

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FUSION PHARMACEUTICALS, INC.
Petitioner,

v.

UNIVERSITÄT HEIDELBERG
Patent Owner

Case No. IPR2023-00551

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

Issue Date: April 20, 2021

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

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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”).
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	<i>targeted radiotherapy of prostate cancer (PCa)</i> , 53 J. Nuclear Med. 170 (2012) (“Hillier 2012”).
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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”).

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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”).
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 Radiopharmaceuticals 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”).

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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”).
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 Pharmacologica 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”).

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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 <i>Coordination Chemistry Reviews</i> 1906 (2009) (“Viola-Villegas”).
1036	Nima Sharifi, et al., <i>Androgen Deprivation Therapy for Prostate Cancer</i> , 294 <i>JAMA</i> 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 <i>Chem. Revs.</i> 2934 (2015) (“Banerjee”).
1039	Arundhati Ghosh & Warren D.W. Heston, <i>Tumor Target Prostate Specific Membrane Antigen (PSMA) and its Regulation in Prostate Cancer</i> , 91 <i>J. Cellular Biochemistry</i> 528 (2004) (“Ghosh”).
1040	Materials Considered by Dr. Abergel.

I. Introduction

Pursuant to 35 U.S.C. §§ 311–19 and 37 C.F.R. § 42.100 et seq., Petitioner Fusion Pharmaceuticals, Inc. (“Fusion”) 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 because each claim would have been obvious to a person of ordinary skill in the art (“POSA”).

The claims of the ’901 patent recite methods of treating patients who have a cancer characterized by overexpression of prostate-specific membrane antigen (“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 .001–.002. 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 .011.

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 .001, .004; *see also* Ex. 1015, Miederer 2008a at .001. 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. ^{225}Ac 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 .002. As a

result, a POSA would have been motivated to use ^{225}Ac -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— ^{225}Ac —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.

II. Mandatory Notices

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

The only real party-in-interest is Fusion Pharmaceuticals, Inc.

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

Petitioner is not aware of any proceedings on the '901 patent or any pending applications claiming priority 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:

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Service on Petitioner may be made by First-Class mail or hand delivery to Goodwin Procter LLP, 620 Eighth Avenue, New York, NY 10018. Petitioner also consents to and prefers electronic service by emailing counsel of record at the above email addresses and DG-Fusion-IPR@goodwinlaw.com.

D. Payment of Fees

Petitioner authorizes the U.S. Patent & Trademark Office to charge Deposit Account No. 506989 for the fee set in 37 C.F.R. § 42.15(a) for this Petition and further authorizes any additional fees to be charged to this Deposit Account.

III. Certification of Grounds for Standing

Pursuant to § 42.104(a), Petitioner certifies that the '901 patent is available for IPR and that the Petitioner is not barred or estopped from requesting IPR on the grounds identified herein.

IV. Overview of Challenge and Precise Relief Requested

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 in combination with Kratochwil
2	9	Obvious over Weineisen 2015 in combination with Kratochwil and Jurcic

This Petition is supported by the declaration of Dr. Rebecca Abergel, Ph.D. (Ex. 1002), an expert in radioisotopes and heavy elements in the context of developing anticancer radiotherapeutics. Dr. Abergel's experience is reflected in her Curriculum Vitae (Ex. 1003) and within her Declaration (Ex. 1002 ¶¶ 1–9).

V. Background

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. Radiopharmaceuticals

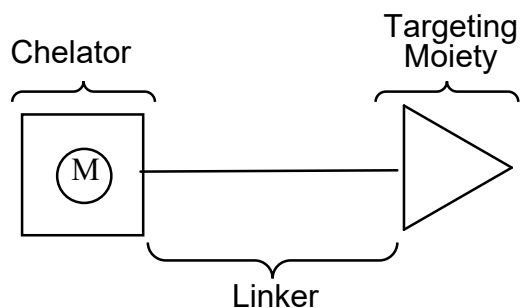
Radioactive elements have been used in medical imaging, diagnostic tests, and radiation therapy for decades. Ex. 1002 ¶¶ 22–24; Ex. 1016.002–.004. Use of radiochemicals for imaging and diagnostics rely on low-energy radiation that can be administered to patients, often systemically, and monitored through detection of the energy emitted from the radioactive decay of the administered radiocompound. Ex. 1002 ¶ 23; Ex. 1012.001–.002. 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 .004.

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 ¶ 24; Ex. 1020.006. Traditional radiation therapy applies radiation from a radioactive source that is external to the patient,

but external radiation therapy has drawbacks. Ex. 1002 ¶ 24; Ex. 1020.002, .005–.006. 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 ¶ 24; Ex. 1020.002–.003.

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. 1013.001–.002; Ex. 1027.011. 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.*

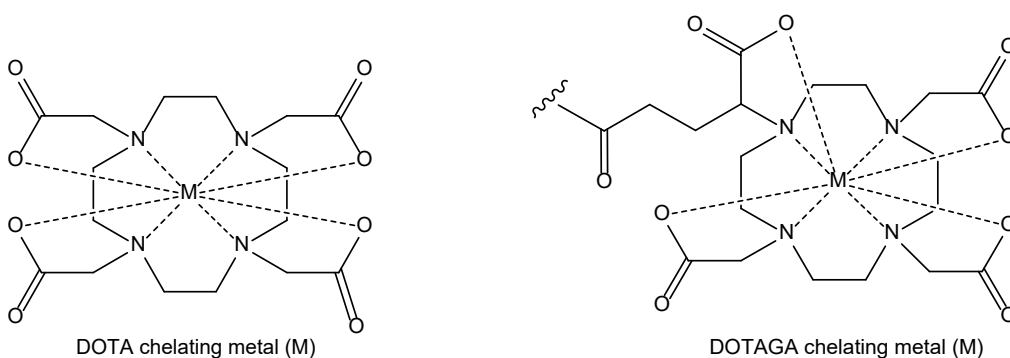
Metallic radionuclides (radioactive atoms in metal chemical families) have been well-studied in cancer therapeutics. Ex. 1002 ¶¶ 24–25; *see* Ex. 1020. Metallic radionuclide-based imaging and therapeutic agents generally follow a design comprising a targeting moiety, a linker, a chelator, and a metallic 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. 1027.011; Ex. 1035, Viola-Villegas at .004, .014, .016.



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. 1014.001–.002; Ex. 1027.011.

B. 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 .006, .008; Ex. 1024, Tukbey at .001; Ex. 1002 ¶ 31. Prior to 2014, treatment options for patients with metastatic prostate cancer were limited to androgen-deprivation therapy and chemotherapy. Ex. 1028.001–.002; Ex. 1002 ¶ 35. 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 .004–.006; Ex. 1002 ¶ 35. 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.

