

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 Owners

Case No. IPR2023-00551
Patent No. 10,980,901 B2

**PATENT OWNERS' RESPONSE
PURSUANT TO 37 C.F.R. §42.120**

TABLE OF CONTENTS

	<u>Page(s)</u>
I. INTRODUCTION	1
II. THE '901 PATENT AND CHALLENGED CLAIMS	3
A. Level of Skill in the Art.....	3
B. Technology Background and Overview of Patent	8
C. Solution Offered by the '901 Patent.....	9
D. Challenged Claims and Claim Construction	17
III. LEGAL STANDARDS	22
IV. FUSION'S PRIOR ART REFERENCES FAIL TO SHOW OBVIOUSNESS.....	24
A. Prior Art References	28
1. Weineisen 2014.....	28
2. Weineisen 2015.....	34
3. Chatalic	37
4. Miederer (Ex. 1015).....	40
5. Jurcic	42
6. Kratochwil.....	45
B. A POSA Would Not Have Been Motivated to Combine Weineisen and Kratochwil	47
C. A POSA Would Not Have Been Motivated to Combine Weineisen, Kratochwil, and Jurcic.....	55
D. Secondary Considerations Support Nonobviousness.....	57
1. The work in the patent has received considerable praise	57
2. The patent invention produced unexpected results.....	63
3. The patent teaches away from convention.....	65
4. The patent resolved a long-felt need.....	65

V.	CONCLUSION.....	68
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TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>CFMT, Inc. v. YieldUp Int’l Corp.</i> , 349 F.3d 1333 (Fed. Cir. 2003)	22
<i>Garmin Int’l, Inc. v. Patent of Cuozzo Speed Techs. LLC</i> , Case No. IPR2012-00001, Paper 15 at 15 (Jan. 9, 2013)	23
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966).....	23
<i>In-Depth Geophysical, Inc. v. ConocoPhillips Co.</i> , IPR2019-00850, Paper 56, *27 (Sept. 3, 2020).....	22
<i>Innogenetics, N.V. v. Abbott Labs.</i> , 512 F.3d 1363 (Fed. Cir. 2008)	24
<i>In re Kahn</i> , 441 F.3d 977(Fed. Cir. 2006)	24
<i>In re Rijckaert</i> , 9 F.3d 1531 (Fed. Cir. 1993)	23
<i>In re Royka</i> , 490 F.2d 981 (C.C.P.A. 1974)	22, 23
<i>Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.</i> , 821 F.3d 1359 (Fed. Cir. 2016)	23
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<i>LG Elecs., Inc. v. Cellular Commc’ns Equip. LLC</i> , IPR2016-00197, Paper 7 at 7-11 (April 29, 2016)	24
<i>Metalcraft of Mayville, Inc. v. Toro Co.</i> , 848 F.3d 1358 (Fed. Cir. 2017)	24

<i>Trivascular, Inc. v. Samuels</i> , 812 F.3d 1056 (Fed. Cir. 2016)	24
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Statutes

37 C.F.R. § 42.104(b)(4).....	22
35 U.S.C. § 103	22, 23
35 U.S.C. § 316(e)	22

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I. **INTRODUCTION**

Pursuant to 37 C.F.R. §42.120, Patent Owners Universität Heidelberg (“UH”) and The European Atomic Energy Community (EURATOM), Represented by The European Commission (“EURATOM”), (collectively, “Patent Owners”), submit their Response to the Petition (Paper No. 2, “Pet.”) for *Inter Partes* Review (“IPR”) of U.S. Patent No. 10,980,901 (the “’901 Patent”) filed by Fusion Pharmaceuticals, Inc. (“Fusion” or “Petitioner”). This submission is timely in accordance with the Notice of Joint Stipulation to Modify Due Dates 1-3 and a Portion of Due Date 5 of the Scheduling Order filed on September 10, 2023 (Paper No. 12).

A. **Summary of Argument**

The Petitioner’s reliance on six disparate references to bring down a patent that has been widely recognized as groundbreaking fails because they provide no reason for a person of ordinary skill in the art (“POSA”) to combine them or for the POSA to believe that the current patent would have any reason to succeed – particularly to the unexpected extent that it did. In its rush to demand invalidation of the claims, Petitioner overlooked the difficulties and pitfalls that had prevented the successful use of the ^{225}Ac radionuclide, not the least of which is the fact that it is – even today – impossible to create a stable ligand with it. As an alpha emitter, the ^{225}Ac releases its alpha particle with enough force to consistently – *every time* – eject it from the chelator holding it. This is an indisputable fact of science that was widely

recognized in the field. But Fusion and its “expert” make no mention of it. Upon its invariable release from its ligand molecule, the daughters of ^{225}Ac (the elements resulting from the atomic degradation of ^{225}Ac , which include ^{221}Fr , ^{217}At , ^{213}Bi , and a last group that is usually ^{213}Po and ^{209}Pb but 2% of the time is ^{209}Tl and ^{209}Pb) would have free reign of the body, pooling in locations like the kidney, spleen, liver, and the bone to cause damage there.

There is no way to prevent this release and cascade. The only way to overcome it is to use a molecule that would have a rapid enough uptake by the cells or removal from the body that it would not have the opportunity to cause this damage. The prior art relied upon by Fusion fails to show the way to that molecule. Instead, the prior art uses large molecules, like Jurcic’s antibodies (Ex. 1011), that remain in the body for days, slowly releasing any alpha emitters from its grasp. The prior art, like Weineisen 2014 and 2015 (Exs. 1027 and 1028), also focuses on using ^{177}Lu , a beta-emitter that would not be released from the molecule upon firing off its much smaller beta particles. These references show that, although ^{225}Ac was known of at the time, it was avoided in favor of the safer beta-emitter alternative which would not be ejected from the ligand and be allowed to roam freely. Fusion’s example of an alpha emitter used with the PSMA I&T ligand is actually the exception that proves the rule, because, rather than using the ^{225}Ac with its five daughter nuclides that would ultimately emit three additional alpha particles and two beta particles, Chatalic (Ex. 1006) attempted to avoid ^{225}Ac ’s danger by using one of its daughter nuclides, ^{213}Bi , that only emits one alpha particle – and therefore never emits one outside of its

ligand. This sidestepped the danger of ^{225}Ac 's free-roaming daughter nuclides and taught the POSAs that they should do the same. Finally, the remaining references Kratochwil (Ex. 1031) and Miederer (Ex. 1031) use an entirely different ligand molecule, the DOTATOC, which is applied to different cancer cells and molecular targets. Since the primary question is whether the ligand would be taken up by the target cells before losing its ^{225}Ac or would be cleared from the body before becoming toxic, experiments with DOTATOC shed no light on how PSMA-ligand molecules (much less PSMA I&T specifically) would work in that regard.

Fusion's argument fails to explain the pathway to the '901 Patent, and instead attempts to mix and match a Frankenstein molecule without regard to what the POSA was thinking at the time.

B. Summary of Case Procedure

Fusion has challenged Claims 1, 2, and 4-13 of '901 Patent claiming that 1) claims 1, 2, 4-8, and 10-13 are obviousness over Weineisen 2015 and Kratochwil; and 2) claim 9 is obviousness over Weineisen 2015, Kratochwil and Jurcic. (Pet., p.5). On August 15, 2023, the Board instituted *inter partes* review on those grounds and issued its schedule. On September 20, 2023, the parties filed a joint stipulation to amend the schedule to allow for filing of the Patent Owner's Response on November 21, 2023.

II. THE '901 PATENT AND CHALLENGED CLAIMS

A. Level of Skill in the Art

Patent Owners disagree with Fusion's asserted level of skill in the art which

should be based on the relevant elements of the patent and the relevant prior art rather than on the expert Fusion was able to find. The '901 Patent relates to a treatment of "PSMA expressing cancers" requiring the use of a particular compound at specific treatment doses, either based on body weight or as a unitary dose. (Ex. 1001:'901 Patent 18:14-20:37.) As such, this is a patent for a clinical product and a clinician would be best suited to opine on its obviousness and how a POSA would have understood the field at the time. Dr. Abergel is not an appropriate expert in this case.

