

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

DECLARATION OF REBECCA ABERGEL, PH.D.

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I, Rebecca Abergel, Ph.D., declare as follows:

1. I have been retained on behalf of Fusion Pharmaceuticals, Inc. (“Fusion Pharmaceuticals”) 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 Fusion Pharmaceuticals is seeking to challenge the patentability of claims 1, 2, and 4–13 of the ’901 patent (the “challenged claims”).

2. Fusion Pharmaceuticals has asked me to consider the patentability of the challenged claims in light of the prior art, and to provide a tutorial on the technology described in the ’901 patent. I make this Declaration based upon my own personal knowledge, information, and belief.

I. QUALIFICATIONS

3. I graduated from the Magistère de Chimie Interuniversitaire at the École Normale Supérieure of Paris, France with a B.S. in Chemistry in 2002. I subsequently earned a Ph.D. in Bio-Inorganic Chemistry in 2006 from the University of California, Berkeley.

4. I have worked in academia since the early 2000s. Following my Ph.D. studies, I was a Post-Doctoral Research Fellow and Research Specialist at the University of California, Berkeley, and a Project Scientist, and Staff Scientist at the Lawrence Berkeley National Laboratory. I am currently an Associate Professor in the Department of Nuclear Engineering at UC Berkeley and the Heavy

Element Chemistry Group Leader within the Lawrence Berkeley National Laboratory's Chemical Sciences Division.

5. My research program is dedicated to developing new chemical tools that will advance our understanding of the chemistry of radioisotopes and heavy elements in the context of (i) the development of new strategies for anticancer, antibacterial, and antiviral radiotherapeutics, (ii) the development of new clinical radionuclide and toxic metal decontamination strategies, (iii) the development of new separation methods for rare earth mining, transuranic waste handling and purification of medical isotopes, and (iv) the development of new methodologies for interrogating the fundamental behavior of heavy and super-heavy elements.

6. I lead a large collaborative effort on the development of new drug products for the treatment of populations contaminated with heavy metals and radionuclides. One of these products was granted an Investigational New Drug status from the U.S. Food and Drug Administration in 2014 and is now in Phase I clinical trial.

7. I currently serve as the chair of the LBNL Radioactive Drug Research Committee and am an associate editor for the *International Journal of Radiation Biology*, a member of the Editorial Board of *Inorganic Chemistry*, and a corresponding member (USA) for *Radioprotection*. I was elected as a Fellow of the American Association for the Advancement of Science in 2019 and received

two U.S. Department of Energy 2020 Secretary of Energy Achievement Honor Awards for my contributions as a member of the National Virtual Biotechnology Laboratory and DOE National Laboratories' COVID-19 Clinical Testing teams.

8. I am the recipient of a Women Chemists Committee ("WCC") Rising Star award from the American Chemical Society (2017), an Early Career award from the U.S. Department of Energy (2014) and was selected as an Innovator under 35 – France by the MIT Technology Review in 2014. I received a Junior Faculty NCRP award (2013) from the Radiation Research Society and a Young Investigator Research Fellowship (2010) from the Cooley's Anemia Foundation.

9. Attached hereto as Exhibit 1003 is a true and correct copy of my Curriculum Vitae and select list of my publications.

II. MATERIALS CONSIDERED

10. Exhibit 1040 includes a list of the materials I considered, in addition to my experience, education, and training, in providing the opinions contained in this declaration.

III. COMPENSATION

11. I am being compensated at my usual rate of \$420 per hour for the time spent preparing this declaration, and my compensation is not contingent on the outcome of this matter or on any of the opinions provided below.

IV. LEGAL PRINCIPLES

12. To assist me in performing my assessment of patentability, Counsel

for Petitioner have informed me about the legal standards for patentability set forth below.

