C_{1-6}\text{alkyl}, OC_{1-6}\text{alkyl}, S=C_{1-6}\text{alkyl}, -Ar_1, \text{ and } C_{1-6}\text{aralkyl};$ $C_{1-6}\text{alkyl}$ can be substituted with 1-3 OH or halo; $Ar_1 = 5\text{- or }6\text{-membered aromatic monocycle}$ with optional substitution and optional heteroatoms $n = 0, 1, 2, 3, \text{ or } 4$
 quinoliny ring	 “represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, wherein there are exactly 2 ring atoms between the N atom and X; said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S; and X represents a C atom” EX1007, 7:15-22.
Substitutions on  $R_{5x}, R_{6x}, \text{ and } R_{7x} = H$	Substitutions on  $R_5, R_6, \text{ and } R_7 = \text{various substitutions, including H}$

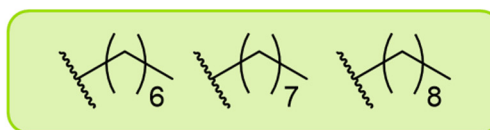
58. A POSA, thus, would have looked to the Jansen FAP- α documents to

understand the meaning of “C(O)alkyl” and “C(O)aryl” in the context of the claimed R_{3x} substituent. And a POSA further would have understood, from the disclosures of the Jansen FAP- α documents, that the “alkyl” groups of the invention signify groups from “from 1 to 6 carbon atoms” and that the term “aryl” would be limited to “5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; said aryl further being optionally substituted with from 1 to 3 substituents.” EX1007, 22:16-43. The graphic below shows the limitations of these two definitions in the context of R_{3x} .

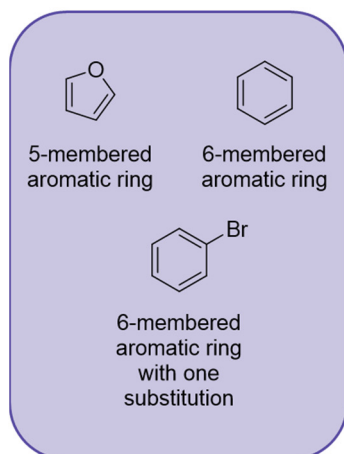
**R_{3x} Substituents
that Fall Within
“Alkyl” Definition**



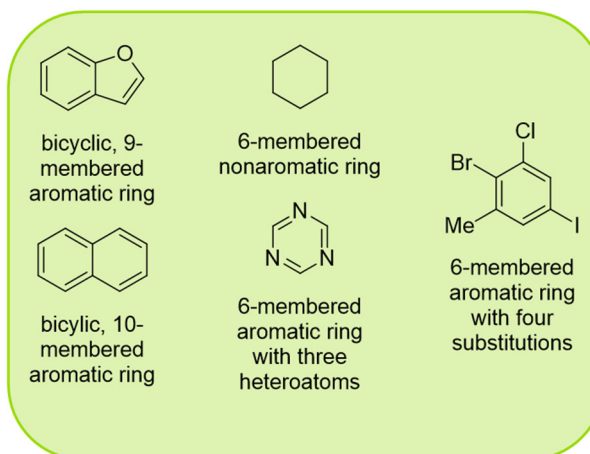
**R_{3x} Substituents that Do
Not Fall Within “Alkyl”
Definition**



**R_{3x} Substituents
that Fall Within
“Aryl” Definition**



**R_{3x} Substituents that do Not Fall
Within “Aryl” Definition**



C. A POSA Would Have Understood The Meaning And Scope Of “Low Molecular Weight” And Thus The Claims Of The ’201 Patent Are Definite.

59. Dr. Martin stated that a POSA would have found the term “low molecular weight” indefinite because “the phrase ‘low molecular weight’ could vary based on the specific field of study,” and “[t]he Patent Owner has not clearly defined this phrase in the ’201 patent or its file history.” EX1002, ¶¶105, 180. I disagree with Dr. Martin. The ’201 patent would have informed a POSA having the appropriate skill in the art (*see* Section V, above) regarding the scope of the claimed invention with a reasonable certainty. Indeed, the ’201 patent makes clear this ordinary meaning of “low molecular weight.”

60. A POSA would have understood the term “low molecular weight” to have its well-accepted, plain and ordinary meaning in the field: compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons. And the specification and prosecution history here are consistent with this meaning. First, the ’201 patent incorporates by reference Pomper: “Suitable linkers are disclosed in . . . U.S. Patent Application Publication No. US2012/0009121 A1 [(EX2018)], for ‘PSMA-Targeting Compounds and Uses Thereof,’ published Jan. 12, 2012, to Pomper et al, each of which is incorporated by reference in its entirety.” EX1001, 17:45-53. Pomper explicitly describes its compounds as “low molecular weight:” “The invention also provides compounds with greater cellular

retention and **low molecular weight.**” EX1006, ¶12 (emphasis added). Dr. Martin also agrees that Pomper is directed to low molecular weight compounds: “In addition, Pomper describes new imaging and therapeutic compounds for targeting cancer and cancer angiogenesis These imaging agents ‘offer better contrast between target tissues and non-target tissues,’ ‘greater cellular retention,’ and ‘low molecular weight.’” EX1002, ¶125.

61. Table 2 below lists the so-called “low molecular weight” compound that Pomper prepares in its disclosures, EX1006, ¶¶207-293, as well as the molecular weights of each compound. For the compounds with reported $[M+1]^+$ values as part of their characterization,⁴ 1 g/mol was subtracted from the reported value to arrive at the calculated molecular weight, as described in EX2013, 6-7 (describing hydrogen as a positively-charged adduct with mass 1). A POSA would have readily been able to perform this routine calculation, as well, as this technique is routinely taught to undergraduate chemistry students. The compounds that did

⁴ I note that $[M+1]^+$ values are obtained through mass spectrometry (MS), a routine method of chemical compound characterization. A POSA would have known that the $[M+1]^+$ values reported in Pomper correspond to the molecular weight of the given compound (M) , plus the mass of one hydrogen atom (+1). EX2013, 6-7. These concepts are taught in basic undergraduate chemistry courses.

not report $[M+1]^+$ values were omitted.

Table 2: Tabulated molecular weights for Pomper compounds that had $[M+1]^+$ values reported.

Example Number	Compound	Reported $[M+1]^+$ weight (g/mol)	Calculated molecular weight (g/mol)
1	SR-V-32	742.77	741.77
2	SR-V-27	1080.55	1049.55
2	SR-V-31	1146	1145
2	SR-V-100	1284.64	1283.64
2	^{69/71} Ga-SR-V-100	1372.52	1371.52
4	SR-VI-34	1328	1327
5	YC-27	1587.6	1586.6
5	YC-VIII-11	1288.9	1287.9
5	YC-VIII-12	1448.4	1447.4
5	YC-VIII-28	1427.6	1426.6
5	YC-VIII-30	1132.5	1131.5
5	YC-VIII-31	992.4	991.4
5	YC-VIII-52	643.3	642.3
5	YC-VIII-74	927.5	926.5
5	YC-VIII-63	1061.4	1060.4
5	YC-IX-92	1143.5	1142.5
6	YC-VIII-36	993.4	992.4

62. As Table 2 shows, this selection of compounds disclosed by Pomper have a range of 642.3 to 1586.6 g/mol. These compounds are explicitly described as “low molecular weight” compounds, both in Pomper itself and by Dr. Martin, when describing Pomper. EX1002, ¶125; EX1006, ¶12. Pomper’s exemplified range is consistent with the plain and ordinary meaning of the term “low molecular weight” as compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons.

63. The plain and ordinary meaning is consistent with the definition offered by the inventor, Dr. Pomper, during prosecution of the ’201 patent. Specifically, Dr. Martin 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.” EX1004, 1215. Thus, based on the prosecution history as well as the specification of the ’201 patent, the ’201 patent shows “low molecular weight” is used according to its plain and ordinary meaning of compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons.

64. Dr. Martin’s indefiniteness analysis is premised on his argument that the “low molecular weight” limitation lacks “reasonable certainty” and that a POSA would not have been “reasonably certain as to the scope of the invention.”

EX1002, ¶¶180, 187. Dr. Martin's analysis of the term "low molecular weight" is flawed. As discussed above, a POSA would have understood, with reasonable certainty, the metes and bounds of the term "low molecular weight" as described in the '201 patent claims, consistent with the prosecution history of the '201 patent. Specifically, a POSA would have understood that the plain and ordinary meaning of the term "low molecular weight" compounds refers to compounds with a "molecular weight of typically from about 50 Daltons to about 1,500 Daltons." EX1004, 1215. And as described in the specification, these "low molecular weight" compounds are contrasted with "antibodies," which "suffer[] from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake." EX1001, 1:56-62. The specification also contrasts low molecular weight compounds from "polymers" which are described as "molecule[s] of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer." EX1001, 48:18-21.

65. Indeed, Dr. Martin's own declaration also contrasts the "low molecular weight" compounds described in the '201 patent, which have molecular weights of typically from about 50 Daltons to about 1,500 Daltons, with polymers, which he describes as a class of compounds having a wide range of molecular

weights. *See, e.g.*, EX1020 (discussing common polymers with molecular weights ranging **from 8,000 Da to 400,000**). Similarly, Dr. Martin describes antibodies in the following way: “[T]he two major classes of antibody molecules have molecular weights of 150,000 and 900,000 Daltons, respectively.” EX1002, ¶182. Both of the ranges that Dr. Martin cites for polymers and antibodies are well above the molecular weight of typically from about 50 Daltons to about 1,500 Daltons for the “low molecular weight” compounds claimed in the ’201 patent, and a POSA would have recognized the same.

