

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CURIUM US LLC,
Petitioner,

v.

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

Case No. IPR2025-01582
Patent No. 10,980,901 B2

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

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2174	Schwartz et al., Renal uptake of bismuth-213 and its contribution to kidney radiation dose following administration of actinium-225-labeled antibody, <i>Phys. Med. Biol.</i> Vol. 56, no. 3, pgs. 721-733 (2011).
2175	Tagawa ST, et al., Anti-prostate-specific membrane antigen-based radioimmunotherapy for prostate cancer, <i>Cancer</i> 2010, 116(4 Suppl):1075-83.

Exhibit No.	Description
2176	Tagawa ST, et al., Bone marrow recovery and subsequent chemotherapy following radiolabeled anti-prostate-specific membrane antigen monoclonal antibody J591 in men with metastatic castration-resistant prostate cancer, <i>Front Oncol</i> 2013, 26:3:214
2177	Tagawa ST, et al., Prostate-Specific Membrane Antigen- Targeting Alpha Emitter via Antibody Delivery for Metastatic Castration-Resistant Prostate Cancer: A Phase I Dose-Escalation Study of 225Ac-J591, <i>J Clin Oncol</i> 2023, 3:JCO2300573
2178	Zalutsky et al., Clinical experience with alpha-particle emitting 211At: treatment of recurrent brain tumor patients with 211At-labeled chimeric antitenascin monoclonal antibody 81C6, <i>J. Nucl. Med.</i> Vol. 49, no. 1, pgs. 30-38 (2008)
2179	Abbas et al., Experimental α -particle radioimmunotherapy of breast cancer using 227Th-labeled p-benzyl- DOTA-trastuzumab, <i>EJNMMI Res.</i> Vol. 1, no. 1, pg.18 (2011)
2180	Parker et al., Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer, <i>N. Engl. J. Med.</i> Vol 369, no. 3, pgs. 213-223
2181	Meredith et al., Dose escalation and dosimetry of first-in-human α radioimmunotherapy with 212Pb-TCMC-trastuzumab, <i>J. Nucl. Med.</i> , vol. 55, no. 10, pgs. 1636-1642 (2014)
2182	Cordier et al., Targeted alpha- radionuclide therapy of functionally critically located gliomas with 213Bi-DOTA- [Thi8, Met(O2)11]- substance P: a pilot trial, <i>Eur. J. Nucl. Med. Mol. Imaging</i> , vol. 37, no. 7, pgs. 1335-1344 (2010)
2183	Müller et al., A unique matched quadruplet of terbium radioisotopes for PET and SPECT and for α - and β - radionuclide therapy: an in vivo proof-of- concept study with a new receptor-targeted folate derivative, <i>J. Nucl. Med.</i> , vol. 53, no. 12, pgs. 1951-1959 (2012).

Exhibit No.	Description
2184	Pimm et al, Blood and tissue kinetics of radiolabelled anti-CEA monoclonal antibody and F(ab)2 and Fab fragments in nude mice with human tumour xenografts: implications for tumour imaging and radioimmunotherapy, <i>Nucl. Med. Commun.</i> , vol. 10, no. 8, pgs. 585-593 (1989)
2185	Sathekge, M., et al., 225Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study, <i>Eur J Nucl Med Mol Imaging</i> 2019, 46:129–138

I. INTRODUCTION

Pursuant to 37 C.F.R. §42.120, Patent Owners Universität Heidelberg and The European Atomic Energy Community (EURATOM), represented by The European Commission (“EURATOM”), (collectively, “Patent Owners” or “POs”), submit their Response to the Petition (Paper No. 2, “Petition”) for *Inter Partes* Review (“IPR”) of U.S. Patent No. 10,980,901 (the “’901 Patent”) filed by Curium US LLC (“Curium” or “Petitioner”).

