

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FUSION PHARMACEUTICALS, INC.,

Petitioner,

v.

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

Patent Owner

Case No. IPR2023-00551

Patent No. 10,980,901 B2

DECLARATION OF DR. THOMAS A. HOPE, MD

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I, Dr. Thomas Hope, MD, declare and state as follows:

I. ASSIGNMENT

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 to express an opinion concerning the obviousness of the patent in suit, U.S. Patent No. 10,980,901 (the “’901 Patent”) in *inter partes* review proceeding Case No. IPR2023-00551 in light of the information provided by Fusion Pharmaceuticals, Inc. and their expert, Dr. Rebecca Abergel, PhD.

I am being compensated for my time in connection with this matter at a rate of \$400/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 of the ’901 Patent.

II. QUALIFICATIONS AND EXPERIENCE

A detailed description of my educational and professional background and qualifications is provided in my *curriculum vitae*, attached as Exhibit 2056. My CV includes a list of positions, awards, honorariums, and publications I have authored up to August of 2023. I have over fifteen years of experience in the field of medical research. My research and professional activities have focused on the development and discovery of novel PET radiopharmaceuticals for the imaging of diseases and disease states and targeted radionuclide therapies for neuroendocrine tumor and prostate cancer treatment.

I graduated from Duke University in 2001 *Summa Cum Laude* with degrees in Economics (B.A.) and Biology (B.S.). In 2007 I graduated from the Stanford University School

of Medicine. I continued my training through a one-year internship in internal medicine at Kaiser San Francisco from 2007-2008 and subsequently completed a residency in diagnostic radiology at the University of California in 2012. I also completed a yearlong clinical fellowship in Body MRI and Nuclear Medicine at the Stanford Medical Center.

While completing my clinical fellowship at Stanford, I accepted a position as an Assistant Professor in Residence in the Department of Radiology and Biomedical Imaging at the University of California, San Francisco, beginning in 2013. I was later promoted to Associate Professor in 2018 and then my current title of full Professor in Residence in 2022. I also worked as a Staff Radiologist at the San Francisco Veterans Affairs Medical Center beginning in 2013 and accepted the title of Chief of Nuclear Medicine there in 2018. I continue to hold my positions at the VA to this day.

I have also held various leadership positions at the University of California, including Co-director of the PET/MRI from 2015 to 2019 and the Associate Chair for Business Strategy from 2020 to 2022. I currently hold the titles of Co-director of the Neuroendocrine tumor Destination Program (since 2016), Director for Molecular Therapy in the Department of Radiology (since 2019), Chair of the Molecular Imaging and Radioligand Therapy Site Committee (since 2019), and Vice Chair of Clinical Operations and Strategy (since 2022).

I have received various awards and honorariums throughout my career beginning with the award of a Trainee Research Prize from the Radiographic Society of North America (RSNA), which I received while in medical school. Since then, I received various awards including the Roentgen Resident/Fellow Research Award from the RSNA, the Wylie J. Dodds Research Award from the Society of Abdominal Radiology, and the Theranostics Investigator Grant from the North American Neuroendocrine Tumor Society, to name a few. I have also received various

recognitions for my work in the field including the Alexander Margulis Society Excellence in Research Award from UCSF, the Marc Tetalman Memorial Award and the Hal O'Brien Rising Star Award from the Society of Nuclear Medicine and Molecular Imaging, the Young Investigator Award from the Prostate Cancer Foundation, and the Outstanding Teacher Award in 2016 and 2017 from the International Society of Magnetic Resonance in Medicine, and most recently, I was the National Association of State Prostate Cancer Coalitions Honoree. I have received eighteen government and private research grants involving neuroendocrine tumors, Prostate Specific Membrane Antigen ("PSMA"), and radiopharmaceutical imaging and therapy.

I have also contributed to various professional organizations to promote the field. I was a member of the Scientific Program Subcommittee of the American Roentgen Ray Society from 2013 to 2016; a board member of the PET Center of Excellence of the Society of Nuclear Medicine and Molecular Imaging from 2015 to 2020; and a member or chairman of the Research Committee of the Society of Abdominal Radiology from 2014 to 2023. I am currently the president of the Correlative Imaging Council, Society of Nuclear Medicine and Molecular Imaging (since 2017), and the vice-president of Therapy Center of Excellence, Society of Nuclear Medicine and Molecular Imaging. I also led the clinical development of ^{68}Ga -PSMA-11 in the United States, leading to two articles in JAMA Oncology, and we obtained in collaboration with UCLA the first New Drug Approval of a PSMA radiopharmaceutical (subsequently approved as Locamets and Illucix) in the United States.

I have published over 150 peer-reviewed publications including many in some of the most important journals in the relevant fields, such as Lancet Oncology, JAMA Oncology, Journal of Nuclear Medicine, and Radiology to name a few. I have also contributed chapters to four books and co-authored my own book in the relevant field, *PET/MRI in Oncology: current*

and clinical applications. I have also been a reviewer for numerous journals, including Lancet, Lancet Oncology, Journal of Clinical Oncology, European Urology, and European Journal of Nuclear Medicine and Molecular Imaging. In 2017 I was a Distinguished Reviewer for the Journal of Magnetic Resonance in Imaging and served on the Editorial Board of the Journal of Nuclear medicine from 2016 to 2021, until I took on my current position there of Associate Editor in 2022.

I have been invited to give over 200 lectures on molecular imaging and radioligand therapies in both domestic and foreign venues. I have also given over sixty lectures as part of my teaching responsibilities at the University of California, including “Imaging Prostate Cancer: where are we going?,” “PSMA at UCSF,” “Introduction to Theranostics,” “Peptide Receptor Radionuclide Therapy,” and “⁶⁸Ga-PSMA-11 PET in prostate cancer.”

My own expertise overlaps with the scientific issues that arise in this case, including the use of PSMA, radionuclide-based therapies, and molecular imaging. As a clinician researcher, I have an in-depth understanding of the confounding issues that may arise in medical research and what may be expected of a new treatment strategy. As a researcher and clinician active at the time of the invention, I also understand what the person of ordinary skill in the art was thinking as viable strategies and the effect that the discoveries described in the invention had on the relevant community. For example, in reaction to the low level of bone marrow toxicity found with certain alpha emitters, I performed microdosimetric modelling on the distribution of alpha emitting radionuclides because I was surprised at the low level of bone marrow toxicity reported in the field. Ex. 2012, Tranel J, Effect of microdistribution of alpha and beta-emitters in targeted radionuclide therapies on delivered absorbed dose in a GATE model of bone marrow, *Phys. Med. Biol.* 66 (2021) 035016. Alpha emitters carried a considerable risk of bone marrow toxicity

compared to beta emitters because of the increased level of energy expected to be deposited there. *Id.* My own work showed unexpected varying levels of marrow toxicity with alpha emitters due to differences in their microdistribution.

III. MATERIALS CONSIDERED

As part of my assignment, I have reviewed the declaration of Dr. Rebecca Abergel, the relevant associated references cited by her declaration, and Dr. Abergel's deposition testimony. I have also reviewed relevant background materials provided by counsel and based on my own understanding of the field. A complete list of the materials that I considered for this declaration is shown in Exhibit 2055.

IV. APPLICABLE LEGAL STANDARDS

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.

It has been explained to me that the patent claims describe the invention made by the inventor and describe 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 the requirements of the claim but refers to another claim and incorporates all of the requirements of the claim to which it refers.

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 having 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.

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 as to why one of ordinary skill in the art would combine the references.

I also understand that when evaluating obviousness, it is not proper to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts. I understand that a reference must be considered for all that it teaches, including disclosures that diverge and teach away from the invention being evaluated.

I understand that it is improper to combine references where 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 that was 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 be productive of 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.

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.

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.

V. PERSON OF SKILL IN THE ART

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.

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 Ac-225-radiopharmaceuticals.” (Ex. 1001, ’901 Patent, at Abstract.) Therefore, I do not entirely agree with Dr. Abergel’s definition of the skills required for a person of skill in the art relevant to the ’901 Patent.

Because this patent relates to a clinical invention, a clinician 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 oncology treatment and specifically with treatments and cancers involving Prostate Specific Membrane Antigen (“PSMA”). While the person of ordinary skill in the art needs to have experience in and knowledge about using radionuclides in treatments, abstract knowledge about 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.

At her deposition, Dr. Abergel agreed that the patent does not claim technology in the kinds of expertise that she initially claimed were necessary for a POSA:

Q. Okay. Now, the patent doesn't claim a new method of synthesizing molecules, does it?

A. I don't believe so.

Q. And it doesn't claim a new method of attaching radionuclides to molecules, does it?

A. I don't believe so.

Q. And it doesn't claim a new method of making radionuclides, right?

A. I don't believe it claims methods of making radionuclides.

Ex. 2011.0010, Abergel Tr. 34:24-35:10.

Q. Well, let me put it this way, then. It doesn't claim a method of synthesis, correct?

A. That's correct.

Ex. 2011.0017, Abergel Tr. 62:16-18.

Q. So a person of ordinary skill, in order to understand this patent, wouldn't need information about radioimmunoconjugation per se.

A. Well, that information is within radiobioconjugation as a more generic term, if you will. So I still believe that a POSA would need to know about conjugation.

Q. Okay. So if they know about radioconjugation but they don't know about radioimmunoconjugation, that would still be sufficient for a person of skill.

A. Sure.

Ex. 2011.0017, Abergel Tr. 61:16-62:1. Therefore, these requirements for a POSA would be superfluous. She also acknowledged that full knowledge of all f- and d- block elements would not be necessary:

Q. But why would they need to know about all of the d-block or f-block elements in order to understand this patent?

A. I'm not sure how to answer your questions, because knowing about all of the elements doesn't mean being an expert in the coordination chemistry of every single element in those series. So general properties would be a basic

understanding. Specific properties about a specific metal in a specific environment may not be needed.