13. I am advised that the following four elements should be considered in conducting an obviousness analysis: (1) the scope and content of the prior art; (2) the differences between the prior art and the claim; (3) the level of ordinary skill in the art; and (4) secondary considerations/objective indicators of non-obviousness. I am advised that a patent claim is unpatentable for obviousness if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in the art to which the subject matter pertains. I am further advised that a patent claim is obvious if a person of ordinary skill in the art would have been motivated to combine the elements of the claim, in view of the prior art and the state of the art and would have had a reasonable expectation of success in doing so. I am advised that the law requires only a reasonable expectation of success and does not require absolute certainty of success.

14. I am advised 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 commonsense approach that is flexible, rather than

adherent to rigid application of legal standards or tests.

15. It is my understanding that obviousness is viewed through the eyes of a person of ordinary skill in the art (“POSA”) as of the time of the invention in question.

16. 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.

V. LEVEL OF ORDINARY SKILL IN THE ART

17. I am advised that in defining a POSA the following factors may be considered: (1) the education level of the inventor; (2) the type of problems encountered in the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field.

18. In my opinion, a POSA as of December 2016 would have been a scientist or clinician, with a Ph.D. or M.D., or a team of such individuals, who alone or in combination had experience with (i) the concept of radioimmunoconjugation, (ii) the chemical behavior of radiometals from the d- and

f-blocks of the Periodic Table, such as ^{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 (iv) the 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.

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 radioactive decay. Radioactive decay, or radioactivity, 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 .002.

20. The two types of radioactive decay relevant for this declaration are

alpha decay and beta 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 the daughter nucleus with two fewer protons.

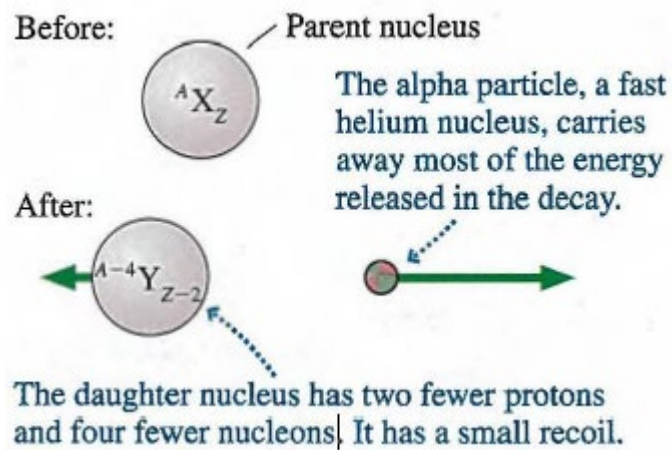


Figure 1. Ex. 1032, Knight at 0.22.

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.

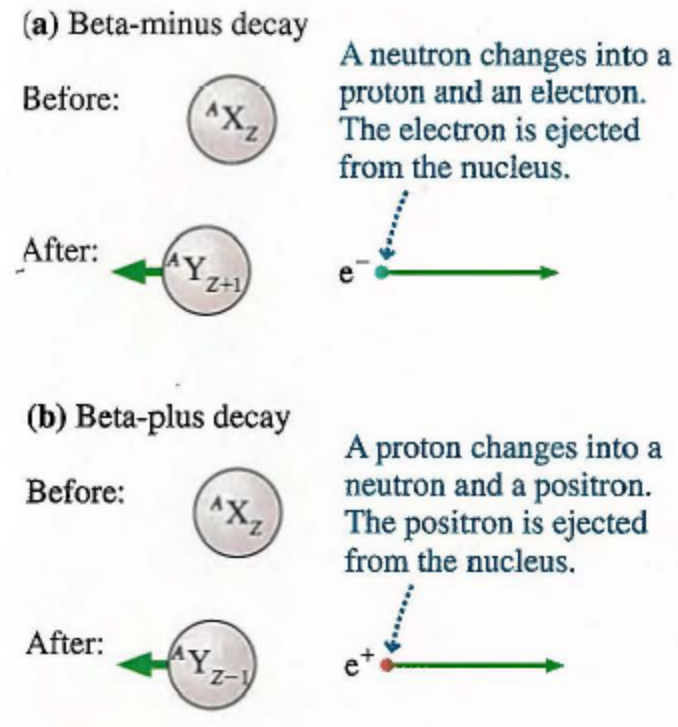


Figure 2. Ex.1032.023.

