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

Patent No. 11,938,201

EXPERT DECLARATION OF STEPHEN F. MARTIN, PH.D., IN SUPPORT OF PETITIONER'S OPPOSITION TO PATENT OWNER'S REQUEST FOR DISCRETIONARY DENIAL OF INSTITUTION

I declare that all statements made herein of my knowledge are true, that all statements made herein on information and belief are believed to be true, and 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.

By: _____ Date: 05/28/2025

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TABLE OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 11,938,201 to Yang et al., issued March 26, 2024, with Sept. 24, 2024, Certificate of Correction ("'201 patent")
1002	Declaration of Dr. Stephen F. Martin
1003	Curriculum Vitae of Dr. Stephen F. Martin
1004	Prosecution History for U.S. Patent No. 11,938,201 (downloaded from USPTO Patent Center)
1005	U.S. Patent Publication No. 2011/0064657 to Pomper et al., published March 17, 2011 ("US '657")
1006	U.S. Patent Publication No. 2012/0009121 to Pomper et al., published Jan. 12, 2012 ("Pomper")
1007	U.S. Patent No. 9,346,814 to Jansen et al., issued May 24, 2016 ("Jansen I")
1008	Petra Dvořáková at al., *Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein*, 60 JOURNAL OF MEDICINAL CHEMISTRY 8385-8394 (2017), available at https://pubs.acs.org/doi/10.1021/acs.jmedchem.7b00767 (last accessed Dec. 19, 2024) ("Dvořáková")

1009	U.S. Patent Publication No. 2010/0098633 to Zimmerman et al., published April 22, 2010 ("Zimmerman")
1010	Keon Jansen et al., *Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold*, 2013(4) ACS MEDICINAL CHEMISTRY, 491-96 (2013) ("Jansen II")
1011	*Product Information: ATTO 488*., ATTO-TEC GMBH (2024) available at https://www.atto-tec.com/fileadmin/user_upload/Katalog_Flyer_Support/ATTO_488.pdf (last accessed Dec. 18, 2024)
1012	*IVISense™ 680 NHS Fluorescent Labeling Kit: NEV11118*, REVVITY, INC., available at https://www.revvity.com/asset-search/tds?part_number=NEV11118 (last accessed Dec. 18, 2024)
1013	*Alexa Fluor™ 790 NHS Ester (Succinimidyl Ester)*, THERMOFISHER SCIENTIFIC, available at https://www.fishersci.com/shop/products/alexa-fluor-790-nhs-ester-succinimidyl-ester/A37569# (last accessed Dec. 18, 2024.
1014	IRDYE 700 DX, U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES, available at https://drugs.ncats.io/drug/C51A2YUX4N (last accessed Dec. 18, 2024)
1015	Ronnie C. Mease et al., *N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: A new Imaging probe for prostate cancer*, 14 CLIN CANCER RES 3036-43 (2008)
1016	Suzanne E. Lapi et al., *Assessment of an 18F-Labeled Phosphoramidate Peptidomimetic as a New Prostate-Specific Membrane Antigen–Targeted Imaging Agent for Prostate*, 50 J NUCL MED 2042-48 (2009)

1017	Ronny Rüger et al., *In Vivo Near-Infrared Fluorescence Imaging Of FAP-Expressing Tumors With Activatable FAP-Targeted, Single-Chain Fv-Immunoliposomes*, 186 JOURNAL OF CONTROLLED RELEASE 1-10 (2014)
1018	Zhi-Yi Chen et al., *Advance of Molecular Imaging Technology and Targeted Imaging Agent in Imaging and Therapy*, BIOMED RESEARCH INT'L 819324 (2014)
1019	A. Feinstein et al., *Conformation of the Free and Antigen-bound IgM Antibody Molecules*, 224 NATURE 1307-09 (1969)
1020	Mark Jordi, *Typical Molecular Weights of Common Polymers*, RQM+ (April 18, 2018), available at https://www.rqmplus.com/blog/typical-polymer-molecular-weights (last accessed Dec. 24, 2024)
1021	Anne Hellebust et al., *Advances in molecular imaging: Targeted Optical Contrast Agents For Cancer Diagnostics*, 7 NANOMEDICINE 429-45 (2012)
1022	Sumith A. Kularatne et al., *Prostate-Specific Membrane Antigen Targeted Imaging and Therapy of Prostate Cancer Using a PSMA Inhibitor as a Homing Ligand*, 6 MOLECULAR PHARMACEUTICS 780-89 (2009)
1023	Yonghwang Ha, *Recent Conjugation Strategies of Small Organic Fluorophores and Ligands for Cancer-Specific Bioimaging*, 248 CHEMICO-BIOLOGICAL INTERACTIONS 36-51 (2016)
1024	Sari Pihlasalo et al., *Method for Determination of Polyethylene Glycol Molecular Weight*, 87 ANALYTICAL CHEMISTRY 3918-22 (2015)

