

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 IPR2025-01582
Patent 10,980,901

DECLARATION OF MICHAEL R. ZALUTSKY, Ph.D.

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I, Michael R. Zalutsky, Ph.D., declare as follows:

1. I have been retained on behalf of Curium US LLC (“Curium”) in connection with its petition for *inter partes* review (“IPR”) of U.S. Patent No. 10,980,901 (“the ’901 patent,” Ex. 1001). I understand that Curium is seeking to challenge the patentability of claims 1, 2, and 4–13 (the “challenged claims”) of the ’901 patent.

2. I have been asked to study and provide my opinions as an independent expert witness regarding the obviousness of the challenged claims of the ’901 Patent in view of the prior art cited herein. I am being compensated at my usual and customary rate for my time. Such compensation, however, does not influence my opinion nor does the outcome of this proceeding impact my compensation.

I. QUALIFICATIONS

3. I currently hold the appointment of Jonathan Spicehandler M.D. Professor of Neuro-Oncology Research at Duke University. I have been a Professor of Radiology, Radiology Oncology, and Biomedical Engineering at Duke University for approximately the last forty years. Before that, I was an assistant professor at Harvard Medical School for five years. I received a Ph.D. in Nuclear Chemistry from Washington University, a Master’s degree from Washington University, and an undergraduate degree from Clark University. I have extensive experience in the field of radiotherapeutics and

radiopharmaceutical chemistry. I have over 400 publications for which I am an author or co-author in the fields of radiopharmaceuticals, radiology, and/or cancer therapy. I have recently co-published with several institutions, including Hokkaido University, Ben Gurion University, QST in Chiba, Japan, Northwestern University, and Johns Hopkins University. I have conducted research on the chemical properties and biological behavior of radiometals, including a number of therapeutic radioisotopes. I have also researched chelating agents that form stable complexes with these radioisotopes, which assists in stability *in vivo* and effective tumor targeting.

4. I also have extensive experience in radiation dosimetry, including preparing calculations for studies performed in preclinical animal models, as well as in human patients. In addition, I have applied micro-dosimetric approaches to calculate radiation dose deposition from alpha emitters, which consider small-scale distribution patterns of the radiopharmaceutical. In addition, as my CV indicates, I have been involved in the design, performance, and interpretation of clinical trials of novel radiotherapeutic agents. For example, I was the first author on the first clinical trial with the alpha-particle emitter Astatine-211 (^{211}At) in patients with glioblastoma.

5. In addition to the above, I have numerous first and senior author publications in other scientific areas overlapping with and/or adjacent to

pharmaceuticals, such as medicine and drug development, which are of relevance and help inform my work on radiopharmaceuticals.

6. I am the founder and Chief Technology Officer (CTO) of a company called Z-Alpha Therapeutics, which focuses on targeted radiotherapy.

7. Attached hereto as Exhibit 1003 is a true and correct copy of my Curriculum Vitae (CV).

II. MATERIALS CONSIDERED

8. In forming my opinions provided in this declaration, I have read and considered the following. I have also relied on my education, knowledge, and experience.

Materials Reviewed	
Exhibit 1001	U.S. Patent No. 10,980,901 (“the ’901 patent”)
Exhibit 1004	File History of U.S. Patent No. 10,980,901
Exhibit 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”).
Exhibit 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 2016a”).
Exhibit 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”).

Materials Reviewed	
Exhibit 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”).
Exhibit 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”).
Exhibit 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”).
Exhibit 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 with Untreated Acute Myeloid Leukemia (AML)</i> , 128 Blood 4050 (2016) (“Jurcic”).
Exhibit 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”).
Exhibit 1013	Michael R. McDevitt, et al., <i>Tumor Therapy with Targeted Atomic Nanogenerators</i> , 294 Science 1537 (2001) (“McDevitt 2001”).
Exhibit 1014	Michael R. McDevitt, et al., <i>Design and synthesis of ²²⁵Ac radioimmunopharmaceuticals</i> , 57 Applied Radiation & Isotopes 841 (2002) (“McDevitt 2002”).
Exhibit 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”).

Materials Reviewed	
Exhibit 1016	Dianne E. Milenic & Martin W. Brechbiel, Targeting of Radio-Isotopes for Cancer Therapy, 3 Cancer Biology & Therapy 361 (2004) (“Milenic”).
Exhibit 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”).
Exhibit 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”).
Exhibit 1019	Martin G. Pomper, et al., <i>^{11}C-MCG: Synthesis, Uptake Selectivity, and Primate PET of a Probe for Glutamate Carboxypeptidase II (NAALADase)</i> , 1 Molecular Imaging 96 (2002) (“Pomper”).
Exhibit 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”).
Exhibit 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”).
Exhibit 1022	David A. Scheinberg & Michael R. McDevitt, <i>Actinium-225 in targeted alpha-particle therapeutic applications</i> , 4 Current Radiopharmceuticals 306 (2011) (“Scheinberg”).
Exhibit 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”).
Exhibit 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”).

Materials Reviewed	
Exhibit 1025	U.S. Patent No. 10,471,160 (“the ‘160 patent”).
Exhibit 1026	U.S. Patent No. 10,398,791 (“the ‘791 patent”).
Exhibit 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”).
Exhibit 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”).
Exhibit 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 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”).
Exhibit 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”).
Exhibit 1032	Randall D. Knight, <i>Physics For Scientists and Engineers</i> 1369–70 (Adam Black et al. eds., vol. 5 2005) (“Knight”).
Exhibit 1033	Liang Zhao, et al., <i>Clinical pharmacology considerations in biologics development</i> , 33 Acta Pharamacologica Sinica 1339 (2012) (“Zhao”).
Exhibit 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”).

Materials Reviewed	
Exhibit 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”).
Exhibit 1036	Nima Sharifi, et al., <i>Androgen Deprivation Therapy for Prostate Cancer</i> , 294 JAMA 238 (2005) (“Sharifi”).
Exhibit 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”).
Exhibit 1038	Sharmila Banerjee, et al., <i>Lutetium-177 Therapeutic Radiopharmaceuticals: Linking Chemistry, Radiochemistry, and Practical Applications</i> , 115 Chem. Revs. 2934 (2015) (“Banerjee”).
Exhibit 1039	Arundhati Ghosh & Warren D.W. Heston, <i>Tumor Target Prostate Specific Membrane Antigen (PSMA) and its Regulation in Prostate Cancer</i> , 91 J. Cellular Biochemistry 528 (2004) (“Ghosh”).
Exhibit 1040	Declaration of Dr. Abergel submitted in IPR2023-00551
Exhibit 1041	Eric W. Price and Chris Orvig, <i>Matching chelators to radiometals for radiopharmaceuticals</i> , 43 Chem. Soc. Rev. 260-290 (2014) (“Price”).
Exhibit 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”).
Exhibit 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”).
Exhibit 1044	Declaration of Dr. Hope submitted in IPR2023-00551

III. LEGAL PRINCIPLES

9. I am not an attorney and will not be offering legal conclusions.

However, I have been informed by Curium's counsel of several principles concerning legal issues relevant to my analysis provided herein and I relied on these principles to arrive at my conclusions.

10. I understand a claim is invalid as obvious under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter of the claim as a whole would have been obvious at the time of the patent's filing date to a Person of Ordinary Skill in the Art (POSA). It is my understanding that the following factors are used to determine whether or not the claimed subject matter would have been obvious: (i) the scope and content of the prior art; (ii) the differences between the prior art and the claimed invention; (iii) the level of ordinary skill in the field of the invention; and (iv) any relevant objective considerations of non-obviousness.

11. I understand that the combination of known elements according to known methods is likely to be obvious when it does no more than yield predictable results, and that any need or problem known in the art at the time of the alleged invention can provide a reason for combining elements. I am further advised that

obviousness is assessed via a flexible approach rather than adherent to rigid application of legal standards or tests.

12. I understand a party asserting obviousness based on a combination of prior art references must demonstrate that one of ordinary skill in the art would have been motivated to combine the teachings of those references to achieve the claimed invention with a reasonable expectation of success. I am advised that the law requires only a reasonable expectation of success and does not require absolute certainty of success.

13. I have been instructed to assume for purposes of my analysis that December 15, 2016, is the relevant date for determining what is “prior art.” In other words, I should consider as “prior art” anything publicly available prior to December 15, 2016. I further understand that, for purposes of this proceeding before the PTAB, only patents and documents that have the legal status of a “printed publication” may be relied on as prior art.

IV. LEVEL OF ORDINARY SKILL IN THE ART

14. I understand that certain issues in an IPR, such as claim construction and whether a claim is invalid as obvious, are assessed from the view of a hypothetical POSA at the time of the invention. I understand there are multiple factors relevant to determining the level of ordinary skill for a POSA, including: (1) the level of education and experience of persons working in the field at the time

of the invention; (2) the sophistication of the technology; (3) the types of problems encountered in the field; and (4) the prior art solutions to those problems.