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 .002–.003. 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 element 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 .001–.002. 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. 1012.002–.003.

24. Additionally, certain radionuclides can be used in medical treatment, most commonly to treat cancer. Ex. 1020, Hubenak at .001. It has long been known that the particles and energy released from radioactive atoms cause damage to DNA, which leads to the death of the impacted cells. *See id.* at .004. 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 .002. This traditional radiation therapy resulted in a number of adverse effects due to the non-specific nature of the treatment. *Id.* at .002, .005–.006. 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 .006.

Once at the target cell, the radioactive decay damages the DNA, and ultimately causes cell death. *Id.* at .004.

25. In both radionuclide imaging and radiopharmaceuticals, 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):

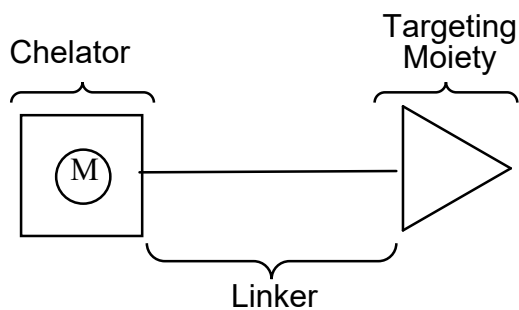


Figure 3

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 .001–.002; Ex. 1027, Weineisen 2014 at .011; Ex. 1035, Viola-Villegas at .004, .014, .016. 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.

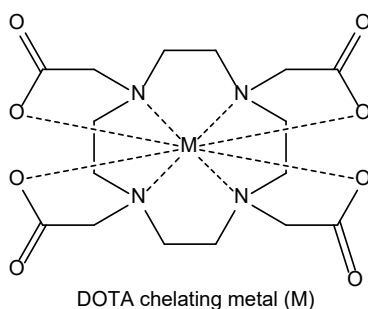


Figure 4

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

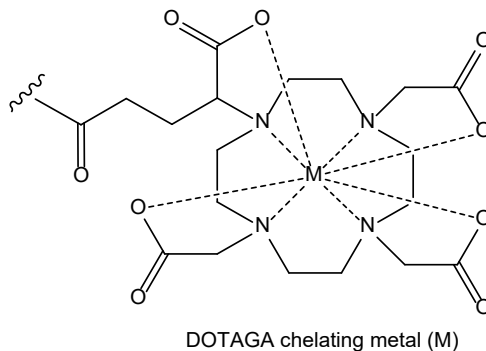


Figure 5

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.

3. Radionuclides

28. 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.

29. Early studies into radiopharmaceuticals focused on the use of beta emitting radionuclides due to their availability and familiarity. Ex. 1016.003.

However, alpha-particle emitting radionuclides are increasingly seen as more desirable in the context of radiopharmaceuticals. *See id.*; Ex. 1030, Miederer 2008b at .002. Alpha particles are substantially larger and contain more energy than the particles emitted during beta decay. *See* Ex. 1030.002; Ex. 1016.003; *see also* Ex. 1017, MIRD Pamphlet at .001. This size difference leads to differences in how these particles behave in the target environment. Ex. 1030.002. The bigger 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 particles resulting from beta decay face less resistance and are able to travel a few hundred cell diameters. *See* Ex. 1016.003. The more localized impact of alpha decay makes it ideally suited for targeted therapy because the impact on the surrounding tissue is minimized, reducing the likelihood of side effects. *See* Ex. 1014.001; Ex. 1030.002. Furthermore, because alpha particles are higher energy than the particles resulting from beta decay, alpha-particle emitters can be administered in lower doses than beta emitters, further reducing the risk of adverse effects. *See* Ex. 1030.002; Ex. 1016.003.