1025	Declaration of Dr. Stephen F. Martin In Support of Petitioner Discretionary Denial Brief
1026	Stephen Martin, Seminar Presentation at Cedars-Sinai, Los Angeles, CA: *Applications of Chemistry to Unmet Medical Needs in Neuroscience* (May 11, 2017)
1027	Stephen Martin, NIH Small Business Technology Transfer Proposal (2017).
1028	Paul J. Trim et al., *Small Molecule MALDI MS Imaging: Current Technologies and Future Challenges*, 104 Methods 127, 129 (2016)
1029	Isotta Chimenti et al., *Biochemistry and Biology: Heart-to-heart to Investigate Cardiac Progenitor Cells*, 1830 Biochimica et Biophysica Acta 2459, 2465 (2013)
1030	Erica J. Carbone et al., *Small Molecule Delivery Through Nonfibrous Scaffolds for Musculoskeletal Regenerative Engineering*, 19 Nanomedicine 1691 (Nov. 2014)
1031	Executive Order 14273, Lowering Drug Prices by Once Again Putting Americans First (Apr. 15, 2025), https://www.whitehouse.gov/presidential-actions/2025/04/lowering-drug-prices-by-once-again-putting-americans-first/

1032	Klobuchar, Grassley Introduce Bipartisan Bills to Reduce Drug Prices by Promoting Competition and Taking on Big Pharma, United States Senator Amy Klobuchar (Mar. 26, 2025), https://www.klobuchar.senate.gov/public/index.cfm/2025/3/klobuchar-grassley-introduce-bipartisan-bills-to-reduce-drug-prices-by-promoting-competition-and-taking-on-big-pharma
1033	Press Release, ITM, ITM Appoints Roger Estafanos as U.S. General Manager and Expands Presence with Opening of U.S. Headquarters in Princeton, New Jersey (Apr. 17, 2023), https://www.itm-radiopharma.com/news/press-releases/press-releases-detail/ITM_Appoints_Roger_Estafanos_as_U.S._General_Manager_and_Expands_Presence_with_Opening_of_U.S._Headquarters_in_Princeton,_New_Jersey-609/
1034	"Ga68-ITM-74D," Synapse, https://synapse.patsnap.com/drug/4e4c9bfab0a3463192ecd5712dcc963f#research (last updated May 25, 2025)
1035	*Company Detail: Bracco S.P.A.*, Italian Business Register, available at https://italianbusinessregister.it/en/company-detail?p_p_id=risultatiricercaimprese_WAR_ricercaPIportlet&p_p_lifecycle=0&p_p_state=normal&_risultatiricercaimprese_WAR_ricercaPIportlet_view=%2Frisultatiricercagratuita%2Fdettaglio_impresa.jsp&_risultatiricercaimprese_WAR_ricercaPIportlet_pageToken=eyJhbGciOiJIUzI1NiIsInR5cCI6IkpXVCJ9.eyJjb3VudCI6MjUwLCJleHAiOjE3NDg0Njg3ODV9.KQL5_TFOcQSBpBu9aYNQYQyXpQhYwqeo1YIPm7kKGLU (last accessed May 27, 2025)

I. Introduction

1. I, Stephen F. Martin, have been retained by counsel for Petitioner ITM Isotope Technologies Munich SE ("Petitioner") as an independent expert consultant in this proceeding before the U.S. Patent and Trademark Office ("USPTO"). I am being compensated for the time I spend on this matter at my customary rate of $800 per hour, but no part of my compensation is dependent on the outcome of this proceeding or any issue in it, or contingent upon my opinions or performance.

2. I submit this Declaration on behalf of Petitioner as an expert in the field of organic chemistry, including bioactive natural products and molecular probes, in the above-identified proceeding. My qualifications in these areas, as well as other areas, were established in my previous December 24, 2024 Declaration (EX1002 at ¶¶ 4-13), including by my *curriculum vitae* (EX1003), and are further established below.

