

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CURIUM US LLC.
Petitioner

v.

UNIVERSITÄT HEIDELBERG AND THE EUROPEAN ATOMIC ENERGY
COMMUNITY (EURATOM), REPRESENTED BY THE EUROPEAN
COMMISSION,
Patent Owner

Case No. IPR2025-01582

U.S. Patent No. 10,980,901

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,980,901**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	SUMMARY OF THE ARGUMENT	2
III.	MANDATORY NOTICES	5
	A. Real Parties-in-Interest (§ 42.8(b)(1)).....	5
	B. Related Matters (37 C.F.R. § 42.8(B)(2))	5
	C. Identification of Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))	5
	D. Service Information Under 37 C.F.R. § 42.8(b)(4).....	5
	E. Payment of Fees	6
IV.	CERTIFICATION OF WORD COUNT UNDER 37 C.F.R. § 42.24(D).....	6
V.	CERTIFICATION OF GROUNDS FOR STANDING	6
VI.	IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(B)(1)	7
VII.	BACKGROUND OF THE STATE OF TECHNOLOGY	8
	A. Radioactive Decay.....	8
	B. Radionuclide Imaging and Radiopharmaceuticals.....	10
	C. Radionuclides	15
	D. Radiopharmaceuticals and the Treatment of Prostate Cancer	17
VIII.	OVERVIEW OF THE ‘901 PATENT	19
	A. Summary of IPR2023-00551	19
	B. Summary of the Original Prosecution.....	20
IX.	CLAIM CONSTRUCTION	22
X.	THE CHALLENGED CLAIMS ARE INVALID AS OBVIOUS.....	22
	A. Scope and Content of Prior Art.....	22
	1. Weineisen 2015 (Exhibit 1028)	22
	2. Kratochwil (Ex. 1031)	24
	3. Jurcic (Exhibit 1011).....	25
	4. Kratochwil 2016 (Exhibit 1045)	26

B.	Person of Ordinary Skill in the Art (“POSA”).....	27
C.	Ground 1: Claims 1, 2, 4–8, and 10–13 are Obvious Over Weineisen 2015 in Combination With Kratochwil.....	27
1.	A POSA would have been motivated to use PSMA I&T in the treatment of prostate cancer with a reasonable expectation of success.....	27
2.	A POSA would have been motivated to use PSMA I&T with ²²⁵ Ac and would have had a reasonable expectation of success.....	30
1.	POSA Would Have Used an Alpha Emitter.....	30
2.	A POSA Would Have Recognized Specific Advantages of ²²⁵ Ac.....	32
3.	A POSA Would Have Had a Reasonable Expectation of Success in Making ²²⁵ Ac-PSMA I&T	35
3.	A POSA would have been motivated to use ²²⁵ Ac-PSMA I&T at the claimed doses	36
4.	A POSA would have been motivated to administer the ²²⁵ Ac-PSMA I&T in repeat doses	40
5.	A POSA would have been motivated to use the ²²⁵ Ac-PSMA I&T to treat PSMA expressing cancers	40
6.	Each and Every Challenged Claim is Unpatentable as Obvious in Light of the Prior Art.....	42
1.	Claim 1.....	42
2.	Claim 2.....	46
3.	Claims 4-7	46
4.	Claims 8, 10-11.....	47
5.	Claims 12-13.....	48
D.	Ground 2: Claim 9 is obvious over Weineisen 2015 in combination with Kratochwil and Jurcic.	50
E.	Ground 3: Claims 1, 2 and 4-13 are Anticipated by Kratochwil 2016	51
1.	Kratochwil 2016 is Prior Art.....	51
1.	Kratochwil 2016 Anticipates Claims 1, 2, 4–8, and 10–13.....	53

1.	Claim 1.....	54
2.	Claim 2.....	55
3.	Claims 4 and 6	55
4.	Claim 5.....	55
5.	Claims 8-11.....	55
6.	Claims 12-13.....	56
XI.	PATENT OWNER’S SECONDARY CONSIDERATION EVIDENCE LACKS A NEXUS AND DOES NOT OVERCOME THE STRONG CASE OF OBVIOUSNESS	56
A.	No Industry Praise for Claimed Invention	57
B.	No Unexpected Results or Teaching Away	60
C.	No Long-Felt Unresolved Need	63
XII.	CONCLUSION.....	64

LIST OF EXHIBITS

EXHIBIT NO.	DESCRIPTION
1001	U.S. Patent No. 10,980,901 (“the ‘901 patent”)
1002	Declaration of Dr. Michael Zalutsky, Ph.D.
1003	Curriculum Vitae of Dr. Michael Zalutsky, Ph.D.
1004	File History of U.S. Patent No. 10,980,901
1005	Marc A. Bjurlin, et al., <i>Imaging and evaluation of patients with high-risk prostate cancer</i> , 12 Nature Reviews Urology 617 (2015) (“Bjurlin”).
1006	Kristell Chatalic, et al., <i>²¹³Bi-labeled PSMA-targeting agents for alpha radionuclide therapy of prostate cancer</i> , 57 J. Nuclear Med. 137 (2016) (“Chatalic”).
1007	Emre Demirci, <i>⁶⁸Ga-PSMA PET/CT imaging of metastatic clear cell renal cell carcinoma</i> , 41 Eur. J. Nuclear Med. Molecular Imaging 1461 (2014) (“Demirci”).
1008	Catherine A. Foss, et al., <i>Radiolabeled Small-Molecule Ligands for Prostate-Specific Membrane Antigen: In vivo Imaging in Experimental Models of Prostate Cancer</i> , 11 Clinical Cancer Rsch. 4022 (2005) (“Foss”).
1009	Shawn Hillier, et al., <i>[¹³¹I] MIP-1375, a small molecule prostate-specific membrane antigen (PSMA) inhibitor for targeted therapy of prostate cancer (PCa)</i> , 52 J. Nuclear Med. 361 (2011) (“Hillier 2011”).
1010	Shawn Hillier, et al., <i>[¹³¹I] MIP-1466, a small molecule prostate-specific membrane antigen (PSMA) inhibitor for targeted radiotherapy of prostate cancer (PCa)</i> , 53 J. Nuclear Med. 170 (2012) (“Hillier 2012”).
1011	Joseph G. Jurcic, et. al., <i>Phase I Trial of Targeted Alpha-Particle Therapy with Actinium-225 (²²⁵Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older</i>

EXHIBIT NO.	DESCRIPTION
	<i>with Untreated Acute Myeloid Leukemia (AML)</i> , 128 Blood 4050 (2016) (“Jurcic”).
1012	Susan J. Mandel, et al., <i>Superiority of Iodine-123 Compared with Iodine-131 Scanning for Thyroid Remnants in Patients with Differentiated Thyroid Cancer</i> , 26 Clinical Nuclear Med. 6 (2001) (“Mandel”).
1013	Michael R. McDevitt, et al., <i>Tumor Therapy with Targeted Atomic Nanogenerators</i> , 294 Science 1537 (2001) (“McDevitt 2001”).
1014	Michael R. McDevitt, et al., <i>Design and synthesis of ²²⁵Ac radioimmunopharmaceuticals</i> , 57 Applied Radiation & Isotopes 841 (2002) (“McDevitt 2002”).
1015	Matthias Miederer, et al., <i>Preclinical Evaluation of the α-Particle Generator Nuclide ²²⁵Ac for Somatostatin Receptor Radiotherapy of Neuroendocrine Tumors</i> , 14 Clinical Cancer Rsch. 3555 (2008) (“Miederer 2008a”).
1016	Dianne E. Milenic & Martin W. Brechbiel, <i>Targeting of Radio-Isotopes for Cancer Therapy</i> , 3 Cancer Biology & Therapy 361 (2004) (“Milenic”).
1017	George Sgourous, et al., <i>MIRD Pamphlet No. 22 (Abridged): Radiobiology and Dosimetry of α-Particle Emitters for Targeted Radionuclide Therapy</i> , 51 J. Nuclear Med. 311 (2010) (“MIRD Pamphlet”).
1018	Natsuko Normura, et al., <i>Prostate specific membrane antigen (PSMA) expression in primary gliomas and breast cancer brain metastases</i> , 14 Cancer Cell Int'l 1 (2014) (“Nomura”).
1019	Martin G. Pomper, et al., <i>¹¹C-MCG: Synthesis, Uptake Selectivity, and Primate PET of a Probe for Glutamate Carboxypeptidase II (NAALADase)</i> , 1 Molecular Imaging 96 (2002) (“Pomper”).

EXHIBIT NO.	DESCRIPTION
1020	Justin R. Hubenak, et al., <i>Mechanisms of injury to normal tissue after radiotherapy: a review</i> , 133 Plastic Reconstructive Surgery 49 (2014) (“Hubenak”).
1021	Jeffery S. Ross, et al., <i>Correlation of Primary Tumor Prostate-Specific Membrane Antigen Expression with Disease Recurrence in Prostate Cancer</i> , 9 Clinical Cancer Rsch. 6357 (2003) (“Ross”).
1022	David A. Scheinberg & Michael R. McDevitt, <i>Actinium-225 in targeted alpha-particle therapeutic applications</i> , 4 Current Radiopharmceuticals 306 (2011) (“Scheinberg”).
1023	David A. Silver, et al., <i>Prostate-specific Membrane Antigen Expression in Normal and Malignant Human Tissues</i> , 3 Clinical Cancer Rsch. 81 (1997) (“Silver”).
1024	Baris Turkbey, et al., <i>Multiparametric Prostate Magnetic Resonance Imaging in the Evaluation of Prostate Cancer</i> , 66 CA: Cancer J. for Clinicians 326 (2016) (“Turkbey”).
1025	U.S. Patent No. 10,471,160 (“the ‘160 patent”).
1026	U.S. Patent No. 10,398,791 (“the ‘791 patent”).
1027	Martina Weineisen, et al., <i>Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer</i> , 4 EJNMMI Rsch. 1 (2014) (“Weineisen 2014”).
1028	Martina Weineisen, et al., <i>⁶⁸Ga-and ¹⁷⁷Lu-labeled PSMA I&T. Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies</i> , 56 J. Nuclear Med. 1169 (2015) (“Weineisen 2015”).
1029	Alla G. Wernicke, et al., <i>Prostate-specific membrane antigen expression in tumor-associated vasculature of breast cancers</i> , 122 APMIS 482 (2014) (“Wernicke”).

EXHIBIT NO.	DESCRIPTION
1030	Matthias Miederer, et al., <i>Realizing the potential of the Actinium-225 radionuclide generator in targeted alpha particle therapy applications</i> , 60 Advanced Drug Delivery Revs. 1371 (2008) (“Miederer 2008b”).
1031	Clemens Kratochwil, et al., <i>Ac-225-DOTATOC - an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors</i> , 56 J. Nuclear Med. 1232 (2015) (“Kratochwil”).
1032	Randall D. Knight, <i>Physics For Scientists and Engineers</i> 1369–70 (Adam Black et al. eds., vol. 5 2005) (“Knight”).
1033	Liang Zhao, et al., <i>Clinical pharmacology considerations in biologics development</i> , 33 Acta Pharamacologica Sinica 1339 (2012) (“Zhao”).
1034	U.S. Dep’t Health & Hum. Servs., <i>Anthropometric Reference Data for Children and Adults: United States, 2015–2018 Series 3</i> , 9 (2021) (“HHS”).
1035	Nerissa Viola-Villegas & Robert P. Doyle, <i>The coordination chemistry of 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (H4DOTA): Structural overview and analyses on structure–stability relationships</i> , 253 Coordination Chemistry Reviews 1906 (2009) (“Viola-Villegas”).
1036	Nima Sharifi, et al., <i>Androgen Deprivation Therapy for Prostate Cancer</i> , 294 JAMA 238 (2005) (“Sharifi”).
1037	Nat’l Cancer Inst., <i>SEER Cancer Stat Facts: Prostate Cancer</i> , seer.cancer.gov, https://seer.cancer.gov/statfacts/html/prost.html (last visited Jan. 31, 2023) (“NCI”).
1038	Sharmila Banerjee, et al., <i>Lutetium-177 Therapeutic Radiopharmaceuticals: Linking Chemistry, Radiochemistry, and Practical Applications</i> , 115 Chem. Revs. 2934 (2015) (“Banerjee”).
1039	Arundhati Ghosh & Warren D.W. Heston, <i>Tumor Target Prostate Specific Membrane Antigen (PSMA) and its</i>

EXHIBIT NO.	DESCRIPTION
	<i>Regulation in Prostate Cancer</i> , 91 J. Cellular Biochemistry 528 (2004) (“Ghosh”).
1040	Declaration of Dr. Rebecca Zalutsky, Ph.D. filed in IPR2023-00551
1041	Eric W. Price and Chris Orvig, <i>Matching chelators to radiometals for radiopharmaceuticals</i> , 43 Chem. Soc. Rev. 260-290 (2014) (“Price”)
1042	Kristell L.S. Chatalic, et al., <i>Towards Personalized Treatment of Prostate Cancer: PSMA I&T, a Promising Prostate-Specific Membrane Antigen-Targeted Theranostic Agent</i> , 6(6) Theranostics, 849-861 (2016) (“Chatalic 2016b”)
1043	Robin M. de Kruijff, et al., <i>A Critical Review of Alpha Radionuclide Therapy – How to Deal with Recoiling Daughters?</i> , 8 Pharmaceuticals, 321-336 (2015) (“de Kruijff”)
1044	Declaration of Dr. Hope, MD filed in IPR2023-00551
1045	Kratochwil et al., “ ²²⁵ Ac-PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer,” <i>Journal of Nuclear Medicine</i> , vol. 57, no. 12, pgs. 1941-1944 (2016) (Kratochwil 2016)
1046	Xofigo® FDA label packaging insert (revised May 2013)

I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311–19 and 37 C.F.R. § 42.100 et seq., Petitioner Curium US LLC. (“Petitioner”) seeks *inter partes* review and cancellation of claims 1, 2, and 4-13 of U.S. Patent No. 10,980,901 (“the ’901 patent”), titled “Treatment of PMSA [sic] Expressing Cancers.” Ex. 1001. This Petition and supporting exhibits demonstrate that there is a reasonable likelihood that all challenged claims are unpatentable to a person of ordinary skill in the art (“POSA”).