30. 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 .007–.008. 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 .002. The [^{225}Ac]DOTA-IgG construct described in McDevitt 2001 was effective in killing a variety of cancer cells. See Ex. 1013.002–.004. Since 2001, ^{225}Ac -based radiopharmaceuticals using other targeting moieties and linkers have garnered interest, including the use of other antibodies, such as anti-HER-2/neu, HuM195, and 3F8 antibodies, tetramers, and small molecules. See, e.g., Ex. 1022.012–.013.

4. Radiopharmaceuticals and the Treatment of Prostate Cancer

31. 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, Turkbey at .001. 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.

32. 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. 1024.001. 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 .001.

33. 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 .005. This difference in expression levels means PSMA-targeting therapies will selectively kill PC cells over healthy cells. *See* Ex. 1008, Foss at .001. Further, high levels of PSMA have been correlated with patients with hormone-refractory disease and primary and nodally metastatic PC. *Id.*; Ex. 1023, Silver at .005. Its presence on malignant PC tumor cells has made PSMA an ideal target for both diagnostic techniques and therapeutic methods. *See* Ex. 1027.011.

34. PSMA functions as an oligonucleotide receptor in prostate cells. Ex. 1008.001. That is, PSMA is a transmembrane protein found primarily in prostate cells and binds oligonucleotides on the exterior of the cells. *Id.* In particular, PSMA selectively binds the oligonucleotide 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 oligonucleotide/small molecule conjugates are more attractive imaging agents. Radiolabeled oligonucleotides/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 .002; Ex. 1008.001.

35. Prior to 2014, most therapies for the treatment of prostate cancer were focused on androgen-deprivation therapy and chemotherapy. Ex. 1028.001–.002. 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 .004–.006. 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 .001; Ex. 1010, Hillier 2012 at .001. Each of these rely on a ¹³¹I radiolabel. Ex. 1009.001; Ex. 1010.001. 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.

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

36. 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

37. 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.*

38. The specification acknowledges some of the known benefits of using alpha emitters like ²²⁵Ac 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.

39. 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

40. 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.

41. 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 ^{225}Ac -radiopharmaceuticals, including ^{225}Ac -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. 1004.402, .406 (June 24, 2020 Non-Final Rejection).

42. The '791 patent claims were directed to a method of treating prostate cancer with ^{177}Lu complexed to the chelator. *See* Ex. 1004.404 (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. 1004.406–.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. 1004.404, .408 (June 24, 2020 Non-Final Rejection).

43. 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).

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.*

44. 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.*

45. 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. 1004.383 (Oct. 26, 2020 Applicant Arguments/Remarks) (emphasis in original). The applicant directed the Examiner to examples in the pending application comparing treatment with ^{225}Ac -radiopharmaceuticals with ^{177}Lu -radiopharmaceuticals, contending that it was a “remarkable difference” that the group treated with ^{177}Lu -radiopharmaceuticals had

a lower response rate than those treated with ^{225}Ac -radiopharmaceuticals. *See* Ex. 1004.383–.384 (Oct. 26, 2020 Applicant Arguments/Remarks).

46. 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. 1004.384 (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. 1004.384 (Oct. 26, 2020 Applicant Arguments/Remarks). As explained in more detail below, I disagree that this difference in efficacy would be surprising or unexpected.

47. The Examiner was not presented with prior art demonstrating the known benefits of using ^{225}Ac 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. 1004.033–.034 (Jan. 11, 2021 Examiner’s Reasons for Allowance).

48. The Examiner allowed the claims without addressing applicant’s nonstatutory double patenting remarks. *See* Ex. 1004.033–.034 (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. 1004.033 (Jan. 11, 2021 Examiner’s Reasons for Allowance).