3. I understand that this Declaration accompanies Petitioner's Brief in Opposition to Patent Owner's Request for Discretionary Denial of Institution of PGR2025-00012 for U.S. Patent No. 11,938,201 ("the '201 patent") (EX1001). In forming my opinions, I have considered the documents and materials cited herein. I additionally have based my opinions on my professional and academic

experience in the broad areas of organic chemistry and chemical biology, including in radiopharmaceutical chemistry as outlined in greater detail below.

II. Summary of Opinions

4. I have been asked by counsel to consider the April 28, 2025 Declarations of Dr. Henry F. VanBrocklin submitted in connection with the Brief in Support of Discretionary Denial ("Brief" or "Br.") and the Patent Owner Preliminary Response ("POPR") prepared by Patent Owner The John Hopkins University ("Patent Owner"). More specifically, I have considered Dr. VanBrocklin's opinions therein regarding the validity of claims 1-3 of the '201 patent.

5. It is my opinion that Dr. VanBrocklin proposes an overly heighted standard of ordinary skill in the art that improperly excludes qualified and capable skilled artisans. I maintain that the POSA definition I articulated in my previous Declaration is the correct one. *See* EX1002 at ¶ 95. It is also my opinion that I would have been a POSA under both my definition and Dr. VanBrocklin's definition by the earliest effective filing date of the '201 patent.

6. As explained below and in my previous Declaration (EX1002), I disagree with Dr. VanBrocklin's opinions related to the validity of the claims of the '201 patent. It remains my opinion that claims 1-3 of the '201 patent would have been obvious to a person of ordinary skill in the art on or before its earliest

possible priority date, and are invalid for lack of enablement, lack of written description, and indefiniteness.

III. Level of Ordinary Skill in the Art

7. In my previous declaration, I explained that, in my opinion, as of October 23, 2017 (the earliest priority date of the '201 patent), 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. EX1002 at ¶ 95. 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. *Id.* 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. *Id.*

8. I understand that Dr. VanBrocklin provided the following definition for a POSA: a person with "**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)." EX2002 at ¶ 22 (emphasis in original).

9. I disagree with Dr. VanBrocklin's assessment of the level of skill of a POSA and maintain that my previously-articulated POSA lens is proper. In particular, considering the pertinent factors including the type of problems encountered in the art and the prior art solutions to those problems, Dr. VanBrocklin's POSA standard is too high.

10. Regarding the types of problems encountered in the art, the '201 patent's express purpose is "[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." EX1001 at Abstract. The background of the invention explains that low molecular weight ligands with "ideal properties for nuclear imaging of FAP-α" are desired. *Id.* at 1:50-67. Then, the patent turns to the design of such ligands: compounds of Formula (I) having a structure B–L–A. *Id.* at 2:1-12. This, too, is the focus of the claims. *See id.* at Claims 1 and 3 (reciting "[a] low molecular weight compound of Formula (I): B–L–A" wherein A is a targeting moiety for FAP-α having a particular structure and B and L are functionally defined as "any optical or radiolabeled function group" and "a linker having bi-functionalization adapted to form a chemical bond with B and A," respectively).

11. Regarding the prior art solutions to those problems, the prior art—including Jansen I, Jansen II, Dvořáková, Zimmerman, and Pomper—similarly focus on the chemical design of agents selective to FAP-α and their use in treating FAP-α related diseases and disorders. *See, e.g.*, EX1007 at Abstract ("The present invention relates to novel inhibitors having high selectivity of specificity for FAP . . . for the treatment and/or prevention of FAP-related disorders . . . ."); EX1010 at Abstract (presenting "the discovery of a new class of FAP inhibitors with a *N*-(4-quinolinoyl)-Gly-(2-cyanopyrrolidine) scaffold"); EX1008 at 2 (describing the design, synthesis, and characterization of targeting ligands for FAP including preparation of a panel of FAP inhibitors and assessing their structure-activity relationships); EX1009 at Abstract ("Novel radiopharmaceuticals that are useful in diagnostic imaging and therapeutic treatment of disease characterized by overexpression of seprase include complexes that contains a proline moiety and a radionuclide adapted for radioimaging and/or radiotherapy."); EX1006 at Abstract ("Prostate-specific membrane antigen (PSMA) targeting compounds are described. Uses of the compounds for imaging, cell sorting, and tumor mapping are also described.").