For example, Dr. Abergel opined that a POSA should have experience in radioimmunoconjugates, because her own experience is limited to labeled antibodies. But the PSMA I&T that Fusion relies on for its obviousness argument is not an immunoconjugate because it is not an antibody. Dr. Abergel admitted at her deposition that she does not have experience with prostate cancer, PSMA, or small molecule radiotherapeutics like PSMA I&T:

Q. Now, have you ever done work with PSMA?

A. I have not.

Q. Okay. Have you ever done work on prostate cancer?

A. I have not.

Q. So do you have experience using ligands for targeting the radiotherapeutic?

A. When you say "ligands," do you say small molecules, peptides?

Q. I would say a small molecule that binds to a receptor?

A. I do have not direct experimental experience with small molecule targeting vectors.

Abergel Deposition Transcript ("Abergel Tr."; Ex. 2011) 23:12-16; 24:5-12.

This is despite the fact that her expert report and Fusion's petition focuses primarily on the assumption that a POSA could make conclusions concerning one small molecule, DOTATOC, to another small molecule, PSMA I&T.

Dr. Abergel also admitted that the patent does not claim new methods of synthesizing molecules or of making or attaching radionuclides, making much of her experience irrelevant and her POSA requirement for experience in the synthesis of chelators simply wrong.

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.

Abergel Tr. 34:24-35:8 (Ex. 2011).

Most problematic is her requirement that the POSA have experience in the “clinical use of radiotherapeutic agents” when she herself has none:

Q. Okay. And so you're not an M.D., correct?

A. I am not an M.D.

Q. Okay. So you haven't administered radiotherapeutics to any patients, correct?

A. That's correct.

Q. Okay. And you haven't treated any patients or diagnosed any patients, correct?

A. That's correct.

Abergel Tr. 12:24-13:6 (Ex. 2011). She also admitted that even in the development of radiopharmaceuticals, her role was outside of the clinical setting. For example, when asked about her involvement in a drug development with a pharmaceutical:

Q. But as far as giving the treatments to patients to test it, you weren't involved in that, were you?

A. I was not.

Q. And in determining whether or not the compounds had clinical utility, you weren't involved in that, were you?

A. I was not directly involved, but I believe that some of my team's findings were used for those determinations.

Q. And when you say your team's findings, do you mean the clinicians?

A. I mean the publications and reports that came out of our studies were used in documents that were submitted to the Food and Drug Administration, for example.

Q. But were you involved in the clinical aspects in producing the data for those reports?

A. I was not.

Abergel Tr. 21:24-21:17 (Ex. 2011). So while Dr. Abergel may know about the synthesis of molecules, she does not have the hands-on experience necessary to understand the difficulties of dosing and how the black box of the human biological system is one that must be determined empirically. Therefore, she does not meet her own standard for a POSA.

Patent Owners' Response is supported by the declaration of Dr. Thomas Hope (Ex. 2010), an expert in the field who has decades of experience using radionuclides as both imaging tools and as therapeutics. He has clinical experience in testing and developing novel PET radiopharmaceuticals for the imaging of diseases and disease states and targeted radionuclide therapies for neuroendocrine tumor and prostate cancer treatment which includes PSMA-binding ligands. His experience is outlined in his Declaration and detailed in his Curriculum Vitae (Ex. 2056.)

Based on the nature of the claimed invention and relevant prior art, 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. (Hope Decl., pg. 11.) Patent Owners do not believe that Dr. Abergel meets these requirements either.

B. Technology Background and Overview of Patent

PSMA (*Prostate Specific Membrane Antigen*) expressing cancers rank among the most frequent cancers. (Ex. 1001, 1:66 – 2:5). In particular, prostate is one of the most common cancer types and a leading cause of cancer death in men. While the survival rate on localized prostate cancer is good, once the cancer has metastasized, the survival prognosis decreases considerably. (Ex. 2054; Center MM, et al., International variation in prostate cancer incidence and mortality rates. *Eur Urol.* 2012;61(6):1079–92.) Late-stage prostate cancer, when the disease is widely disseminated, limits the availability of treatments. *Id.*

In spite of considerable efforts spent on various approaches during the last decades, these PSMA expressing cancers are still among those for which a reliable and efficient therapy remained elusive. Radiopharmaceuticals are particularly interesting for treating various cancers. Radiopharmaceuticals typically comprise a combination of: (1) a targeting moiety (ligand), (2) a chelating moiety, and often (3) a linker between the two. The targeting moiety (1) is specific to certain target markers (predominantly) expressed by target cells, and the chelating moiety (2) is

able to chelate (bind) a radionuclide. The radiopharmaceutical (*i.e.*, the combination of the targeting and chelating moieties with a radionuclide) is thus able to target and bind to the desired site of such cells to destroy the cell it's bound to or nearby cells, such as cancer cells. (Ex. 1001, 1:2-55). As Fusion's expert states in her Declaration, "[s]election 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." (Ex. 1002.015, ¶27) That is, all of the factors play a part in the functioning of the radiotherapeutic to treat a specific cancer, with a modification in any one of them having (sometimes surprising) effects on the radiotherapeutic's functioning.

C. Solution Offered by the '901 Patent

Within this context, the '901 Patent describes the surprising discovery that treating patients having PSMA expressing cancers with an low dosage of one or more specific Ac-225-radiopharmaceuticals (*i.e.*, with alpha-emitting Ac-225 radionuclide compounds having a specific targeting moiety and a chelating moiety, that is administered in the specific claimed effective amount), allows for an unexpectedly strong anticancer effect resulting in remission of the cancer with low hematotoxicity. This result was surprising on multiple levels. First, that an unusually low dose of 6-10 MBq could provide an effective treatment was surprising. Second

the results went beyond mere treatment but complete remission of the prostate cancer, bringing the markers for cancer below detectable levels after only 3-4 treatments. '901 Patent 13:65-14:2; 14:10-13; 17:53-61. Third, there was no significant hematotoxicity found in measurements of the platelets, white blood cells, or hemoglobin. These last two points were the most remarkable because there is usually a direct correlation between a radiopharmaceutical's efficacy and toxicity. (Hope Decl., pg. 37.) A clinician must usually use a very high dosage to achieve the kind of complete remission seen in the Patent which also increases the toxicity.

These results were also surprising because of the widely recognized issue with alpha-emitter release from the chelator allowing radionuclides free reign throughout the body, which could cause extensive damage throughout. As Dr. Hope explains, this was 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 from ^{225}Ac is much greater than that needed to expel beta particles from ^{177}Lu and can dislodge the alpha-emitting nuclide, while a beta-emitter holds firm. (Hope Decl., pg. 24.)

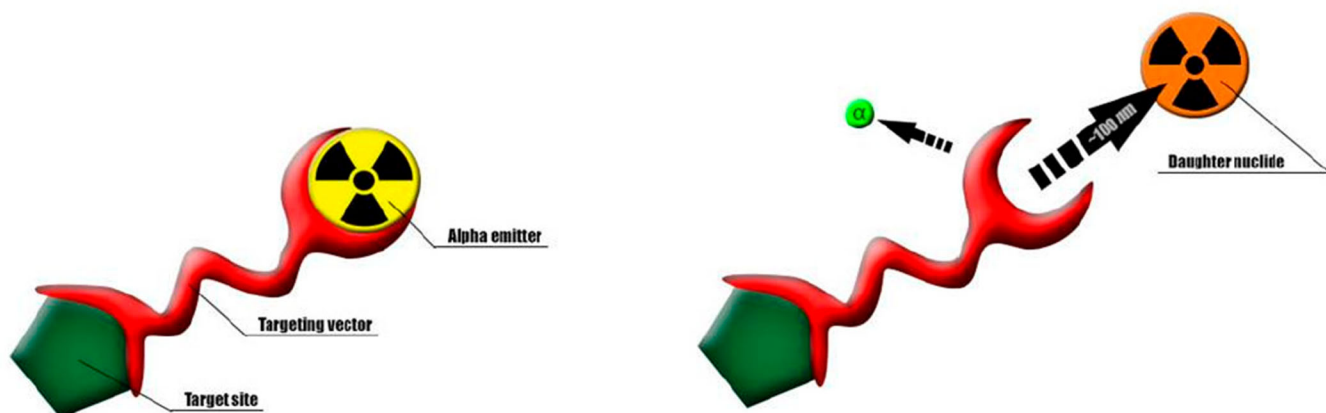


Figure 1. Schematic representation of a recoiling daughter radionuclide detaching from a targeting agent as a consequence of alpha decay.