Importantly, the obviousness grounds of rejection presented in this Petition are the same grounds of rejection the PTAB has previously determined reached the threshold for institution challenging the same claims of the ’901 Patent. *See* IPR2023-00551, *Fusion Pharmaceuticals, Inc. v. Universität Heidelberg et. al.*, Paper No. 8 at 29 (PTAB August 15, 2023) (“an *inter partes* review of claims 1, 2, and 4–13 of the ’901 patent is instituted with respect to all grounds set forth in the Petition.”)¹. However, IPR2023-00551 was settled post-institution before a Final Written Decision was reached. *See id.* at Paper No. 21 (PTAB March 12, 2024).

In addition, Patent Owner argued in IPR2023-00551 that a paper the inventors co-authored and published before the ’901 Patent (Ex. 1045) discloses the challenged claims of the ’901 Patent. IPR2023-00551, Paper No. 15 at 57. However,

¹ The instant Petitioner was not involved with IPR2023-00551 and not related to any of the parties involved in that proceeding.

four other co-authors on this prior paper are not listed as inventors of the '901 Patent; and thus, this paper is prima facie prior art under 35 U.S.C. §102(a)(1). Ex. 1045 at 1. Patent Owner has not provided any evidence that this paper falls within an exception listed in 35 U.S.C. §102(b)(1). Absent such evidence, there can be no debate that this paper anticipates all of the challenged claims in view of Patent Owner's statements in IPR2023-00551

The instant petition is also supported by the declaration of Dr. Michael Zalutsky, a chaired professor at Duke University with decades of experience and hundreds of publications in the field of radiology, particularly radiation oncology. Ex. 1002 at ¶3-7; Ex. 1003 (Dr. Zalutsky's CV). Dr. Zalutsky reviewed the expert declarations submitted by both Dr. Abergel and Dr. Hope in IPR2023-00551 and substantially agrees with the declaration submitted by Dr. Abergel in support of the petitioner in that proceeding. Ex. 1002 at ¶18; *see also* Ex. 1040 (Dr. Abergel declaration) and Ex. 1044 (Dr. Hope declaration).²

II. SUMMARY OF THE ARGUMENT

The claims of the '901 patent recite methods of treating patients who have a cancer characterized by overexpression of prostate-specific membrane antigen

² The Institution Decision in IPR2023-00551 cites approvingly of Dr. Abergel's testimony throughout the decision. *See* IPR2023-00551, Paper No. 8 at 18-20, 23 and 25.

(“PSMA”) by administering ^{225}Ac complexed with certain radiopharmaceutical targeting compounds at certain dosages. While the claims recite a variety of compounds that can be used as the radiopharmaceutical targeting compound, the challenged claims extend to cover a radiopharmaceutical targeting compound that was known in the prior art—a compound referred to as PSMA I&T. Prior to the earliest filing date of the ‘901 patent, PSMA I&T had been identified as a promising compound for use in targeted radiation treatment of PSMA expressing cancers. *See, e.g.*, Ex. 1028, Weineisen 2015 at 1-2. The radionuclide ^{225}Ac had also previously been used with radiopharmaceuticals to effectively treat a variety of cancers, including PSMA expressing cancers. *See, e.g.*, Ex. 1013, McDevitt 2001; Ex. 1031, Kratochwil; *see also* Ex. 1027, Weineisen 2014 at 11.

As explained in more detail below, a POSA would have been motivated to combine ^{225}Ac with PSMA I&T in the treatment of PSMA expressing cancers. Alpha-emitting radionuclides like ^{225}Ac were known to be ideally suited for targeted cancer therapy because alpha emissions have high potency and travel short distances, impacting only the cells directly adjacent to the target site. *See* Ex. 1017, MIRD Pamphlet at 1, 4; *see also* Ex. 1015, Miederer 2008a at 1. Therefore, a POSA would have been motivated to use an alpha emitter, like ^{225}Ac , in combination with PSMA I&T to treat patients who had PSMA expressing cancers and would have reasonably expected the combination to be safe and effective.

The challenged claims additionally specify dosage amounts and dosage regimens for the claimed radiopharmaceuticals. But these limitations do not distinguish the challenged claims from what was known in the art. ²²⁵Ac radiotherapies had demonstrated promising results within the claimed dosage ranges in phase I and phase II clinical trials for cancer treatments prior to the earliest filing date of the challenged patent. *See* Ex. 1011, Jurcic. And, PSMA I&T chelated with similar alpha-emitting radionuclides had been shown to be effective and safe within the claimed dose ranges. *See* Ex. 1006, Chatalic at 2. As a result, a POSA would have been motivated to use ²²⁵Ac-PSMA I&T at doses within the claimed ranges and would have reasonably expected treatment at these doses to be safe and effective.

The challenged claims of the '901 patent are directed to the use of a known radiopharmaceutical that was proven to be effective in targeting radionuclides to PSMA expressing cancer cells—PSMA I&T—in combination with a known radionuclide proven to be effective in the treatment of cancer—²²⁵Ac—at doses proven to be safe and effective. A POSA would have been motivated to combine these known elements in a method of treating patients with PSMA expressing cancers and would have had a reasonable expectation of success. Therefore, the Board should find all challenged claims unpatentable as obvious in light of the prior art.

III. MANDATORY NOTICES

A. Real Parties-in-Interest (§ 42.8(b)(1))

The Petitioner and real party in interest is Curium US LLC.

B. Related Matters (37 C.F.R. § 42.8(B)(2))

The '901 Patent was previously challenged in IPR2023-00551. The Board instituted this proceeding, but the proceeding terminated due to a settlement before a Final Written Decision was issued.

Petitioner is not aware of other proceedings relating to the '901 Patent.

C. Identification of Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

Petitioner designates the following lead and backup counsel:

Lead Counsel	Backup Counsel
James P. Murphy Reg. No. 55,474 Polsinelli PC 1000 Louisiana Street Suite 6400 Houston, Texas 77002 Tel: (713) 374-1631 jpmurphy@polsinelli.com	Patrick Muffo Reg. No. 60,342 Polsinelli PC 150 N. Riverside Plaza Suite 3000 Chicago, Illinois 60606 Tel: (312) 873-2988 pmuffo@polsinelli.com

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Physical mailing service information is as follows:

James Murphy
Polsinelli PC
1000 Louisiana Street
Suite 6400
Houston, Texas 77002

Petitioner also consents to service by e-mail at the above e-mail addresses provided for lead and backup counsel.

E. Payment of Fees

All required fees have been paid with the filing of this Petition. Petitioner further authorizes the U.S. Patent & Trademark Office to charge Deposit Account No. 50-1662 for any fees, including the fee set forth in 37 C.F.R. § 42.15(a) for this Petition.

IV. CERTIFICATION OF WORD COUNT UNDER 37 C.F.R. § 42.24(D)

Petitioner certifies that the word count in this Petition, including all footnotes and annotations, is 13,997 words as counted by the word-processing program (Microsoft Word for Office 365) used to generate this Petition, where such word count excludes the table of contents, mandatory notices, certificate of service, list of exhibits, and this certificate of word count. This Petition is in compliance with the 14,000-word limit set forth in 37 C.F.R. § 42.24(a)(1)(i).

V. CERTIFICATION OF GROUNDS FOR STANDING

Petitioner certifies that the '774 patent is available for *inter partes* review. Petitioner is not barred or estopped from requesting an *inter partes* review of the '901 patent claims on the grounds identified in this Petition. 37 C.F.R. § 42.104(a).

VI. IDENTIFICATION OF GROUNDS FOR WHICH REVIEW IS REQUESTED UNDER 37 C.F.R. § 42.104(B)(1)

Petitioner requests institution of IPR based on the following grounds:

Ground	Claims	References and Type of Challenge
1	1, 2, 4–8, and 10–13	Obvious over Weineisen 2015 ³ in combination with Kratochwil ⁴
2	9	Obvious over Weineisen 2015 in combination with Kratochwil and Jurcic ⁵
3	1, 2, 4–13	Anticipation over Kratochwil 2016 ⁶

³ Ex. 1028 - Martina Weineisen, et al., *⁶⁸Ga-and ¹⁷⁷Lu-labeled PSMA I&T. Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies*, 56 J. Nuclear Med. 1169 (2015) (“Weineisen 2015”).

⁴ Ex. 1031 - Clemens Kratochwil, et al., *Ac-225-DOTATOC - an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors*, 56 J. Nuclear Med. 1232 (2015) (“Kratochwil”).

⁵ Ex. 1011 - Joseph G. Jurcic, et. al., *Phase I Trial of Targeted Alpha-Particle Therapy with Actinium-225 (²²⁵Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML)*, 128 Blood 4050 (2016) (“Jurcic”).

⁶ Ex. 1045 - Kratochwil et al., “225 Ac-PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer,” *Journal of Nuclear Medicine*, vol. 57, no. 12, pgs. 1941-1944 (2016) (Kratochwil 2016).

VII. BACKGROUND OF THE STATE OF TECHNOLOGY⁷

The '901 patent is directed to methods of using radiotherapeutics in the treatment of cancer. In this treatment, a radionuclide is delivered to the cancer cells through the use of a targeting compound. The targeting compound holds the radionuclide and directs it to the target cancer cells where the radionuclide can exert its therapeutic effect. A brief background of the relevant scientific principles is provided below.

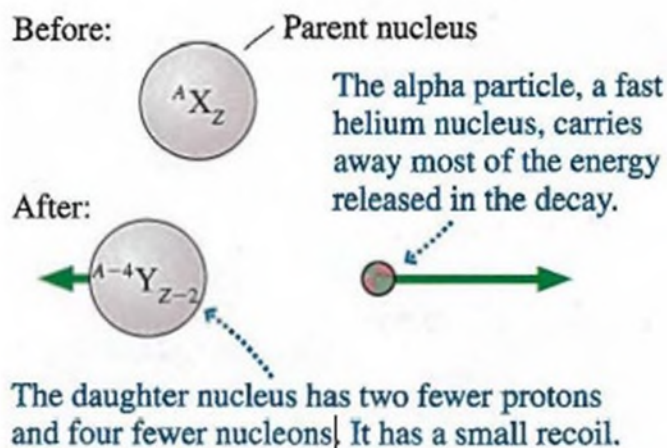
A. Radioactive Decay

Each atom of a particular element has the same number of protons. Ex. 1002 ¶19. For example, every carbon atom has 6 protons. However, the number of neutrons in the atom's nucleus may differ, e.g., a carbon can have 6, 7, or 8 neutrons. Atoms of the same element with differing numbers of neutrons are isotopes. Certain isotopes of elements are known to be unstable and readily break apart. Ex. 1002 ¶19. This process is referred to as radioactive decay. Radioactive decay, or radioactivity, is the process in which unstable atoms, also known as radionuclides, spontaneously release energy, and often particles. Ex. 1002 ¶19. Radioactive decay occurs through specific processes dependent on the specific atom that is decaying. That is, each

⁷ Cited references not named in a ground of rejection are cited for the purpose of showing the state of the art and the background knowledge of a POSITA. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013).

unstable isotope generally has a predictable decay pattern based on the type of decay it undergoes. Ex. 1002 ¶19; Ex. 1022, Scheinberg at 2.

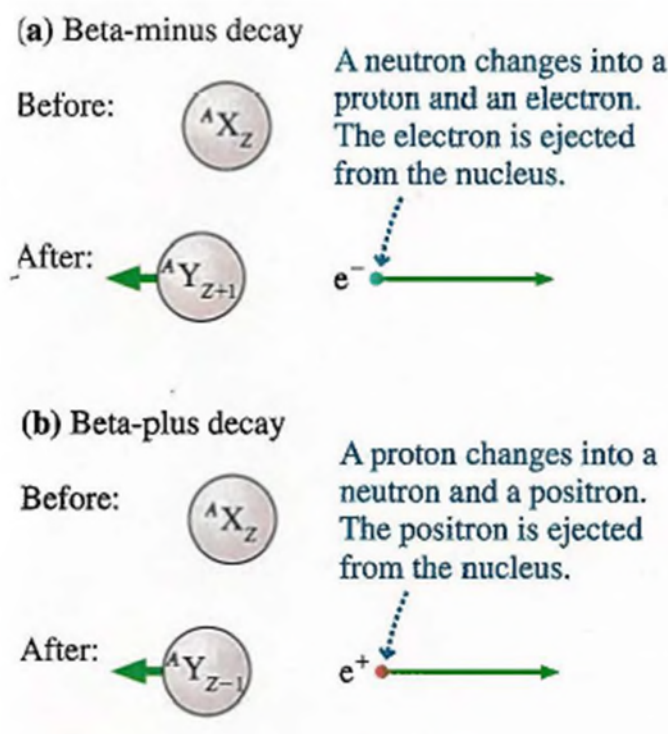
The two types of radioactive decay relevant for this matter are alpha decay and beta decay. Ex. 1002 ¶20. In either case, the “parent” radioactive atom decays and becomes one or more “daughter” atom(s), which can subsequently undergo further radioactive decay. Ex. 1002 ¶20. When an atom undergoes alpha decay, its nucleus ejects an “alpha particle.” Ex. 1002 ¶20. For example, when alpha decay occurs in an atom, the parent nucleus emits an alpha particle made up of two protons and two neutrons, the equivalent of a helium nucleus (Fig. 1). Ex. 1002 ¶20. This alpha decay results in the daughter nucleus with two fewer protons. Ex. 1002 ¶20.



Ex. 1032 at Fig. 1

When an atom undergoes beta decay, it releases a beta particle (either a negatively charged electron or positively charged positron). Ex. 1002 ¶21. For example, when an atom undergoes beta-minus decay, a neutron in its nucleus breaks

apart into a proton and an electron (see Fig. 2). Ex. 1002 ¶21. The electron is emitted from the nucleus, and the proton remains as part of the daughter nucleus, Y. Ex. 1002 ¶21.