12. A POSA under my standard would:

(a) understand the compounds described in the prior art and their component parts, would be aware of how to find and understand

literature showing how diagnostic agents can be linked to targeting groups for imaging;

(b) understand the structures and chemistry of FAP-α targeting moieties;

(c) understand the structures and chemistry of possible linkers suitable for forming a chemical bond or connection between two moieties;

(d) understand the structures and chemistry of optical and radiolabeled functional groups, the characteristics that would make these functional groups suitable for applications such as optical imaging, positron-emission tomography imaging, single-photon emission computer tomography imaging, and radiotherapy;

(e) be able to design, synthesize, and evaluate compounds comprising diagnostic moieties joined by a linker to FAP-α targeting moieties, including radiolabeled compounds or radiopharmaceuticals, for imaging;

13. Therefore, in my understanding, the subject matter of the ’201 patent and the prior does not require *multiple years of formal training and practical experience in radiopharmaceuticals and in using molecular imaging techniques* as alleged by Dr. VanBrocklin. The patent—and the claims—are focused on chemical compounds and the design and synthesis thereof, as is the prior art. To the extent

those compounds are intended for use as radiotherapeutics, a POSA under my definition having an Bachelor's degree in organic chemistry or a related field, two to five years of experience employing organic chemistry as a tool for the development of molecules with targeted biological activity, and "*understanding of processes employed for synthesis and evaluation of imaging and radiotherapeutic agents"* would be sufficiently versed in the technology. Years of additional formal training and/or experience in radiopharmaceuticals and molecular imaging techniques is, in my opinion, overkill.

14. While I disagree with Dr. VanBrocklin's POSA standard, I nevertheless note that I meet that standard given my practical experience evaluating and using agents, including radiopharmaceuticals, for molecular and biomedical imaging, as outlined below.

15. I was involved in two different collaborative experiments involving radiopharmaceuticals, including therapeutic agents, with radioisotopes ^{3}H and ^{11}C, and using molecular imaging techniques, including proton emission tomography (PET). For example, as I presented in a 2017 seminar, I studied sigma 2 receptor (σ_2R) targeting agents for treatment of central nervous system disorders, such as Alzheimer's disease and traumatic brain injury. EX1026 at 5, 10, 13. In one study, I utilized a ^{11}C-labeled therapeutic agent in PET imaging to evaluate uptake of the therapeutic across the blood-brain barrier in monkeys and to monitor its

displacement in the presence and absence of a small molecule blocker. *Id.* at 18. Likewise, as shown in a 2017 research proposal, I have also used a ^{3}H-labeled σ_2R-targeting agent to image localization of σ_2R in rodent brain and to monitor its displacement with another σ_2R-binding ligand. *See* EX1027 at 11-12.

16. Finally, even if Dr. VanBrocklin's POSA standard is adopted, my opinions as provided in my previous declaration would not substantively change.

IV. Claim Construction

17. I previously analyzed the plain and ordinary meaning of the words in the claim in the context of the patent specification as it would be understood by one of ordinary skill in the art. EX1002 at ¶ 97. Based on that analysis, I determined that the phrase "low molecular weight" could vary based on the specific field of study and types of molecules, whether they be antibodies, polymers, carbohydrates, or secondary metabolites. *Id.* at ¶ 105. Therefore, I found the claims to lack reasonable certainty. *Id.* I also determined that the phrases "C(O)Alkyl" and "Aryl" would be understood by a POSA as including alkyl groups of any length and aryl groups not limited to any particular length, size, or substitution. *Id.* at ¶¶ 106-11.

A. "Low molecular weight"

18. I understand that Dr. VanBrocklin now asserts that my conclusions are wrong. With respect to the phrase "low molecular weight," I understand that Dr.

VanBrocklin asserts that 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." EX2002 at ¶ 60. As explained in my previous Declaration, I disagree that the Patent Owner clearly defined the phrase "low molecular weight" in the '201 patent or its file history. *See* EX1002 at Section VIII.E. In the absence of a clear definition provided by the Patent Owner, the phrase "low molecular weight" could reasonably be interpreted differently by scientists. *See id.* Therefore, it remains my opinion that the phrase "low molecular weight" lacks the reasonable clarity that I understand to be required by a patent claim.