Ex. 2007.004: de Kruijff, RM, et al., A Critical Review of Alpha Radionuclide Therapy—How to Deal with Recoiling Daughters?, *Pharmaceuticals* 2015; 8, 321-336. 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) experiences 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; (Hope Decl., pg. 24.) Therefore, any carrier molecule to which the alpha-emitter is bound will lose the daughter radionuclide once the alpha particle is released with little to no chance of them recombining, allowing the radioactive daughter nuclide to roam. *Id.* For ^{225}Ac , there are five generations of daughter nuclides before it become stably nonradioactive (^{221}Fr , ^{217}At , ^{213}Bi , and a last group that is usually ^{213}Po and ^{209}Pb but 2% of the time is ^{209}Tl and ^{209}Pb). These

will emit another three alpha particles and two beta particles before the line stabilizes. To be clear, because of the huge amount of energy produced by the alpha particle, and the fact that all alpha emitters will eventually emit one, the release of an alpha emitter like ^{225}Ac is not just a possibility, it is an *eventuality*.

Although Dr. Abergel was fully aware of this recoil issue making the use of alpha emitters like ^{225}Ac dangerous, she makes no mention of it in her declaration. She only passingly acknowledges the reality of the recoil because it is in a figure that she lifted from another source. (Abergel Decl. at 7-8):

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.

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

At her deposition, she was also asked about Ex. 2007, the de Kruijff, RM reference explaining the disadvantages of the recoil effect. She agreed that this energy was enough to expel the ²²⁵Ac daughter nuclide 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.

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

The problem of alpha-emitters escaping their targeting carriers was widely recognized. (Hope Decl., pg. 27.) Miederer, the author cited by Fusion in its Ex. 1015, noted in his 2004 paper when introducing his ^{225}Ac conjugate antibody 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. 2021.008. 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 goes on to explain that the “release of the daughters from ^{225}Ac ” was a “key drawback” because “such daughters may not be retained in tumor tissue” and would increase the chances of side-effects. *Id.* In a 2008 review, Miederer cites to examples in which the ^{225}Ac and then its released daughters were “distributed to liver and bone and the subsequent release of its daughters contributed to acute radiotoxicity.” Ex. 1030.003. And again, in the paper that Fusion relies on

as one of its primary references, Ex. 1015, Miederer says 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 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.” Ex. 1015.002. When asked about this passage, Dr. Abergel could not disagree with its assessment. Abergel Tr. 72:19-73:10. Dr Abergel acknowledged that this was a concern for the POSA community:

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.

Abergel Tr. 71:1-11.

In fact, Dr. Abergel was one of them. In her November 2016 review paper, Active Actinium, she writes that 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 ” and recommends solutions such as nanoparticles. Ex.

2008: DeBlonde, GJ, Abergel, RJ, *Nat Chem.*, 2016 Oct 21;8(11):1084. Six years later, in 2022, Dr. Abergel writes in a review article that she *still* sees the release of the daughter nuclides as a problematic hurdle in the use of ^{255}Ac : “Although pre-clinical and clinical studies have highlighted the therapeutic benefits of these conjugates, there are still challenges that need to be solved, such as kinetics and stability of the complexes[], and retention of the daughters.” Ex. 2009: Pallares RM and Abergel RJ, Development of radiopharmaceuticals for targeted alpha therapy: Where do we stand? *Front. Med.* 2022; 9:1020188.

D. Challenged Claims and Claim Construction

Patent Owner does not currently believe that any claim construction beyond the plain and ordinary meaning is necessary, but reserves its right to respond to any implicit or explicit claim construction put forward by Petitioner

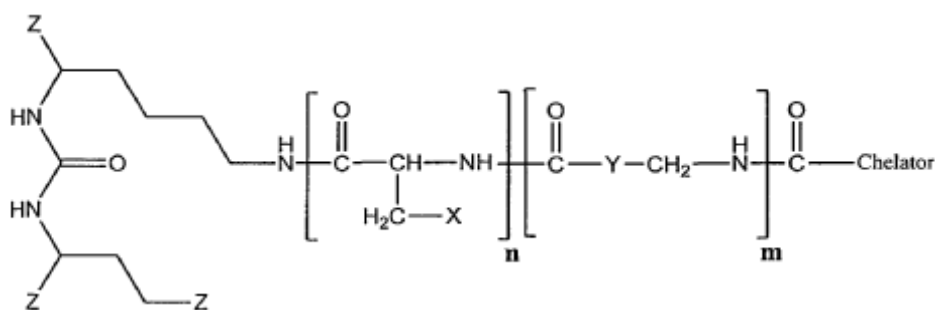
Claim 1 of the '901 Patent recites a method for treating PSMA expressing cancers comprising administering a specifically recited “effective amount” of an Ac-225 radiopharmaceutical. The claim includes a Markush group defining a specific group of covered ligands that chelate the Ac-225 radionuclide, which include ligands satisfying Formulae (A), (B), (C), (D), and (E). Remaining challenged claims 2 and 4-13 depend directly or indirectly from claim 1.

Claim 1 states:

A method for treating PSMA expressing cancers, wherein the method

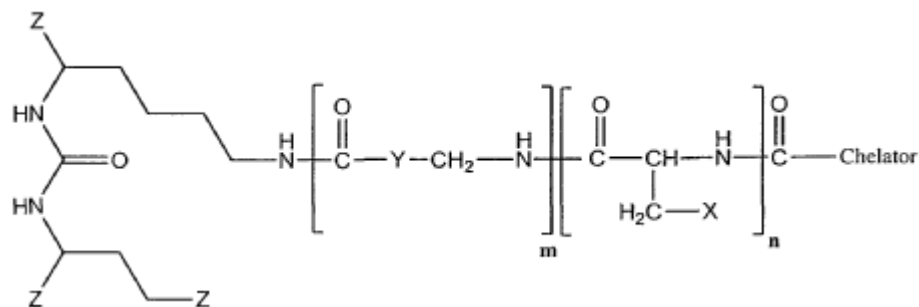
comprises administering to a patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B), (C), (D) or (E):

Formula (A)



or

Formula (B)



with:

- | | |
|-----------|--|
| n: | 0,1 |
| m: | 1,2,3,4 |
| Z: | -CO ₂ H, -SO ₂ H, -SO ₃ H, -SO ₄ H, -PO ₂ H,
-PO ₃ H, -PO ₄ H ₂ |
| X: | naphthyl, phenyl, biphenyl, indolyl
(=2,3-benzopyrrolyl), benzothiazolyl |
| Y: | aryl, alkylaryl, cyclopentyl, cyclohexyl, |

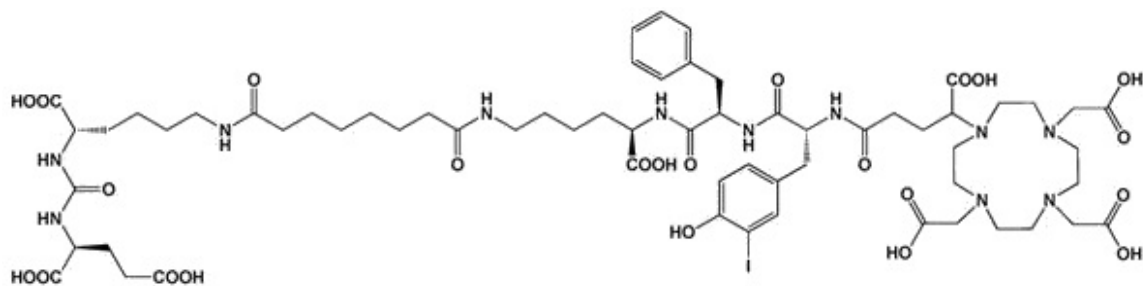
Chelator:

cycloheptyl
 1,4,7,10-tetraazacyclododecane-
 N,N',N'',N'''-tetraacetic acid (DOTA),
 N,N''-bis[2-hydroxy-5-(
 (carboxyethyl)benzyl]ethylenediamine-
 N,N''-diacetic acid (HBED-CC),
 1,4,7-triazacyclononane-1,4,7-triacetic
 acid (= NOTA),
 2-(4,7-bis(carboxymethyl)-1,4,7-
 triazonan-1-yl)pentanedioic acid
 (NODAGA),
 2-(4,7,10-tris(carboxymethyl)-
 1,4,7,10-tetraazacyclododecan-1-
 yl)pentanedioic acid (DOTAGA),
 1,4,7-triazacyclononane phosphinic
 acid (TRAP),
 1,4,7-triazacyclononane-1-[methyl(2-
 carboxyethyl)phosphinic acid]-4,7-
 bis[methyl(2-
 hydroxymethyl)phosphinic acid]
 (NOPO),
 3,6,9,15-
 tetraazabicyclo[9.3.1.]pentadeca-
 1(15),11,13-triene-3,6,9-triacetic acid
 (PCTA),

