

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CURIUM US, LLC

Petitioner,

v.

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

Patent Owner

Case No. IPR2025-01582

Patent No. 10,980,901 B2

DECLARATION OF DR. MICHAEL A. GORIN, M.D.

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I, Dr. Michael A. Gorin, MD, declare and state as follows:

I. ASSIGNMENT

1. I have been retained by Universität Heidelberg and The European Atomic Energy Community (Euratom), represented by The European Commission (collectively Heidelberg), as an independent consultant and expert witness in this proceeding. I have been asked to investigate and express an opinion concerning the obviousness of the patent in suit, U.S. Patent No. 10,980,901 (the "'901 Patent"), in the inter partes review proceeding Case No. IPR2025-01582 in light of the information provided by Curium US LLC and their expert, Dr. Michael Zalutsky, PhD.

2. I am being compensated for my time in connection with this matter at a rate of \$500/hr. My compensation is not in any way contingent upon the opinions that I express or the outcome of this proceeding. I have no financial or personal interest in the outcome of this proceeding regarding the '901 Patent.

II. QUALIFICATIONS AND EXPERIENCE

3. My curriculum vitae, attached as Exhibit 2156, provides a detailed description of my educational and professional background and qualifications. My CV includes a list of positions, awards, patents, grants, clinical trials, publications, and invited lectures current through August 2026. I have over a decade of experience in the fields of urology, urologic oncology, and molecular imaging research. My research and clinical activities have focused on the development and clinical translation of novel molecular imaging agents for the detection and characterization of prostate and kidney cancer, with particular emphasis on agents targeting

cellular mitochondrial content, Prostate-Specific Membrane Antigen (“PSMA”), and Carbonic Anhydrase IX (“CAIX”).

4. I graduated from the University of Michigan in 2007 with a Bachelor of Science with Distinction in Cell and Molecular Biology. In 2011, I graduated from the University of Miami Leonard M. Miller School of Medicine with a Doctor of Medicine degree with Distinction in Research and as a member of the Alpha Omega Alpha (ΑΩΑ) Honor Medical Society. I went on to complete my postgraduate medical education at Johns Hopkins, beginning with a general surgery internship (2011–2012), followed by a urology residency (2012–2017), which included a dedicated year of clinical and translational research, and a fellowship in endourology and minimally invasive surgery (2017–2019). My training included clinical rotations at The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, and Johns Hopkins Children’s Center. I am board-certified by the American Board of Urology and hold an active medical license in the State of New York. I am also a member of the American Urological Association and the Endourological Society.

5. I currently hold the position of Associate Professor in the Milton and Carroll Petrie Department of Urology at the Icahn School of Medicine at Mount Sinai in New York, a position I have held since 2022. In 2025, I was also appointed Associate Professor in the Windreich Department of Artificial Intelligence and Human Health at the Icahn School of Medicine at Mount Sinai. Prior to joining Mount Sinai, I served as an Assistant Professor in the Department of Urology at the Johns Hopkins University School of Medicine from 2017 to 2020 and then as a Clinical Assistant Professor of Urology at the University of Pittsburgh School of Medicine from 2021 to 2022.

6. I have been the recipient of multiple awards and professional honors during my academic and clinical career. These include the Drs. Carl and Barbara Alving Endowed Award for Outstanding Biomedical Research from the University of Miami Leonard M. Miller School of Medicine, as well as the Frank L. Coulson Jr. Resident Clinical Excellence Award and the William F. Rienhoff, Jr., M.D. Scholar Award from Johns Hopkins University School of Medicine. My research has also received awards at scientific meetings, including Best Poster at the Society of Urologic Oncology Annual Meeting, Best Clinical Research Poster at the National Kidney Foundation of Maryland Scientific Session, and Best Paper at the Annual Meeting of the Engineering & Urology Society. Most recently, in 2026, I was named a Castle Connolly Top Doctor. I have served as the principal investigator or co-principal investigator on multiple research grants and clinical trials involving urologic cancers and molecular imaging. I was the recipient of a grant from the AUA Care Foundation for the development of a novel method for detecting circulating tumor cells in patients with renal cell carcinoma and a grant from the National Kidney Foundation of Maryland for studying ^{99m}Tc -Sestamibi SPECT imaging for the preoperative diagnosis of renal oncocytoma. I also served as principal investigator on the Patrick C. Walsh Research Fund project evaluating PSMA-targeted ^{18}F -DCFPyL PET/CT for the detection of clinically significant prostate cancer in men presenting with an elevated PSA.

7. In addition, I have served as lead co-investigator and principal investigator on multiple investigator-initiated and industry-sponsored clinical trials involving PSMA-targeted molecular imaging. Notably, I was the lead investigator of the first clinical trial investigating ^{18}F -DCFPyL PET/CT in high-risk patients prior to radical prostatectomy. I then went on to play a key leadership role in the design and implementation of the landmark OSPREY (ClinicalTrials.gov ID NCT02981368) and CONDOR (ClinicalTrials.gov ID NCT03739684)

trials that led to FDA approval of this agent, now commercially known as PYLARIFY. Since the time of its initial approval in 2021, PYLARIFY has been used to image over 750,000 men with prostate cancer. At present, I am the co-principal investigator of the CLARIFY trial (ClinicalTrials.gov ID NCT06056830) of ^{64}Cu -SAR-bisPSMA, a novel bi-motif ligand of PSMA with a higher binding affinity and longer half-life than currently available ^{18}F and ^{68}Ga -labeled agents, which we believe will translate to a higher sensitivity than these already available agents.

8. As the result of my research, I am a named inventor on two issued U.S. patents: U.S. Patent No. 12,570,944, *Devices and Methods for Magnetic Isolation and Analysis of Rare Cells*, and U.S. Patent No. 10,857,246, *Nuclear Imaging and Radiotherapeutics Agents Targeting Carbonic Anhydrase IX and Uses Thereof*. The latter patent relates directly to my research on the development of CAIX-targeted molecular imaging agents for detecting clear cell renal cell carcinoma, the most common subtype of kidney cancer. My work on CAIX-targeted imaging has included the development and preclinical evaluation of novel radiolabeled agents, including a dual-motif inhibitor labeled with ^{111}In and ^{64}Cu for SPECT and PET imaging of clear cell renal cell carcinoma, respectively. The ^{111}In -labeled CAIX targeting agent is currently undergoing study in a first-in-human trial at Johns Hopkins (ClinicalTrials.gov ID NCT07062549).

9. I have published extensively in the peer-reviewed scientific literature. My publication record includes over 300 original research articles, systematic reviews, meta-analyses, narrative reviews, editorials, consensus statements, and case reports. My Google Scholar h-index is 65, with more than 17,000 total citations, placing me among the top 10% of cited clinicians according to Doximity. In addition, Semantic Scholar has credited my work with

540 “highly influential citations,” reflecting the impact of my scholarship on subsequent research.

10. Many of my publications relate directly to PSMA-targeted molecules relating to prostate cancer, CAIX-targeted imaging of kidney cancer, and the use of novel nuclear medicine techniques for renal mass characterization. Much of my work also pertains to the novel use of PSMA-targeted agents in patients with non-prostate malignancies, including renal and urothelial cancers. I currently serve as Editor-in-Chief of *BJUI Compass* and as an editorial board member of the *BJU International*. In 2025, I was appointed Section Editor for Artificial Intelligence and Digital Health Tools at *Urologic Oncology: Seminars and Original Investigations*.

11. I have also contributed chapters to leading medical textbooks. Notably, I was the first invited author to contribute a dedicated chapter on nuclear imaging to Campbell-Walsh-Wein Urology, the definitive reference textbook in the field of urology. My chapter, “Genitourinary Tract Imaging: Basic Principles of Nuclear Medicine,” has appeared in the 12th and 13th editions of Campbell-Walsh-Wein Urology, published by Elsevier in 2020 and 2025, respectively. I also co-edited the textbook *Diagnosis and Surgical Management of Renal Tumors*, published by Springer in 2019.

12. I have contributed to professional organizations dedicated to advancing the field of molecular imaging and nuclear medicine in urology. I have served as a committee member of the Society of Nuclear Medicine and Molecular Imaging Prostate Cancer Outreach Working Group since 2021. From 2023 to 2025, I served on a joint committee of the European Association of Nuclear Medicine and the Society of Nuclear Medicine and Molecular Imaging, developing a procedure standard for nuclear imaging for renal masses. In 2025, I was appointed

to the American College of Radiology committee developing the PSMA-Targeted PET Reporting and Data System.

13. I have been invited to deliver numerous lectures at national and international meetings on topics including “Novel Imaging Techniques in Renal Cell Carcinoma,” “PSMA-targeted PET/CT Imaging of Prostate Cancer,” “Risk Stratification of Localized Renal Tumors Utilizing Molecular Imaging,” “PSMA-targeted PET/CT Imaging of Prostate and Kidney Cancer,” and “Renal Mass Biopsy and Molecular Imaging.” These lectures reflect the breadth and depth of my expertise in the clinical application of molecular imaging to urologic malignancies.

14. My expertise overlaps with the scientific issues that arise in this case, including the use of PSMA-targeted imaging agents, molecular imaging of kidney and prostate cancer, nuclear medicine imaging principles, and the development of novel radiolabeled agents for cancer detection. As a clinician-scientist who has led clinical trials, developed imaging agents, obtained patents in this area, and published extensively on these topics, I have an in-depth understanding of the relevant science and the state of the art during the relevant time period.

III. MATERIALS CONSIDERED

15. As part of my assignment, I have reviewed the declaration of Dr. Michael Zalutsky, the relevant associated references cited by his declaration, and Dr. Zalutsky’s deposition testimony. I have also reviewed relevant background materials provided by counsel and have relied on my own understanding of the field. A complete list of the materials that I considered for this declaration is shown in Exhibit 2157.

16. I have also reviewed the declarations of Dr. Rebecca Abergel, Ph.D., and Dr. Thomas Hope, M.D., provided in the previous IPR involving the '901 Patent. I agree with Dr. Hope's opinions on the claims, prior art, technology, and why Claims 1, 2, and 4-13 of the '901 Patent are valid and not obvious. I have adopted the majority of Dr. Hope's opinions and have expanded on some of the points. I also include references to Dr. Abergel's deposition where relevant since she was provided as an expert in opposition to the '901 Patent.

IV. APPLICABLE LEGAL STANDARDS

17. I am not an attorney and will not offer opinions on the law. Rather, I am offering a technical assessment and opinion. I have been informed by counsel of the legal standards for determining patentability, which I have employed in forming my opinions that are recited in this declaration.

18. It has been explained to me that the patent claims describe the invention made by the inventor and what the patent owner owns and what the owner may prevent others from using. I understand that an independent claim sets forth all the requirements that must be met to be covered by that claim. I further understand that a dependent claim does not itself recite all of its requirements but refers to another claim and incorporates all the requirements of the claim to which it refers.

19. A claim is invalid as obvious under 35 U.S.C. § 103 if the differences between the claim sought to be patented and the prior art are such that 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. I have been informed 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, often called secondary considerations.

20. 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 and that the skilled artisan would have had a reasonable expectation of success in doing so. It is my understanding that it is not enough to show that one skilled in the art could combine elements of multiple references or that all of the elements of the invention may have been known separately in the prior art, but instead there must be some reason that would have prompted a person of ordinary skill in the art to combine the elements in the way the claimed invention does. I understand that there must be some reasoned explanation for why one of ordinary skill in the art would combine the references.

21. I also understand that when evaluating obviousness, it is improper to selectively use only certain parts of a single reference that support a specific position while ignoring other relevant sections. I understand that a reference must be considered in its entirety, including any disclosures that diverge from or teach against the invention being evaluated.

22. I understand that it is improper to combine references when the references teach away from their combination. I understand that a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference or would be led in a direction divergent from the path taken by the applicant. It is also my understanding that the degree of teaching away will depend on the particular facts; in general, a reference will teach away if it suggests that the line of development

flowing from the reference's disclosure is unlikely to produce the result sought by the applicant. I understand that a reference teaches away, for example, if (1) the combination would produce a seemingly inoperative device, or (2) the references leave the impression that the product would not have the property sought by the applicant or would no longer achieve the intended purpose(s) of the references being modified or combined. If the reference teachings lead to any of these results, then the modification would generally not be obvious.

23. It is my further understanding that obviousness cannot be based on a hindsight combination of components selected from prior art references nor consider what was learned only from the teachings of the patent. In particular, I understand that it is improper to use the patent claims as a road map for selecting and combining items of prior art. In other words, one should avoid using the challenged patent as a guide through the prior art references, combining the right references in the right way so as to achieve the result of the claims at issue. Instead, one must put oneself in the place of a person of ordinary skill at the time the invention was made and consider only what was known before the invention was made.

24. I also understand that a patent is not rendered obvious merely because a person of ordinary skill in the art could have tried a particular approach. Rather, "obvious to try" generally requires that the prior art identify a finite number of predictable options and provide a reason and guidance to pursue the claimed approach with a reasonable expectation of success. Where the prior art presents numerous alternatives, substantial uncertainty, or an unpredictable field of endeavor, the fact that a skilled person could have experimented with a particular option does not, by itself, establish that the option would have been obvious. I understand the fields of chemistry, biotechnology, and pharmacology are considered unpredictable fields.

25. I understand that the secondary considerations include: commercial success of a product due to the merits of the claimed invention; a long-felt need for the solution provided by the claimed invention; unsuccessful attempts by others to find the solution provided by the claimed invention; copying of the claimed invention by others; unexpected and superior results from the claimed invention; acceptance by others of the claimed invention as shown by praise from others in the field or from the licensing of the claimed invention; teaching away from the conventional wisdom in the art at the time of the invention; and other evidence tending to show non-obviousness.

26. I understand that part of the secondary considerations analysis includes the question of “nexus,” which concerns whether the secondary factors (praise, commercial success, superior results, etc.) are attributable to the novel claimed features rather than unclaimed features. The secondary factor need not be linked to every claimed feature, so long as there is a connection to the novel claimed features.

V. PERSON OF SKILL IN THE ART

27. I have been asked to address the issues from the perspective of a person having ordinary skill in the art (“POSA”) in the field of the ’901 Patent at the time that its application was filed, which I have been informed was December 15, 2016. I have applied this timeframe as being the relevant time for the perspective of a POSA.

28. As stated in the ’901 Patent, the field of the invention generally relates to “a method for treating PSMA [Prostate Specific Membrane Antigen]-expressing cancers, wherein the method comprises administering to a patient in need thereof an effective amount of one or more ²²⁵Ac-radiopharmaceuticals.” (Ex. 1001, ’901 Patent, at Abstract.) Accordingly, as

explained below, I do not agree with Dr. Zalutsky's definition of the skills required for a person of skill in the art relevant to the '901 Patent.

29. Because this patent relates to a clinical invention, a clinician with experience in molecular imaging and/or theranostic agents would be better suited to understand and appreciate the invention and determine whether the efficacy described in the patent was obvious or unexpected. In particular, a person of ordinary skill in the art should have experience in the diagnosis and clinical management of prostate cancer, specifically with agents targeting Prostate Specific Membrane Antigen ("PSMA"). While the POSA needs to have experience in and knowledge about using radionuclides in treatments, abstract knowledge of the chemical behavior of radionuclides is not necessary. I also do not believe that a person of ordinary skill in the art would need to have experience in the chemistry of designing and synthesizing molecules, although they would need a basic understanding of how those molecules are used in radiopharmaceuticals. I do not believe that a purely chemistry background would be appropriate to appreciate the aspects of this clinical patent.

30. Dr. Zalutsky provides four elements that a person of ordinary skill in the art could have experience with, including:

- the concept of radiolabeling,
- the chemical behavior of radiometals (e.g., ^{111}In , ^{177}Lu , and ^{225}Ac),
- the design, synthesis, and use of chelators that form kinetically and thermodynamically stable complexes with the radiometals, **and/or**
- the evaluation or clinical use of radiotherapeutic agents.

31. When asked about this definition at deposition, Dr. Zalutsky confirmed that the patent does not include or claim the design, synthesis, or purity of the compound:

Q. The design, synthesis, and use of chelators that form kinetically and thermodynamically stable complexes with the radiometals. The patent doesn't claim synthesis of chelators, correct?

A. Right; in fact, it has nothing -- no information about synthesis, purity; none of that, totally lacking.

Q. Of the chelator?

A. Of the chelator or the compound, totally lacking.

Q. It doesn't claim the purity, right?

A. Nope.

Q. It doesn't claim synthesis?

A. No, it does not.

(Ex. 2139.029, Zalutsky Tr. 108:10-23)

32. Therefore, these requirements for a POSA would be unnecessary. Dr. Zalutsky further testified that a POSA would need only one of the four attributes to qualify as a POSA:

Q. Okay, at the end of part three, you have an and slash or. So does that mean that a person of ordinary skill could have just one of these four attributes?

A. Yes.

Q. And that would make them a person of ordinary skill in the art?

A. Yes.

Q. And then for part four, you have the evaluation or clinical use of radiotherapeutic agents. So if somebody is just skilled in the evaluation of radiotherapeutic agents, that would make them a person of ordinary skill in the art?

A. Yes.

(Ex. 2139.029, Zalutsky Tr. 109:15-22)

33. This would mean that a person would need only experience with the concept of radiolabeling to qualify as a POSA in the field of the '901 Patent invention. I disagree. I believe that Dr. Zalutsky's definition is overinclusive and does not represent the skill set to work in the field.

34. Because the patent concerns the use of specific doses of PSMA-targeting molecules for the treatment of cancer, it is my view that a POSA should have: (1) clinical experience with radiopharmaceuticals; (2) an understanding of radiopharmaceutical dosimetry in human subjects; (3) knowledge of the radiobiology of radiopharmaceuticals; (4) an understanding of the design and conduct of clinical dose-finding studies; and (5) clinical experience in the management of prostate cancer or other PSMA-expressing cancers. The prior art's teaching is interpreted from the perspective of a POSA. My analysis is thus based on the perspective of a POSA having this level of knowledge and skill at the relevant time of the invention.

VI. TECHNICAL BACKGROUND

A. Dosimetry

35. The term dosimetry describes the scientific process of measuring the absorbed dose to tissue from either an internal or external source of radiation. In medicine, this term is typically applied to external beam radiation therapy, diagnostic imaging such as computed tomography, or radiopharmaceutical therapy. Dosimetry in the setting of radiopharmaceutical therapies is used to determine the appropriate administered activity based on the expected safety and efficacy of a radiopharmaceutical therapy. A radiopharmaceutical includes a radionuclide, which is the atom that delivers the radiation, and a ligand, which holds the radionuclide for delivery. The ligand typically has an affinity for a target protein or structure so that it will bind to the target to deliver the radionuclide to that location. If the radionuclide is a radiometal, the ligand may also include a chelator to capture the radiometal and a linker between the chelator and the ligand. The chelator is charged such that it can bind to the radiometal at several points to form coordinate bonds and effectively hold the radiometal in a pocket. Each of these parts play a

role in the function of the radiopharmaceutical and they can affect each other through, for example, steric interactions or affecting the overall charge of the molecule.

36. In radiopharmaceutical therapies, a number of factors go into the determination of the appropriate administered activity, including the form of emitted energy from the radionuclide, the half-life of the radionuclide, and the biodistribution of the radiopharmaceutical in both tumor and normal tissue, including the distribution of the intact radiopharmaceutical, its radiometabolites, and, where applicable, its radioactive daughter products. Where a radionuclide is targeted to a specific tissue by some binding mechanism or molecule, there are additional factors, including receptor affinity and residence time / clearance, which are impacted by the stability and uptake of the radiopharmaceutical. These factors all combine to result in an “absorbed dose,” which is the amount of radiation energy deposited in a tissue divided by the mass of the tissue. This differs from the “administered activity,” which is the amount of radiation given to a patient. The absorbed dose is the most important factor in the efficacy and safety of a radiopharmaceutical therapy. Therefore, the *in vivo* affinity, clearance, stability, cellular internalization, and target-specific or non-specific uptake of the specific radiopharmaceutical must be determined, typically empirically, to calculate the absorbed dose.

37. Efficacy is the capacity of a drug to produce a desired effect, typically the reduction or treatment of an illness. This is balanced against the tolerability of the drug, which is how much of the drug may be safely administered before the unwanted effects (often referred to as side effects) become intolerable to the patient or even dangerous to the patient. In the case of radiopharmaceuticals, these unwanted effects are typically due to radiation absorbed by normal tissues rather than the interaction of the drug with its target receptor per se. The expert in the

previous IPR against the '901 Patent, Dr. Abergel, initially provided a similar definition at her deposition 1:

Q. And what does it mean by a tolerable dose?

A. I would define "tolerable dose" as a dose that does not result in such toxicity effects that it impacts the life of the patient negatively.

Q. And how would you measure the tolerability of a dose?

A. There are several ways. One is just quality of life, symptoms, but also maybe body weight loss, and then you could go down to specific markers.

Q. And so the tolerability dose of, say, a radiopharmaceutical is going to be different from the efficacious dose. Isn't that right?

A. That's right.

(Ex. 2080, Abergel Tr. 40:10-22)

38. Dr. Zalutsky also distinguished between the effective dose and the maximum tolerated dose ("MTD"):

Q. And so the maximum tolerable dose doesn't really provide any guidance on what the efficacious dose would be, correct? Correct?

A. Well, it sets boundaries.

Q. Well, the efficacious dose can be higher than the maximum tolerable dose, can't it?

A. Right

(Ex. 2139.023, Zalusky Tr. 86:6-12)

Q. I understand that. But that dose that would be effective could be beyond the point where you would be harming the patient, and so you can't really use it.

Mr. Murphy: Objection, form.

The Witness: The -- there are compounds where the first dose or the lowest dose which is effective is above the maximum tolerated dose.

Q. Right, and there are compounds where it's below the maximum tolerated dose, right?

A. Right.

Q. Because the two are really independent of each other.

A. Generally so, yes.

Q. And so the efficacious dose could be far below the maximum tolerable dose, right?

A. Right.

Q. And so if I were to say that my maximum tolerable dose is at a certain level, and I say that I do have some efficacious effect, that doesn't mean it's at the maximum tolerable dose, right?