19. I understand that Dr. VanBrocklin has equated the term "low molecular weight" and "small molecule" in an attempt to find a definition for "low molecular weight" in the art. EX2001 at ¶ 41. But even taking it as true that these two terms are synonymous, this only further establishes my previous conclusion that the meaning of "low molecular weight" is indefinite. Like the phrase "low molecular weight," the phrase "small molecule" has different meanings to scientists in various fields and has changed over time. *See, e.g.*, Paul J. Trim et al., *Small Molecule MALDI MS Imaging: Current Technologies and Future Challenges*, 104 Methods 127, 129 (2016) ("Trim") (EX1028). Indeed, definitions of "small molecule" vary throughout the literature depending on the author and the

application. *See, e.g.*, *id.* ("Here [small molecule] is taken to be any molecule with a molecular weight under 2000 g/mol in its native form."); Isotta Chimenti et al., *Biochemistry and Biology: Heart-to-heart to Investigate Cardiac Progenitor Cells*, 1830 Biochimica et Biophysica Acta 2459, 2465 (2013) ("Chimenti") (EX1029) ("A small molecule, in the fields of pharmacology and biochemistry, is a low molecular weight organic compound . . . . Their molecular weight is approximately 800 Da . . . ."); Erica J. Carbone et al., *Small Molecule Delivery Through Nonfibrous Scaffolds for Musculoskeletal Regenerative Engineering*, 19 Nanomedicine 1691 (Nov. 2014) ("Carbone") (EX1030) ("In biomedical sciences, small molecule refers to a non-peptide biologically active organic compound with a molecular size usually less than 1,000 Da."). Thus, I maintain my position that "low molecular weight" has no single specific definition, and scientists, even those in the same field, reasonably and routinely interpret the phrase differently.

20. Furthermore, I understand that Dr. VanBrocklin has relied on Pomper as supporting his definition of "low molecular weight" as "about 50 Daltons to about 1,500 Daltons." EX2002 at ¶¶ 59−64. In particular, Dr. VanBrocklin points to 17 compounds disclosed in Pomper and having molecular weights between 642.3 and 1586.6 g/mol and asserts that this confirms his proposed definition. The chart provided by Dr. VanBrocklin is reproduced below:

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**

EX2002 at 40.

21. Pomper's disclosure of these 17 compounds does not change my opinion regarding the definition—or lack thereof—of "low molecular weight."

First, Pomper does not expressly refer to these 17 compounds as "low molecular weight." Nor does Pomper suggest that these 17 compounds are intended to exemplify "low molecular weight" compounds or that compounds having molecular weights above "about 1500 g/mol" would fall outside the scope of Pomper's intended invention. Indeed, the molecular weight of 1586.6 g/mol for Compound YC-27 is already near the upper boundary of "about 1500 g/mol," if not already exceeding it.

22. The flaws in Dr. VanBrocklin's opinions—and the claims of the '201 patent—become even more apparent when the various definitions in the art for the synonymous term "small molecule" are applied to Pomper's example compounds. For example, according to Chimenti's definition of the synonymous phrase "small molecule" as "less than 800 Da," only 2 of 17 Pomper compounds would be considered "low molecular weight." *See* EX1029 at 2465 (defining "small molecule" as less than 800 Da); EX2002 at ¶ 61. Similarly, under Carbone's definition of "less than 1,000 Da," only 5 of 17 Pomper compounds would be considered "low molecular weight." *See* EX1030 at 2 (defining "small molecule" as less than 800 Da); EX2002 at ¶ 61. And, under Trim's broader definition of "under 2000 g/mol," all 17 of Pomper's compounds would be considered "low molecular weight." EX1028 at 129. In my opinion, a skilled artisan, reading the claims of the '201 patent would be unable to make an informed and confident

determination of what constitutes a "low molecular weight" compound and what does not.

23. Therefore, I maintain that the term "low molecular weight" is ambiguous and lacks reasonable clarity. Dr. VanBrocklin's reliance on the phrase "small molecule" and Pomper's exemplary compounds further demonstrate the ambiguity present in this vague phrase.