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 .001; Ex. 1002 ¶ 34. 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 ¶ 33; Ex. 1008.001; Ex. 1019, Pomper at .005. 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. 1008.001; Ex. 1002 ¶ 33. Indeed, PSMA was considered an “excellent target” for targeted radioligand therapy. *See* Ex. 1027.011; Ex. 1028.001; Ex. 1002 ¶¶ 33, 55–61. By at least 2016, PSMA-targeted radiopharmaceuticals had been “highly optimized” for therapeutic applications. *See* Ex. 1027.011; Ex. 1028.001; Ex. 1002 ¶¶ 59–61.

VI. 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. For purposes of this petition, Petitioner assumes any patent or printed publication dated prior to December 15, 2016 qualifies as prior art.

A. Specification

The '901 patent specification describes the alleged invention as “a method for treating PSMA expressing cancers, wherein the method comprises administering to [a] patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals.” Ex. 1001 at Abstract; Ex. 1002 ¶ 37. The specification further describes that the ²²⁵Ac-radiopharmaceutical “is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or

wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.” Ex. 1001 at Abstract; Ex. 1002 ¶ 37.

The inventors acknowledge the known benefits of using alpha emitters like ²²⁵Ac in radiopharmaceuticals to treat of PSMA expressing cancers, disclosing that the “short range (<100 micrometers) action of the Ac-225 alpha emitters” combined with “the very efficient and specific targeting of the Ac-225-radiopharmaceuticals to PSMA” allows for “very good results of destruction of cancer cells without notable damage to non-target tissues.” Ex. 1001 at 12:19–23; Ex. 1002 ¶ 38. Nevertheless, the inventors assert that the use of radiopharmaceuticals comprising ²²⁵Ac as the radionuclide “has been surprisingly found” to “provide considerably...better therapeutic results [than] corresponding radiopharmaceuticals with other radionuclides, especially with the particular administration dosages of the present invention.” Ex. 1001 at 11:36–42; Ex. 1002 ¶ 38. To support this assertion, the inventors disclose that “[e]xperiments have been conducted to compare the efficiency of the Ac-225-radiopharmaceuticals” (²²⁵Ac-PSMA-617) with “non-Ac-225-radiopharmaceuticals comprising the same targeting compound, but chelated...with...a [different] radionuclide” (¹⁷⁷Lu-PSMA-617). Ex. 1001 at 16:12–18 (“A6. Comparative Examples”); Ex. 1002 ¶ 39. The inventors state that “[t]he group treated with Lu-177-PSMA-617 had a

lower response rate in comparison to the one treated with Ac-225-PSMA-617,” and that this was a “remarkable difference taking into account similar hematological toxicity and the more advanced patients selected for Ac-225-radiopharmaceutical therapy.” Ex. 1001 at 16:42–51; Ex. 1002 ¶ 39.

A. Prosecution History

During prosecution of the '901 patent, the Examiner rejected all pending claims, which covered, *inter alia*, a method of treating PSMA expressing cancers by administering a compound within a broad genus of ²²⁵Ac-radiopharmaceuticals at a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or as a unitary dosage of from 3 MBq to 30 MBq. *See* Ex. 1004, '901 File History at .398–.412 (June 24, 2020 Non-Final Rejection); Ex. 1002 ¶ 41. The Examiner based this rejection of these 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. 1004.402, .406 (June 24, 2020 Non-Final Rejection); Ex. 1002 ¶ 41.

The claims of the '791 patent are directed to radiopharmaceuticals to treat prostate cancer with ¹⁷⁷Lu complexed to the chelator. Ex. 1004.404 (June 24, 2020 Non-Final Rejection); Ex. 1002 ¶ 42. The claims of the '160 patent are directed to particular targeting compounds complexed with specific radionuclides and a method of their use in tracing, imaging, and treating prostate cancer. Ex.

1004.406–.408 (June 24, 2020 Non-Final Rejection); Ex. 1002 ¶ 42. The claims of the '791 and '160 patents overlap with the claims rejected by the Examiner—and those that later issued in the '901 patent—in that they cover the radiopharmaceutical specifically identified in claim 3 of the '901 patent, which is not challenged in this petition. *See* Ex. 1004.400–.411 (June 24, 2020 Non-Final Rejection); Ex. 1001 at 25:17–41; Ex. 1002 ¶ 42.

The Examiner explained that the rejected claims were not patentably distinct from the claims of the '791 and '160 patents because “both sets of claims are directed to the same art specific subject matter.” Ex. 1004.402, .406 (June 24, 2020 Non-Final Rejection); Ex. 1002 ¶ 41. The Examiner concluded, “[t]he difference between the instant and the issued claims is in scope only.” Ex. 1004.404, .408 (June 24, 2020 Non-Final Rejection); Ex. 1002 ¶ 42.

The applicant responded that the '791 and '160 patents “focus on the provision of a targeted chelator to which multiple different radionuclides can be complexed.” *See* Ex. 1004.382 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1002 ¶ 43. Specifically, the '160 patent “claims a metal complex including ‘a radionuclide,’ and in separate claims list 14 different illustrative radionuclides,” and the '791 patent “claims only ¹⁷⁷Lu complexed to the chelator compound.” Ex. 1004.382 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1002 ¶ 43. The applicant contended, “[i]n contrast, the present claims recite only ²²⁵Ac.” *See* Ex.

1004.382 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1002 ¶ 43. The applicant further noted that although the '791 and '160 patents disclosed multiple radionuclides, including ^{225}Ac , the examples in the '791 and '160 patents used radionuclides ^{68}Ga for imaging and ^{177}Lu for cancer therapy, rather than ^{225}Ac . *See* Ex. 1004.382 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1002 ¶ 44. The applicant claimed that “both the claims and the disclosures of the [patents] are relatively silent about dosages.” *See* Ex. 1004.382 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1002 ¶ 44.

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. 1004.383 (Oct. 26, 2020 Applicant Arguments/Remarks) (emphasis in original); Ex. 1002 ¶ 45. 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. 1004.383–.384 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1002 ¶ 45. 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.” Ex. 1004.383–.384 (Oct. 26, 2020 Applicant Arguments/Remarks) (emphasis in original); Ex. 1002 ¶ 45. 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. 1004.384 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1002 ¶ 46. 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.” Ex. 1004.384 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1002 ¶ 46.