N'-{5-[Acetyl(hydroxy)amino]pentyl}-
 N-[5-({4-[(5-aminopentyl)-
 (hydroxy)amino]-4-
 oxobutanoyl} amino)pentyl]-N-
 hydroxysuccinamide (DFO),
 diethylenetriaminepentaacetic acid
 (DTPA),
 Trans-cyclohexyl-
 diethylenetriaminepentaacetic acid
 (CHX-DTPA),
 1-oxa-4,7,10-triazacyclododecane-
 4,7,10-triacetic acid (oxo-Do3A) p-
 isothiocyanatobenzyl-DTPA (SCN-Bz-
 DTPA),
 1-(p-isothiocyanatobenzyl)-3-methyl-
 DTPA (1B3M),
 2-(p-isothiocyanatobenzyl)-4-methyl-
 DTPA (1M3B), or
 1-(2)-methyl-4-isocyanatobenzyl-
 DTPA (MX-DTPA)

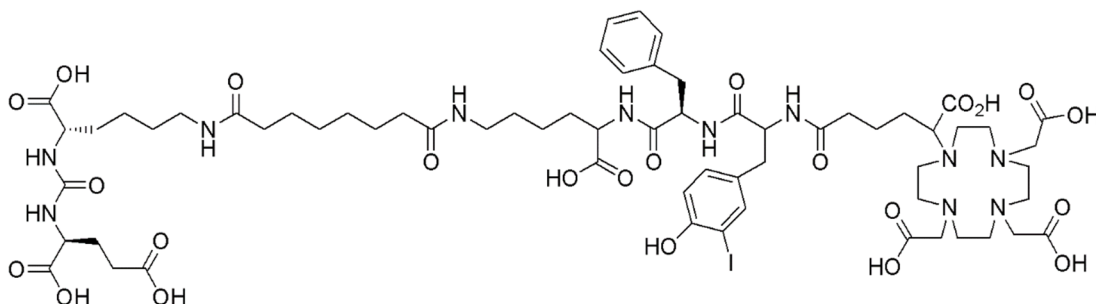
or

Formula (C)



or

Formula (D)



,

or

Formula (E)

(PSMA antibody)-Chelator or (PSMA minibody)-Chelator;

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

As will be readily appreciated, the claims plainly recite a narrow specific class of ligands in combination with a specific radionuclide applied at specific low dosages

to target a specific class of cancer. The dependent claims go further, reciting specific cancers (claims 2, 4-8, 10-14) and an even more narrow effective dosage (claim 9).

III. LEGAL STANDARDS

In an inter partes review, “the petitioner shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.” 35 U.S.C. § 316(e). To that end, Fusion “must ‘specify where each element of the claim is found in the [relied upon] prior art patents.’” *In-Depth Geophysical, Inc. v. ConocoPhillips Co.*, IPR2019-00850, Paper 56, *27 (Sept. 3, 2020) (quoting 37 C.F.R. § 42.104(b)(4)).

The Petition relies solely on obviousness, and more specifically upon combinations of two or more references for each ground. Section 103 of the Patent Act provides that “[a] patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention **as a whole** would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.” 35 U.S.C. § 103 (emphasis added). If a single element of a claim is absent from the prior art, the claim cannot be considered obvious. *See CFMT, Inc. v. YieldUp Int’l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (“[O]bviousness requires a suggestion of all limitations in a claim.”) (citing *In re Royka*, 490 F.2d

981, 985 (C.C.P.A. 1974)); *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (reversing obviousness rejection where prior art did not teach or suggest all claim limitations); *Garmin Int'l, Inc. v. Patent of Cuozzo Speed Techs. LLC*, Case No. IPR2012-00001, Paper 15 at 15 (Jan. 9, 2013) (refusing to institute an IPR under 35 U.S.C. § 103 where prior art did not disclose all claim limitations).

Assessing obviousness requires considering: (1) the “level of ordinary skill in the pertinent art,” (2) the “scope and content of the prior art,” (3) the “differences between the prior art and the claims at issue,” and (4) “secondary considerations” of non-obviousness such as long-felt but unsolved needs, failure of others, unexpected results, commercial success, copying, licensing, and praise by others. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). An obviousness determination requires a reason to combine “accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

The conclusion of obviousness based on a combination of references must be supported with explicit analysis of a reason to combine those references. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The Federal Circuit has stated that such reasons must be more than “mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal

conclusion of obviousness.” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006); *accord Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 (Fed. Cir. 2008) (agreeing with the district court’s reasoning that “some kind of motivation must be shown from some source, so that the jury can understand why a person of ordinary skill would have thought of either combining two or more references or modifying one to achieve the patented method”); *see also LG Elecs., Inc. v. Cellular Commc’ns Equip. LLC*, IPR2016-00197, Paper 7 at 7-11 (April 29, 2016) (faulting a petition’s obviousness analysis for lack of sufficient articulated reasons with rational underpinnings for modifying references to achieve particular elements required in the claims). Proving obviousness requires “explanation as to how” and “*why* the references would be combined to produce the claimed invention.” *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016) (original emphasis). When a petitioner fails to provide “any explanation as to how or why the references would be combined to arrive at the claimed invention, we are left with only hindsight bias that *KSR* warns against.” *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017) (citing *KSR*, 550 U.S. at 421).

IV. FUSION’S PRIOR ART REFERENCES FAIL TO SHOW OBVIOUSNESS

Fusion’s entire arguments for obviousness are fundamentally flawed because they fail to take into account at least two factors. First, as explained above, they

ignore the widely held concern that ^{225}Ac cannot be stably held by a chelator. (Hope Decl., pg. 23-29.) When ^{225}Ac releases its first alpha particle the recoil effect will invariably release the atom (which has now changed into its daughter particle ^{221}Fr) from the chelator which will then travel through the body to release three more alpha particles and two beta particles. (Hope Decl., pgs. 26, 59, 78.) Released actinium and its daughter nuclides have been found to pool in liver and bone and cause radiotoxicity there. Ex. 1030.004. This possibility of releasing multiple alpha and beta particles in healthy tissue would make a POSA hesitant to use ^{225}Ac , and other alpha-emitters, in human treatments.

As Dr. Abergel's own writings show, POSAs have been concerned about using ^{225}Ac for some time and have attempted to find alternate methods to control the daughters. Ex. 2008; 2009.002. This fact also completely demolishes Fusion's claim that the radionuclides are interchangeable. As Dr. Abergel knew when she wrote her Declaration, the two nuclides, ^{177}Lu and ^{225}Ac , will act completely differently as part of a ligand. While ^{177}Lu , a beta-emitter, is held firmly in its chelator, ^{225}Ac will escape the first chance it gets – which may be anyplace in the body.

This also undermines Dr. Abergel's and Fusion's claim that ^{225}Ac is an inherent improvement over ^{213}Bi and ^{177}Lu because it will release so many more particles to damage the target tumor. 1002 at ¶83. As Dr. Abergel acknowledged at her deposition, whether that advantage materializes is dependent upon the radiopharmaceutical reaching its target and becoming internalized:

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.

Abergel Tr. 110:19-111:5; 111: 10-111:21.

This realization shifts the discussion from Fusion's focus on the chelator being able to hold the radionuclide (which it cannot if it is ^{225}Ac) to whether the radiopharmaceutical can get inside the tumor before the nuclide is released. As Dr. Abergel asserts, that is dependent on the "[s]election of each of the radionuclide, chelator, linker and targeting moiety" and the "particular cancer a patient may have" (Ex. 1002.015, ¶27) – a much more complex affair than just switching the radionuclide as Fusion has claimed.

The second factor they overlook is that the components of a radiopharmaceutical – the choice of chelator, the targeting moiety, the linker, radionuclide, and which cancer it is for – renders it unique such that each has specific affinity, internalization rates, number of targets, etc., that cause them to act differently when interacting with the tumor. This undermines the assumption that the administrative dose, the amount given to a patient, can inherently predict the tumor's absorbed dose, the amount taken into the tumor. Although two radiopharmaceuticals may be given at the same dose, one may only deliver 20% to the tumor while another delivers 50% of its dose, resulting in different absorbances and possibly different efficacies.