A. Summary of Argument

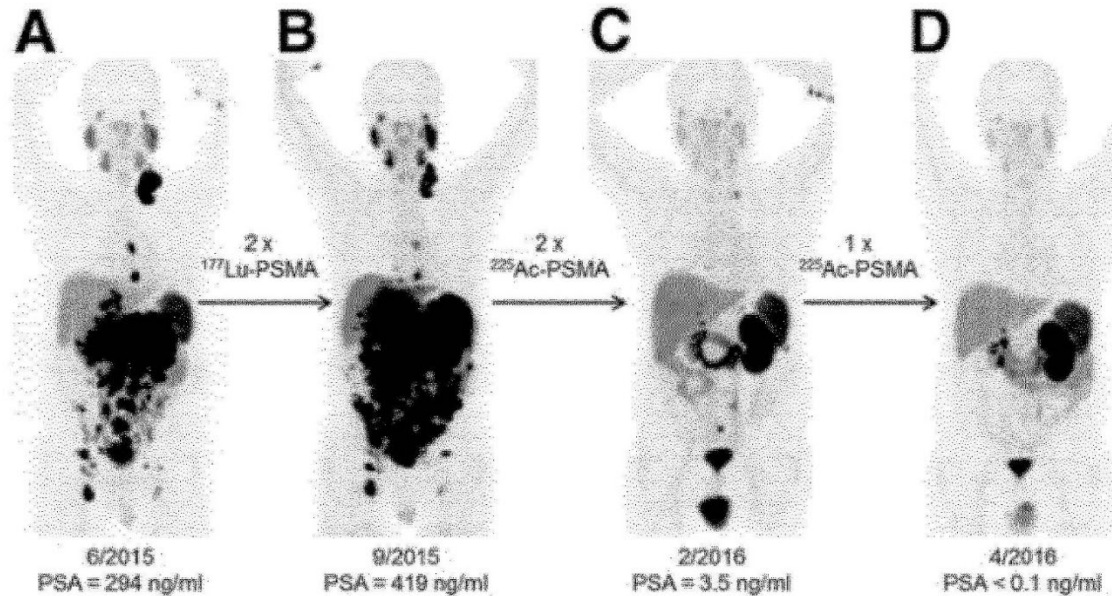
The ’901 Patent covers PSMA-targeting ^{225}Ac -radiopharmaceuticals for treating cancers. Petitioner essentially argues that combining PSMA-I&T with actinium-225, (“ ^{225}Ac ”) among all available PSMA-targeting molecules and radionuclides was obvious to try. But Petitioner relies on hindsight to combine disparate prior art involving different radionuclides, molecules, diseases, and radiation doses into a version of the ’901 Patent invention.

A POSA would not have been motivated to combine Petitioner’s prior art or reasonably expected the claimed combinations and dosages to achieve the ’901 Patent’s reported clinical results. As the prior art reflects, changes in cancer type, targeting ligand, chelator, radionuclide, or dosing parameters materially and unpredictably affect clinical performance.

The field, including articles by Petitioner’s expert, Dr. Zalutsky, taught away from ^{225}Ac . Alpha-emitter radiometals like ^{225}Ac require chelators to bind them to

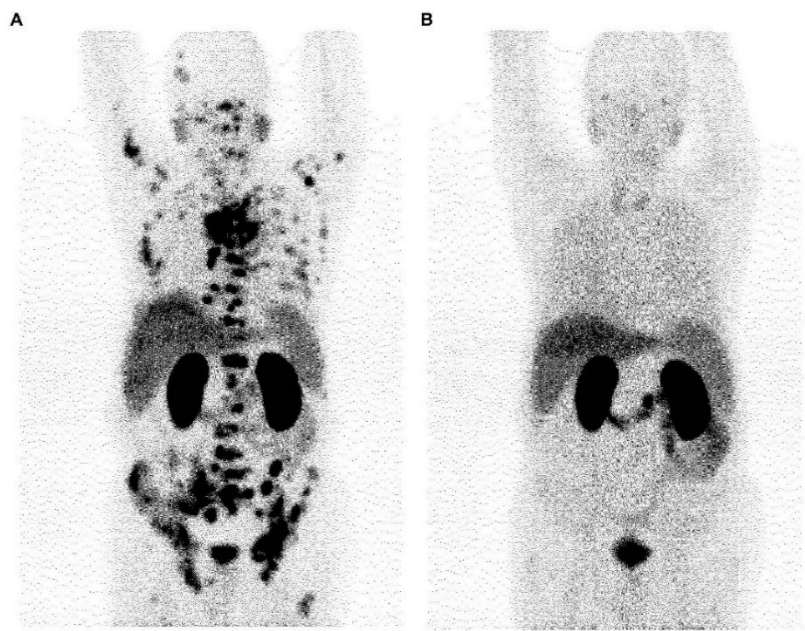
targeting molecules. But alpha decay was understood to create a significant risk of releasing daughter molecules before the radionuclide reached its target because alpha-emitters are *always* ejected from their chelator upon releasing their first alpha particle, potentially freeing the daughter radionuclide to wander the body, damaging healthy tissue, particularly the kidneys where it ^{213}Bi accumulates. Actinium-225 daughters then emit three more alpha and two more beta particles, making them more damaging than other alpha-emitters or typically used beta-emitting radionuclides.