The Examiner then allowed the claims with minimal explanation and did not address the applicant’s nonstatutory double patenting remarks. *See* Ex. 1004.033–.034 (Jan. 1, 2021 Notice of Allowance); Ex. 1002 ¶ 48.

B. The Challenged Claims

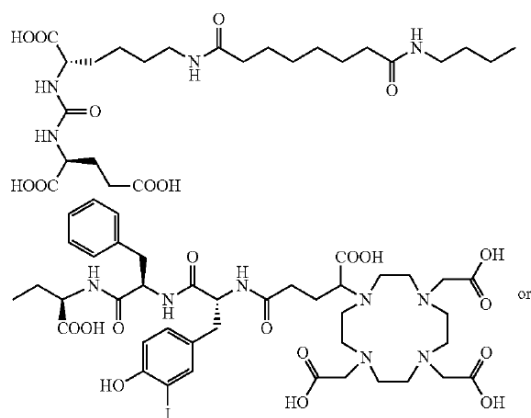
The ’901 patent issued with thirteen claims, twelve of which are challenged here. Independent claim 1 reads:

1. A method for treating PSMA expressing cancers, wherein the method comprises administering to a patient in need thereof an

effective amount of one or more Ac-225-radiopharmaceuticals,
said one or more Ac-225-radiopharmaceuticals comprising Ac-
225 chelated with a targeting compound of Formula (A), (B),
(C), (D) or (E):

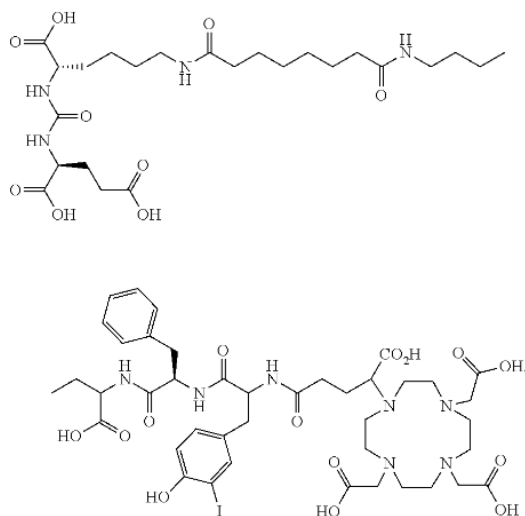
...

Formula (C)



...

Formula (D)



...

wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a dosage of from 25 kBq to 400 kBq/kg of body weight of said patient or wherein the effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.

Ex. 1001 at 18:13–20:37; Ex. 1002 ¶ 50. Formula C listed in claim 1 is the compound referred to as PSMA I&T. Formula D listed claim 1 is PSMA I&T with an undefined stereocenter.

Claims 2 and 4–13 depend from claim 1 either directly or indirectly, and include further limitations regarding specific targeting compounds (claim 2), the type of cancer being treated (claims 4, 5, 6, and 7), dosage ranges (claims 8, 9, 10, and 11), and dosing schedule (claims 12 and 13). *See* Ex. 1001 at 20:38–25:16 (claim 2); Ex. 1001 at 25:42–26:43 (claims 4–13); Ex. 1002 ¶ 51–54.

VII. Claim Construction

For this Petition, Petitioner asserts that the claim terms should be given their plain and ordinary meaning because, to the extent certain claim terms are subject to multiple interpretations, those questions do not affect the grounds advanced here.

Nothing in this Petition should be construed as an admission that the claims, read in light of the specification and the prosecution history, inform a POSA with reasonable certainty about the scope of the invention. Petitioner reserves its right to assert that the claims of the '901 patent are invalid for indefiniteness.

VIII. The Challenged Claims Are Invalid as Obvious

A patent claim is invalid as obvious if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time of the alleged invention to a person having ordinary skill in the art. 35 U.S.C. § 103(a). Obviousness is a question of law premised on underlying issues of fact, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective evidence, such as commercial success, long-felt need, and the failure of others. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007); *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 17–18 (1966).

“A party seeking to invalidate a patent as obvious must demonstrate...‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.’” *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014)

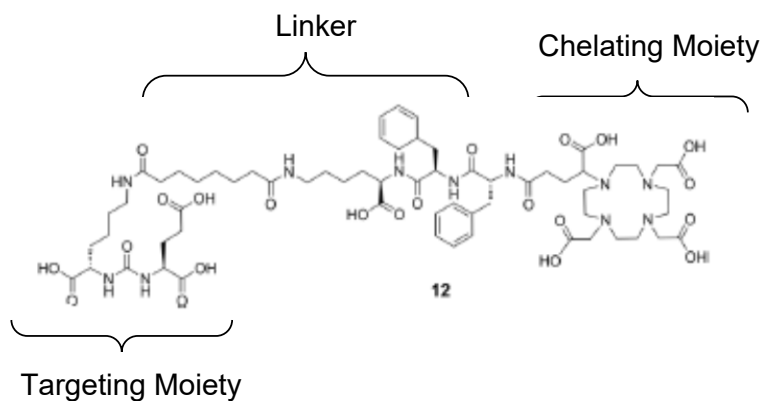
(quoting *Procter & Gamble Co v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009)). Where a claim “simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious.” *KSR Int’l Co.*, 550 U.S. at 417 (citation omitted) (internal quotation marks omitted). That is because “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 416. Such is the case here. All elements of the challenged claims were known in the prior art, and a POSA would have been motivated to combine these elements in the claimed manner with a reasonable expectation of success.

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 ¹⁷⁷Lu and ²²⁵Ac. 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.

i. Weineisen 2014 (Exhibit 1027)¹

Weineisen 2014, published in 2014, is prior art to the '901 patent and was not considered by the Patent Office during prosecution. Weineisen 2014 discloses the synthesis of a “PSMA ligand allowing for...complexation...with therapeutic M^{3+} -radiometals, e.g. ^{177}Lu , ^{90}Y or ^{225}Ac .” Ex. 1002 ¶ 56; Ex. 1027.011. This PSMA ligand, referred to as DOTAGA-ffk(Sub-KuE) (Compound “12”), comprises: a chelating moiety (DOTAGA), a linker, and a PSMA-targeting moiety (Sub-KuE):



Ex. 1027.009 (annotated); Ex. 1002 ¶ 56.

Weineisen 2014 demonstrates that the chelating moiety of DOTAGA-ffk(Sub-KuE) readily complexes with the beta-particle emitter ^{177}Lu to form the

¹ Martina Weineisen, et al., *Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer*, 4 EJMMI Rsch. 63 (2014).