The uniqueness of the radiopharmaceutical combination also results in a change to one part affecting another. Changing the radionuclide affects not only the level of radiation but can also affect the targeting moiety. And changing portions supposedly unrelated to binding can still affect the binding of the radiopharmaceutical. As discussed further below, the Weineisen 1027 and 1028

papers show that the POSA cannot simply switch out one part of the radiopharmaceutical without possibly affecting the others in unpredictable ways. Changing the radioligand can affect the overall effectiveness of the radiopharmaceutical outside of just its level of radiation and releasing it from the ligand.

While these are the clearest and most permeating reasons for the failure of Fusion's claim of obviousness, which are sufficient to overcome their Petition, there are other reasons that are described below.

A. Prior Art References

1. Weineisen 2014

Rather than support Fusion's argument that it would have been obvious and natural to introduce ^{225}Ac to the PSMA I&T molecule, Weinisen teaches a POSA that there was a good possibility that it would not work or would not work well. (Ex. 1027.010).

Weineisen 2014 describes the creation of new radionuclide carrier molecules (DOTA-FFK(Sub-KuE), DOTAGA-FFK(Sub-KuE), DOTAGA-ffk(Sub-KuE)) with the same targeting moiety for PSMA and the results of *in vitro* and mouse experiments with those compounds. The Weinisen lab performed competition experiments to determine the carriers' affinity for PSMA, measured by an IC_{50} – the amount of the molecule necessary to inhibit the binding of another molecule by half. Although the molecules all had the same targeting moiety for PSMA the radioligand

(or non-radioactive version) affected the molecule's affinity.

Table 1 from Weineisen 2014 (Ex. 1027)

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 ([¹²⁵I]-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).

For example, as seen in Weineisen's Table 1 above, the IC₅₀ of Ga-bound DOTA-FFK(Sub-KuE) was more than double that of unbound DOTA-FFK(Sub-KuE) - 13.1 nM for unbound DOTA-FFK(Sub-KuE) vs. 29.5 nM for Ga-bound DOTA-FFK(Sub-KuE). *Id.* And even more remarkably, the IC₅₀ of Lu-bound DOTA-FFK(Sub-KuE) was more than quadruple that of unbound DOTA-FFK(Sub-KuE) - 13.1 nM for unbound DOTA-FFK(Sub-KuE) vs. 54.7 nM for Lu-bound DOTA-FFK(Sub-KuE). *Id.*

When asked about this data, Dr. Abergel agreed that there were significant differences arising from the use of the radionuclides:

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.

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.

Abergel Tr. 128:19-129:9.

Weineisen 2014 also found that changing the radionuclide affected the ligand

rate of internalization with ^{177}Lu -bound ligands showing a higher rate than ^{68}Ga -bound ligands. According to Dr. Abergel, when asked about Table 2 of Weineisen 2014, 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.

Abergel Tr. 129:24-130:22.

This data demonstrates three things to a person of ordinary skill in the art.
(Hope Decl., pgs. 51-52.)

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, linker, 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.

Abergel Tr. 131:8-24.

Because of this, and because Weineisen 2014 only studied ^{177}Lu and ^{68}Ga , a POSA would not be able to guess how another radionuclide – like ^{225}Ac – would have functioned in the Weineisen 2014 ligands, or any other ligand. Instead, the variability of Weineisen 2014's results would inform the POSA that the reported work would only apply 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 . There is no way that a POSA looking at the result from Weineisen 2014, would conclude that radionuclides are interchangeable. (Hope Decl., pgs. 53-55.)

But another source of unpredictability is the use of mice for the internalization and biodistribution work. The fact is that, while convenient, mice are a poor model

for biological studies because they lack genetic diversity and do not provide the level of information necessary to fully understand the full scope of radiopharmaceutical effects. For example, the primary side effect of the '901 patent invention was dry mouth, making salivary glands the dose limiting organ. (Hope Decl., pgs. 14, 62, 70.) But Weineisen 2014, while recognizing that PSMA was present salivary glands (Ex. 1027.001).

2. **Weineisen 2015**

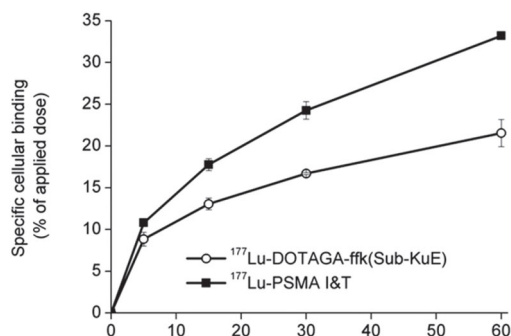
Weineisen 2015 must be viewed in light of Weineisen 2014 since the former is a continuation of the work of the latter. Weineisen also showed using different radionuclides with the same ligands can dramatically affect binding affinity and internalization of the constructs in different ways, and that using different ligands with the same radionuclides can also result in different binding affinity and internalization. (Hope Decl., pgs. 55-56.)

Stated more simply, changing the radionuclide of a construct – or changing the ligand – leads to unpredictable results. (Hope Decl., pg. 56.)

Weineisen 2015 showed that a small modification to the linker region – which plays no role in the ligand other than connecting the targeting moiety to the chelator – can dramatically affect properties and performance – such as binding affinity and biodistribution – of the ligand. (Hope Decl., pg. 56.) Ex. 1028.003. The disclosed PSMA-I&T ligand simply added an iodine and an OH group to a pendant phenyl group on the linker moiety. Ex. 1028.003. As Figure 2 from Weineisen below shows,

these simple chemical additions to an otherwise inactive and non-functional part of the ligand nearly doubled the binding affinity of the ligand despite the unchanged targeting moiety being located all the way at the other end of the molecule and the same radionuclide being used. (Hope Decl., pg. 56.) (Ex. 1028.002-004) These small changes to the ligand also resulted in dramatically higher binding to the cells even though the linker would not normally have been expected to play any a role in binding. (Hope Decl., pg. 56.)

Figure 2 Weineisen 2015 (Ex. 1028.004)



Weineisen 2015 also compared uptake of ligands having the same targeting moiety but different chelated radionuclides and found that uptake differed between different radionuclides – despite being chelated to the same ligand. ((Hope Decl., pg. 56.) Ex. 1028.007.) As shown by Figure 3 from Weineisen 2015 below, while ⁶⁸Ga-PSMA-I&T and ¹⁷⁷Lu-PSMA-I&T showed marginally different binding affinity to PSMA, Weineisen 2015 found a significant difference in the amount of uptake in mice organs between the ⁶⁸Ga and ¹⁷⁷Lu radioligands, with ¹⁷⁷Lu-PSMA-I&T usually being taken up in greater amounts, particularly in bone. (Hope Decl., pg. 56); Ex.1028.005.

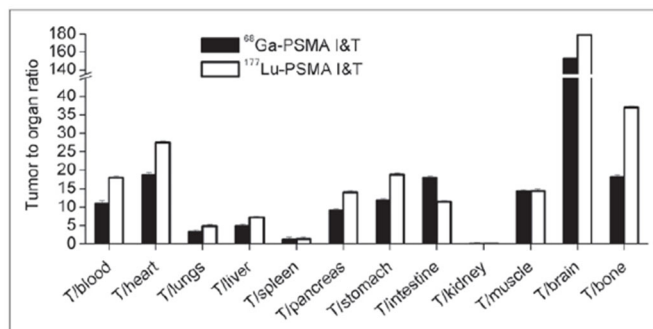
Figure 3 Weineisen 2015 (Ex. 1028.005)

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.