A. Right.

(Ex. 2139.024, Zalusky Tr. 88:15-89:11)

39. Where the administered activity reaches its limit of tolerability is the “maximum tolerable dose.” The toxicity effect that limits the dose is referred to as “dose-limiting toxicity.” For example, in the radiopharmaceuticals reported in the '901 Patent, the dose-limiting toxicity is dry mouth (i.e., xerostomia). Where a particular organ is most sensitive to the radiopharmaceutical and represents the greatest risk, that organ is usually referred to as the “dose-limiting organ.” For example, in the radiopharmaceuticals reported in the '901 Patent, the dose-limiting organ is the salivary glands. For radiopharmaceutical therapies, the bone marrow is frequently the dose-limiting organ. Ex. 1017.012. Dr. Abergel, the previous petitioner's expert, agreed that for a non-ligand-bound radionuclide like ^{225}Ac , the liver, kidney, and bone were the most likely sites of accumulation:

Q. Okay. So let's say you had actinium that was free floating in the body. Where would it most likely pool?

A. Most likely in the liver and in the skeleton. And that would be -- it also depends on the organism. So I'm assuming you're asking about humans.

Q. Let's say yes.

A. So liver, kidney, and skeleton.

Ex. 2080.0008, Abergel Tr. 25:10-17.

40. The efficacy of a drug typically increases with the administered activity because the absorbed dose will usually increase with the amount of radioactivity administered to the patient. But this also brings the patient closer to the limits of tolerability. There is no guarantee

that a drug will reach any significant level of efficacy before reaching its maximum tolerated dose. That is, the upper limit of acceptable toxicity may be lower than the lowest dose needed to reach an effective dose. Determining the maximum tolerated dose is unrelated to determining the administered activity required for efficacy, and if the maximum tolerated dose is less than that required for efficacy, the radiopharmaceutical will not be clinically useful.

41. Dr. Zalutsky's own publications confirm the divide between the maximum tolerable dose and the effective amount. In one of Dr. Zalutsky's papers, he was testing a PSMA-targeting molecule with the alpha-emitter ^{211}At attached. 2158.001 (Kiess, et al. (2S)-2-(3-(1-Carboxy-5-(4- ^{211}At -Astatobenzamido)Pentyl) Ureido)-Pentanedioic Acid for PSMA-Targeted α -Particle, J Nucl Med 2016; 57:1569–1575). Although he determined that 37 kBq was the maximum tolerated dose for the compound, he could not show an effect from the compound until the dose reached 111 kBq. In this case, the effective dose was well above the MTD, showing that they can be separate factors.

Q. Okay, and so with the -- with the mice in that first paragraph, the one entitled anti-tumor efficacy in micrometastatic models, so those mice with tumors were untreated or they received 37, 111, 185, or 370 kilobecquerels of radiation, correct?

A. Correct.

Q. And you found that at 37, which is the maximum tolerated dose, there was really no effect on their survival?

A. Right.

Q. And it wasn't until you went up to 111 that these number of days increased to 72, correct?

A. Yep, yes.

Q. Okay, so in order to get an efficacious dosage, you had to go beyond the maximum tolerated dose, correct?

Mr. Murphy: Objection, objection, form.

The Witness: With this first generation compound, yes; in subsequent research, subsequent publications, we took what we learned from this paper,

modified chemical structures, and were able to come up with compounds that were more efficacious with less toxicity. They were PSMA compounds also labeled with astatine. This is first generation.

Q. And in this case, you had to exceed what you determined to be the maximum tolerated dose in order to get an effect?

A. With this first generation compound, yes.

Q. And so the level at which you can get an effective dose is a separate question from what the maximum tolerated dose is, correct?

Mr. Murphy: Objection, form.

The Witness: The level at which you can get an effective dose; yes, it can be different.

(Ex. 2139.008, .009, Zalusky Tr. 24:21-25:8; 25:15-26:1; 27:4-13)

42. This is a particular challenge for targeted radiopharmaceuticals because numerous factors may affect the efficacy and tolerability of a given drug. These include the affinity and specificity of the ligand for its intended target, uptake in both target and non-target tissues, and the balance between therapeutic efficacy and toxicity resulting from radiation delivered by the radionuclide and, where applicable, its radiometabolites and radioactive daughter products. As such, even when the same ligand is used for tissue targeting, changing the radionuclide can dramatically alter the therapeutic profile of the radiopharmaceutical, potentially transforming an effective cancer therapy into one that is ineffective, unacceptably toxic, or even lethal.

43. Ex. 2159, Vallabhajosula et al., “Prediction of Myelotoxicity Based on Bone Marrow Radiation-Absorbed Dose: Radioimmunotherapy Studies Using ⁹⁰Y- and ¹⁷⁷Lu-Labeled J591 Antibodies Specific for Prostate-Specific Membrane Antigen,” J. Nucl. Med., vol. 46, no. 5, pgs. 850-858 (2005); Ex. 2160, Cloutier, et al., MIRD Pamphlet No. 21, Dose Estimate Report No. 2, “Summary of Current Radiation Dose Estimates to Humans from ⁶⁶Ga-, ⁶⁷Ga-, ⁶⁸Ga-, and ⁷²Ga-citrate,” J. Nucl. Med., vol. 14, no. 10, pgs. 755-756 (1973).

44. Therefore, while there may be guidance on the number of traversal events or the amount of absorbed dose required to result in cell death (see Ex. 1017.004), the administered activity necessary to achieve those numbers and amounts for any given radiopharmaceutical cannot be reliably determined without experimentation. As explained in Dr. Zalutsky's reference, Ex. 1017, a publication of the Committee on Medical Internal Radiation Dose ("MIRD"), idealized in vitro experiments "give way to complex activity and tissue geometries." Ex. 1017.009 (Sgourous, et al., MIRD Pamphlet No. 22 (Abridged): Radiobiology and Dosimetry of α -Particle Emitters for Targeted Radionuclide Therapy, Sgourous, G. et al., J Nucl. Med. 2010; 51:311–328). Even with modeling, "[d]etermining the activity distribution [] remains difficult." Ex. 1017.010.

45. These considerations are particularly important when considering the subject matter of the '901 Patent because it involves the use of the alpha-emitting radionuclide ^{225}Ac . ^{225}Ac decays through a chain that includes multiple radioactive daughter radionuclides, which may redistribute independently from the original targeted radiopharmaceutical and thereby contribute to radiation exposure in both tumor and normal tissues. This situation presents additional challenges in predicting biodistribution, dosimetry, efficacy, and toxicity. In this respect, ^{225}Ac differs from radionuclides such as ^{177}Lu , which is used in the FDA-approved radiopharmaceutical ^{177}Lu -PSMA-617 for the treatment of prostate cancer and does not present the same complication from a decay chain of multiple radioactive daughter radionuclides. The behavior of a ^{225}Ac -labeled targeted radiopharmaceutical, and thus its safety and efficacy at a particular administered activity, therefore cannot simply be assumed from experience with the same or a similar targeting ligand labeled with a different radionuclide. These challenges associated with alpha-emitting radiopharmaceuticals were recognized by Sgourous, who explained

that, “in contrast to most targeted therapy trials to date, collection of biodistribution data for dosimetry from pretreatment imaging studies will not be possible for most α -particle–emitting radionuclides with therapeutic potential.” Ex. 1017.012–013.

B. Limitations of Preclinical Models for Radiopharmaceutical Therapies

46. Many radiopharmaceuticals begin with testing with cell lines to determine basic functions of the molecule such as target affinity, uptake, internalization, retention, cytotoxicity, etc. However, the predictive power of cell lines in human treatment is extremely limited because cell cultures are clones based on a single progenitor cell and are therefore homogenous. Cell culture experiments are also poor tools for measuring the efficacy of radiopharmaceuticals because the radiopharmaceuticals in the cell culture solution need not specifically bind to the cells to have some cell-killing effect. In fact, in a cell culture experiment, the radionuclide could be entirely released from the radiopharmaceutical but still be in solution close enough to the cells to have an effect and possibly be taken up by the cultured cells as part of the media, resulting in a false positive effect. For example, in 2001, McDevitt reported that a monoclonal antibody bound to ^{225}Ac was effective at killing leukemia, lymphoma, breast, ovarian, neuroblastoma, and prostate cancer cells in vitro. Ex. 1013. But in 2005, the same lab reported that once the ^{225}Ac decays, the “daughters, once formed, are unlikely to associate with the antibody-DOTA construct due to high atomic recoil-energy as a result of α -decay [], possible rupture of the chelate, and different chemical properties of the daughters.” Ex. 2161.001, Jaggi, SJ, et al. Efforts to Control the Errant Products of a Targeted In vivo Generator, *Cancer Res.* 2005; 65: (11). This lab also noted that the “free daughters produced in the vasculature from the circulating unbound antibody or the antibody bound to the surface of a target cell could diffuse or be transported to various target organs, where they can accumulate and cause radiotoxicity.” *Id.*

47. Cell culture experiments also cannot reflect a radiopharmaceutical's internalization or tumor binding that would be seen in the human body. In a cell culture, radiopharmaceuticals have immediate access to the target cells as soon as they are put into solution. But in the human body, a radiopharmaceutical must travel through the body to its intended site of action. In the human body, the radiopharmaceutical is confronted with a host of alternative binding sites and perhaps limited access to the desired site. It may also become the subject of metabolism or the microenvironment may change the conformation of the target or ligand, which would not occur in the optimized conditions of a petri dish. In a cell culture, where the radiopharmaceutical is in the cell media, obstacles don't exist because the radiopharmaceutical is already close to the cells, there are ample cells in the culture to bind to, there are few, if any, alternative binding sites, and the radioactivity permeates the media even if not targeted. In the human body, however, these tasks are infinitely more complicated, as the compounds may need to travel quite a distance to reach the target, there may be competing compounds attempting to bind to the same cells and receptors, and the radionuclide may escape or be released from the compound before it reaches the target site.

48. Cell cultures also cannot model the effect of the radiopharmaceuticals on healthy organs or their pooling in other organs that results in the dose-limiting organ toxicity. As noted by the Jaggi lab, ^{225}Ac 's daughter nuclide, ^{213}Bi , is known to accumulate in the renal cortex, resulting in nephrotoxicity. *Id.* Animals treated with ^{225}Ac suffer from anemia and renal failure. *Id.*

49. While mice are the most commonly used animal model, they are also limited in their ability to represent humans, particularly in the field of oncology. For example, cancer studies in mice often use a xenograft, which is a homogeneous culture of cancerous cells. Ex.

2111.001, Denison, TA, Tumor Heterogeneity and its Implication to Drug Delivery, J. Control. Release 2012, 164(2): 187-191. Human cancers, by contrast, are heterogeneous and dynamic diseases that undergo branched clonal evolution over time, including in response to selective pressures imposed by successive lines of therapy. Xenograft models therefore reproduce the complexity and heterogeneity of human cancer only to a limited extent. Moreover, conventional xenograft models generally require immunodeficient animals and thus cannot fully reproduce the interactions between a therapy, the tumor, and an intact immune system that occur in human patients. *Id.* at 187–188. These limitations reduce the ability of xenograft models to predict the magnitude and consistency of treatment responses in humans, particularly where different tumor cell populations may exhibit differing degrees of sensitivity or resistance to a therapy.

50. Whether a disease state is modeled using xenografts or through other approaches, such as genetic modification or exposure to mutagens, the animals used in these studies generally lack the degree of genetic diversity found in human populations. Moreover, mice also fail to provide the full scope of tolerability information. Some toxicities, like kidney toxicity, take months to develop in humans, meaning that a much higher rate of kidney toxicity is required to detect it in animals. Animals are also unable to provide information on subjective discomfort like dry mouth resulting from damage to the salivary glands. And when toxicity or biodistribution data was obtained from mice, in 2016 there was “no standardized way for extrapolating time-integrated activity coefficients from animal data to humans.” Ex. 1028.007.

51. Separate from toxicity, tumor uptake of drugs is often artificial in mice. In fact, it is not uncommon for research to implement xenograft models that significantly overexpress the target (SSTR, PSMA, etc.) in order to make sure that the radiopharmaceutical is taken up in the

model. This will of course overestimate the efficacy of a treatment relative to what may be seen in clinical applications.

52. Taken together, these limitations of animal models in cancer research make it exceptionally difficult to determine the optimal administered amount of a drug –whether a radiopharmaceutical or other class of drug – without subsequent empiric work performed in humans. For many drugs, this initial translation step from animals to humans is the point of failure for the tested compound, as no such safe therapeutic dose of the drug can be achieved. Perhaps Dr. Richard Klausner, then director of the National Cancer Institute, said it best: “The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades--and it simply didn’t work in humans.” Cimons et al., “Cancer Drugs Face Long Road From Mice to Men,” Los Angeles Times, <https://www.latimes.com/archives/la-xpm-1998-may-06-mn-46795-story.html> (1998).

53. As a result of the inherent differences between mice and humans, much of the data and results cannot be carried over from one to the other. And the data cannot be used to support any generic conclusions regarding data extrapolation from mouse to human. For example, in Dr. Zalutsky’s reference Ex. 1015 (“Miederer 2008a”), Miederer 2008a reports the limit of tolerability for ^{225}Ac -DOTATOC to be 20 kBq/mouse and compares this with 1000 kBq/mouse for ^{177}Lu -DOTATOC as a reference for a ^{177}Lu to ^{225}Ac conversion factor of $(1000/20)\sim 50$. Ex. 1015.001. However, Miederer 2008a also compares 12 kBq/mouse of ^{225}Ac -DOTATOC to 450 kBq/mouse of ^{177}Lu -DOTATOC as a reference for a ^{177}Lu to ^{225}Ac conversion factor of 37.5. *Id.*006. Contrast this with Kratochwil’s finding that treatments of 18.5, 25, and 40 MBq of ^{225}Ac -DOTATOC were tolerable in humans. Specifically, compared to what is understood to be a fairly low and safe dose of 7,400 MBq of ^{177}Lu -DOTATOC in humans, this

equates to three different ratios in humans for this DOTATOC construct of 400 (7400/18.5), 296 (7400/25), and 185 (7400/40). Ex. 2162, Forrer, F, et al., Treatment with ^{177}Lu -DOTATOC of Patients with Relapse of Neuroendocrine Tumors After treatment with ^{90}Y -DOTATOC, *J Nucl Med.* 2005; 46:1310–1316. Add to this that while 7,400 MBq has become the treatment standard for ^{177}Lu -DOTATOC in humans, the tolerable level of this construct could be higher, creating a disparity between mouse and human treatment and tolerance ratios even wider than the order of magnitude noted in aspects of this example exercise. This confusion and unreliability in the conversion of data from mice to humans prevents these kinds of studies from concluding that pharmaceuticals are safe and/or effective in humans

54. Additionally, as can be seen in the above exercise, converting the administered activity from mouse to human is rather complicated. Indeed, as the data in Miederer 2008a, Kratochwil, and Weineisen 2015 show, no consistent conversion factor or other calculation can be used to convert a mouse dose to a human dose. This is true even when the compared radiopharmaceuticals include the same ligand – as demonstrated in the above exercise. Add to this a wholly different ligand – e.g., a PSMA-targeting ligand – and the conversion and extrapolation become infinitely more complicated. The '901 Patent illustrates this point. Specifically, the '901 Patent describes the complete failure of the above-referenced administered activity of 7,400 MBq (7.4 GBq) of ^{177}Lu -PSMA-617 to treat “Patient B.” (Ex. 1001.018.) This demonstrates not only that mouse to human extrapolation is far too complicated to provide any accurate information, but also that mouse data for one construct is not instructive for human treatments using a different construct.

55. Again, these sorts of differences and confounding issues result in treatments that often seem promising in mice but are clinical failures in humans. Ex. 2121, Morton, JJ, et al.

Humanized mouse xenograft models: narrowing the tumor-microenvironment gap, *Cancer Res.* 2016; 76(21): 6153–6158.

C. Predictability of Radiopharmaceutical Efficacy Based on Structure

56. While form determines a molecule's function, it is notoriously difficult to predict the function of a molecule from its atomic structure. One's ability to do so has had major limitations historically, and some of the biggest breakthroughs in chemical structural prediction have come in only the last few years due to advances in artificial intelligence. But even with these advances, the problem of predicting the biological behavior of a molecule from its structure is a different, and much more complex, problem than that of predicting structure alone. For example, in Dr. Zalutsky's Weineisen 2014 (Ex. 1027) reference, Weineisen found that its ^{68}Ga -11 compound – having an L-amino acid spacer between the chelator and PSMA ligand – was rapidly metabolized. Ex. 1027.012. To correct for this, Weineisen replaced portions of the L-amino acid spacer with its D-amino acid counterpart, which resulted in “high metabolic stability in vivo.” *Id.* However, Weineisen also found that this change in the linker resulted in an increase in the uptake of the radionuclide-bound molecules over the molecules with the original L-amino acid spacer. Ex. 1027.010-011. Weineisen later found in Weineisen 2015 (Ex. 1028) that simple modifications to a benzene ring on the linker – far from the PSMA targeting moiety – increased the binding affinity of a PSMA I&T construct as compared to the D-amino acid linker DOTAGA construct (i.e., the one reported in Weineisen 2014 (Ex. 1027)). (Ex. 1028.004.) Weineisen attributed this to an increase in the lipophilic interaction of the molecule with PSMA (Ex. 1028.002). Ex. 1028.004.

57. Similarly, the addition or choice of a radionuclide can have unpredictable results on PSMA binding even though the radionuclide (in its chelator) is on the other side of the

radiopharmaceutical. In Weineisen 2014, Weineisen found that the addition of ^{68}Ga to the DOTA-FFK (Sub-KuE) ligand dramatically decreased binding affinity to PSMA by more than half, and the addition of ^{177}Lu decreased it by nearly four times. *Id.* This effect was not seen with other radiopharmaceuticals tested in Weineisen 2014. *Id.* Weineisen provides no explanation for this phenomenon.

D. Predictability of Off-target Binding based on Chemical Composition

58. Off-target accumulation of radioactivity in healthy organs is a major concern in the development of radiopharmaceuticals for cancer treatment, and experimental evaluation of this problem is an essential aspect for any novel radiopharmaceutical. Special attention is typically paid to the kidneys, spleen, and bone marrow, since these organs may accumulate considerable quantities of radioactive material and may therefore receive radiation doses, which could be limiting. Therefore, the potential translation of a radiopharmaceutical to human use can be greatly impacted by its biodistribution. Importantly, the biodistribution of a given radiopharmaceutical cannot be reliably predicted from prior studies of the free radionuclide, the same radionuclide attached to a different ligand, or the same ligand labeled with a different radionuclide.

59. For example, in Weineisen 2014 (Ex. 1027), the biodistribution of ^{68}Ga -PSMA-targeting compounds in mice was investigated, and significantly higher uptake was observed in the kidney and spleen than in the tumor. Ex. 1027.012. In the subsequent Weineisen 2015 study, the lab evaluated both ^{68}Ga -PSMA I&T and ^{177}Lu -PSMA I&T in mice and observed that kidney uptake was >10-fold higher than tumor uptake with ^{68}Ga -PSMA I&T and >13-fold higher than tumor uptake with ^{177}Lu -PSMA I&T, whereas splenic uptake was approximately equal to tumor uptake. Ex. 1028.004. Extrapolating these data to humans, Weineisen estimated the highest

absorbed radiation doses to be to the kidneys, adrenals, uterus, spleen, and pancreas. Ex. 1028.005. These results highlight the necessity of experimental assessment of the actual radiolabeled molecule itself to establish the safety and translational potential of a new radiopharmaceutical, as neither the magnitude nor the organ-specific pattern of its biodistribution can be predicted with confidence from studies of the radionuclide or ligand in a different context. This problem is further compounded by the aforementioned challenges of translating results from contrived animal studies to humans.

E. Stability of Chelated Alpha Emitters

60. POSAs at the time of the invention in 2016 were aware of the high likelihood of alpha-emitting isotope separation from their carrier molecules (e.g., the chelator), allowing free daughters to circulate throughout the body. This is due to the fact that alpha emitters expel an alpha particle, consisting of two protons and two neutrons, causing the daughter nuclide to recoil with approximately 100 keV of kinetic energy—roughly 1,000 times greater than the energy required to break a typical chemical bond. This results in an average travel of 100 μm of the daughter nuclide away from the carrier molecule. Ex. 1043.003, de Kruijff, RM, et al., A Critical Review of Alpha Radionuclide Therapy—How to Deal with Recoiling Daughters?, *Pharmaceuticals* 2015; 8, 321-336. Therefore, any carrier molecule to which the alpha-emitter is bound will lose the daughter radionuclide once the alpha particle is released. *Id.* The chance that the daughter radionuclide will recombine with the carrier is small, resulting in the usually radioactive daughter nuclides circulating in the patient's body. This was in contrast to beta emitters like ^{177}Lu , which emit beta particles with the mass of electrons and can be stably held by chelators linking them to targeting molecules.

61. Expulsion of an α -emitting daughter radionuclide from a carrier intended to target it to a tumor means that only the α -particle emission preceding the recoil-induced ejection can be assured of occurring at the intended target, assuming that it arrives at the target before decay occurs. Subsequent decay events may occur away from the target, potentially exposing healthy tissues to radiation. For α emitters whose remaining decay chains are short, such as ^{213}Bi when administered as the therapeutic radionuclide, release of the daughter radionuclide from its carrier following decay was expected to be less consequential because the dominant ^{213}Bi decay pathway proceeds by β^- emission to ^{213}Po , which rapidly undergoes α decay to ^{209}Pb , followed by only one additional β^- decay to stable ^{209}Bi . In contrast, following ^{225}Ac 's initial α decay (i.e., the potential ejection event), its principal decay pathway produces three additional α particles and two β^- particles before ultimately reaching stable ^{209}Bi . *See* Schwartz, J, et al., Renal uptake of bismuth-213 and its contribution to kidney radiation dose following administration of actinium-225-labeled antibody, *Phys Med Biol.* 2011; 56(3): 721–733. Because the free ^{213}Bi daughter produced in the ^{225}Ac decay chain was known to accumulate in the bone, liver, and kidneys, there was serious concern regarding the potential toxicity associated with the use of ^{225}Ac as a therapeutic radionuclide. *Id.*; Ex. 2163, Dorso, L, et al., Long-Term Toxicity of ^{213}Bi -Labelled BSA in Mice, *PLoS ONE* 2016; 11, e0151330. In light of this, because only the α -particle emission preceding ejection can be assured of reaching the target, radionuclides that emit less radiation after that initial emission may have been a preferred strategy.

62. The problem of alpha-emitters escaping their targeting carriers was widely recognized, as the previous petitioner's expert, Dr. Abergel, acknowledged:

Q. Okay. And so wasn't this an enormous issue for the use of actinium-225 that it would be released once it fired its first alpha particle?

MS. CIPRIANO: Objection; assumes facts not in evidence.