Ex. 2011.0010, Abergel Tr. 34:14-23.

[Q.] So you still believe that a person of skill needs to know about all of the elements in the f-block and the d-block?

MS. CIPRIANO: Objection; misstates --

A. It doesn't say "all of the elements." It says "chemical behavior of radiometals."

Q. Okay.

A. So maybe you could be more specific and say "relevant to radiotherapy," but...

Ex. 2011.0017, Abergel Tr. 63:15-23.

I also do not believe that a background in radioimmunoconjugation is sufficient for a person of ordinary skill since the patent does not focus on immunoconjugates (which is the combination of antibody sequences with other molecules), but primarily relates to ligand conjugates such as those non-antibody sequences that bind to PSMA. In fact, Dr. Abergel's expert declaration focuses on the molecule PSMA I&T, which is not an immunoconjugate, but a conjugate of a small molecule ligand.

Because the patent involves the use of specific doses of PSMA-targeting molecules for the treatment of cancer, the relevant person of skill in the art should have experience in dosimetry studies using radiopharmaceuticals. Specifically, a POSA should have (1) clinical experience with radiopharmaceuticals, (2) experience in dosimetry modeling of radiopharmaceuticals, (3) knowledge in radiation-biology of radiopharmaceuticals, (4) an understanding of dose finding studies of radiopharmaceuticals, and (5) clinical experience with prostate cancer or other PSMA-expressing cancers.

I understand that the teaching of the prior art is viewed through the eyes of a person of ordinary skill in the art. 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.

Finally, while I cannot speak to Dr. Abergel's experience with "the development of new strategies for anticancer, antibacterial, and antiviral radiotherapies," as she lists in her declaration (Ex. 1002 at 2), I do not believe that any of the other experience she lists is relevant to this patent. For example, this patent and the technology surrounding it does not relate to "separation methods for rare earth mining, transuranic waste handling and purification of medical isotopes," or "toxic metal decontamination strategies." At Dr. Abergel's deposition, she agreed that the patent does not involve these matters:

Q. So looking at ii, you say "The development of new clinical radionuclide and toxic metal decontamination strategies." Do you see that?

A. I see that.

Q. So this patent doesn't relate to decontamination strategies, right?

A. That's right.

Q. Okay. For iii, you say "The development of new separation methods for rare earth mining, transuranic waste handling, and purification of metal isotopes." Do you see that?

A. I do.

Q. So this patent isn't related to the separation methods of rare earth mining, right?

A. That's right.

Q. Or transuranic waste handling, right?

A. That's right.

Ex. 2011.0015, Abergel Tr. 53:9-54:3.

I also believe that the patent has less to do with the "methodologies for interrogating the fundamental behavior of heavy and super-heavy elements" than the use of radiopharmaceuticals with specific radionuclides as Dr. Abergel agreed in her deposition above. Ex. 2011.0017, Abergel Tr. 63:15-23. This patent is also not focused on the creation or isolation of radioisotopes. Therefore, it is unclear to me how Dr. Abergel's experience is relevant to this patent.

VI. TECHNICAL BACKGROUND

A. Dosimetry

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 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. 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. Where a radionuclide is targeted to a specific tissue by some binding mechanism or molecule, there are the additional factors including receptor affinity and residence time / clearance, which is 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 that is 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 treatment based on radionuclides (referred to as “radiopharmaceuticals”). 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.

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. Dr. Abergel initially provided a similar definition at her deposition¹:

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.

Where the administered activity reaches its limit of tolerability is the “maximum tolerable dose.” And the toxicity effect that limits the dose is the “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 agreed that for a free-floating radionuclide like ²²⁵Ac, the liver, kidney, and bone were the most likely sites of collection:

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.

¹ I understand that Dr. Abergel later argued that a tolerability limit must implicate the death of the subject or irreversible damage. I do not agree with that definition and her initial definition which include weight loss and quality of life, and I also do not agree with those later statements.

A. So liver, kidney, and skeleton.

Ex. 2011.0008, Abergel Tr. 25:10-17.

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 efficacious dose. Determining the maximum tolerated dose is not related 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.

This is a particular problem for targeted radiopharmaceuticals because various factors may prevent effective function. Moreover, the same administered activity of different radionuclides can result in vastly different results so that the same administered activity of a radiopharmaceutical can cure a patient with one radionuclide but be lethal with another. And the relationship between appropriate administered activity for two such disparate radionuclides attached to the same ligand is not clear. Although a radionuclide emitting a higher energy particle, like an alpha particle, would be administered at a lower activity than a beta-emitting particle, the ratio between two such administered activities is not clear and not necessarily preserved across targets, ligands, or tumor types. Additionally, administering the same activity level of radionuclides with different half-lives or particle emission energies can result in a different amount of absorbed dose to tumor and tissue. Ex. 2013, Vallabhajosula et al., “Prediction of Myelotoxicity Based on Bone Marrow Radiation-Absorbed Dose: Radioimmunotherapy Studies Using ^{90}Y - and ^{177}Lu -Labeled J591 Antibodies Specific for

Prostate-Specific Membrane Antigen,” J. Nucl. Med., vol, 46, no. 5, pgs. 850-858 (2005); Ex. 2014, Cloutier, et al., MIRD Pamphlet No. 21, Dose Estimate Report No. 2, “Summary of Current Radiation Dose Estimates to Humans from ^{66}Ga -, ^{67}Ga -, ^{68}Ga -, and ^{72}Ga -citrate,” J. Nucl. Med., vol. 14, no. 10, pgs. 755-756 (1973).

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.² As explained in Dr. Abergel’s Ex. 1017 (Sgourous, et al., MIRD Pamphlet No. 22 (Abridged): Radiobiology and Dosimetry of α -Particle Emitters for Targeted Radionuclide Therapy, Sgouros, G. et al., *J Nucl. Med.* 2010; 51:311–328), for clinical applications, idealized *in vitro* experiments “give way to complex activity and tissue geometries.” Ex. 1017.009. Even with modeling, “[d]etermining the activity distribution [] remains difficult.” Ex. 1017.010. Even in 2022, Dr. Abergel herself acknowledges the difficulty of aligning an administered activity to the necessary absorbed dose: “While radiobiology and dosimetry for external-beam radiotherapy are well-established, their direct extrapolation to targeted radiotherapy is problematic, as the characteristics of the latter are rather different (i.e., mixed and heterogeneous irradiation, long exposure times, and low absorbed dose rates).” Pallares RM and Abergel RJ, Development of radiopharmaceuticals for targeted alpha therapy: Where do we stand? *Front. Med.* 2022; 9:1020188. In particular, “targeted alpha therapy, dosimetry calculations are more challenging than in other types of targeted radiotherapy, since

² Sgouros acknowledges this fact: “specific parameters such as the average number of α -particle traversals to induce a lethal event or the D_0 value. . . are highly sensitive to experimental factors such as the geometry of the cells, the thickness or diameter of the cell nucleus, the distribution of DNA within the nucleus (i.e., the phase of the cell cycle), and the number and spatial distribution of the α -particle sources relative to the target nuclei.” Ex. 1017.004

the daughter nuclides need to be considered, and they may have different pharmacokinetic profiles and chemical properties.” *Id.*

When asked about these factors in her paper, Dr. Abergel agreed that these would differ from molecule to molecule and tumor to tumor:

Q. Right. But you're talking here about the radiotherapy -- the targeted radiotherapy, and you're saying it's problematic because of these factors in the parentheses.

MS. CIPRIANO: Objection; misstates the document.

Q. Mixed and heterogeneous irradiation, long exposure times, and low absorbed dose rates. Isn't that right?

A. That's right.

Q. Okay. And so these are factors that go into the ultimate exposure of the tumor to the radiation, correct?

A. That's correct.

Q. And these will be different from molecule to molecule and tumor to tumor, correct?

MS. CIPRIANO: Objection to the extent it's not talking about what this document says.

A. They may be different. That's correct.

Ex. 2011.0046, Abergel Tr. 178:10-179: 3.

As pointed out by Sgouros, “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. This was because, like ^{225}Ac , many of the “ α -emitting radiotherapeutics decay to α -emitting daughter nuclides whose distribution may not be that of the carrier.” Ex. 1017.012. This requires a consideration of the daughter nuclides and requires “a greater emphasis on preclinical studies and extrapolation of results obtained from such studies to the human.” *Id.*

B. Limitations of Preclinical Models for Radiopharmaceutical Therapies

While mice are the most commonly used animal model, they are 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 homogenous culture of cancerous cells. Ex. 2015.001, Denison,

TA, Tumor Heterogeneity and its Implication to Drug Delivery, *J. Control. Release* 2012, 164(2): 187-191. But because human cancer is a dynamic disease resulting from mutations in the genome, cancer cells are heterogenous. *Id* at 187-188. This is why treatments fashioned after mice models produce inconsistent treatment effects, with some cancer cells responding to the treatment while others are resistant.

Standard laboratory mice, by design, also lack the genetic diversity found in humans. As such, a treatment that works for one laboratory mouse is likely to work for another. But there are wide disparities in what works from one human patient to another. 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.

Another main limitation 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 a mouse model are too short to model these effects. Additionally, it is not possible to measure toxicities such as dry mouth in animal models, which are dose limiting in humans. Separate from toxicity, tumor uptake is artificial in mice. In animal models, researchers chose xenograft models that significantly overexpress the target (SSTR, PSMA, etc) in order to make sure that the radiopharmaceutical is taken up in the model, which will overestimate the efficacy of a treatment relative to what may be seen in clinical applications. Therefore the maximum tolerated doses in

mice can be significantly different than that seen in humans, and the therapeutic window cannot be predicted from results in mice. The optimal administered activity is determined by both efficacy and toxicity, which defines the therapeutic window. The goal is to give an effective administered activity that does not result in unacceptable toxicity. These references demonstrate that the tumors can be effectively targeted with radiopharmaceuticals, but provide no information on what the effective and safe administered activity would be, and more important whether the administered activity required for efficacy is below the threshold required to be safe. 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.” Cimon 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).