15. In order to determine the characteristics of a hypothetical POSA at the time of the claimed invention, I have considered these above factors. I have considered the prior art (referred to in the “Materials Considered” section of this declaration), the types of problems encountered in the art and the solutions to those problems, the sophistication of the technology involved, and the educational background and experience of those actively working in the relevant field at the time of the invention.

16. In my opinion, a POSA as of December 15, 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. 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.

17. Based on the above definition, I obtained the requisite education and experience of a POSA at least by December 15, 2016.

V. DR. ABERGEL'S PRIOR DECLARATION REGARDING THE '901 PATENT

18. I have reviewed Dr. Abergel's and Dr. Hope's declarations submitted in IPR2023-00551 and generally agree with Dr. Abergel's opinions on why claims 1, 2, and 4–13 of the '901 patent are unpatentable. *See* Ex. 1040 and Ex. 1045. Therefore, with respect to the '901 patent, I have adopted much of Dr. Abergel's analysis in my own analysis set out below for why a POSA would find claims 1, 2, and 4–13 of the '901 patent as unpatentable.

VI. TECHNICAL BACKGROUND

A. Radiopharmaceuticals

1. Radioactive Decay

19. The building blocks of every atom are electrons, neutrons, and protons. Each atom of a particular element has the same number of protons. 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. This process is referred to as radioactive decay. Radioactive decay is the process in which unstable atoms, also known as radionuclides, spontaneously release energy, and often particles. Radioactive decay occurs through specific processes dependent on the specific atom that is decaying. That is, each unstable isotope

generally has a predictable decay pattern based on the type of decay it undergoes.

Ex. 1022, Scheinberg at 2.

20. The two types of radioactive decay relevant for this declaration are alpha-particle decay and beta-particle decay. In either case, the “parent” radioactive atom decays and becomes one or more “daughter” atom(s), which can subsequently undergo further radioactive decay. When an atom undergoes alpha decay, its nucleus ejects an “alpha particle.” 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). This alpha decay results in a daughter nucleus with two fewer protons.

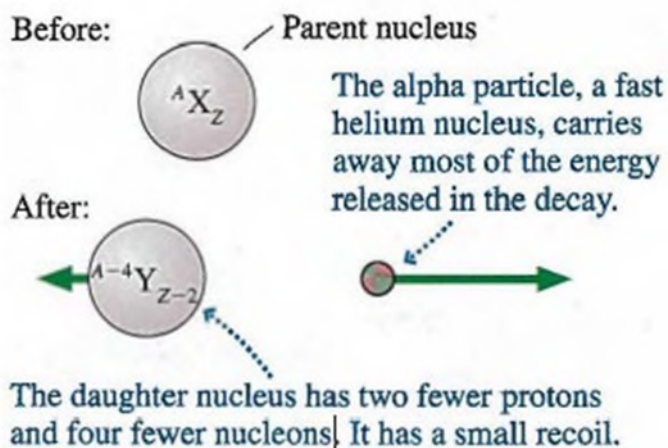


Figure 1. Ex. 1032, Knight at 22.

21. When an atom undergoes beta decay, it releases a beta particle (either a negatively charged electron or positively charged positron). 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). The electron is emitted from the nucleus and the proton remains as part of the daughter nucleus, Y.

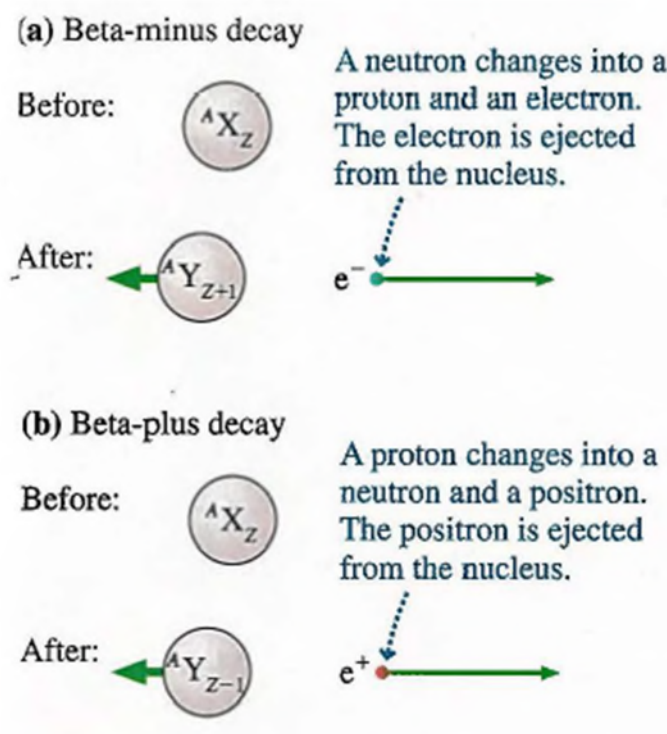


Figure 2. Ex.1032 at 23.

2. Radionuclide Imaging and Radiopharmaceuticals

22. Over the past several decades, scientists have developed uses for radioactive materials to improve medical imaging and treatment. See Ex. 1016, Milenic at 2-3. Specifically, the particle(s) and energy released during radioactive decay can be harnessed to allow for imaging of the interior of the human body and to provide treatment of diseases and disorders, particularly cancer. See *id.*

23. Medical imaging with radionuclides is accomplished by injecting a radioactive molecule into a patient and using sensitive equipment to detect the

location and strength of radioactive emissions within the body. For example, a radionuclide can be injected into a patient's artery, and the flow of that material through the artery can be used to detect a blockage. Radionuclides can also be used for more targeted imaging by coupling the radioactive imaging agent with a targeting agent to allow for imaging of a specific target organ or type of cell. For instance, administration of a radioactive isotope of iodine, ^{123}I , into a patient's blood allows for imaging of the thyroid gland. Ex. 1012, Mandel at 1-2. Due to natural regulation of the iodine, the body will concentrate the ^{123}I in the thyroid gland and specialized equipment can image the gland by detecting the iodine's radioactivity. Ex. 1012 at 2-3.

24. Additionally, certain radionuclides can be used in medical treatment, most commonly to treat cancer. Ex. 1020, Hubenak at 1. It has long been known that the particles and energy released from radioactive atoms cause damage to DNA, which can lead to the death of the impacted cells. *See id.* at 4. Radiation therapy has used this pathway in the treatment of cancer for decades, where an external radiation source is directed at a patient's tumor but must penetrate through the patient's skin and other organs to reach the targeted tissue. *See id.* at 2. This traditional radiation therapy often resulted in a number of adverse effects due to the non-specific nature of the treatment. *Id.* at 2, 5-6. As a result, targeted radiotherapy was developed, in which radiopharmaceuticals can be used to kill

cancer cells by delivering radionuclides to the target tumor cells. *See id.* at 6. Once at the target cell, the radioactive decay damages the DNA, and ultimately causes cell death. *Id.* at 4.

25. In both radionuclide imaging and radiopharmaceutical therapy, the challenge lies in the ability to selectively target the desired tissue/cells. To achieve this goal, scientists have developed ways to attach radionuclides to molecules that bind to specific targets based on the desired outcome. Both non-metallic and metallic radionuclides can be used. 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):

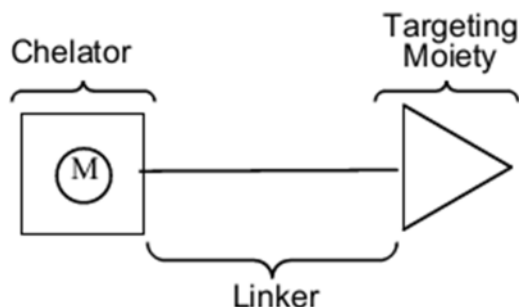


Figure 3

26. The radionuclide is incorporated into these molecules through a process called chelation. Chelation is a unique kind of molecular interaction, in which a charged metal atom (a metal ion) interacts with heteroatoms (N, S, O, etc.) of the chelator. For example, dodecane tetraacetic acid (“DOTA”) (Fig. 4), is a well-known chelator, capable of forming complexes with many different types of

radionuclides, such as ^{177}Lu , ^{90}Y , and ^{225}Ac , upon deprotonation. *See, e.g.*, Ex. 1014, McDevitt 2002 at 1-2; Ex. 1027, Weineisen 2014 at 11; Ex. 1035, Viola-Villegas at 4, 14, 16. The typical molecular structure of a metal complex of DOTA is shown below (Fig. 4). DOTA can also incorporate a substituting group on one carboxylic acid, leaving only three accessible carboxylic acid moieties for chelation.

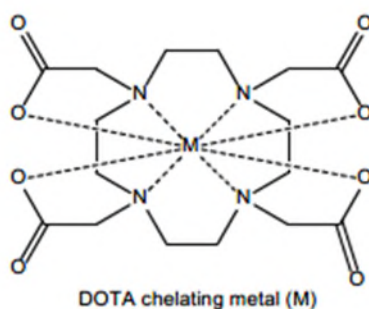


Figure 4

Another well-known chelator used in radiopharmaceuticals is DOTAGA. This substituted DOTA derivative is pictured below (Fig. 5) in its metal complex form.