C. The Challenged Claims

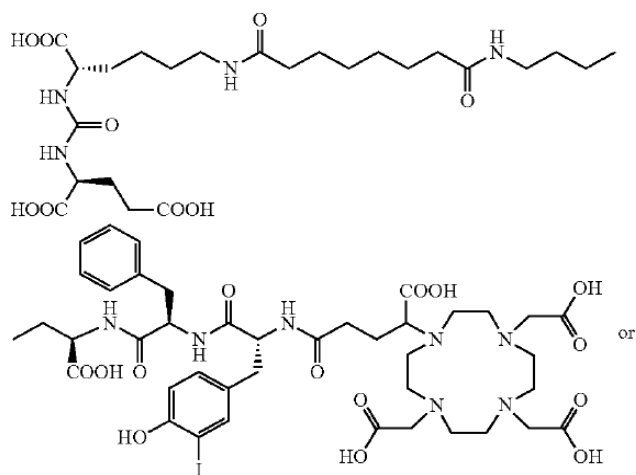
49. I understand that Fusion is challenging claims 1, 2, and 4–13 of the ’901 patent as unpatentable.

50. Independent claim 1 reads:

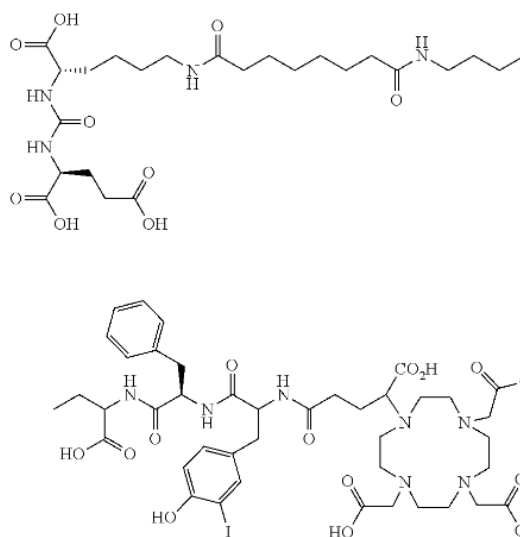
1. A method for treating PSMA expressing cancers, wherein the method comprises administering to a patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (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

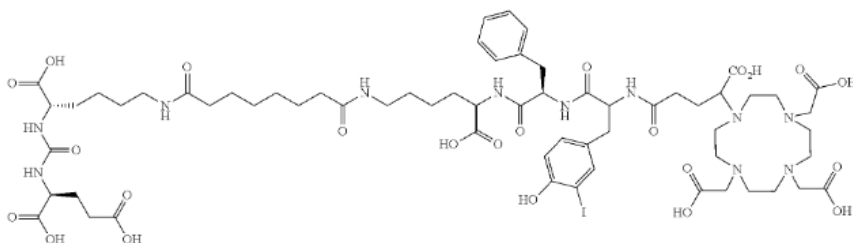
effective amount of said one or more Ac-225-radiopharmaceuticals is administered as a unitary dosage of from 3 MBq to 30 MBq to said patient.

Ex. 1001 at 18:13–20:37.

51. 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.

52. 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.

53. 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.

54. 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.

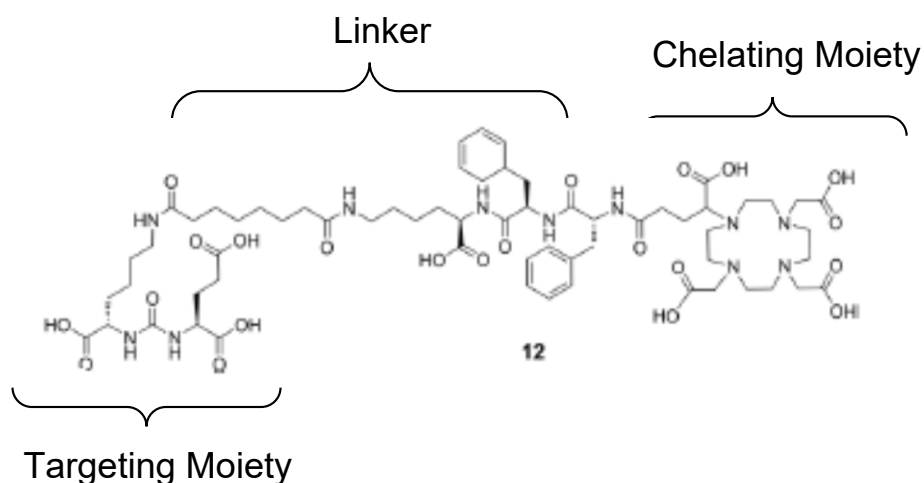
Ex. 1001 at 26:37–43.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