As a result of the inherent differences between mouse and human, 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. Abergel’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 (1MBq=)1000 kBq/mouse for ^{177}Lu -DOTATOC as a reference for a conversion factor of $(1000/20) \sim 50$. However, Miederer 2008a also compares 12kBq/mouse of ^{225}Ac -DOTATOC to 450 kBq/mouse of ^{177}Lu -DOTATOC as a reference for a conversion factor of 37.5. 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, 296 and 185 ($7400/18.5=400$; $7400/25=296$; and $7400/40=185$). Ex. 2016, 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.

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 becomes 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.

These sorts of differences and confounding issues result in treatments that often seem promising in mice but are clinical failures in humans. Ex. 2017, Morton, JJ, et al. Humanized mouse xenograft models: narrowing the tumor-microenvironment gap, *Cancer Res.* 2016; 76(21): 6153–6158.

The same applies for models based on cell cultures because cell cultures are clones based on a single progenitor cell and are therefore homogenous. Cell culture experiments are also poor tools to measure 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. 2018.001, 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.*

Cell cultures also cannot model the effect of the radiopharmaceuticals on healthy organs or their pooling in other organs that result 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.*

C. Predictability of Radiopharmaceutical Efficacy based on Structure

While form determines a molecule's function, it is notoriously difficult to predict the function of a molecule from its atomic structure. This is because the connection between the known atoms and the final tertiary structure is not always clear, and because small changes in structure may produce results outside of the intended effect. For example, in Dr. Abergel'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.

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.

Table 1 PSMA affinities (IC₅₀) of the compounds investigated		
Ligand		IC₅₀ [nM]
HBED-CC-Ahx-KuE		5.7 ± 0.5
[^{nat} Ga]HBED-CC-Ahx-KuE		6.1 ± 0.8
DOTA-FFK(Sub-KuE)	(10)	13.1 ± 2.3
[^{nat} Ga]DOTA-FFK(Sub-KuE)	(^{nat} Ga- 10)	29.5 ± 6.6
[^{nat} Lu]DOTA-FFK(Sub-KuE)	(^{nat} Lu- 10)	54.7 ± 6.1
DOTAGA-FFK(Sub-KuE)	(11)	10.2 ± 1.5
[^{nat} Ga]DOTAGA-FFK(Sub-KuE)	(^{nat} Ga- 11)	12.1 ± 3.9
[^{nat} Lu]DOTAGA-FFK(Sub-KuE)	(^{nat} Lu- 11)	15.1 ± 1.5
DOTAGA-ffk(Sub-KuE)	(12)	13.9 ± 0.4
[^{nat} Ga]DOTAGA-ffk(Sub-KuE)	(^{nat} Ga- 12)	15.9 ± 0.5
[^{nat} Lu]DOTAGA-ffk(Sub-KuE)	(^{nat} Lu- 12)	13.1 ± 2.2
Binding assays were performed using LNCaP cells (150,000/well) and ([¹²⁵ I]-BA) KuE (c = 0.2 nM) as the radioligand. Cells were incubated in HBSS (1% BSA) at 4°C for 1 h. Data are expressed as mean ± SD (n = 3).		

D. Stability of Chelated Alpha Emitters

In 2016, damage to healthy organs by the accumulation of free isotopes in non-target organs was a significant concern with the use of radiopharmaceuticals in cancer treatment. In particular, the kidney, spleen, and bone marrow typically showed high accumulations of radioactivity. For example, in Weineisen 2014 (Ex. 1027), the researchers examined the biodistribution of ⁶⁸Ga in mice and found higher distributions of radiation in the kidneys and spleen than in the tumor. Ex. 1027.012. In its follow up Weineisen 2015 article, the lab found that the biodistribution in mice of the ⁶⁸Ga-PSMA I&T and ¹⁷⁷Lu-PSMA I&T was respectively over 10 and 13 times higher in the kidney than in the tumor, with the spleen holding approximately the same amount as the tumor. Ex. 1028.004. Extrapolating this to humans, Weineisen estimated that the highest amount of radiation would be seen in the kidney, adrenals, uterus, spleen, and pancreas. Ex. 1208.005.

Alpha-emitting isotopes in particular were a topic of concern because of the high likelihood that they would separate from the carrier molecule (e.g., the chelator), allowing free daughter radionuclides to circulate throughout the body. This is a particular concern with alpha-emitters as opposed to beta-emitters, because while beta-emitters like ^{177}Lu emit small beta particles that are the mass of electrons, alpha-emitters expel a particle made up of two protons and two neutrons, each 2000 times heavier than an electron. This means that the energy needed to expel the much larger alpha particle is much greater than that needed by beta emitters to expel beta particles.

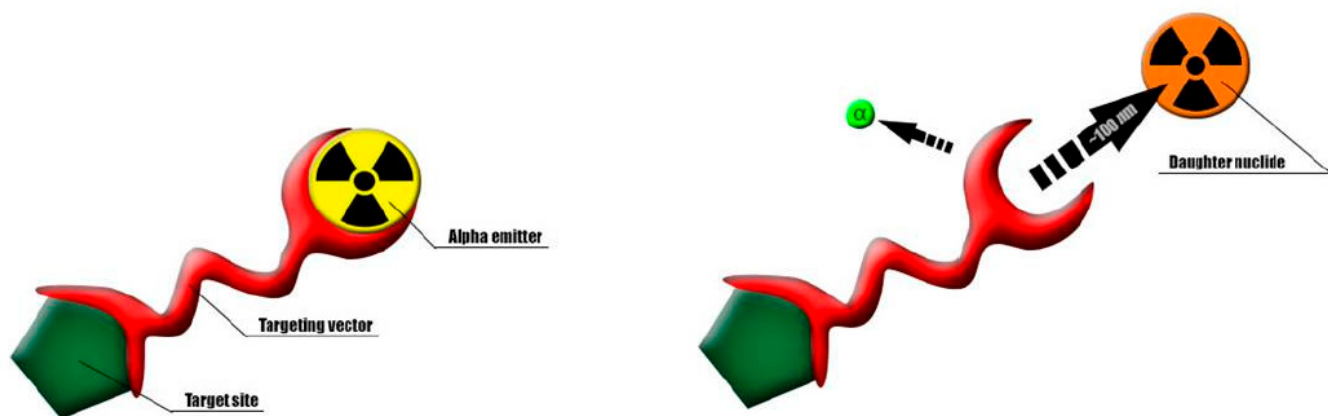


Figure 1. Schematic representation of a recoiling daughter radionuclide detaching from a targeting agent as a consequence of alpha decay.

As illustrated above, when the alpha particle is emitted, the alpha daughter nuclide (the atom the radionuclide becomes after losing the mass of the alpha particle) experience approximately 100 keV – 1000 times more energy than is needed to break the binding energy of any chemical compound – and travels an average of 100 nm – typically far beyond the parameters of the carrier molecule (e.g., chelator). Ex. 2007.003 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.

Although Dr. Abergel passingly acknowledged the reality of the recoil in her declaration (Abergel Decl. at 7-8) because it was in a diagram that she cited, she left out any mention that this recoil was an issue:

Q. Okay. And then on page 7, in the middle of page 7, you give an example of an alpha particle, correct?

A. That's right.

* * *

Q. You say -- underneath the example of the alpha particle, it says "The daughter nucleus has two fewer protons and four fewer nucleons. It has a small recoil." Do you see that?

A. I do.

Q. Okay. What do you mean by the -- what does that mean by the "recoil"?

MS. CIPRIANO: Objection to the extent it mischaracterizes the figure.

A. It means that there's an energy associated with that nuclear reaction and that the alpha particle carries some -- there's conservation of energy and conservation of momentum. And your alpha particle carries some energy and has a momentum. The emitting nucleus that becomes something else also has -- carries some energy and has an opposite momentum.

Q. Okay. So it moves.

A. It moves.

Q. Okay. That doesn't happen with the beta emitter, right?

A. Not to the same extent.

Q. Okay. So when you say "not to the same extent," do you mean that for every action there's an opposite yet equal reaction but it's pretty tiny?

A. Right.

Ex. 2011.0018, Abergel Tr. 66:2-5; 66:20-67:19.

When asked about the Ex. 2007, the de Kruijff, RM reference, she agreed that this energy was enough to expel the ²²⁵Ac from the chelator on the ligand molecule and that the resulting daughter nuclides could cause considerable harm:

Q. Okay. So the author here says, in the third sentence, referring to the emission of alpha particles. "This energy is in most cases at least 100 keV, more than a thousand times larger than the binding energy of any chemical compound." Do you see that?

A. I do.

Q. Do you disagree with that?

MS. CIPRIANO: Objection; foundation.

A. I don't disagree with that.

Q. And then it goes on to say "This simply means that bond rupture will always occur subsequent to alpha decay, implying that the released daughters, which are often themselves alpha emitters, might cause considerable harm, as seen in some of the clinical trials with, e.g., for example, AS patients." Do you see that?

A. I see that.

Q. Do you disagree with that?

A. I don't disagree with this. It might cause considerable harm. Those are not -- a strong statement in my mind, so I don't disagree.

* * *

[Q.] So we agree that the amount of energy from a recoil would be enough to break the actinium or its daughter element out of the chelator that's holding it, right?