The well-known dangers of ^{225}Ac made the '901 Patent results published in Kratochwil 2016 unexpected, eliciting praise, including from Petitioner's expert. The '901 Patent data show complete remission in four patients with extensive metastatic prostate cancer. Figure 14 from the '901 Patent (reproduced here as Figure 1) shows superimposed PET/CT scans, with dark splotches indicating metastasized prostate cancer sites (Ex. 1001, 15:38-49). Two treatments with the closest prior art, using radioactive ^{177}Lu , failed to prevent further spread of prostate cancer (compare A to B), while two treatments with the claimed ^{225}Ac radioactive molecule (^{225}Ac -PSMA-617) almost completely cleared the cancer from the patient's body (compare B to C) and a third drove it into remission (Compare C to D):

Figure 1

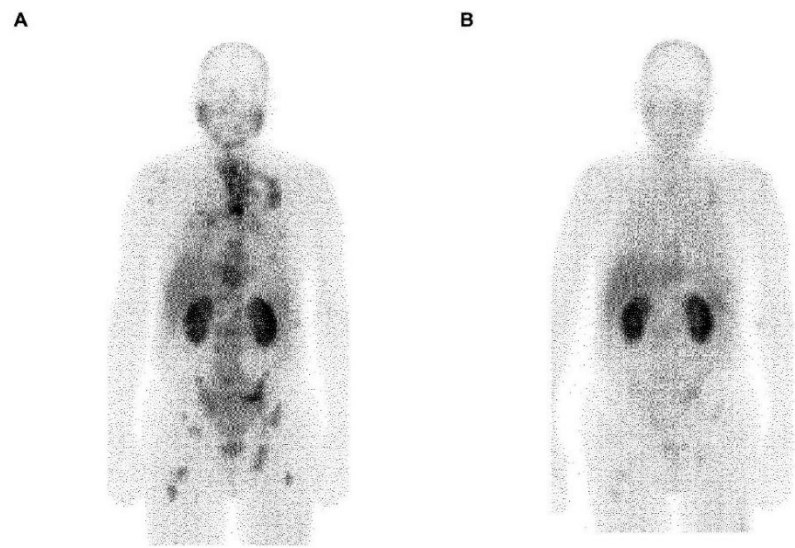
(Ex. 1001, Figure 14; 17:42-53). These results appear in the inventors' Kratochwil 2016 publication. (Ex. 1045.003). The '901 Patent's Figures 4-6 and 12, reproduced below (with "A" representing before and "B" after treatment with the patented invention), further corroborate Kratochwil 2016, confirming these unexpected results in four other patients:

Figure 2



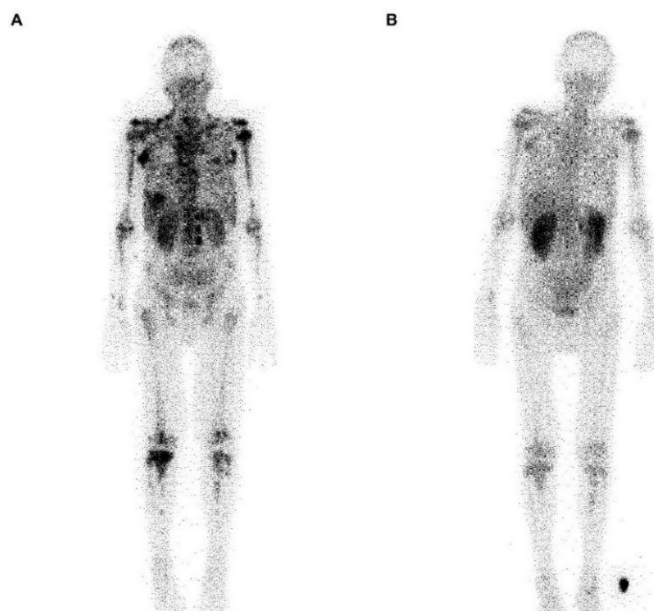
(*Id.* Fig. 4).