66. In light of this disclosure, a POSA would have understood the meaning of the term “low molecular weight” as referring to compounds with a molecular weight of typically from about 50 Daltons to about 1,500 Daltons, even under Dr. Martin’s wrong POSA definition. It then follows that Dr. Martin fails to show that the ’201 patent claims are indefinite, as a POSA would readily have been able to understand the bounds of the claimed invention as compounds of the formula B-L-A from about 50 to about 1,500 Daltons, and that a compound with higher molecular weight than about 1,500 Daltons would fall outside the scope of the claims. In addition, given the high precision of analytical techniques that a POSA under either Dr. Martin’s or my definition would have known how to use, such as mass spectrometry, EX2013, 5-8, a POSA would have had no trouble determining the molecular weight of a given B-L-A compound to see if it falls

under the typical about 50 to about 1,500 Da scope of “low molecular weight.”

VIII. CLAIMS 1-3 OF THE '201 PATENT WOULD NOT HAVE BEEN OBVIOUS IN VIEW OF JANSEN I AND/OR JANSEN II, TAKEN IN VIEW OF ZIMMERMAN AND POMPER, OR DVOŘÁKOVÁ, TAKEN IN VIEW OF POMPER.

A. FAP Background And State Of The Art Before October 23, 2017

67. Fibroblast-activation protein- α (FAP), also referred to as seprase or FAP- α , is a transmembrane serine protease expressed almost exclusively in pathological conditions, such as cancerous tumors, and is often used as a marker for pro-tumorigenic stroma. EX2013, 3-4. FAP is expressed on the stroma (the supportive framework of an organ or tissue) of cells and is typically undetectable or low in healthy cell tissues, but overexpressed in cancer cells, where it has been detected in over 90% of cancer stroma examined. EX2013, 4; EX1010, 1.

68. FAP is a member of the prolyl peptidase family that includes prolyl oligopeptidase (PREP) and dipeptidyl peptidases (DPP) DPP^{IV}, DPP^{II}, and DPP^{IX}. EX2012, 3; EX1008, 1-2. FAP shares structural homology with all members of the prolyl peptidase family, with the closest protease to FAP being DPP^{IV}, which shares 52% amino acid sequence identity with FAP. EX1008, 2; EX1007, 1:42-51; EX1010, 491. This structural similarity between FAP and PREP and the DPPs makes the PREP and the DPPs proteases a common off-target for FAP-targeting moieties, with many FAP-targeting compounds “in general also display[ing] significant affinity for one or several DPPs.” EX1010, 1-2; EX1008, 2; EX1007,

1:42-51.

69. FAP inhibitors (FAPis) and FAP antibodies are classes of molecules that target FAP, either for diagnostic or therapeutic applications. EX1010, 1-2.

Before October 2017, a variety of potential FAPi-targeting small-molecule agents had been discovered, including pyrrolidine-3-carbonitrile-based and pyrrolidin-3-yl-boronic acid-based moieties, sometimes also featuring naphthyl, quinolinyl, or pyridyl aryl groups conjugated to the heterocycle. EX1007, Abstract, Table 4; EX1010, Abstract, Tables 2-3; EX1009, Abstract, Examples 1-12.

70. In evaluating a FAP-targeting imaging or therapeutic agents using FAPis, *affinity* for FAP is an important property. Affinity for a given binding site measures how tightly a given target binds to the target protein/enzyme, and is measured using the term *half-maximal inhibitory concentration*, or IC_{50} . EX1009, ¶185. Lower IC_{50} numbers signify better binding to the target and signify a more potent targeting moiety. EX1009, ¶185; EX1008, 2.

71. Given the similarities in structure between FAP and related family members such as DPP^{IV} and PREP, another important consideration for targeted imaging and therapeutic compound design is the selectivity that a given compound displays for FAP, as “[t]he non-specific binding of FAP, due to sharing peptide substrate with other postpropyl peptidase, is the limitation for the fabrication of FAP targeted imaging probe for in vivo studies.” EX2011, 11. Selectivity for FAP

is calculated by first measuring the IC₅₀ of a compound for the desired target, FAP, and for undesirable targets, such as PREP or DPP^{IV}. The ratio of these IC₅₀ values (binding affinity) is referred to as the selectivity index (SI) of the compound for FAP. EX1007, Table 3, 78:5-31. 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. EX2011, 11; EX1010, 1-2; EX1008, 2; EX1007, 1:42-51. FAP-targeting agents with higher affinity and selectivity properties generally exhibit better performance. EX2011, 11; EX1010, 1-2; EX1008, 2; EX1007, 1:42-51.

B. Dr. Martin Does Not Explain How Or Why A POSA Would Have Selected Particular Compounds Or How A POSA Would Have Modified The Selected Compounds

72. I have been informed that, in evaluating obviousness of chemical compounds, it is often helpful to use an analysis referred to as “lead compound” analysis. I understand that this analysis involves identifying a compound(s) most promising to modify (i.e., “the lead compound(s)”), and then determining whether the prior art would have provided a POSA with a reason to modify the lead compound(s) to make the claimed compound, with a reasonable expectation of success. As discussed below, Zimmerman, Jansen I, and Jansen II disclose a panoply of possible FAPi compounds that could be used as a starting point (based on their affinity and selectivity) to be modified. Dr. Martin does not mention or

address most of the disclosed compounds. Nor does Dr. Martin explain **how** or **why** a POSA would have selected a particular compound or compounds for further modification.

1. Dr. Martin Did Not Explain How A POSA Would Have Selected “A” From Jansen I/Jansen II To Arrive At The Claimed Invention.

73. Dr. Martin does not dispute that a POSA reading Jansen I and Jansen II would have been faced with the panoply of 4-quinoline-based FAPis (corresponding to the claimed “A” moiety). EX1007, Table 3; EX1010, Table 3; EX1002, ¶¶55-56, 63-65. Indeed, Jansen I describes twenty eight (28) 4-quinolinyl compounds, and Jansen II—sixteen (16) additional 4-quinolinyl compounds (for a total of $28 + 16 = 44$ 4-quinolinyl “A” compounds). EX1007, Table 3; EX1010, Table 3. Jansen I and Jansen II also report affinity (IC_{50}) and selectivity (FAP/PREP) values for the 44 compounds, and those values vary **dramatically** among the compounds.

74. Jansen II’s 4-quinolinyl compounds show an IC_{50} variation of over three orders of magnitude, from compound 31 ($IC_{50} = 0.0071 \mu M$) to compound 20 ($IC_{50} = 5.9 \mu M$) to compound 22 ($IC_{50} > 10 \mu M$). EX1010, Table 3. The FAP/PREP selectivity of the compounds disclosed in Jansen II is calculated in

Table 3 below.⁵ The coloring scheme in the table below is: for affinity, in order of worse-performing to better-performing: $>1\ \mu\text{M}$, red; between 1 and $0.1\ \mu\text{M}$, orange; between 0.1 and 0.01, green; <0.01 , blue. For selectivity, in order of worse-performing to better performing: <10 , red; between 10 and 100, orange; between 100 and 1000, green; >1000 , blue.

⁵ Here, I use the same method for calculating FAP/PREP affinity for the compounds of Jansen II as in Jansen I, which is simply dividing the PREP IC_{50} by the FAP IC_{50} . EX1007, 5:35-55; EX1004, 1199-1205 (Pomper Declaration). A POSA would have known how to perform such calculations because the FAP/PREP ratio is a key measurement of affinity for the compounds of both Jansen I and Jansen II. EX1007, 5:35-55. My calculations are included in Appendix A.

Table 3: Tabulated FAP affinity and FAP/PREP selectivity for the Jansen II quinolinyl A moieties.

Compound #	FAP affinity (μM)	FAP/PREP Selectivity
7	0.0103	83
19	0.670	1.0
20	5.900	9.1
21	$1 < \text{IC}_{50} < 10$	$0.4 < \text{SI} < 0.04$
22	> 10	< 0.1
23	0.770	24
24	0.160	240
25	0.010	1700
26	0.011	> 4500
27	0.014	60.
28	0.012	51
29	0.010	60.
30	0.009	660
31	0.007	190
32	0.006	190
33	0.190	1.8
34	0.370	1.0

75. The quinolinyl compounds of Jansen I display this disparate performance as well. Table 4 below shows the reported FAP affinity and

FAP/PREP selectivity for these compounds, with green colors showing more desirable values, and red values indicating less desirable values, and found a similarly disparate set of results for the quinolinyl compounds.

Table 4: Tabulated FAP affinity and FAP/PREP selectivity for the Jansen I quinolinyl A moieties.

Compound #	FAP affinity (μM)	FAP/PREP Selectivity
1	0.0032	562
2	0.0103	83
3	0.67	1
5	5.9	9
6	0.0103	59
7	0.014	60
8	0.12	59
9	0.19	1.8
10	0.37	1
11	0.0092	677
12	0.0062	193
13	0.0071	197
21	0.0099	1700
22	0.011	>4500
23	0.0043	2100
24	0.0085	970

Compound #	FAP affinity (μM)	FAP/PREP Selectivity
25	0.070	280
25 ⁶	0.059	34
26	0.064	135
27	0.0069	72
31	6	>16
32	3.4	1.7
33	0.028	120
38	0.16	230

76. Dr. Martin did not explain how a POSA would have selected a particular compound or compounds (the claimed “A” moiety) for developing an imaging or radiotherapeutic agent from the variety of Jansen II or Jansen I compounds. As I explained in paragraphs 70-71, a POSA would have understood that affinity and selectivity are important metrics for evaluating the performance of FAP targeting compounds: compounds with low selectivity may have potential off-target side effects, and compounds with low affinity may lack potency for FAP-targeting, whereas compounds with high affinity and selectivity generally exhibit

⁶ Jansen I assigns the same compound number – 25 – to two different compounds.

better performance. EX2011, 11; EX1010, 1-2; EX1008, 2; EX1007, 1:42-51.