A. Right.

Q. And you agree with the statement from this document that the alpha emitters, the daughter elements might cause considerable harm, correct?

A. Yes, I agree.

Ex. 2011.0019, Abergel Tr. 69:3-23; 70-17-25.

Expulsion of an alpha-emitter from a carrier intended to target the radionuclide means that only the first alpha particle emission has any chance of being targeted to the tumor. Any additional decay event will occur distantly from its target, and likely in healthy tissue. For emitters that are close to their stability point, like ^{213}Bi , ejection of the radionuclide from its carrier is less dangerous because it only has one additional beta particle to emit before it becomes stable. This is not so for ^{225}Ac . ^{225}Ac will release four additional alpha particles and two beta particles before stabilizing. 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. As mentioned above, radionuclides were known to

accumulate in the bone, liver, and kidney, including ^{225}Ac 's daughter radionuclide, ^{213}Bi . *Id.*; Ex.2020, Dorso, L, et al., Long-Term Toxicity of ^{213}Bi -Labelled BSA in Mice, *PLoS ONE* 2016; 11, e0151330. So the daughter radionuclides of ^{225}Ac emitted after the first alpha particle emission would likely end up in the kidney, raising serious nephrotoxicity concerns. In light of this, since an alpha emitter may only be effective against the target for its first alpha emission, using radionuclides that will ultimately emit less radiation after that initial emission may have been a preferred strategy.

The problem of alpha-emitters escaping their targeting carriers was widely recognized, which Dr. Abergel acknowledges:

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. 2011.0019, Abergel Tr. 71:1-11.

In 2004, Miederer (the same author of Abergel's Ex. 1015) noted when introducing his antibody- ^{225}Ac 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. 2021.001, 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.* at 2. These loose daughter nuclides would increase the chances of side-effects and prevent the accurate estimation of appropriate administered activities. *Id.*

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.” When asked about this passage, Dr. Abergel 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. 2011.0019, Abergel Tr. 71:24-72:7; 72:19-73:10. That same year, in his review paper on ^{225}Ac , Miederer discussed one example of ^{225}Ac being released from the chelator HEHA that

resulted in ^{225}Ac migrating to the bone and liver followed by “acute radiotoxicity” from ^{225}Ac and its daughter nuclides. Ex. 1030.003.

Even Dr. Abergel recognized in 2016 that, while ^{225}Ac held promise, the “rising challenge for chemists resides in the handling of ^{225}Ac intermediates and potentially harmful recoiling daughter nuclides — ^{221}Fr , ^{217}At , and ^{213}Po .” DeBlonde, GJ, Abergel, RJ, *Nat Chem.*, 2016 Oct 21;8(11):1084. However, the solution she discussed in 2016 was the use of structures very different from chelators and radioligands to better retain or recapture ^{225}Ac and its alpha cascade – these structures were dubbed “nanosafes” and included encapsulating nanoparticles or scavenging carriers. *Id.* Even six years later in 2022, Dr. Abergel still considers 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.” Pallares RM and Abergel RJ, Development of radiopharmaceuticals for targeted alpha therapy: Where do we stand? *Front. Med.* 2022; 9:1020188. She and her colleagues wrote that “minimizing daughter release is a fundamental step to extend the use of targeted alpha therapy beyond metastatic non-responding patients,” and again suggested nanoparticles as the key. *Id.* So, the difficulties and challenges posed by recoiling ^{225}Ac daughter nuclides were, and remain to this day, a widely recognized problem that some – apparently including Dr. Abergel – continue to recognize as remaining unresolved.

As even Dr. Abergel admits in her own articles, the field was concerned that the use of ^{225}Ac in targeted radiopharmaceuticals was problematic at best and dangerous at worst.

VII. THE KRATOCHWIL PATENT

The '901 Patent describes the surprising discovery that treating patients having PSMA-expressing cancers with 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.

These results were obtained despite the generally acknowledged danger and obstacle of ^{225}Ac 's daughter nuclides escaping the compound, migrating to healthy organs, and causing irreparable organ damage.

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 from claim 1 so that each claim also recites the elements of Claim 1.

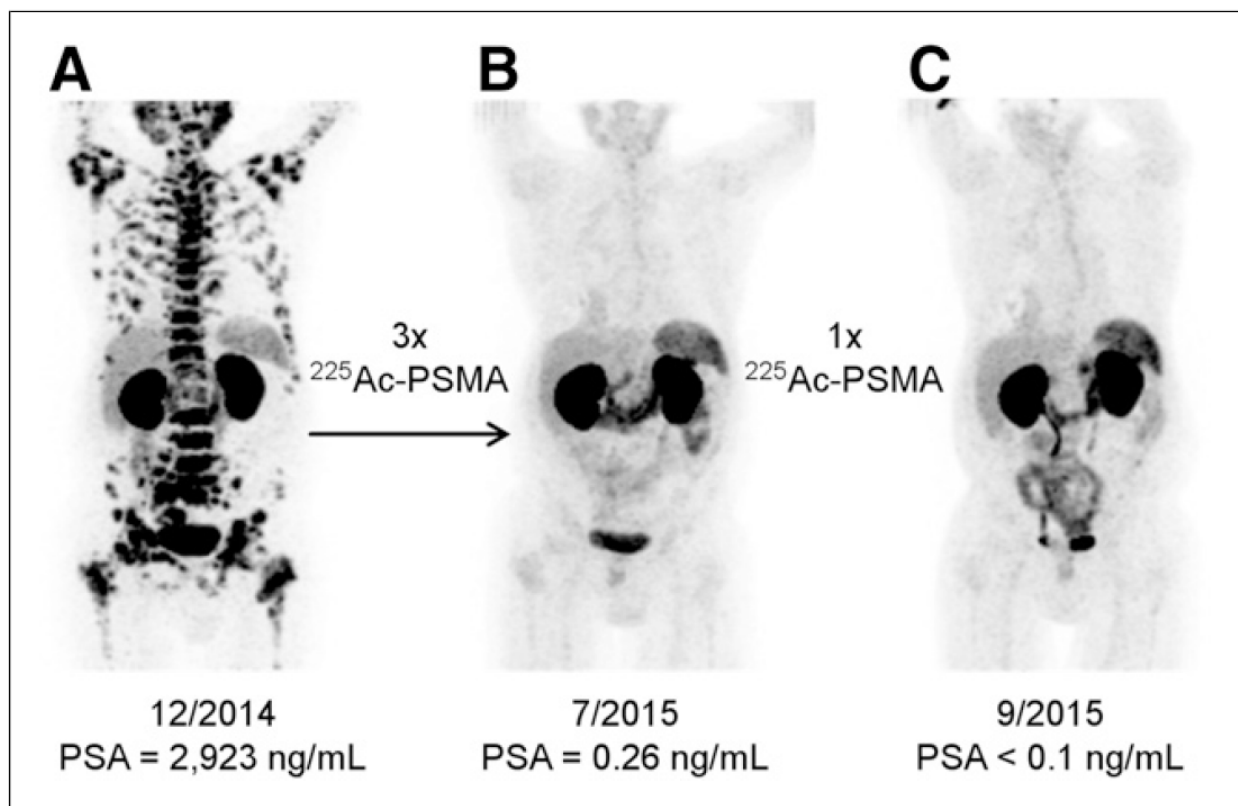
Claim 1 recites "[a] method for treating PSMA expressing cancers, wherein the method comprises administering to a patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E)," and then depicts Formulae A-E.

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

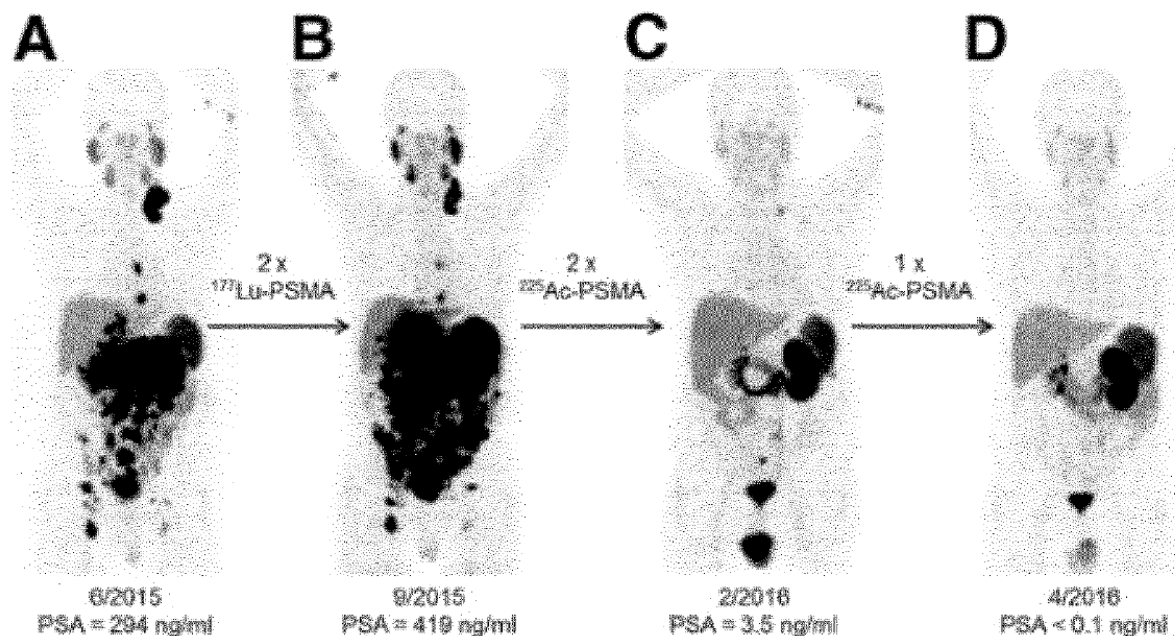
The invention described in the '901 Patent is reflected in a journal article published by Kratochwil's lab just before the Patent filing, Ex. 2022, "²²⁵Ac-PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer, published July 7, 2016, in the *Journal of Nuclear 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. 2022.002-3, Ex1001.007-8. 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. 2022.002; Ex1001.007. The figure also includes the measurement of prostate-specific antigen ("PSA"), which is a protein produced by malignant cells of the prostate gland. The higher the amount of PSA in the blood, the more extensive the tumor spread. 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)



The second patient was also given $^{225}\text{Ac-PSMA-617}$ at a dosage of 6.4 MBq (100 kBq/kg) three times over a three-month period. Ex. 2022.002-3; Ex1001.008. 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 $^{177}\text{Lu-PSMA-617}$ treatment (*compare* Fig. 3A baseline to Fig. 3B). *Id.* The $^{177}\text{Lu-PSMA-617}$ 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)



Figures 13 and 15 of the Patent correspond to Figures 2 and 4 of the Kratochwil paper, respectively. Ex. 2022.002-3; Ex1001.008-9.