A. Weineisen 2014

55. 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.

56. Weineisen 2014 discloses a bifunctional construct capable of targeting PSMA and chelating a radionuclide. Ex. 1027.001. Weineisen 2014 includes work 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. 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. 1027.009 (annotated).

57. 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. 1027.008. Wineisen 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, Wineisen 2014 measured ^{177}Lu -12’s affinity for PSMA (IC_{50}), specificity for PSMA-expressing cells, and internalization into prostate cells. Ex. 1027.008–010. As shown in Wineisen 2014, ^{177}Lu -12 exhibits high affinity for its target protein, PSMA, ($\text{IC}_{50} = 13.1 \text{ nM}$) with little off-target binding (less than 0.5%). Ex. 1027.010. Additionally, ^{177}Lu -12 proved to be rapidly internalized into PSMA expressing cells. Ex. 1027.014. These data allowed the authors to conclude that DOTAGA-ffk(Sub-KuE) “possesses remarkable potential for a PSMA based theranostics concept.” *Id.*

B. Wineisen 2015

58. Martina Wineisen, 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) (“Wineisen 2015”), published in 2015.

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

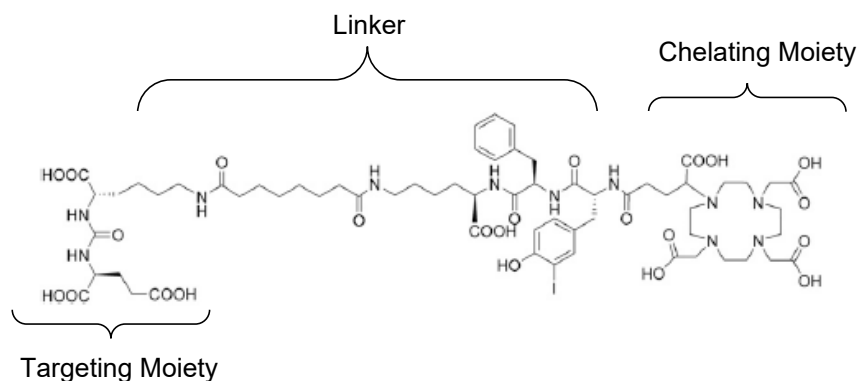


Figure 6

Ex. 1028, Weineisen 2015 at .002.

60. 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. 1028.002. In *in vitro* studies, [^{177}Lu]PSMA I&T possessed an almost twofold increase in PSMA binding as compared to ^{177}Lu -**12**. Ex. 1028.003–.004. The increase PSMA affinity conferred a ~72% increase in internalization of [^{177}Lu]PSMA I&T as compared to ^{177}Lu -**12**. Ex. 1028.004. These data disclosed in Weineisen highlight [^{177}Lu]PSMA I&T superiority compared to previous radioligands.

61. Furthermore, in contrast to Weineisen 2014, which did not undertake *in vivo* studies with ^{177}Lu -**12**, Weineisen 2015 discloses a proof-of-concept study

comprising administering [^{177}Lu]PSMA I&T to two human patients with metastatic castrate-resistant prostate cancer. Ex. 1028.006. In this study, [^{177}Lu]PSMA I&T showed “high, specific and rapid uptake in all previously identified tumor lesions.” Ex. 1028.007. 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 “ ^{177}Lu -PSMA I&T endoradiotherapy was feasible, safe, and effective in metastatic PC.” Ex. 1028.008.