Ex. 1032 at Fig. 2

B. Radionuclide Imaging and Radiopharmaceuticals

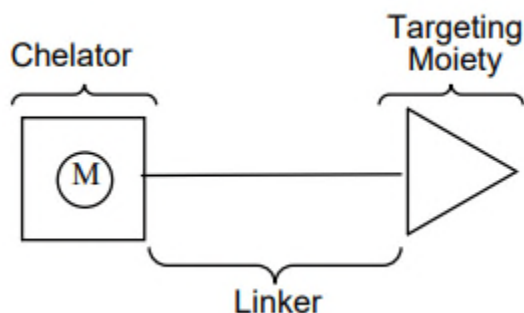
Radioactive elements have been used in medical imaging, diagnostic tests, and radiation therapy for decades. Ex. 1002 ¶¶22–24; Ex. 1016 at 2-4. Use of radiochemicals for imaging and diagnostics rely on low-energy radiation that can be administered to patients, often systemically, and monitored through detection of the energy emitted from the radioactive decay of the administered radiocompound. Ex. 1002 ¶23; Ex. 1012 at 1-2. Radiation therapy, on the other hand, often relies on high

energy radiation to cause enough cellular damage to kill unhealthy tissue. Ex. 1002 ¶24; Ex. 1020, Hubenak at 4.

Because high energy radiation will damage any tissue to which it is exposed, using radiation as a form of therapy requires the energy be specifically targeted to the unhealthy tissue. *See* Ex. 1002 ¶25; Ex. 1020 at 6. Traditional radiation therapy applies radiation from a radioactive source that is external to the patient, but external radiation therapy has drawbacks. Ex. 1002 ¶25; Ex. 1020 at 2, 5-6. Particularly, the treatment is limited in how far the radiation can penetrate into the body, reducing its efficacy, and can impact the healthy tissues surrounding the targeted area, increasing its adverse effects. Ex. 1002 ¶25; Ex. 1020 at 2-3.

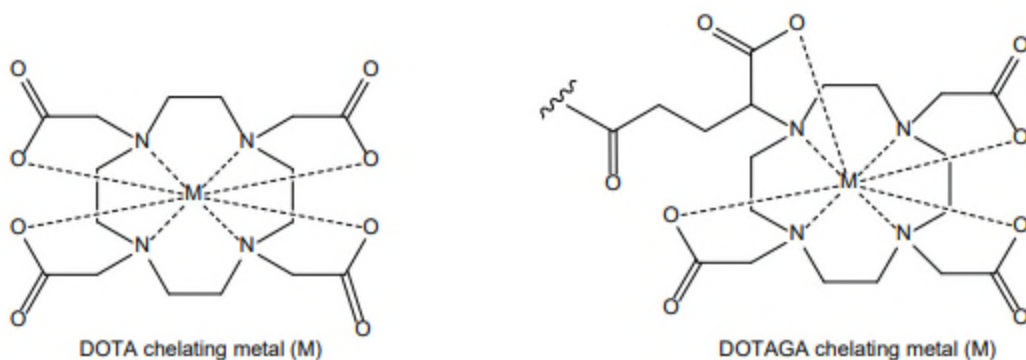
In the past several decades, scientists have developed sophisticated targeting mechanisms to both increase the efficacy of radiation therapy and decrease the side effects associated with radiation by delivering radioactive atoms directly to unhealthy cells within the body. This is achieved by linking a targeting moiety to a radioactive atom. Ex. 1002 ¶27; Ex. 1013 at 1-2; Ex. 1027 at 11. The targeting moiety guides the radioactive atom to the target cells, where the atom decays, delivering localized radiotherapy and killing the target cells while limiting damage to surrounding healthy cells. Ex. 1002 ¶27. Ideally, the chosen targeting moiety selectively interacts with a target that is unique to cancer cells and not found elsewhere in healthy tissue. *See id.*

Metallic radionuclides (radioactive atoms in metal chemical families) have been well-studied in cancer therapeutics. Ex. 1002 ¶¶24–25; *see* Ex. 1020. Metallic radionuclide-based imaging and therapeutic agents generally follow a design comprising a targeting moiety, a linker, a chelator, and a metallic radionuclide (“M” below):



Ex. 1002 ¶25 (Fig. 3).

The chelator portion of the molecule functions to hold the radionuclide in place with a number of ionic interactions between the radionuclide and portions of the chelator and is attached to the targeting moiety via the linker. Ex. 1002 ¶27. There are many chelator molecules that are known and used in medical treatment and imaging with radionuclides. For example, molecules called DOTA and DOTAGA are well-known chelators, capable of forming complexes with many different types of radiometals such as ^{177}Lu , ^{90}Y , and ^{225}Ac . Ex. 1002 ¶26; *see, e.g.*, Ex. 1027 at 11; Ex. 1035, Viola-Villegas at 4, 14, 16.



Both DOTA and DOTAGA have been incorporated into larger radiopharmaceutical compounds to serve as the chelator moiety to hold the radiometal. Ex. 1002 ¶26; Ex. 1014 at 1-2; Ex. 1027 at 11.

In some of radionuclides that undergo alpha decay, including ^{225}Ac , the radionuclide may decay with an energy high enough to separate the radionuclide from the chelator. Ex. 1002 ¶28. This phenomenon is commonly referred to as the recoil effect. Ex. 1002 ¶28. The recoil effect can potentially lead to toxicity because the daughter isotope produced from the alpha decay is no longer bound to the targeting compound and therefore may travel to other areas of the body and cause damage to healthy tissues. Ex. 1002 ¶28; *see generally* Ex. 1043.

The recoil effect of ^{225}Ac was known at the time of the invention. Ex. 1002 ¶29. De Kruijff notes several studies that showed a range of outcomes due to toxicity caused by the recoil effect but largely indicates that safe and effective treatments may be reasonably achieved. Ex. 1002 ¶29. For example, ^{225}Ac -labeled Humanized Anti-CD33 Monoclonal Antibody HuM195 was shown to be safe in humans at doses

of ≤ 0.1 MBq/kg. Ex. 1043 at 3; Ex. 1002 ¶29. Another *in vivo* study in animal models utilizing antibodies J591 and B4 conjugated to DOTA to treat prostate carcinoma and disseminated lymphoma “indicated a clear benefit of alpha radiation at low administered activities with no toxic effects.” Ex. 1043 at 9; Ex. 1002 ¶29. As such, at the time of filing, a POSA would have been aware that the potential benefit of ^{225}Ac -labeled radiolabeling for the treatment of cancer likely outweighed small potential side effects, including daughter recoil effect. Ex. 1002 ¶29.

It is also worth noting that an alpha emitter therapy, ^{223}Ra dichloride (known as Xofigo®), had been previously approved by the FDA in the United States for the treatment of metastatic castration-resistant prostate cancer with symptomatic bone metastases. Ex. 1002 ¶30; Ex. 1046. Importantly, the previous approval of the ^{223}Ra alpha emitter therapy occurred years earlier than the priority date of the ‘901 patent. Ex. 1002 ¶0. Since ^{223}Ra exhibits a daughter recoil effect similar to ^{225}Ac , one of skill in the art at the time the ‘901 patent was filed would have readily appreciated that the therapeutic benefit of alpha emitter therapy, including ^{225}Ac , may outweigh any potential negative(s) associated with a daughter recoil effect. Ex. 1002 ¶30. As such, the use of ^{225}Ac as claimed in the ‘901 patent was a common-sense solution. Ex. 1002 ¶30.

C. Radionuclides

Radionuclide targeting agents can carry a variety of different radioactive metals, each with their unique decay pattern. Ex. 1002 ¶31. The energy of the particles emitted during the different types of radioactive decay varies based on identity of the metal and its isotope. Ex. 1002 ¶31. Therefore, the radioactive metal used in the complex can be customized depending on the desired result. Ex. 1002 ¶31.

Early studies into radiopharmaceuticals focused on the use of beta emitting radionuclides due to their availability and familiarity. Ex. 1002 ¶32; Ex. 1016 at 3. However, alpha-particle emitting radionuclides are increasingly seen as more desirable in the context of radiopharmaceuticals. Ex. 1002 ¶32; Ex. 1016 at 3.; Ex. 1030, Miederer 2008b at 2. Alpha particles are substantially larger and contain more energy than the particles emitted during beta decay. Ex. 1002 ¶32; Ex. 1030 at 2; Ex. 1016 at 3; *see also* Ex. 1017, MIRD Pamphlet at 1. This size difference leads to differences in how these particles behave in the target environment. Ex. 1002 ¶32; Ex. 1030 at 2. The bigger alpha particles face more resistance in the body and are therefore only capable of traveling the distance of a few cell diameters. Ex. 1002 ¶32; Ex. 1030 at 2. In contrast, the smaller particles resulting from beta decay face less resistance and are able to travel a few hundred cell diameters. Ex. 1002 ¶32; Ex. 1016 at 3. The more localized impact of alpha decay makes it ideally suited for

targeted therapy because the impact on the surrounding tissue is minimized, reducing the likelihood of side effects. Ex. 1002 ¶32; Ex. 1014 at 1; Ex. 1030 at 2. Furthermore, because alpha particles are higher energy than the particles resulting from beta decay, alpha-particle emitters can be administered in lower doses than beta emitters, further reducing the risk of adverse effects. Ex. 1002 ¶32; see Ex. 1030 at 2; Ex. 1016 at 3.

A number of radionuclides were being investigated prior to the filing of the '901 patent in 2016. Ex. 1002 ¶33. For example, a common beta emitter used in radiotherapeutics was ^{177}Lu . [^{177}Lu]DOTA complexes were linked to a variety of targeting moieties. Ex. 1002 ¶33; Ex. 1038, Banerjee at 7-8. However, as the advantages of alpha emitters were appreciated, alpha emitters like ^{225}Ac and ^{213}Bi gained favor, and the principles and constructs developed with beta emitters were applied for use with alpha emitters. Ex. 1002 ¶33. For example, McDevitt 2001 showed that ^{225}Ac could form stable complexes with the chelator DOTA and subsequently linked those complexes to a targeting moiety. Ex. 1002 ¶33; Ex. 1013, McDevitt 2001 at 2. The [^{225}Ac]DOTA-IgG construct described in McDevitt 2001 was effective in killing a variety of cancer cells. Ex. 1002 ¶33; see Ex. 1013 at 2-4. Since 2001, ^{225}Ac -based radiopharmaceuticals using other targeting moieties and linkers have garnered interest, including the use of other antibodies, such as anti-HER-2/neu, HuM195, and 3F8 antibodies, tetramers, and small molecules. Ex. 1002

¶33; Ex. 1022 at 12-13. Price described DOTA and derivatives of DOTA (including DOTAGA) as “the gold standard” for forming complexes with ^{225}Ac , as well as being a good match for complexing with ^{177}Lu and ^{111}In . Ex. 1002 ¶33; *see* Ex. 1041 at 8-9.

D. Radiopharmaceuticals and the Treatment of Prostate Cancer

Prostate cancer (“PC”) is one of the most commonly diagnosed malignancies in men and is one of the leading causes of death of men. Ex. 1037, NCI at 6, 8; Ex. 1024, Tuckey at 1; Ex. 1002 ¶34. Prior to 2014, treatment options for patients with metastatic prostate cancer were limited to androgen-deprivation therapy and chemotherapy. Ex. 1028 at 1-2; Ex. 1002 ¶38. However, these therapies were known to cause potentially serious adverse effects including bone loss, metabolic changes, muscle loss, hot flashes, and increased cardiovascular disease. Ex. 1036, Sharifi at 4–6; Ex. 1002 ¶38. As a result, scientists in the field were working to develop additional therapeutic options for patients with metastatic prostate cancer. *See, e.g.*, Ex. 1028; 1002 ¶¶35, 38.

The discovery of prostate-specific membrane antigen (PSMA) significantly improved diagnosis and treatment of prostate cancer. PSMA is a transmembrane protein, meaning it resides within the membrane of cells with a portion exposed to the exterior of the cell and a portion exposed to the interior of the cell. Ex. 1008, Foss at 1; Ex. 1002 ¶37. PSMA has been shown to be highly expressed on the surface

of prostate cancer cells but remains at low levels on the surface of healthy prostate cells. Ex. 1002 ¶36; Ex. 1008 at 1; Ex. 1019, Pomper at 5. Therefore, therapeutics that target PSMA will preferentially engage with prostate cancer cells over normal prostate cells, making PSMA an ideal target for selective treatment of prostate cancer. Ex. 1008 at 1; Ex. 1002 ¶36. Indeed, PSMA was considered an “excellent target” for targeted radioligand therapy. *See* Ex. 1027 at 11; Ex. 1028 at 1; Ex. 1002 ¶¶36, 59-65. By at least 2016, PSMA-targeted radiopharmaceuticals had been “highly optimized” for therapeutic applications. *See* Ex. 1027 at 11; Ex. 1028 at 1; Ex. 1002 ¶¶63-65.

Indeed, PSMA I&T specifically was shown to be a promising theranostic agent for the treatment of prostate cancer. Ex. 1002 ¶39. For example, Chatalic 2016 investigated ¹¹¹In-PSMA I&T, which showed a dose-dependent uptake in PSMA-expressing tumors, kidneys, spleen, adrenals, lungs, and salivary glands. Ex. 1002 ¶39, 67; *see* Ex. 1042 at 1. The study investigated dosages of 0.1, 0.3, 1, and 10 nmol/mouse Ex. 1002 ¶39. Chatalic 2016 also noted that the structure of PSMA I&T has “a favorable effect on the binding properties of urea-based small-molecule PSMA inhibitors” owed to the DOTAGA chelator and “the presence of a 3-iodo-D-tyrosine in the linker.” Ex. 1002 ¶39; Ex. 1042 at 9. The study also investigated co-administration of 2-PMPA with ¹⁷⁷Lu-PSMA I&T to reduce kidney uptake but found that the co-administration significantly reduced therapeutic

efficacy. Ex. 1002 ¶39; see Ex. 1042 at 11. Ultimately, the study concluded that “PSMA I&T is a highly promising theranostic agent for radionuclide imaging and therapy of [prostate cancer].” Ex. 1042 at 12.