Because the bones are one area in which unbound ^{225}Ac and its daughters may relocate to, 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 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.

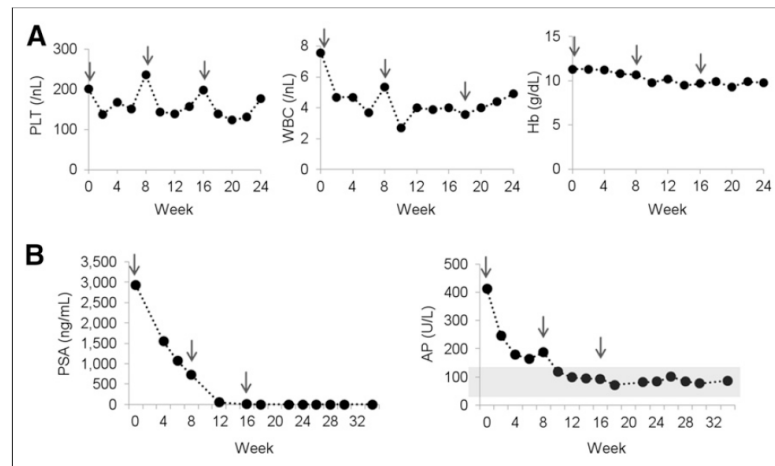
Q. And it could reduce the amount of hemoglobin because it's destroying the platelets that are in the red marrow, correct?

A. Possibly.

Ex. 2011.0014, Abergel Tr. 49:11-24.

Along with a steady decline in tumor markers to undetectable levels, these figures show no significant decrease in the patients' blood cell counts, white blood cell counts, and hemoglobin levels, indicating hematotoxicity. Ex. 2022.002-3; Ex1001.008-9.

'901 Patent Figure 13 (Kratochwil Paper Fig. 2)

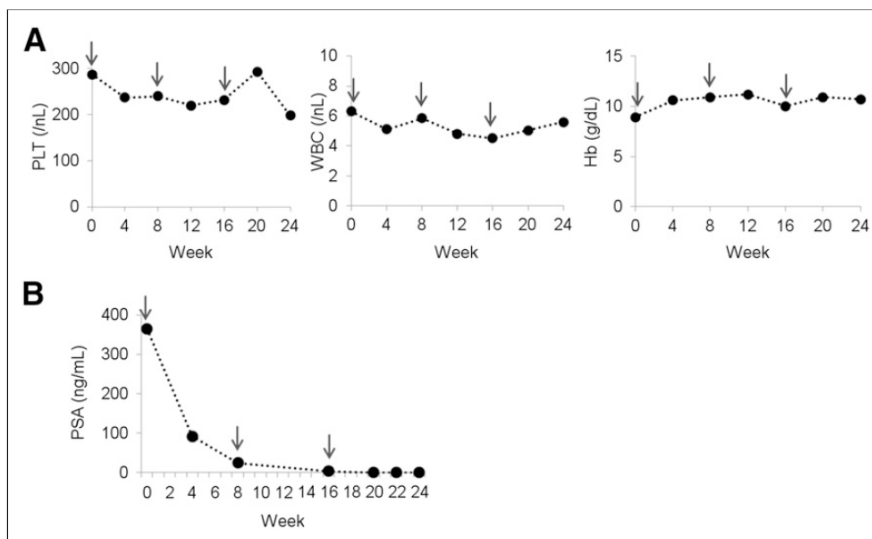


The data in Figure 13A for the first patient indicates the dates of treatment with arrows, which show a decrease in blood counts and white blood cells directly after treatment, but a quick recovery over two months. *Id.* The patient platelet count never drops below 100/ml which is considered a grade 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. 2023, 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. 2022.002-3; Ex1001.007-9.

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)

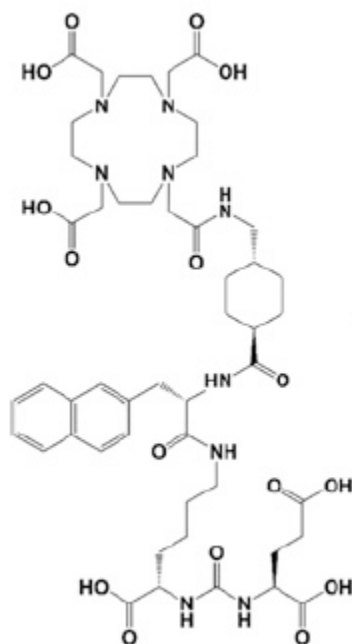


B. The Kratochwil Paper Embodies the '901 Patent Claims

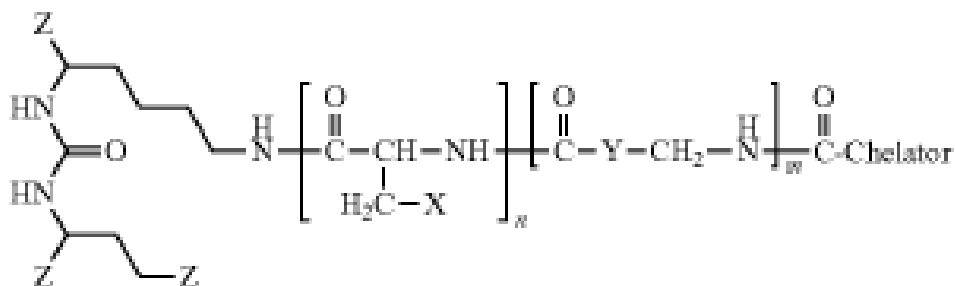
I have been informed that a product or method embodies a patent when it has all of the elements described in the claims of the patent. It is my opinion that the treatment method in the Kratochwil paper embodies the claims of the '901 patent. Specifically, it embodies challenged Claims 1, 2, 4-6, and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

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. 1011.018. 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. 2022.002-3. The Kratochwil paper administers the ^{225}Ac -PSMA-617 radiopharmaceutical to patients in need of cancer treatment as required by Claim 1.

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.2024. The structure of PSMA-617 is:



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

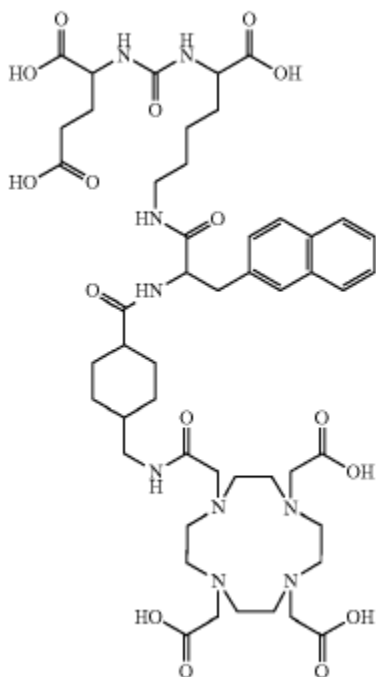


For the PSMA-617 ligand, the variable Chelator is the DOTA moiety, the variable Y is an aryl, X is the naphthyl moiety, and the Zs are -CO₂H groups.

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.2022.002 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.

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 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.2022.002. 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. Ex.2044, 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

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.

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.

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.*

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.*

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.*

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

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.

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. 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. When asked about it, Dr. Abergel has 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. 2011.0012, 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. 2011.0013, Abergel Tr. 47:7-17.

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. 2025, <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.

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. 2026, 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. 2027, <https://www.eanm.org/congresses-events/awards-grants/winners/>

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 ¹⁷⁷Lu-PSMA-617 presented progression (B). In contrast, restaging after the second (C) and third (D) cycles of α -emitting ²²⁵Ac-PSMA-617 gave an impressive response.” Ex. 2028, Alam, MR, et al., A Review of ¹⁷⁷Lutetium-PSMA and ²²⁵Actinium-PSMA as Emerging Theranostic Agents in Prostate Cancer, *Cureus* 2022; 14(9): e29369. The author also included a chronological listing of clinical studies using ²²⁵Ac with PSMA targeting molecules with the Kratochwil paper listed as the first two entries. Dr. Kratochwil's work with the ²²⁵Ac-PSMA-617 radiopharmaceutical was the first of its kind, and then others followed suit.

Author	Total number of patients	Frequency of best PSA decline of $\geq 50\%$ (%)	Frequency of objective remission (%)	Median overall survival (months)
Kratochwil et al. [55]	14	63%	NR	NR
Kratochwil et al. [56]	38	82%	13%	>12
Sathekge et al. [57]	17	70%	NR	NR
Sathekge et al. [58]	73	65%	NR	18
Khreish et al. [59]	20	49%	21%	12
Yadav et al. [60]	28	39%	9%	17

TABLE 3: Overview of overall survival, progression-free survival, and complete response in the recently published literature on 225Actinium prostate-specific membrane antigen targeted alpha-particle treatment.