Figure 3



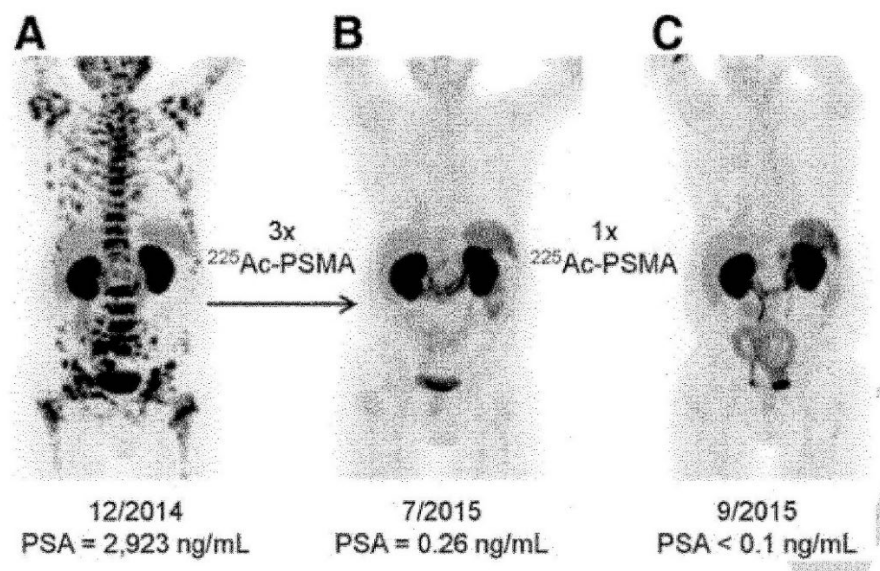
(*Id.* Fig. 5).

Figure 4



(*Id.* Fig. 6).

Figure 5



(*Id.* Fig. 12).

Prostate-Specific Antigen (“PSA”) levels have been used since the late 1980s

and are the standard clinical indicator of prostate cancer risk, treatment efficacy, and recurrence after therapy. (Exs. 2135.002; 2136.001, .006-7). PSA levels in the several-hundred ng/mL range signal advanced, likely metastatic disease and shortened survival. (Exs. 2137.003; 2135.003; 2138 ¶79). Figures 1 and 5 show patients with PSA levels of 2923 and 419 ng/ml, respectively, placing them in advanced metastatic stages. Three treatments with the claimed ^{225}Ac radiopharmaceuticals reduced both PSA levels below 1 ng/ml for at least 16 weeks after the last dose.

As Dr. Gorin explains, because bone marrow is frequently the dose limiting organ for radiopharmaceuticals and ^{225}Ac is known to accumulate in bone (Ex. 2138 ¶¶39, 58, 120), the inventors examined platelet (thrombocyte) and white-blood-cell counts and found them largely unaffected (Figures 6 & 7, below). (*Id.* ¶¶85-88). Kidney damage was also a long-term concern of PSMA-radiopharmaceutical treatment, but the dose limiting side-effect was dry mouth (xerostomia), with very low renal toxicity occurring only in patients with a history of it. (*Id.* ¶58-59, 61-64, 95, 120182; Ex. 2098.007;).

Figure 6 (Ex. 1001, Fig 7)