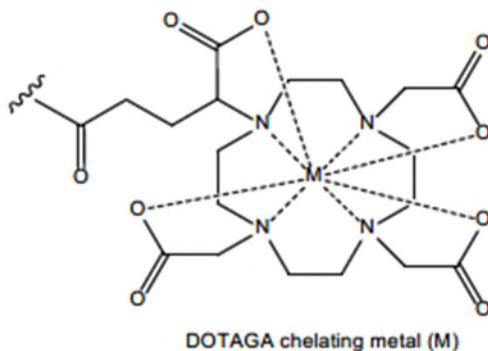


Figure 5

DOTAGA comprises an additional carboxylic acid as compared to DOTA. As shown in these figures, the nitrogen and oxygen atoms of both DOTA (Fig. 4) and DOTAGA (Fig. 5) ligands form coordinate bonds (shown as dotted lines) to hold the metal ion (labeled as “M”) in place.

27. The metal-chelator complex is attached through a linker to a “targeting moiety.” The targeting moiety is used to direct the rest of the molecule to a particular part of the body. For example, the targeting moiety might be an antibody known to bind to a protein on the surface of a specific type of tumor cell or a small molecule that binds to proteins only found on cancer cells. Selection of each of the radionuclide, chelator, linker, and targeting moiety is key to ensure the radiopharmaceutical is effective in the treatment of the particular cancer a patient may have.

28. In some radionuclides that undergo alpha decay, including ^{225}Ac , the radionuclide has multiple alpha emitting daughters which due to the recoil effect separate the daughter radionuclides from the chelator. The recoil effect can potentially lead to toxicity because the daughter radionuclides produced from the initial alpha decay are no longer bound to the targeting compound, and therefore may travel to other areas of the body and cause damage to healthy tissues. *See generally* Ex. 1043.

29. The recoil effect of ^{225}Ac was known at the time of the invention. 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. 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. Another *in vivo* study in animal models utilizing antibodies J591 and B4 conjugated to DOTA to treat prostate carcinoma and disseminated lymphoma, respectively, “indicated a clear benefit of alpha radiation at low administered activities with no toxic effects.” Ex. 1043.009. As such, at the time of filing, a POSA would have been aware that the potential benefit of ^{225}Ac -labeled radiopharmaceuticals for the treatment of cancer likely outweighed potential side effects, including those related to the daughter recoil effect.

30. 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. Importantly, the previous approval of the ^{223}Ra alpha emitter therapy occurred years earlier than the priority date of the ‘901 patent. 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. As such, the use of ²²⁵Ac as claimed in the '901 patent was a common-sense solution.

3. Radionuclides

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

32. Early studies into radiopharmaceuticals focused on the use of beta emitting radionuclides due to their availability and familiarity. Ex. 1016 at 3. However, alpha-particle emitting radionuclides are increasingly seen as more desirable in the context of therapeutic radiopharmaceuticals. *See id.*; Ex. 1030, Miederer 2008b at 2. Alpha particles are substantially larger and contain more energy than beta particles. *See* 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. 1030 at 2. The bigger and more highly charged alpha particles face more resistance in the body and are therefore only capable of traveling the distance of a few cell diameters. *Id.* In contrast, the smaller beta particles face less resistance and are able to travel a few hundred cell diameters. *See* Ex. 1016 at 3. The more localized impact of alpha decay makes it

ideally suited for targeted radiotherapy because the impact on the surrounding tissue is minimized, reducing the likelihood of side effects. *See* Ex. 1014 at 1; Ex. 1030 at 2. Furthermore, because alpha particles have higher energies 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 while maintaining therapeutic efficacy. *See* Ex. 1030 at 2; Ex. 1016 at 3.

33. A number of radionuclides were being investigated prior to the filing of the '901 patent in 2016. 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. 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. 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. 1013, McDevitt 2001 at 2. The [^{225}Ac]DOTA-IgG construct described in McDevitt 2001 was effective in killing a variety of cancer cells. *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, tetramers, and small molecules. *See, e.g.*, 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 . *See* Ex. 1041 at 8-9.

4. Radiopharmaceuticals and the Treatment of Prostate Cancer

34. 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, Turkbey at 1. Accordingly, there has been interest in finding ways to diagnose and treat this malicious disease; radionuclide-based diagnostics and treatments began gaining traction in the early 2010s.

35. Despite PC’s prevalence, up to the mid-2010s, diagnostic tools for the disease remained limited, relying on invasive methods such as blood tests and prostate biopsy analysis. Ex. 1024 at 1. While effective, such methods were not ideal for disease progression monitoring as they are inconvenient and difficult to rapidly administer. MRI can be a convenient alternative to these more invasive methods. However, standard MRI techniques have difficulty differentiating between the 15% of PC patients with a poor prognosis that require treatment versus those with an indolent form of the disease. Ex. 1005, Bjurlin at 1.

36. The discovery of a protein that is found on the surface of many prostate cancer cells helped shift this paradigm. Prostate-specific membrane antigen (“PSMA”) has been shown to be highly expressed on PC cells, whereas it

remains at low levels on healthy prostate cells, making it an ideal target for therapeutics. Ex. 1019, Pomper at 5. This difference in expression levels means PSMA-targeting therapies will selectively kill PC cells over healthy cells. See Ex. 1008, Foss at 1. Further, high levels of PSMA have been correlated with patients with hormone-refractory disease and primary and metastatic PC. *Id.*; Ex. 1023, Silver at 5. Its presence on malignant PC tumor cells has made PSMA an ideal target for both diagnostic techniques and therapeutic methods. See Ex. 1027 at 11.

37. PSMA is a transmembrane protein found primarily on the exterior of prostate cancer cells and can bind to specific molecules on the cells. Ex. 1008.001 In particular, PSMA selectively binds N-acetyl-L-aspartyl-L-glutamate and has been used as a target in a variety of radiolabeled conjugates. While radiolabeled antibody conjugates are often used for diagnosis and treatment of tumors, radiolabeled peptide-small molecule conjugates are more attractive imaging agents. Radiolabeled peptide/small molecules have increased access to tumors and shorter serum half-lives, leading to lower background noise as compared to radiolabeled antibodies. Ex. 1033, Zhao at 2; Ex. 1008 at 1.

38. Prior to 2014, most therapies for the treatment of prostate cancer were focused on androgen-deprivation therapy and chemotherapy. Ex. 1028 at 1-2. However, these therapies were often plagued by undesirable side effects, including bone loss, metabolic changes, muscle loss, hot flashes, and increased

cardiovascular disease. Ex. 1036, Sharifi at 4-6. Additionally, prior to 2014, only two therapeutics had been evaluated that took advantage of a small molecule PSMA-inhibitor as a targeting moiety, [¹³¹I]MIP-1375 and [¹³¹I]MIP-1466. *See, e.g.*, Ex. 1009, Hillier 2011 at 1; Ex. 1010, Hillier 2012 at 1. Each of these rely on a ¹³¹I radiolabel. Ex. 1009 at 1; Ex. 1010 at 1. In these contexts, the targeting radiotherapeutic binds to PSMA and then is internalized within the cell. The radionuclide subsequently undergoes radioactive decay. The emissions from the decay cause damage within the cell, for example, to the DNA, ultimately resulting in cell death. As described in more detail below, since 2014, the field has rapidly developed a variety of strategies for the treatment of PC that successfully employ radiopharmaceuticals that target PSMA.

39. PSMA I&T specifically was shown to be a promising theranostic agent for the treatment of prostate cancer. 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. *See* Ex. 1042 at 1. The study investigated dosages of 0.1, 0.3, 1, and 10 nmol/mouse. 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.” *See* 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. *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].” *See* Ex. 1042 at 12.

VII. U.S. PATENT NO. 10,980,901 AND THE CHALLENGED CLAIMS

40. I have read the ‘901 patent, entitled “Treatment of PMSA [sic] Expressing Cancers.” According to its cover page, the ‘901 patent claims priority to a PCT application filed on December 15, 2016.

A. The Specification

41. The ‘901 patent generally relates to using radiopharmaceuticals for cancer treatment. Ex. 1001 at 1:14–17. The ‘901 patent is directed to “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. The ‘901 patent specification further provides that 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.” *Id.*

42. The specification acknowledges some of the known benefits of using alpha emitters like ^{225}Ac in radiopharmaceuticals. For example, the specification discloses that the “the very efficient and specific targeting of the Ac-225-radiopharmaceuticals to PSMA combined [with] the short range (<100 micrometers) action of the Ac-225 alpha emitter allows for very good results of destruction of cancer cells without notable damage to non-target tissues.” Ex. 1001 at 12:19–23. Despite these known benefits, the inventors claimed radiopharmaceuticals comprising ^{225}Ac have been “surprisingly found” to “provide considerably and significantly better therapeutic results [than] corresponding radiopharmaceuticals with [non-alpha emitting] radionuclides, especially with the particular administration dosages of the present invention.” Ex. 1001 at 11:36–42.