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 her deposition, Dr. Abergel 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. 2011.0009, Abergel Tr. 30:19-31:5.

According to Pubmed, a commonly used scientific research database, the Kratochwil paper has been cited by 299 academic papers since its publication in December of 2016.

According to Google Scholar, which performs a broader search to include, for example, books and websites, it has been cited 861 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. Abergel relies on to show obviousness (see Table below). 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 60% of the Kratochwil paper’s citations.

Reference	Pubmed Ex.2029	Google Scholar Ex. 2030
Kratochwil, C. et al. ²²⁵ Ac-PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer, <i>J. Nucl. Med.</i> 2016, 57, 1941 – 1944 (Ex.2029.001; Ex. 2030.001)	299	861
Martina Weineisen, et al., Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer, <i>EJNMMI Research</i> 2014, 4:63(Ex.2029.002; Ex. 2030.003)	71	207
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, <i>J Nucl Med</i> 2015; 56:1169–1176 (Ex.2029.003; Ex. 2030.005)	181	536
Kristell Chatalic, et al., 213Bi-labeled PSMA-targeting agents for alpha radionuclide therapy of prostate cancer, <i>J. Nuc. Med.</i> 2016, 57 (supplement 2) 137. (Ex.2030.004)	N/A	2
Matthias Miederer, et al., Preclinical Evaluation of the α -Particle Generator Nuclide ²²⁵ Ac for Somatostatin Receptor Radiotherapy of Neuroendocrine Tumors, <i>Clin Cancer Res</i> 2008,14(11), 3555-3561. (Ex.2029.007; Ex. 2030.005)	62	153
Joseph G. Jurcic, et. al., Phase I Trial of Targeted Alpha-Particle Therapy with Actinium-225 (²²⁵ Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC)in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML), <i>Blood</i> 2016, 128 (22): 4050 (Ex. 2030.006)	N/A	47

Clemens Kratochwil, et al., <i>Ac-225-DOTATOC - an empiric dose finding for alpha particle emitter based radionuclide therapy of neuroendocrine tumors</i> , <i>J. Nuclear Med.</i> 2015, 56 (supplement 3) 1232. (Ex. 2030.008)	N/A	45
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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 cite 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 97% of its contemporaries and scores in the 98th percentile compared to all tracked articles regardless of time. Ex. 2031.003, 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 fiftieth 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

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. But this was not the case here.

Although Dr. Abergel 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 ^{225}Ac 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. 2032, 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. 2019, 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 ^{225}Ac had multiple daughter nuclides that would emit non-bound, non-targeted alpha particles, increasing toxic exposure. But surprisingly, this expected toxicity did not manifest.

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.

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.

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. 2033, 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. 2034, 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. 2035, “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.

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.

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. 2036, Zalutsky et al., “Clinical experience with alpha-particle emitting 211At: treatment of recurrent brain tumor patients with 211At-labeled chimeric antitenascin monoclonal antibody 81C6,” *J. Nucl. Med.* Vol. 49, no. 1, pgs. 30-38 (2008); Ex. 2037, Abbas et al., “Experimental α -particle radioimmunotherapy of breast cancer using 227Th-labeled p-benzyl-DOTA-trastuzumab,” *EJNMMI Res.* Vol. 1, no. 1, pg.18 (2011); Ex. 2038, Parker et al., “Efficacy and Safety of Radium-223 Dichloride in Symptomatic Castration-resistant Prostate Cancer Patients With or Without Baseline Opioid Use From the Phase 3 ALSYMPCA Trial,” *Eur. Urol.* Vol. 70, no. 5, pgs. 875-883 (2016); Ex. 2039, Meredith et al., “Dose escalation and dosimetry of first-in-human α radioimmunotherapy with 212Pb-TCMC-trastuzumab,” *J. Nucl.*

Med., vol. 55, no. 10, pgs. 1636-1642 (2014); Ex. 2040, 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. 2041, 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. 2019, 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. 2018, “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.

VIII. NEITHER DR. ABERGEL NOR THE ART SHE RELIES ON DEMONSTRATES THAT THE CLAIMS OF THE '901 PATENT WERE OBVIOUS

The prior art references that Dr. Abergel relies upon fail to show that the '901 Patent was obvious either individually or in combination. Dr. Abergel 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, she reads far too much into passing mentions of ^{225}Ac .

A. Weineisen 2014

Dr. Abergel's reliance on Wineisen'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. Wineisen 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 Wineisen lab performed competition experiments to test the *in vitro* binding of the ligand molecules. They determined the IC_{50} 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. IC_{50} – 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 IC_{50} , 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, IC_{50} is a good measure of the binding affinity of the radioligand to the target that would otherwise bind to the control ligand.

The Wineisen 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. For example, the IC_{50} 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 IC_{50} 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.*

Table 1 PSMA affinities (IC₅₀) of the compounds investigated		
Ligand		IC₅₀ [nM]
HBED-CC-Ahx-KuE		5.7 ± 0.5
[^{nat} Ga]HBED-CC-Ahx-KuE		6.1 ± 0.8
DOTA-FFK(Sub-KuE)	(10)	13.1 ± 2.3
[^{nat} Ga]DOTA-FFK(Sub-KuE)	(^{nat} Ga-10)	29.5 ± 6.6
[^{nat} Lu]DOTA-FFK(Sub-KuE)	(^{nat} Lu-10)	54.7 ± 6.1
DOTAGA-FFK(Sub-KuE)	(11)	10.2 ± 1.5
[^{nat} Ga]DOTAGA-FFK(Sub-KuE)	(^{nat} Ga-11)	12.1 ± 3.9
[^{nat} Lu]DOTAGA-FFK(Sub-KuE)	(^{nat} Lu-11)	15.1 ± 1.5
DOTAGA-ffk(Sub-KuE)	(12)	13.9 ± 0.4
[^{nat} Ga]DOTAGA-ffk(Sub-KuE)	(^{nat} Ga-12)	15.9 ± 0.5
[^{nat} Lu]DOTAGA-ffk(Sub-KuE)	(^{nat} Lu-12)	13.1 ± 2.2
Binding assays were performed using LNCaP cells (150,000/well) and ([¹²⁵ I]-BA) KuE (c = 0.2 nM) as the radioligand. Cells were incubated in HBSS (1% BSA) at 4°C for 1 h. Data are expressed as mean ± SD (n = 3).		

When asked about this data, Dr. Abergel agreed 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. 2011.0033, 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. 2011.0033, Abergel Tr. 128:19-129:9.

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.

According to Dr. Abergel, when asked about Table 2 of Wineisen 2014, Dr. Abergel noted that this internalization affect could have been separate from the affinity affect, 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 2. We see that the DOTAGA-FFK, sub-KuE, also shows a difference between using gallium and lutetium, correct?

A. That's correct.

Ex. 2011.0034, Abergel Tr. 129:24-130:22.

This data demonstrates three things to a person of ordinary skill in the art.

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.

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.

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.

When asked, Dr. Abergel 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. 2011.0034, Abergel Tr. 131:8-24.

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 .

Despite these shortcomings, Dr. Abergel 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 M^{3+} -radiometals, e.g. ^{177}Lu , ^{90}Y or ^{225}Ac for endoradiotherapy.” (Ex. 1027.011). In light of this, and contrary to Dr. Abergel'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 M^{3+} -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 understood that ^{225}Ac either – or both – does not form “stable complexes” or is not useful “for therapy.” 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.

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.

Finally, Weineisen 2014 does not disclose any of the elements recited in the '901 Patent claims and therefore cannot be used to argue obviousness. This reference does not use PSMA-I&T – upon which Dr. Abergel bases her obviousness argument – or ^{225}Ac . Dr. Abergel 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

We must view Weineisen's follow up 2015 publication (Ex. 2028) in light of the 2014 paper. Indeed, Dr. Abergel herself views Weineisen 2015 as a follow up to Weineisen 2014. (Ex. 1002.031.) 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.

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.

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, Wineisen 2015 found a significant difference in the amount of uptake between the ^{68}Ga and ^{177}Lu constructs, with ^{177}Lu -PSMA-I&T usually being taken up in greater amounts, particularly in bone.

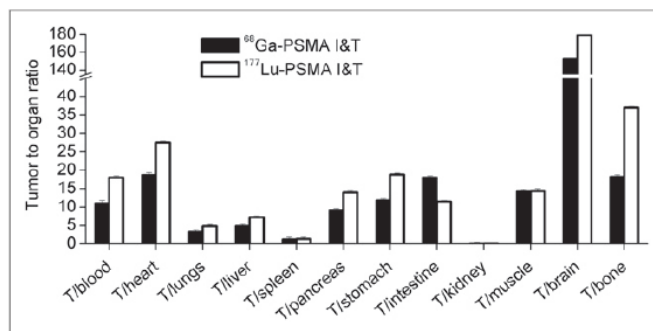


FIGURE 3. Tumor-to-organ ratios of dual-tracer biodistribution of ⁶⁸Ga- and ¹⁷⁷Lu-PSMA I&T at 1 h after injection in LNCaP tumor-bearing CD-1 *nu/nu* mice (*n* = 4). T/ = tumor-to-.

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. 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. 2011.0035, Abergel Tr. 136:15-137:4

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 .

Importantly, Wineisen 2015 makes no mention of ^{225}Ac in this follow-up writing. This is consistent with my discussion above of Wineisen 2014's deliberate exclusion of ^{225}Ac from the first studies in 2014. And even if the POSA got the impression that Wineisen'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. Abergel argues that it would have been obvious to combine ^{225}Ac with Wineisen 2015's PSMA-I&T construct, it apparently did not occur to Wineisen herself – despite her clearly being aware of ^{225}Ac as a potential “therapeutic M^{3+} radiometal [I]”.³ Therefore, Wineisen 2014 and 2015 explicitly teach that the most promising radionuclide for these treatments was ^{177}Lu , and implicitly teach that ^{225}Ac was not suitable.