VIII. OVERVIEW OF THE ‘901 PATENT

The ‘901 patent is titled “Treatment of PMSA [sic] Expressing Cancers,” and claims priority to a PCT application filed on December 15, 2016. Ex. 1001. The Board previously reviewed and summarized the specification and challenged claims of the ‘901 Patent. See IPR 2023-00551, Paper No. 8 at 3-7.

A. Summary of IPR2023-00551

The Board made a number of findings on contested issues in its institution decision IPR2023-00551 that are relevant to the instant proceeding. Most importantly, the Board determined that the obviousness grounds of rejection presented herein have a reasonable likelihood of rendering obvious each of challenged claims 1, 2, 4-13.

As part of that analysis, the Board considered Patent Owner’s arguments summarized by the Board as below:

Patent Owner contends that in arriving at the presently claimed methods from the disclosure of Weineisen 2015 would require several steps such as a motivation to use an alpha-emitter instead of a beta emitter, the specific selection of ²²⁵Ac as the alpha emitter, the recited ²²⁵Ac doses, applying the treatment to PSMA expressing cancers, and showing a reasonable expectation of success.

IPR2023-00551, Paper No. 8 at 23. The Board addressed each of these contentions raised by Patent and found none of them persuasive. *Id.* at 24-26.

Patent Owner filed a response post-intuition reiterating many of these same arguments in an effort to get the Board to change its position. *See* IPR2023-00551, Paper No. 15. Patent Owner also raised secondary considerations were it relied on the alleged praise of Kratochwil 2016, which Patent Owner argued embodies the challenged claims. *Id.* at 57. of the '901 Patent. However, IPR2023-00551 was terminated due to settlement before the Board issued a Final Written Decision or considered any of Patent Owner's arguments filed in its response.

B. Summary of the Original Prosecution

During the original prosecution of the '901 patent, the Examiner rejected all pending claims on nonstatutory double patenting over U.S. Patent Nos. 10,398,791 ("the '791 patent," Ex. 1026) and 10,471,160 ("the '160 patent," Ex. 1025). *See* Ex. 1004 at 402-406. To distinguish the pending claims from the '791 and '160 patents, the applicant stated, "[t]o arrive at the method and dosage recited in the present claims from either the description or claims of the '791 and '160 patents, the ordinary artisan would have needed to specifically select radionuclide Ac-225 and a dose that is **significantly lower** than the broadest range suggested in the [']791 and [']160 patents." Ex. 1004 at 383 (emphasis in original).

Applicant also directed the Examiner to examples in the specification of the pending patent application, which compare treatment using a chelator with radionuclide ^{177}Lu at a dose as used in the '791 and '160 patents to treatment with a chelator with radionuclide ^{225}Ac at a dose as recited in the pending claims. Ex. 1004 at 383-384. The applicant contended that it was a “remarkable difference” that “the group treated with Lu-177-PSMA-617 had a **lower response rate** in comparison to the one treated with Ac-225-PSMA-617.” *Id.* (emphasis in original). Applicant further directed the Examiner to Figure 14 of the application, which depicts “the partial response of a patient to treatment with 7.4 GBq of the Lu-177-comprising chelator and subsequent remission after treatment with 6.4 MBq (100 kBq per kg body weight) of the Ac-225 comprising chelator.” Ex. 1004 at 384 (Oct. 26, 2020 Applicant Arguments/Remarks). Applicant contended, “[t]hose of ordinary skill in the art would not have expected such a strong response to be obtainable for Ac-225-radiopharmaceuticals at the low dosages recited in the present claims. *Id.*..

The Examiner then allowed the claims with minimal explanation and did not address the applicant’s nonstatutory double patenting remarks. *See* Ex. 1004 at 33-34.

IX. CLAIM CONSTRUCTION

Petitioner agrees with the Board's and Patent Owner's statement from the prior IPR that no claim construction is required to resolve the grounds raised. *See* IPR2023-00551, Paper No. 8 at 15 (Board) and Paper No. 15 at 17 (Patent Owner).

X. THE CHALLENGED CLAIMS ARE INVALID AS OBVIOUS

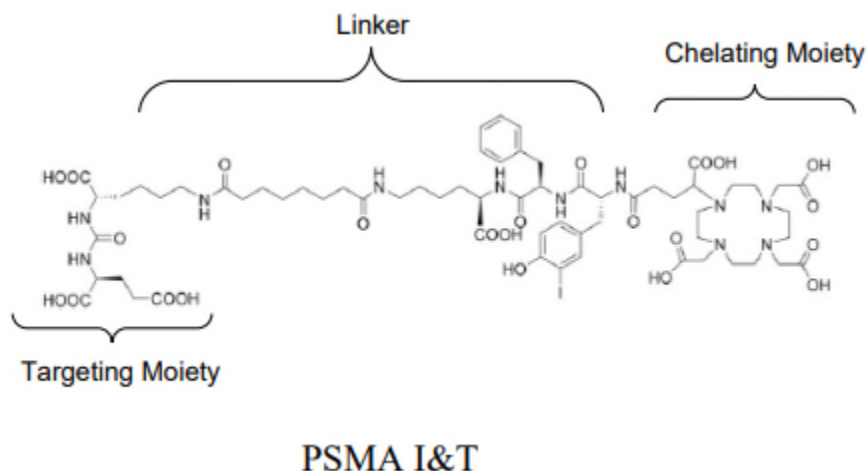
A. Scope and Content of Prior Art

As discussed in more detail below, prior to December 2016, a POSA would have been familiar with targeting radiopharmaceuticals that contained a chelating moiety, a linker, and a PSMA targeting moiety. A POSA would have known that these compounds had been successfully complexed with a variety of radiometals, including ^{177}Lu and ^{225}Ac . A POSA would have also been aware that these radiopharmaceutical complexes had been tested for their utility in targeting PSMA for the treatment of PSMA-expressing cancers and were shown to be safe and effective in those studies at a range of doses.

1. Weineisen 2015 (Exhibit 1028)

Weineisen 2015, published in 2015, is prior art to the '901 patent and was not considered by the Patent Office during prosecution. Weineisen 2015 reports on the continued work of the same group that authored Weineisen 2014. Ex. 1002 ¶¶59–61; Ex. 1028. Weineisen 2015 discloses a different radiopharmaceutical, referred to

as PSMA I&T, that demonstrated improved ability to bind to PSMA. Ex. 1002 ¶¶62–65; Ex. 1028 at 6-7. The structure of PSMA I&T is shown below.



Ex. 1028 at 2; Ex. 1002 ¶¶63.

PSMA I&T is structurally similar to compound 12, the ligand disclosed in Weineisen 2014. Ex. 1002 ¶¶60-61 and 64; Ex. 1028 at 2. PSMA I&T comprises a chelating moiety (DOTAGA), a linker, and a PSMA-targeting moiety (Sub-KuE). Ex. 1002 ¶¶63-64; Ex. 1028 at 2. The only differences between PSMA I&T and compound 12 are small changes to the linker, specifically, two substituents, a hydroxyl and iodo, were added to compound 12 to arrive at PSMA I&T. Ex. 1028 at 2; Ex. 1002 ¶¶63-64. Weineisen 2015 teaches that PSMA I&T is superior when compared with similar radioligands that were previously available, including compound 12. Ex. 1028 at 3-4; Ex. 1002 ¶¶64. For example, in *in vitro* studies, [^{177}Lu]PSMA I&T demonstrated an almost two-fold increase in PSMA binding

compared to ^{177}Lu -12, conferring a ~72% increase in internalization of [^{177}Lu]PSMA I&T compared to ^{177}Lu -12. Ex. 1028 at 3-4; Ex. 1002 ¶64.

Weineisen 2015 also discloses a proof-of-concept study in which [^{177}Lu]PSMA I&T was administered to two human patients with metastatic castrate-resistant prostate cancer. Ex. 1028 at 6; Ex. 1002 ¶65. In this study, [^{177}Lu]PSMA I&T showed “high, specific and rapid uptake in all previously identified tumor lesions.” Ex. 1028 at 7; Ex. 1002 ¶65. The patients showed “impressive molecular treatment response,” and exhibited improved clinical outcomes, including reduced pain, lower levels of Prostate Specific Antigen (“PSA,” an important indicator in prostate cancer), and reduced disease burden. Ex. 1028 at 7; Ex. 1002 ¶65. In view of these data, Wineisen 2015 teaches that “ ^{177}Lu -PSMA I&T endoradiotherapy was feasible, safe, and effective in metastatic PC.” Ex. 1028 at 8; Ex. 1002 ¶65.

2. *Kratochwil (Ex. 1031)*

Kratochwil, published in 2015, is prior art to the ‘901 patent. Kratochwil discloses a dose escalation study of ^{225}Ac -DOTATOC radionuclide therapy. Ex. 1031 at 1; Ex. 1002 ¶¶73-74. As noted above, ^{225}Ac -DOTATOC had been shown to be superior to its ^{177}Lu -DOTATOC counterpart in Miederer’s *in vivo* mouse studies, *see* Ex. 1015 at 4-5, but had not yet been tested in humans. Ex. 1002 ¶69. Kratochwil describes trials in which thirty-four human patients with neuroendocrine tumors received treatment with ^{225}Ac -DOTATOC at various unit doses and intervals. Ex.

1031 at 1; Ex. 1002 ¶75. Kratochwil observed that the maximum tolerable dose of a single cycle of ^{225}Ac -DOTATOC was considered to be 40 MBq. Ex. 1031 at 2; Ex. 1002 ¶75. For repeated doses, patients tolerated 25 MBq every 4 months or 18.5 MBq every 2 months. Ex. 1031 at 2; Ex. 1002 ¶75. Kratochwil concluded that these doses represented “a well tolerable treatment protocol for [targeted alpha-therapy]” with ^{225}Ac -DOTATOC that “demonstrated promising treatment efficacy in various patients.” Ex. 1031 at 2; Ex. 1002 ¶76.

3. *Jurcic (Exhibit 1011)*

Jurcic, published in 2016, is prior art to the ‘901 patent and was not considered by the Patent Office during prosecution. Jurcic discloses a phase I clinical trial for ^{225}Ac -Lintuzumab, an antibody coupled with ^{225}Ac . Ex. 1011 at 1; Ex. 1002 ¶¶70-71. Like the other radiopharmaceuticals discussed above, ^{225}Ac -Lintuzumab comprises a chelating moiety (DOTA) with a radionuclide (^{225}Ac), a linker, and a targeting moiety that is an antibody (Lintuzumab). Ex. 1011 at 1; Ex. 1002 ¶71. Thirty-eight patients with acute myeloid leukemia (“AML”) were split into four cohorts, each receiving one of the four dose levels tested. Ex. 1011 at 2; Ex. 1002 ¶71. The doses of radioactivity used in this study are summarized below in both $\mu\text{Ci/kg}$ and kBq/kg .⁸

⁸ As explained by Dr. Zalutsky, 1 $\mu\text{Ci/kg}$ equals 37 kBq/kg . Ex. 1002 ¶ 67.

<u>μCi/kg (kBq/kg)</u>
<u>0.5 (18.5)</u>
<u>1.0 (37)</u>
<u>1.5 (55.5)</u>
<u>2.0 (74)</u>

Ex. 1002 ¶71; *see* Ex. 1011 at 2.

Treatments at all dosage levels tested in Jurcic were well tolerated, with only two patients exhibiting dose-limiting toxicity. Ex. 1011 at 2; Ex. 1002 ¶72. Additionally, the treatment induced remission in older patients with untreated AML. Ex. 1011 at 3; Ex. 1002 ¶72. While Jurcic concluded that all dose levels could be safely and effectively used in patients, the 2.0 μCi/kg (74 kBq/kg) dose was identified as a promising dose for a phase II monotherapy study. Ex. 1011 at 2–3; Ex. 1002 ¶72.

4. *Kratochwil 2016 (Exhibit 1045)*

Kratochwil 2016, published in July 2016, is prior art to the ‘901 patent. As Patent Owner argued in IPR2023-00551, that “[t]he invention described in the ‘901 Patent is reflected in a journal article [Kratochwil 2016] published by Kratochwil’s lab *just before the Patent filing.*” PO Resp. at 33 (emphasis added). Likewise, Patent Owner’s expert, Dr. Hope, states that Kratochwil 2016 discloses an embodiment of the ‘901 Patent that uses ²²⁵Ac-PSMA-617 dosed at 100 kBq per kilogram of body weight to treat prostate cancer. Ex. 1044 at 33-35 (citing Ex. 1045).

B. Person of Ordinary Skill in the Art (“POSA”)

A POSA as of December 2016 would have been a scientist or clinician, with a Ph.D. or M.D., or a team of such individuals, who alone or in combination had experience with (i) the concept of radiolabeling, (ii) the chemical behavior of radiometals (e.g., ^{111}In , ^{177}Lu and ^{225}Ac), (iii) the design, synthesis, and use of chelators that form kinetically and thermodynamically stable complexes with the radiometals, and/or (iv) the evaluation or clinical use of radiotherapeutic agents. Ex. 1002 ¶¶14-16. The POSA would have easily understood the prior art references referred to herein and would have had the capability to draw reasonable inferences from them. *Id.* Dr. Zalutsky obtained the requisite education and experience of a POSA at least by December 15, 2016. Ex. 1002 ¶17.