B. "C(O)Alkyl" / "Aryl"

24. Regarding the claim terms "C(O)alkyl" and "aryl," I understand that Dr. VanBrocklin disagrees with my conclusion that the terms have no limit[1] and argues instead that a POSA would understand a limit to exist based on the incorporation by reference of Jansen I. EX2002 at ¶¶ 54-58. However, the passage of the '201 patent that Dr. VanBrocklin relies upon is itself non-limiting, stating that "***[r]epresentative*** targeting moieties for FAP-α are disclosed in [Jansen I] . . .

[1] While it is my opinion that the claim terms "C(O)alkyl" and "aryl" have no explicit limit, I recognize that there may be an implicit limit imposed by the claim phrase "low molecular weight." As I have discussed elsewhere in my declarations, it is my opinion that the claim phrase "low molecular weight" is indefinite. *See* Section IV.A., *supra*; EX1002 at Section VIII.E. However, to the extent the phrase "low molecular weight" is found to have a defined range, it would logically follow that the size of the "C(O)alkyl" and "aryl" groups cannot be so large that the molecular weight of a compound would exceed the upper threshold of that defined range. Therefore, if "low molecular weight" is found to have a specific range, it is my opinion that the scope of the terms "C(O)alkyl" and "aryl" would not be unlimited, although the scope of these terms would still be very large.

which [is] incorporate[d] by reference in [its] entirety." EX1001 at 8:25-32 (emphasis added). The definition of "alkyl" in Jansen I is also expressly non-limiting. *See* EX1007 at 22:18-20 ("***Generally***, alkyl groups of this invention comprise from 1 to 6 carbon atoms") (emphasis added). Moreover, the definition that Dr. VanBrocklin proposes is expressly contradicted by the definition of "alkyl" that appears in the specification of the '201 patent, which includes examples having between one and ten carbon atoms (i.e., C_1-C_{10}) and between one and twenty carbon atoms (i.e., C_1-C_{20}). *See* EX1001 at 39:43-50 ("[A]lkyl . . . ha[s] the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term 'alkyl' refers to C_1-C_{20} inclusive . . . ."). Therefore, I do not find that these definitions from Jansen I, even if incorporated by reference, change my analysis of the phrase "alkyl" as used within the '201 patent specification, nor do they change my ultimate conclusion that the phrase "alkyl," which lacks a designation of the number of carbon atoms, as used in the claims is unlimited.

25. Dr. VanBrocklin's proposed construction for "aryl" and its underlying analysis based on the incorporation of Jansen is similarly flawed. His proposed construction of "a 5- or 6-membered aromatic monocycle" cannot be correct. The '201 patent explicitly exemplifies aryls having at least 1 to 3 aromatic rings. *See* EX1001 at 42:64-67 (defining "aryl" as "an aromatic hydrocarbon substituent that

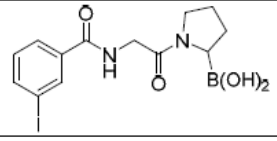
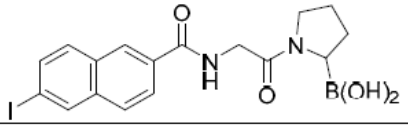
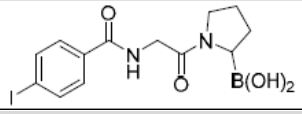
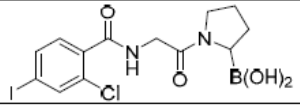
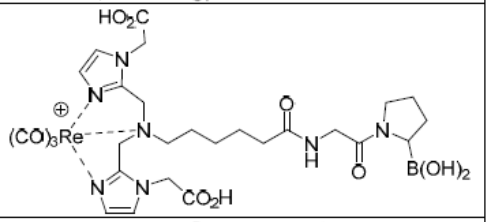
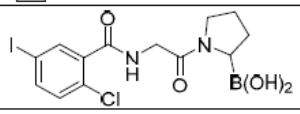
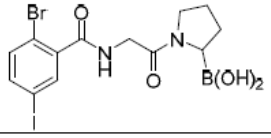
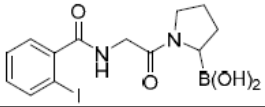
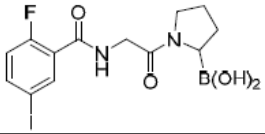
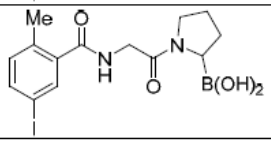
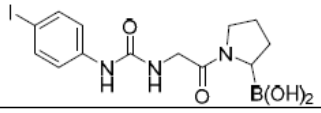
can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently."); *see also id.* at 43:7-16 (describing "[n]on-limiting examples of aryl . . . groups," including several with multiple rings). Therefore, I also maintain my previous conclusion that aryl groups as claimed in the '201 patent are not strictly limited to any particular size or substitution.