A. It is an issue that has been discussed in many settings. Yes.

Q. So if it's been discussed in many settings, doesn't that mean that a lot of people were worried about it?

A. Yes.

Ex. 2080.0019, Abergel Tr. 71:1-11.

63. In 2004, Miederer (the same author of Zalutsky's Ex. 1015) noted when introducing his ^{225}Ac -antibody conjugate that "the 3 α -emitting daughter elements generated have the potential for significant toxicity as these nuclides are no longer bound to the carrier IgG." Ex. 2072.001, Miederer, M, et al., Pharmacokinetics, Dosimetry, and Toxicity of the Targetable Atomic Generator, ^{225}Ac -HuM195, in Nonhuman Primates, J. Nucl. Med. 2004; 45:129–137. Miederer understood that the "release of the daughters from ^{225}Ac " was a "key drawback" because "such daughters may not be retained in tumor tissue." *Id.*002. These loose daughter nuclides would increase the chances of side effects and prevent the accurate estimation of appropriate administered activities. *Id.*

64. Several years later in 2008, Miederer 2008a recognized that this was still a problem. Ex. 1015.002. While lauding the potential of ^{225}Ac and chelators, he noted that "after disintegration, the retention of daughter isotopes within the chelate is highly unlikely, either due to the physical recoil energy or the different chemical properties of the first daughter nuclide." *Id.* Miederer 2008a acknowledged – years later – that the α -emitting daughter nuclides are still "capable of relocating within the organism and accumulation of ^{213}Bi originating from the bloodstream into the kidneys with subsequent radiation damage has been shown in nonhuman primates." *Id.*002. When asked about this passage, Dr. Abergel, the previous petitioner's expert, could not disagree with the danger Miederer 2008a described:

Q. It says "However, after disintegration, the retention of daughter isotopes within the chelate is highly unlikely, either due to the physical recoil energy or the different chemical properties of the first daughter nuclide 221 Fr." Do you see that?

A. Yes.

Q. Now, this document is one of the ones you relied on for your declaration, correct?

A. Yes.

Q. So he's showing concern about the release of the daughter elements after actinium releases its initial alpha particle, correct?

A. That's right.

Q. So he goes on to say "Despite their relatively short half-lives, the alpha-emitting daughter nuclides, 221 Fr, and its subsequent daughters 217 As and 213 Bi, are capable of relocating within the organism and accumulation of 213 Bi originate from the bloodstream into the kidneys with subsequent radiation damage has been shown in non-human primates." Do you see that?

A. I see that.

Q. Do you disagree with that?

MS. CIPRIANO: Objection; calls for speculation.

A. I don't disagree with this statement per se.

Ex. 2080.0019, Abergel Tr. 71:24-72:7; 72:19-73:10.

65. That same year, in his review paper on actinium, Miederer discussed one example of ²²⁵Ac being released from the chelator HEHA that resulted in ²²⁵Ac migrating to the bone and liver followed by "acute radiotoxicity" from ²²⁵Ac and its daughter nuclides. Ex. 1030.003.

66. Like the rest of the community, Dr. Zalutsky was concerned about the emission of the daughter nuclides from ²²⁵Ac. In 2011, he noted that the problem with ²²⁵Ac's "particle emitting radioactive daughters" is "severe" because of the daughters' longer half-lives, allowing them to wander further than other alpha emitters' daughters. Ex. 2148.002 (Zalutsky, MR, Pruszyński, M Astatine-211: Production and Availability, Curr Radiopharm. 2011 July; 4(3): 177–185.). Even after the success of the ²²⁵Ac-PSMA-617, Dr. Zalutsky was still showing concern in 2021: "The fact that ²²⁵Ac emits four α-particles per decay likely contributes to its excellent therapeutic effectiveness but also to its normal toxicity because the in vivo fate of its

radioactive daughters is difficult to control.” Ex. 2153.003-4 (Vaidynathan, G, et al., Synthesis and Preliminary Evaluation of ^{211}At -labeled Inhibitors of Prostate-Specific Membrane Antigen for Targeted Alpha Particle Therapy of Prostate Cancer, Nucl Med Biol. 2021; 94-95: 67–80).

And in 2022:

A possible issue with α -emitters, such as ^{225}Ac , is that multiple α -emitting daughters are generated from their parents, and in each case the energy imparted by the nuclear recoil effect is orders of magnitude greater than chemical bonds. That energy makes the release of the radioactive daughters from the targeting vector extremely likely, which can then lead to unintended irradiation of nontarget tissues.

Ex. 2147.001 (Mease, CR, et al. An Improved ^{211}At -Labeled Agent for PSMA-Targeted α -Therapy, J Nucl Med 2022; 63:259–267).

67. One reaction to the difficulty of controlling alpha emitters like ^{225}Ac was to find alternatives. Dr. Zalutsky did so by turning away from radiometals and using radiohalogens instead. In 2016, just before the publication of the Kratochwil 2016 paper containing the data from the '901 Patent, Dr. Zalutsky published a paper commenting that ^{211}At was preferable because it had a short half-life that did not outlive the small molecule carriers and because of its “absence of α -particle–emitting daughters, which can lead to excessive radiation doses to normal tissues when released from the parent molecule.” Ex. 2140.004 (Rowe, S, Prostate-Specific Membrane Antigen–Targeted Radiohalogenated PET and Therapeutic Agents for Prostate Cancer, J Nucl Med 2016; 57:90S–96S). I have been told that one sign of non-obviousness is teaching away from the invention, and Dr. Zalutsky’s constant promoting of radiohalogen ^{211}At

and emphasizing its features distinguishing it from ^{225}Ac would teach away from the use of ^{225}Ac .

68. Dr. Abergel, the previous expert, also tried alternative ways to capitalize on α -emitters while avoiding ^{225}Ac 's "potentially harmful daughter nuclides — ^{221}Fr , ^{217}At , ^{213}Bi , and ^{213}Po ." Ex. 2114, DeBlonde, GJ, Abergel, RJ, Nat Chem., 2016 Oct 21;8(11):1084. The solution she suggested in 2016 to retain ^{225}Ac and its daughters was the use of structures called "nanosafes" made from encapsulating nanocarriers or scavenging carriers, very different from chelators and radioligands. *Id.* Like Dr. Zalutsky, even six years later in 2022, Dr. Abergel still considered daughter nuclides to be a problematic hurdle in the use of ^{225}Ac : "Although pre-clinical and clinical studies have highlighted the therapeutic benefits of these conjugates, there are still challenges that need to be solved, such as kinetics and stability of the complexes [...], and retention of the daughters." Ex. 2115, Pallares RM and Abergel RJ, Development of radiopharmaceuticals for targeted alpha therapy: Where do we stand? Front. Med. 2022; 9:1020188.

69. Although Dr. Zalutsky promoted avoiding ^{225}Ac and chelators, he now says that Price (Ex. 1041) would have given a POSA a reasonable expectation of success in using DOTA or DOTA-derivative chelators with ^{225}Ac . I disagree, because, while Price does say that DOTA is the "gold standard" of chelators to be used with ^{225}Ac , it does not solve the recoil problem, which was the main concern.

70. Additionally, Price's label of "gold standard" does not go as far as Dr. Zalutsky suggests. It is telling that on Price's table of radiometals that DOTA binds (Table 2), Price does not provide a Log K_{ML} for ^{225}Ac . 1041.008. Price also has a question mark beside the "Proposed

Geometry” of ^{225}Ac ’s binding with DOTA and comments that the study of its coordination chemistry with ^{225}Ac is difficult. *Id.* Price gives DOTA the gold standard mark for use with ^{225}Ac not because it is “good” with DOTA. In fact, Price appears to lack sufficient information (e.g., LogK_{ML} and coordination data) to say how well the chelator binds. It is given the “gold standard” label only because it is currently being used with ^{225}Ac and is better than the previously used HEHA and PEPA. 1041.021. Since none of the chelators could resist the recoil effect, using DOTA would just be making the most out of a bad selection.

71. Dr. Zalutsky overstates the promise of Price. Price never says that DOTA “works well” with ^{225}Ac (Zalutsky Decl. ¶83) and makes no comment about DOTAGA. Only DOTA receives the gold standard label for ^{225}Ac . Because Price bases his labeling on which chelators are currently being used with the radiometals, he could not apply it to DOTAGA because no one had used DOTAGA with ^{225}Ac by 2014. A POSA would not just assume that DOTAGA was equivalent to DOTA – if that was the case, then there would be no reason to make DOTAGA. Because PSMA-I&T uses DOTAGA in its structure, Price’s gold standard tag for DOTA means nothing here. Price would not provide a motivation to combine ^{225}Ac with DOTA or DOTAGA, and Dr. Zalutsky gives no explanation as to why it would motivate a combination with PSMA I&T as opposed to any other compound that had DOTA or DOTAGA in it.

72. Additionally, Price does not capture all the reasons that a particular chelator may be chosen. Even if DOTA were the gold standard for chelation of ^{225}Ac , its role is more complex. For example, Dr. Zalutsky’s own work shows that a chelator moiety may be added for its effect on the overall ligand, which is further modified by the presence of a radiometal. Dr. Zalutsky modified an experimental ligand’s chelator from DOTA to DOTAGA on his own investigative molecules not to bind ^{211}At , which was covalently bound, but instead for its functional effect on

the molecule. (Ex. 2139.012-12, .009, Zalusky Tr. 41:24-42:11 42:13-18) More specifically, this chemical modification increased PSMA affinity by 50% and quadrupled cellular uptake. (Ex. 2108.012-13.) A year later, he was still uncertain as to whether the improvement was due to steric hindrance or a change in molecular charge (Ex. 2135.010), demonstrating that choosing a chelator is not just about metal binding and that the results are unpredictable.

73. Dr. Zalutsky also claims that the ^{223}Ra product, Xofigo, would have caused a POSA to appreciate that the therapeutic benefit would outweigh any negatives. (Zalutsky Decl. ¶30) I disagree. There is little comparison between ^{223}Ra and ^{225}Ac . As Dr. Zalutsky acknowledged, ^{223}Ra is a natural calcium analog with short-lived daughters.

Q. But as we discussed earlier, the radium is a calcium analog, right?
A. Right.

Q. Okay, so the radium that goes into the bone, though, like, for example, with the Xofigo that you mention here, when it releases its daughters, do you know what the half-lives of those daughters are?
A. Yeah, they're short.

Q. But to get the radium into the bone, which is the target, there's no additional molecule that's attached to the radium, correct?
A. That's correct.
Q. But with the actinium, you'd have to have it on a chelator of some kind to target it to, in this case, PSMA, correct?
A. Correct.

(Ex. 2139.032, Zalusky Tr. 120:7-9; 120:19-23; 121:11-21)

74. So, unlike ^{225}Ac , ^{223}Ra inherently “mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases,”

rapidly integrating into metastasized bone without targeting molecules. (Ex. 1046.009.) Since it is not reliant on any targeting ligand, there is no danger of it being misdirected. Ten minutes after injection, 88% of ^{223}Ra is cleared from the blood and 94% within an hour. (Ex. 2112.005). Because the half-lives of ^{223}Ra 's first two daughters are 4 seconds and 1.8 milliseconds, respectively, they release their alpha particles close to where the ^{223}Ra releases its alpha particle. (Ex. 2136.022) But ^{225}Ac 's first daughter has a half-life of 4.8 minutes, more than enough time to travel to another part of the body and do damage. Radium-223 would not have offered any reassurance to or guidance to POSAs concerning any other alpha-emitter.

VII. THE KRATOCHWIL PATENT

75. The '901 Patent describes the surprising discovery that treating patients having PSMA-expressing cancers with a low dose of alpha-emitting ^{225}Ac radionuclide compounds having a specific targeting moiety and a chelating moiety administered in the specific claimed effective amount yields unexpectedly impressive and unprecedented efficacy with surprisingly low hematotoxicity.

76. These results were obtained despite the generally acknowledged danger and obstacle of Ac 's daughter nuclides escaping the compound, migrating to healthy organs, and causing irreparable organ damage.

77. Patent Claim 1 of the '901 Patent recites a method for treating PSMA-expressing cancers comprising administering a specifically recited "effective amount" of a PSMA-specific ^{225}Ac radiopharmaceutical. The claim includes what I have been told is a Markush group defining a specific list of covered ligands that chelate the ^{225}Ac radionuclide, which include

ligands satisfying Formulae A through E. Remaining challenged claims 2 and 4-13 depend directly or indirectly on claim 1 so that each claim also recites the elements of Claim 1.

78. Claim 1 recites “[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),” and then depicts Formulae A-E.

79. As will be readily appreciated, the claims plainly recite a narrow and specific class of ligands in combination with a specific radionuclide applied at specific low dosages to target a specific and narrow class of cancer. The dependent claims go further, reciting specific cancers, molecular structures, even narrower effective dosages, and dosing schedules.

A. The '901 Patent is Embodied by the 2016 Kratochwil Paper

80. The invention described in the '901 Patent is reflected in a journal article published by Kratochwil's lab just before the Patent filing, Ex. 1045, “225Ac-PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer, published July 7, 2016, in the Journal of Nuclear Medicine (the “Kratochwil paper”). In this publication, Kratochwil first publishes the '901 Patent's Figures 12 and 14, demonstrating the efficacy of the claimed treatment. Ex. 1001, Figs. 4-6, 12, 14; Ex. 1045, Figs. 1 and 3. Figures 1 and 3 of the publication, which are the same as Figures 12 and 14, respectively, in the '901 Patent, show PET/CT scans of patients before and after treatment with the claimed ²²⁵Ac-PSMA-617 compound. The first patient (Fig. 12 of the '901 Patent/Fig. 1 of the publication) has extensive metastasis of his prostate tumor throughout the body as detected using radioactive

⁶⁸Ga-PSMA tracer (Fig. A). Ex. Ex1001.007; 1045.002. The figure also includes the measurement of prostate-specific antigen (“PSA”), which is a protein produced by malignant cells of the prostate gland. PSA levels have been used since the late 1980s and are the standard clinical indicator of prostate cancer risk, treatment efficacy, and recurrence after therapy. Ex. 2135.002, Nordstrom, M. *et al*, Identification of plasma protein profiles associated with risk groups of prostate cancer patients, *Proteomics Clin. Appl.* 2014 December; 8(0): 951-962; Ex. 2136.001, .006-7, Afshar-Oromieh, A., *et al*, The Rise of PSMA Ligands for Diagnosis and Therapy of Prostate Cancer, *J. Nucl. Med.* 2016; 57:79S-89S, DOI: 10.2967/jnumed.115.170720. The higher the amount of PSA in the blood, the more extensive the tumor spread. PSA levels in the several-hundred ng/mL range signal advanced, likely metastatic disease and shortened survival. Ex. 2137.003, Berney, DM *et al*, Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome, *British Journal of Cancer* (2016) 114, 1078-1083, doi: 10.1038/bjc.2016.86; Ex. 2135.003. After three treatments of the ²²⁵Ac-PSMA-617 compound at 9-10 MBq (100 kBq/kg) over a three-month period, the tumor is visually undetectable by PET/CT scanning, and the indicator molecule for the presence of the prostate tumor, PSA, has plummeted from 2,923 ng/mL to less than 1 ng/mL (Fig. B). An additional cycle of treatment reduced the PSA to below the detectable range (Fig. C). *Id.* ’901 Patent Figure 12 (Kratochwil Paper Fig. 1)

81. The second patient was also given ²²⁵Ac-PSMA-617 at a dosage of 6.4 MBq (100 kBq/kg) three times over a three-month period. Ex. 1001.008; Ex. 1045.002-3. After 2 months the tumor was largely gone from the PET/CT scans, and the patient’s PSA had dropped from 419 ng/mL to 3.5 ng/mL (Fig. C). *Id.* After another treatment, the PSA fell below the detectable range and the tumors were entirely gone from the PET/CT scan (Fig. D). *Id.* Notably, the second

patient had begun treatment by receiving the same PSMA-617 ligand but chelating a different radionuclide – ^{177}Lu – but the tumor was entirely resistant to the ^{177}Lu -PSMA-617 treatment (compare Fig. 3A baseline to Fig. 3B). *Id.* The ^{177}Lu -PSMA-617 compound not only failed to reduce the amount of tumor, but the tumor in fact clearly spread, and the PSA count increased from 294 ng/mL to 419 ng/mL. *Id.* '901 Patent Figure 14 (Kratochwil Paper Fig. 3)

82. Figures 13 and 15 of the Patent correspond to Figures 2 and 4 of the Kratochwil paper, respectively. Ex. 1001.008-9; Ex. 1045.002-3.

83. I disagree with Dr. Zalutsky's comment during his deposition that the figures in the '901 Patent do not show that the tumors were targeted. Dr. Zalutsky complained during the deposition that he did not understand how the imaging was done because actinium cannot be imaged and contended that it could not be determined that the ^{225}Ac -PSMA-617 had targeted the tumor:

Q. And so they confirmed on their own that the tumors had been properly targeted, correct?

Mr. Murphy: Objection, form.

The Witness: Post-therapeutic emission scans. Scans of what? With what? You can't scan actinium-225, so it's not clear what they're talking about here. See, they're talking about the targeting -- I see. They're talking about the targeting of the imaging agent, not about the actinium-225, because you can't image actinium-225.

By Mr. Boetticher:

Q. All right, say that again?

A. The post-therapeutic emission scans were not done with the actinium-225. They were done with something else.

Q. Right, but they --

A. They --

Q. -- they were done to confirm that the actinium had properly targeted the tumor.

A. And how would they -- I don't understand how that happens, because they're using something else to target the tumor that they're imaging. The actinium-225 is not being imaged.

Q. So once they are able to confirm that the tumor has been properly targeted, they're able to say that in a particularly preferred aspect, the invention relates to a treatment of disseminated cancer or cancer cells, and that it was a very efficient and specific targeting of the AC-225 radiopharmaceuticals to PSMA combined to the short-range, less than 100 micrometers, action of the AC-225.

Mr. Murphy: Objection, form.

The Witness: They confirmed that the tumor shrank. They confirmed -- they confirmed that they injected actinium-225, PSMA-617, but they did not confirm that the actinium-225 actually targeted the tumor. No evidence for that except indirect -- indirect evidence the tumor PSA brought.

By Mr. Boetticher:

Q. Is an indirect evidence evidence?

A. It is indirect evidence.

Q. But it's evidence, nonetheless.

A. It is one of the classes of evidence, certainly.

(Ex. 2139.044, Zalusky Tr. 167:18-168:2; 168:12-169:7)

84. A POSA would understand that the disappearance of the PSMA+ tumors in multiple patients after treatment with the ^{225}Ac -PSMA-617 is evidence that the compound is responsible for the destruction of the tumors. The tumors were imaged with ^{68}Ga -PSMA-11, as explained in the '901 Patent. Ex. 1001.016. For a POSA, who understands that in biology, not all effects are going to be directly visible, the rigorous reproduction of the compound's effect in multiple patients is sufficient evidence that the destruction of the tumor is due to the compound binding PSMA and killing the cancer cells.

85. Because the bones are one area to which unbound ^{225}Ac and its daughters may relocate, one side effect of its use in a radiopharmaceutical could be damage to the red and white blood cells produced there (referred to as "bone marrow toxicity" or "hematotoxicity"). Dr. Abergel, the expert that previously challenged the '901 Patent, also acknowledges that these are possible side effects:

Q. So earlier we talked about the effects that actinium might have if it was in the skeleton. Do you remember that?

A. Right.

Q. Would one of the effects be damaging the red blood cells that are made in the red marrow?

A. It could be an effect.

Q. And could it also damage the white blood cells that are made in the bone marrow?

A. It could be an effect.

Q. And it could reduce the amount of hemoglobin because it's destroying the platelets that are in the red marrow, correct?

A. Possibly.

Ex. 2080.0014, Abergel Tr. 49:11-24.

86. Along with a steady decline in tumor markers to undetectable levels, Kratochwil 2016's figures show no significant decrease in the patients' peripheral blood cell counts, indicating that little to no hematotoxicity occurred with the therapy. Ex. 1001.008-9; Ex. 1045.002-3. '901 Patent Figure 13 (Ex. 1045.002, Fig. 2)

87. The data in Figure 13A for the first patient indicates the dates of treatment with arrows, which show a decrease in blood counts and white blood cells directly after treatment, but a quick recovery over two months. *Id.* The patient platelet count never drops below 100/nL, which is considered a grade 1 adverse event. Adverse events are graded from 0 to 5 with grade 0 being the absence of an adverse event and grade 5 being death related to an adverse event from the treatment. Ex. 2164, Common Terminology Criteria for Adverse Events (CTCAE), V. 5.0, November 27, 2017, U.S. Dept. Health & Human Services. A grade 1 adverse event is considered only a mild, asymptomatic observation. Meanwhile, tumor markers like PSA dropped steadily to nothing over several weeks. Ex. 1001.007-9; Ex. 1045.002-3.

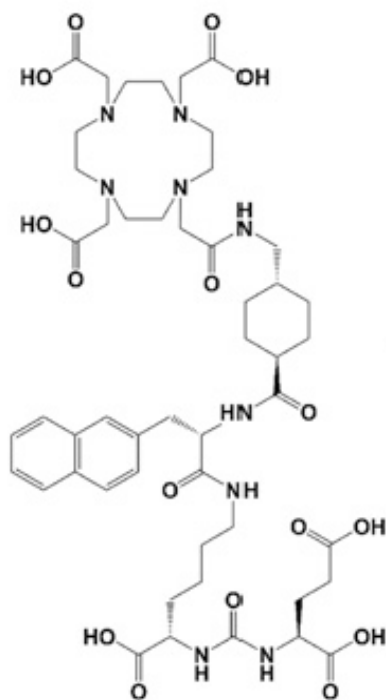
88. The data in Figure 4 of the publication and Figure 15 of the '901 Patent shows essentially the same results for the second patient with little or no decrease in red or white blood cell counts after treatment, no decrease in hemoglobin throughout treatment, and a steady decrease of tumor markers to baseline. '901 Patent Figure 15 (Kratochwil Paper Fig. 4)

B. The Kratochwil Paper Embodies the '901 Patent Claims

89. I have been informed that a product or method embodies a patent when it has all of the elements described in the claims of the patent. It is my opinion that the treatment method in the Kratochwil paper embodies the claims of the '901 patent. Specifically, it embodies challenged Claims 1, 2, 4-6, and 8-13.