Thus, when selecting FAP-targeting compounds for further development, a POSA would have evaluated at least whether any particular compounds exhibited a beneficial combination of FAP affinity and selectivity. EX2011, 11; EX1010, 1-2; EX1008, 2; EX1007, 1:42-51. However, Dr. Martin did not explain that a POSA would have even evaluated the FAP affinity and selectivity data reported in Jansen I and Jansen II when selecting compounds for further modification, let alone whether or how a POSA would have used the affinity and/or selectivity values reported in the references to select a suitable “A” moiety to arrive at the claimed invention.

77. Compounding Dr. Martin’s failure to explain which of these compounds a POSA would have selected, the FAP/PREP selectivity of Jansen I’s and Jansen II’s compounds is broad, spanning indices of 4545 (Jansen II compound 26) to compounds that are actually more selective for PREP compared to FAP (Jansen II compound 22). Further, high FAP affinity compounds do not always correspond to high selectivity compounds. For example, Jansen II compound 30 displays high affinity (0.009 μ M), but only a middling selectivity index (660). Conversely, compounds with high selectivity do not always display high FAP affinity, such as Jansen II compound 24, which displayed triple the specificity compared to the unsubstituted compound 7 (specificity indices of 24

versus 83, respectively), but performed an order of magnitude worse in terms of affinity (affinities of 0.160 μM versus 0.0103 μM , respectively). EX1010, Table 3. Dr. Martin fails to explain how a POSA would have navigated these competing, and sometimes contradictory, performance metrics in selecting a compound for modification.

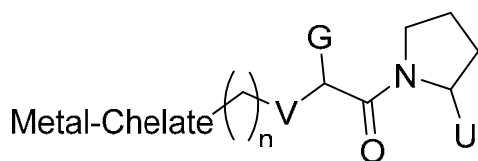
78. Dr. Martin fails to explain how or why a POSA (under any POSA definition) would have selected a FAPi or FAPis from the multitude of choices presented by Jansen I and Jansen II. And although many of these choices in Jansen I and II exhibited an inconsistent combination of FAP affinity and selectivity (with some having high affinity but relatively lower selectivity, and vice versa), Dr. Martin does not explain whether affinity or selectivity would be more important, or how these metrics would need to be judged in light of one another, for the selection of an appropriate “A” group to combine with a suitable linker and “B” moiety. Thus, Dr. Martin fails to explain why or how a POSA would have known to select a suitable “A” group from the numerous choices presented by Jansen I and Jansen II to arrive at the claimed invention.

2. Dr. Martin did not explain how a POSA would have selected “B” and “L” from Zimmerman to arrive at the claimed invention.

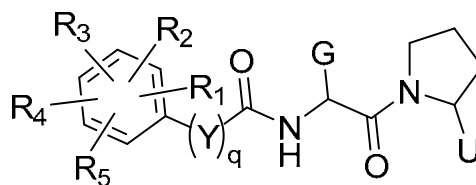
79. Following Dr. Martin’s logic in Ground I, in addition to selecting FAPi(s) (“A”) from the many choices of Jansen I/Jansen II, a POSA would have

had to select which Zimmerman's linker(s) ("L") and optical group(s) ("B") to use to prepare the claimed compounds ("B-L-A"). Dr. Martin, once again, does not explain how a POSA would have made such a choice for each L and B. But the choices would have been numerous, as I explain below.

80. Zimmerman discloses thirty-four (34) compounds having two general structures:

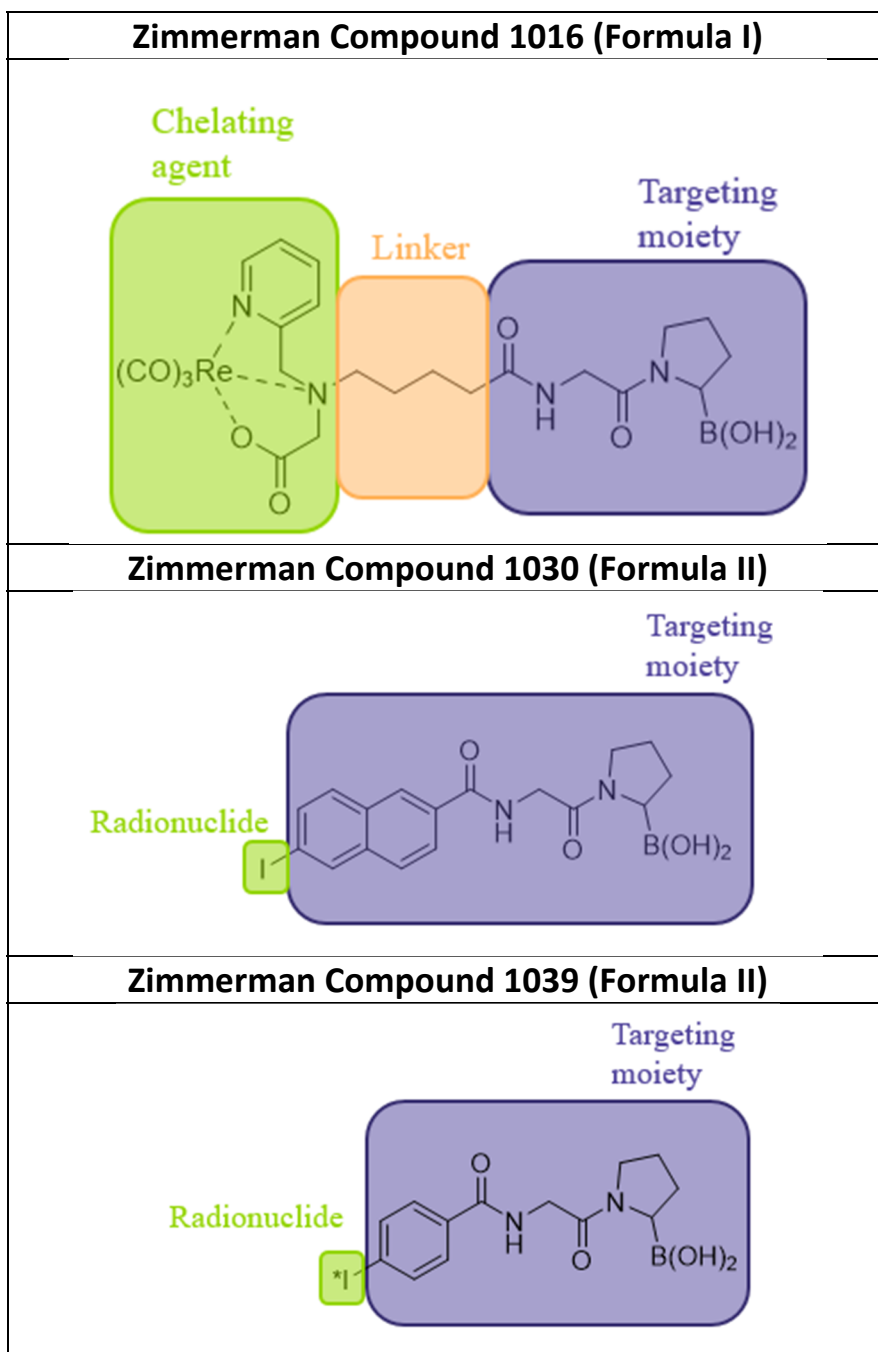


Formula I
EX1009, Abstract.



Formula II
EX1009, Abstract.

81. Zimmerman's compounds of Formula I and Formula II belong to two different structural classes. The table below illustrates structural difference between the two classes.



82. The compounds of Formula I and Formula II also differ in the potential radionuclides that each compound can incorporate. Each of the compounds of Formula I contain metal-chelates, linked to the FAPi via a linker

allowing for the incorporation of metal ions to the compound. Conversely, the Formula II compounds allow for imaging or therapy through use of radionuclides, particularly radiohalogens, which are covalently bonded to the compound without such a linker. EX1009, ¶¶8-28. The IC₅₀ values of compounds of Formula I and Formula II are reproduced below in Zimmerman Table 2, are annotated to show which compounds are of which Formula.

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

Formula I

Formula II

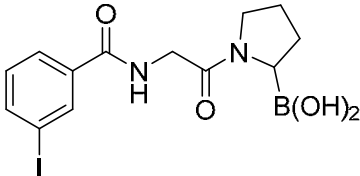
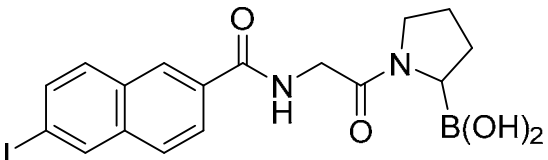
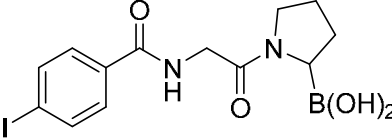
Formula I

Formula II

EX1009, Table 2, p. 34 (annotated).

83. A POSA would have recognized that the best-performing compounds in Zimmerman are those of Formula II. This is because the best affinity, an IC₅₀ of 2 nM, was displayed by compounds 1025 and 1030 (compounds of Formula II). EX1009, Table 2, p. 34 (annotated). Moreover, ten (10) of the top eleven (11) highest affinities are displayed by the compounds of Formula II, rather than Formula I. EX1009, Table 2, p. 34. Table 5 below summarizes the top eleven highest-affinity compounds in Zimmerman (a POSA would have easily performed this analysis as well by simply reviewing the data in Zimmerman):⁷

Table 5: Tabulated highest affinity compounds of Zimmerman.