Abergel Tr. 136:15-137:4

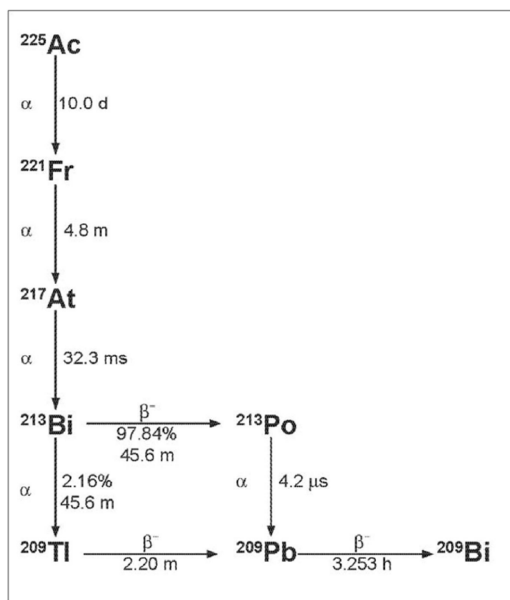
The POSA would therefore not consider radionuclides to be interchangeable when devising a treatment method for a particular cancer. Nor would the POSA consider the ligand structures to be interchangeable. (Hope Decl., pg. 57-58.) Instead, the POSA would expect from Weineisen 2014 and Weineisen 2015 that swapping the radionuclide – for example, ^{225}Ac for ^{177}Lu – would have unpredictable results.

3. Chatalic

Contrary to Fusion's assertions, Chatalic (Ex. 1006) would likely guide a POSA *away* from using alpha-emitters and ^{225}Ac .

First, given the known tendency of ^{225}Ac 's daughter nuclides to leave the ligand, Chatalic's use of ^{213}Bi -PSMA-I&T to inject into mice to test against xenografted cancer cells is less an endorsement of alpha-emitters and more an avoidance of ^{225}Ac . As shown in the decay chart below, ^{225}Ac decays six times, releasing four alphas and two betas. Because ^{213}Bi is a downstream daughter of ^{225}Ac , only one more alpha and beta are released before the atom stabilizes. By using

^{213}Bi , only one more alpha will be released while the ^{213}Bi is in the ligand, making it much safer than using ^{225}Ac . Knowing this, the POSA would conclude that Chatalic intentionally teaches the use of ^{213}Bi *instead of* ^{225}Ac to avoid ^{225}Ac 's known and unresolved inherent dangers.



Ex. 1022.025.

Second, as also seen in the above decay chain, ^{213}Bi releases two betas for every alpha emission, with the beta usually (97%) emitting first. This creates uncertainty in determining the efficacy of alpha particle emissions apart from the beta particle from ^{213}Bi . At her deposition, Dr. Abergel admitted that it there was no way to tell from Chatalic's abstract how much of the DNA damage reported by Chatalic was from the beta or alpha particles:

Q. But they don't have any evidence it was the alpha particle. It could have been the beta particles as well.

A. There is no evidence in the abstract.

Q. So there's no evidence in this abstract showing whether or not the damage was caused by beta particles or alpha particles.

MS. CIPRIANO: Objection; misstates her testimony.

A. I -- no. No.

Abergel Tr. 156: 1-4; 156:7-12.

Finally, the activity used by Chatalic was so large for a mouse that it would make a POSA wonder about the radioligand's efficacy. Chatalic injected the mice – which typically weigh about 25 grams – with 5 MBq ^{213}Bi -PSMA I&T. (Hope Decl., pg. 60.) 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. (Hope Decl., pg. 60.) To put this in perspective, Claim 1 of the '901 Patent recites a unitary dosage of 3-30 MBq of ^{225}Ac , (Ex. 1001.019. and the experiments on human subjects in Weineisen 2015 used 5,700 and 8000 MBq of ^{177}Lu . 1028.003. 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. (Hope Decl., pg. 60.) 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. (Hope Decl., pg. 60.) In fact, Chatalic describes using 10 nmol of 2-PMPA or 4 mg gelofusin “for

renal protection,” indicating deep concern about toxicity from the ^{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 .

And ultimately, anything obtained from Chatalic is of questionable relevance to the human treatment described in the '901 Patent because Chatalic’s work was with mice implanted with xenografts. Both laboratory mice and xenografts lack the genetic diversity seen in the patient population. (Hope Decl., pgs. 17-21, 60-61.) Real world cancers are heterogenous and the same class of cancer can differ from patient to patient and even within patients because they contain mutations. (Hope Decl., pgs. 45-46). This model shortcoming is one reason that cancer cures work in mice but fail completely in humans. It unclear how Chatalic’s 5MBq of radiation would equate to a human study or if it could have any relevance.

4. Miederer (Ex. 1015)

Miederer describes experiments with the compound DOTATOC, which has a DOTA chelator and a somatostatin analog for binding to somatostatin receptors for the treatment of neuroendocrine tumors. The targeting moiety and purpose of this ligand is completely different from the one described by Weineisen for treating PSMA-expressing prostate cancer cells.

Miederer compares the efficacy and tolerability of the DOTATOC with ^{177}Lu or ^{225}Ac . While Miederer finds that the ^{225}Ac -DOTATOC was better at halting progression of the xenograft tumor than ^{177}Lu -DOTATOC, Miederer also highlights

the hazards of using the ^{225}Ac radionuclide which would deter and discourage the POSA from applying that radionuclide elsewhere. Miederer 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 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 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 invention was that renal side effects were very low with only low-grade side effects and renal failure 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 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.

5. **Jurcic**

Jurcic provides no guidance to the POSA leading to the ‘901 Patent. Jurcic uses an antibody, lintuzumab, which would have very different pharmacodynamics and pharmacokinetics because of its size and slower clearance. (Hope Decl., pgs. 64-66.) If anything, Jurcic would have dissuaded a POSA from using ^{225}Ac , because Jurcic used an entire year of medicine to prevent “radiation-induced nephrotoxicity” indicating a strong fear of kidney damage from treatment. (Ex. 1011.002.)

The antibody is also not directed to PSMA or the same diseases in Fusion’s other references. Jurcic uses an antibody directed to CD33 as a treatment for leukemia. This would not provide any insight into how PSMA I&T would work.

But the worst is that Jurcic combines his ^{225}Ac -lintuzumab with a low dose of cytarabine (“LDAC”) often used for leukemia treatments but had no negative control. Ex.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. *Id.* But without a control a POSA could not tell from his paper whether the effects are from the LDAC or the ^{225}Ac -lintuzumab. (Ex. 1011.001-1011.002.) That is, a POSA has no clue as to the efficacy of the ^{225}Ac -lintuzumab. Fortunately, when asked about this, Dr. Abergel agreed that to understand the effects of the ^{225}Ac -lintuzumab in Jurcic,

it would have to be compared to LDAC treatment 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.

Abergel Tr. 157:12-22

In a previous study by Burnett using the same protocol with LDAC alone, as Dr. Abergel suggests, Burnett 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
Ex. 1011. 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	11%
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, <i>Cancer</i> 2007;109:1114-24	18%
Ex. 2048. 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	9%
Ex. 2049. Tilly, H, et al., Low-dose cytosine arabinoside treatment for acute nonlymphocytic leukemia in elderly patients, <i>Cancer</i> 1985; 55(8):1633-6	50%
Ex. 2050. 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	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 ^{225}Ac -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 ^{225}Ac -antibody construct had a **negative** effect, reducing the efficacy and effectiveness of the cytarabine. With this, the POSA would have understood the ^{225}Ac -antibody treatment – and 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, suggesting the ^{225}Ac -antibody construct had, at best, little or no effect on treatment. And since there was not effect, a person of ordinary skill would not have followed the treatment regimen offered by Jurcic for ^{225}Ac or with any other treatments. 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.

6. 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 that were also tolerated. (Ex. 1031.002.) These doses only show how much radiation the patient can receive before the side effects become intolerable – they do not disclose or teach efficacious or effective doses for the radiopharmaceutical. 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 the maximum tolerable dose. 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.

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. Therefore, Kratochwil provides no guidance as to what a proper dose would be for ^{225}Ac -DOTATOC, much less for ^{225}Ac -PSMA-I&T.