C. Ground 1: Claims 1, 2, 4–8, and 10–13 are Obvious Over Weineisen 2015 in Combination With Kratochwil

- 1. A POSA would have been motivated to use PSMA I&T in the treatment of prostate cancer with a reasonable expectation of success*

As explained above, by 2014, PSMA-targeted radiotherapy had emerged as a promising treatment option for metastatic prostate cancer. Ex. 1027 at 11; Ex. 1028 at 1. Targeted radiotherapy methods had been developed using either antibodies or small molecules as targeting moieties, but small molecule targeting had benefits over using antibodies. Ex. 1002 ¶¶37, 78. For example, small molecules were known to have shorter half lives in patients’ serum, reducing potential adverse effects from the

radionuclide in non-targeted parts of the body. Ex. 1002 ¶¶37, 78; Ex. 1033, Zhao at 2; Ex. 1008 at 1.

In selecting a potential chelating ligand for a PSMA-targeting radiotherapy, a POSA would have recognized PSMA I&T to be a promising radiopharmaceutical. Ex. 1002 ¶¶79-80. A POSA would have appreciated that Weineisen 2015 concluded that PSMA I&T exhibited ideal characteristics for PSMA-targeted therapy, including increased PSMA affinity and significantly improved internalization efficiency, over prior work on similar compounds. *Id.*; Ex. 1028 at 3-4.

Additionally, using human studies, Weineisen 2015 confirmed that endoradiotherapy with PSMA I&T bound to ^{177}Lu (“ ^{177}Lu PSMA I&T”) was “feasible, safe, and effective” to treat prostate cancer. Ex. 1028 at 8. A POSA would have recognized that human studies are reserved for only the safest and most promising therapies. Ex. 1002 ¶81. By selecting PSMA I&T for human studies, Weineisen 2015 highlighted PSMA I&T as a promising candidate for radiotherapy of PSMA-expressing cancers like prostate cancer. Ex. 1002 ¶81.

Further, Chatalic underscores the attractiveness PSMA I&T as a radioligand and shows that others in the field were interested in improving upon this therapy. From all the radioligands available in the prior art, Chatalic selected PSMA I&T to be used as a ligand for an alpha emitter. Ex. 1006 at 1; Ex. 1002 ¶82. The studies

disclosed in Chatalic would have highlighted for a POSA that PSMA I&T continued to be a safe and effective ligand for radiotherapy. Ex. 1002 ¶82.

Price also underscores that DOTA and derivatives including DOTAGA work well with ^{225}Ac , and so a POSA would have a reasonable expectation of success in making ^{225}Ac -PSMA I&T because the PSMA I&T has a DOTAGA chelator. Ex. 1002 ¶83; Ex. 1041 at 9. Notably, the claims of the '901 patent do not require a requisite level of purity or stability for ^{225}Ac -PSMA I&T, nor do they require any clinical endpoint for the treatment itself. Ex. 1002 ¶83. Rather, the claims are broadly directed to a treatment using known compounds that are known to be useful for such treatment. Thus, to a POSA, Price would provide a reasonable motivation to combine and a reasonable expectation of success. Ex. 1002 ¶83.

As Dr. Zalutsky explains, the real-world evidence shows that a POSA would have been motivated to select PSMA I&T as a ligand when developing a radiotherapy based on Weineisen 2015's disclosure that PSMA I&T is a safe and effective ligand for the treatment of cancer. Ex. 1002 ¶¶81–83; *see also* Ex. 1028 at 6, 8; Ex. 1006 at 1-2. Therefore, a POSA would have been motivated to select the PSMA I&T ligand disclosed in Weineisen 2015 as the basis for an improved PSMA expressing cancer therapy with a reasonable expectation of success. ¶84.

2. A POSA would have been motivated to use PSMA I&T with ²²⁵Ac and would have had a reasonable expectation of success

Although Weineisen 2015 explicitly discloses using PSMA I&T with beta-emitting radionuclides (⁶⁸Ga and ¹⁷⁷Lu), a POSA would have understood that alpha-emitting radionuclides like ²²⁵Ac have the advantages of high potency and specificity. Ex. 1017 at 1; Ex. 1002 ¶¶85–86. These properties have made alpha emitters the “subject of considerable investigation” for targeted cancer therapeutics. Ex. 1017 at 1. As a result, and as explained in more detail below, a POSA would have been motivated to complex ²²⁵Ac with PSMA I&T to improve on the radiopharmaceuticals disclosed in Weineisen 2015 and would have had a reasonable expectation of success in doing so.

1. POSA Would Have Used an Alpha Emitter

As an initial matter, a POSA would have known that alpha particles can have a greater cytotoxic impact on cancer cells within the body than beta particles. Ex. 1002 ¶93; Ex. 1015 at 1. Alpha emissions release more energy and cause more cellular damage than beta emissions. Ex. 1002 ¶93. As Miederer explained, ²²⁵Ac is “characterized by extremely high cytotoxic activity on the cellular level.” Ex. 1015 at 1; Ex. 1002 ¶93. Additionally, unlike beta particles, alpha particles are only able to travel short distances within the body. Ex. 1014 at 1; Ex. 1002 ¶32, 94. This limited range reduces damage to healthy cells surrounding the cancer cells, thereby decreasing side effects. Ex. 1014 at 1; Ex. 1002 ¶32, 94. As Dr. Zalutsky explains, a

POSA would have recognized alpha emitters' advantageous therapeutic properties and considered alpha emitters, like ^{225}Ac , attractive potential alternatives to beta emitters. Ex. 1002 ¶¶32, 94. Therefore, a POSA would have been motivated to use an alpha emitter in an improved prostate cancer radiotherapeutic.

In addition, the POSA would have been motivated to use a targeting compound with a DOTA or DOTA-derivative chelator such as DOTAGA and therefore would have been drawn to PSMA I&T. Ex. 1002 ¶¶98. As discussed above, it was known at the time of the invention that DOTA and derivatives of DOTA including DOTAGA were “the gold standard” for complexation with ^{225}Ac . Ex. 1002 ¶¶98; see Ex. 1041 at 9. Further, the claims of the '901 patent are not limited to a particular purity or stability of the radiopharmaceutical. Moreover, a POSA would have preferred a small molecule/peptide like PSMA I&T over an antibody because it was known that the high temperatures required for chelating ^{225}Ac with DOTA are unfavorable for some antibodies. Ex. 1002 ¶¶98.

The POSA would have been confident that PSMA I&T could be successfully used with alpha emitters, like ^{225}Ac . Ex. 1002 ¶¶86-92. Weineisen 2014 suggested ^{225}Ac would be acceptable for use with the compounds the Weineisen group was studying. Ex. 1027 at 11; Ex. 1002 ¶¶89. Weineisen 2014 stated that the goal of the disclosed studies was to develop a “PSMA ligand allowing for...complexation...with therapeutic M^{3+} -radiometals, e.g., ^{177}Lu , ^{90}Y or ^{225}Ac .” Ex. 1027 at 11; Ex. 1002

¶86. A POSA would have understood that Weineisen's chelator compounds could complex with any M^{3+} radiometal, including the specifically listed radiometals. Ex. 1002 ¶86.

Indeed, prior to December 2016, PSMA I&T had already been complexed with alpha emitting radiometals in treatments for prostate cancer. For instance, Chatalic studied PSMA I&T complexed with alpha emitter ^{213}Bi in prostate cancer preclinical studies. Ex. 1006 at 1-2; Ex. 1002 ¶82. Chatalic taught that "therapeutic efficacy could be significantly enhanced by using alpha-emitting radionuclides" and concluded that ^{213}Bi PSMA I&T showed "promising preliminary results," including "good tumor targeting and induction" Ex. 1006 at 1-2.

Therefore, a POSA would have had a reasonable expectation of success using PSMA I&T with a number of different radionuclides, including alpha-particle emitters, to target PSMA expressing cells *in vivo*. Ex. 1002 ¶¶91 and 94.

2. *A POSA Would Have Recognized Specific Advantages of ^{225}Ac*

Apart from general advantages of alpha emitting radionuclides, a POSA would have been specifically motivated to use ^{225}Ac in an improved prostate cancer therapy.

First, the prior art taught that ^{225}Ac showed increased efficacy as compared to ^{177}Lu . Ex. 1015 at 1-2; Ex. 1002 ¶69. For example, Miederer directly compared beta emitter ^{177}Lu with alpha emitter ^{225}Ac in the same carrier molecule, DOTATOC. Ex.

1015 at 2; Ex. 1002 ¶69. Miederer taught that because ^{225}Ac 's alpha emission is higher energy than ^{177}Lu 's beta emission, ^{225}Ac would have “extremely high cytotoxic activity on the cellular level” and therefore could be a more effective treatment for tumors in patients with metastasized neuroendocrine tumors. Ex. 1015 at 1; Ex. 1002 ¶69. Miederer used *in vivo* studies to conclude that “ ^{225}Ac -DOTATOC activities were shown to be nontoxic (12–20 kBq), reduced the growth of neuroendocrine tumors, and showed improved efficacy compared with ^{177}Lu -DOTATOC,” highlighting the “beneficial effect(s) of ^{225}Ac -DOTATOC over ^{177}Lu -DOTATOC.” Ex. 1015 at 1, 6; Ex. 1002 ¶69. This comparison alone would have motivated a POSA to use ^{225}Ac in a targeted radiotherapeutic.

Second, a POSA would have understood that ^{225}Ac has benefits over other well-characterized alpha emitters. Chatalic disclosed that ^{213}Bi PSMA I&T showed promise in preclinical studies and underscored the benefits of using an alpha emitter with PSMA I&T. Ex. 1006 at 1-2; Ex. 1002 ¶67. But a POSA would have recognized that ^{213}Bi has drawbacks compared with ^{225}Ac . Ex. 1002 ¶87. For example, ^{213}Bi has a short half-life, requiring that the radiotherapy be prepared immediately before administration to prevent loss of potency. *Id.* Further, the POSA would have been motivated to use a targeting compound with a DOTA or DOTA-derivative chelator such as DOTAGA, and therefore would have been drawn to PSMA I&T. As discussed above, it was known at the time of the invention that DOTA and

derivatives of DOTA including DOTAGA were “the gold standard” for complexation with ^{225}Ac . *See* Ex. 1041 at 9; Ex. 1002 ¶88.

A POSA would have understood that ^{225}Ac had been shown to be significantly more potent than ^{213}Bi when compared in the same targeting construct. Ex. 1022 at 1, 4; Ex. 1002 ¶89. A POSA would also have understood that ^{225}Ac does not exhibit many of ^{213}Bi ’s drawbacks. Ex. 1002 ¶89. For instance, ^{225}Ac produces more alpha emissions than ^{213}Bi and has a substantially longer half-life than ^{213}Bi . Ex. 1002 ¶89; Ex. 1022 at 1. Accordingly, the POSA would have been motivated to use ^{225}Ac with PSMA I&T in an improved cancer treatment. Ex. 1002 ¶89.

Lastly, it was also known at the time of the invention that ^{225}Ac could be safe and effective in treating cancers. Ex. 1002 ¶90. For example, a Phase I trial demonstrated that ^{225}Ac -labeled Humanized Anti-CD33 Monoclonal Antibody HuM195 was safe at doses of $\leq 0.1 \text{ MBq/kg}$ – which falls within the claimed dose range – to treat patients with advanced myeloid malignancies. Ex. 1002 ¶90. The compound was then cleared for Phase I/II clinical trials by the FDA to study the response rate, progression-free survival, and overall survival. *See* Ex. 1043 at 3. The POSA would have therefore understood that ^{225}Ac could be used safely and effectively as a radiotherapeutic. Ex. 1002 ¶90.

3. *A POSA Would Have Had a Reasonable Expectation of Success in Making ²²⁵Ac-PSMA I&T*

A POSA would have understood that the chelating moiety of PSMA I&T could successfully complex with any of the widely used M³⁺-radiometals. Indeed, using one radionuclide instead of another, particularly swapping ²²⁵Ac for ¹⁷⁷Lu, had been well-established by 2016. *See supra* Section X.C.ii.2; Ex. 1002 ¶91; *see also* Ex. 1013. Notably, claims 1, 2, and 4-13 of the ‘901 patent are not limited to any particular reaction conditions or any particular purity or stability level. Nor are claims 1, 2, and 4-13 limited to any specific targeting compound and chelating group combination.

Although synthesis of ²²⁵Ac-chelator complexes requires harsher reaction conditions, e.g., higher temperatures, than those needed to synthesize the analogous ¹⁷⁷Lu complexes, a POSA would not have been deterred. Ex. 1014 at 6; Ex. 1002 ¶92. Despite these differences in synthesis, ²²⁵Ac-DOTA/DOTAGA complexes and ¹⁷⁷Lu-DOTA constructs demonstrated similar stability under biological conditions. Ex. 1014 at 6; Ex. 1002 ¶92. Accordingly, a POSA would have had a reasonable expectation of success in being able to complex ²²⁵Ac with PSMA I&T and doing so would have been within the routine skill of a POSA. Ex. 1002 ¶92; *see, e.g.*, Ex. 1013; Ex. 1014. As noted above, the ‘901 patent claims do not require any threshold level of purity or stability to be achieved.

3. *A POSA would have been motivated to use ^{225}Ac -PSMA I&T at the claimed doses*

A POSA contemplating dosage amounts for the ^{225}Ac -PSMA I&T radiopharmaceutical would have based the dosage on the amount of the radionuclide that needs to be delivered to the target site to achieve the therapeutic effect. Ex. 1002 ¶95. The POSA would have looked to prior art regarding the doses of ^{225}Ac necessary to kill cancer cells without being overly toxic to the patient. *Id.*

As a practical matter, before the priority date of the '901 patent, a POSA would have been familiar with the ^{177}Lu Lutathera® product, the dosing of which was known and published in the literature at least as early as 2014 and 2015. Ex. 1002 ¶96. A POSA would also have known that ^{225}Ac and other alpha emitters in radiotherapies: (1) were known to have significantly higher potency than beta emitters like ^{177}Lu , leading to lower doses needed for alpha emitters; and (2) alpha emitters can only travel limited distances, and therefore cause less damage to cells surrounding the target cells. Ex. 1002 ¶96. It would therefore have been routine optimization to extrapolate the significantly lower desired dosage of ^{225}Ac , based on what was known of Lutathera® in order to arrive at the claimed dosages of the '901 patent. Ex. 1002 ¶96.