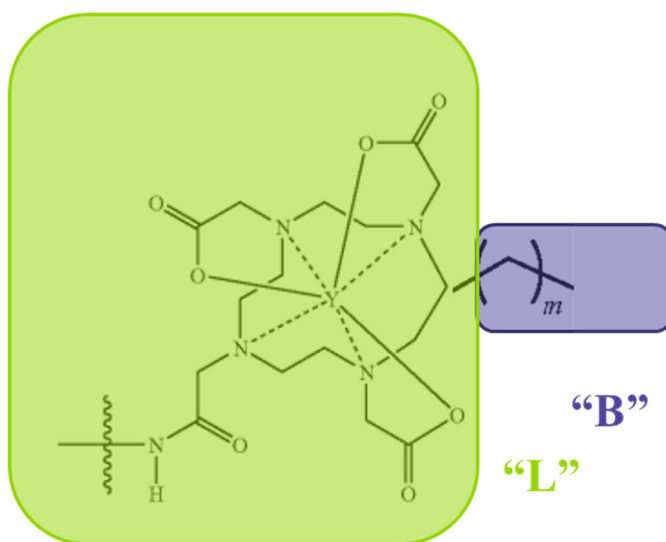
Zimmerman Compound No.	IC ₅₀ (nM)	Formula	Structure
1025	2	II	
1030	2	II	
1024	3	II	

⁷ This top 11 ranking provides a representative number of the best-performing compounds.

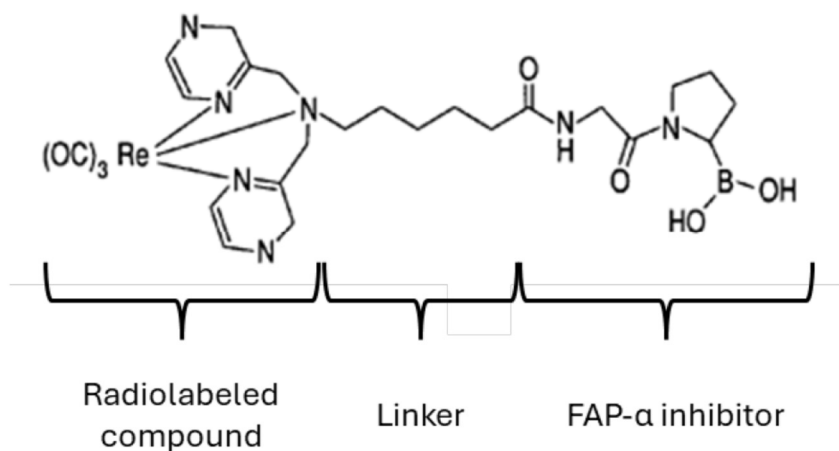
Zimmerman Compound No.	IC ₅₀ (nM)	Formula	Structure
1026	3	II	
1020	4	I	
1027	5	II	
1028	5	II	
1023	7	II	
1029	8	II	
1032	11	II	
1034	11	II	

84. Despite an undisputable superiority of the compounds of **Formula II**

in Zimmerman, Dr. Martin testified (without any explanation as to why) that a POSA (under any POSA definition) would have somehow selected a compound of **Formula I** for further development, and does not even mention or reference the compounds of Formula II in obviousness Ground I. EX1002, ¶119. From the above, a POSA would have recognized that, overwhelmingly, the compounds of Formula II are superior to the compounds of Formula I. Zimmerman itself highlighted compounds with “IC₅₀ values in the low nanomolar range, e.g. 1024, 1040, and 1030,” all of which are compounds of Formula II. EX1009, ¶185. Notably, it was Zimmerman’s compound 1024 that was selected for further clinical testing by Meletta (2015). However, in discussing Zimmerman, Dr. Martin points to the linkers (“L” in the challenged claims) and the metal-chelate moieties (“B” in the challenged claims) having the following structure (EX1002, ¶¶120-121):



85. Both of those structures are found in the compounds of Formula I.
EX1009, ¶87. Crucially, neither of them is present in the compounds of Formula II.
EX1009, ¶111. Dr. Martin, again, without any explanation as to why, focuses on one specific compound of Formula I in Zimmerman (EX1002, ¶124):



86. In sum, Dr. Martin offers no explanation as to why a POSA would have focused on Zimmerman’s compounds of Formula I in selecting “L” and “B” to combine with the many compounds of Jansen I/Jansen II.

C. Claims 1-3 of the '201 Patent Would Not Have Been Obvious in View of Jansen I and/or Jansen II, Taken in View of Zimmerman and Pomper (Ground I).

1. Dr. Martin Fails to Explain how a POSA would have Combined Zimmerman, Jansen I and/or Jansen II, and Pomper to Arrive at the Claimed Invention

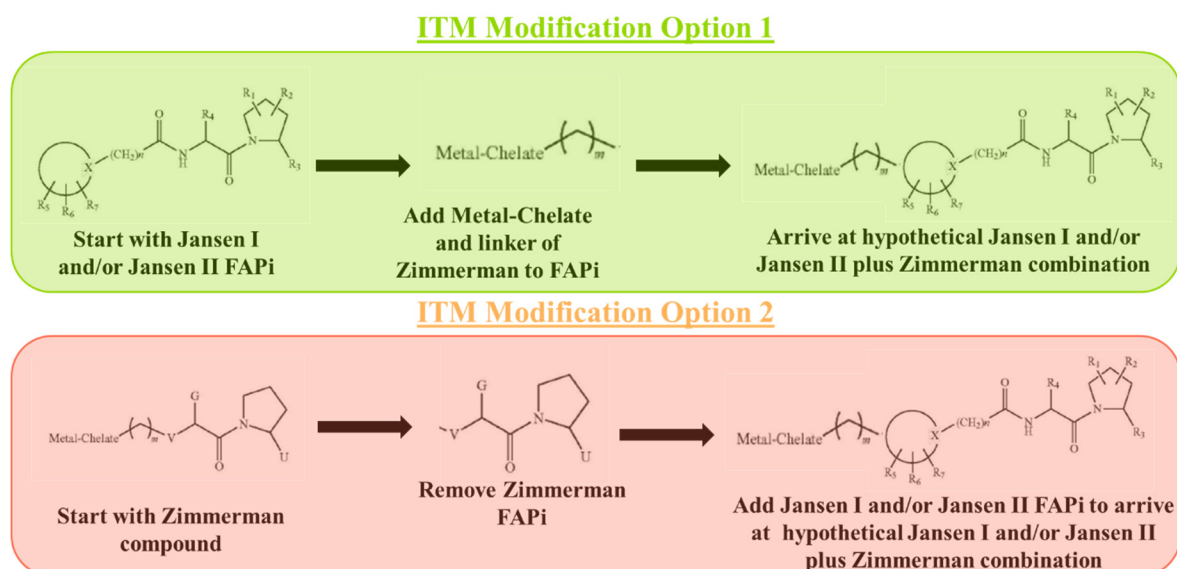
87. Dr. Martin argues that Jansen I and II disclose quinolinyl “A” FAPis but are missing the “B” and “L” moieties, which are disclosed in Zimmerman and

Pomper. EX1002, ¶¶115-117. He also states that “A POSA at the time of filing the ’201 patent application would have been motivated to prepare the FAP- α inhibitor described in Jansen I and/or Jansen II. A POSA also would have been motivated to attach the FAP- α inhibitor of Jansen I and/or Jansen II to a radiolabeled compound via a linker for diagnostic imaging based on Zimmerman and Pomper,” EX1002, ¶127, as shown in Option 1 in the graphic below. But, contradicting himself, Dr. Martin further argues that Zimmerman teaches “the components B and L” and that “a POSA would be motivated to **swap** the proline-based FAP inhibitor of Zimmerman with the higher performing quinoline-modified FAP inhibitors or Jansen I and/or Jansen II[,]” as shown in Option 2 in the graphic below. EX1002, ¶¶124, 128 (emphasis added). Upon reviewing Dr. Martin’s testimony, Dr. Martin does not explain whether a POSA would have started with Jansen I and/or Jansen II, and then add the “L” and “B” groups disclosed in Zimmerman, or if a POSA would have started with the A-L-B compounds of Zimmerman, and then modify the A group to be one of Jansen I and/or Jansen II.

88. But to follow those paths, a POSA would have had to have different reasons. Starting from Jansen I/Jansen II and modifying it with Zimmerman’s linker and optical moiety would be based on POSA’s wanting to turn a FAPi into an imaging or therapeutic agent. But starting from Zimmerman’s optical agents and modifying it with Jansen I/Jansen II’s FAPi would be based on POSA’s

wanting to improve upon Zimmerman's optical agent by using a more selective FAPi.

89. The graphic below shows the difference between these two paths. From the image below, it is clear that there are two potential combinations that Dr. Martin suggests making, and that he does not sufficiently explain which of these options a POSA would have taken – or indeed, which of these options that he proposes.



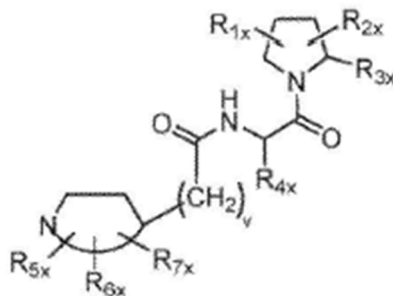
2. Dr. Martin Fails To Show That A POSA Would Have Had A Reason To Modify The Jansen I And/Or Jansen II FAPis To Arrive At The Claimed Invention.

90. In his obviousness argument for Ground I, Dr. Martin fails to explain why a POSA, under any POSA definition, would have been motivated to modify any of Jansen I/Jansen II compounds to remove the beneficial substituents on the

quinolinyl ring. Indeed, it is more likely that removing such substitutions would actually destroy the selectivity of the FAPi for FAP over PREP. Dr. Martin does not explain why a POSA would have selected the unsubstituted quinolinyl groups – compound 7 in Jansen II and compounds 1 and 2 in Jansen I – in the face of higher-affinity and selectivity compounds with substitutions. As discussed above in Section VII.B.1, the FAPis presented by Jansen I and Jansen II display a broad range of affinities and selectivities, which would make it difficult for a POSA to select a FAPi to modify. And as discussed in Jansen II, the broad ranges of FAPi performance are due to the varying quinolinyl substitutions: “we have shown that introduction of substituents at the 5-position of the quinolinoyl ring system is a possible means of maximizing inhibitor selectivity with respect to PREP.”