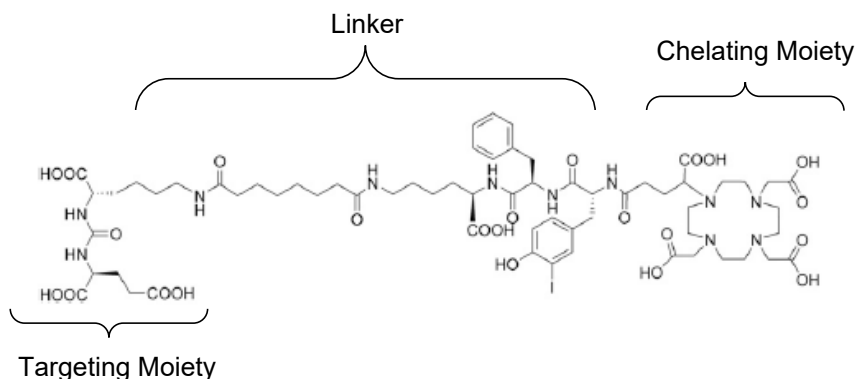
radiopharmaceutical [^{177}Lu]DOTAGA-ffk(Sub-KuE) (“ ^{177}Lu -**12**”). Ex. 1027.008; Ex. 1002 ¶ 57. Weineisen 2014 further examined properties relevant to how ^{177}Lu -**12** would perform in the body. Ex. 1027.008–.010; Ex. 1002 ¶ 57. For instance, using a cell-based *in vitro* assay, Weineisen 2014 measured ^{177}Lu -**12**’s affinity for PSMA, specificity for PSMA-expressing cells, and internalization into prostate cells. Ex. 1027.008–.010; E. 1002 ¶ 57. Weineisen 2014 found that ^{177}Lu -**12** exhibits high affinity for PSMA, with little off-target binding. Ex. 1027.010; Ex. 1002 ¶ 57. ^{177}Lu -**12** was also shown to be rapidly internalized into PSMA expressing cells. Ex. 1027.014; Ex. 1002 ¶ 57. Weineisen 2014 concludes that DOTAGA-ffk(Sub-KuE) “possesses remarkable potential for a PSMA based theranostics concept.” Ex. 1027.014; Ex. 1002 ¶ 57.

*ii. Weineisen 2015 (Exhibit 1028)*²

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. 1028. Weineisen 2015 discloses a different radiopharmaceutical, referred to as PSMA

² Martina Weineisen, et al., *^{68}Ga - and ^{177}Lu -labeled PSMA I&T: Optimization of a PSMA-Targeted Theranostic Concept and First Proof-of-Concept Human Studies*, 56 J. Nuclear Med. 1169 (2015).

I&T, that demonstrated improved ability to bind to PSMA. Ex. 1002 ¶¶ 58–61; Ex. 1028.006–.007. The structure of PSMA I&T is shown below.



PSMA I&T

Ex. 1028.002; Ex. 1002 ¶ 59.

PSMA I&T is structurally similar to compound **12**, the ligand disclosed in Weineisen 2014. Ex. 1002 ¶ 60; Ex. 1028.002. PSMA I&T comprises a chelating moiety (DOTAGA), a linker, and a PSMA-targeting moiety (Sub-KuE). Ex. 1002 ¶¶ 59–60; Ex. 1028.002. 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. 1028.002; Ex. 1002 ¶¶ 59–60. Weineisen 2015 teaches that PSMA I&T is superior when compared with similar radioligands that were previously available, including compound **12**. Ex. 1028.003–.004; Ex. 1002 ¶ 60. For example, in *in vitro* studies, [^{177}Lu]PSMA I&T demonstrated an almost two-fold increase in PSMA binding compared to

¹⁷⁷Lu-12, conferring a ~72% increase in internalization of [¹⁷⁷Lu]PSMA I&T compared to ¹⁷⁷Lu-12. 1028.003–.004; Ex. 1002 ¶ 60.

Weineisen 2015 also discloses a proof-of-concept study in which [¹⁷⁷Lu]PSMA I&T was administered to two human patients with metastatic castrate-resistant prostate cancer. Ex. 1028.006; Ex. 1002 ¶ 61. In this study, [¹⁷⁷Lu]PSMA I&T showed “high, specific and rapid uptake in all previously identified tumor lesions.” Ex. 1028.007; Ex. 1002 ¶ 61. 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. 1028.007; Ex. 1002 ¶ 61. In view of these data, Wineisen 2015 teaches that “¹⁷⁷Lu-PSMA I&T endoradiotherapy was feasible, safe, and effective in metastatic PC.” Ex. 1028.008; Ex. 1002 ¶ 61.

*iii. Miederer (Exhibit 1015)*³

Miederer, published in 2008, is prior art to the '901 patent and was not considered by the Patent Office during prosecution. Miederer discloses that many

³ Matthias Miederer, et al., *Preclinical evaluation of the α -particle generator nuclide ²²⁵Ac for somatostatin receptor radiotherapy of neuroendocrine tumors*, 14 Clinical Cancer Resch. 3555 (2008).

patients with metastasized neuroendocrine tumors did not respond to radiotherapy using a radiopharmaceutical, referred to as DOTATOC,⁴ complexed with the beta-emitting ¹⁷⁷Lu. Ex. 1015.006; Ex. 1002 ¶ 65. Miederer hypothesized that because ²²⁵Ac's alpha emission releases more energy than ¹⁷⁷Lu's beta emission, ²²⁵Ac would have “extremely high cytotoxic activity on the cellular level,” and therefore could be a more effective treatment for tumors in these patients. Ex. 1015.001; Ex. 1002 ¶ 65. To examine the efficacy of ²²⁵Ac-DOTATOC, Miederer discloses studies on mice implanted with xenograft tumors. Ex. 1015.004; Ex. 1002 ¶ 65. These studies demonstrate that ²²⁵Ac-DOTATOC was more effective at preventing tumor growth than ¹⁷⁷Lu-DOTATOC. Ex. 1015.004–.005; Ex. 1002 ¶ 65. Additionally, initial mouse studies show that up to 60 kBq of ²²⁵Ac-DOTATOC was tolerated without toxicity. Ex. 1015.004. These *in vivo* data highlight the “beneficial effect(s) of ²²⁵Ac-DOTATOC over ¹⁷⁷Lu-DOTATOC.” Ex. 1015.006; Ex. 1002 ¶ 65. Miederer concludes, “²²⁵Ac-DOTATOC activities were shown to be nontoxic (12–20 kBq), reduced the growth of neuroendocrine tumors, and

⁴ Like PSMA I&T and DOTAGA-ffk(Sub-KuE) discussed above, DOTATOC is radiopharmaceutical ligand comprising a chelating moiety, a linker, and a peptide-based targeting moiety. Ex 1002 ¶ 65.