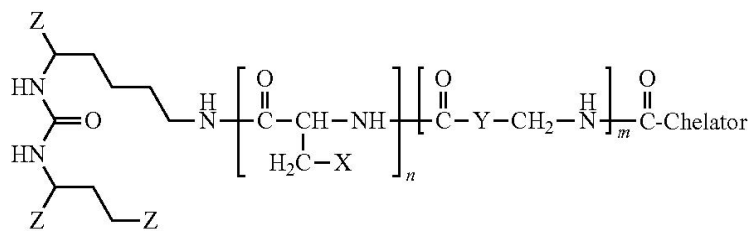
90. Claim 1 describes a “method for treating PSMA expressing cancers” which relates to the Kratochwil paper which describes “PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer.” Ex. 1045. Prostate cancer is well-known to express its namesake Prostate Specific Membrane Antigen (PSMA). The Kratochwil paper demonstrates this by using a PET radiopharmaceutical, ^{68}Ga -PSMA-11, to detect the cancer in its PET/CT scans. Ex. 1045.002-3. The Kratochwil paper administers the ^{225}Ac -PSMA-617 radiopharmaceutical to patients in need of cancer treatment as required by Claim 1.

91. The Kratochwil paper uses PSMA-617 which was first described by the Kratochwil lab in Benesova, M, et al., Preclinical Evaluation of a Tailor-Made DOTA-Conjugated PSMA Inhibitor with Optimized Linker Moiety for Imaging and Endoradiotherapy of Prostate Cancer, J Nucl Med 2015; 56:914–920. Ex.2078. The structure of PSMA-617 is:



(PSMA-617)

92. This falls under Formula A described in Claim 1 with the variable portions, Chelator, X, Y, and Z being represented by Ex. 1001.018:



93. For the PSMA-617 ligand, the variable Chelator is the DOTA moiety, the variable Y is an aryl, X is the naphthyl moiety, and the Zs are -CO₂H groups.

94. The Kratochwil paper shows that 9-10 MBq of the radiopharmaceutical every two months for the first patient and 6.4 MBq of the radiopharmaceutical every two months for the second patient were effective amounts to completely remove the tumors from the respective patients without significant bone toxicity. Ex. 1045.002. These dosage amounts represented 100 kBq/kg. Therefore, the effective dosage in the Kratochwil paper falls within the administered activities of 25-400 kBq/kg of body weight and a unitary dosage of 3-30 MBq recited in Claim 1. The Kratochwil 2016 paper, which uses the same data from the '901 Patent, shows that the patients did not respond to ^{177}Lu -PSMA-617 and in fact worsened. However, they did respond to the claim ^{225}Ac -PSMA-617 and went into complete remission. That there was complete remission with ^{225}Ac -PSMA-617, but not ^{177}Lu -PSMA-617, demonstrates the improvement resulted from combining ^{225}Ac and the PSMA-617 targeting molecule at that dose, establishing a nexus between the patent's claimed treatment combinations and Kratochwil 2016's results. I understand that such a nexus and unexpected results are often established by comparing the invention to the closest prior art, which a POSA would understand was done in this case.

95. Importantly, the '901 Patent requires an "effective amount," not just an efficacious amount. Efficacy is the ability of the drug to prevent or remove a disease, but effectiveness is how the drug performs in the real world, which can be affected by a number of factors, including the toxicity of the drug. A drug with a high toxicity may be ineffective because the patient will refuse the drug or may die from it, even though it still has a high efficacy. The '901 Patent requires not just an amount of the drug that would have a positive effect on tumors, but would be effective with a reasonable level of toxicity. The low level of hematotoxicity and complete remission of the tumor using such a low dose shows a remarkable effectiveness at treating the cancer. Indeed, the '901 Patent demonstrates complete remission with only minor

salivary gland toxicity manifesting as xerostomia. Ex.1045.002. Not only is this low level of toxicity surprising, unexpected, and remarkable, but the lack of renal toxicity is particularly impressive and unexpected since the free daughter nuclides would have been expected to pool in the kidneys. However, Kratochwil showed that kidneys only received a third of the activity of the salivary glands. Ex. 2101.004, Kratochwil, C, et al., Targeted α -Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{225}Ac -PSMA-617: Dosimetry Estimate and Empiric Dose Finding, J Nucl Med 2017; 58:1624–1631. A long-term retrospective study confirmed this surprising result by reviewing data from seven different treatment centers using ^{225}Ac -PSMA targeting molecules and found that only 5% of patients suffered from renal toxicity. Sathekge, M. , et al. Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study Lanc. Onc., 25 (2), 2024, p. 175-183.

96. Claim 2, which further limits the range of molecular structure includes the specific PSMA-617 structure as an option Ex. 1001.019: '901 Patent at 20:40-65. So the method described in the Kratochwil paper meets Claim 2.

97. Claim 4 provides a specific listing of PSMA expressing cancers to be treated, including prostate cancer, and Claim 6 limits the cancer to specifically prostate cancer. *Id.* at 22. As noted above, the Kratochwil paper describes treatment of “metastatic castration-resistant prostate cancer,” and therefore meets both of these Claims.

98. Claim 5 includes the treatment of disseminated cancers. The Kratochwil paper meets this requirement because the PET/CT scan of the treated patients shows that both patients began with metastasized cancers throughout their bodies which were then treated. *Id.*

99. Claims 8 through 11 narrow the dosage range based on body weight and the unit dosage, but the dosages used in Kratochwil still fall within those claimed ranges. *Id.* Claims 8 and 9 require 30-250 kBq/kg of body weight and 50-200 kBq/kg of body weight, respectively. *Id.* The 100 kBq/kg of body weight described in the Kratochwil paper falls within these Claims. *Id.* Claims 10 and 11 recite unitary dosages of 4-25 MBq and 5-20 MBq, respectively, which encompass the 6.4 and 9-10 MBq doses used for the patients in the Kratochwil paper. *Id.*

100. Claims 12 and 13 depend from Claims 8 and 10, respectively, and require that the administering of the effective amount is repeated after 15-90 days. *Id.* The Kratochwil paper described administering new dosages every two months – which would be 60 days – and thus falls within these two claims as well. *Id.*

101. Dr. Zalutsky was asked about this during his deposition and he agrees that the Kratochwil 2016 Paper embodies the '901 Patent.

Q. Okay, so my question for you is, you've looked at the 901 patent, correct?

A. Yes, I have.

Q. And you've read this as well, correct?

A. Right.

Q. Would you say that the technology in this paper is an embodiment of the claims of the 901 patent?

Mr. Murphy: Objection, form.

The Witness: Yes.

Ex. 2139.045, .009, Zalutsky Tr. 171:9-18.

102. Additionally, a POSA would understand that the effects of the treatment described in the '901 Patent are the result of the features of the claimed compound. The Kratochwil 2016 Paper and the '901 Patent compare the effectiveness of the ²²⁵Ac-PSMA-617 compound to its closest compound, ¹⁷⁷Lu-PSMA-617. Although Figure 14 shows that the ¹⁷⁷Lu treatment did not

work and actually allowed the cancer to progress, the ^{225}Ac treatment removed it entirely. There do not appear to be any aspects of the procedure that could have caused this effect, so a POSA would understand that the difference in effect here is due to the combination of a PSMA-targeting ligand with ^{225}Ac provided at the correct dosage to remove the cancer cells. As I will discuss below, these results produced a great deal of surprise in the field, which led to a great deal of praise for the claimed compound. This surprise and praise are due to the treatment results and a POSA would understand that the results stem from this particular compound given in this particular way, because the control, the ^{177}Lu compound, did not have that effect.

C. The Patented Invention was Highly Praised for its Unexpected Results

103. Because the Kratochwil paper is an embodiment of most of the claims of the '901 Patent, any praise of the Kratochwil paper would reflect upon the '901 Patent invention. I have been told that praise is a secondary (or objective) factor that supports the non-obviousness of a patented invention.

104. As a person of skill in the art working in the field of oncology, and in particular radiology and prostate cancer, at the time of the Kratochwil paper and the '901 Patent, I know from personal experience that the community found the Kratochwil paper to be groundbreaking and the results to be unexpectedly impressive. In fact, when I initially heard of this work, I will admit that I was skeptical at the time that using ^{225}Ac would succeed where ^{177}Lu failed. But the results were undeniable. Figures 1 and 3 (the '901 Patent's Figures 12 and 14, respectively) quickly became iconic in the field of oncology and nuclear medicine. During the two years after the Kratochwil paper's publication, I saw it included in scores of presentations. The expert that previously challenged the '901 Patent, Dr. Abergel, agreed that Figure 12, for example, was

widely cited in presentations in the field and compared favorably to previous radiopharmaceutical results:

Q. Had you seen this figure before you were engaged as an expert in this case?

A. I had.

Q. Where had you seen this figure before?

A. In many places.

Q. So it was a fairly popular figure?

A. It is a popular figure.

Q. So it received a lot of attention in the field, correct?

A. That's correct.

Ex. 2080.0012, Abergel Tr. 44:16-25.

Q. And so the people, as you recall, when they presented this data, were they speaking of it favorably?

MS. CIPRIANO: Objection; outside the scope of the declaration.

A. They mostly speak of it as an example of what actinium-225 can achieve.

Q. And when they were talking about it as an example of what it could achieve, were they indicating that it was an impressive result?

A. I mean, yes. It's an impressive result compared to other results.

Ex. 2080.0013, Abergel Tr. 47:7-17.

105. In fact, of the dozens of papers published that month in Journal of Nuclear Medicine, Figure 3 was selected to be on the cover, as is often done for the most groundbreaking data. Ex. 2074, <https://jnm.snmjournals.org/content/57/12.cover-expansion>. This particular honor is unlikely to be granted to a discovery that would have been considered obvious.

106. The community continued to praise and positively comment on the unexpected results of Dr. Kratochwil's data for several years afterwards. In 2017, the European Journal of Nuclear Medicine and Molecular Imaging noted that "225Ac-PSMA-617 was chosen for the special award of the radiopharmaceutical of the year at the 30th Annual Congress of the

European Association of Nuclear Medicine (EANM) in Vienna, Austria. The data for this promising compound for alpha radiation therapy in advanced prostate cancer were presented by Kratochwil et al.” Ex. 2123, Fanti, S, et al. Highlights of the 30th Annual Congress of the EANM, Vienna 2017: “Yes we can – make nuclear medicine great again,” Eur. J. Nuc. Med. Mol. Im. 2018; 45:1781–1794. This award, the EANM Marie Curie Award, is one of the most highly recognized research awards from the European Association for Nuclear Medicine. Ex. 2124, <https://www.eanm.org/congresses-events/awards-grants/winners/>

107. In a 2022 review in Cureus, the author noted, again reproducing Figure 3 from the Kratochwil paper, that “Compared to initial tumor spread (A), restaging after two cycles of β -emitting ^{177}Lu -PSMA-617 presented progression (B). In contrast, restaging after the second (C) and third (D) cycles of α -emitting ^{225}Ac -PSMA-617 gave an impressive response.” Ex. 2126, Alam, MR, et al., A Review of ^{177}Lu -PSMA and ^{225}Ac -PSMA as Emerging Theranostic Agents in Prostate Cancer, Cureus 2022; 14(9): e29369. The author also included a chronological listing of clinical studies using ^{225}Ac with PSMA targeting molecules with the Kratochwil paper listed as the first two entries. Dr. Kratochwil’s work with the ^{225}Ac -PSMA-617 radiopharmaceutical was the first of its kind, and then others followed suit.

108. The degree of response to the Kratochwil paper data and the community’s desire to follow suit is best quantified by the number of times it is cited in other publications. The number of times a paper is cited is a quantification of its influence in the field and the importance of the work. If the paper is cited, then it is being widely discussed and likely followed. At the deposition of the expert that previously challenged the ’901 Patent, Dr. Abergel, she agreed that this is one measure of a paper’s influence on the community:

Q. But in terms of the community, the influence of the article, how would you measure that?

A. You could measure that by looking at the number of citations.

Q. And the citations represent the number of times that other people have referenced the article, correct?

A. That's correct.

Q. And so usually an article that has influence or has an important finding will be cited more often. Is that correct?

A. I think it could be the generality. Yes.

Ex. 2080.0009, Abergel Tr. 30:19-31:5.

109. According to PubMed, a commonly used scientific research database maintained by the National Library of Medicine, as of October 2025 the Kratochwil paper had been cited by 419 academic papers since it first appeared online ahead of print in July of 2016. Ex. 2131.

According to Google Scholar, which performs a broader search to include, for example, books and websites, it has been cited 1224 times. To put this in perspective, and compare the number to references that are supposedly in the field, the Kratochwil paper is cited more than any of the six primary references that Dr. Zalutsky relies on to show obviousness (see Table below).¹

Reference	PubMed Citations	Google Scholar Citations
Ex. 1045 Kratochwil 2016	419 Ex. 2131	1224 Ex. 2094
Ex. 1027: Weineisen 2014	85 Ex. 2166	238 Ex. 2167
Ex. 1028: Weineisen 2015	224 Ex. 2132	643 Ex. 2033
Ex. 1006: Chatalic	0	2 Ex. 2168
Ex. 1015: Miederer	65 Ex. 2169	256 Ex. 2170
Ex. 1011: Jurcic	0	59 Ex. 2171
Ex. 1031: Kratochwil	0	63 Ex. 2172

¹ The Chatalic (1006), Jurcic (Ex. 1011), and Kratochwil (Ex. 1031) references are only abstracts and presentations and therefore do not appear on the PubMed system but do appear on Google Scholars.

110. In fact, excluding Weineisen 2015, the citations of the other five references combined come to around half that of the Kratochwil paper. Only Weineisen 2015, which was published in June of 2015 – a year and a half before the Kratochwil paper – reaches just over 50% of the Kratochwil 2016’s citations. Ex.2131 Ex. 2094

111. Kratochwil, C. et al. 225Ac-PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer, J. Nucl. Med. 2016, 57, 1941 – 1944 (Ex. 2131.001; Ex. 2094.001)

112. Martina Weineisen, et al., Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer, EJNMMI Research 2014, 4:63 (Ex.2166; Ex. 2067)

113. 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, J Nucl Med 2015; 56:1169–1176 (Ex.2131.003; Ex. 2094.005)

114. Kristell Chatalic, et al., 213Bi-labeled PSMA-targeting agents for alpha N/A 2 radionuclide therapy of prostate cancer, J. Nuc. Med. 2016, 57 (supplement 2) 137. (Ex.2168)

115. Matthias Miederer, et al., Preclinical Evaluation of the α -Particle 62 153 Generator Nuclide 225Ac for Somatostatin Receptor Radiotherapy of Neuroendocrine Tumors, Clin Cancer Res 2008,14(11), 3555-3561. (Ex.2169; Ex. 2070)

116. Joseph G. Jurcic, et. al., Phase I Trial of Targeted Alpha-Particle N/A Therapy with Actinium-225 (²²⁵Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML), *Blood* 2016, 128 (22): 4050 (Ex.2171)

117. Clemens Kratochwil, et al., Ac-225-DOTATOC - an empiric dose finding N/A 45 for alpha particle emitter based radionuclide therapy of neuroendocrine tumors, *J. Nuclear Med.* 2015, 56 (supplement 3) 1232. (Ex.2172)

118. Another way to quantify the influence of the Kratochwil paper is to compare it to the average number of citations in the field or that particular journal. The site Altmetric looks at a broad range of citations to compile a quantification of the amount of attention given to an article. Comparing the Kratochwil paper to other papers from that period (within six weeks before and after), it is cited more than 96% of its contemporaries and scores in the 98th percentile compared to all tracked articles regardless of time. Ex. 2095.003. Comparing it to other articles from the *Journal of Nuclear Medicine*, it is the third most cited article from that period (six weeks before and after) and the fifty-seventh most cited article compared to all of the *Journal of Nuclear Medicine*'s publications. *Id.*

<https://www.altmetric.com/details/9534712/citations>. This level of citation is unlikely to be garnered by findings that were obvious or expected.

D. The Effectiveness of the Invention Was Uncertain and Surprising

119. The citation numbers indicate that those of ordinary skill in the art understood how important and remarkable the Kratochwil paper – and thus the '901 Patent – was. They understood it was important because the results in the Kratochwil paper and the '901 Patent were unexpected and surprising. The efficacy of the ²²⁵Ac-PSMA-617 molecule was remarkably high.

The PET/CT scans and PSA measurements show a complete remission of the cancer. As I mentioned earlier, usually such extreme efficacy is counterbalanced by extreme toxicity, decreasing the drug's effectiveness. This is because being able to completely kill tumor cells with radiation typically requires dangerous levels of radiation. So the clinician must typically choose between using higher levels of radiation to kill the tumor and risk side-effects or using lower levels to avoid the toxicity but risk an ineffective treatment. But this was not the case here. In fact, part of the unexpected aspect of the '901 Patent was that it achieved such impressive remission, with low toxicity, and at a low dose. I know that Dr. Zalutsky argues that a low dose would be expected because alpha particles are more powerful, but nothing in the field indicated that it could be that low and that effective.

120. Although Dr. Zalutsky argues that the shorter emission length of the alpha particle would reduce non-specific damage to healthy organs, that argument would not hold for the organs in which PSMA is found, like the salivary glands, or other areas where ²²⁵Ac and its daughter nuclides are known to collect, like the bone marrow, the kidneys, the liver, and the spleen. Ex. 1022.006-7; Ex. 1030.004; Ex. 2173, Afshar-Oromieh et al., "The Theranostic PSMA Ligand PSMA-617 in the Diagnosis of Prostate Cancer by PET/CT: Biodistribution in Humans, Radiation Dosimetry, and First Evaluation of Tumor Lesions," J. Nucl. Med., vol. 56, no. 11, 1697-1705 (2015). Because the kidney is where the agent is excreted and the salivary glands have physiologic uptake, these organs would bear the brunt of the toxicity, and would be expected to be damaged by the high intensity alpha particles. *Id.*; Ex. 2174, Schwartz et al., "Renal uptake of bismuth-213 and its contribution to kidney radiation dose following administration of actinium-225-labeled antibody," Phys. Med. Biol. Vol. 56, no. 3, pgs. 721-733 (2011). This expected toxicity would be magnified by the fact that the ²²⁵Ac had multiple

daughter nuclides that would emit non-bound, non-targeted alpha particles, increasing toxic exposure. But surprisingly, this expected toxicity did not manifest.

121. Another surprising outcome was that ^{225}Ac -PSMA-617 did so well while the ^{177}Lu -PSMA-617 failed so completely. The second patient had been previously treated with two cycles of 7.4 GBq of ^{177}Lu -PSMA-617, which not only failed to decrease the tumor progression, but the tumor actually spread even further after treatment. Indeed, after the treatment with ^{177}Lu -PSMA-617, the amount of detectable PSA increased from 294 ng/mL to 419 ng/mL. A person of ordinary skill in the art of clinical oncology understands that it is not unheard of for a tumor to be resistant to a method of treatment. Because tumor cells are mutagenic, even tumors that fall within the same category may vary widely from patient to patient such that one patient responds to treatment while another does not. However, it is not expected that one radiation therapy would succeed so remarkably well – to the point of remission – where another had not only failed so completely, but the tumor actually spread even further.

122. In this data, the previously attempted treatment used the same ligand, PSMA-617, so it had the same targeting moiety, chelator, and linker. The ^{177}Lu chelated to this ligand would be expected to target and have the same access to the same tumor cells as the subsequent ^{225}Ac construct unless there was an unknown radionuclide effect on binding like that described in Weineisen 2015. Moreover, as explained before, the recoil effect of alpha particle emission meant that there was a very good chance that the ^{225}Ac -PSMA-617 would lose the ^{225}Ac radionuclide before being taken up into the target tumor cells. That free radionuclide would then be a source of toxicity. The success of the compound was dependent on what happened to the daughter radionuclides after the initial decay event, which was unknown.

123. It is also apparent from looking at the prior art that potential benefits of using ^{225}Ac over other radionuclides were not obvious at the time of filing the application for the '901 Patent. Nor was the combination of ^{225}Ac with either PSMA-617 or PSMA I&T obvious. At the time of filing the application for the '901 Patent the community was focused primarily on other radionuclides, such as ^{177}Lu , ^{90}Y , ^{131}I , and ^{223}Ra . For example, beginning in 2010, the work of Tagawa was focused on developing the PSMA antibody J591 as a radiopharmaceutical. Ex. 2175, Tagawa ST, et al., "Anti-prostate-specific membrane antigen-based radioimmunotherapy for prostate cancer," *Cancer* 2010, 116(4 Suppl):1075-83. But Tagawa only used ^{90}Y , ^{177}Lu , and even ^{89}Zr , and did not even attempt to use ^{225}Ac until late 2023. Compare Ex. 2176, Tagawa ST, et al., "Bone marrow recovery and subsequent chemotherapy following radiolabeled anti-prostate-specific membrane antigen monoclonal antibody J591 in men with metastatic castration-resistant prostate cancer," *Front Oncol* 2013, 26:3:214 and Ex. 2177, "Prostate-Specific Membrane Antigen-Targeting Alpha Emitter via Antibody Delivery for Metastatic Castration-Resistant Prostate Cancer: A Phase I Dose-Escalation Study of ^{225}Ac -J591," *J Clin Oncol* 2023, 3:JCO2300573.

124. In fact, a search on PubMed for papers discussing PSMA-I&T and ^{225}Ac show that although Weineisen published on the creation of the PSMA-I&T tracer in June of 2015, no paper discusses its combination with ^{225}Ac until June of 2020, and no studies are completed until September of 2020. It seems unlikely that there would be such a long wait for its production if the combination were obvious. Meanwhile, a search for PSMA-I&T and ^{177}Lu for the same time period produces twenty articles evaluating the compound. Therefore, although researchers could have combined PSMA-I&T with ^{225}Ac instead of ^{177}Lu , approximately twenty papers were

published studying the ^{177}Lu combination, and zero were published studying the ^{225}Ac combination.