EX1010, 4. Specifically, Jansen II showed that “[m]ost remarkably, the selectivity with respect to PREP of these inhibitors sharply increases ($SI_{[FAP/PREP]} > 1000$)” when “a chlorine or bromine substituent [is introduced] at the 5-position of the quinoline ring such as in analogues 25 and 26.” EX1010, 3.

91. I note that the quinolinyl part of the claimed “A” moiety is unsubstituted, other than by “L.” Claim 1 recites that “A is a targeting moiety for FAP- α , wherein A has the structure of:



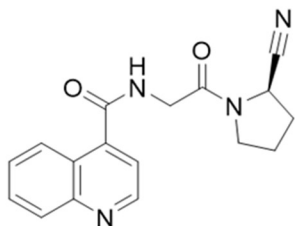
wherein ... R_{5x} , R_{6x} and R_{7x} are each H; [and]



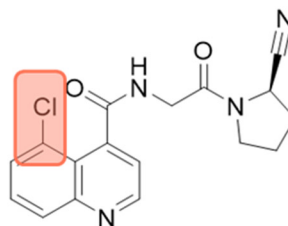
represents a quinolinyl ring[.]” EX1001, pp. 46, 47. Because each of R_{5x} , R_{6x} and R_{7x} are defined to be H, the quinolinyl ring is unsubstituted, other than the linker moiety.

92. In light of the clearly superior data for substituted FAPis presented by Jansen I and Jansen II, a POSA would have selected a substituted FAPi, rather than a naked quinolinyl group, to modify. However, Dr. Martin does not explain why a POSA would have selected the unsubstituted quinolinyl groups – compound 7 in Jansen II and compounds 1 and 2 in Jansen I – in the face of higher-affinity and selectivity compounds with substitutions, to arrive at the claimed invention. For example, Jansen II compound 25 shows comparable or better FAP affinity and two orders of magnitude higher affinity compared to Jansen II compound 7, as shown below. And Jansen I compound 23 shows comparable or better FAP affinity to Jansen I compound 3, while displaying drastically improved selectivity ($SI_{[FAP/PREP]}$)

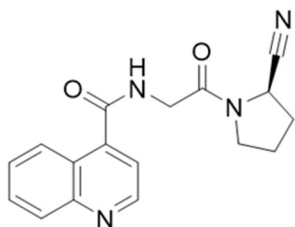
of 2100 for compound 23 versus 83 for compound 3, respectively), as shown below.



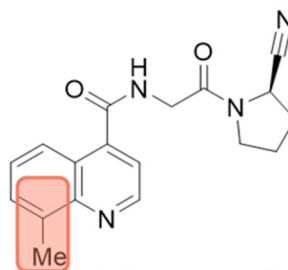
Jansen II Compound 7
FAP IC₅₀ = 0.0103 μM
SI_[FAP/PREP] = 83



Jansen II Compound 25
FAP IC₅₀ = 0.010 μM
SI_[FAP/PREP] = 1700

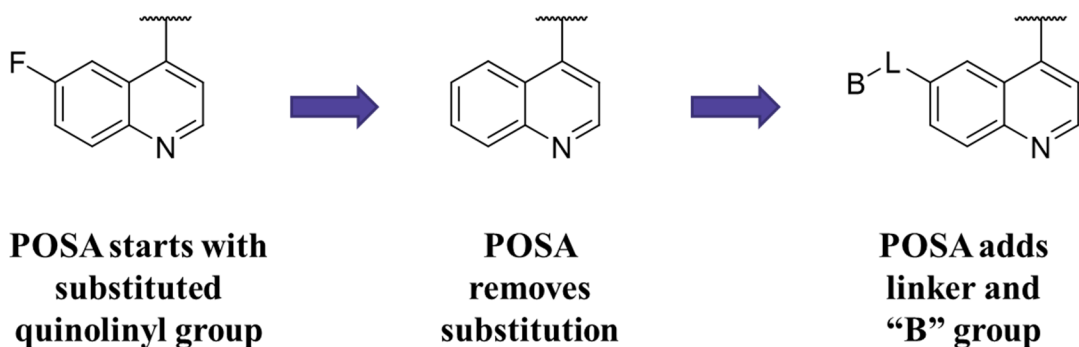


Jansen I Compound 2
FAP IC₅₀ = 0.0103 μM
SI_[FAP/PREP] = 83

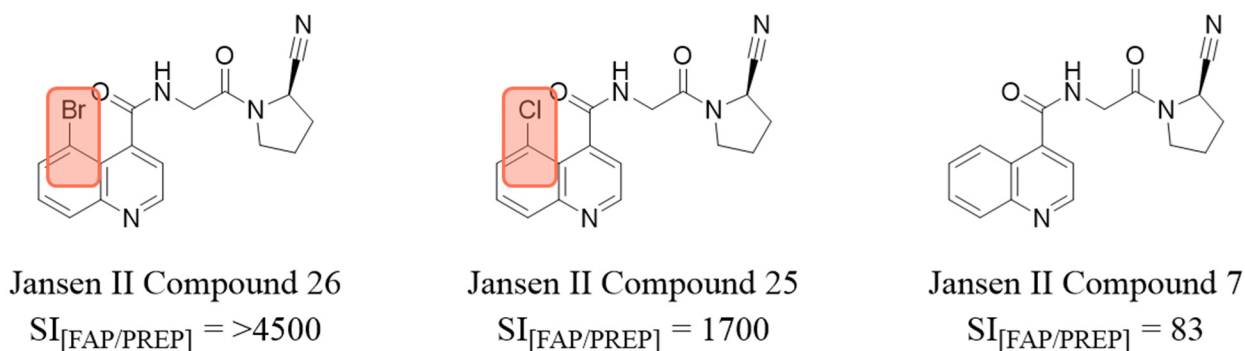


Jansen I Compound 23
FAP IC₅₀ = 0.0043 μM
SI_[FAP/PREP] = 2100

93. Furthermore, if a POSA would have selected one of the better performing compounds from Jansen I/Jansen II, such as compounds 22 or 23 from Jansen I, or compound 25 from Jansen II, to arrive at the claimed invention, the POSA would have then had to **remove** the substituent first, before adding the linker and “B” moiety. The graphic below shows this hypothetical modification.



94. But Jansen II explicitly states that “selectivity with respect to PREP of these inhibitors **sharply increases**” when substituted with Br or Cl in the 5-position. EX1010, 3. Indeed, as seen below, even just modifying the substituent from Br- to Cl- at the same position (Jansen II compounds 26 and 25, respectively) reduces selectivity from >4500 to 1700. EX1010, Table 3. Removing the substituent completely from this position (Jansen II compound 7) **destroys selectivity**, with a $SI_{[FAP/PREP]}$ of 83 for Compound 7. EX1010, Table 3.



95. As discussed above, Dr. Martin fails to explain why a POSA, even under Dr. Martin’s incorrect POSA lens, would have been motivated to modify any of Jansen I/Jansen II compounds to remove the beneficial substituents on the quinolinyl ring. Indeed, it is more likely that removing such substitutions would

actually destroy the selectivity of the FAPi for FAP over PREP.

3. Dr. Martin Fails to Show that a POSA Would Have Had a Reasonable Expectation of Success in Combining Jansen I and/or Jansen II, Zimmerman, and Pomper.

96. The only reason Dr. Martin offers for why a POSA would have had a reasonable expectation of success in arriving at the claimed invention is because “Jansen II clearly teaches that the quinoline-modified FAP inhibitors have improved performance over the proline-based FAP inhibitors.” EX1002, ¶128. But Dr. Martin fails to explain why a POSA would have reasonably expected that combining the different FAPis, radiolabeled groups, and linkers disclosed in Jansen I, Jansen II, Zimmerman, and Pomper could even have been done without the guidance in the patent, or would have resulted in the claimed compounds.

97. For example, Dr. Martin does not explain why a POSA would have had a reasonable expectation that the claimed compounds could even be synthesized at all. Dr. Martin does not explain what synthetic steps a POSA would have taken, and under which conditions, to modify Jansen I/Jansen II’s compounds with the linker and optical moiety of Zimmerman. Nor does Dr. Martin explain why a POSA would have “a reasonable expectation that such compounds would work for their desired purpose” except with a conclusory statement that the “prior art [taught] that the use of radiolabeled compounds presented advantages in diagnostic imaging and therapeutic treatment of diseases, and the teachings of the

prior art that quinoline-modified FAP inhibitors have improved performance.

EX1002, ¶114. But, as discussed above, the most specific quinoline-modified FAPis of Jansen I and/or Jansen II were substituted quinolinyl moieties, which are not included in the claimed invention. And the best-performing compounds for radiotherapy or imaging in Zimmerman did not employ linkers, meaning that they also did not fall within the scope of the claimed invention. Thus, even if a POSA would have put these compounds together to arrive at the claimed invention, a POSA would not have reasonably expected the compounds to perform well for their intended purpose, given the teachings of the prior art that such compounds did not perform well in terms of selectivity and affinity.

D. Claims 1-3 of the '201 Patent Would Not Have Been Obvious in View of Dvořáková and Pomper.

1. Dr. Martin Fails to Show a POSA Would Have Been Motivated to Modify Dvořáková with Pomper to Create a Low Molecular Weight Compound.