V. Ground I

26. I previously opined that claims 1-3 of the '201 patent would have been obvious to a POSA in view of Jansen I and/or Jansen II, taken in view of Zimmerman and Pomper. EX1002 at ¶ 112.

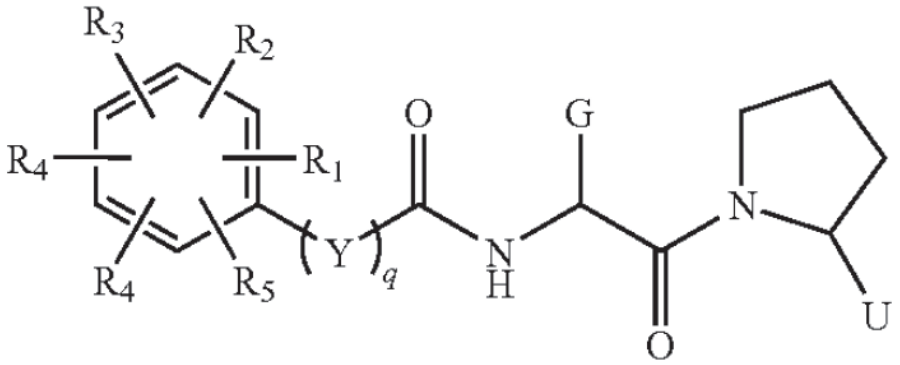
27. I understand that, in response, Dr. VanBrocklin asserts that Zimmerman discloses compounds of Formula I having linkers and compounds of Formula II without linkers, and that Zimmerman's data show that compounds of Formula II without linkers exhibited overwhelmingly better FAP targeting properties. EX2002 at ¶ 79-86. In support, Dr. VanBrocklin asserts that ten of the eleven compounds with the highest reported affinities do not have a linker. *See* EX2002 at ¶ 83. The chart relied upon by Dr. VanBrocklin for this proposition is reproduced below:

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	
1026	3	II	
1020	4	I	
1027	5	II	
1028	5	II	
1023	7	II	
1029	8	II	
1032	11	II	
1034	11	II	

28. In my opinion, a POSA would not draw the strong conclusions that Dr. VanBrocklin and Patent Owner assert using the partial data in Table 5. As an initial matter, I disagree with Dr. VanBrocklin's classification of the compounds of Formula II as being without linkers. The genus of Formula II, reproduced below, clearly includes a linker, as represented by at least the structure Y_q:

II



where:

U is —$B(OH)_2$, —CN, —CO_2H, or —$P(O)(OPh)_2$;

G is H, alkyl, substituted alkyl, carboxyalkyl, heteroalkyl, aryl, heteroaryl, heterocycle, or arylalkyl;

Y is a bond, —O—, —CH_2—, —OCH_2—, —CH_2O—, NR, —NR—CH_2, or CH_2—NR—, wherein R is H, Me or CH_2CO_2H;

q is an integer ranging from 0 to 24; and

R_1, R_2 , R_3 , R_4 and R_5 are independently hydrogen, halogen, cyano, carboxyl, alkyl, alkylamino, alkoxy, or substituted or unsubstituted amino, provided that at least one of R_1, R_2, R_3, R_4 and R_5 is a radiohalogen.

EX1009 at ¶¶ 111-17.

Additionally, Zimmerman teaches that "glycine and/or other appropriate amino acid can be incorporated as a linker." For example, Schemes 2 and 4 of Zimmerman depict the syntheses of functionalized proline-$M^{+}(CO)_3$ complexes utilizing an amino acid linker (*e.g.,* a glycine residue) attached to the pyrrolidine ring of compound 1003. *Id.* at ¶¶ 126-27 and 131-32. Although these schemes show routes to compounds of Formula I, the same amino acid (*e.g.,* a glycine) linker is present in compounds of Formula II, the preparation of which from the same glycine-linked pyrrolidine derivative 1003 is shown in Scheme 5. *Id.* at ¶ 135. Each compound included in Dr. VanBrocklin's Table 5—including all the compounds of Formula II in Table 5—incorporate a glycine linker, further demonstrating the error in Dr. VanBrocklin's mischaracterization of the compounds of Formula II as not having a linker.