showed improved efficacy compared with ^{177}Lu -DOTATOC.” Ex. 1015.001; Ex. 1002 ¶ 65.

iv. Chatalic (Ex. 1006)⁵

Chatalic, published in 2016, is prior art to the '901 patent and was not considered by the Patent Office during prosecution. Chatalic discloses using PSMA I&T with ^{213}Bi , a radiometal that emits alpha particles. Ex. 1002 ¶ 63; Ex. 1006.001. Using xenograph mouse studies, Chatalic found that unitary dosage administration of 5 MBq of ^{213}Bi PSMA I&T induced tumor cell DNA damage within 1 hour of administration. Ex. 1006.001–.002; Ex. 1002 ¶ 63. Chatalic concluded that ^{213}Bi PSMA I&T had “good tumor targeting and induction of [DNA double strand breaks] in PSMA-expressing...xenografts.” Ex. 1006.002; Ex. 1002 ¶ 63.

⁵ Kristell Chatalic, et al., *^{213}Bi -labeled PSMA-targeting agents for alpha radionuclide therapy of prostate cancer*, 57 J. Nuclear Med. 137 (2016).

v. *Kratochwil (Ex. 1031)*⁶

Kratochwil, published in 2015, is prior art to the '901 patent. Kratochwil discloses a dose escalation study of ²²⁵Ac-DOTATOC radionuclide therapy. Ex. 1031.001; Ex. 1002 ¶ 70. As noted above, ²²⁵Ac-DOTATOC had been shown to be superior to its ¹⁷⁷Lu-DOTATOC counterpart in Miederer's *in vivo* mouse studies, *see* Ex. 1015.004–.005, but had not yet been tested in humans. Kratochwil describes trials in which thirty-four human patients with neuroendocrine tumors received treatment with ²²⁵Ac-DOTATOC at various unit doses and intervals. Ex. 1031.001; Ex. 1002 ¶ 71. Kratochwil observed that the maximum tolerable dose of a single cycle of ²²⁵Ac-DOTATOC was considered to be 40 MBq. Ex. 1031.002; Ex. 1002 ¶ 71. For repeated doses, patients tolerated 25 MBq every 4 months or 18.5 MBq every 2 months. Ex. 1031.002; Ex. 1002 ¶ 71. Kratochwil concluded that these doses represented “a well tolerable treatment protocol for [targeted alpha-therapy]” with ²²⁵Ac-DOTATOC that “demonstrated promising treatment efficacy in various patients.” Ex. 1031.002; Ex. 1002 ¶ 72.

⁶ 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. (2015).

vi. *Jurcic (Exhibit 1011)*⁷

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 ²²⁵Ac-Lintuzumab, an antibody coupled with ²²⁵Ac. Ex. 1011.001; Ex. 1002 ¶ 67. Like the other radiopharmaceuticals discussed above, ²²⁵Ac-Lintuzumab comprises a chelating moiety (DOTA) with a radionuclide (²²⁵Ac), a linker, and a targeting moiety that is an antibody (Lintuzumab). Ex. 1011.001; Ex. 1002 ¶ 67. Thirty-eight patients with acute myeloid leukemia (“AML”) were split into four cohorts, each receiving one of the four dose levels tested. Ex. 1011.002; Ex. 1002 ¶ 67. The doses of radioactivity used in this study are summarized below in both µCi/kg and kBq/kg:⁸

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

⁷ 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).

⁸ As explained by Dr. Abergel, 1 µCi/kg equals 37 kBq/kg. Ex. 1002 ¶ 67.

Ex. 1002 ¶ 67; *see* Ex. 1011.002.

Treatments at all dosage levels tested in Jurcic were well tolerated, with only two patients exhibiting dose-limiting toxicity. Ex. 1011.002; Ex. 1002 ¶ 68.

Additionally, the treatment induced remission in older patients with untreated AML. Ex. 1011.003; Ex. 1002 ¶ 68. 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. 1011.002–.003; Ex. 1002 ¶ 68.

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

A POSA as of December 2016 would have been a scientist or clinician, having a Ph.D. or M.D., or a team of such individuals, who alone or in combination had experience with (i) the concept of radioimmunoconjugation, (ii) the chemical behavior of radiometals from the d- and f-blocks of the Periodic Table such as ¹¹¹In, ¹⁷⁷Lu, and ²²⁵Ac, (iii) the design, synthesis, and use of chelators that form kinetically and thermodynamically stable complexes with the radiometals, and (iv) the clinical use of radiotherapeutic agents. Ex. 1002 ¶ 18. 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.*

**C. Ground 1: Claims 1, 2, 4–8, and 10–13 are obvious over
Weineisen 2015 in combination with Kratochwil**

- i. A POSA would have been motivated to use PSMA I&T in the treatment of prostate cancer*

As explained above, by 2014, PSMA-targeted radiotherapy had emerged as a promising treatment option for metastatic prostate cancer. Ex. 1027.011; Ex. 1028.001. 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 ¶¶ 34, 74. 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 ¶¶ 34, 74; Ex. 1033, Zhao at .002; Ex. 1008.001.

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 ¶ 76. 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. 1028.003–.004.

Additionally, using human studies, Weineisen 2015 confirmed that endoradiotherapy with PSMA I&T bound to ¹⁷⁷Lu (“[¹⁷⁷Lu]PSMA I&T”) was

“feasible, safe, and effective ” to treat prostate cancer. Ex. 1028.008. A POSA would have recognized that human studies are reserved for only the safest and most promising therapies. Ex. 1002 ¶ 77. 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 ¶ 77. As Dr. Abergel 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 ¶¶ 77–79; see also Ex. 1028.006, .008; Ex. 1006.001–.002. 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.

ii. 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. 1017.001; Ex. 1002 ¶¶ 85–86. These properties have made alpha emitters the “subject of considerable investigation” for targeted cancer therapeutics. Ex. 1017.001. 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. The POSA Would Have Been Motivated to Use 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 ¶ 85; Ex. 1015.001. Alpha emissions release more energy and cause more cellular damage than beta emissions. Ex. 1002 ¶ 85. As Miederer explained, ²²⁵Ac is “characterized by extremely high cytotoxic activity on the cellular level.” Ex. 1015.001; Ex. 1002 ¶ 85. Additionally, unlike beta particles, alpha particles are only able to travel short distances within the body. Ex. 1014.001; Ex. 1002 ¶ 29, 86. This limited range reduces damage to healthy cells surrounding the cancer cells, thereby decreasing side effects. Ex. 1014.001; Ex. 1002 ¶ 29, 86. As Dr. Abergel explains, a POSA would have recognized alpha emitters’ advantageous therapeutic properties and considered alpha emitters, like ²²⁵Ac, attractive potential alternatives to beta emitters. Ex. 1002 ¶ 86. Therefore, a POSA would have been motivated to use an alpha emitter in an improved prostate cancer radiotherapeutic.