98. Dr. Martin argues that a POSA would have been motivated to create a “low molecular weight” version of Dvořáková’s compound, iBody, “by, for example, reducing the number of FAP-targeting and ATTO488 groups, using a linker with a lower molecular weight, and eliminating the biotin groups.” EX1002, ¶¶139-140. But a POSA would not have been motivated to remove the multiple dye units, targeting units, and affinity anchors that Dvořáková employs because Dvořáková teaches that those multiple repeating units confer beneficial properties

b)

iBody 1
($M_n = 110,600$)

Chemical structure of iBody 1 ($M_n = 110,600$) is shown, featuring a central core and multiple arms. The structure is labeled with its molecular weight ($M_n = 110,600$). The arms are functionalized with various groups, including a central core, a methyl group, a hydroxyl group, and a central carbon atom. The arms are labeled with their respective units: ~4 ATTO488 units, ~18 biotin units, and ~13 inhibitor units.

100. These numbers are approximations because, polymeric compounds, as opposed to low molecular weight compounds, are heterogeneous, with variable structures. The values of four dye units and thirteen FAPi units are average numbers, determined in bulk by measuring the total amount of each unit using a fluoride selective electrode (for the inhibitor units), or spectrophotometry (for ATTO488 and biotin). These bulk measurements were then “converted into a number of units per iBody” using the known molecular weights of the individual components and the polymer to arrive at average units per iBody, with an average molecular weight of 110,600 Da. EX1008, 7, EX2007, S9-S10. This large molecular weight is over two orders of magnitude higher than the low molecular weight compounds disclosed in Zimmerman, Jansen I and II, and Pomper, as well as the compounds in the claimed invention. To arrive at the claimed invention, a POSA would have had to remove the polymeric HMPA backbone, and remove on average 3 FAPi inhibitor units, 18 biotin units, and on average 3 ATTO units from iBody, to arrive at the claimed “low molecular weight” compound. But there is no indication in Dvořáková, nor would a POSA (under any POSA definition) have reasonably expected, that Dvořáková’s compound would maintain its imaging functionality when using a single FAP-targeting unit. Indeed, data in Dvořáková suggest that a compound with a single FAPi unit (compound 1) has reduced selectivity compared to a compound with 13 FAPi units (iBody), with respective

selectivities of 765 and >4500. EX1008, FIG. 2c.

101. Additional cited art also supports the usefulness of multimeric imaging agents prior to October 2017. For example, Carlucci reported that: “[m]ultimerization of peptide-based ligands may **improve the binding characteristics** by increasing local ligand concentration and by improving dissociation kinetics,” and Tweedle teaches that “[b]iological activity was evident in the heterodimers **where none or very little** existed in homodimers, monomers or monomer mixtures[.]” EX2010, 1; EX2009, 1. Similarly, Tassa states that “The **multivalent conjugation** of targeting ligands on the surface of nanoparticles is **presumed to enhance binding** to the desired target... We report that even weak small molecule targeting ligands can **significantly enhance** target-specific avidity (by up to 4 orders of magnitude) through multivalent interactions and also observe a much broader range of kinetic effects than has been previously reported[.]” EX1008, 1.

102. All of these teachings describe situations in which compounds with multiple functional moieties were preferred over compounds with just one targeting or imaging/therapeutic agent. Indeed, the low molecular weight compound of Meletta showed poor FAP-targeting, in contrast to the high-molecular weight compounds such as those discussed in Dvořáková, which displayed high selectivity and affinity for FAP. EX2006, 1, 9-10. Thus, a POSA

aware of the literature surrounding targeted imaging or therapy would not be motivated to reduce the number of FAP-targeting groups from approximately 4 to 1.

103. In this same vein, the “affinity anchor” of biotin would be removed completely in the proposed Dvořáková-Pomper combination, removing noncovalent interactions between the target protein and the imaging agent. As described in Šácha, which describes iBodies in more detail, “[s]pecific recognition, immobilization, and imaging of a protein of interest **require** a specific targeting ligand (e.g., an inhibitor), **an affinity anchor**, and an imaging probe attached to the polymer backbone (Figure 1a). As an affinity tag, we chose **biotin** because it can be readily used for high affinity immobilization on a variety of commercially available resins.” EX2005, 1 (emphasis added). Indeed, Šácha specifically teaches that biotin is used “for both visualization and immobilization” of the target protein. EX2005, 4. And Šácha specifically shows that lower numbers of biotins and inhibitor units on the iBody polymer backbone reduces affinity for the target compound, with iBody 1 (19 inhibitor units, 51 biotin units) displaying a K_i ⁸ value

⁸A K_i value, short for inhibition constant, is a measure of how tightly a compound binds to a given protein. Like IC_{50} , it is a measure of a compound’s potency. EX2004, Abstract, 1.

of 0.0043, whereas iBody compounds with fewer such units displayed K_i values at least three orders of magnitude worse: iBody 2 (6 inhibitor moieties, and 7 biotins) showed a K_i of 7.9, and iBody 3 (7 inhibitor units, 9 biotin units) showed a K_i of 18.9. EX2005, Table 1. When Šácha compares iBody to a compound, compound 1, containing just one inhibitor unit, similar destruction in affinity is observed:

“attachment of several molecules of compound 1 to the HPMA copolymer led to a significant drop in the K_i value [$K_i(\text{compound 1})=2.0$ nM vs. $K_i(\text{iBody 1})=4.3$ pM].

This nearly three-order-of-magnitude decrease in K_i can be explained by the synergic effect of **several inhibitor molecules on the polymer scaffold and increased local inhibitor concentration** (19 inhibitor molecules per polymer chain).” EX2005, 2 (emphasis added).

104. Based on the teachings of Dvořáková and Šácha, a POSA would have viewed the effect of removing biotin and FAPis from the HMPA scaffold as detrimental to the desired function of the imaging agent.

105. In addition to the biotin and FAPis, the teachings of Dvořáková tout the benefits of the polymeric backbone, but Dr. Martin argues that a low molecular weight, non-polymeric compound linker would be preferred. A POSA would not have been motivated to modify this key structural polymeric component.

Dvořáková teaches:

“[s]ynthetic HPMa conjugates are well-characterized compounds for biomedical applications and have long been used as carriers for drug delivery to solid tumors, often making use of the enhanced permeability and retention (EPR) effect. Importantly, the molecular weight of the HPMa backbone can be easily adjusted to specifically tailor the pharmacokinetic properties.”

EX1008, 1. A POSA reading Dvořáková would not be motivated to modify the polymeric iBody in line with Pomper’s teachings, as these non-polymeric forms could lose the EPR effect and would not allow for easy adjustment of backbone size. Based on these perceived disadvantages, a POSA, even under Dr. Martin’s incorrect POSA definition, would not have modified the Dvořáková compound in line with the teachings of Pomper. EX1008, 2.

2. Dr. Martin Fails To Show A Reasonable Expectation Of Success In A Dvořáková/Pomper Combination.

106. Dr. Martin’s cursory analysis when addressing the reasonable expectation of success for Ground II fails to take into account the clear teachings of Dvořáková and Šácha, which tout the benefits of both the HMPA backbone and the multiple biotin and inhibitor units. Dr. Martin addresses the reasonable expectation of success for Ground II with just two sentences: “Based on Pomper’s teachings about the benefits of a low molecular weight compound, a POSA would have reasonably expected a low molecular weight version of iBody 1 to work for the desired purpose. Thus, the art would have taught and motivated a POSA to

design and prepare a low molecular weight compound with high affinity and selectivity for FAP that would serve as an imaging or therapeutic agent, and a POSA would have had a reasonable expectation that such compounds would work for their desired purpose.” EX1002, ¶¶140-141. These sentences form the entirety of Dr. Martin’s analysis of a POSA’s reasonable expectation of success in Ground II. In light of these teachings, a POSA (even under Dr. Martin’s incorrect definition) would not have had a reasonable expectation of success in starting with the targeted iBody compound of Dvořáková, and then paring it down by removing key targeting groups.

107. As discussed above, a POSA reading the teachings of Dvořáková and Šácha would have known that the multiple FAP-targeting moieties and biotin units confer increased selectivity compared to compounds with one FAP-targeting group. EX1008, FIG. 2c; EX2005, 2. Similarly, a POSA would have also expected to lose the touted beneficial properties of using a polymeric iBody backbone if swapping it out for a low molecular weight version: the “EPR effect” and “easy adjustment of backbone size.” EX1008, 1. And it was well-known in the art that multimeric compounds could exhibit better selectivity and binding compared to monomeric compounds. EX2010, 1; EX2009, 1; EX2008, 1 EX2005, 2. Taken in sum, a POSA (even under Dr. Martin’s incorrect definition) would not have expected beneficial effects when removing key aspects of the iBody compounds –

namely, the polymeric backbone, multiple FAP units, and multiple biotin units – in pursuit of synthesizing a low molecular weight version of iBody. Dr. Martin fails to address this issue, and in doing so, fails to meet his burden of showing a reasonable expectation of success in this prior art combination.

E. Dr. Martin Ignored Unexpectedly Superior Results Achieved with the Claimed Compounds.

108. During prosecution of the '201 patent, named inventor Dr. Martin Pomper submitted a declaration providing FAP selectivity data for nearly a dozen FAPi compounds covered by the claims of the '201 patent as compared to FAP selectivity data for a number of prior art FAPi compounds, including comparisons to Zimmerman. EX1004, 1195-1206. According to Dr. Pomper, “[s]urprisingly, the specificity of the compounds covered by the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds” in the prior art. EX1004, 1195-1206. In fact, as reported by Dr. Pomper, some of the claimed FAPi compounds had a FAP selectivity *five* orders of magnitude higher than that of the prior art, reference compounds. EX1004, 1195-1206. The “higher specificity of the compounds” was an unexpected and highly beneficial result over the prior art, showing non-obviousness of the claimed invention. EX1004, 1195-1206.