125. There was also little certainty as to which of several alpha emitters should be used at the time. The literature was considering ^{223}Ra , ^{213}Bi , ^{211}At , ^{227}Th , ^{149}Tb , ^{203}Pb , ^{212}Pb , and ^{225}Ac . Ex. 1017; Ex. 2178, Zalutsky et al., “Clinical experience with alpha-particle emitting ^{211}At : treatment of recurrent brain tumor patients with ^{211}At -labeled chimeric antitenascin monoclonal antibody 81C6,” *J. Nucl. Med.* Vol. 49, no. 1, pgs. 30-38 (2008); Ex. 2179, Abbas et al., “Experimental α -particle radioimmunotherapy of breast cancer using ^{227}Th -labeled p-benzyl- DOTA-trastuzumab,” *EJNMMI Res.* Vol. 1, no. 1, pg.18 (2011); Ex. 2180, Parker et al., Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer, *N. Engl. J. Med.* Vol 369, no. 3, pgs. 213-223; Ex. 2181, Meredith et al., “Dose escalation and dosimetry of first-in-human α radioimmunotherapy with ^{212}Pb -TCMC-trastuzumab,” *J. Nucl. Med.*, vol. 55, no. 10, pgs. 1636-1642 (2014); Ex. 2182, Cordier et al., “Targeted alpha- radionuclide therapy of functionally critically located gliomas with ^{213}Bi -DOTA- [Thi8, Met(O2)11]-substance P: a pilot trial,” *Eur. J. Nucl. Med. Mol. Imaging*, vol. 37, no. 7, pgs. 1335-1344 (2010); Ex. 2183, Müller et al., “A unique matched quadruplet of terbium radioisotopes for PET and SPECT and for α - and β - radionuclide therapy: an in vivo proof-of- concept study with a new receptor-targeted folate derivative,” *J. Nucl. Med.*, vol. 53, no. 12, pgs. 1951-1959 (2012). But there were many articles warning against using ^{225}Ac because of the expected toxicity complications. Ex. 2174, Schwartz et al., “Renal uptake of bismuth-213 and its contribution to kidney radiation dose following administration of actinium-225-labeled antibody,” *Phys. Med. Biol.*, vol. 56, no. 3, pgs. 721-733 (2011); Jaggi et al., Ex. 2161, “Efforts to control the errant products of a targeted in vivo generator,” *Cancer Res.*, vol. 65, no. 11, pgs. 4888-4895 (2005); de Kruijff et al, “A Critical

Review of Alpha Radionuclide Therapy-How to Deal with Recoiling Daughters?”, Pharmaceuticals (Basel), vol. 8, no. 2, pgs. 321-336 (2015). And even if ^{225}Ac had been selected, the researcher was left with a guessing game as to the selection of a proper dose because other compounds would likely have different binding and biodistribution properties.

E. The Invention Led to Copying by Others in the Field

126. As I explained above, the Kratochwil 2016 Paper received a lot of attention because of its remarkably good results. This led to many others following in the footsteps of the invention, not only in using ^{225}Ac but also PSMA. In 2023, Dr. Zalutsky again wrote about the Kratochwil 2016 Paper, describing the results as “superior clinical results.” (Ex. 2144.002.) In fact, he acknowledged that since the Kratochwil 2016 paper, “ α -emitters have been attracting increased interest due to their higher therapeutic efficacy” *Id.*

127. The most obvious example of copying is the 2021 paper by Dr. Harun Ilhan’s group. This group, 5 years after the publication of the Kratochwil 2016 Paper created the same claimed molecule that Dr. Zalutsky says render the patent invalid: ^{225}Ac -PSMA I&T. This group copied not only the molecule described in the ’901 Patent, but also the protocol by treating a prostate cancer patient with ^{177}Lu -PSMA-I&T followed by the ^{225}Ac version of the molecule. Similar to the ’901 Patent results, the ^{177}Lu treatments saw initial decrease in PSA, the molecule used to track prostate cancer progression, but then began to rise. The treatment with ^{225}Ac -PSMA I&T was about as impressive as those in the ’901 Patent, showing that the surprising results are not limited to the single molecule, but seems to align with other forms of the claimed molecule.

VIII. NEITHER DR. ZALUTSKY NOR THE ART HE RELIES ON DEMONSTRATES THAT THE CLAIMS OF THE ’901 PATENT WERE OBVIOUS

128. The prior art references that Dr. Zalutsky relies upon fail to show that the '901 Patent was obvious either individually or in combination. Dr. Zalutsky generally overlooks their teachings that the radiopharmaceuticals using ^{177}Lu or other beta-emitters were the safer alternatives, that the radiopharmaceuticals in the prior art are not comparable to that in the '901 Patent, or that there is some unpredictability in the development and use of constructs for treatment. Instead, he reads far too much into passing mentions of ^{225}Ac .

A. Weineisen 2014

129. Dr. Zalutsky's reliance on Weineisen's 2014 paper from the EJNMMI Research is misplaced. This reference instead perfectly illustrates why researchers could not extrapolate the research from one carrier molecule to another, or from one radionuclide to another. Weineisen 2014 describes the creation of new carrier molecules for radionuclides and the results of in vitro and mouse experiments with those compounds. Of particular note are the binding experiments. (Ex. 1027.010). The Weineisen lab performed competition experiments to test the in vitro binding of the ligand molecules. They determined the IC₅₀ of the ligands - measured against a control ligand, a high affinity PSMA radioligand (^{125}I)-BA)KuE – by incubating them together to see how much of the ligand was needed to prevent binding of the control ligand to PSMA. IC₅₀ – or half-maximal inhibitory concentration – is the concentration of the radioligand needed to inhibit binding of the control ligand to PSMA by 50% or more. The higher the IC₅₀, the higher the concentration of the radioligand needed to inhibit binding of the control ligand to PSMA. Because inhibition of the binding of the control ligand is an indication of the competing radioligand being bound to the same target, IC₅₀ is a good measure of the binding affinity of the radioligand to the target that would otherwise bind to the control ligand.

130. The Weineisen lab found that although constructs may have the same binding motif for PSMA, the selection of other components of the radioligand could dramatically affect binding affinity. In each case the metal reduced it. For example, the IC50 of Ga bound DOTA-FFK(Sub-KuE) was more than double that of unlabeled DOTA-FFK(Sub-KuE) - 13.1 nM for empty DOTA-FFK(Sub-KuE) vs. 29.5 nM for Ga bound DOTA-FFK(Sub-KuE). *Id.* And even more remarkably, the IC50 of Lu bound DOTA-FFK(Sub-KuE) was more than quadruple that of empty DOTA-FFK(Sub-KuE) - 13.1 nM for unlabeled DOTA-FFK(Sub-KuE) vs. 54.7 nM for Lu bound DOTA-FFK(Sub-KuE). *Id.*

131. When asked about this data, Dr. Abergel, the previous expert that challenged the '901 Patent, had to agree that there were significant differences arising from the use of the radionuclide:

Q. So if we look at the third, fourth, and fifth line on Table 1, on the far right, we see the numbers 13.1, 29.5, and 54.7. Do you see that?

A. Yes.

Q. And so this is all for the DOTA-FFK sub-KuE, but they differ in that the first one has no metal in it, the second one has gallium, and the third one has lutetium, correct?

A. That's correct.

Q. And so even though these are the same molecules, the same carriers, we see that by adding different metals to the chelator, we dramatically affect the affinity of the ligand. Isn't that right?

MS. CIPRIANO: Objection to the extent it misstates the document.

A. There is a significant difference between the free chelator and the metal complexes. That's right.

Q. And we also see a difference between the two metal complexes, with gallium having an affinity of 29.5 and lutetium having 54.7.

A. In this particular case, that's correct.

Ex. 2080.0033, Abergel Tr. 127:19-128:14.

Q. Although between the empty DOTAGA-FFK and the lutetium-containing FFK -- DOTAGA-FFK, we do see a large difference, don't we?

A. We do see a significant difference.

Q. So a person of skill reading this would understand that using a radionuclide in a molecule can affect its ligand-binding ability, correct?

A. That's correct.

Q. And they would also conclude that using different types of metals in the chelators would also affect the ligand's binding ability, correct?

A. That may affect, depending on the ligands. From this particular table, it does not affect the DOTAGA constructs. It affects the DOTA constructs.

Q. But it could affect it.

A. It could.

Ex. 2080.0033, Abergel Tr. 128:19-129:9.

132. Weineisen 2014 also found that changing the radionuclide affected the ligand rate of internalization with ¹⁷⁷Lu-bound ligands showing a higher rate than ⁶⁸Ga-bound ligands. Dr. Abergel, the previous expert, and I are in accord that affinity and internalization are separate factors. For example, when asked about Table 2 of Weineisen 2014, Dr. Abergel noted that this internalization effect could have been separate from the affinity effect, creating another direction of unpredictability:

Q. So internalization is linked to the idea of affinity, correct?

A. Not necessarily.

Q. Okay. Explain how it's not.

A. It depends on the mechanism of internalization.

Q. Okay. So you could have something that has high affinity but low internalization or low affinity and high internalization, correct?

A. That's right.

Q. So when we look at this chart, we see that, again, the gallium and lutetium for the DOTA-FFK molecule are significantly different, correct?

A. That's correct.

Q. And as you just explained, that difference is not necessarily because of the difference in affinity. It could be due to the difference in internalization or uptake, correct?

A. That's correct.

Q. And then we look at the next line down. That's lines 4 and 5 on Table. We see that the DOTAGA-FFK, sub-KuE, also shows a difference between using gallium and lutetium, correct?

A. That's correct.

Ex. 2080.0034, Abergel Tr. 129:24-130:22.

133. These data demonstrate three things to a person of ordinary skill in the art.

134. First, even when chelated to the same ligand, different radionuclides can result in dramatic changes in the binding and internalization of the radiopharmaceutical. This is true even though the radionuclide is distant from the binding site. And differences in binding can affect the efficacy and effectiveness of the radiopharmaceutical.

135. Second, because different radionuclides have different and separate effects on binding affinity and internalization, the binding affinity of any given radioligand – i.e., the combination of radionuclide, chelator, and targeting moiety – cannot be predicted from data related to a different radionuclide.

136. Third, because these differences in affinity and internalization were more pronounced for some constructs than for others, the POSA could not – and would not – assume that the same radionuclide would perform or behave similarly when chelated to different ligands. And since these differences are not consistent either in constructs with the same radionuclide but different ligands or in constructs with the same ligand but different radionuclides, the POSA would have understood that the performance and behavior of any given radiopharmaceutical in a biological system – particularly in the human body – could not be predicted with any reasonable degree of accuracy.

137. When asked, Dr. Abergel, the expert who previously challenged the validity of the '901 Patent, admitted that the effects of a radionuclide on the characteristics of the ligand are unpredictable:

Q. Okay. And so a person of skill, again, would conclude that having different radionuclides in even the same ligand-binding molecule can result in different internalization rates.

A. That's right.

Q. So I think that we can agree, based on the differences that we see between the

radionuclides and your comment about how the three-dimensional structure may differ from what we see on paper, that determining whether or not a radionuclide will affect the binding and the internalization parameters is complicated.

MS. CIPRIANO: Objection; calls for speculation.

A. It may be complicated. Yes.

Q. And, in fact, there's a certain level of unpredictability to it, correct?

A. That's correct.

Ex. 2080.0034, Abergel Tr. 131:8-24.

138. Armed with this, and because Weineisen 2014 only studied ^{177}Lu and ^{68}Ga , a POSA contemplating use of a radionuclide that was not studied in Weineisen 2014 – like ^{225}Ac – would not have known or even been able to hazard a guess as to how that radionuclide would affect binding affinity or performance of radiopharmaceuticals employing the ligands Weineisen 2014 studied – or any other ligand for that matter. Instead, the variability of Weineisen 2014's results would inform the POSA that the reported work should only be applied to the specifically studied ligands – DOTA-FFK(sub-KuE), DOTAGA-FFK(sub-KuE) and DOTAGA-ffk(sub-KuE) – and to the specifically studied radionuclides – ^{177}Lu and ^{68}Ga .

139. Despite these shortcomings, Dr. Zalutsky argues that Weineisen 2014 would have taught the POSA to use ^{225}Ac because Weineisen 2014 mentions it once – along with other radionuclides – as allegedly chelatable by DOTA. But the single mention of ^{225}Ac in Weineisen 2014 would not have suggested this to the POSA. That mention of ^{225}Ac comes in a sentence describing the “approach” of the research, and not the actual research itself: “Our approach was therefore focused on the development of a PSMA ligand allowing for both, complexation with, e.g. ^{68}Ga or ^{111}In for PET or SPECT and with therapeutic M3+-radiometals, e.g. ^{177}Lu , ^{90}Y or ^{225}Ac for endoradiotherapy.” (Ex. 1027.011). Weineisen's statement of an “approach” to developing a PSMA ligand capable of complexing with therapeutic M3+ radiometals does not teach that the ligands developed and evaluated in Weineisen 2014 were compatible with all M3+

radiometals. Nor does this statement teach or demonstrate that those ligands could successfully chelate ^{225}Ac in particular.

140. In light of this, and contrary to Dr. Zalutsky's conclusion, the fact that the Weineisen 2014 lab mentioned ^{225}Ac – and other radionuclides, including ^{177}Lu and ^{90}Y – but chose to study only ^{177}Lu (and further reference ^{90}Y) – to the exclusion of ^{225}Ac – and instead focus studies on ^{177}Lu and ^{68}Ga would have actually informed the POSA that ^{177}Lu , ^{90}Y and ^{68}Ga were the better, safer bets. For example, when discussing the constructs, Weineisen 2014 states that DOTA and its analogues “form stable complexes with a broad range of radiometals, for therapy most importantly ^{90}Y and ^{177}Lu .” (Ex. 1027.002 (emphasis added).) Here, Weineisen 2014 again specifically excludes ^{225}Ac – despite it being listed earlier in the document in the same group of therapeutic radiometals with the now specifically mentioned ^{177}Lu and ^{90}Y . And again, when explaining that the constructs would “allow labelling with both diagnostic and therapeutic radionuclides, e.g., ^{68}Ga for PET imaging and $^{177}\text{Lu}/^{90}\text{Y}$ for therapy after conjugation of DOTA,” Weineisen 2014 again excludes ^{225}Ac . *Id.* Given Weineisen 2014's mention of ^{225}Ac as a “therapeutic M3+-radiometal” together with ^{177}Lu and ^{90}Y , and then consistent exclusion of ^{225}Ac when discussing the formation of “stable complexes” and use “for therapy,” the POSA would have had reason to doubt that ^{225}Ac forms “stable complexes” or is useful “for therapy” with these ligands. With these teachings, then, the POSA would not have been motivated to select ^{225}Ac for further study or use, especially with the knowledge that the selection of radionuclide could have unknown effects on binding and performance, and the knowledge that ^{225}Ac presents unique recoiling daughter nuclide safety and toxicity concerns.

141. Weineisen 2014 also uses cell culture and mice studies – and not human trials. Weineisen therefore also fails to inform the POSA whether the studied compounds could be

effectively and safely used in humans. For example, Weineisen 2014 measures the internalization of the studied constructs in cell culture after 1 hour and found 14-44% internalization. (Ex.1027.011.) But the POSA would not expect this petri dish experiment to reflect the internalization that would be seen in the human body. This is because in a cell culture the constructs have unfettered and immediate access to the cells as soon as put in solution. This is not the case in the human body. In the human body, a radiopharmaceutical must travel to the site and bind to the site after which – ideally – the radionuclide is delivered to the target cell for radiotherapy. In a cell culture, where the radiopharmaceutical is in the cell media, obstacles don't exist because the radiopharmaceutical is already close to the cells, there are ample cells in the culture to bind to, and the radioactivity permeates the media even if not targeted. In the human body, however, these tasks are infinitely more complicated, as the compounds may need to travel quite a distance to reach the target, there may be competing compounds attempting to bind to the same cells and receptors, and the radionuclide may escape or be released from the compound before it reaches the target site. And in the case of ^{225}Ac , these tasks are complicated even further due to alpha recoil which significantly increases the chance that the radionuclide will escape the compound before reaching the target site, and poses increased risk of serious damage to the patient.

142. Finally, Weineisen 2014 does not disclose any of the elements recited in the '901 Patent claims, and so supplies no teaching that would have led a POSA to the claimed subject matter. This reference does not use PSMA- I&T – upon which Dr. Zalutsky bases his obviousness argument – or ^{225}Ac . Dr. Zalutsky never claims that any of the constructs in the reference satisfy the formulae or elements of the '901 Patent claims. But in addition to not disclosing any of the claim elements, Weineisen 2014 also does not describe human treatments

or dosages for any ^{225}Ac -based treatments – and in fact would have suggested to the POSA not to use ^{225}Ac -based treatments.

B. Weineisen 2015

143. We must view Weineisen's follow up 2015 publication (Ex. 1028) in light of the 2014 paper. Again, Weineisen 2014 showed that using different radionuclides with the same ligands can dramatically affect binding affinity and internalization of the constructs in different ways, and that using different ligands with the same radionuclides can also dramatically affect binding affinity and internalization. Stated more simply, changing the radionuclide of a construct – or changing the ligand – leads to unpredictable results.

144. Weineisen 2015 in fact contributes to this understanding by showing that a small modification to the linker region – which plays no role in the construct other than connecting the targeting moiety to the chelator – can also dramatically affect properties and performance – such as binding affinity and biodistribution – of the construct. Ex. 1028.003. The disclosed PSMA-I&T construct simply includes an iodine and an OH group added to a pendant phenyl group on the linker moiety. These simple chemical additions to an otherwise inactive and non-functional part of the ligand nearly doubled the binding affinity of the construct despite the binding moiety (i.e., the targeting moiety) being located all the way at the other end of the molecule. (Ex. 1028.002 and 1028.003.) These small changes to the construct also resulted in dramatically higher uptake by the cells even though the linker would not have been expected to play any a role in uptake.

145. Weineisen 2015 also compared uptake of constructs having the same ligand but different chelated radionuclides and found that uptake differed between different radionuclides –

despite being chelated to the same ligand. (Ex. 1028.007.) While ^{68}Ga -PSMA-I&T and ^{177}Lu -PSMA- I&T showed marginally different binding affinity to PSMA, Weineisen 2015 found a significant difference in the amount of uptake in mice organs between the ^{68}Ga and ^{177}Lu constructs, with ^{177}Lu - PSMA- I&T usually being taken up in greater amounts in the tumor, spleen, and kidney. (Ex. 1028.004.)

146. The differences between the ^{68}Ga and ^{177}Lu constructs are most likely due to steric interactions between the chelator and the rest of the ligand in which the differently sized ^{68}Ga and ^{177}Lu are having different effects. At deposition, Dr. Zalutsky offered a different explanation — which he called “my speculation” — that PSMA-I&T’s DOTAGA could not hold the smaller ^{68}Ga as well as the ^{177}Lu , so that the ^{68}Ga detached and the measured signal decreased regardless of the ligand’s binding. Either explanation makes the same point here: changing only the radionuclide altered the compounds behavior in a way a POSA could not have predicted.

Q. So, changes in the nuclide that the chelator is holding can have effects on its - the placement of the molecule in tissue, correct? Am I saying that correctly?

A. You're saying it correctly, but it's incorrect. So the story is that we are only interested in a way in the radioactive part of the molecule because that is what is used for imaging and what is used for therapy. So, you know, to interpret the biodistribution, you have to know what has happened to the gallium-68. You know, if gallium-68 were bound to another molecule with -- with a DOTA instead of a NOTA, you would predict a similar problem. Although, you know, steric hindrance and all these other factors have to be considered.

Q. So you're saying that less of the gallium-PSMA-I&T is in the kidney because - because the gallium leaked from the PSMA-I&T?

A. That would be my speculation, and if you look at the tumor uptake, you will see the tumor uptake is considerably lower than the lutetium.

Q. And then you won't be able to measure the gallium because it's not there, even if the molecule has been taken up?

A. No, you're only looking at -- gallium is the only thing you're looking at when you're counting.

Q. I understand that, but what I'm getting at is that because you're only measuring the gallium, the PSMA-I&T could still be taken up into the kidney, but there's no gallium to measure?

A. Absolutely, yes, sorry.

Ex. 2139.019, .020, .009, Zalusky Tr. 67:13-69:12; 70:1-10

147. This seems unlikely, given that there is no evidence that ^{68}Ga has a significantly lower stability in DOTA than ^{177}Lu . Weineisen 2014 showed that the Ga-bound construct in fact had the lower IC₅₀ – 29.5 nM, versus 54.7 nM for the Lu-bound construct – measured by competition experiments that did not rely on the signal from Ga or Lu but from a third radionuclide, ^{125}I . (Ex. 1027.010) While these studies concern a different ligand, they indicate that a Ga-bound construct may bind PSMA more avidly than its Lu-bound counterpart and still show lower uptake *in vivo*, which is itself evidence that binding affinity does not reliably predict biodistribution. Additionally, Price, a reference that Dr. Zalutsky relies on to show that DOTA was the “gold standard” for chelating ^{225}Ac , shows that ^{68}Ga and ^{177}Lu have comparable thermodynamic affinities for DOTA – 21.3 and 21.6-23.5, respectively. (Ex. 1041.008, Table 2). Either the stability is very different for PSMA-I&T’s DOTAGA – a definite possibility but counter to Dr. Zalutsky’s other assertions – or there is a significant difference in *in vivo* instability due to size differences sufficient to halve the signal, or, as the Weineisen 2014 competition data indicate, the chelated radiometal alters the construct’s behavior *in vivo* in ways that binding affinity alone does not predict. Any one of these explanations — steric interactions, decreased stability, or *in vivo* effects on binding — would indicate that the compatibility of radionuclides to ligands is difficult if not impossible to predict.

148. If the difference in size between ^{68}Ga and ^{177}Lu , approximately 40% for an absolute difference in radius of 24 pm, is an issue for any of these, then the difference between ^{177}Lu and ^{225}Ac would be at least as significant: the absolute difference in radius is larger still, 26 pm, even if it is a smaller proportion of the larger ion (approximately 30%).

149. In light of Weineisen 2014 and 2015, the POSA would not have reasonably expected even very similar radioligand constructs – such as those with the same radionuclide but different ligand structures, or those with the same ligand structure but different radionuclides – to perform identically or comparably in the body. The previous expert that challenged this patent, Dr. Abergel, agreed at her deposition that changing the radionuclide could result in very different characteristics:

Q. So a person of ordinary skill in the art looking through the two Weineisen papers and comparing them would conclude that you can change out the radionuclide in a molecule and get very different affinities and uptake.

A. In the case of lutetium and gallium, yes.

Q. And it's possible that if you put something else in you would get the same effect, correct?

A. That's correct.

Q. And it's also -- they also see that even if you have the same radionuclide, putting that in a different molecule will give you different --

A. Yes.

Q. -- affinity and uptake.

A. That's correct.

Ex. 2080.0035, Abergel Tr. 136:15-137:4

150. The POSA would therefore not consider radionuclides to be interchangeable when devising a treatment method for a particular cancer. Nor would the POSA consider the ligand structures to be interchangeable. Instead, as I've demonstrated here, from Weineisen 2014 and Weineisen 2015 the POSA could not predict the results from swapping the radionuclide – for example, ^{225}Ac for ^{177}Lu .