43. To support this contention, the specification discloses experiments conducted to “compare the efficiency of Ac-225-radiopharmaceuticals” (Ac-225-PSMA-617) with “non-Ac-225-radiopharmaceuticals comprising the same targeting compound[] but chelated [with a different radionuclide]” (Lu-177-PSMA-617). Ex. 1001 at 16:12–18 (“A6. Comparative Examples”). The inventors stated 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.

B. The Prosecution History

44. I have reviewed portions of the Prosecution History of the ‘901 patent. Below, I summarize the key points of the Prosecution History that pertain to the Challenged Claims.

45. During prosecution of the ‘901 patent, the Examiner rejected all pending claims, which were directed to a method of treating PSMA expressing cancers by administering ²²⁵Ac-radiopharmaceuticals, including ²²⁵Ac-PSMA I&T, at specific dosages. *See* Ex. 1004, ‘901 File History at 398-412 (June 24, 2020 Non-Final Rejection). The Examiner rejected these claims in light of U.S. Patent Nos. 10,398,791 (the “‘791 patent,” Ex. 1026) and 10,471,160 (the “‘160 patent,” Ex. 1025), explaining that “[a]lthough the claims at issue are not identical,” to the claims of the ‘791 and ‘160 patents, “they are not patentably distinct from each other,” because the claims were “directed to the same art specific subject matter.” Ex. 1004 at 402-406 (June 24, 2020 Non-Final Rejection).

46. The ‘791 patent claims were directed to a method of treating prostate cancer with ¹⁷⁷Lu complexed to the chelator. *See* Ex. 1004 at 404 (June 24, 2020 Non-Final Rejection). The ‘160 patent claims covered a radionuclide and a method of using them to treat prostate cancer. *See* Ex. 1004 at 406-408 (June 24,

2020 Non-Final Rejection). The claims of the ‘791 and ‘160 patents cover the compound specifically identified in claim 3 of the ‘901 patent. Ex. 1001 at 25:17–41. The Examiner concluded that the difference between the pending claims and the ‘791 and ‘160 patent claims “is in scope only.” Ex. 1004 at 404-408 (June 24, 2020 Non-Final Rejection).

47. 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 at 382 (Oct. 26, 2020 Applicant Arguments/Remarks). The applicant stated that 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 ^{177}Lu complexed to the chelator compound.” *Id.* The applicant stated, “[i]n contrast, the present claims only recite ^{225}Ac .” *Id.*

48. Although the applicant acknowledged that the ‘791 and ‘160 patents disclosed multiple radionuclides, including ^{225}Ac , the applicant noted that the examples in the ‘791 and ‘160 patents used radionuclides ^{68}Ga for imaging and ^{177}Lu for cancer therapy, rather than ^{225}Ac , and that both the claims and disclosures are “relatively silent about dosages.” *Id.*

49. The applicant further 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 (Oct. 26, 2020 Applicant Arguments/Remarks) (emphasis in original). The applicant directed the Examiner to examples in the pending application comparing treatment with ²²⁵Ac-radiopharmaceuticals with ¹⁷⁷Lu-radiopharmaceuticals, contending that it was a “remarkable difference” that the group treated with ¹⁷⁷Lu-radiopharmaceuticals had a lower response rate than those treated with ²²⁵Ac-radiopharmaceuticals. See Ex. 1004 at 383-384 (Oct. 26, 2020 Applicant Arguments/Remarks).

50. The 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.” Ex. 1004 at 384 (Oct. 26, 2020 Applicant Arguments/Remarks). As explained in more detail below, I disagree that this difference in efficacy would be surprising or unexpected.

51. The Examiner was not presented with prior art demonstrating the known benefits of using ²²⁵Ac and other alpha emitters in radiotherapies, including:

(1) alpha emitters were known to have higher potency than beta emitters like ^{177}Lu , leading to lower doses needed for alpha emitters; (2) alpha emitters can only travel limited distances, and therefore cause less damage to cells surrounding the target cells. *See* Ex. 1004 at 33-34 (Jan. 11, 2021 Examiner's Reasons for Allowance).

52. The Examiner allowed the claims without addressing applicant's nonstatutory double patenting remarks. *See* Ex. 1004 at 33-34 (Jan. 1, 2021 Notice of Allowance). The Examiner provided minimal explanation for the allowance, stating that the closest prior art "differ[ed]...in chemical structure of the variable linker," which "results in change of lipophilic interactions in the linker regions, as well as binding affinity to prostate-specific membrane antigen (PSMA) protein." Ex. 1004 at 33 (Jan. 11, 2021 Examiner's Reasons for Allowance).

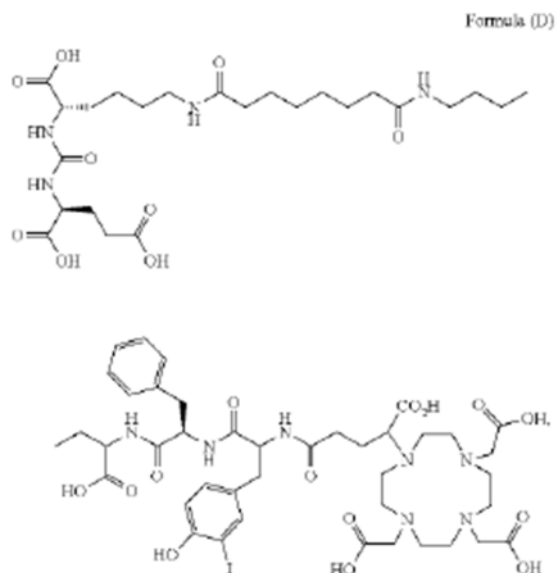
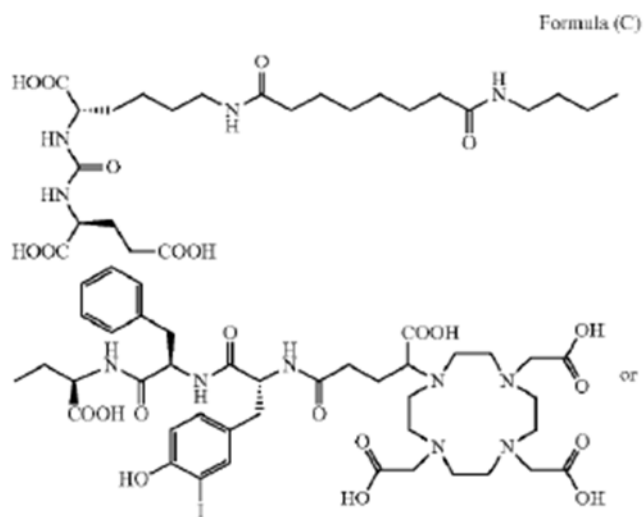
C. The Challenged Claims

53. I understand that Curium is challenging claims 1, 2, and 4–13 of the '901 patent as unpatentable.

54. 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):



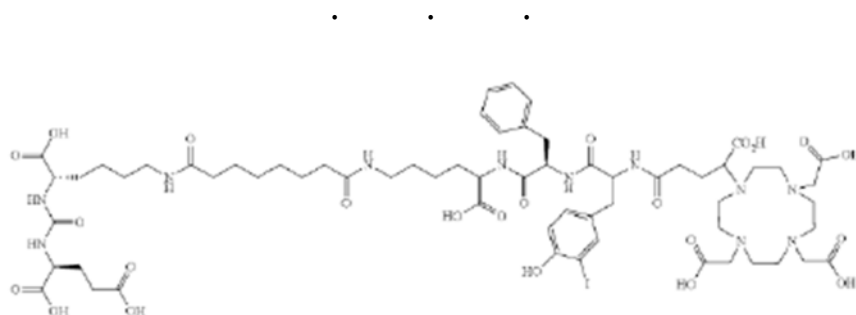
wherein the effective amount of said one or more Ac-225-
radiopharmaceuticals is administered as a dosage of from 25 kBq to
400 kBq/kg of body weight of said patient or wherein the effective

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.

55. Claim 2 depends from claim 1 and includes further limitations regarding specific targeting compounds. Claim 2 provides:

2. The method of claim 1, wherein the one or more Ac-225-radiopharmaceuticals are selected from:



Ex. 1001 at 20:38–25:16.

56. Claims 4–7 depend from claim 1 and include further limitations regarding types of cancer treated.

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 25:42–26:25.

57. Dependent claims 8–11 include further limitations regarding dosage range and administration.

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.
9. The method of claim 8, wherein the dosage ranges from 50 kBq to 200 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 26:26–36.

58. Dependent claims 12–13 include further limitations regarding dosing schedule.

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 26:37–43.