As ^{225}Ac had garnered interest as a radiopharmaceutical, multiple models and schema had been used to estimate the absorbed dose of radioactivity from administration of ^{225}Ac prior to 2016. *Id.* For instance, in 2010, the Committee on

Medical Internal Radiation Dose (“MIRD”) circulated an expansive pamphlet that outlines the radiobiology and dosimetry of alpha-particle emitters for targeted radionuclide therapy. Ex. 1002 ¶97; Ex. 1017. From that guidance, a POSA would have appreciated the radiobiology, toxicity, and relative biological effectiveness considerations impacting dosimetry of alpha-emitters. Ex. 1002 ¶97. The pamphlet teaches the therapeutic potential, toxicity, and dosimetry of a variety alpha emitters for human studies, including ^{225}Ac . *Id.*; Ex. 10172.

A POSA would also have understood that by 2015, human studies of radiotherapies using ^{225}Ac to treat cancer had already begun. Ex. 1002 ¶98; *see, e.g.*, Ex. 1031. These studies highlight that the dose required for treatment is tied to the amount of radiation that is released by the radiotherapy, measured in the units $\mu\text{Ci/kg}$ or kBq/kg . Ex. 1002 ¶98; *see, e.g.*, Ex. 1031.

A POSA determining the appropriate dose of ^{225}Ac -PSMA I&T would look to the doses used in human studies using structurally similar ^{225}Ac small molecule radiopharmaceuticals. Ex. 1002 ¶98. Kratochwil, for example, would have directed the POSA to use doses in the claimed range. Ex. 1002 ¶98; Ex. 1031 at 2. Kratochwil discloses a dose escalation study to determine suitable doses of ^{225}Ac -DOTATOC for treatment of neuroendocrine tumors. Ex. 1002 ¶98; Ex. 1031 at 2. Like ^{225}Ac -PSMA I&T, ^{225}Ac -DOTATOC comprises a DOTA chelating moiety, a linker, and an oligopeptide-based targeting moiety complexed with ^{225}Ac . Ex. 1002 ¶98.

Further, as discussed above, at least one therapy utilizing ^{225}Ac was determined to be safe in human trials at a dose of $\leq 0.1 \text{ MBq/kg}$, i.e., $\leq 100 \text{ kBq/kg}$. Ex. 1022 ¶99; Ex. 1043 at 3. Therefore, the POSA would have appreciated that ^{225}Ac -DOTATOC would be a suitable comparator for ^{225}Ac -PSMA I&T. Kratochwil concluded that unit doses of 18.5 MBq and 25 MBq of ^{225}Ac -DOTATOC were well tolerated in humans. *Id.*; Ex. 1031 at 2. Accordingly, a POSA would have been motivated to use a similar unit dosage—18.5 MBq or 25 MBq or a dose of $\leq 100 \text{ kBq/kg}$ —for a therapy using ^{225}Ac -PSMA I&T. Ex. 1002 ¶109.

Furthermore, a POSA would have understood that the unit dose disclosed in Kratochwil (18.5 MBq or 25 MBq) could be translated to a body weight dose that also falls within the claimed dosage range. Ex. 1002 ¶99. It was routine in the art to calculate suitable body weight doses based on unit doses. Ex. 1002 ¶99. For example, the average weight of an adult male patient in the United States is 90 kg. Ex. 1034, HHS at 9; Ex. 1002 ¶99. Using this calculation, an 18.5 MBq unit dose of ^{225}Ac -DOTATOC would be equal to administering a dose of 206 kBq/kg to a 90 kg patient.⁹ Ex. 1002 ¶99. Similarly, a 25 MBq unit dose is equal to administering a dose of 278 kBq/kg to a 90 kg patient.¹⁰ *Id.* Therefore, a POSA would also have

⁹ $18.5 \text{ MBq} * (1000 \text{ kBq/MBq}) = 18500 \text{ kBq}$. $18500 \text{ kBq}/90 \text{ kg} = \sim 206 \text{ kBq/kg}$.

¹⁰ $25 \text{ MBq} * (1000 \text{ kBq/MBq}) = 25000 \text{ kBq}$. $25000 \text{ kBq}/90 \text{ kg} = \sim 278 \text{ kBq/kg}$

been motivated to use a per weight dose at either 206 kBq/kg or 278 kBq/kg, depending on dosing frequency. *Id.*

A POSA would have further understood that lower doses could also be effective in light of Jurcic's Phase I clinical trial. Ex. 1002 ¶100; Ex. 1011 at 2. Jurcic examined four doses of a ^{225}Ac -based radiotherapeutic: 18.5 kBq/kg, 37 kBq/kg, 55.5 kBq/kg, and 74 kBq/kg. Ex. 1011 at 2-3 (converted from $\mu\text{Ci/kg}$); Ex. 1002 ¶100. All four doses were determined to be safe and effective, and the 74 kBq/kg dose was selected to be used in the phase II trial. Ex. 1011 at 2-3; Ex. 1002 ¶100. Therefore, a POSA would have known that a dose of around 74 kBq/kg of ^{225}Ac -PSMA I&T would also have been acceptable in an improved cancer treatment. Ex. 1002 ¶100.

Contrary to the representations in the '901 patent, a POSA would have not been surprised that lower doses of ^{225}Ac were needed to show effect as compared to ^{177}Lu . As explained above, alpha emitters were known to release more energy and therefore be more cytotoxic than an equivalent amount of a beta emitter. *See supra* Section X.C.ii.1; Ex. 1002 ¶93; Ex. 1017 at 1. Additionally, Meiderer demonstrated that ^{225}Ac -DOTATOC is more effective than ^{177}Lu -DOTATOC at preventing tumor growth. Ex. 1015 at 4-5; Ex. 1002 ¶69. Therefore, a POSA would have expected that lower doses of an ^{225}Ac radiopharmaceutical, as compared to ^{177}Lu , would be

required for efficacy, and would have been motivated to use doses similar to those previously shown to be safe and effective. Ex. 1002 ¶101.

4. A POSA would have been motivated to administer the ^{225}Ac -PSMA I&T in repeat doses

A POSA contemplating a suitable dosing schedule for ^{225}Ac -PSMA I&T would have understood that repeat dosing was routine practice in cancer therapy Ex. 1002 ¶¶75-76, 116. For instance, Kratochwil taught that dosing 18.5 MBq of a ^{225}Ac radiopharmaceutical every two months (i.e., approximately 60 days) was “a well tolerable treatment protocol” for targeted alpha-therapy. Ex. 1031 at 2; Ex. 1002 ¶¶75-76, 116. A POSA would have understood that this repeat dosing regimen “demonstrated promising treatment efficacy in various patients.” Ex. 1031 at 2; Ex. 1002 ¶76. As a result, a POSA would have understood that similar repeated dosing of ^{225}Ac -PSMA I&T would be well tolerated and appropriate. Ex. 1002 ¶¶98, 116. Accordingly, a POSA would have been motivated to repeat administration of 18.5 MBq of ^{225}Ac -PSMA I&T after approximately 60 days for targeted radiotherapy and would have had a reasonable expectation of success. Ex. 1031 at 2; Ex. 1002 ¶116.

5. A POSA would have been motivated to use the ^{225}Ac -PSMA I&T to treat PSMA expressing cancers

Although PSMA overexpression is most commonly associated with prostate cancer, a POSA would have understood that PSMA had been shown to be overexpressed in a number of cancers, including breast and renal cancer. Ex. 1002

¶102. For over a decade, scientists recognized that PSMA expression in tumors was correlated to a high risk of disease progression. *See* Ex. 1002 ¶102; *see, e.g.*, Ex. 1021, Ross. Scientists recognized that the overexpression of PSMA used in the imaging and therapy of prostate cancer could be leveraged to develop targeted therapies for other tumor cells that present more PSMA on their cell surface than non-cancerous cells. Ex. 1002 ¶102.

For example, by 2014, a POSA would have understood that breast cancer metastases showed elevated levels of PSMA and would have recognized PSMA's potential as a candidate target for breast cancer therapies. *Id.*; Ex. 1029, Wernicke 2014 at 5; Ex. 1018, Nomura at 6. And, by 2014, PSMA-targeting constructs had been successfully used in the imaging of metastatic renal cell carcinoma. Ex. 1007, Demirci at 1; Ex. 1002 ¶102. Accordingly, a POSA would have been motivated to use the improved ^{225}Ac PSMA I&T to treat any PSMA-expressing cancer, such as prostate cancer, breast cancer, or renal cancer. Ex. 1002 ¶102.

Further, the POSA would have recognized that the treatment of PSMA-expressing cancers would not be limited to encapsulated, solid tumors. Ex. 1002 ¶103; *see also* Ex. 1028 at 2-4. PSMA-expressing solid tumors have been shown to expand beyond their native tissue environment. *Id.*; Ex 1039, Ghosh at 2. For example, PSMA-expressing breast cancer is known to migrate (i.e., metastasize) to other parts of the body. Ex. 1002 ¶103; Ex. 1007 at 1; Ex. 1018 at 6; *see* Ex. 1029 at

1. Because targeted therapy targets the protein expressed on the outside of a cell, rather than being confined to a specific tissue, the therapy will direct itself to anywhere a PSMA-expressing cancer cell has disseminated. Ex. 1002 ¶103; Ex. 10297; Ex. 1028 at 2-4. A POSA would have understood that targeted therapy has the advantage of impacting solid tumors as well as disseminated cells, unlike localized radiation therapies which only treat discrete areas. Ex. 1002 ¶103. Therefore, the POSA would have been motivated to use the improved ²²⁵Ac-PSMA I&T radiopharmaceutical to treat any cancer— whether encapsulated or disseminated—that overexpressed PSMA, including breast and prostate cancer, and would do so with a reasonable expectation of success in light of the knowledge of PSMA expression. See Ex. 1002 ¶¶92-93.

6. Each and Every Challenged Claim is Unpatentable as Obvious in Light of the Prior Art

Claims 1, 2, and 4-8 cover the use of ²²⁵Ac-PSMA I&T in the treatment of PSMA expressing cancers at doses known in the prior art. As explained above, a POSA would have been motivated to complex PSMA I&T with ²²⁵Ac and use that complex to treat PSMA expressing cancers at doses within the claimed ranges. Therefore, claims 1, 2, and 4-8 are unpatentable as obvious in light of the prior art.

1. Claim 1

Independent claim 1 is directed to a method of administering certain ²²⁵Ac radiopharmaceuticals to a patient at specified dosage amounts. Ex. 1001 at 18:13-

20:37; Ex. 1002 ¶105. Formula C listed in claim 1 is PSMA I&T (Ex. 1001 at 19:20-39) as disclosed in Weineisen 2015 (Ex. 1028 at 2). Ex. 1002 ¶105. Formula D listed claim 1 is PSMA I&T with an undefined stereocenter, which would also cover the PSMA I&T compound disclosed in Weineisen 2015. Ex. 1001 at 19:39-20:15; Ex. 1002 ¶105.

As discussed above, a POSA would have understood that PSMA I&T was recognized as a promising chelating ligand for small-molecule PSMA-targeting therapies. *See supra Section X.C.i*; Ex. 1002 ¶106. For instance, Chatalic recommended radiopharmaceuticals comprising PSMA I&T for additional studies. Ex. 1006 at 2; Ex. 1002 ¶106. PSMA expressing cancers were a known target for PSMA I&T, and as such, the POSA would have been motivated to use this improved PSMA-targeting radiopharmaceutical in an improved method of treating of PSMA-expressing cancers. Ex. 1002 ¶107.

It would also have been obvious to a POSA to complex the alpha emitter ²²⁵Ac with PSMA I&T. Ex. 1002 ¶108. As discussed above, Weineisen 2015 disclosed PSMA I&T complexed with beta emitter ¹⁷⁷Lu, but the POSA would have appreciated that alpha emitters were known to be superior to beta emitters in that they were more potent and caused fewer side effects. *Supra Section X.C.ii.1*. The POSA would have been confident in substituting ²²⁵Ac for ¹⁷⁷Lu because, for example, Miederer shows that ¹⁷⁷Lu and ²²⁵Ac can be used interchangeably in a

chelator targeting molecule. *See* Ex. 1015 at 5-6; Ex. 1002 ¶108. When used in the same targeting compound, ^{225}Ac and ^{177}Lu showed similar stability profiles, but ^{225}Ac exhibited increased efficacy compared to the ^{177}Lu analog. Ex. 1015 at 5-6; Ex. 1002 ¶108. Therefore, the POSA would have been motivated to complex ^{225}Ac with PSMA I&T with a reasonable expectation of success.

The POSA seeking to use ^{225}Ac -PSMA I&T for treating cancer would have been motivated to use doses within the claimed ranges. Ex. 1002 ¶109. The dose of radiation recited in claim 1 is “from 25 kBq to 400 kBq/kg of body weight of said patient” or “a unitary dosage of from 3 MBq to 30 MBq.”¹¹ Ex. 1001 at Abstract. As discussed above, Kratochwil discloses a unitary dose of 18.5 MBq or 25 MBq, which is equivalent to a dose of approximately 206 kBq/kg and 278 kBq/kg for an average male patient. *See supra* Section X.C.iii.; Ex. 1002 ¶110; Ex. 1031 at 2. Therefore, the claimed dosage ranges of “from 25 kBq to 400 kBq/kg of body weight of said patient” or “a unitary dosage of from 3 MBq to 30 MBq,” both overlap with the dosage amounts that a POSA would have been motivated to use for a ^{225}Ac

¹¹ The dose limitations of claim 1 are included in the alternative, requiring one or the other to infringe. As such, the claim is unpatentable if the claim is obvious with any single alternative limitation. *See In re Theresa*, 720 F. App’x 634, 637 (Fed. Cir. 2018); *see also Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001). As discussed in this petition, both the dosage limitations in claim 1 would have been obvious to a POSA, but the Board need only find that one dose limitation is obvious in order to find claim 1 unpatentable.

radiopharmaceutical, making the claimed ranges *prima facie* obvious. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). “[E]ven a slight overlap in [the claimed and prior art] range[s] establishes a *prima facie* case of obviousness.” *Id.*; see also *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) (finding prior art disclosing a single value within a claimed range invalidated the claimed range that encompassed the prior art value). “[W]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence of teaching away, unexpected results or criticality,” or other pertinent evidence of nonobviousness. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (citations omitted) (internal quotations marks omitted). There is no such evidence that would overcome the presumption of obviousness here—the prior art taught toward doses of ^{225}Ac that fall within the claimed range and the results of using these well-characterized doses would have been entirely expected in light of the prior art.