The POSA would have been confident that PSMA I&T could be successfully used with alpha emitters, like ²²⁵Ac. Ex. 1002 ¶¶ 81–84. Weineisen 2014 suggested ²²⁵Ac would be acceptable for use with the compounds the

Weineisen group was studying. Ex. 1027.011; Ex. 1002 ¶ 83. Wineisen 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. 1027.011; Ex. 1002 ¶ 81. A POSA would have understood that Wineisen’s chelator compounds could complex with any M^{3+} radiometal, including the specifically listed radiometals. Ex. 1002 ¶ 81.

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. 1006.001–.002; Ex. 1002 ¶ 78. 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. 1006.001–.002. 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 ¶ 78.

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. 1015.001–.002; Ex. 1002 ¶ 65. For example, Miederer directly compared beta emitter ^{177}Lu with alpha emitter ^{225}Ac in the same carrier molecule, DOTATOC. Ex. 1015.002; Ex. 1002 ¶ 65. 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. 1015.001; Ex. 1002 ¶ 65. 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. 1015.001, .006; Ex. 1002 ¶ 65. 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. As discussed above, 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. *See supra* Section VIII.A.iv; *see also* Ex. 1006.001–.002; Ex. 1002 ¶ 63. But a POSA would have recognized that ^{213}Bi has drawbacks compared with ^{225}Ac . Ex. 1002 ¶ 82. For example, ^{213}Bi

has a short half-life, requiring that the radiotherapy be prepared immediately before administration to prevent loss of potency. *Id.*

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. 1022.001, .004; Ex. 1002 ¶ 83. A POSA would also have understood that ^{225}Ac does not exhibit many of ^{213}Bi 's drawbacks. Ex. 1002 ¶ 83. For instance, ^{225}Ac produces more alpha emissions than ^{213}Bi and has a substantially longer half-life than ^{213}Bi . Ex. 1002 ¶ 83; Ex. 1022.001. Accordingly, the POSA would have been motivated to use ^{225}Ac with PSMA I&T in an improved cancer treatment. Ex. 1002 ¶ 83.

3. A POSA Would Have Had a Reasonable Expectation of Success in Making ^{225}Ac -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 M^{3+} -radiometals. Indeed, using one radionuclide instead of another, particularly swapping ^{225}Ac for ^{177}Lu , had been well-established by 2016. *See supra* Section VIII.C.ii.2; Ex. 1002 ¶ 84; *see also* Ex. 1013. Although synthesis of ^{225}Ac -chelator complexes requires harsher reaction conditions, e.g., higher temperatures, than those needed to synthesize the analogous ^{177}Lu complexes, a POSA would not have been deterred. Ex. 1014.006; Ex. 1002 ¶ 84. Despite these differences in synthesis, ^{225}Ac -DOTA/DOTAGA complexes and ^{177}Lu -DOTA constructs demonstrated similar

stability under biological conditions. Ex. 1014.006; Ex. 1002 ¶ 84. Accordingly, a POSA would have had a reasonable expectation of success in being able to complex ^{225}Ac with PSMA I&T and doing so would have been within the routine skill of a POSA. Ex. 1002 ¶ 84; *see, e.g.*, Ex. 1013; Ex. 1014.

iii. 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 ¶ 87. 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.*

Because ^{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 ¶ 88; 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 ¶ 88.

The pamphlet teaches the therapeutic potential, toxicity, and dosimetry of a variety of alpha emitters for human studies, including ^{225}Ac . *Id.*; Ex. 1017.002.

A POSA would also have understood that by 2015, human studies of radiotherapies using ^{225}Ac to treat cancer had already begun. Ex. 1002 ¶ 89; *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 ¶ 89; *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 ¶ 89. Kratochwil, for example, would have directed the POSA to use doses in the claimed range. Ex. 1002 ¶ 89; Ex. 1031.002. Kratochwil discloses a dose escalation study to determine suitable doses of ^{225}Ac -DOTATOC for treatment of neuroendocrine tumors. Ex. 1002 ¶ 89; Ex. 1031.002. 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 ¶ 89. 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. 1031.002. Accordingly, a POSA would have been motivated to

use a similar unit dosage—18.5 MBq or 25 MBq—for a therapy using ²²⁵Ac-PSMA I&T. Ex. 1002 ¶ 89.

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 ¶ 90. It was routine in the art to calculate suitable body weight doses based on unit doses. Ex. 1002 ¶ 90. For example, the average weight of an adult male patient in the United States is 90 kg. Ex. 1034, HHS at .009; Ex. 1002 ¶ 90. Using this calculation, an 18.5 MBq unit dose of ²²⁵Ac-DOTATOC would be equal to administering a dose of 206 kBq/kg to a 90 kg patient.⁹ Ex. 1002 ¶ 90. Similarly, a 25 MBq unit dose is equal to administering a dose of 278 kBq/kg to an 90 kg patient.¹⁰ *Id.* Therefore, a POSA would also have 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 ¶ 91; Ex. 1011.002. Jurcic examined four doses of a ²²⁵Ac-based radiotherapeutic: 18.5 kBq/kg, 37 kBq/kg, 55.5 kBq/kg, and 74 kBq/kg. Ex. 1011.002–.003 (converted from

⁹ 18.5 MBq * (1000 kBq/MBq) = 18500 kBq. 18500 kBq/90 kg = ~206 kBq/kg.

¹⁰ 25 MBq * (1000 kBq/MBq) = 25000 kBq. 25000 kBq/90 kg = ~278 kBq/kg

μCi/kg); Ex. 1002 ¶ 91. 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. 1011.002–.003; Ex. 1002 ¶ 91. Therefore, a POSA would have known that a dose of around 74 kBq/kg of ²²⁵Ac-PSMA I&T would also have been acceptable in an improved cancer treatment. Ex. 1002 ¶ 91.

Contrary to the representations in the '901 patent, a POSA would have not been surprised that lower doses of ²²⁵Ac were needed to show effect as compared to ¹⁷⁷Lu. 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 VIII.C.ii.1; Ex. 1002 ¶ 29; Ex. 1017.001. Additionally, Meiderer demonstrated that ²²⁵Ac-DOTATOC is more effective than ¹⁷⁷Lu-DOTATOC at preventing tumor growth. Ex. 1015.004–005; Ex. 1002 ¶ 65. Therefore, a POSA would have expected that lower doses of an ²²⁵Ac radiopharmaceutical, as compared to ¹⁷⁷Lu, 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 ¶ 91.