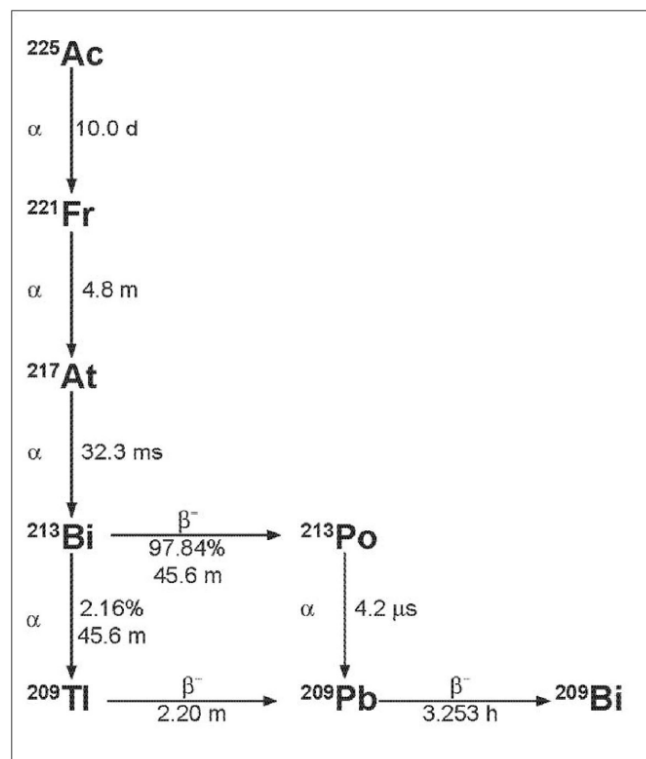
C. Chatalic

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

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 alpha-radiation into surrounding organs, thereby causing irreparable damage to healthy

³ In fact, no ^{225}Ac -PSMA-I&T appeared in publication as a suggested treatment until 2020. Ex. 2042, 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.

organs. 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 . But 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.* 201; 4(4): 306–320.

Second, far from encouraging use of alpha emitters, Chatalic would actually deter the POSA from using alpha emitters. Specifically, Chatalic described injecting mice – which typically weigh about 25 grams – with 5 MBq ^{213}Bi -PSMI I&T. In a human patient – who would weigh about 85-90 kg on average in North America – this dosage would translate to $(85/.025 \times 5=)17,000$ MBq. 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, it appears that Chatalic uses a presumed 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 their 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-PPMPA 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 .

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.

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)

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.

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.

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.

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.

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. Abergel 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.

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}As , 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. 2044, 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. 2045, 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

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

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 Fusion’s proffered grounds for obviousness, as well as in many of the other references relied on by Dr. Abergel. 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. 2046, 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.

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.

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. Abergel – because it is not targeted to PSMA. Instead, Jurcic is directed to a treatment for leukemia, and leukemia cells with lintuzumab, which is targeted to the CD33 protein found on leukemia cells.

The significant differences in the treatment and disease discussed in Jurcic and the remaining references relied on by Fusion and Dr. Abergel 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. Abergel) would be cleared out much more quickly further emphasizes the completely different and irrelevant nature of Jurcic's disclosure.

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. Abergel'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.

But perhaps Jurcic's biggest failure is that it demonstrates that ^{225}Ac either does nothing or is slightly detrimental. Jurcic does not use the ^{225}Ac -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. Abergel lacks a proper control of the isolated pharmaceuticals. When asked about this, Dr. Abergel agreed that to understand the effects of the ^{225}Ac -lintuzumab, it would have to be compared to LDAC alone:

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. 2011.0041, Abergel Tr. 157:12-22

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. 2047, 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 Actinium-225 (²²⁵ Ac)-Lintuzumab and Low-Dose Cytarabine (LDAC) in Patients Age 60 or Older with Untreated Acute Myeloid Leukemia (AML), <i>Blood</i> (2016) 128 (22): 4050. Ex. 1011.	11%
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, <i>Cancer</i> 2007;109:1114–24. Ex. 2047	18%
Winter, JN, et al., Low-dose cytosine arabinoside (Ara-C) therapy in the myelodysplastic syndromes and acute leukemia. <i>Cancer</i> 1985; 56(3):443-9. Ex. 2048	9%
Tilly, H, et al., Low-dose cytosine arabinoside treatment for acute nonlymphocytic leukemia in elderly patients, <i>Cancer</i> 1985; 55(8):1633-6. Ex. 2049.	50%
Cheson, BD, et al., A critical appraisal of low-dose cytosine arabinoside in patients with acute non-lymphocytic leukemia and myelodysplastic syndromes, <i>J Clin Oncol</i> 1986; 4(12):1857-64. Ex. 2050	16-32% (summarizing articles)

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 actually concluded that the ²²⁵Ac-antibody construct had a **negative** effect, reducing the efficacy and effectiveness of the cytarabine. 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 is the average success rate for cytarabine alone. This still suggests that the ^{225}Ac -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. Abergel.

Also, since the POSA would have understood that the ^{225}Ac -antibody construct actually had a negative effect on the cytarabine treatment, 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 ostensibly impeded the work of cytarabine, the POSA would have – at best – found the doses in Jurcic instructive as to what doses **not** to use.

F. Kratochwil

The Kratochwil reference is a simple abstract providing follow up information on the tolerability of Ac-225-DOTATOC. (Ex. 1031.001.) For this construct, Kratochwil reports a maximum tolerable dose (MTD) of 40 MBq, and fractional doses of 25 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 maximum tolerable dose. 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. 2011.0044, Abergel TR. 169:230170:17. Kratochwil only referred to the numbers he provided as the Maximum Tolerable Dose (MTD) or tolerated doses. He never provides any numbers for an effective or efficacious dose.

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.

As a specific case in point, the 2016 Kratochwil 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. But Kratochwil only mentions chronic kidney toxicity. (Ex. 1031.001.) This is because DOTATOC would not have the same qualitative or quantitative toxicity as a PSMA targeting ligand. 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.

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

I disagree with Dr. Abergel's assertion that the prior art she describes renders the '901 Patent claims obvious. Dr. Abergel supports her 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. Abergel'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.

First, I do not agree that Dr. Abergel has demonstrated her assertion that the POSA would have been motivated to select PSMA I&T over many other potential PSMA-targeting ligands. While Dr. Abergel has cited papers using PSMA I&T, such as Weineisen 2015 and Chatalic, she 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 she 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 she has argued that these methods were also effective. 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. 2033, Tagawa, ST, et al., Anti-prostate-specific membrane antigen-based radioimmunotherapy for prostate cancer, *Cancer* 2010;116(4 Suppl):1075-83; Ex. 2035, 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. Abergel’s “improved” radioligand, Dr. Abergel 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. Abergel herself 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.)

Dr. Abergel does not demonstrate that PSMA I&T was better than these small molecule and antibody alternatives. She 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.” (Abergel 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.

Dr. Abergel's reference to Chatalic does nothing to support her claim since there were – and still are – many researchers using small molecules and antibodies in PSMA studies. Although Dr. Abergel repeats her 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. This indicates to the POSA that alpha-emitting PSMA I&T radiopharmaceuticals must be used at very high concentrations to achieve effect that he demonstrated in his 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.

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.

Second, but equally important, Dr. Abergel 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

^{225}Ac daughter nuclides being released and the subsequent toxicities, and these references were trying to work around this significant issue.

Ironically, Dr. Abergel 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." (Abergel Decl. ¶77.) I agree. But that means that Weineisen demonstrates that the safest and most promising radionuclide was ^{177}Lu , not ^{225}Ac .

Dr. Abergel 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. Abergel'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. Abergel's reference to the DOTATOC study by Miederer 2008a does not counter this point because it is a wholly different ligand.

Dr. Abergel 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. Kruijff, Ex. 2007.003. Although Dr. Abergel argues that the ^{225}Ac would reduce side effects, she admitted that this assumed the radioligand would be delivered to the target cell:

Q. You say "The more localized impact of alpha decay makes it ideally suited for targeted therapy because the impact on the surrounding tissue is minimized, reducing the likelihood of side effects." Do you see that?

A. I do.

Q. Now, doesn't this line assume that the actinium remains within the molecule and is fully delivered to the tumor?

A. Yes. It is describing the effect of the alpha particles emitted from the radionuclide in the same location as the compared diameter.

Q. But if you're thinking in terms of just comparing a beta-emitting nuclide and an alpha-emitting nuclide in the same location, then if those two nuclides are in some healthy organ, in fact, the alpha-emitting nuclide would cause more damage, wouldn't it?

A. That's right. Yes.

Q. So in that case, this sentence would be wrong because it doesn't reduce the likelihood of side effects.

MS. CIPRIANO: Objection to the extent it takes the document out of context.

A. If the targeting is not achieved.

Q. And you say in your declaration that actinium reduces the likelihood of side effects, correct?

A. I say that alpha decay is better suited for targeted therapy because it is more localized in terms of its effects when compared to beta decay.

Q. But that statement only holds true if it's been targeted to the tumor, not if it's in healthy organs because it's been released from the chelator, correct?

A. That's correct.

Ex. 2011.0029-30, Abergel Tr. 110:19-111:5; 111:10-21; 113:7-16. 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. 2018, 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 ^{225}Ac for ^{213}Bi in Chatalic's construct would increase – not decrease – side effects and risk to the patient.