151. Importantly, Weineisen 2015 makes no mention of ^{225}Ac in this follow-up publication. This is consistent with my discussion above of Weineisen 2014's deliberate exclusion of ^{225}Ac from the first studies in 2014. And even if the POSA got the impression that Weineisen's casual mention of ^{225}Ac in the 2014 paper was a suggestion to use ^{225}Ac , then that impression would have completely faded with the 2015 paper. Although Dr. Zalutsky argues that it would have been obvious to combine ^{225}Ac with Weineisen 2015's PSMA-I&T construct, it apparently did not occur to Weineisen herself – despite her clearly being aware of ^{225}Ac as a potential “therapeutic M3+ radiometal”]. Therefore, Weineisen 2014 and 2015 identify ^{177}Lu as the radionuclide of choice for these treatments, and give the POSA no basis to expect that ^{225}Ac would be suitable.

152. Since neither Weineisen 2014 nor 2015 use ^{225}Ac in any dosage, they do not teach an effective dosage for ^{225}Ac -PSMA-I&T as required by the '901 Patent. Weineisen 2015's use of ^{177}Lu -PSMA-I&T, at 1000 times the administered dose and effective dose claimed in the '901 Patent, provides no guidance to a POSA that would lead them to the claimed dosage. There are too many factors involved that decide the effective dose (e.g., affinity, internalization, metabolism, cell geometries, etc.) for a dosage for a one radionuclide to be converted to another. For example, because ^{177}Lu beta particles have a much greater range than alpha particles, they can have an effect on tumor cells that a ^{225}Ac -radioligand may not be able to reach because the target is sequestered. As I explained previously, there is no standard conversion for ^{177}Lu dosages to ^{225}Ac dosages. Dr. Zalutsky argues that a POSA would know that a radiopharmaceutical using ^{225}Ac would have a lower administrative dose than one using ^{177}Lu , but they would not know how low because the administrative dose for any radiopharmaceutical must be determined empirically.

C. Chatalic

153. Chatalic is an abstract that offers no guidance in the use of ^{225}Ac and largely steers the POSA away from using this radionuclide. Chatalic injects mice with ^{213}Bi -PSMA-I&T to study its ability to target and damage xenografted cancer cells. (Ex. 1006.)

154. First, Chatalic's use of ^{213}Bi is not an endorsement of – or even a suggestion to use – other alpha emitters, including ^{225}Ac . Quite the contrary, using ^{213}Bi was likely Chatalic's attempt to avoid the known and significant problems and challenges presented by ^{225}Ac , namely its recoiling daughter nuclides. As explained above, the greatest obstacle to using ^{225}Ac was that its recoiling daughter nuclides would break free from the radioligand construct and release high-energy α -radiation into surrounding organs, thereby causing irreparable damage to healthy tissues. In fact, no ^{225}Ac -PSMA-I&T appeared in publication as a suggested treatment until 2021. Ex. 2120, Lin M, et al., Prostate-Specific Membrane Antigen-Targeted Radiopharmaceuticals in Diagnosis and Therapy of Prostate Cancer: Current Status and Future Perspectives, Cancer Biother Radiopharm 2021 Apr;36(3):237-251. This was long after the publication of the '901 Patent. As seen from the ^{225}Ac decay scheme below, ^{225}Ac decays six times, releasing four alpha particles and two beta particles, until becoming a stable ^{209}Bi . Because ^{213}Bi is one of ^{225}Ac 's daughter nuclides, its use sidesteps the daughter nuclide problem by beginning with a radiometal much further down the decay chain. Compared to ^{225}Ac 's six decays, ^{213}Bi decays via a branched mechanism and releases one alpha and two beta particles. As can be seen from this comparison, using ^{213}Bi would be significantly safer than using ^{225}Ac . Specifically, even if ^{213}Bi were to escape the ligand, the amount of energy subsequently released would be significantly lower than with ^{225}Ac , thus mitigating and minimizing the risk of recoil damage. Knowing this, the POSA would have concluded that Chatalic intentionally selected ^{213}Bi instead of ^{225}Ac to avoid ^{225}Ac 's

known and unresolved inherent dangers. Ex. 1022.025, Scheinberg, DA, et al., Actinium-225 in targeted alpha-particle therapeutic applications, Curr Radiopharm. 2011; 4(4): 306–320.

155. Second, far from encouraging use of alpha emitters, Chatalic would actually deter the POSA from using such radionuclides. Specifically, Chatalic described injecting mice – which typically weigh about 25 grams – with 5 MBq ^{213}Bi -PSMA I&T. In a human patient – who would weigh about 85-90 kg on average in North America – a simple body-weight scaling of that dose would give $(85/.025 \times 5)=17,000$ MBq. I do not offer that figure as a reliable mouse-to-human conversion – as I explain above, no consistent conversion factor exists – but only to show the order of magnitude of the activity Chatalic administered. To put this in perspective, Claim 1 of the '901 Patent recites a unitary dosage of 3-30 MBq of ^{225}Ac , and the experiments on human subjects in Weineisen 2015 used 5,700 and 8000 MBq of ^{177}Lu . In comparing these dosage levels, Chatalic uses an alpha emitter at doses well above – indeed more than double – even a beta emitter level to achieve the reported effect. The POSA reading Chatalic would thus conclude that the dangerously high amount of radiation was necessary to obtain the reported result and that its dose-limiting toxicity would make other alpha emitters – and particularly ^{225}Ac with its significantly higher alpha radiation – useless. In fact, Chatalic describes using 10 nmol of 2- PMPA or 4 mg gelofusin “for renal protection,” indicating deep concern about toxicity from the presumed ^{213}Bi alpha emitter. And as ^{225}Ac is a much more potent alpha emitter than ^{213}Bi , the POSA faced with Chatalic’s deep concern about toxicity from ^{213}Bi would certainly not have ventured a treatment with the far more dangerous and toxic ^{225}Ac .

156. Finally, Chatalic studies the ^{213}Bi compounds only in mice. As I discuss elsewhere in this Declaration, one of the main limitations of mouse models is that they do not adequately model toxicity profiles that are seen in humans. For example, kidney toxicity often

occurs in delayed fashion with radiopharmaceuticals in humans, but the time course of treatments in Chatalic's mouse model were too short to model these effects. Specifically, while Chatalic was clearly concerned about kidney toxicity – as evidenced by the co-administration of renal protective drugs – Chatalic evaluated the tumor cells only at 1 hour and 24 hours after administration. And Chatalic apparently did not evaluate kidney toxicity at either of these points – or any other point in the study – despite clearly being concerned about it. As the optimal administered activity is determined by both efficacy and toxicity – which defines the therapeutic window – Chatalic's failure to study or report on toxicity severely limits the application of his findings to any treatment protocol.

157. As proof of this, Chatalic concludes from the mouse studies only that “preclinical evaluation” of the ^{213}Bi compounds “revealed good tumor targeting and induction of DSBs [DNA double strand breaks].” Ex. 1006.002. And Chatalic specifically states that “further evaluation of the therapeutic efficacy and toxicity of Bi-labeled tracers” for treatment of metastasized prostate cancer would be needed. *Id.* This reinforces my above comments that mouse models are not sufficient to determine therapeutic efficacy and toxicity in humans.

D. Miederer 2008a (Ex. 1015)

158. Miederer 2008a not only describes a treatment that is different from the one in the '901 Patent, Miederer 2008a also concerns a disease very different from the one in the '901 Patent. This means that Miederer 2008a provides the POSA with no useful guidance on the use of ^{225}Ac with PSMA-targeting ligands.

159. Miederer 2008a describes a treatment for neuroendocrine tumors and targets somatostatin receptors with somatostatin analogues linked to a chelator. While Miederer 2008a

may also use a targeted radioligand therapy, its similarities to the '901 Patent end there. Miederer 2008a uses a completely different ligand and treats a completely different disease – neuroendocrine tumors not PSMA expressing cancers. These diseases and targets are too different for Miederer 2008a to provide any meaningful guidance to the POSA regarding therapies or treatment modalities for PSMA expressing cancers. As such, the POSA would not have found the '901 Patent obvious based on any information from Miederer 2008a.

160. The POSA would understand that the different diseases could differ in numerous ways, making Miederer 2008a inapplicable to PSMA expressing cancers, for example, prostate cancer. These factors include: • susceptibility to radiation treatment; • the number and availability of target receptors; • the speed of proliferation; • tendency to metastasize; • the specificity of the target molecule; • the adaptability of the cancer to avoid treatment; • cellular uptake of the radiopharmaceutical; • the homogeneity of the cancer; • the tendency of the drug or radionuclide to pool in healthy organs; and • side effects from the radioligand itself binding to targets not involved with the tumor.

161. These factors and more make it difficult, if not impossible, to carry over treatment data from one cancer type to another. As a simple example, one of the few side effects of the invention embodied in the 901 Patent was damage to the salivary glands leading to xerostomia (dry mouth) because PSMA is found there. This became the dose-limiting organ determinative of the treatment's effectiveness – rather than the expected kidney, liver, or bone marrow. A somatostatin study would give no clue as to the importance of this organ to PSMA-ligand based treatments because other organs could be the dose-limiting organs in that study.

162. Additionally, the differences in the radioligands themselves prevent the Miederer 2008a findings from providing any guidance. As demonstrated by Weineisen 2014 and 2015, a modification in almost any part of a small molecule can affect the resulting ligand's binding. Dr. Zalutsky proposes the most radical of changes – changing the ligand itself – and just assumes – without any study or research – that it would work equally well. But Weineisen 2014 and 2015 teach otherwise.

163. Miederer 2008a also highlights the hazards of using the ^{225}Ac radionuclide which would deter and discourage the POSA from applying that radionuclide elsewhere. Miederer 2008a explains that “due to the high toxicity of ^{225}Ac and its daughter nuclides, ^{221}Fr , $^{217}\text{A}[t]$, and ^{213}Bi , unwanted side effects are to be expected.” (Ex. 1015.005.) This was because “after disintegration, the retention of daughter isotopes within the chelate is highly unlikely, either due to the physical recoil energy or the different chemical properties of the first daughter nuclide ^{221}Fr .” Ex. 1015.002. Miederer 2008a explains that this makes the ^{225}Ac daughter nuclides “capable of relocating within the organism” and that “accumulation of ^{213}Bi [a daughter nuclide] originating from the bloodstream into the kidneys with subsequent radiation damage has been shown in nonhuman primates.” *Id.* Miederer 2008a recommends “renal protection from the accumulation of ^{225}Ac daughter nuclides” using additional scavengers such as chelating agents or by promoting diuresis to push the radioligand through the system with either furosemide or chlorothiazide. (Ex. 1015.006.) But one of the surprising results of the '901 Patent was that renal side effects were very low with only low-grade side effects and renal injury only occurring in those patients that had a history of such. Ex. 2101, Kratochwil, C, et al., Targeted α -Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{225}Ac -PSMA-617: Dosimetry Estimate and Empiric Dose Finding, J Nucl Med 2017; 58:1624–1631; Ex. 2098, Sathekge, M, et al.,

Predictors of Overall and Disease-Free Survival in Metastatic Castration-Resistant Prostate Cancer Patients Receiving ^{225}Ac -PSMA-617 Radioligand Therapy, J Nucl Med 2020; 61:62–

69. As these results are completely counter to the toxicity results that Miederer 2008a reports as “expected,” the POSA would have found the ’901 Patent data exhibiting unprecedented treatment success coupled with very low toxicity to be unexpected and surprising.

E. Jurcic

164. Jurcic has a number of confounding issues making its data irrelevant to the invention of the ’901 Patent.

165. First, Jurcic uses the antibody lintuzumab with a ^{225}Ac radionuclide. Antibodies are large molecules – not small molecules as disclosed in the Weineisen 2015 and Kratochwil references that are cited in Curium’s proffered grounds for obviousness, as well as in many of the other references relied on by Dr. Zalutsky. And antibodies have dramatically different pharmacodynamics and kinetics than small molecules. For example, the POSA would understand that large molecules like antibodies take longer to clear from the body and thus require a significantly different approach to treatment. Ex. 2184, Pimm et al, “Blood and tissue kinetics of radiolabelled anti-CEA monoclonal antibody and F(ab)2 and Fab fragments in nude mice with human tumour xenografts: implications for tumour imaging and radioimmunotherapy,” Nucl. Med. Commun., vol. 10, no. 8, pgs. 585-593 (1989). Antibodies remain in the system much longer than small molecules, so the dose, efficacy, and toxicity reported for an antibody like lintuzumab would have no bearing on the dose, efficacy, and toxicity for a small molecule PSMA-targeting ligand.

166. This is driven home by Jurcic using furosemide alongside the antibody construct and spironolactone for a year after treatment to prevent “radiation-induced nephrotoxicity.” (Ex. 1011.002.) The antibody would remain present for days or weeks, and the ^{225}Ac daughters would be slowly ejected from the antibody construct due to the recoil effect with the ^{225}Ac daughter nuclides being cleared by the kidney. This would extend the exposure time of the body – and particularly the kidneys – to prolonged radiation. Although Jurcic states that an alpha emitter may result in more specific tumor cell killing and less damage to normal tissue, the use of furosemide and spironolactone demonstrates the concern that this treatment subjects normal, healthy tissue and organs to considerable long-term risk of irreparable damage. The POSA would have found potential kidney injury from ^{225}Ac and its daughters a significant potential concern.

167. Second, Jurcic’s antibody construct is not instructive as to the technologies in Weineisen 2015 or Kratochwil – or indeed the other references discussed by Dr. Zalutsky – because it is not targeted to PSMA. Instead, Jurcic is directed to a treatment for leukemia cells with lintuzumab, which targets the CD33 protein.

168. The significant differences in the treatment and disease discussed in Jurcic and the remaining references relied on by Curium and Dr. Zalutsky raise a whole host of reasons why the POSA would not use the teachings of Jurcic in an effort to improve or modify the technology disclosed in any of the other references. The POSA could not assume that the antibody would bind with the same affinity as the small molecules in the other references. This and the fact that the antibody would remain in the body for so long mean that Jurcic provides zero guidance on a dosing regimen for a radically different treatment compound targeted to a completely different target receptor for the treatment of a completely different disease. And the fact that the small molecule ligands disclosed in Weineisen 2015 and Kratochwil (and most of the remaining

references discussed by Dr. Zalutsky) would be cleared out much more quickly further emphasizes the completely different and irrelevant nature of Jurcic's disclosure.

169. Also, because leukemia is not a solid tumor, the POSA would expect the dosage for treating that disease to be very different from that for a solid tumor, such as those discussed in Dr. Zalutsky's remaining references. Therefore, the POSA could not – and would not – rely on the dosage information provided in Jurcic to devise a dosage regimen for the very different treatments in the remaining references for treating very different diseases.

170. But perhaps Jurcic's biggest failure is that its design cannot show what, if anything, the ²²⁵Ac-lintuzumab contributed. Jurcic does not use the ²²⁵Ac-lintuzumab alone, but rather in combination with a low dose of cytarabine ("LDAC"), which is often used to treat leukemia. (Ex. 1011.001-1011.002.) Jurcic found that the combination of the radioimmunoconjugate with 20 mg of cytarabine twice a day for 10 days every 4-6 weeks resulted in complete remission in 11% of the study subjects. But the data relied on by Dr. Zalutsky lacks a proper control of the isolated pharmaceuticals. When asked about this, both Dr. Abergel and Dr. Zalutsky suggested that to understand the effects of the ²²⁵Ac-lintuzumab, you would have to look at similar LDAC experiments but without ²²⁵Ac-lintuzumab :

Q. So they're not just giving the 225-Ac-Lintuzumab. They're also giving a low dose of cytarabine, aren't they --

A. That's right.

Q. -- alongside it?

And so when we look at the results for this study, how do we know whether the results were caused by the LDAC, the low-dose cytarabine, or the 225-Ac-Lintuzumab?

A. You compare the results with other data where you have only one agent, like the LDAC.

Ex. 2080.0041, Abergel Tr. 157:12-22

171. Dr. Zalutsky also suggested that to understand Jurcic requires looking at comparable studies done without the ²²⁵Ac-lintuzumab:

Q. Well, you say that we can see some complete responses here, but we don't have a zero control to compare it to, do we?

A. This was not designed to determine efficacy, so you could do historical comparisons. You could certainly do historical comparisons.

Q. What do you mean by historical comparisons?

A. Patients that received only the cytarabine, and were followed had similar levels of disease, all that. I don't know if they discussed historical controls, but clearly that's not ideal. You -- you would like to have a parallel arm, but again, you can't do that.

[Q.] You said that I could look at historical studies. So if I looked at other studies that used low-dose Cytarabine, and I found that they were more efficacious, I would conclude that the Lintuzumab didn't do anything.

Mr. Murphy: Objection, form.

By Mr. Boetticher:

Q. Correct?

A. You could make that conclusion.

(Ex. 2139.028, Zalutsky Tr. 104:5-17; 105:11-19)

172. But a previous such study by Burnett using the same cytarabine protocol (as a mono- therapy with LDAC alone) found a complete remission rate of 18% with cytarabine alone. Ex. 2116, Burnett, AK, et al., A Comparison of Low-Dose Cytarabine and Hydroxyurea With or Without All-trans Retinoic Acid for Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome in Patients Not Considered Fit for Intensive Treatment, Cancer 2007;109:1114–24. In fact, Burnett cites to a host of other papers that did as well as or better than Jurcic with cytarabine (a/k/a cytosine arabinoside) alone, reporting complete remission rates of 9-50% as summarized in the table below: Reference Reported CR Jurcic, JG, et al., Phase I Trial of Targeted Alpha-Particle Therapy with 11% Actinium-225 (²²⁵Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML), Blood (2016) 128 (22): 4050. Ex. 1011. Burnett, AK, et al., A Comparison of Low-Dose

Cytarabine and Hydroxyurea 18% With or Without All-trans Retinoic Acid for Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome in Patients Not Considered Fit for Intensive Treatment, *Cancer* 2007;109:1114–24. Ex. 2116 Winter, JN, et al., Low-dose cytosine arabinoside (Ara-C) therapy in the 9% myelodysplastic syndromes and acute leukemia. *Cancer* 1985; 56(3):443-9. Ex. 2117 Tilly, H, et al., Low-dose cytosine arabinoside treatment for acute 50% nonlymphocytic leukemia in elderly patients, *Cancer* 1985; 55(8):1633-6. Ex. 2118. Cheson, BD, et al., A critical appraisal of low-dose cytosine arabinoside in 16-32% patients with acute non-lymphocytic leukemia and myelodysplastic (summarizing syndromes, *J Clin Oncol* 1986; 4(12):1857-64. Ex. 2119 articles)

173. Based on this, the POSA would conclude that any remission effect seen in the Jurcic research was due to the cytarabine – not the ²²⁵Ac-antibody construct – because no improvements were shown over previous studies using that drug alone. In fact, because Jurcic’s results were lower than most other studies using cytarabine alone, the POSA would have had no reason to attribute any benefit to the ²²⁵Ac-antibody construct. With this, the POSA would have understood the ²²⁵Ac-antibody treatment – and the entire year of treatment with spironolactone – to not only be a waste of time and resources, but also a completely unnecessary and inadvisable exposure of the patient to damaging radiation. Even considering the total number of remissions, including incomplete remissions, reported in Jurcic, the success rate was still only 28%, which falls within the range reported for cytarabine alone. This still suggests that the ²²⁵Ac-antibody construct had little or no effect – or even negative effect – on treatment. But again, since Jurcic’s treatment requires exposure of the patient to damaging radiation and the risk of damaging toxicity, the POSA would not have found Jurcic’s treatment regime instructive on improving or modifying the treatments discussed in the remaining references discussed by Dr. Zalutsky.

174. Also, since the POSA would have had no basis to credit the ^{225}Ac -antibody construct with any benefit, that POSA would not have found the dose information in Jurcic at all helpful or instructive as to what doses to use with other treatment modalities. To the contrary, as the addition of the ^{225}Ac -antibody construct showed no demonstrable benefit over cytarabine alone, the POSA would have – at best – found the doses in Jurcic uninformative. Therefore, Jurcic does not include any guidance on an effective dose for ^{225}Ac or for ^{225}Ac -PSMA-I&T as required by the '901 Patent claims because its data does not show that the ^{225}Ac -lintuzumab compound had any effect and, even if it did, it would not provide guidance on the completely different compound claimed in the '901 Patent. Jurcic would not give a POSA a reasonable expectation of success in creating the '901 Patent invention either alone or in combination with the other prior art.

F. Kratochwil

175. The Kratochwil reference is a simple abstract providing follow up information on the tolerability of ^{225}Ac -DOTATOC. (Ex. 1031.001.) For this construct, Kratochwil reports an MTD of 40 MBq, and fractional doses of MBq every 4 months and 18.5 MBq every 2 months. (Ex. 1031.002.) These doses only show how much radiation the patient can receive without developing intolerable side effects – they do not disclose or suggest the efficacious or effective doses for the discussed construct. Therefore, this abstract would have no bearing on the doses a POSA would have chosen as effective. Instead, the POSA would have readily understood that the effective or efficacious doses may be lower or higher than that put forth in the Abstract as the MTD. My understanding is that Dr. Abergel agreed to this understanding:

[Q.] When determining the proper dose, there's a trade-off between efficacy and tolerability.

A. That's correct.

Q. And the reason is because you want to increase the dose to the point where it's efficacious, but you're getting it closer to that limit of tolerability, correct?

A. That's correct.

Q. But the two doses of efficacy and tolerability are not the same, correct?

A. That's correct.

MS. CIPRIANO: Objection; incomplete hypothetical.

Q. The point of efficacy could be much lower or much higher than the tolerable dose.

A. That's correct.

Q. So when somebody determines what the maximum tolerable dose is, it doesn't tell you what the efficacious or effective dose is, correct?

A. That's correct.

Ex. 2080.0044, Abergel TR. 169:230170:17.

176. Kratochwil only referred to the numbers he provided as the MTD or tolerated doses. He never provides any numbers for an effective or efficacious dose. To the extent that Dr. Zalutsky relies on any implication that Kratochwil found efficacy in the study, a POSA would be at a loss as to what dosages provided efficacy. A MTD study requires providing different doses of a compound to different patients and determining whether the side effects are intolerable. This necessarily requires exceeding what is eventually determined to be the MTD. Therefore, if any efficacy was found, it could have been at doses higher than the MTD. In fact, it is more likely to be seen above the MTD since efficacy is more likely at higher doses.