C. Chatalic

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

63. Chatalic discloses the use of PSMA I&T with the alpha particle emitter ^{213}Bi . Ex. 1006, Chatalic at .001. Using xenograph mouse studies, Chatalic observed that within 1 hour of administration of 5 MBq of ^{213}Bi PSMA I&T had induced DNA damage within tumor cells. Ex. 1006.001–.002. The authors conclude that ^{213}Bi PSMA I&T had “good tumor targeting and induction of [DNA double strand breaks] in PSMA-expressing LNCaP xenografts.” Ex. 1006.002.

D. Miederer

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

65. Miederer teaches that many patients did not respond to radiotherapy using the beta-emitting $^{177}\text{Lu}(\text{DOTATOC})$, despite evidence that it was a promising treatment for metastasized neuroendocrine tumors. Ex. 1015, Miederer 2008a at .006. 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. 1015.001. 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. 1015.001. Miederer reports initial mouse studies showing that up to 60 kBq of ^{225}Ac -DOTATOC was tolerated without toxicity. Ex. 1015.004. 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. 1015.004–005. 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. 1015.001, .006.

E. Jurcic

66. 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.

67. 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 .001. 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. 1011.002. 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 $\mu\text{Ci/kg}$ and kBq/kg ¹:

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

See id.

68. 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. 1011.003. While the maximum tolerated dose was never achieved, Jurcic and co-workers conclude that all doses can be safely and effectively used and planned to use the $2.0 \mu\text{Ci/kg}$ (74kBq/kg) dose in a phase II monotherapy study. Ex. 1011.002–.003.

F. Kratochwil

69. 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.

70. Kratochwil discloses a dose escalation study of ²²⁵Ac-DOTATOC

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

radionuclide therapy. Ex. 1031, Kratochwil at .001. ^{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.*

71. 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. 1031.002. 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.*

72. 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

73. 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

74. 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 oligonucleotides as targeting moieties, a POSA would have understood that an oligonucleotide targeting portion would be preferred. As previously discussed, oligonucleotide/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* ¶ 34; *see also* Ex. 1033.002; Ex. 1008.001.

75. 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.

76. 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. 1028.003–.004. 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. 1028.007. A POSA would have expected that increased accumulation of a therapeutic to its desired target would confer a greater therapeutic efficiency.

77. Additionally, Weineisen 2015 used [¹⁷⁷Lu]PSMA I&T in human studies. Ex. 1028.006. 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 a safe and effective in prostate cancer patients, representing a promising new lead radiotherapy. Ex. 1028.008.

78. 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. 1006.001. 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. 1006.002.

79. 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

80. While Weineisen 2015 describes the use of PSMA I&T with radionuclides that undergo beta decay (⁶⁸Ga and ¹⁷⁷Lu), Ex. 1028.001, 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. 1006.001–.002. 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*.

81. 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. 1027.011. Due to the nature of the chelator moiety used in Weineisen’s compounds, a POSA would have appreciated that any 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.

82. 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 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 .

83. 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. 1027.011. 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. 1022.001, .004. 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. 1013.004. Accordingly, the POSA would have been motivated to use ^{225}Ac with PSMA I&T in an improved cancer treatment.

84. 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, using one radionuclide instead of another, particularly swapping ^{225}Ac for ^{177}Lu , had been established by 2016. Ex. 1013. 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. 1014.006. 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. 1013.002. Indeed, these studies show the two radiopharmaceuticals are equally stable under biological conditions, showing that the synthesis reaction conditions did not have an impact on stability.

85. 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* ¶ 29; Ex. 1014.001–.002. 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. 1015.001. 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).

86. Furthermore, alpha particles are ~8,000 larger than beta particles. As explained above, their size prevents alpha particles from traveling long distances within the body, reducing the damage caused to healthy cells in the vicinity. *Supra* ¶ 29; Ex. 1014.001. 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* ¶ 29; Ex. 1014.001. 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

87. 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.