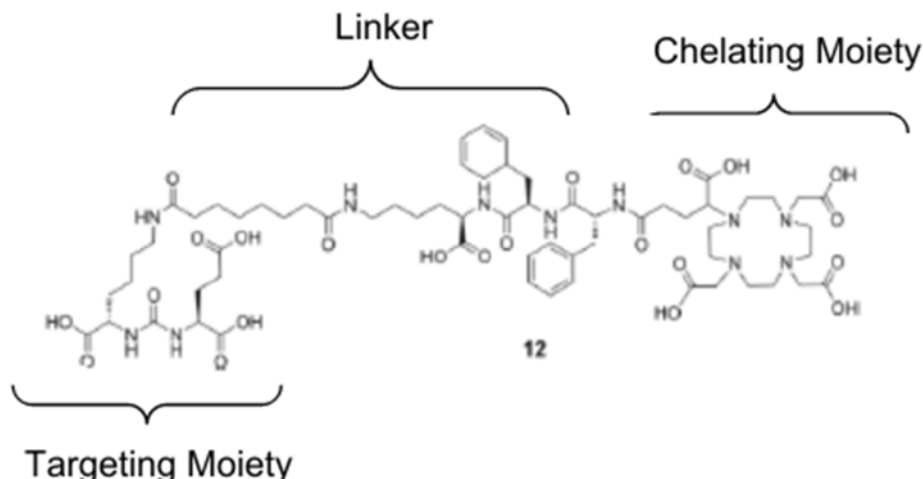
VIII. SCOPE AND CONTENT OF THE PRIOR ART

A. Weineisen 2014

59. Martina Weineisen, et al., *Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer*, 4 EJNMMI Rsch. 1 (2014) (“Weineisen 2014”), published in 2014.

60. Weineisen 2014 discloses a bifunctional construct capable of targeting PSMA and chelating a radionuclide. Ex. 1027 at 1. Weineisen 2014 includes work to develop a “PSMA ligand allowing for.. .complexation.. .with therapeutic M³⁺-radiometals, e.g. ¹⁷⁷Lu, ⁹⁰Y or ²²⁵Ac.” Ex. 1027 at 11. The disclosed ligand,

referred to as DOTAGA-ffk(Sub-KuE) (“12”), comprises a chelating moiety (DOTAGA), a linker, and a PSMA-targeting moiety (Sub-KuE):



Ex. 1027 at 9 (annotated).

61. In addition to describing the synthesis of DOTAGA-ffk(Sub-KuE), Weineisen 2014 shows that the chelating moiety of DOTAGA-ffk(Sub-KuE) readily complexes with the beta-particle emitter ^{177}Lu , achieving a >95% radiochemical yield. Ex. 1027 at 8. Weineisen 2014 goes on to examine the properties relevant to how the resultant radiopharmaceutical, [^{177}Lu]DOTAGA-ffk(Sub-KuE) (“ ^{177}Lu -12”), will perform inside the body. In particular, using a cell-based *in vitro* assay, Weineisen 2014 measured ^{177}Lu -12’s affinity for PSMA (IC₅₀), specificity for PSMA-expressing cells, and internalization into prostate cancer cells. Ex. 1027 at 8-10. As shown in Weineisen 2014, ^{177}Lu -12 exhibits high affinity for its target protein, PSMA, (IC₅₀ = 13.1 nM) with little off-target binding (less than 0.5%). Ex. 1027 at 10. Additionally, ^{177}Lu -12 proved to be

rapidly internalized into PSMA expressing cells. Ex. 1027 at 14. These data allowed the authors to conclude that DOTAGA-ffk(Sub-KuE) “possesses remarkable potential for a PSMA based theranostics concept.” *Id.*

B. Weineisen 2015

62. 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”), published in 2015.

63. Weineisen 2015 discloses efforts to improve a ligand’s ability to bind to PSMA. These efforts culminated in the development of PSMA I&T:

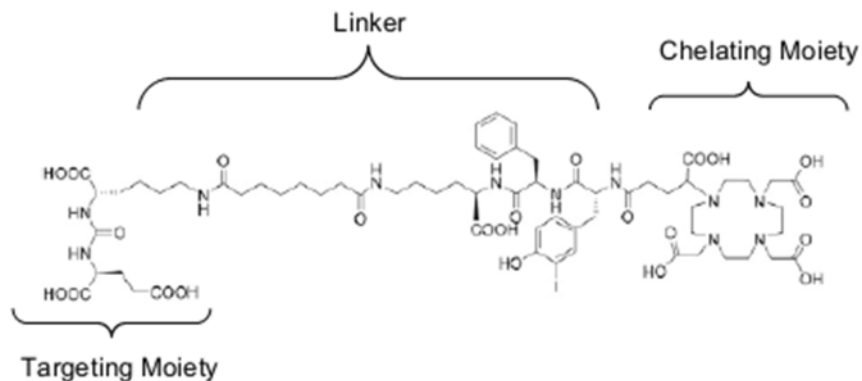


Figure 6

Ex. 1028, Weineisen 2015 at 2.

64. Similar to the ligand disclosed in Weineisen 2014, 12, PSMA I&T comprises a chelating moiety (DOTAGA), a linker, and a PSMA-targeting moiety (Sub-KuE) . *Id.* The only differences between PSMA I&T and compound 12 are

small changes to the linker. Specifically, two small substituents, a hydroxyl and iodo, were added to 12 to increase PSMA binding and internalization of the radiopharmaceutical. Ex. 1028 at 2. In *in vitro* studies, [¹⁷⁷Lu]PSMA I&T possessed an almost twofold increase in PSMA binding as compared to ¹⁷⁷Lu-12. Ex. 1028 at 3-4. The increase PSMA affinity conferred a ~72% increase in internalization of [¹⁷⁷Lu]PSMA I&T as compared to ¹⁷⁷Lu-12. Ex. 1028 at 4. These data disclosed in Weineisen highlight [¹⁷⁷Lu]PSMA I&T superiority compared to previous radioligands.

65. Furthermore, in contrast to Weineisen 2014, which did not undertake *in vivo* studies with ¹⁷⁷Lu-12, Weineisen 2015 discloses a proof-of-concept study comprising administering [¹⁷⁷Lu]PSMA I&T to two human patients with metastatic castrate-resistant prostate cancer. Ex. 1028 at 6. In this study, [¹⁷⁷Lu]PSMA I&T showed “high, specific and rapid uptake in all previously identified tumor lesions.” Ex. 1028 at 7. The patients showed “impressive molecular treatment response,” exhibiting important clinical responses, such as reduction in pain, drops in Prostate Specific Antigen (“PSA”) (an important indicator in prostate cancer), and reduction of disease burden . *Id.* In light of these data, the authors conclude that “¹⁷⁷Lu-PSMA I&T endoradiotherapy was feasible, safe, and effective in metastatic PC.” Ex. 1028 at 8.

C. Chatalic

66. Kristell Chatalic, et al., *²¹³Bi-labeled PSMA-targeting agents for alpha radionuclide therapy of prostate cancer*, 57 J. Nuclear Med. 137 (2016) (“Chatalic 2016a”), published in May 2016.

67. Chatalic 2016a discloses the use of PSMA I&T with the alpha particle emitter ²¹³Bi. Ex. 1006, Chatalic 2016a at 1. Using xenograft mouse studies, Chatalic observed that within 1 hour of administration, 5 MBq of ²¹³Bi PSMA I&T had induced DNA damage within tumor cells. Ex. 1006 at 1-2. The authors conclude that ²¹³Bi PSMA I&T had “good tumor targeting and induction of [DNA double strand breaks] in PSMA-expressing LNCaP xenografts.” Ex. 1006 at 2.

D. Miederer

68. Matthias Miederer, et al., Preclinical Evaluation of the α -Particle Generator Nuclide ²²⁵Ac for Somatostatin Receptor Radiotherapy of Neuroendocrine Tumors, 14 Clinical Cancer Res. 3555 (2008) (“Miederer 2008a”) published in 2008.

69. Miederer teaches that many patients did not respond to radiotherapy using the beta-emitting ¹⁷⁷Lu(DOTATOC), despite evidence that it was a promising treatment for metastasized neuroendocrine tumors. Ex. 1015, Miederer 2008a at 6. Similar to PSMA I&T and DOTAGA-ffk(Sub-KuE) discussed above, DOTATOC is a radiotherapy ligand made up of a DOTA, a linker, and a peptide

targeting moiety. Because of the DOTA's ability to chelate a variety of radionuclides including ^{225}Ac , Miederer proposed swapping ^{225}Ac for ^{177}Lu . See Ex. 1015 at 1. Miederer hypothesized 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 these patients. Ex. 1015 at 1. Miederer reports initial mouse studies showing that up to 60 kBq of ^{225}Ac -DOTATOC was tolerated without toxicity. Ex. 1015 at 4. To examine the efficacy of ^{225}Ac -DOTATOC, Miederer discloses studies on mice implanted with xenograft tumors. *Id.* These studies show that ^{225}Ac -DOTATOC is more effective at preventing tumor growth as compared with ^{177}Lu -DOTATOC. Ex. 1015 at 4-5. In light of these *in vivo* data, Miederer concludes 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.

E. Jurcic

70. Joseph G. Jurcic, et. al., *Phase I Trial of Targeted Alpha-Particle Therapy with Actinium-225 (^{225}Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML)*, 128 Blood 4050 (2016) ("Jurcic"), published in January 2016.