B. A POSA Would Not Have Been Motivated to Combine Weineisen and Kratochwil

For Ground 1, Fusion claims that the combination of Weineisen 2015 and Kratochwil would render Claims 1, 2, and 4-13 obvious. But, Fusion's argument is based on a number of false presumptions. First, Fusion presumes that the ^{225}Ac was the perfect radionuclide without any downsides, which could be easily exchanged with the ^{177}Lu that Weineisen 2015 taught. As explained above, POSAs, including Dr. Abergel, knew that ^{225}Ac had significant downsides because when it released its first alpha particle, it (or rather the daughter nuclide resulting from the decay, ^{221}Fr) would be ejected from the chelator. Ex. 2007.003. That released daughter nuclide, and its subsequent generations, could then roam free and be able to release three more alpha particles and two beta particles. While the goal of the targeted radiopharmaceutical is to release the radionuclide's particle near or in the tumor, there is no guarantee that this will happen, and the downside of it not happening has

significant repercussions. Actinium-225 and its daughter nuclides have been reported to pool in the liver and the bone and to cause radiotoxicity. Ex. 1003.003. Actinium was not interchangeable with Lutetium or Gallium because it represented a qualitatively different threat to the patient.¹

This leads to Fusion's second fallacy, that all radiopharmaceuticals are the same. Fusion has formed its argument in terms of providing just ²²⁵Ac and has assumed that if the administered dose is the same then the absorbed dose will be the same and efficacy will be the same. But that is not the case. As Dr. Abergel stated: "[s]election 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." When asked about this at her deposition, she agreed that a radiopharmaceutical is dependent on all of its parts for efficacy as well as selection of the target cancer, not just the radionuclide:

Q. So on the next page, 12, paragraph 27. In that last sentence of paragraph 27, you say "Selection of each of the radionuclide, chelator, linker, and target moiety is key to ensure the radiopharmaceutical is

¹ Although, even without the recoil effect, the radionuclides should not be treated as interchangeable since they differ in size, decay rate, decay pathway to stability, particle emissions and whether they ever reach stability. As we saw with Weineisen, different radionuclides can indirectly change the workings of their radioligands.

effective in the treatment of a particular cancer a patient may have." Do you see that?

A. Yes.

Q. And do you still stand by that?

A. I do.

Q. And so what you're saying here is that the radionuclide, the chelator, the linker, and the targeting moiety are each important to the process of making the radiopharmaceutical effective, correct?

A. That's correct.

Q. And so, for example, if the targeting moiety was less effective, the overall molecule would be less effective, correct?

A. That's correct.

Q. And so you could -- if you could switch out a radionuclide, that might also affect the overall effectiveness of the molecule, correct?

A. That's correct.

Q. And that effectiveness is viewed in terms of that particular cancer, correct?

A. That's correct.

Q. And so, for example, if you had a radionuclide, chelator, linker, and targeting moiety, it may work for one cancer but not work for another.

A. That's correct -- well, hold on. Say that again. I'm sorry.

Q. So if you had a combination of radionuclide, chelator, linker, and

targeting moiety --

A. That's right. That's correct.

Q. -- they might work for one cancer --

A. Yes.

Q. -- but not for the other, right?

A. That's correct.

Abergel Tr. 98:24-100:10. Because Fusion ignores this simple point, it repeatedly frames the combination and comparison of radiopharmaceuticals as just “doses of ^{225}Ac ” (*see e.g.*, Pet. 35, 36, 38, 44, 47, 51) when they are actually doses of DOTATOC or PSMA-617 with ^{225}Ac attached. These molecules would have, for example, different affinities, uptakes, and solubilities and they would have different targets on different cancers with different levels of accessibility and populations. Just as knowing a proper dosage for morphine would not tell you the proper dosage of aspirin to take, knowing the dosing on ^{225}Ac -DOTATOC would not tell the POSA the dosing range on ^{225}Ac -PSMA-617. The amount required of each is based on their individual, unique characteristics.

Thus, Fusion’s invocation of the overlapping range rule is inapplicable here because the patent and, for example, Kratochwil are not providing a range of the same thing. The Kratochwil reference describes DOTATOC molecules with ^{225}Ac attached while the '901 Patent is describing PSMA-ligand-based molecules with ^{225}Ac attached. That they both have the same radionuclide does not change the fact that the range represents different molecules, so they do not “overlap” as Fusion

insists. That the molecules are measured in radioactivity is immaterial because each molecule's dose range is based on the molecule's ability to be absorbed in the tumor and its resulting efficacy. That the measurements may overlap is as immaterial as saying that the measurement of a pound of nails overlaps with a pound of books.

More specifically, Kratochwil would not guide a POSA to add ^{225}Ac to PSMA I&T because, beyond the inherent issues with ^{225}Ac releasing its daughter nuclides, Weineisen 2014 and 2015 had already taught that radionuclides are not interchangeable in the PSMA-ligand molecules. As described above, Weineisen found that adding ^{68}Ga or ^{177}Lu to its PSMA ligands resulted in very different affinity or internalization. A POSA would not know if a ^{225}Ac would work better or worse in the PSMA I&T because the affinity and uptake could be affected. Given the inherent instability of ^{225}Ac in chelators, it likely would not have been worth the risk.

Although Weineisen 2014 mentions ^{225}Ac in passing, Weineisen 2015 makes no mention of ^{225}Ac and is not following up on it in Weineisen. Had a POSA gotten the impression that Weineisen's casual mention of ^{225}Ac in the 2014 paper was a suggestion to use ^{225}Ac , then that impression would have completely faded with the 2015 paper. (Hope Decl., pg. 58.) Although Dr. Abergel argues that it would have been obvious to combine ^{225}Ac with Weineisen 2015's PSMA-I&T construct, it apparently did not occur to Weineisen herself – despite her clearly being aware of

²²⁵Ac as a potential “therapeutic M³⁺ radiometal[1]”.² Therefore, Weineisen 2014 and 2015 explicitly teach that the most promising and safest radionuclide for these treatments was ¹⁷⁷Lu. Dr. Abergel even makes that point when she says that human studies like those done in Weineisen 2015 are “reserved for only the safest and most promising therapies.” Abergel Decl. at ¶77. The promising therapy was not just PSMA I&T, it was ¹⁷⁷Lu-PSMA-I&T, teaching that ¹⁷⁷Lu was the safe choice.

Kratochwill also will not combine with Weineisen to inform the dosage because 1) as mentioned above, it does not provide an effective dose, only a tolerable dose, 2) if there were a dose provided, it would be for DOTATOC, which can shed no light on PSMA-I&T. Determining the administrative dose is not based solely on the radionuclide activity but more so on the ability of the targeting moiety to bring the radionuclide to the tumor. Sgourous (Ex. 1017) indicates that determining the dosage is largely empirical because of “complex activity and tissue geometries.” (Ex. 1017.009.) Where there is information to base the dosing on, it is focused on the targeting moiety elements like the number of sites per cell, the fraction of cells

² In fact, no ²²⁵Ac-PSMA-I&T appeared in publication as a suggested treatment until 2020. 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.

that express the target, the distribution of binding sites per cell among the targeted cells, binding and dissociation constants for cell targeting, internalization rate, and lethal dose in targeted and nontargeted cells. (Ex. 1017.009).

Kratochwil's DOTATOC is an analog of somatostatin for binding such 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, with a differently expressed target molecule, this reference provides no insight as to the tolerable, effective, or efficacious doses that might relate to the patented invention. (Hope Decl., pgs. 68-70.) The efficacy of a radiotherapeutic is not based on just the amount of radiation added, but also its delivery to the target, which is based on the targeting moiety, which for DOTATOC is completely different from PSMA ligands. (Hope Decl., pgs. 68-70.) Since the POSA would know this, they would know they would not have a reasonable expectation of success basing their dosing of PSMA I&T on DOTATOC. The POSA would not have adopted the dose from Kratochwil's NET 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. 1001.017. But Kratochwil only mentions chronic kidney toxicity. (Ex. 1031.001.) This is because DOTATOC would not have the same qualitative or quantitative effects 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. Ex.1031.001; 1001.017.

The person of skill would have also understood that just because a radionuclide worked with one molecule, it would not work the same with another molecule. For example, Miederer (Ex. 1030) used ^{225}Ac on two different molecules, DOTA-biotin and DOTATOC (Ex. 1030.008) and found that toxicity was widely divergent. Lethal toxicity was observed at 60 kBq after 180 days with ^{225}Ac -DOTATOC but not until 740 kBq at 110 days with ^{225}Ac -Dota-Biotin. So, a POSA knew that a nuclides like ^{225}Ac on DOTATOC could not simply be put onto another molecule that was functionally different, like PSMA I&T, and expect to get equivalent results.

Adding Chatalic to the mix does not help because, as explained above, ^{213}Bi was likely used to avoid the pitfalls of ^{225}Ac . The ^{213}Bi nuclide would only have one alpha emission, making it much safer than ^{225}Ac , indicating to a POSA that ^{225}Ac should be avoided in favor of ^{213}Bi . Chatalic’s experiment also did little to put alpha

emitters in a positive light since the amount of radiation used was very high and there was no way to tell how much of the efficacy was due to the alpha emissions and how much was due to the beta. *See IV.A.3 supra*.