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

A POSA contemplating a suitable dosing schedule for ²²⁵Ac-PSMA I&T would have understood that repeat dosing was routine practice in cancer therapy. Ex. 1002 ¶ 89, 106. For instance, Kratochwil taught that dosing 18.5 MBq of a

²²⁵Ac radiopharmaceutical every two months (i.e., approximately 60 days) was “a well tolerable treatment protocol” for targeted alpha-therapy. Ex. 1031.002; Ex. 1002 ¶¶ 71–72, 106. A POSA would have understood that this repeat dosing regimen “demonstrated promising treatment efficacy in various patients.” Ex. 1031.002; Ex. 1002 ¶ 72. As a result, a POSA would have understood that similar repeated dosing of ²²⁵Ac-PSMA I&T would be well tolerated and appropriate. Ex. 1002 ¶¶ 89, 106. Accordingly, a POSA would have been motivated to repeat administration of 18.5 MBq of ²²⁵Ac-PSMA I&T after approximately 60 days for targeted radiotherapy and would have had a reasonable expectation of success. Ex. 1031.002; Ex. 1002 ¶ 106.

v. A POSA would have been motivated to use the ²²⁵Ac-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 ¶ 92. For over a decade, scientists recognized that PSMA expression in tumors was correlated to a high risk of disease progression. *See* Ex. 1002 ¶ 92; *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 ¶ 92.

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 .005; Ex. 1018, Nomura at .006. And by 2014, PSMA-targeting constructs had been successfully used in the imaging of metastatic renal cell carcinoma. Ex. 1007, Demirci at .001; Ex. 1002 ¶ 92. Accordingly, a POSA would have been motivated to use the improved ²²⁵Ac PSMA I&T to treat any PSMA-expressing cancer, such as prostate cancer, breast cancer, or renal cancer. Ex. 1002 ¶ 92.

Further, the POSA would have recognized that the treatment of PSMA-expressing cancers would not be limited to encapsulated, solid tumors. Ex. 1002 ¶ 93; *see also* Ex. 1028.002–.004. PSMA-expressing solid tumors have been shown to expand beyond their native tissue environment. *Id.*; Ex 1039, Ghosh at .002. For example, PSMA-expressing breast cancer is known to migrate (i.e., metastasize) to other parts of the body. Ex. 1002 ¶ 93; Ex. 1007.001; Ex. 1018.006; *see* Ex. 1029.001. 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 ¶ 93; Ex. 1029.007; Ex. 1028.002–.004. 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 ¶ 93. Therefore, the POSA would have been motivated to use the improved ^{225}Ac -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.

vi. 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 ^{225}Ac -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 ^{225}Ac 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 ^{225}Ac radiopharmaceuticals to a patient at specified dosage amounts. Ex. 1001 at 18:13–20:37; Ex. 1002 ¶ 95. Formula C listed in claim 1 is PSMA I&T (Ex. 1001 at 19:20–39) as disclosed in Weineisen 2015 (Ex. 1028.002). Ex. 1002 ¶ 95. 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 ¶ 95.

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 VIII.C.i; Ex. 1002 ¶ 96. For instance, Chatalic recommended radiopharmaceuticals comprising PSMA I&T for additional studies. Ex. 1006.002; Ex. 1002 ¶ 96. 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 ¶ 97.

It would also have been obvious to a POSA to complex the alpha emitter ^{225}Ac with PSMA I&T. Ex. 1002 ¶ 98. As discussed above, Weineisen 2015 disclosed PSMA I&T complexed with beta emitter ^{177}Lu , 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 VIII.C.ii.1. The POSA would have been confident in substituting ^{225}Ac for ^{177}Lu because, for example, Miederer shows that ^{177}Lu and ^{225}Ac can be used interchangeably in an chelator targeting molecule. *See* Ex. 1015.005–.006; Ex. 1002 ¶ 98. 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. 1015.005–.006; Ex. 1002 ¶ 98. 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 ¶ 99. 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 VIII.C.iii.; Ex. 1002 ¶ 100; Ex. 1031.002. 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 radiopharmaceutical, making the claimed ranges *prima facie* obvious. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). “[E]ven a

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.

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.

2. Claim 2

Claim 2 depends from claim 1 and narrows the specified targeting compounds. Ex. 1002 ¶ 102; Ex. 1001 at 20:38–2516. 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 ¶ 102; Ex. 1001 at 20:38–2516. 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 VIII.C.vi.1; 1002 ¶ 102. 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 VIII.C.vi.1. Wineisen 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 VIII.A.ii; Ex. 1028.002–.004; Ex. 1002 ¶ 103. A POSA would have known that metastatic prostate cancer would express PSMA and would be considered a disseminated cancer. Ex. 1002 ¶ 103. Additionally, as Dr. Abergel 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 Wineisen 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 VIII.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 ¶ 104. 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. 1031.002; Ex. 1002 ¶ 104; *see supra* Section VIII.A.v. 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 VIII.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 ¶ 106.

As discussed above, claims 8 and 10 would have been obvious to a POSA in light of Weineisen 2015 and Kratochwil. *See supra* Section VIII.C.vi.4. The additional repeat-dosage limitation added in claims 12 and 13 would also have been obvious to a POSA. Ex. 1002 ¶ 106.

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. 1031.002; Ex. 1002 ¶ 106. 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 ¶ 106. 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 ¶ 106. 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 VIII.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 ¶ 104; Ex. 1001 at 26:29–30.

As discussed above, a POSA would have been aware of several published reports studying the administration of ^{225}Ac . *See generally supra* Section VIII.A; Ex. 1002 ¶ 104. 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. 1031.002; *see also* Ex. 1002 ¶ 90 (converting from MBq). For example, Jurcic discloses successfully administering an ^{225}Ac radiotherapeutic at doses ranging from 18.5 kBq/kg to 74 kBq/kg to a human patient. Ex. 1011.002 (converted from $\mu\text{Ci/kg}$); Ex. 1002 ¶ 104. 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. 1011.002–.003; Ex. 1002 ¶ 68. 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 ¶ 104.