109. Dr. Martin does not dispute that this heightened FAP specificity of the claimed compounds described in Dr. Pomper’s declaration was unexpected and

beneficial. EX1002, ¶¶131-136. For Ground I, Dr. Martin states that “the alleged unexpected results provided by Patent Owner during prosecution are not commensurate in scope with the ’201 patent claims.” EX1002, ¶16. Dr. Martin goes on to say that these results cannot support non-obviousness. EX1002, ¶16. Yet, as discussed below, Dr. Martin’s conclusions regarding the unexpected results are based on an incorrect POSA lens. Dr. Martin also fails to mention, let alone address, that Dr. Pomper’s unexpected results evidence likewise shows non-obviousness of the claims over the prior art in Ground II. EX1002, ¶¶137-157.

110. Dr. Martin states that “given the broad scope of the claims,” there are “thousands, if not millions or more, possible linkers, optical dyes, radiolabeling groups, and combinations thereof encompassed by the broad functional language used in the claims.” EX1002, ¶¶133-134. According to Dr. Martin, “11 examples are not sufficient to represent the full scope of the very broad claims.” EX1002, ¶133. But Dr. Martin does not identify any compound or A, L, or B moiety that would not perform similarly to the 11 disclosed by Dr. Pomper.

111. Further, the ’201 patent specification states that the Jansen I prior art reference describes “A” moieties for use in the claimed invention, and that the Pomper prior art reference describes “suitable linkers” for the L moiety. In addition the ’201 patent specification lists a wide variety of known radiolabeled functional groups for the B moiety. EX1001, 8:25-38, 17:45-54, 17:55-30:67. A POSA would

have readily expected that the known A, B, and L moieties disclosed in the specification and in the prior art would behave similarly to the specific moieties used in Dr. Pomper's tested compounds.

IX. THE '201 PATENT CLAIMS HAVE SUFFICIENT WRITTEN DESCRIPTION.

A. Dr. Martin's Written Description Analysis Wrongly Focuses On A Functional Definition Of The Compounds.

112. Dr. Martin's written description analysis solely depends on whether the '201 patent provides sufficient description for "the broad functional language recited in the claims." EX1002, ¶¶177-178. For example, Dr. Martin states: "[d]espite using this **broad functional language**, the '201 patent provides only two working examples falling within the scope of the claims and does not even describe why or how these two compounds **perform the claimed functions**," and that "[t]he '201 patent also fails to provide any additional guidance permitting a POSA to determine what characteristics are most likely to meet these **functional limitations**." EX1002, ¶178 (emphasis added). But as explained in Section VII.A above, the claims recite low molecular weight compounds that are defined **structurally**, having formula B-L-A. It is only the specific "B" and "L" moieties that must be selected based on their individual functional characteristics—i.e., suitability for imaging/radiotherapy and bifunctionalization adapted to form a chemical bond between A and B, respectively. EX1001, 46-47. Thus, because Dr.

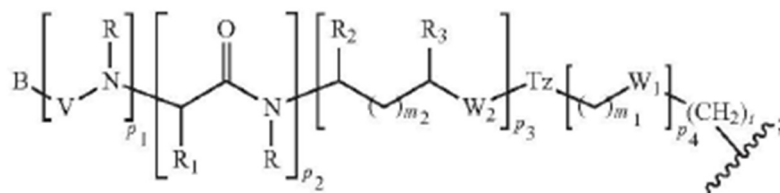
Martin looked for support for the functions that the claimed compounds are not required to perform— suitability for optical imaging **and** bifunctionalization adapted to form a chemical bond with B and A—Dr. Martin’s conclusion that “the claims of the ’201 patent lack written description” is incorrect. EX1002, ¶ 177.

B. Dr. Martin Did Not Show That There Is A Lack Of A Representative Number Of Species Disclosed In The ’201 Patent.

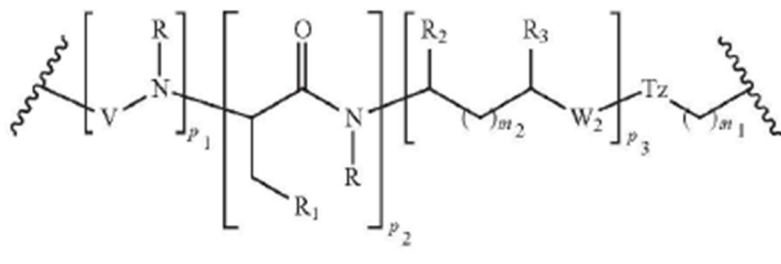
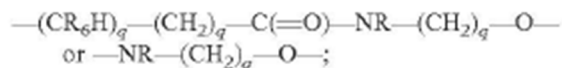
113. Dr. Martin concluded “the ’201 patent fails to provide an adequate written description for claims 1-3” because the “patent provides only two working examples falling within the scope of the claims.” EX1002, ¶¶179-180. Dr. Martin is wrong because, in addition to the working examples, the specification provides an extensive description for the claimed A, B, and L moieties, which are combined into a novel A-L-B combination. EX1001, 18-27. While there is functional language defining the “B” and “L” groups, it is clear from the patent specification that extensive guidance is given as to the structures that perform the recited function for these moieties and thus can be included in the claimed compounds. And Dr. Martin does not dispute that the ’201 patent specification adequately describes the “A” groups that are included in the claimed compounds.

114. For example, the ’201 patent specification devotes two pages to descriptions of suitable linkers, in addition to an example showing an example of “B” and “L” being put together, teaching that suitable linkers include a variety of alkyl-, PEG-, and amide-containing linkers. EX1001, 18-20. Specifically, the ’201

patent specification shows an exemplary combination of L and B represented



structurally: , with each substituent also structurally defined. EX1001, 18. There are also generic linker structures, including the following structures:



. EX1001, 19. And there are 15 specific

exemplary linker structures disclosed with a variety of substituents and substitutions. EX1001, 19-20.

115. Further, the '201 patent specification devotes eight (8) pages to suitable "B" moieties alone. The '201 patent specification teaches that suitable "B" moieties include, *e.g.*, a variety of radioisotopic groups, such as ^{18}F , ^{124}I , ^{125}I , ^{131}I , and ^{211}At -containing groups; various chelating agents, such as DOTA, DOTA derivatives, NOTA, and NOTA derivatives; and optical dyes, such as BODIPY, the VivoTag family, and the AlexaFluor family. EX1001, 20:17, 55-65; 21:20, 9-11;

24:25, 19-25. EX1001, 19-27. Specifically, the '201 patent specification describes four (4) radioisotopes to be used with six (6) generic radiolabeled prosthetic groups, as well as ten (10) specific radioisotope/prosthetic group combinations. EX1001, 20-21. There are also thirty-two (32) examples of chelator “B” moieties (EX1001, 21-24), and 13 optical dyes disclosed. EX1001, 24-27. The patent specification also lists out thirty-eight (38) commercially-available potential dyes for the “B” moiety: “In some embodiments, the fluorescent dye moiety comprises carbocyanine, indocarbocyanine, oxacarbocyanine, thiocarbocyanine and merocyanine, polymethine, coumarine, rhodamine, xanthene, fluorescein, boron-dipyrromethane (BODIPY), Cy5, Cy5.5, Cy7, VivoTag-680, VivoTag-S680, VivoTag-S750, AlexaFluor660, AlexaFluor680, AlexaFluor700, AlexaFluor750, AlexaFluor790, Dy677, Dy676, Dy682, Dy752, Dy780, DyLight547, Dylight647, HiLyte Fluor 647, HiLyte Fluor 680, HiLyte Fluor 750, IRDye S00CW, IRDye S00RS, IRDye 700DX, ADS780WS, ADS830WS, and ADS832WS.” EX1001, 24. This detailed and varied treatment increases the depth of what “B” and “L” moieties a POSA would have considered for inclusion in the claimed compounds.

116. The specification also incorporates by reference a multitude of other references that provide even further examples of such suitable moieties: “Suitable linkers are disclosed in U.S. Patent Application Publication No. US2011/0064657 A1, for ‘Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA),

Biological Evaluation, and Use as Imaging Agents,’ published Mar. 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. US2012/0009121 A1 [Pomper], for ‘PSMA-Targeting Compounds and Uses Thereof,’ published Jan. 12, 2012, to Pomper et al, each of which is incorporated by reference in its entirety.” EX1001, 20. Both of these references list dozens of exemplary compounds, with varied linkers and chelating or radiolabeled groups, adding to the description of “L” and “B” moieties in the specification.

117. A POSA with actual, practical experience in radiopharmaceutical development and nuclear imaging or radiotherapeutics, and in using molecular imaging techniques, would thus readily ascertain from the specification’s disclosures the known B and L moieties that would be suitable in the recited compounds combining these known moieties—and would thus likewise readily understand that the inventors of the ’201 patent possessed the recited subject matter.

118. Dr. Martin argues that “[t]he ’201 patent also fails to provide any additional guidance permitting a POSA to determine what characteristics are most likely to meet these functional limitations.” EX1002, ¶178. However, Dr. Martin fails to provide any evidence to show that such teaching would be necessary for a POSA to understand that the specification describes the claimed invention, nor does he point out any “B” or “L” groups that allegedly would not perform

imaging/therapeutic or linking functions, respectively. In sum, the specification adequately describes the claimed compounds, which are defined by their structure.

X. THE '201 PATENT CLAIMS ARE ENABLED.

A. Dr. Martin's Enablement Analysis Wrongly Focuses on a Functional Definition of the Compounds.

119. As discussed above in Section VII.A, the claims here are defined and construed *structurally*—i.e., they recite a low molecular weight compound having formula B-L-A—with the functional language reserved *only* for the B and L moieties that are themselves extensively described within the specification.

120. Rather than considering that the claimed compounds are defined structurally, Dr. Martin performed the enablement analysis as if the claimed compounds are *required* to perform particular functions. EX1002, ¶176. Table 6 below shows how Dr. Martin's enablement analysis relies on the wrongly assumed functional requirement:

Table 6: Excerpts from Dr. Martin’s declaration showing wrongly assumed functional requirements.