Miederer (Ex. 1015) also does not help to justify the combination because, like Kratochwil, it is exclusively focused on DOTATOC. As explained above with Kratochwil, the difference in targeting moiety, cancer type, and target, prevents a POSA from concluding that because ^{225}Ac worked on DOTATOC it would work on PSMA I&T. That DOTATOC is able to use both ^{177}Lu and ^{225}Ac , says nothing about PSMA I&T.

Therefore, there is nothing that would recommend the combination of Kratochwil with Weineisen 2015 for the creation of ^{255}Ac -PSMA-I&T. Moreover, Fusion has never explained *why* a POSA would want to combine these divergent references other than to make the invention indicating that the combination is purely hindsight.

C. **A POSA Would Not Have Been Motivated to Combine Weineisen, Kratochwil, and Jurcic**

The reasons for not combining Kratochwil and Weineisen discussed in Section IV.B above are the same for this combination and are incorporated into this section as well.

Remarkably, although Weineisen and Kratochwil provide no insight together

because they relate to completely different cancers, targets, and molecules, Fusion believes that tossing another, more divergent, reference will somehow clarify the issue. Jurcic uses an antibody (while Weineisen and Kratochwill use small molecules), it targets CD33 (while Weineisen targets PSMA and Kratochwill targets somatostatin), which is intended to treat the liquid cancer, leukemia (while Weineisen treats prostate cancer and Kratochwil treats NET which are both solid cancers). These references have nothing in common other than Fusion's desire to unite them.

If the dosage of Kratochwil's DOTATOC would not provide guidance for PSMA I&T, then Jurcic's antibody is even less useful. Antibodies have a slower rate of clearance, as acknowledged by Dr. Abergel:

Q. Do antibodies get cleared fairly quickly?

A. In a few days, depending on the antibody.

Q. How does the clearance of antibodies compare to small molecules?

A. It's slower.

Q. Just to be sure we're clear, which one is slower, the small molecule or the antibody?

A. The antibody is slower.

Abergel Tr. 94:20-95:2. Since the antibody is slower to clear, radiation exposure from it is spread out over a longer time, which would affect the dosage provided. It would certainly be different from what a more quickly cleared small molecule like PSMA I&T would need. So, a POSA would not expect to get any guidance on ²²⁵Ac-

PSMA-I&T dosage from Jurcic.

Moreover, as explained above, Jurcic does not actually shed enough light on the efficacy of the ^{225}Ac -lintuzumab to encourage a POSA to use ^{225}Ac because it was co-administered with LDAC and there is no proper control for the experiment. But a POSA would know that the results in Jurcic are no better than the LDAC alone, which would disincentivize a POSA from using ^{225}Ac .

D. Secondary Considerations Support Nonobviousness

1. The work in the patent has received considerable praise

As laid out by Dr. Hope, the journal article ^{225}Ac -PSMA-617 for PSMA-Targeted α -Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer by the inventor, Dr. Clemens Kratochwil, as the first author describes an embodiment of the patent. Ex. 2022; (Hope Decl., pgs. 35-39.) 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. The paper and the work within it have garnered an enormous amount of praise and attention. Even Dr. Abergel wrote a review *six years later* and included figure 1 from Kratochwil's paper. 2009.006.

In fact, Figures 1 and 3 (the '901 Patent's Figures 12 and 14, respectively) quickly became iconic in the field of oncology and radiology, being cited in numerous publications and presentations. Dr. Abergel confirmed that the figures were widely touted and the results were impressive compared 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.

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.

Abergel Tr. 47:7-17.

The month it was published in the *Journal of Nuclear Medicine*, the article received the honor of having its Figure 3 on the cover.



[https://jnm.snmjournals.org/content/57/12.cover-expansion.](https://jnm.snmjournals.org/content/57/12.cover-expansion)

The praise and attention for the unexpected result continued for years. 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. <https://www.eanm.org/congresses-events/awards-grants/winners/> Ex. 2027; (Hope Decl., pg. 41.) Over the years, various authors have also recognized how remarkable the result 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 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 Actinium 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 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.
- “Compared to initial tumor spread (A), restaging after two cycles of β -

emitting ^{177}Lu -PSMA-617 presented progression (B). In contrast, restaging after the second (C) and third (D) cycles of α -emitting ^{225}Ac -PSMA-617 gave an impressive response.” Ex. 2028 Alam, MR, et al., A Review of ^{177}Lu tetium-PSMA and ^{225}Ac tinium-PSMA as Emerging Theranostic Agents in Prostate Cancer, *Cureus* **2022**; 14(9): e29369.

- “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 Feuerecker, B., et al., Clinical Translation of Targeted α -Therapy: An Evolution or a Revolution? *J Nucl Med* **2023**; 64:685–692

Citations to a paper are an objective measurement of a paper’s importance to a field, its influence, and its groundbreaking nature. 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.

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. Ex. 2029. According to Google Scholar, which performs a broader search to include, for example, books and websites, it has been cited 861 times. Ex. 2030. This is more than any of the six primary references that Dr. Abergel relies on to show obviousness (see Table below) and, excluding Weineisen 2015, more than twice the others combined. 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
Ex. 2022 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, pg. 1; Ex. 2030, pg. 1)	299	861
Ex. 1027: Weineisen 2014 Reference (Ex. 2029, pg. 3; Ex. 2030, pg. 2)	71	207
Ex. 1028: Weineisen 2015 Reference (Ex. 2029, pg. 5; Ex. 2030, pg. 3)	181	536
Ex. 1006: Chatalic Reference (Ex. 2030, pg. 4)	0	2
Ex. 1015: Miederer Reference (Ex. 2029, pg. 7; Ex. 2030, pg. 5)	62	153
Ex. 1011: Jurcic Reference (Ex. 2030, pg. 6)	0	47

Ex. 1031: Kratochwil Reference (Ex. 2030, pg. 8)	0	45
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The site Altmetric can compare a paper's cites to the average number of citations in the field or that particular journal. 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. 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. Ex. 2031 <https://www.altmetric.com/details/9534712/citations>. This level of citation is unlikely to be garnered by findings that were obvious or expected.

2. **The patent invention produced unexpected results**

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. Ex. 1001.007-008. Even more remarkable was that this treatment was so completely successful after the complete failure of treatment with a ¹⁷⁷Lu construct. Indeed, the treatment with the ¹⁷⁷Lu construct actually resulted in the cancer continuing to grow and spread. Ex. 1001.008; 17:42-57. That another radiation treatment could be

applied after such potent ¹⁷⁷Lu resistance and be as successful as the '901 Patent, is truly remarkable. 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 fails to apply the correct standard and ignores the results themselves. She claims the *results* were not unexpected because a POSA would have *conceived of the invention*. Since Dr. Abergel is not applying the correct standard, her opinion on this matter should be given no weight.

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.

Abergel Tr. 180:8-181:4.

3. The patent teaches away from convention

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. 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 radioligand is taken up by tumor cells fast enough that the daughter nuclides are either internalized, cleared, or partitioned to protect tissues, cells, and organs. Previous research found that ^{225}Ac and its daughters pool in bone causing radiotoxicity. Ex. 1030. But the '901 Patent shows no reduction in white blood cells, platelets, or hemoglobin after months of treatment. Ex. 1001.008-009. These remarkable results were contrary to the conventional wisdom at the time.

4. The patent resolved a long-felt need

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. (*Id* 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 has 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.

V. CONCLUSION

In view of the foregoing, claims 1, 2 and 4-13 are patentable, and Fusion has not met its burden to prove otherwise. Accordingly, Patent Owners respectfully request that the Board confirm the patentability of the Challenged Claims.

DATED: November 21, 2023, Respectfully submitted,
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Pursuant to 37 C.F.R. §42.24(d), the undersigned hereby certifies that this paper contains 13,710 words, excluding the portions exempted under 37 C.F.R. §42.24(a)(1), according to the word count feature of the word-processing system used to prepare this paper.

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CERTIFICATE OF SERVICE

I hereby certify that on November 21, 2023, a copy of this **PATENT OWNERS' RESPONSE** and all previously unserved supporting materials (Exhibits 2007-2042 and 2044-2057), was served by email on the following correspondence addresses of record for Petitioner, pursuant to 37 C.F.R. § 42.6(e):

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