177. Additionally, like Miederer 2008a, which also used DOTATOC, Kratochwil's experiment relates to a molecule directed to somatostatin receptors on neuroendocrine tumors – not to PSMA on PSMA-expressing cancers. Because DOTATOC has a different structure from the constructs claimed in the '901 Patent, binds a different target, and involves a different cancer type, this reference provides no insight as to the tolerable, effective, or efficacious doses that might relate to the patented invention. Additionally, Kratochwil's DOTATOC ligand is significantly different than Weineisen 2015's PSMA I&T ligand and Jurcic's lintuzumab ligand,

and is used to treat yet another different disease – neuroendocrine tumors compared to Weineisen’s metastatic prostate cancer and Jurcic’s acute myeloid leukemia. As established above, even though a construct may use the same radionuclide, differences in the ligand significantly affect properties and performance. As the POSA would know this, the POSA would not have adopted the dose from Kratochwil’s neuroendocrine tumor treatment for use with a very different radioligand in the treatment of a very different cancer.

178. Kratochwil's administered activity cannot be extrapolated to ^{225}Ac -PSMA-I&T because the two agents bind different targets, expressed at different densities in different tissues.

179. The MIRD Pamphlet that Dr. Zalutsky relies on as authority for his dosimetry argument (Zalutsky Decl. ¶97), makes target properties, not the radionuclide, the controlling variables. Cell killing is highly sensitive to cancer cell characteristics (e.g., cell geometry, nuclear size, DNA distribution, and spatial arrangement of target to the nuclei (Ex. 1017.004)) and to specific ligand and target features (e.g., cellular targeting kinetics, binding site distribution per cell, ligand affinity, and internalization (Ex. 1017.013)). MIRD accordingly prescribes a target-driven program starting with determining "the number of sites per cell and fraction of cells expressing target", "distribution of binding sites per cell", affinity, internalization, and "median lethal dose in targeted versus nontargeted cells" before progressing to human studies. (Ex. 1017.013). Kratochwil determined MTD for ^{225}Ac -DOTATOC, not MTD or effectiveness for other, unrelated targets.

180. PSMA and SST are not comparable. SSTRs occur at high density in neuroendocrine tumors, (Ex. 1038.019,) whereas PSMA density increases in prostate cancer (Ex. 1038.017). ^{68}Ga -DOTATOC shows high uptake in healthy liver, adrenals, and kidney, and

highest of all in spleen. Ex. 2143, Boy, et al. “⁶⁸Ga-DOTATOC PET/CT and somatostatin receptor (sst1–sst5) expression in normal human tissue: correlation of sst2 mRNA and SUV_{max}” Eur. J. Nucl. Med. Mol. Imaging Vol. 38, no. 7, pgs 1224–1236 (2011). ⁶⁸Ga-PSMA I&T shows low uptake in liver, spleen and small intestine but high uptake in kidney and salivary glands. (Ex. 1028.005-006).

181. Different target densities result in different amounts of administered activity reaching dose-limiting organs, resulting in different MTDs and efficacies between SSTR-directed peptides and a PSMA-directed ligands. As a specific case in point, the Kratochwil 2016 paper (discussed above) and the '901 Patent report xerostomia (dry mouth) as the dose-limiting toxicity and the salivary glands as the dose-limiting organ. Ex. 1001.017; Ex. 2096.026, Table 5; Ex. 1045.002. But Kratochwil only mentions chronic kidney toxicity. (Ex. 1031.001.) This is because DOTATOC, an SSTR-targeting ligand, has different qualitative and quantitative effects than a PSMA-targeting ligand. Exs. 1031.001; 1001.017; 1044.072. And these differences are highlighted by the difference in toxicity here – chronic kidney toxicity with Kratochwil’s DOTATOC construct vs. minor salivary gland toxicity with the patented constructs. Just as Kratochwil could not have indicated the importance of xerostomia to the patented PSMA-based invention, it would have offered no relevant guidance regarding its effective dose.

182. Petitioner's own references show the extrapolation fails even *within* the somatostatin class. Changing the ligand from DOTATOC to DOTANOC shifted SSTR subtype affinity and produced "higher uptake in normal tissues," increasing the whole-body dose. (Ex. 1038.020). If affinity changes within a single receptor family prevent dose extrapolation, Petitioner cannot bridge SSTR to PSMA.

IX. THE CHALLENGED CLAIMS OF THE '901 PATENT ARE NOT RENDERED OBVIOUS BY THE ASSERTED PRIOR ART

183. I disagree with Dr. Zalutsky's assertion that the prior art he describes renders the '901 Patent claims obvious. Dr. Zalutsky supports his contention by repeatedly stating that the POSA would have been motivated to improve the technology of radiotherapeutics. But the motivation to do something to improve the field is always present as it is the primary function of science. The more relevant question is whether Dr. Zalutsky's evidence shows that the POSA would have been motivated to improve the technology in the manner claimed in the '901 Patent with the results described in the '901 Patent. I believe that the answer is no.

184. First, I do not agree that Dr. Zalutsky has demonstrated his assertion that the POSA would have been motivated to select PSMA I&T over many other potential PSMA-targeting ligands. While Dr. Zalutsky has cited papers using PSMA I&T, such as Weineisen 2015 and Chatalic, he has also cited and considered papers using other small molecules, such as Weineisen 2014 (Ex. 1027), Demirci (Ex. 1007), Foss (Ex. 1008), Hillier 2011 (Ex. 1009), and Hillier 2012 (Ex. 1010). And he has also cited papers using antibodies rather than small molecules, such as Jurcic, McDevitt 2001 (Ex. 1013), McDevitt 2002 (Ex. 1014), and Banerjee (Ex. 1038). And he has argued that these methods were also effective. He has also acknowledged that, at the time of the invention, other researchers were using many other scaffolds for binding PSMA such as "thiols, carbamates, phosphoramidates, phosphinic acids, and ureas." (Ex. 2138.001.)

Q. So it says here, several scaffolds have been used in the synthesis of small molecule PSMA inhibitors. These include thiols, carbamates, phosphoramidates, phosphinic acids, and ureas, right? So at that time, a person of ordinary skill, they were looking at a number of these different things in order to synthesize small PSMA molecule inhibitors. Is that right?

A. Some people were looking in this direction, and others were looking in other directions.

(Ex. 2139.011, Zalusky Tr. 34:22-35:7)

185. I also know that leading researchers like Scott Tagawa have been studying the use of antibody J591 in radiopharmaceuticals since 2010, and they apparently still believe this antibody to be a viable option in radiopharmaceuticals. See Ex. 2175, Tagawa, ST, et al., Anti-prostate-specific membrane antigen-based radioimmunotherapy for prostate cancer, *Cancer* 2010;116(4 Suppl):1075-83; Ex. 2177, Tagawa, ST, et al., Prostate- Specific Membrane Antigen-Targeting Alpha Emitter via Antibody Delivery for Metastatic Castration-Resistant Prostate Cancer: A Phase I Dose-Escalation Study of 225Ac-J591, *J Clin Oncol* 2023;JCO2300573. Even if we accept that the POSA would have chosen PSMA as the target for Dr. Zalutsky's "improved" radioligand, Dr. Zalutsky has not explained why that POSA would have specifically chosen PSMA I&T from among the litany of small molecule and antibody options that Dr. Zalutsky himself listed and considered. For example, Hillier 2011 (Ex. 1009) and Hillier 2012 (1010) report that MIP-1375 and MIP-1466 both inhibited tumor growth at "clinically relevant" doses. (Ex. 1009.002; Ex. 1010.002). And the J591 antibody for PSMA has been able to recognize PSMA with nearly 100% specificity and sensitivity. (Ex. 1039.002.)

186. Dr. Zalutsky does not demonstrate that PSMA I&T was better than these small molecule and antibody alternatives. He argues that PSMA I&T was approved for use in human studies, and that such approval is "reserved for only the safest and most promising therapies." (Zalutsky Decl. ¶77.) But this does not differentiate PSMA I&T from PSMA antibodies that were also being tested in humans. *See* Bone marrow recovery and subsequent chemotherapy

following radiolabeled anti-prostate-specific membrane antigen monoclonal antibody j591 in men with metastatic castration-resistant prostate cancer, *Front Oncol* 2013, 26:3:214.

187. Dr. Zalutsky's reference to Chatalic does nothing to support his claim since there were – and still are – many researchers using small molecules and antibodies in PSMA studies. Although Dr. Zalutsky repeats his mantra that Chatalic showed PSMA I&T to be “safe and effective,” Chatalic did nothing of the sort since Chatalic did not report any toxicology results and, as explained above, uses an extremely high dose of ^{213}Bi – 5 MBq on a mouse. (Ex. 1006.002) This indicates to the POSA that alpha-emitting PSMA I&T radiopharmaceuticals must be used at very high concentrations to achieve the effect that she demonstrated in her manuscript. Chatalic then determined the biodistribution of the radionuclide and DNA damage to the tumors by sacrificing the animals to collect the tumors at 1 hour and 24 hours – there is no indication that the animals would have survived this high dose beyond that timeline.

188. What's more, Chatalic was not looking only at PSMA I&T. Chatalic also evaluated the PSMA nanobody JVZ-008, which was found equivalent. So the POSA would have been equally directed to JVZ-008 instead of PSMA I&T.

189. Second, but equally important, Dr. Zalutsky does not explain why the POSA would have been compelled to combine PSMA I&T with ^{225}Ac when everyone else at the time seemed to be actively avoiding ^{225}Ac . The Miederer 2008 papers (Ex. 1015 & 1030) show that ^{225}Ac could be acquired from multiple places, including Oak Ridge National Laboratory (ORNL) in Oak Ridge, TN, and the Institute for Transuranium Elements in Karlsruhe, Germany (Ex. 1030.002). Despite this availability, and although Weineisen 2014 mentioned ^{225}Ac , Weineisen did not use ^{225}Ac in 2014 or 2015. And instead of using ^{225}Ac , Chatalic used ^{213}Bi in her study in

2016 in an apparent attempt to circumvent the recoiling issue and production of multiple generations of alpha-emitting daughter nuclides. The fact is that the community was still concerned about the Ac daughter nuclides being released and the subsequent toxicities, and these references were trying to work around this significant issue.

190. Ironically, Dr. Zalutsky argues the significance of Weineisen 2015's use of ^{177}Lu -PSMA- I&T in patients by noting that "human studies are reserved for only the safest and most promising therapies." (Zalutsky Decl. ¶77.) I agree. But that means that Weineisen demonstrates that the safest and most promising radionuclide was ^{177}Lu , not ^{225}Ac .

191. Dr. Zalutsky also relies on Weineisen 2015's report of the high accumulation of ^{177}Lu - PSMA-I&T in target cells to argue the benefits of the construct. But Weineisen 2015 pointed out that this high PSMA-I&T accumulation was only for ^{177}Lu , and not for the other studied radionuclide, ^{68}Ga . This would tell the POSA that using a different radionuclide might decrease the accumulation. Counter to Dr. Zalutsky's assertion that it was known that radionuclides are interchangeable, Weineisen 2015 shows that they are not. Specifically, Weineisen 2015 shows that changing the radionuclide could be detrimental to the function, performance, and properties of the molecule. And Dr. Zalutsky's reference to the DOTATOC study by Miederer 2008a does not counter this point because it is a wholly different ligand.

192. Dr. Zalutsky attempts to make the secondary alpha emissions from recoiling ^{225}Ac daughter nuclides a positive motivating factor to use ^{225}Ac – as though that would undoubtedly increase cytotoxicity. But the POSA understood that once the first alpha particle was released, the recoil would be enough to push the daughter nuclides free of the construct, and

these free daughter nuclides would be free to leave the tumor site and redistribute to and damage healthy organs. de Kruijff, Ex. 1043.003.

193. But the POSA at the time understood that these freely roaming daughter nuclides would potentially increase side effects by allowing them to pool in healthy organs and cause irreparable damage. Ex. 1030.003; Schwartz et al., “Renal uptake of bismuth-213 and its contribution to kidney radiation dose following administration of actinium-225-labeled antibody,” *Phys. Med. Biol.*, vol. 56, no. 3, 721-733 (2011); Ex. 2161, Jaggi et al., “Efforts to control the errant products of a targeted in vivo generator,” *Cancer Res.*, vol. 65, no. 11, pgs. 4888-4895 (2005). The POSA, therefore, would have been concerned that replacing ^{213}Bi with ^{225}Ac in Chatalic’s construct would increase – not decrease – side effects and risk to the patient.

194. Dr. Zalutsky’s argument seems to be that the POSA would have known that ^{225}Ac could be combined with PSMA I&T. But I do not understand that to be the standard for establishing obviousness – any two components could be combined. The correct inquiry – as I understand it – is whether there was a motivation or suggestion to combine these specific components in the specifically claimed way to treat the specifically claimed disease at the specifically claimed dose. There was not. ^{225}Ac was considered dangerous. The researchers Dr. Zalutsky cites understood this. And their intentional avoidance of ^{225}Ac despite knowledge of it as a “therapeutic M3+- radiometal” confirms the lack of motivation to use ^{225}Ac together with PSMA I&T in the specific treatment and dose claimed in the ’901 Patent.

195. My understanding is that a patent or claim is not rendered obvious just because POSAs were aware of the components and could have combined them. This is especially true in this case because there are nearly an infinite number of possible molecules, not just PSMA I&T, and a

substantial number of radionuclides. I have already listed several references that Dr. Zalutsky cited that were looking at different molecules other than PSMA I&T: Weineisen 2014 (Ex. 1027), Demirci (Ex. 1007), Foss (Ex. 1008), Hillier 2011 (Ex. 1009), and Hillier 2012 (Ex. 1010). Also, in Dr. Zalutsky's 2016 paper he listed several molecular families that were the basis of PSMA-targeting molecules: "Several scaffolds have been used in the synthesis of small molecule PSMA inhibitors; these include thiols, carbamates, phosphoramidates, phosphinic acids, and ureas." Ex. 2140 (Prostate-Specific Membrane Antigen–Targeted Radiohalogenated PET and Therapeutic Agents for Prostate Cancer) Dr. Zalutsky confirmed this list and even suggested that there were other avenues as well:

Q. So it says here, several scaffolds have been used in the synthesis of small molecule PSMA inhibitors. These include thiols, carbamates, phosphoramidates, phosphinic acids, and ureas, right?

So at that time, a person of ordinary skill, they were looking at a number of these different things in order to synthesize small PSMA molecule inhibitors. Is that right?

A. Some people were looking in this direction, and others were looking in other directions.

Q. And so my question is, these different things, the thiols, the carbamates, the phosphoramidates, the phosphinic acids, and ureas were all things that a person of ordinary skill in the art was using at the time to make small-molecule PSMA inhibitors, right?

A. That's correct.

(Ex. 2139.011, Zalutsky Tr. 34:22-35:7 35:19-25)

196. To put this in perspective, each of these categories can represent dozens to thousands of molecules. Multiply this by the various combinations with radionuclides. A quick list with both beta and alpha emitters: ^{177}Lu , ^{90}Y , ^{68}Ga , ^{47}Sc , ^{149}Tb , ^{161}Tb , ^{111}In , ^{153}Sm , ^{166}Ho , ^{165}Dy , ^{169}Er – but these are just the radiometals, Dr. Zalutsky has spent the last decade arguing in favor of radiohalogens, which would build up the list even further. Dr. Zalutsky has provided no reason

to go with any particular molecule or any particular radionuclide other than the foregone assumption that the POSA would want what is found in the patent.

197. Third, Dr. Zalutsky takes a non-clinical, overly simplistic approach to determining dose. He claims that the POSA would just look at the literature and select a dose based on the amount of radioligand that needs to get to the target site to achieve therapeutic effect. (Zalutsky Decl. ¶87.) But Dr. Zalutsky skips a step. As explained before, a lot of factors go into the difference between the administered activity (what Dr. Zalutsky would have the physician administer) and the absorbed dose at the tumor site (which decides actual efficacy). These include the affinity of the radioligand for the target, the tendency of the radioligand to degrade, the ability of the body to clear the radioligand, the number of binding sites on the tumor cells, and the resistance of the tumor to treatment, just to name a few. Given so many unpredictable variables, the administered activity must be determined empirically. And since every radiopharmaceutical will differ in its ability to be absorbed at the site, a POSA cannot rely on the dosing range of one pharmaceutical for guidance on an entirely different one.

198. At his deposition, Dr. Zalutsky recognized that the absorbed dose differs from the administered activity and is dependent on factors like the delivery system:

Q Okay, and so the administered activity is different from the absorbed dose?

A **Absolutely.**

Q And so you may give a certain amount for the administered activity, and the absorbed dose could be much, much lower or nothing, depending on where you're looking.

A **Yes, it's also different units, so.**

Q The absorbed dose that you will get for a particular tissue can be influenced by the delivery system such as the molecule that the radiation is attached to, correct?

Mr. Murphy: Object to form.

The Witness: Correct.

Q You could administer the same activity with two different molecules but get different absorbed doses at a particular tissue, correct?

Mr. Murphy: Objection; form.

The Witness: That's correct.

(Ex. 2139.009, .010, Zalusky Tr. 29:10-17; 30:16-21; 30:23-31:3)

199. Sgouros (Ex. 1017) does not support Dr. Zalutsky's contentions. Sgouros was not intended to magically provide the administered activity value as Dr. Zalutsky implies. The publication teaches that determining the administered activity is difficult because of "complex activity and tissue geometries." (Ex. 1017.009.) Sgouros admits that "[d]etermining the activity distribution [] remains difficult." (Ex. 1017.010.)

200. To the extent that Dr. Zalutsky implies that Sgouros (Ex. 1017.002) provides any dose guidance at all – let alone for all uses of the listed radionuclides – I disagree. While this review article may provide a table of examples from the literature, the reference does not provide, for example, any guidance as to how to extrapolate those examples out of their own context, or provide any conclusions as to resulting efficacy, effectiveness, or toxicity from such an exercise. Also, obviously, the doses for one pharmaceutical or illness cannot be applied across the board to different pharmaceuticals and different illnesses. This is because the appropriate dose for each pharmaceutical and each illness will involve different factors that affect internal delivery of the pharmaceutical and absorbance at the tumor site. In particular, the one example of ²²⁵Ac on the second page of Sgouros involves a treatment for acute myelogenous leukemia (AML) targeting the CD33 protein. AML is a liquid tumor. Therefore, the dosing used in that example for a pharmaceutical that binds a completely different target (CD33, not PSMA) and a

cancer that is qualitatively different (liquid, not solid), would provide no guidance for the solid PSMA- expressing tumors described in Weineisen 2015 and in the '901 Patent.

201. Similarly, the tolerated doses reported in Kratochwil (Ex. 1031) relate to a DOTATOC construct for the treatment of neuroendocrine tumor, not prostate cancer, and not a PSMA expressing cancer. (Ex. 1031.) Analogous to Sgouros targeting CD33 for the treatment of a different disease, this DOTATOC construct targets somatostatin receptors for treatment of yet another different disease. So like in Sgouros, the properties and performance of this molecule will also differ from the constructs in Weineisen 2015 and the '901 Patent claims in numerous ways – like the affinity for the target, how much of the target is expressed on the cells, and the clearance rate after administration. So this reference also cannot be used to estimate the dose required for efficacy or effectiveness in the treatment of PSMA expressing cancers using a completely different construct. A POSA would not expect the mixing and matching of the elements of these radiopharmaceuticals to succeed.

202. Jurcic similarly provides no guidance as to dosing. Jurcic relates to an antibody rather than a small molecule, binds to a different target, and is a treatment for an entirely different disease (AML). And to make matters worse, a comparison of Jurcic to previous studies shows no demonstrable benefit from the Jurcic dose of the antibody construct compared to the co-administered drug used alone. So any dose information provided in Jurcic is not relevant. And in fact, the POSA would have seen Jurcic, at best, as what not to do.

B. The Challenged Claims of the '901 Patent Are Not Obvious

203. I have reviewed Dr. Zalutsky's prior art and his analysis of the claims and disagree with his conclusion that the claims are obvious. I have been informed that for claims to

be obvious, every element of the claim must be found in the prior art and there must be some motivation to combine those references with a reasonable expectation of success. I do not believe that Dr. Zalutsky's explanations meet this standard.

1. Claim 1

204. I do not believe that Dr. Zalutsky has shown that Claim 1 is obvious.

205. Dr. Zalutsky provides no reason or motivation to add ^{225}Ac to the PSMA I&T ligand in light of the understanding at the time that ^{225}Ac has a recoil effect that would force its release from the ligand. This would have let the daughter nuclides loose in the patient's body to indiscriminately emit three more alpha particles and two more beta particles which would not be targeted to tumor cells, thus increasing irreparable damage to healthy tissue or organs. The POSA would have understood that this would prevent Weineisen 2015's PSMA I&T from functioning as intended because, according to Dr. Zalutsky, PSMA I&T "was specifically designed to target PSMA-expressing cells." But as ^{225}Ac would allow the daughter nuclides to wander through the body unchecked, these daughter nuclides would not target the PSMA-expressing cells. Instead, they would cause damage to whichever healthy tissue, organs, or cells are nearby after relocating. And these daughter nuclides were known to pool in the bone or kidney, so they would be most likely to cause significant damage in those organs.

206. Dr. Zalutsky relies on Weineisen 2015 (Ex. 1028) as disclosing PSMA I&T even though Weineisen uses ^{177}Lu and does not suggest ^{225}Ac .

207. Ostensibly to support his reliance on Weineisen 2015, Dr. Zalutsky also notes that Chatalic (Ex. 1006) describes PSMA I&T as "promising." I disagree. Chatalic used a high dose of the radiopharmaceutical to achieve the reported effect, which likely would have resulted in

significant toxicity in humans. Chatalic also co-administered 10 nmol 2-PMPA together with the reported ^{213}Bi -PSMA-I&T. This was co-administered to provide renal protection, indicating the expected nephrotoxicity from such a high dose of ^{213}Bi .

208. I also disagree because Chatalic tested both PSMA I&T and the nanobody JVZ-008 and reported uptake for both (5.75 ± 2.70 %ID/g and 2.68 ± 0.56 %ID/g) along with comparable tumor-to-kidney ratios. Chatalic did not distinguish JVZ-008 from PSMA I&T for additional study. Dr. Abergel, the expert of the previous petitioner against this patent, acknowledged this at her deposition:

209. Thus, it is my opinion that Chatalic at best suggested JVZ-008 and PSMA I&T with equal force and did not provide any reason to select one over the other.

210. Dr. Zalutsky relies on Miederer 2008a (Ex. 1015) as allegedly teaching the interchangeability of ^{225}Ac for ^{177}Lu . This is not convincing. Miederer 2008a used an entirely different construct, DOTATOC, which was directed to a completely different disease, targeted a completely different receptor, and had a very different structure than PSMA I&T or any other ligand claimed in the '901 Patent. And the POSA would not have read Miederer 2008a as suggesting that ^{177}Lu and ^{225}Ac are interchangeable, as suggested by Dr. Zalutsky – particularly in light of the teaching in Weineisen 2014 and Weineisen 2015 that changing the radionuclide would result in dramatic changes in the binding affinity and uptake.