Citation in Dr. Martin’s Declaration (EX1002)	Quote from Dr. Martin’s Declaration
¶160	“This broad functional language permits a virtually unlimited number of potential candidate compounds that would need to be made and tested to determine whether the compound falls within the scope of the claims.”
¶167	“The ’201 patent does not even describe why or how the two disclosed examples—XY-FAP-01 and XY-FAP-02—perform the claimed functions , or why other compounds do not.”
¶170	“At this level of skill, the functional limitations recited in the challenged claims would require a POSA to perform countless lengthy, sometimes challenging or difficult or unpredictable experiments to determine whether the claims are satisfied. ”
¶171	“Further, the ’201 patent does not describe which features— structural or otherwise— would be needed for the compound to perform the claimed functions for the B moiety, i.e., be “suitable for” optical imaging, PET imaging, SPECT imaging, or radiotherapy, or for the linker moiety, i.e., “bi-functionalization adapted to form a chemical bond with B and A.”

121. However, as explained above with respect to written description, not only did Dr. Martin mistakenly attribute “the claimed functions” to the claimed compounds, but Dr. Martin also never explained what he believes the “claimed functions” **of the recited compounds** actually are. Thus, a POSA would have disagreed with Dr. Martin’s enablement analysis.

B. Dr. Martin Fails to Show Undue Experimentation Would be Required.

122. Dr. Martin argues that “it would require undue experimentation for a POSA to make and use the full scope of the invention as claimed.” EX1002, ¶158. But Dr. Martin fails to appreciate the proper full scope of the claims that must be enabled, fails to appreciate the skill level of a POSA, and fails to understand the predictability of the invention as claimed.

1. Dr. Martin Misrepresented the True Size of the Claimed Genus and the Skill Level of a POSA in Concluding that the Claims are not Enabled.

123. Dr. Martin argues that the scope of the claimed invention is “vast.” EX1002, 164. Dr. Martin’s conclusion is based on his argument that a POSA would have interpreted the “alkyl” and “aryl” groups for R_{3x} to be “virtually unlimited” with a “countless number of possibilities.” EX1002, ¶162. But as discussed above in Section VII.B, Dr. Martin is wrong, and a POSA, under any POSA definition, would have understood the terms “C(O)alkyl” and “C(O)aryl” for substituent R_{3x} to have a limit.

124. But Dr. Martin’s enablement analysis also underestimates the level of skill of a POSA. EX1002, ¶¶170-174. As discussed above, Dr. Martin’s POSA definition lacks practical experience in the field of imaging or radiotherapeutics and developing compounds for such applications. And Dr. Martin did not provide any evidence that a POSA would have had to engage in undue experimentation in order to practice the claimed invention. Moreover, Dr. Martin’s enablement analysis overlooks the extensive disclosures in the specification and fails to provide any evidence supporting his finding of undue experimentation.

2. Dr. Martin Underestimated the Predictability of the Invention, and the Level of Guidance Provided by the Specification.

125. In his enablement analysis, Dr. Martin did not consider the state of the art at least as of July 23, 2023. Specifically, Dr. Martin failed to take into account the knowledge that a POSA would have had when selecting suitable A, L, and B groups to practice the claimed invention at least as of July 23, 2023.

126. At least as of July 23, 2023, ample evidence existed to guide the POSA in practicing the claimed invention. First, the publication of disclosures US2011/0064657, “Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA), Biological Evaluation, and Use as Imaging Agents,” published Mar. 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. US2012/0009121 A1, for “PSMA-Targeting Compounds and Uses Thereof,”

published Jan. 12, 2012, to Pomper et al, are examples of publications that a POSA would have looked to for guidance in selecting suitable linker moieties. Indeed, the contents of these publications are incorporated by reference to the disclosure of the '201 patent, providing dozens of examples of linkers, a fact that Dr. Martin does not address. Similarly, suitable imaging or therapeutic agents that could be used were well-known, and included dyes, chelating agents, and radioactive groups – far from the “virtually unlimited” scope opined by Dr. Martin. EX1002, ¶¶92, 165. Dr. Martin did not explain why a POSA under any POSA definition would not have been able to routinely and predictably select “B” and “L” moieties for use in a low molecular weight compound of the recited structure.

127. Moreover, Dr. Martin does not argue that simply **making** the claimed compounds would require undue experimentation, nor does he establish that **practicing** the full scope of the invention would require testing. EX1002, ¶167. Without explanation, Dr. Martin merely assumes that “the '201 patent calls for a make-and-screen approach[,]” EX1002, ¶171, but this assumption appears to be based on his faulty premise that the claims impose a functional requirement that must be screened for. Not only does Dr. Martin not explain what type of screening would be required, he fails to show that any screening would necessitate undue experimentation. For example, Dr. Martin does not explain why a POSA would have needed to engage in any experimentation other than tasks that would have

been routine for a POSA equipped with the guidance in the specification, such as selecting and adjusting known moieties for creating and using the claimed compounds, which, as discussed above, are defined by their structure, not function. And Dr. Martin does not provide even a single example of a low molecular weight compound of the claimed “B-L-A” structure that a POSA could not have made or used.

128. JHU, however, provided examples of other compounds encompassed by the challenged claims that **could be made and used** following the guidance in the specification. Specifically, during prosecution of the '201 patent Dr. Pomper submitted a declaration discussing nine additional compounds. EX1004, 1203-1205 (Pomper Declaration). The Pomper declaration showed that a variety of “L” (at least 10) and “B” (at least 5), when incorporated into the claimed B-L-A compounds, showed high FAP selectivity indices. EX1004. Dr. Martin did not explain why these additional, **structurally-diverse**, examples do not show enablement.

129. Further, Dr. Martin does not explain what “countless lengthy, sometimes challenging or difficult or unpredictable experiments,” EX1002, ¶¶170, 174, would be required to practice the scope of the invention. As discussed above, given the extensive guidance provided in the '201 patent specification, selection of suitable A, L, and B moieties could not constitute undue experimentation because

selection of such moieties given the guidance in the specification would be routine for someone who had multiple years of both formal training and actual, practical experience in i) nuclear or optical imaging, or ii) radiotherapeutics (collectively, radiopharmaceuticals), radiopharmaceutical development, and in using molecular imaging techniques.

130. Dr. Martin fails to point out any specific embodiments of the recited low molecular weight compounds of formula A-L-B that would require experimentation to make and use, and fails to explain why additional working examples would be needed to enable the full scope of the claimed invention. In sum, Dr. Martin fails to show that a POSA would have had to engage in undue experimentation when making and using the full scope of the claimed invention.

XI. THE CLAIMED INVENTION IS DEFINITE.

A. A POSA Would Have Understood the Scope of the Term “Low Molecular Weight.”

131. Dr. Martin states that the term “low molecular weight” limitation lacks “reasonable certainty” and that a POSA would not have been “reasonably certain as to the scope of the invention.” EX1002, ¶¶180, 188. Dr. Martin’s analysis of the term “low molecular weight” is flawed. A POSA would have understood, with reasonable certainty, the metes and bounds of the term “low molecular weight” as described in the ’201 patent claims, consistent with the prosecution history of the ’201 patent and the state of the art at least as of July 18,

2023. In this analysis, I refer to my discussion in the Claim Construction Section VII.C, wherein I conclude that a POSA, under any POSA definition, would have recognized the plain and ordinary term “low molecular weight” as referring to compounds with a “molecular weight of typically from about 50 Daltons to about 1,500 Daltons. Based on this claim construction, I conclude that a POSA would have been reasonably certain of the metes and bounds of the claimed invention.

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 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.

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.

APPENDIX A: JANSEN II SELECTIVITY CALCULATIONS

The selectivity index (SI) of the Jansen II compounds for FAP vs. PREP ($SI_{[FAP/PREP]}$) was calculated as described in Jansen II. EX1010, 2-3. Specifically, $SI_{[FAP/PREP]}$ was determined by dividing the FAP IC_{50} value by the PREP IC_{50} value as reported in Jansen II, Table 4, and then rounding the resultant value to the appropriate number of significant figures (the highest number of significant figures for each set of IC_{50} values). A sample calculation for Compound 7 is shown below.

$$SI_{[FAP/PREP]_{Cpd. 7}} = \frac{PREP IC_{50} (\mu M)_{Cpd. 7}}{FAP IC_{50} (\mu M)_{Cpd. 7}} = \frac{0.86 \mu M}{0.0103 \mu M} = 83.49514563 \rightarrow 83$$

Jansen II Compound Number	FAP IC_{50} (μM)	PREP IC_{50} (μM)	$SI_{[FAP/PREP]}$ unrounded	$SI_{[FAP/PREP]}$ rounded
7	0.0103	0.86	83.49514563	83
19	0.67	0.64	0.955223881	0.96
20	5.9	53.6	9.084745763	9.1
21	$1 < IC_{50} < 10$	0.35	$0.35 < SI < 0.035$	$0.4 < SI < 0.04$
22	> 10	1	< 0.1	< 0.1
23	0.77	18.5	24.02597403	24
24	0.16	38	237.5	240
25	0.0099	16.8	1696.969697	1700
26	0.011	> 50	> 4500	> 4500
27	0.014	0.84	60	60

Jansen II Compound Number	FAP IC₅₀ (μM)	PREP IC₅₀ (μM)	SI_[FAP/PREP] unrounded	SI_[FAP/PREP] rounded
28	0.014	0.71	50.71428571	51
29	0.0103	0.61	59.22330097	60
30	0.0092	6.1	663.0434783	660
31	0.0072	1.4	194.4444444	190
32	0.0062	1.2	193.5483871	190
33	0.19	0.35	1.842105263	1.8
34	0.37	0.36	0.972972973	0.97