71. Jurcic discloses the doses and dosing frequency used in a phase I clinical trial for ^{225}Ac -Lintuzumab, a radiolabeled antibody and low-dose cytarabine. Ex. 1011, Jurcic at 1. Similar to the other radiopharmaceuticals discussed above, ^{225}Ac -Lintuzumab comprises a chelating moiety (DOTA) with a radionuclide (^{225}Ac), a linker, and a targeting moiety (Lintuzumab). *Id.* A total of 38 patients with acute myeloid leukemia were broken into cohorts, with four dose levels tested. Ex. 1011, at 2. Two fractions of ^{225}Ac -Lintuzumab were administered one week apart. *Id.* The doses of radioactivity used in this study are summarized below in both $\mu\text{Ci}/\text{kg}$ and kBq/kg ¹:

$\mu\text{Ci}/\text{kg}$ (kBq/kg)
0.5 (18.5)
1.0 (37)
1.5 (55.5)
2.0 (74)

See id.

72. Treatment was well tolerated across all dosage levels, with only two patients exhibiting dose-limiting toxicity. *Id.* Additionally, the treatment induced remission in older patients with untreated AML. Ex. 1011 at 3. While the maximum tolerated dose was never achieved, Jurcic and co-workers conclude that

¹ $1 \mu\text{Ci} = 37 \text{ kBq}$. Therefore, $0.5 \mu\text{Ci} * 37 \text{ kBq}/\mu\text{Ci} = 18.5 \text{ kBq}$. $1.0 \mu\text{Ci} * 37 \text{ kBq}/\mu\text{Ci} = 37 \text{ kBq}$. $1.5 \mu\text{Ci} * 37 \text{ kBq}/\mu\text{Ci} = 55.5 \text{ kBq}$. $2.0 \mu\text{Ci} * 37 \text{ kBq}/\mu\text{Ci} = 74 \text{ kBq}$.

all doses can be safely and effectively used and planned to use the 2.0 $\mu\text{Ci/kg}$ (74 kBq/kg) dose in a phase II monotherapy study. Ex. 1011 at 2-3.

F. Kratochwil

73. 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”), published in May 2015.

74. Kratochwil discloses a dose escalation study of ^{225}Ac -DOTATOC radionuclide therapy. Ex. 1031, Kratochwil at 1. ^{225}Ac -DOTATOC is a targeted radiopharmaceutical which comprises the targeting agent octreotide linked to a ^{225}Ac -chelated DOTA. The goal of this empiric dose escalation was to find the maximum tolerated dose of single cycle and fractionated doses for this targeted alpha therapy. *Id.*

75. In this study, thirty-four human patients with progressive neuroendocrine tumors received treatment with ^{225}Ac -DOTATOC at various unit doses and intervals. *Id.* Kratochwil determined that the maximum tolerated dose of a single cycle of ^{225}Ac -DOTATOC was 40 MBq. Ex. 1031 at 2. For repeat (fractionated) doses, Kratochwil found that patients tolerated a dosing regimen of 25 MBq every 4 months or 18.5 MBq every 2 months. *Id.*

76. Kratochwil concluded that these doses represented a well-tolerated treatment protocol for targeted alpha therapy that “demonstrated promising treatment efficacy in various patients.” *Id.*

IX. ALL CHALLENGED CLAIMS WOULD HAVE BEEN OBVIOUS IN LIGHT OF THE PRIOR ART

77. By 2016, a POSA working in the radiopharmaceutical field would have recognized that prostate cancer treatment could benefit from improved targeted radiotherapeutics. A POSA would have been motivated to develop an improved prostate cancer treatment using prior art compounds combined with radionuclides that had been shown to be effective in cancer treatment. As a result, a POSA would have arrived at a method falling within the scope of the challenged claims with a reasonable expectation of success.

A. A POSA Would Have Been Motivated to Use PSMA I&T

78. A POSA looking for an improved radiotherapy for the treatment of prostate cancer would have understood that targeted radiotherapy would be preferred over a more generalized treatment and would have known that a number of studies had been published regarding molecules used to target radionuclides. While the literature disclosed using both antibodies and peptides as targeting moieties, a POSA would have understood that a peptide targeting portion would be preferred. As previously discussed, peptide/small molecule-based conjugates have shorter half-lives in serum, leading to a substantially decreased risk in non-specific

toxic interactions of the radiotherapeutic with other parts of the body. *Supra* ¶ 37; *see also* Ex. 1033 at 2; Ex. 1008 at 1.

79. A POSA developing a treatment for prostate cancer would have also chosen PSMA as a target. As noted above, PSMA was a well-known target for both diagnosis and treatment of prostate cancer. Several studies had been performed showing PSMA's viability as a promising target for further study. *See, e.g.*, Ex. 1027; Ex. 1028.

80. In light of this knowledge, a POSA would have been motivated to select the PSMA I&T ligand disclosed in Weineisen 2015 as the basis for an improved cancer therapy. A POSA would have recognized that PSMA I&T was the culmination of Weineisen and co-workers' efforts to develop an effective PSMA-targeted radiopharmaceutical. Indeed, PSMA I&T shows desirable properties for a PSMA-targeting radiotherapy, such as increased PSMA affinity and significantly enhanced internalization efficiency. Ex. 1028 at 3-4. For example, as discussed in Weinstein 2015, increased affinity coupled with enhanced internalization in *in vitro* studies translated to a twofold-higher accumulation of PSMA I&T in PSMA-expressing tissues, including metastases of metastatic Castration-Resistant Prostate Cancer (mCRPC), and lower non-specific interactions compared to previous PSMA targeting-therapeutics. Ex. 1028 at 7. A

POSA would have expected that increased accumulation of a therapeutic to its desired target would confer a greater therapeutic efficiency.

81. Additionally, Weineisen 2015 used [¹⁷⁷Lu]PSMA I&T in human studies. Ex. 1028 at 6. Due to ethical and safety concerns, human studies are reserved for only the safest and most promising therapies. By selecting PSMA I&T for human studies, Weineisen 2015 highlighted the construct as a radiotherapy of particular interest. The data from the human studies showed that PSMA I&T was safe and effective in prostate cancer patients, representing a promising new lead radiotherapy. Ex. 1028 at 8.

82. 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. Additionally, 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. *See* Ex. 1006 at 2.

83. Price also underscores that DOTA and derivatives including DOTAGA work well with ²²⁵Ac, and so a person having ordinary skill in the art would have a reasonable expectation of success in making ²²⁵Ac-PSMA I&T because the PSMA I&T has a DOTAGA chelator. Ex. 1041 at 9. Notably, the claims of the '901 patent do not require a requisite level of purity or stability for

²²⁵Ac-PSMA I&T, nor do they require any clinical endpoint for the treatment itself. The claims are merely directed to the abstract idea of treatment with 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.

84. Therefore, 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 and would have had a reasonable expectation that such efforts would be successful.

B. A POSA Would Have Been Motivated to Use PSMA I&T with ²²⁵Ac

85. While Weineisen 2015 describes the use of PSMA I&T with radionuclides that undergo beta decay (⁶⁸Ga and ¹⁷⁷Lu), Ex. 1028 at 1, a POSA would have understood that use of PSMA I&T would not have been limited on only those radionuclides. For example, Chatalic and co-workers showed use of PSMA I&T was not limited to use with beta emitters, disclosing PSMA I&T complexed with alpha emitter ²¹³Bi as a potential lead in preclinical studies. Ex. 1006 at 1-2. Therefore, a person of ordinary skill in the art would have understood that PSMA I&T could be used with a number of different radionuclides, including both alpha-particle and beta emitters to PSMA expressing cells *in vivo*.

86. Specifically, a person of ordinary skill in the art would have been motivated to use ^{225}Ac with PSMA I&T. At the outset of their efforts, Weineisen and co-workers sought 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. Due to the nature of the chelator moiety used in Weineisen’s compounds, a POSA would have appreciated that a M^{3+} -radiometal could be complexed with the targeting compounds. By December 2016, their bifunctional construct PSMA I&T had achieved that goal and been successfully used as a ligand for both alpha-emitting and beta-emitting radionuclides. *See, e.g.*, Ex. 1028; Ex. 1006.

87. Indeed, as discussed above, ^{213}Bi PSMA I&T showed promise in preclinical studies, but ^{213}Bi has known drawbacks. In particular, ^{213}Bi produces fewer alpha emissions per decay than other alpha-particle emitters and has a half-life of only 46 min. ^{213}Bi ’s shortened half-life presents a logistical challenge for its use as a radiotherapeutic because the radiotherapy must be prepared immediately before administration to prevent loss of potency. Therefore, a POSA would have been motivated to substitute another alpha emitter with a longer half-life than ^{213}Bi .

88. 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. 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 a small molecule/peptide would penetrate more rapidly into tumors and clear more rapidly from tissue compared to antibodies. *Id.* In addition, a small molecule/peptide would be more economical to produce at GMP grade than an antibody and thus more commercially viable.