211. That DOTATOC would work for both ^{225}Ac and ^{177}Lu is immaterial to whether both would work for the entirely different molecule PSMA I&T because the toxicity profile is completely different for PSMA than it is for the somatostatin receptors targeted by DOTATOC. Also, as Weineisen 2014/2015 showed, even small changes in a molecule can increase its

sensitivity to different nuclides, resulting in very different efficacies. Switching to an entirely different molecule – DOTATOC to PSMA I&T – is more than a small change.

212. The same applies to Dr. Zalutsky's reliance on the Kratochwil reference (Ex. 1031). This reference was also directed to the DOTATOC ligand. Dr. Zalutsky incorrectly claims that there was an "overlap" between the Kratochwil tolerated doses for DOTATOC and the doses recited in the '901 Patent for PSMA targeting constructs. As an experienced clinician, I would not consider this an "overlap" because they are two completely different radiopharmaceuticals for treating completely different diseases. The POSA would not rely on the recommended dose of one drug in selecting a dose for a completely different drug. The dose for a pharmaceutical must be based on information about the specific pharmaceutical, not an unrelated second pharmaceutical, and especially not an unrelated second pharmaceutical indicated for treatment of a completely different disease or illness.

213. Dr. Zalutsky considers the dosing question superficially by focusing on the administered activity. And he concludes that the dose for DOTATOC in Kratochwil (Ex. 1031) would simply be applied to the invention in the '901 Patent. But the administered activity must be based on the expected absorbed dose, which is the amount the tumor and normal tissue are expected to absorb. The absorbed dose is based on the characteristics of the radiopharmaceutical and the disease being treated, which differ from one construct and disease to another. The POSA would not conclude that the dose from the ^{225}Ac -DOTATOC would have the same tumor and normal tissue uptake as a ^{225}Ac -PSMA I&T. Quite the contrary, the POSA would expect the uptake to be different. Therefore, the POSA would not have determined the dose in the manner suggested by Dr. Zalutsky. Instead, the POSA would have to have determined administered

activity empirically, with a starting point based on the specific characteristics of the construct and the tumor being targeted.

214. As Miederer 2008a and Kratochwil concern different radiopharmaceuticals – i.e., those that bind somatostatin receptors, not PSMA – these references fail to provide any guidance on the dose required for efficacy or effectiveness in a radiopharmaceutical that binds PSMA.

215. For these reasons, I do not agree with Dr. Zalutsky's analysis and conclusions. And I do not believe that the POSA would have combined Weineisen 2015 (PSMA I&T) with Kratochwil (²²⁵Ac) as suggested by Dr. Zalutsky and Curium.

2. Claim 2

216. I have been informed that Claim 2 is a dependent claim and depends from Claim 1, so it includes all the elements of Claim 1 and further narrows Claim 1 by adding new requirements or selectively narrowing the requirements in Claim 1.

217. Claim 2 narrows the selection of formulae from Claim 1 and includes, among other things, PSMA I&T. Because Claim 1 is incorporated into Claim 2, my explanation for why Claim 1 is not obvious applies to Claim 2 as well.

3. Claims 4-5

218. I have been informed that Claims 4 and 5 each depend from Claim 1, so they include all the elements of Claim 1 and further narrow Claim 1 by adding new requirements or selectively narrowing the requirements in Claim 1.

219. Claims 4 and 5 narrow the selection of cancers to a specific list in Claim 4, or to disseminated cancers in Claim 5. Because Claim 1 is incorporated into Claims 4 and 5, my explanation for why Claim 1 is not obvious applies to Claims 4 and 5 as well.

4. *Claims 6-7*

220. I have been informed that Claims 6 and 7 are dependent claims depending from Claim 4 which depends from Claim 1, so they include all the elements of Claims 1 and 4 and further narrow the elements in these Claims by adding new requirements or selectively narrowing the requirements in Claims 1 and 4.

221. Claims 6 and 7 narrow the selection of cancers in Claim 4 to the specific cancers of prostate cancer in Claim 6 and breast cancer in Claim 7. Because Claim 1 is incorporated into Claims 6 and 7, my explanation for why Claim 1 is not obvious applies to Claims 6 and 7 as well.

5. *Claims 8-9*

222. I have been informed that Claims 8 and 9 are dependent claims depending from Claim 1, so they include all the elements of Claim 1 and further narrow the elements in these Claims by adding new requirements or selectively narrowing the requirements in Claim 1.

223. Claims 8 and 9 narrow the dose ranges based on body weight from Claim 1 to 30-250 kBq/kg of body weight in Claim 8, and 50-200 kBq/kg of body weight in Claim 9. Because Claim 1 is incorporated into Claims 8 and 9, my explanation for why Claim 1 is not obvious applies to Claims 8 and 9 as well. Specifically, I reiterate my explanation that the POSA would not base the dose of a pharmaceutical on the dose of another pharmaceutical with a very different design, and especially not one which binds to a different target molecule, and treats an unrelated

and completely different disease. As I explain throughout this Declaration, different drugs have different biodistributions and different toxicities within the human body, and these differences become widened even further when differences in the treated diseases are taken into account. For these reasons, those of ordinary skill in the art would not apply dosages either across diseases, or across drugs. And in this case, those of ordinary skill in the art would not have applied the dose of an antibody-based conjugate used to treat acute myeloid leukemia (from Jurcic) or the dose of a DOTATOC-based conjugate to treat neuroendocrine tumors (from Kratochwil) to a treatment for prostate cancer (from Weineisen 2015).

224. I note that Dr. Zalutsky illustrates his misconception when he says that “a POSA would have been motivated to use doses of ^{225}Ac that have been previously shown to be safe and effective.” However, when discussing a targeted α therapy like the one recited in the ’901 Patent, a clinician does not “use a dose of ^{225}Ac .” The pharmaceutical is not just ^{225}Ac . It has a complex molecular structure designed specifically to direct it to a target whose characteristics are also taken into account to determine the appropriate efficacious or effective dose. Dr. Zalutsky is again mistakenly focusing on the administered activity and treating all ^{225}Ac compounds the same rather than focusing on the calculated absorbance which dictates what the administered activity should be.

225. Dr. Zalutsky also mistakenly relies on Jurcic, asserting that the POSA would have been motivated to use Jurcic’s dose for the PSMA I&T ligand disclosed in Weineisen 2015. This fails on several fronts. First, as explained above, the Jurcic reference did not show that the reported dose was safe and effective because Jurcic’s design cannot show that the radioimmunoconjugate added anything to what cytarabine achieved on its own. But also, as I explained above with respect to Sgouros, the POSA would not rely on an antibody treatment for

leukemia as guidance for a PSMA-targeting treatment for prostate cancer. The diseases and drugs are too different to reliably extrapolate the dose information from one to the other.

6. Claims 10-11

226. I have been informed that Claim 10 is dependent on Claim 1 and that Claim 11 is dependent on Claim 10. Accordingly, Claims 10 and 11 each incorporate all of the limitations of Claim 1. Claim 10 further narrows Claim 1 by adding additional limitations and/or narrowing certain limitations of Claim 1, and Claim 11 further narrows Claim 10 by adding additional limitations and/or further narrowing the limitations of Claim 10.

227. Claims 10 and 11 narrow the dose ranges based on unitary dosages in Claim 1 to 4-25 MBq in Claim 10, and 5-20 MBq in Claim 11. Because Claim 1 is incorporated into Claims 10 and 11, my explanation for why Claim 1 is not obvious applies to Claims 10 and 11 as well. Specifically, I reiterate my explanation that the POSA would not base the dose of a pharmaceutical on the dose of another pharmaceutical with a very different molecular design, especially one which binds to a completely different target molecule, and treats an unrelated and completely different disease. Therefore, the POSA would not have been motivated to use the doses for DOTATOC allegedly described in Kratochwil (Ex. 1031) for the PSMA I&T construct described in Weineisen 2015 (Ex. 1028).

7. Claims 12 and 13

228. I have been informed that Claims 12 and 13 are dependent on Claims 8 and 10, respectively, which are further dependent on Claim 1, so Claim 12 includes all the elements of Claims 1 and 8 and Claim 13 includes all the elements of Claims 1 and 10 and they further narrow the elements in these Claims by adding new requirements or selectively narrowing the requirements.

229. Claims 12 and 13 introduce the requirement that the dosage be repeated every 15-90 days. Dr. Zalutsky relies on Kratochwil (Ex. 1031) as allegedly disclosing this feature. But I repeat my explanation that a POSA would not rely on a reference like Kratochwil – which relates to the DOTATOC somatostatin binder for treating neuroendocrine tumors – to determine the dosing or treatment regimen for a completely different drug, binding to a completely different target, to treat a completely different disease. For example, the POSA would not have applied Kratochwil’s dosage of a DOTATOC construct for the treatment of neuroendocrine tumors to the PSMA I&T construct for treating the very different prostate cancer disclosed in Weineisen 2015 (Ex. 1028).

230. Specifically, I reiterate my explanation that the POSA would not base the dose of a pharmaceutical on the dose of another pharmaceutical with a very different molecular design, especially one which binds to a completely different target molecule and treats an unrelated and completely different disease. Therefore, the POSA would not have been motivated to use the doses allegedly described in Kratochwil (Ex. 1031) for the PSMA I&T construct described in Weineisen 2015 (Ex. 1028).

C. A POSA Would Have No Motivation to Combine Dr. Zalutsky’s References

231. For the reasons I state above, a POSA would have had no reason to combine Dr. Zalutsky’s diverse references to arrive at the invention of the ’901 Patent and certainly not with the results that the Patent provides. A POSA would not have necessarily expected the ²²⁵Ac of the Kratochwil reference (Ex. 1031) to work with the PSMA I&T of Weineisen 2015 (Ex. 1028) because the DOTATOC and PSMA I&T ligands are completely different. They have unrelated structures designed to recognize different receptors on different cells for different cancers. DOTATOC is a somatostatin analog designed to bind to somatostatin receptors to treat

neuroendocrine tumors. PSMA I&T is designed to bind to PSMA receptors to treat cancers other than neuroendocrine tumors.

232. As Dr. Zalutsky said in his Declaration, “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.” (Zalutsky Decl. ¶27.) This is because these elements come together to uniquely interact with a cancer to treat it. Changing any one will change the efficacy of treatment. The POSA would not expect that the components from one would necessarily work with the other. This is particularly true in light of Weineisen 2014/2015’s examples showing that slight modifications to the structure or changing the radionuclide can change the affinity and internalization of the radiopharmaceutical. The ^{225}Ac nuclide is chemically related to ^{177}Lu , but Ac^{3+} is substantially larger than Lu^{3+} , and a POSA would expect that size difference to have unknown effects on the binding of the PSMA I&T ligand. That Weineisen 2014 (Ex. 1027) mentions the use of ^{225}Ac in passing has far less of an influence than the fact that ^{225}Ac was not used or even mentioned in its follow up paper, Weineisen 2015.

233. At her deposition, Dr. Abergel, the expert that previously challenged the ’901 Patent, agreed that different molecules will have different characteristics resulting in a different relationship between the administered activity and the absorbed dose:

Q. When we're giving a radiotherapy, our goal, if I understand correctly, is to try to get as much of the dose to the tumor as possible, correct?

A. Correct.

Q. And so there's a difference between the administrative dose and the absorbed dose of the tumor because the radiation or the radiotherapeutic is lost in various ways. It breaks down. It leaves the chelator. It doesn't bind properly, for example. Correct?

A. That's correct.

Q. And also, what affects the difference is the ability of the -- if it's a targeted radiotherapeutic -- to bind to or be internalized.

A. That's correct.

Q. Because different therapeutics will have different rates of internalization and binding, correct?

A. That's correct.

Q. And different tumors might have different rates of internalization.

A. That's correct.

Q. So if you are looking at the internalization and binding to one tumor with one molecule, you can't assume that you're going to have the same internalization and binding with another molecule of another tumor, correct?

A. Correct.

Ex. 2080.0043, Abergel Tr. 167:7-168:7.

234. Therefore, the POSA also would not have expected the PSMA I&T to have the same administered activity as the DOTATOC to achieve efficacy because they are completely different molecules which would interact with their respective cancers in completely different ways. Dr. Zalutsky's claim in his declaration that they would be the same is purely hindsight.

235. The POSA also would not have used the teachings of Miederer 2008a (Ex. 1015) as motivation to combine Kratochwil and Weineisen 2015 because Miederer 2008a only compares the same ligand with different radionuclides. That different radionuclides were capable of use within DOTATOC has nothing to do with whether the radionuclides would have been useable within PSMA I&T. This is because, again, the toxicity profile and biodistribution would be different across radiopharmaceuticals and across treated diseases. These differences mean that the POSA would not have been able to predict treatment efficacy and effectiveness – including toxicity and biodistribution – of the hypothesized ²²⁵Ac-PSMA I&T radiopharmaceutical for any particular disease, including metastatic castrate-resistant prostate cancer (as disclosed in Weineisen 2015).

236. Additionally, the characteristics of a ligand, such as the affinity and internalization, happen on a cellular level when it interacts with its target. One ligand's method of interacting with its target (on a specific cancer, with a specific target, and a specific targeting moiety) has no bearing on another ligand (for a different cancer, with a different target, and a different targeting moiety). Dr. Zalutsky assumes too much about the way the biological system works – which is notoriously unpredictable.

237. The POSA also would not have relied on Chatalic (Ex. 1006) or Jurcic (Ex. 1011) to guide its decision to combine Kratochwil and Weineisen 2015, because Chatalic shows that the use of alpha emitters is questionable. Chatalic uses 5 MBq ^{213}Bi on a mouse, which is a very high administered activity, and fails to provide any assessment of toxicity and safety, or even survivability. As explained above, proportionally, it is far beyond what the '901 Patent uses, so Chatalic would have taught away from the dosage claimed by the Patent. It would also tell a POSA that large doses of alpha-emitters may be necessary to achieve efficacy. And since Chatalic provides no data or discussion of toxicity, safety, or survivability, the POSA would have been deterred from combining the ^{225}Ac from Kratochwil with Weineisen 2015's PSMA I&T because they would likely assume that, just as Weineisen 2014/2015 suggested, changing the radionuclide had detrimental effects on the efficacy requiring the large radiation dose. Meanwhile, a POSA would have recognized that Jurcic's combination of the ^{225}Ac antibody with LDAC performed no better than LDAC alone. This would further support the conclusion from Chatalic that large doses of alpha emitters were needed to get an effect.

238. Moreover, Jurcic also suffers from the problem that ^{225}Ac -lintuzumab, an antibody, was far too different from the small molecules in the other references to offer any guidance. Its cell interaction, internalization, and clearance from the body would be very

different resulting in different pharmacokinetics and pharmacodynamics. So a POSA would not rely on it to determine a dose.

D. Secondary Considerations Show that the '901 Patent is Non-obvious

239. I have been informed that objective factors or secondary considerations can also demonstrate that a patent is not obvious. These secondary considerations include:

- commercial success of a product due to the merits of the claimed invention;
- a long felt need for the solution provided by the claimed invention;
- unsuccessful attempts by others to find the solution provided by the claimed invention;
- copying of the claimed invention by others;
- unexpected and superior results from the claimed invention;
- acceptance by others of the claimed invention as shown by praise from others in the field or from the licensing of the claimed invention;
- teaching away from the conventional wisdom in the art at the time of the invention;

240. As I discussed in Section VII above, the '901 Patent, as embodied in the 2016 Kratochwil paper, has received considerable attention and praise. Figure 3 of the Kratochwil paper became iconic and was included in presentation after presentation as an example of a resounding success. It was included on the cover of the Journal of Nuclear Medicine and to this

day it is included in nearly every Review article on radiotherapy. Over the years, various authors have indicated how remarkable the results from the Kratochwil Paper are:

- “**First in-human** studies of PSMA-617 labeled with the long-lived α emitter ^{225}Ac ($t_{1/2}$ = 9.9 days) have shown remarkable therapeutic efficacy in PCa patients resistant to ^{177}Lu -PSMA or in whom treatment with β emitters was contraindicated because of diffuse red marrow infiltration.” Ex. 2125.002, Nonnekens, J., et al., ^{213}Bi -Labeled Prostate-Specific Membrane Antigen- Targeting Agents Induce DNA Double-StrandBreaks in Prostate Cancer Xenografts, *Canc. Bioth. Rad.* 2017, 32 (2), 67-73.
- “Katochwil et al. **first described a remarkable therapeutic effect** of ^{225}Ac - PSMA-617 in patients with late stage prostate cancer (Fig. 3).” Ex. 2127.003, Feuerecker, B., et al., Clinical Translation of Targeted α -Therapy: An Evolution or a Revolution? *J Nucl Med* 2023; 64:685–692
- “Since the **seminal** paper by Kratochwil *et al.* establishing its feasibility, ^{225}Ac -labeled PSMA ligands have gained momentum.” Ex. 2128.003, Lepareur, N., An overview of current phase 3 radiopharmaceutical therapy clinical trials, *Front. Med.* 2025; 12:1-6.
- “About TAT-targeting PSMA, the **surprising therapeutic effects** of ^{225}Ac]Ac-PSMA-617 were reported in clinical studies in 2016 (Fig. 11).” (x. 2130.010),Munekane, M, et al. Recent advances in the development of ^{225}Ac - and ^{211}At -labeled radioligands for radiotheranostics, *Anal. Sci.* 40:803-826.
- “Recent clinical trials using ^{225}Ac -labeled PSMA ligands (^{225}Ac]AcPSMA-617 or ^{225}Ac]Ac-PSMA-I&T) have achieved **remarkable therapeutic results.**” Ex. 2186.001, Alan-Selcuk, N. *et al.*, Clinical Experience with ^{225}Ac]Ac-PSMA Treatment in Patients with ^{177}Lu]Lu-PSMA–Refractory Metastatic Castration-Resistant Prostate Cancer, *J*

- “An incredible example of this occurred when β -resistance was overcome with α -particle therapy with Ac-225-PSMA ... led to complete tumor eradication and a return to normal levels of PSA.” Ex. 2187.009, Kauffman, N. et al., Intra-Arterial Delivery of Radiopharmaceuticals in Oncology: Current Trends and the Future of Alpha-Particle Therapeutics, *Pharmaceutics* 2023 Apr; 15(4):1138
- “A recent clinical study highlighted the ability of alpha-radiotherapy to overcome treatment resistance to beta-particle therapy, **prompting a paradigm shift.**” Ex. 2188.006, Okamoto, S. *et al.*, Clinical Perspectives of Theranostics, *Molecules* 2021 Apr; 26(8):2232
- “Despite previous chemotherapy exposure and extensive bone metastases,... side effects to bone marrow were **remarkably mild**”, and “the **impressive responses** in patients with end-stage disease **should spark major efforts** to perform further clinical studies”. Ex. 2189.002, Oyen, W.J. and de Bono, J.S., Targeted α -Based Treatment of Metastatic Castration-Resistant Prostate Cancer: Revolutionizing Systemic Radiotherapy?, *J Nucl Med* 2016 Dec; 57(12): 1838-1839

241. While researchers will often refer to their own work as “promising,” it is unusual to get such a large number of unrelated researchers all describing the work as “seminal” and “surprising.”

242. In fact, the Kratochwil paper is one of the most widely cited papers from the Journal of Nuclear Medicine and scored in the 98th percentile of all cited papers from that Journal. Given such widespread, high praise, I believe the invention claimed in the ‘901 Patent

has achieved the secondary consideration of “acceptance by others of the claimed invention as shown by praise from others in the field or from the licensing of the claimed invention.”

243. Of course, part of the reason for such high praise is that the results were surprisingly superior to what was expected. Dr. Kratochwil’s data showed that the tumor completely disappeared after three cycles of treatment over six months. Even more remarkable was that this treatment was so successful after the failure of treatment with a ^{177}Lu construct. Indeed, the treatment with the ^{177}Lu construct actually resulted in the cancer continuing to grow and spread. That another radiation treatment could be applied after such potent ^{177}Lu resistance and be as successful as the treatment recited in the ‘901 Patent, is truly remarkable and unprecedented. Even if we accept Dr. Zalutsky’s arguments of obviousness, there is nothing that suggests that there would be a complete remission of cancer throughout the entire body after only three or four treatments.

244. These results also taught away from the conventional wisdom at the time. The POSA understood that alpha emitters experience substantial recoil resulting in the release of daughter nuclides from the carrier molecule. These daughters would then roam freely within the body and damage healthy tissue, cells, and organs. This was clearly a significant concern in the community and literature at the time of the ‘901 Patent. Based on this understanding, the POSA would have expected the invention claimed in the ‘901 Patent to have considerable toxic side effects. However, it appears that in the treatment claimed in the ‘901 Patent invention, the potential toxicity associated with the redistribution of the ^{225}Ac daughter radionuclides in surrounding tissue, cells, and organs was not realized. This resulted in lower-than-expected toxicity. Given these remarkable and unexpected results which were contrary to the conventional wisdom at the time, I believe the invention claimed in the ‘901 Patent has achieved the

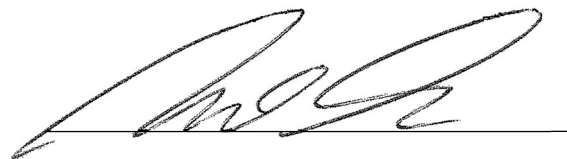
secondary considerations of “unexpected and superior results from the claimed invention” and “teaching away from the conventional wisdom in the art at the time of the invention.”

245. Moreover, as Dr. Zalutsky lays out in his Declaration, prostate cancer had long needed a better method of treatment. Up to the mid-2010s the diagnostic methods relied on blood tests and biopsy analysis with it being difficult to determine the proper course of treatment. (Zalutsky Decl. at 14-15.) Prior to 2014, therapies for prostate cancer were focused on androgen-deprivation therapy and chemotherapy, which, like most cancer treatments, had considerable and damaging side effects. (Zalutsky Decl. at 16.)

X. CONCLUSION

Based on the reasons given above, I disagree with Dr. Zalutsky’s opinion that any of the claims the ’901 Patent are obvious. I reserve my right to amend or supplement my Declaration in response to the Petitioner’s response or any additional opinions offered by Dr. Zalutsky.

DATED: August 24, 2027

A handwritten signature in black ink, appearing to read 'M. Gorin', is written over a horizontal line.

Dr. Michael A. Gorin, MD