29. Moreover, the data do not support Dr. VanBrocklin's assertion that the compounds of Formula II demonstrate "undisputable superiority." *See* EX2002 at ¶ 84. The compound with the fifth highest affinity (1020) in Dr. VanBrocklin's Table 5 is of Formula I.[2] *See* EX1009 at ¶ 185, Table 2; EX2002 at ¶ 83.

[2] Although Compound 1020 has the fifth highest affinity as reported in Zimmerman, a POSA would understand that there are limitations of this *in vitro* assay, including experimental error, and would not rely on these data to definitively determine that Compound 1020 (IC_{50} = 4 nM) has lower affinity than, for example, Compounds 1025 (IC_{50} = 2 nM) or 1030 (IC_{50} = 2 nM). Instead, a

Additionally, other compounds with high reported affinity, such as Compound 1014 (IC_{50} = 21 nM) and Compound 1018 (IC_{50} = 20 nM), are of Formula I. *See* EX1009 at ¶ 185, Table 2; EX2002 at ¶ 83. Moreover, several compounds of Formula II, including Compound 1061 (IC_{50} = 24,540 nM), Compound 1044 (IC_{50} = 23,680 nM), and Compound 1048 (IC_{50} = 7,414 nM) have very poor affinities.

30. Zimmerman does not expressly disparage the compounds of Formula I, and, in my opinion, the data are certainly not "overwhelmingly" in favor of the compounds of Formula II, especially in view of the limited structural variations in those compounds. A POSA reading Zimmerman would understand that all of the compounds disclosed therein contain linkers and that compounds of both Formula I and Formula II are viable.

31. Therefore, I maintain my position that the '201 patent would have been obvious to a POSA in view of Jansen I and/or Jansen II, taken in view of Zimmerman and Pomper.

VI. Ground II

32. I previously opined that claims 1-3 of the '201 patent would have been obvious to a POSA in view of the teachings of Dvořáková and Pomper. *See* EX1002 at ¶ 137. Dvořáková discloses every limitation of claim 1 except "low

POSA would conclude that compounds with low single-digit nanomolar IC_{50} values have comparable levels of affinity.

molecular weight." *See id.* Pomper, however, teaches the benefits of low molecular weight compounds and a POSA would have been motivated to modify Dvořáková's disclosed compounds to have a lower molecular weight based on Pomper's teachings. *See id.*

33. I understand that Dr. VanBrocklin disagrees, arguing that a POSA would not have been motivated to synthesize low molecular weight versions of Dvořáková's compounds. EX1002 at ¶ 98-107. In particular, Patent Owner, citing Dr. VanBrocklin, asserts that "Dvořáková would have taught a POSA that iBody exhibited beneficial FAP targeting and imaging properties because it used multiple such moieties and a higher molecular weight linker, causing iBody to have high molecular weight." Br. at 43 (citing EX2002 at ¶¶ 99-105).

34. In my opinion, this is an improper reading of Dvořáková. Dvořáková does not attribute its beneficial properties to its high molecular weight. To the contrary, Dvořáková touts the "highly module and versatile" nature of the iBody. EX1008 at 8386; *see also id.* at 8386-87 (praising the multi-purpose functionality of the iBody, as exemplified by its specific targeting and visualization of FAP using ATTO488 and its ability to be immobilized via biotin). Dvořáková also states that "conjugates containing virtually any desired compound can be easily prepared" and that "[i]mportantly, the molecular weight of the HMPA backbone can be easily adjusted to specifically tailor the pharmacokinetic properties." *Id.* at

8386. These teachings in Dvořáková would not have taught away from low molecular weight compounds. In fact, these teachings would have encouraged a POSA to take advantage of a high affinity FAP binding molecule such as compound 2 (*id.* at 8389 (Fig. 2)), which possesses a linker, and attach an imaging or radiolabeled moiety to synthesize and test a low molecular weight compound according to the teachings of Pomper.

35. Thus, I maintain my position regarding the obviousness of the ’201 patent given the teachings of Dvořáková and Pomper.

VII. Conclusion

36. For the reasons discussed in my previous Declaration (EX1002) and herein, it is my opinion that each of claims 1-3 of the ’201 patent is invalid.