88. 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 alpha emitters, including ^{225}Ac .

Ex. 1017.002

89. 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. Accordingly, a POSA would have been motivated to use a similar unit dose of 18.5 MBq or 25 MBq for ^{225}Ac -PSMA I&T.

90. 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 .009. 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 an 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.

91. 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. 1011.002–.003 (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. 1011.003. 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 ²²⁵Ac-PSMA I&T to Treat PSMA Expressing Cancers

92. 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 .001. Scientists, however, found elevated levels of PSMA in breast cancer metastases and glioma. Ex. 1029, Wernicke at .005. In addition, PSMA-targeting constructs have been successfully used in the imaging of metastatic renal cell carcinoma. Ex. 1007, Demirci at .001–.002. Therefore, the same overexpression of PSMA as seen and used in the imaging and therapy of PC could be used for targeted therapies for any tumor cells that present more PSMA on their cell surface than non-cancerous cells. Accordingly, a POSA would have been motivated to use the improved PSMA-targeted radiopharmaceutical, ²²⁵Ac-PSMA I&T, to treat PSMA-expressing cancers, including PC, breast cancer, renal cancer or glioma, with a reasonable expectation of success.

93. 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 .002 (“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 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 .005–.006; 1029.007. 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. 1029.007; Ex. 1007.001; Ex. 1018.005. 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. 1028.002–.004; *see supra* ¶¶ 60–61. 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 ²²⁵Ac-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

94. 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 ²²⁵Ac-PSMA I&T in the treatment of PSMA expressing cancers at doses of

²²⁵Ac known in the prior art, it is my opinion that these claims are invalid as obvious.

1. Claim 1

95. Claim 1 is directed to a method of administering certain identified ²²⁵Ac 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. 1028.002. Formula D listed 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.

96. As discussed above, PSMA I&T was a promising targeting compound and was subsequently recommended for additional studies by Chatalic. Ex. 1006.002.

97. 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. 1028.002–.003.

98. While Weineisen 2015 discloses [¹⁷⁷Lu]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. 1015.005–.006. 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* ¶ 82.

99. The dose of radiation recited 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.

100. 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. 1031.002.

101. 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

102. 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 method of claim 1 would have been obvious to a POSA. Therefore, claim 2 would also have been obvious.

3. Claims 4–7

103. 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. 1028.002–.004; *see supra* ¶¶ 60–61. 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* ¶¶ 92–93; Ex. 1029.005, .007; Ex. 1018.004–.006; Ex. 1007.001; Ex. 1029.002, .004. Therefore, claims 4–7 would also have been obvious to a POSA.

4. Claims 8–9

104. 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* ¶¶ 89–91. Kratochwil discloses administration of ^{225}Ac at a dose of 205 kBq/kg, Ex. 1031.002 (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. 1011.002 (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

105. 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* ¶¶ 89–91. Kratochwil discloses a unitary dosage of 18.5 MBq of radiation when using an ^{225}Ac radiopharmaceutical comprising an oligonucleotide targeting moiety, a value that is encompassed by both ranges recited in claims 10 and 11. 1031.002. 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

106. 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* ¶¶ 103–04. 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* ¶ 89. For example, Kratochwil discloses dosing 18.5 MBq of a ^{225}Ac radiopharmaceutical comprising an oligonucleotide targeting moiety every two

months (i.e., ~60 days). Ex. 1031.002. 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. NO SECONDARY CONSIDERATIONS SUPPORT THE NON-OBVIOUSNESS OF THE CHALLENGED CLAIMS

107. I am not aware of any secondary consideration that show the challenged claims to be non-obvious.

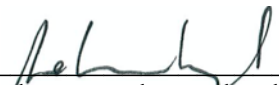
XI. CONCLUSION

108. 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.

XII. DECLARATION

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

Dated: February 7, 2023

By: 
Rebecca Abergel, Ph.D.