89. The POSA would have understood that ^{225}Ac would be a promising substitute. Notably, Weineisen 2014 suggested ^{225}Ac as one of the radionuclides that would be acceptable for use in the family of compounds studied, of which PSMA I&T is part. Ex. 1027 at 11. A POSA would have also recognized that ^{225}Ac would overcome many of the drawbacks of ^{213}Bi . For example, ^{225}Ac , and its resultant decay chain, produces more alpha emissions than ^{213}Bi and has a substantially longer half-life of about 10 days. Ex. 1022 at 1, 4. Further, studies that directly compare ^{225}Ac to ^{213}Bi in the same antibody constructs have shown that ^{225}Ac is substantially more potent than the ^{213}Bi analog. Ex. 1013 at 4. Accordingly, the POSA would have been motivated to use ^{225}Ac with PSMA I&T in an improved cancer treatment.

90. It was also known at the time of the invention that ^{225}Ac could be safely administered in treating cancers. 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. 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 administered a radiotherapeutic.

91. The POSA would have had a reasonable expectation of success in making a ^{225}Ac -PSMA I&T complex based on the prior art disclosures of similar combinations. As noted above, the general idea of using one radionuclide instead of another, particularly swapping ^{225}Ac for ^{177}Lu , had been established by 2016. Ex. 1013. Claims 1, 2, and 4-13 of the '901 patent are not limited to any particular reaction conditions or any particular purity, stability level, or efficiency. Nor are claims 1, 2, and 4-13 limited to any specific targeting compound and chelating group combination.

92. While reaction conditions to prepare ^{225}Ac -DOTA/DOTAGA complexes are harsher than those needed for the corresponding ^{177}Lu complexes, synthesis of ^{225}Ac -DOTA/DOTAGA complexes, and their attachment to targeting moieties, would have been routine to a POSA in 2016. *See, e.g.*, Ex. 1013; Ex.

1014. And despite these harsher reaction conditions, e.g., higher temperatures, than preparation of the analogous [^{177}Lu]DOTA complexes, a POSA would not have been deterred. Ex. 1014 at 6. The known [^{225}Ac]DOTA constructs exhibited similar stability to [^{177}Lu]DOTA constructs in an assay that mimics the conditions inside the human body. Ex. 1013 at 2. Given that the ‘901 patent claims do not require any threshold level of purity, stability, or efficiency there would have been a reasonable expectation of success. Indeed, these studies show the two radiopharmaceuticals are generally stable under biological conditions, showing that the synthesis reaction conditions did not have an impact on stability.

93. Additionally, a POSA would have understood that radionuclides that undergo alpha decay could provide improved potency and reduce unwanted side effects. As noted above, alpha-particle emitters were known for their potentially improved therapeutic efficacy as compared to beta emitters. *See supra* ¶ 32; Ex. 1014 at 1-2. Alpha emission is higher in energy than beta emission, therefore alpha particles can do more damage to cells within the body than beta particles. For example, as Miederer notes, the alpha emitter ^{225}Ac is “characterized by extremely high cytotoxic activity on the cellular level.” Ex. 1015 at 1. By directly comparing [^{177}Lu]-DOTATOC with [^{225}Ac]-DOTATOC, Miederer showcases the increased efficacy of an alpha emitter (^{225}Ac) compared to a beta emitter (^{177}Lu).

94. Furthermore, alpha particles are ~8,000 larger than beta particles. As explained above, their size and charge prevents alpha particles from traveling long distances within the body, reducing the damage caused to healthy cells in the vicinity. *Supra* ¶ 32; Ex. 1014 at 1. Targeted delivery of alpha emitters to cancer cells leads to specific damage to cancerous cells with reduced off-target effect as compared to beta emitters. *Supra* ¶ 32; Ex. 1014 at 1. Therefore, a POSA would have had a reasonable expectation of success in making a ^{225}Ac -PSMA I&T and would have expected that the resulting radiopharmaceutical would be an effective cancer treatment.

C. A POSA Would Have Been Motivated to Use ^{225}Ac -PSMA I&T at the Doses Within the Claimed Ranges

95. A POSA looking to use the improved radiopharmaceutical to treat cancer would have looked to the literature to understand the appropriate doses that would be needed. The dosages necessary would be predominantly based on the amount of the radionuclide that needs to be delivered to the target site to achieve the therapeutic effect. Therefore, the POSA would look to information regarding the doses of ^{225}Ac necessary to kill cancer cells.

96. As a practical matter, before the priority date of the '901 patent, one of skill in the art 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. One of skill in the art 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. 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.

97. More specifically, because ^{225}Ac had garnered interest as a radiopharmaceutical, multiple schema and models had been made to estimate the absorbed dose of radioactivity from administration of ^{225}Ac . 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. 1017. From that guidance, a POSA would have understood the considerations related to radiobiology, toxicity, and relative biological effectiveness. Indeed, the pamphlet teaches the therapeutic potential, toxicity, and dosimetry for human studies of a variety of alpha emitters, including ^{225}Ac . Ex. 1017 at 2.

98. As of 2015, human studies of radiotherapies using ^{225}Ac had begun. *See, e.g.*, Ex. 1031. These studies highlight that the dose is tied to the amount of radiation that is released by the radiotherapy, using the units $\mu\text{Ci/kg}$ or kBq/kg . *Id.*

Early studies in humans of a ^{225}Ac radiopharmaceutical would have provided the POSA with additional information regarding appropriate doses for ^{225}Ac because similar radiopharmaceuticals would possess similar tolerated doses. In initial studies, Kratochwil determined that unit doses of 18.5 MBq and 25 MBq of an ^{225}Ac -DOTATOC, a targeting radiopharmaceutical, were well tolerated. Ex. 1031.002. Like PSMA I&T, DOTATOC comprises a DOTA chelating moiety, a linker, and an oligopeptide-based targeting moiety. 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. 1043 at 3. Accordingly, a POSA would have been motivated to use a similar unit dose of 18.5 MBq or 25 MBq, or a dose of $\leq 100 \text{ kBq/kg}$ for ^{225}Ac -PSMA I&T.

99. Additionally, the POSA would have understood that a unit dose could be translated to a body weight dose. For example, the average weight of an adult male patient in the United States is 90 kg. Ex. 1034, HHS at 9. This means that the 18.5 MBq unit dose is equivalent to administering ^{225}Ac -DOTATOC at a dose of 206 kBq/kg to a 90 kg patient:

$$18.5 \text{ MBq} \times \frac{1000 \text{ kBq}}{1 \text{ MBq}} = 18500 \text{ kBq}$$

$$18500 \text{ kBq} / 90 \text{ kg} = \sim 206 \text{ kBq/kg}$$

Similarly, the 25 MBq unit dose is equivalent to administering ^{225}Ac -DOTATOC at a dose of 278 kBq/kg to a 90 kg patient:

$$25 \text{ MBq} \times \frac{1000 \text{ kBq}}{1 \text{ MBq}} = 25000 \text{ kBq}$$

$$25000 \text{ kBq} / 90 \text{ kg} = \sim 278 \text{ kBq/kg}$$

Accordingly, a POSA would have been motivated to use a unit dose at either 206 or 278 kBq/kg, depending on the frequency of dosing.

100. A POSA would have also understood that lower doses had also been shown to be effective. Jurcic's clinical trial examined four doses (18.5 kBq/kg, 37 kBq/kg, 55.5 kBq/kg, and 74 kBq/kg), all four of which were determined to be safe and effective. Ex. 1011 at 2-3 (converted from $\mu\text{Ci/kg}$ —see footnote 1, above). Of these, the 74 kBq/kg dose was selected to be used in the phase II trial. Ex. 1011 at 3.

101. Therefore, the POSA would have been similarly motivated to administer ^{225}Ac PSMA I&T at the doses shown to be safe and effective in Jurcic. Additionally, in light of the MIRD Pamphlet, Kratochwil's initial human studies, and Jurcic's phase I clinical trial, the POSA would have had a reasonable expectation of success in using dosage amounts in the ranges previously disclosed in Kratochwil and Jurcic because the calculations of radiation of dosing had undergone extensive study, and studies in humans had already determined the safety and efficacy of doses in this range.

D. A POSA Would Have Been Motivated to Use the ^{225}Ac -PSMA I&T to Treat PSMA Expressing Cancers

102. While PSMA is most commonly associated with prostate cancer, a POSA would have understood that PSMA has been shown to be overexpressed in a number of cancers, including breast cancers. As early as 2003, it was understood that increased PSMA expression in tumors was correlated with a high risk of PC disease progression. Ex. 1021, Ross at 1. Scientists, however, found elevated levels of PSMA in breast cancer metastases and glioma. Ex. 1029, Wernicke at 5. In addition, PSMA-targeting constructs have been successfully used in the imaging of metastatic renal cell carcinoma. Ex. 1007, Demirci at 1-2. Therefore, the same overexpression of PSMA as seen and used in the imaging and therapy of PC could be used for other targeted therapies. Accordingly, a POSA would have been motivated to use the improved PSMA-targeted radiopharmaceutical, ^{225}Ac -PSMA I&T, to treat PSMA-expressing cancers, including PC, breast cancer, renal cancer or glioma, with a reasonable expectation of success.