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 ¶ 104; Ex. 1001 at 26:29; Ex. 1011.002. 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. There Is No Secondary Evidence That Can Overcome a Finding of Obviousness

Petitioner is not aware of any relevant secondary considerations that have a nexus to, or are commensurate in scope, with any of the challenged claims. Ex. 1002 ¶ 107. Even if Patent Owner comes forward with alleged evidence of secondary considerations of non-obviousness, secondary considerations cannot overcome the strong case of obviousness discussed above. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

IX. Section 325(d) Does Not Support Discretionary Denial

Patent Owner may argue that the Board should deny this petition under 35 U.S.C. § 325(d) because the Examiner considered substantially the same arguments during prosecution, but the Board should reject this argument. First, the prior art relied on in this petition is not the same or substantially the same as that considered during prosecution. *See* Ex. 1002 ¶¶ 41–42. Second, even if it were, the Examiner erred in their consideration of the knowledge of a POSA with respect to substituting radionuclides in chelator complexes and the knowledge in the field regarding the doses of ²²⁵Ac that were safe and effective. *See* Ex. 1002 ¶¶ 46–47; Ex. 1004.383–.384 (Oct. 26, 2020 Applicant Arguments/Remarks); Ex. 1004.404–.406, .408–.410 (June 24, 2020 Non-Final Rejection).

According to the framework set forth in *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, the Board considers “(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential).

Only one piece of prior art cited in this petition was presented to the patent office during prosecution of the '901 patent—Kratochwil is the only reference supporting the grounds of invalidity in this Petition that was before the examiner. The arguments presented in this petition are also not substantially the same as those considered during prosecution. As discussed above, the prior art patents cited by the Examiner disclose one of the compounds covered by the challenged claims (PSMA-617) complexed with ^{177}Lu . While the references that were before the examiner are similar in scope to the disclosures of Weineisen 2015—that is, they disclose a PSMA-targeting radiopharmaceutical complexed with ^{177}Lu —the similarity between the art and arguments considered during prosecution and that presented in this petition ends there. As set forth above, the challenged claims are unpatentable as obvious based on Weineisen 2015 in light of prior art that discloses that (1) chelator targeting compounds could be easily used with a variety of radionuclides; (2) alpha emitters would have been preferred over beta emitters; and (3) alpha emitters like ^{225}Ac were known to be more potent than beta emitters like ^{177}Lu , such that lower dosages of alpha emitters would be required. *See supra* Section VIII.C.vi. This prior art was not submitted to the patent office during prosecution, and there is no evidence that the Examiner considered prior art covering substantially the same subject matter or the arguments presented in this petition. Therefore, there is no basis for discretionary denial in light of the

prosecution history. *Oticon Med. AB v. Cochlear Ltd.*, IPR2019-00975, Paper 15 at 19–20 (P.T.A.B. Oct. 19, 2019) (precedential).

Even if the Board were to find that the arguments considered by the Examiner are substantially the same as arguments presented in this petition, the Examiner erred in their analysis. The Examiner’s analysis did not take into account the full breadth of knowledge of a POSA or that this knowledge would have motivated a POSA to combine the prior art to arrive at the claimed method, as discussed above. Thus, even if the Board finds similarities between the arguments presented here and during prosecution, the Examiner’s errors during prosecution support institution here.

More specifically, the Examiner made two material errors in considering the disclosures of the ’791 and ’160 patents during prosecution. First, the Patent Owner incorrectly told the Examiner that the identification of ^{225}Ac for use in the radiopharmaceutical distinguished the prior art from the presented claims. Ex. 1004.382 (Oct. 26, 2020 Applicant’s Remarks/Arguments). Along these lines, the Examiner seems to have improperly ignored the teachings in the ’791 and ’160 patents that the claimed targeting molecule could be used with ^{225}Ac . *See, e.g.*, Ex. 1025, ’160 patent at 51:5–7 (claim 7 claims “[t]he metal complex of claim 6, wherein the radionuclide is selected from ^{89}Zr , ^{44}Sc , ^{111}In , ^{90}Y , ^{68}Ga , ^{177}Lu , $^{99\text{m}}\text{Tc}$, ^{64}Cu , ^{67}Cu , ^{153}Gd , ^{155}Gd , ^{157}Gd , ^{213}Bi , or ^{225}Ac .”) (emphasis added); Ex. 1026, ’791

patent at 21:65–22:7 (“Depending on whether the inventive Formula (Ia) and/or (Ib) compounds are to be used as radio-imaging agents or radio-pharmaceuticals different radionuclides are complexed to the chelator. Illustrative radionuclides include...²²⁵Ac.”); *id.* at 22:5–6 (“According to one aspect of this invention, the radionuclide is...²²⁵Ac”). The Examiner was likewise not made aware of the prior art that specifically discussed use of other radionuclides in similar targeting molecules or of the fact that a POSA would have found it routine to substitute one metallic radionuclide for another in a chelating targeting molecule. Ex. 1004.383–.384 (Oct. 26, 2020 Applicant Arguments/Remarks); *see also* Ex. 1002 ¶¶ 80–83. Thus, the Examiner’s consideration was, at best, incomplete.

Second, the Examiner only considered the claimed dosage ranges in light of prior art disclosing dosage ranges for a different radionuclide (¹⁷⁷Lu). As explained in detail above, a POSA would have had sufficient information to determine appropriate dosage amounts of ²²⁵Ac, and it would not have been surprising to a POSA that the ²²⁵Ac dosage amounts were substantially lower than those used for ¹⁷⁷Lu. *See supra* Section VIII.C.iii. Therefore, the Examiner erred in concluding that the claimed dosage ranges were patentable in light of the prior art.

As a result, there is no basis under § 325(d) for the Board to deny institution of this petition.

X. Conclusion

In light of the prior art disclosing PSMA I&T as a promising radiopharmaceutical for PSMA expressing cancers and the prior art disclosing the use of ²²⁵Ac in radiation therapy, Petitioner respectfully requests that the Board institute this proceeding and find the challenged claims of the '901 patent unpatentable as obvious.

Respectfully submitted,

Dated: February 13, 2023

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition for *Inter Partes* Review of U.S. Patent 10,980, 901 complies with the type-volume limits of 37 C.F.R. § 42.24(a)(1)(i) because it contains 11,335 words as calculated by the word processing system used to prepare this Petition, excluding the words in the Table of Contents, Table of Authorities, List of Exhibits, Mandatory Notices, Certification under 37 C.F.R. § 42.24(d), and Certificate of Service, as set forth in 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I certify that on this 13th day of February, 2023, I caused to have served a copy of the Petition together with all of the exhibits identified in the above Table of Exhibits and Petitioner's Power of Attorney by USPS Priority Mail Express on the following addresses for patent owner and their representatives that are listed in the United States Patent and Trademark Office's public records :

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