Taken together, a POSA would have been motivated to use PSMA I&T (formula C and D of claim 1) as disclosed in Weineisen 2015 complexed with ^{225}Ac to treat PSMA-expressing cancers at the doses required by claim 1 as disclosed in Kratochwil, and the POSA would have been able to perform such a method with a

reasonable expectation of success. Therefore, claim 1 is unpatentable as obvious in light of Weineisen 2015 in combination with Kratochwil. Ex. 1002 ¶111.

2. *Claim 2*

Claim 2 depends from claim 1 and narrows the specified targeting compounds. Ex. 1002 ¶112; Ex. 1001 at 20:38-25:16. Formula C of claim 2 is PSMA I&T, and Formula D of claim 2 is PSMA I&T with an undefined stereocenter. Ex. 1002 ¶112; Ex. 1001 at 20:38–25:16. As discussed above, the use of PSMA I&T in the method of claim 1 would have been obvious to a POSA. *See supra Section X.C.vi.1*; 1002 ¶112. Therefore, claim 2 is also unpatentable as obvious in light of Weineisen 2015 and Kratochwil.

3. *Claims 4-7*

Claims 4-7 depend from claim 1 and further specify the type(s) of PSMA expressing cancer to be treated with the claimed method:

4. The method of claim 1, wherein said PSMA expressing cancers are selected among prostate cancer, conventional renal cell cancers, cancers of the transitional cells of the bladder, testicular-embryonal cancers, neuroendocrine cancers, colon cancers, brain tumors and breast cancers.
5. The method of claim 1, wherein the cancer is a disseminated cancer.
6. The method of claim 4, wherein said PSMA expressing cancer is prostate cancer.
7. The method of claim 4, wherein said PSMA expressing cancer is breast cancer.

Ex. 1001 at 25:42-26:24.

As discussed above, claim 1 would have been obvious to a POSA in light of Weineisen 2015 and Kratochwil. *See* Section X.C.vi.1. Weineisen 2015 discloses studies that examine both the pharmacology and efficacy of PSMA I&T in *in vitro* and *in vivo* studies, specifically focusing on metastatic prostate cancer. *See supra* Section X.A.i; Ex. 1028 at 2-4; Ex. 1002 ¶113. A POSA would have known that metastatic prostate cancer would express PSMA and would be considered a disseminated cancer. Ex. 1002 ¶113. Additionally, as Dr. Zalutsky explains, PSMA was known to be expressed on a variety of cancers, including metastatic breast cancer, and a POSA would have been motivated to use a PSMA-targeting radiopharmaceutical to treat any PSMA-expressing cancer. *Id.* Therefore, a POSA would have been motivated to use the method of claim 1 to treat the cancers listed in claims 4-7, rendering each of these claims also unpatentable as obvious in light of Weineisen 2015 and Kratochwil. *Id.*

4. *Claims 8, 10-11*

Claims 8, 10 and 11 directly or indirectly depend from claim 1 and require the radiopharmaceutical be administered in narrower dosage ranges:

8. The method of claim 1, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 30 kBq to 250 kBq/kg of body weight.

10. The method of claim 1, wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 4 MBq to 25 MBq.

11. The method of claim 10, wherein the unitary dosage ranges from 5 MBq to 20 MBq.

Ex. 1001 at 26:25-36.

As discussed above, claim 1 would have been obvious to a POSA in light of Weineisen 2015 and Kratochwil. *See supra Section X.C.vi.1.* A POSA would have been motivated to use doses of a ^{225}Ac radiopharmaceutical that are in line with doses of ^{225}Ac that have been previously shown to be safe and effective. Ex. 1002 ¶¶114-115. Kratochwil discloses administering a unitary dosage of 18.5 MBq of radiation using an ^{225}Ac radiopharmaceutical that is structurally similar to ^{225}Ac -PSMA I&T. Ex. 1031 at 2; Ex. 1002 ¶¶114-115; *see supra Section X.A.ii.* Further, Kratochwil's unitary dosage is equivalent to a body weight dosage of approximately 206 kBq/kg in an average male patient. *See supra Section X.C.iii.* Therefore, like claim 1, the ranges required by claims 8, 10, and 11 are *prima facie* obvious because they each include doses that are disclosed in the prior art, and there is no evidence that the prior art taught away from the claimed values or that the claimed values provide any unexpected benefits over the prior art. *See Titanium Metals*, 778 F.2d at 782; *In re Peterson*, 315 F.3d at 1329. As a result, claims 8, 10, and 11 are unpatentable as obvious in light of Weineisen 2015 and Kratochwil.

5. Claims 12-13

Claims 12-13 depend from claims 8 and 10, respectively, and claim specific repeat-dosing schedules:

12. The method of claim 8, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

13. The method of claim 10, wherein administering of the effective amount of said one or more Ac-225-radiopharmaceuticals to the patient is repeated after 15 to 90 days.

Ex. 1001 at 26:37-42; Ex. 1002 ¶116.

As discussed above, claims 8 and 10 would have been obvious to a POSA in light of Weineisen 2015 and Kratochwil. *See supra Section X.C.vi.4.* The additional repeat-dosage limitation added in claims 12 and 13 would also have been obvious to a POSA. Ex. 1002 ¶116.

Kratochwil discloses that administering 18.5 MBq (which is equivalent to approximately 206 kBq/kg) of an ²²⁵Ac radiopharmaceutical every 2 months, was well tolerated. Ex. 1031 at 2; Ex. 1002 ¶116. Therefore, a POSA would have been motivated to use the doses and administration schedule for an ²²⁵Ac radiopharmaceutical that was similar to those disclosed in Kratochwil. Ex. 1002 ¶116. Kratochwil's dosing schedule of 18.5 MBq (206 kBq/kg) repeated after 60 days falls within the "15 to 90 days" range recited in claims 12 and 13, and there is no evidence that prior art taught away from such a schedule or that the claimed range

provides any unexpected benefits over the prior art. Ex. 1002 ¶116. Thus, claims 12 and 13 are unpatentable as obvious in light of Weineisen 2015 and Kratochwil. *See In re Peterson*, 315 F.3d at 1329.

D. Ground 2: Claim 9 is obvious over Weineisen 2015 in combination with Kratochwil and Jurcic.

Claim 9 depends from claim 8, and further narrows the dosage range:

9. The method of claim 8, wherein the dosage ranges from 50 kBq to 200 kBq/kg of body weight.

As discussed above, claim 8 would have been obvious to a POSA in light of Weineisen 2015 and Kratochwil. *See supra Section X.C.vi.4.* The additional limitation further narrowing the dosage range to “from 50 kBq to 200 kBq/kg of body weight” would have also been obvious to a POSA. Ex. 1002 ¶114; Ex. 1001 at 26:29-30.

As discussed above, a POSA would have been aware of several published reports studying the administration of ²²⁵Ac. *See generally supra Section X.A;* Ex. 1002 ¶114. While Kratochwil discloses safety and efficacy at weight-based doses of approximately 206 kBq/kg to 278 kBq/kg, other studies examined lower weight-based doses. Ex. 1031 at 2; *see also* Ex. 1002 ¶99 (converting from MBq). For example, Jurcic discloses successfully administering an ²²⁵Ac radiotherapeutic at doses ranging from 18.5 kBq/kg to 74 kBq/kg to a human patient. Ex. 1011 at 2 (converted from µCi/kg); Ex. 1002 ¶114. Jurcic reported that all dose levels could

be safely and effectively used in patients and identified the 74 kBq/kg dose as a promising dose for further study. Ex. 1011 at 2-3; Ex. 1002 ¶72. Therefore, a POSA would also have been motivated to administer ²²⁵Ac-PSMA I&T at doses similar to those shown to be effective in Jurcic, specifically doses around 74 kBq/kg, and would have reasonably expected success in doing so. Ex. 1002 ¶114.

The claimed range of doses in claim 9 overlaps with the dose range disclosed in Jurcic and includes the dose that was identified in Jurcic as being promising for further study. Ex. 1002 ¶114; Ex. 1001 at 26:29; Ex. 1011 at 2. Therefore, claim 9 is *prima facie* obvious. See *In re Peterson*, 315 F.3d at 1329; *Titanium Metals*, 778 F.2d at 782. There is no evidence that the claimed range has unexpected benefits over the prior art, and the prior art taught toward, not away from, values within the claimed range. Thus, claim 9 is unpatentable as obvious in light of *Weineisen 2015*, *Kratochwil*, and *Jurcic*.

E. Ground 3: Claims 1, 2 and 4-13 are Anticipated by Kratochwil 2016

1. Kratochwil 2016 is Prior Art

In IPR2023-00551, as part of its secondary consideration argument, Patent Owner states that “[t]he invention described in the ’901 Patent is reflected in a journal article [Kratochwil 2016] published by Kratochwil’s lab *just before the Patent filing.*” PO Resp. at 33 (emphasis added). As such, Kratochwil 2016 is *prima facie* prior art under 35 U.S.C §102(a)(1) since it was “described in a printed

publication” on July 7, 2016 before the ’901 Patent was filed on December 15, 2016. Ex. 1045 at 1 (“Published online Jul. 7, 2016.”); *see also* Ex. 1001 at 1 (listing Kratochwil 2016 as published on “Jul. 7, 2016”).

In addition, Patent Owner has not provided any evidence that Kratochwil 2016 is subject to an exception under 35 U.S.C §102(b)(1). Kratochwil 2016 is “by another” as it includes four co-authors that are not listed as inventors on the ’901 Patent. Ex. 1045 at 1 (listing as co-authors Mirjam Weis, Frederik A. Verburg, Felix Mottaghy and Klaus Kopka). Here, there is no evidence that any of these co-authors “obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor” in accordance with the exception under 35 U.S.C §102(b)(1).

As explained by another Board panel when dealing with an inventor’s earlier paper that includes non-inventor co-authors, a Patent Owner would need to provide evidence that the disclosed subject matter of the paper qualifies for an exception under §102(b)(2) to apply. IPR2023-01064, *Murray & Poole Ent. Ltd. v. Int. De Cardiologie De Montreal*, Paper No. 9 at 54-56 (PTAB Jan 16, 2024); *see also EmeraChem Holdings v. Volkswagen*, 859 F.3d 1341, 1345 (Fed. Cir. 2017); MPEP 2155.01 (discussing nature of evidence that “may” establish an exception under §102(b)(1)(A)).

If anything Kratochwil 2016 suggests at least Dr. Kopka’s work contributed to the disclosed subject matter by expressly referencing Dr. Kopka’s patent

application “for PSMA-617 (regardless of the radiolabeling nuclide).” *See* Ex. 1045 at 4. Dr. Kopka is not listed as an inventor of the ’901 Patent. Nor is there any evidence to suggest that co-authors Mirjam Weis, Frederik A. Verburg, Felix Mottaghy, and Klaus Kopka did not contribute to the subject matter disclosed in Kratochwil 2016. Indeed, most of these co-authors are not listed as being members of the same organizations as inventors of the ’901 Patent, but rather are associated with different organizations suggesting they would have made independent contributions to the disclosed subject matter. *Id.*

Therefore, the Kratochwil 2016 paper is prior art as it was published before the ’901 Patent and there is no evidence that Kratochwil 2016 falls within an exception provided by §102(b)(1).

1. Kratochwil 2016 Anticipates Claims 1, 2, 4–8, and 10–13

In IPR2023-00551, as part of its secondary consideration argument, Patent Owner admits that Kratochwil 2016 is an embodiment of the ’901 Patent. IPR2023-00551, Paper No. 15 at 57. Thus, if Kratochwil 2016 is prior art, then Patent Owner has admitted that Kratochwil 2016 anticipates the challenged claims, which is confirmed by the testimony of Dr. Hope, who was Patent Owner’s expert.

In particular, Dr. Hope testified that Kratochwil 2016 embodies all of the challenged claims of the ’901 Patent:

It is my opinion that the treatment method in the Kratochwil paper embodies the claims of the '901 patent. Specifically, it embodies challenged Claims 1, 2, 4-6, and 8-13.

Ex. 1044 at 37. For the reasons provided below, and as admitted by Patent Owner, Kratochwil 2016 anticipates each of claims 1, 2, 4-13.

1. Claim 1

Dr Hope testifies that Kratochwil 2016 discloses administering “²²⁵Ac-PSMA-617 radiopharmaceutical to patients in need of cancer treatment as required by Claim 1.” Ex. 1044 at 37; Ex. 1045 at 2-3. In addition, Dr. Hope testified that the structure of PSMA-617 “falls under Formula A described in Claim 1” where “the variable Chelator is the DOTA moiety, the variable Y is an aryl, X is the naphthyl moiety, and the Zs are -CO₂H groups.” Ex. 1044 at 38. Next, Dr. Hope testifies that Kratochwil 2016 discloses dosage amounts of “9-10 MBq of the radiopharmaceutical every two months for the first patient and 6.4 MBq of the radiopharmaceutical every two months for the second patient” which represent 100kBq/kg and therefore “falls within the administered activities of 25-400 kBq/kg of body weight and a unitary dosage of 3-30 MBq recited in Claim 1.” Ex. 1044 at 39; Ex. 1045 at 2.