103. Further, the POSA would have recognized that the treatment of PSMA-expressing cancers would not be limited to encapsulated, solid tumors. PSMA-expressing solid tumors have been shown to expand beyond their native tissue environment. See Ex. 1039, Ghosh at 2 (“PSMA can be used as a target of imaging agent[s] to detect metastatic tumor site, or PSMA can also be used to detect prostate cancer cells in the circulation or lymphatics.”). For example,

PSMA-expressing breast cancer is known to migrate (i.e., metastasize) to other parts of the body, taking PSMA along. Ex. 1018, Nomura at 5-6; 1029 at 7. Because targeted therapy targets the protein expressed on the outside of a cancer cell, rather than being confined to a specific tissue, the therapy will find a PSMA-expressing cancer cell even if it has disseminated. Ex. 1029 at 7; Ex. 1007 at 1; Ex. 1018 at 5. As discussed above, Weineisen 2015 discloses *in vitro* and *in vivo* studies examining the pharmacology and efficacy of PSMA I&T to treat metastatic prostate cancer, which a POSA would have considered a disseminated cancer. Ex. 1028 at 2-4; *see supra* ¶¶ 64-65. 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, often missing metastases. Therefore, a POSA would have been motivated to use ^{225}Ac -PSMA I&T to treat any PSMA expressing cancer, including disseminated cancers, with a reasonable expectation of success.

E. Each Challenged Claim is Invalid as Obvious

104. I understand that a patent claim is invalid as obvious if it covers obvious subject matter. Because the challenged claims of the '901 patent cover the use of ^{225}Ac -PSMA I&T in the treatment of PSMA expressing cancers at doses of ^{225}Ac known in the prior art, it is my opinion that these claims are invalid as obvious.

1. Claim 1

105. Claim 1 is directed to a method of administering certain identified ^{225}Ac radiopharmaceuticals to a patient at specified dosage amounts. 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. Formula D listed in claim 1 is PSMA I&T with an undefined stereocenter. Ex. 1001 at 19:39–20:15. It is my opinion that the use of PSMA I&T in method of claim 1 would have been obvious to a POSA as of December 15, 2016.

106. As discussed above, PSMA I&T was a promising targeting compound and was subsequently recommended for additional studies by Chatalic. Ex. 1006 at 2.

107. The method of claim 1 is directed to the treatment of PSMA-expressing cancers. PSMA expressing cancers were a known target for PSMA I&T. As discussed above, PSMA I&T was specifically designed to target PSMA-expressing cells. Additionally, 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 PSMA-expressing prostate cancer. Ex. 1028 at 2-3.

108. While Weineisen 2015 discloses [^{177}Lu]PSMA I&T, moving from a beta emitter like ^{177}Lu to the alpha emitter ^{225}Ac with DOTA/DOTAGA-containing targeting compounds as recited in claim 1 would have been obvious to a POSA.

Indeed, Miederer shows that when used in the same targeting compound, ^{225}Ac and ^{177}Lu have similar stabilities, but ^{225}Ac was shown to have increased efficacy compared to the ^{177}Lu analog. Ex. 1015 at 5-6. As noted above, ^{225}Ac is seen as a more viable radionuclide in radiotherapeutics when compared to ^{213}Bi , particularly because of ^{225}Ac 's longer half-life, resulting in lower required dosing and easier handling in the clinic. *Supra* ¶ 87.

109. The dose of radiation recited in claim 1 is 25 kBq to 400 kBq/kg of body weight of the patient. This dosage range for ^{225}Ac overlaps with the range that a POSA would have been motivated to use for ^{225}Ac . As discussed above, Kratochwil discloses at least 2 doses of ^{225}Ac , 205 kBq/kg and 278 kBq/kg, that fall within the range recited in claim 1. I understand that this overlap with the prior art is sufficient to find the dosage range obvious.

110. While I understand claim 1 lists the dosage as a unitary dosage, as an alternative to the per kg dose, the range of the unitary dosage in claim 1 is 3 MBq to 30 MBq. This unitary dosage amount would also have been within the range that a POSA would have been motivated to use. For example, the unitary dosages of radiation disclosed in Kratochwil are 18.5 MBq and 25 MBq in its human studies. Ex. 1031 at 2.

111. Therefore, it is my opinion that the use of Formula C or D in the method of claim 1 would have been obvious to a POSA.

2. Claim 2

112. Claim 2 depends from claim 1 and narrows the specified compounds. 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. *Id.* As discussed above, the use of PSMA I&T in the method of claim 1 would have been obvious to a POSA. Therefore, claim 2 would also have been obvious.

3. Claims 4–7

113. Claims 4–7 depend from claim 1 and further specify the type(s) of cancer treated with the claimed method. Ex. 1001 at 25:42-26:24. Claim 4 recites prostate cancer and breast cancer, among others. Ex. 1001 at 25:42-26:18. Claim 5 recites treatment of a disseminated cancer. Ex. 1001 at 26:19-20. Claim 6 recites treatment of prostate cancer. Ex. 1001 at 26:21-22. Claim 7 recites treatment of breast cancer. Ex. 1001 at 26: 23-24. As discussed above, 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. Ex. 1028 at 2-4; *see supra* ¶¶ 64-65. A POSA would have known that metastatic prostate cancer would be considered a disseminated cancer. Additionally, as noted above, PSMA was a known target for therapy and diagnosis of a number of cancers, including metastatic breast cancer and glioma, metastatic renal carcinoma, and other disseminated cancers. *See, e.g., supra* ¶¶ 102-103; Ex.

1029 at 5, 7; Ex. 1018 at 4, 6; Ex. 1007 at 1; Ex. 1029 at 2, 4. Therefore, claims 4-7 would also have been obvious to a POSA.

4. Claims 8–9

114. Claim 8 depends from claim 1 and requires the radiopharmaceutical be administered in the dosage range of 30 to 250 kBq/kg of body weight. Ex. 1001 at 26:25-29. Claim 9 depends from claim 8 and further narrows the recited dosage range to 50 to 200 kBq/kg of body weight. Ex. 26:29-30. As discussed above, a POSA would have been motivated to use doses of ^{225}Ac that have been previously shown to be safe and effective. *Supra* ¶¶ 98-100. Kratochwil discloses administration of ^{225}Ac at a dose of 205 kBq/kg, Ex. 1031 at 2 (converted from MBq), and Jurcic discloses successfully administering a radiotherapeutic with a radiation strength of 55.5 kBq/kg and 74 kBq/kg to a human patient, Ex. 1011 at 2 (converted from $\mu\text{Ci/kg}$). A POSA would have been motivated to use doses similar to the doses previously studied and would have had a reasonable expectation of success in doing so. Thus, claims 8 and 9 would also have been obvious to a POSA.

5. Claims 10–11

115. Claim 10 depends from claim 1 and requires the radiopharmaceutical be administered as a unitary dosage in the range of 4 MBq to 25 MBq of radiation. Ex. 26:31-33. Claim 11 depends from claim 10 and narrows the required unitary

dosage to a range of 5 MBq to 20 MBq of radiation. Ex. 26:34-35. As discussed above, POSA would have been motivated to use doses of ^{225}Ac that have been previously shown to be safe and effective. *Supra* ¶¶ 98-100. Kratochwil discloses a unitary dosage of 18.5 MBq of radiation when using an ^{225}Ac radiopharmaceutical comprising a peptide targeting moiety, a value that is encompassed by both ranges recited in claims 10 and 11. Ex. 1031 at 2. A POSA would have been motivated to use doses similar to the doses previously studied and would have had a reasonable expectation of success in doing so. Therefore, claims 10 and 11 would also have been obvious to a POSA.

6. Claims 12–13

116. Claims 12 and 13 depend from claims 8 and 10, respectively, and further require repeating the administration of an ^{225}Ac -radiopharmaceutical after 15-90 days. Ex. 1001 at 26:37-42. As discussed above, the methods of claims 8 and 10 would have been obvious to a POSA. *Supra* ¶¶ 114-115. Additionally, a POSA would have understood that ^{225}Ac radiopharmaceuticals have been repeatedly administered safely and would have been motivated to administer repeat doses. *Supra* ¶ 98. For example, Kratochwil discloses dosing 18.5 MBq of a ^{225}Ac radiopharmaceutical comprising an peptide targeting moiety every two months (i.e., ~60 days). Ex. 1031 at 2. Kratochwil taught that this dosing regimen was well tolerated. *Id.* A POSA would have been motivated to use doses similar to the

doses previously studied and would have had a reasonable expectation of success in doing so. Therefore, claims 12 and 13 would also have been obvious to a POSA.

X. CONCLUSION

117. For the reasons above, it is my opinion that claims 1, 2, and 4-13 of the '901 patent are obvious in view of the prior art. I reserve the right to amend or supplement these opinions in reply to Patent Owner's response.

XI. DECLARATION

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: September 26, 2025


By: _____
Michael R. Zalutsky, Ph.D.