Dr. Abergel'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. Abergel cites understood this. And their intentional avoidance of ^{225}Ac despite knowledge of it as a “therapeutic M^{3+} -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.

Third, Dr. Abergel takes a non-clinical, overly simplistic approach to determining dose. She 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. (Abergel Decl. ¶87.) But Dr. Abergel skips a step. As explained before, a lot of factors go into the difference between the administered activity (what Dr. Abergel 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 their 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.

Sgourous (Ex. 1017) does not support Dr. Abergel's contentions. Sgourous was not intended to magically provide the administered activity value as Dr. Abergel implies. The

publication teaches that determining the administered activity is difficult because of “complex activity and tissue geometries.” (Ex. 1017.009.) Sgourous admits that “[d]etermining the activity distribution [] remains difficult.” (Ex. 1017.010.) Dr. Abergel herself recognized this as recently as 2022. She wrote that in “targeted alpha therapy, dosimetry calculations are more challenging than in other types of targeted radiotherapy, since the daughter nuclides need to be considered, and they may have different pharmacokinetic profiles and chemical properties.” Pallares RM and Abergel RJ, Development of radiopharmaceuticals for targeted alpha therapy: Where do we stand? *Front. Med.* 2022; 9:1020188.

To the extent that Dr. Abergel implies that Sgourous (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 Sgourous 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.

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. 3031.) Analogous to Sgourous 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 Sgourous, 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.

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 that the Jurcic dose of the antibody construct had either no effect or a negative effect 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.

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

I have reviewed Dr. Abergel's prior art and her analysis of the claims and disagree with her 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 one of the prior art references and there must be some motivation to combine those references. I do not believe that Dr. Abergel's explanations meet this standard.

1. *Claim 1*

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

Dr. Abergel 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. Abergel, 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.

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

Ostensibly to support her reliance on Weineisen 2015, Dr. Abergel 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 .

I also disagree because Chatalic tested both PSMA I&T and the nanobody JVZ-008 and found that they had equivalent uptake (5.75 ± 2.70 %ID/g and 2.68 ± 0.56 %ID/g) and tumor to kidney ratios. Chatalic did not distinguish JVZ-008 from PSMA I&T for additional study. Dr. Abergel acknowledged this at her deposition:

Q. So, again, Chatalic's data doesn't show that the 213 bismuth PSMA I&T and the 213 bismuth JVC 008 are better or worse than each other, correct?

A. That's correct. It doesn't suggest that.

Ex. 2011.0039, Abergel Tr. 150:2-5.

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.

Dr. Abergel 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. Abergel - 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.

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.

The same applies to Dr. Abergel's reliance on the Kratochwil reference (Ex. 1031). This reference was also directed to the DOTATOC ligand. Dr. Abergel 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.

Dr. Abergel considers the dosing question superficially by focusing on the administered activity. And she 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 is 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. Abergel. 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.

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.

For these reasons, I do not agree with Dr. Abergel’s analysis and conclusions. And I do not believe that the POSA would have combined Weineisen 2015 (PSMA I&T) with Kratochwil (^{225}Ac) as suggested by Dr. Abergel and Fusion.

2. *Claim 2*

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.

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*

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.

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*

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.

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 4 and 5 as well.

5. *Claims 8-9*

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.

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).

I note that Dr. Abergel illustrates her misconception when she 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. Abergel 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.

Dr. Abergel 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 the radioimmunoconjugate had no effect – and perhaps even had a negative effect – above what cytarabine could do on its own. But also, as I explained above with respect to Sgourous, 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*

I have been informed that Claim 10 is dependent on Claim 1 and Claim 11 is dependent on Claim 10, so they include all the elements of Claim 1 and further narrow the elements in

Claims 1 and/or 11 by adding new requirements or selectively narrowing the requirements in Claims 1 and/or 11.

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

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.

Claims 12 and 13 introduce the requirement that the dosage be repeated every 15-90 days. Dr. Abergel 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).

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).

B. A POSA Would Have No Motivation to Combine Dr. Abergel's References

For the reasons I state above, a POSA would have had no reason to combine Dr. Abergel'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 Kratochwill reference (Ex. 1031) to work with the PSMA I&T of Weineisen 2015 (Ex. 2028) 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.

As Dr. Abergel said in her 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." Abergel Decl. at ¶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 in the same family as ^{177}Lu , but since it is below it on the periodic table a POSA would expect it to differ in size and have unknown effects on the binding of the PSMA I&T ligand. That Weineisen 2014 (Ex. 2027) 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.

At her deposition, Dr. Abergel 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. 2011.0043, Abergel Tr. 167:7-168:7.

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. Abergel's claim in her declaration that they would be the same is purely hindsight.

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).

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. Abergel assumes too much about the way the biological system works – which is notoriously unpredictable.

The POSA also would not have relied on Chatalic (Ex. 1006) or Jurcic (Ex. 1011) to guide their decision to combine Kratochwil and Weineisen 2015, because Chatalic shows that the use of alpha emitters is questionable. Chatalic uses 5MBq ²¹³Bi 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 PMSA 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 dosage of antibody with ^{225}Ac had done nothing because its combination with LDAC was 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.

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.

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

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;

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. 2051.002, 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.
- “The ^{225}Ac labeled derivative, ^{225}Ac -PSMA-617, developed and characterized by the JRC Karlsruhe in 2013, has shown a remarkable therapeutic efficacy in heavily pre-treated metastatic castration-resistant prostate cancer (mCRPC) patients.” Ex. 2052.002, Sathekge, M., et al., ^{225}Ac -PSMA-617 in chemotherapy-naïve patients with advanced prostate cancer: a pilot study, *Eur J Nucl Med Mol Imaging* 2019, 46:129–138.
- “Kratochwil et al. first described a remarkable therapeutic effect of ^{225}Ac -PSMA-617 in patients with late stage prostate cancer (Fig. 3).” Ex. 2053.003, Feurecker, B., et al., Clinical Translation of Targeted α -Therapy: An Evolution or a Revolution? *J Nucl Med* 2023; 64:685–692

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.”

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 ¹⁷⁷Lu construct. Indeed, the treatment with the ¹⁷⁷Lu construct actually resulted in the cancer continuing to grow and spread. That another radiation treatment could be applied after such potent ¹⁷⁷Lu resistance and be as successful as the treatment recited in the ‘901 Patent, is truly remarkable and unprecedented. Even if we accept Dr. Abergel’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.

Dr. Abergel’s explanation for why the results were not unexpected does not actually address the results themselves and indicates that she is not applying the correct standard:

Q. So did your counsel -- so were you made aware of what secondary considerations are?

MS. CIPRIANO: So objection to the extent it calls for privileged information. But you can answer the question to the extent you understand it.

A. So my understanding is that there are other considerations in addition to the existing literature to assessing whether something is novel and worth patenting. So yeah.

Q. Okay. Did you consider unexpected results?

A. I considered the possibility of unexpected results. Yes.

Q. Okay. What did you conclude?

A. I did not believe that the results or the claims in the patents were unexpected.

Q. And why was that?

A. Because, as we've discussed all day, I think person of skills would have thought of using actinium-225, and the proposed treatment regimen would have been the starting point based on the available literature at the time.

Ex. 2011.0046, Abergel Tr. 180:8-181:4.

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 ²²⁵Ac 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."

Moreover, as Dr. Abergel lays out in her 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. (Abergel 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. (Abergel Decl. at 16.) At her deposition, when Dr. Abergel was asked about this need, she agreed that there was a long-felt need for improvement:

Q. Okay. And then in paragraph 35, you continue with the history. "Prior to 2014, most therapies for the treatment of prostate cancer were focused on androgen-deprivation therapy and chemotherapy," right?

A. That's right.

Q. And these were plagued by undesirable side effects, including bone loss, metabolic change, muscle loss, hot flashes, and increased cardiovascular disease, right?

A. That's right.

Q. So, again, it seems like there was a long-felt need to improve upon these systems, right?

MS. CIPRIANO: Objection; calls for a legal conclusion.

A. There's always a need for improvement, so....

Q. It had been sitting for quite some time, since before 2010, correct?

A. That is correct.

Abergel Tr. 122:6-23. She also insisted researchers had begun considering ²²⁵Ac as a possible treatment radionuclide since 2001, pointing to her Ex. 1013:

Q. But it gaining favor was something that was fairly recent in 2016, correct?

A. I would say that it was maybe about 20 years old. This paper that you cited that I referred to and that you brought here is from 2001, so it's already 15 years before this patent.

Q. Okay.

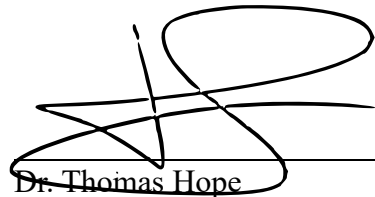
A. So I would say a couple decades.

Abergel Tr. 120:16-23. But no researcher had implemented them truly successfully until the '901 Patent, showing that the Patent fulfilled a long-felt need that others had not met despite an interest in doing so.

X. Conclusion

Based on the reasons given above, I disagree with Dr. Abergel'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. Abergel.

DATED: November 21, 2023



Dr. Thomas Hope

CERTIFICATE OF SERVICE

I hereby certify that on November 21, 2023, a copy of this **PATENT OWNER'S RESPONSE AND SUPPLEMENTAL EVIDENCE TO PETITIONER'S OBJECTIONS TO EVIDENCE**, was served by email on the following correspondence addresses of record for Petitioner, pursuant to 37 C.F.R. § 42.6(e):

DG-Fusion-IPR@goodwinlaw.com

lcipriano@goodwinlaw.com

ouitto@goodwinlaw.com

gtruong@goodwinlaw.com

ChristopherHaley@goodwinlaw.com

Evan Boetticher
Registration No. 63,184
Counsel for Patent Owners