Therefore, Kratochwil discloses an embodiment within the broad ranges recited in claim 1 of the '901 Patent, which is all that is required for anticipation. *See Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015) (“When

a patent claims a range, as in this case, that range is anticipated by a prior art reference if the reference discloses a point within the range”).

2. *Claim 2*

Dr Hope testifies “Claim 2, which further limits the range of molecular structure includes the specific PSMA-617 structure as an option...so the method described in the Kratochwil paper meets Claim 2.” Ex. 1044; Ex. 1001 at 20:40-65.

3. *Claims 4 and 6*

Dr Hope testifies Kratochwil 2016 “describes treatment of ‘metastatic castration-resistant prostate cancer,’ and therefore meets both of these Claims [4 and 6]” while recite treatment of certain cancers including prostate cancer. Ex. 1044 at 40; Ex. 1045 at 1.

4. *Claim 5*

Dr Hope testifies “Claim 5 includes the treatment of disseminated cancers. The Kratochwil paper meets this requirement because the PET/CT scan of the treated patients shows that both patients began with metastasized cancers throughout their bodies which were then treated.” Ex. 1044 at 40; Ex. 1045 at Fig. 1, Fig. 3 and 2-3.

5. *Claims 8-11*

Dr Hope testifies that “Claims 8 through 11 narrow the dosage range based on body weight and the unit dosage, but the dosages used in Kratochwil still fall within those claimed ranges. [Ex. 1045 at 2-3]. Claims 8 and 9 require 30-250

kBq/kg of body weight and 50-200 kBq/kg of body weight, respectively. *Id.* The 100 kBq/kg of body weight described in the Kratochwil paper falls within these Claims. *Id.* Claims 10 and 11 recite unitary dosages of 4-25 MBq and 5-20 MBq, respectively, which encompass the 6.4 and 9-10 MBq doses used for the patients in the Kratochwil paper.” Ex. 1044 at 40-41; Ex. 1045 at 2-3.

6. *Claims 12-13*

Dr Hope testifies “Claims 12 and 13 depend from Claims 8 and 10, respectively, and require that the administering of the effective amount is repeated after 15-90 days. The Kratochwil paper described administering new dosages every two months – which would be 60 days – and thus falls within these two claims as well.” Ex. 1044 at 41; Ex. 1045 at 2-3.

XI. PATENT OWNER’S SECONDARY CONSIDERATION EVIDENCE LACKS A NEXUS AND DOES NOT OVERCOME THE STRONG CASE OF OBVIOUSNESS

In IPR2023-00551, Patent Owner submitted what it contends is evidence of secondary considerations of non-obviousness. IPR2023-00551, Paper No. 8 at 57-67. Yet, Patent Owner does not establish that the purported evidence of secondary considerations has a nexus to the claimed invention. *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (“[t]he patentee bears the burden of showing that a nexus exists”). In fact, Patent Owner provides no indication for how

its evidence relates to any specific claim limitation. Without this nexus, the Patent Owner's secondary consideration arguments carry little to no weight.

Even if Patent Owner could establish a nexus, the purported evidence does not overcome the strong case of obviousness presented in this Petition.

A. No Industry Praise for Claimed Invention

Patent Owner's argument for praise is based on alleged praise for the Kratochwil 2016 article that forms the basis of the anticipation rejection for Ground 3 above.

Assuming Kratochwil 2016 is not prior art, Patent Owner's argument relies on the legally flawed assumption that "any praise of the Kratochwil paper would reflect upon the '901 Patent invention." PO Resp. at 57. Yet, the law requires that "[e]vidence of secondary considerations must be reasonably commensurate with the scope of the claims." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). In particular, Patent Owner has not shown that the narrow embodiment in Kratochwil 2016 is commensurate with the broad scope of the '901 Patent claims. *Allergan, Inc. v Apotex, Inc.*, 754 F.3d 952, 963 (Fed. Cir. 2014) ("Neither the district court nor appellees explain the nexus between this finding and the broad scope of '029 patent's claimed invention. The '029 patent's claimed invention is not unique to PGF analogs that bind the variant FP receptor").

The claims of the '901 Patent are not limited to any specific treatment while encompassing multiple radiopharmaceutical formulas and broad dosage ranges. Kratochwil 2016 discloses treating a singular disease (prostate cancer), using a singular radiopharmaceutical formula ($^{225}\text{AC-PSMA-617}$) at a singular dosage (100 kBq of body weight). As in *Allergan*, the narrow and limited disclosure of this evidence cannot be commensurate with the “full scope” of the claimed invention. *Allergan*, 754 F.3d at 963. As such, Kratochwil 2016 can invalidate the claims since it discloses an embodiment within the scope of the ranges claimed, but it cannot serve as evidence of praise for secondary considerations since this singular embodiment is not commensurate with the breadth of the claims.

First, claim 1 of the '901 Patent is not bounded by being used as a method for any specific treatment or outcome, which means the claims encompass being used for any possible treatment. Indeed, claim 4 confirms the breadth of claim 1 as claim 4 limits the scope to a list of eight specific treatments. Ex. 1001 at 25:42-43 and 26:16-18. One of the treatments listed in claim 4 is “prostate cancer”, which is the only treatment discussed in Kratochwil 2016. Any evidence of alleged praise related to the treatment of prostate cancer is not evidence of praise for all other possible treatments encompassed by claim 1 (or even the other seven treatments listed in claim 4).

Next, claim 1 of the '901 Patent recites a radiopharmaceutical comprising “Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D), or (E).” Ex. 1001 at 18:18-19. Thus, the scope of the claim encompasses using any one of these five different formulas for the targeting compound, but Kratochwil 2016 only discloses a single radiopharmaceutical formula, namely ^{225}Ac -PSMA-617, which “falls under Formula A” according to Dr. Hope. Ex. 1044 at 38. Yet, the only claim of the '901 Patent limited to using ^{225}Ac -PSMA-617 is claim 3 – which is not challenged in this Petition. See Ex. 1001 at 25:17-19. Claim 1, and the other challenged claims, encompass radiopharmaceutical formulas other than ^{225}Ac -PSMA-617. Thus, there is no nexus between the alleged praise of ^{225}Ac -PSMA-617 and the challenged claims.

Indeed, all of the articles cited by Patent Owner for industry praise refer to the specific ^{225}Ac -PSMA-617 radiopharmaceutical formula used in Kratochwil 2016 rather than all of the other radiopharmaceutical formulas encompassed by the claims. See IPR2023-00551, Paper No. 15 at 59-61 (“ ^{225}Ac -PSMA-617 was chosen for the special award...”); (“First in-human studies of PSMA-617 labeled with the long-lived α emitter ^{225}Ac ...have shown remarkable therapeutic efficacy”); (“ ^{225}Ac -PSMA-617...has shown a remarkable therapeutic efficacy”); (“cycles of α -emitting ^{225}Ac -PSMA-617 gave an impressive response.”); (“remarkable therapeutic effect of

²²⁵Ac-PSMA-617”). This alleged praise of ²²⁵Ac-PSMA-617 has no nexus to the challenged claims which encompass other radiopharmaceutical formulas.

Lastly, claim 1 of the '901 Patent recites administering a dosage of ²²⁵Ac radiopharmaceuticals in a range “from 25kBq to 400kBq/kg of body weight” where said dosage is administered as a unitary dosage in the range of “from 3 MBq to 30 MBq.” Ex. 1001 at 20:32-37. In contrast, Kratochwil 2016 administered a dosage of ²²⁵Ac radiopharmaceuticals of 100 kBq per kilogram body weight and provided as a unitary dose between 6-10 MBq. Ex. 1045 2 (“patient A was treated with 3 cycles of 9–10 MBq (100 kBq per kilogram of body weight) of ²²⁵Ac-PSMA-617”) and *id.* at 3 (“patient [B] received 3 cycles of 6.4 MBq (100 kBq per kilogram of body weight)”).

Any praise associated with the very specific dosage of 100 kBq/kg of body weight provided as a unitary dosage between 6-10 MBq is not commensurate with the claimed dosage range of 25kBq to 400kBq/kg of body weight provided as a unitary dosage between 3-30 MbQ. Indeed, the claimed dosage range for bodyweight is four times smaller on the low end and four times larger on the high end relative to the dosage provided in Kratochwil 2016.

B. No Unexpected Results or Teaching Away

Patent Owner argues that the result of treatment with ²²⁵Ac is unexpected in how well it worked relative to the “failure of treatment with a ¹⁷⁷Lu construct” and

that these “results also taught away from the conventional wisdom at the time.” PO Resp. at 63-65. These arguments are little more than a rehash of Patent Owner’s argument for why a POSA would not have been motivated to combine the prior art. However, the reasons provided in this Petition regarding the motivation to combine and reasonable expectation of success of Ground 1 (supported by the testimony of Dr. Zalutsky), demonstrate that a POSA would have expected the results disclosed in the ’901 Patent motivating a POSA to pursue the claimed invention.

As discussed above, a POSA would have been aware of the benefits of alpha emitters like ^{225}Ac for a prostate treatment including increased cytotoxicity and shorter travel distances compared to known treatments using beta emitters like ^{177}Lu . Ex. 1002 ¶¶85-86; Ex. 1014 at 1; Ex. 1015 at 1. Indeed, prior to Kratochwil paper, Chatalic disclosed that “therapeutic efficacy could be significantly enhanced by using alpha-emitting radionuclides” to treat prostate cancer. Ex. 1006 at 1-2; Ex. 1002 ¶82. In addition, Weineisen 2014 showed that a PSMA ligand could be complexed with the alpha emitted ^{225}Ac . Ex. 1027 at 11; Ex. 1002 ¶86. In short, the benefits of and ability to use ^{225}Ac to treat PSMA expressing prostate cancer were known prior to Kratochwil 2016 and the ’901 Patent.

Furthermore, Kratochwil 2016 expressly undercuts the Patent Owner’s argument that the results were unexpected. In particular, Kratochwil 2016 states that

the *in vivo* result described in the paper “matches the theoretic considerations” based on prior studies:

The ligand PSMA-617 induces fast cellular internalization, with 54% and 75% of the total cell-associated activity internalized after 1 h and 3 h, respectively, of incubation in the LNCaP cell line (2). For the PSMA-targeted and then internalized antibody ^{225}Ac -J591, sufficient tumor retention of the ^{225}Ac daughter nuclides has already been demonstrated in vitro (15). Thus, *radioligand therapy with ^{225}Ac -PSMA-617 ideally matches the theoretic considerations* for targeted α -therapy of mCRPC.

Ex. 1045 at 3 (emphasis added).

The fact that the actual outcome “matched” the theoretic outcome shows that the results were expected rather than unexpected. While Kratochwil 2016 may have been the first to publish *in vivo* results for treating prostate cancer with ^{225}Ac -PSMA-617, the results obtained by Kratochwil 2016 were predictable in light of the prior studies in light of the knowledge of a POSA.

With respect to the difference in treatment outcome of using alpha emitter ^{225}Ac compared to beta emitter ^{177}Lu , this also was a predictable as this difference between alpha emitters and beta emitters had already been demonstrated in other studies as expressly acknowledged in Kratochwil 2016. Ex. 1045 at 3 (“In patients with neuroendocrine tumors refractory to ^{177}Lu -labeled somatostatin analogs, it has *already been demonstrated* that targeted α -therapy can break radioresistance to β -radiation (8).”) (emphasis added). This is consistent with Chatalic which disclosed

that “alpha-emitting radionuclides” showed improved therapeutic effects. Ex. 1006 at 1-2. Thus, there was nothing unexpected by the differing outcomes of using alpha emitter ^{225}Ac compared to beta emitter ^{177}Lu .

C. No Long-Felt Unresolved Need

At best, Patent Owner argues that “prostate cancer had long needed a better method of treatment.” PO Resp. at 65-66. Yet, this generalized unresolved need to treat prostate cancer has no nexus to the claims of the '901 patent, which are not directed to any specific treatment, let alone prostate cancer. As discussed earlier, only claim 3 (which is not challenged in this Petition) recites prostate cancer and even then, prostate cancer is recited in a list with eight other potential treatments of the claimed invention.

In addition, there is no evidence that a method of using ^{225}Ac radiopharmaceuticals to treat cancer was a long-felt unresolved need. Instead, of any scientific or technical barriers to performing such a method, the barrier to using this method was an economic one due to the limited supply of ^{225}Ac as acknowledged in Kratochwil 2016. Ex. 1045 at 3 (“Nevertheless, the limited availability of ^{225}Ac is still a key challenge for its clinical translation, and this shortage has to be solved before large studies are feasible.”). The alleged invention of the '901 Patent does not purport to have solved the problem of limited availability of ^{225}Ac at the time of the invention.

XII. CONCLUSION

Petitioner respectfully requests that the Board institute this proceeding and find claims 1, 2, and 4-13 of the '901 patent are unpatentable.

Respectfully submitted,

Dated: September 26, 2025

/James P. Murphy/
James P. Murphy
Reg. No. 55,474
Polsinelli PC
1000 Louisiana Street
Suite 6400
Houston, Texas 77002
Tel: (713) 374-1631
jpmurphy@polsinelli.com
Counsel for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e)(4)(i) *et seq.* and 42.105(b), the undersigned certifies that on September 26, 2025, complete copies of this Petition for *Inter Partes* Review including all supporting exhibits and Petitioner's Power of Attorney are being served by USPS Priority Mail Express® on the following counsel of record for U.S. Patent 10,980,901:

Lewis Roca Rothgerber Christie LLP

PO Box 29001

Glendale, CA 91209-9001

Petitioner has also served electronic copies of the same via email on counsel listed for Patent Owner in IPR2023-00551 as indicated below:

S. Art Hasan

AShan@LewisRoca.com

Lauren E. Schneider

LSchneider@LewisRoca.com

Evan E. Boetticher

EBoetticher@LewisRoca.com

/Ericka McNeil/

Ericka McNeil

Polsinelli, PC

1000 Louisiana Street, Suite 6400

Houston, Texas 77002

Tele: (713) 374-1600