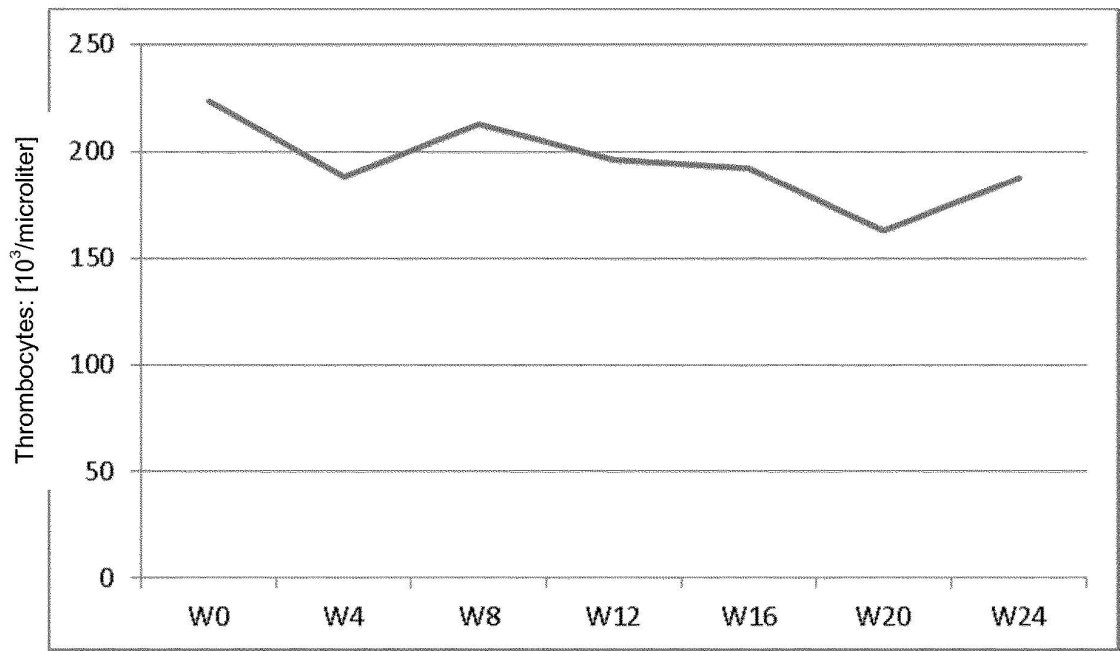
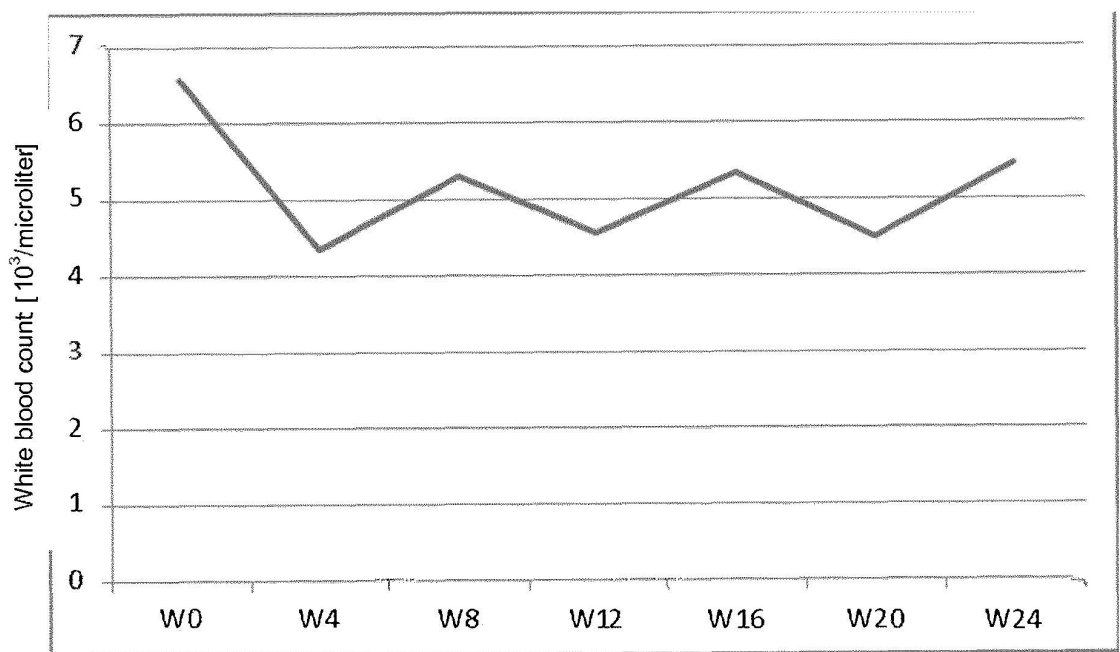


Figure 7 (Ex. 1001, Fig 8)



(Ex. 1001 Fig. 7, 8).

These data in the '901 Patent and Kratochwil 2016 embody one of the most important advances in cancer treatment, particularly prostate cancer, in decades. Petitioner points to no prior art suggesting such a surprising, dramatic result was possible.

Petitioner's prior art fails to teach the '901 Patent's crucial elements of a "method for treating PSMA expressing cancers" comprising "an effective amount" of "Ac-225-radiopharmaceuticals," particularly "wherein the effective amount" is "25 kBq to 400 kBq / kg of body weight" or "a unitary dosage of from 3 MBq to 30 MBq."

Weineisen 2015 teaches ^{177}Lu , not the claimed ^{225}Ac radiopharmaceutical, at unitary doses of 5.7 and 8.0 GBq—1000x higher than the claimed effective dose. It also teaches that modifying targeting molecules or switching radionuclides can affect effectiveness. (Exs. 1028.003, .006; 2138 ¶¶54, 143-152)

Kratochwil uses another ligand (DOTATOC) binding another target (somatostatin receptors) in another cancer. (Ex. 2138 ¶¶175-182). A POSA would not have relied on Kratochwil's somatostatin-receptor-binding ligand dose for a very different radioligand binding a very different target, PSMA, in a different cancer. (*Id.* ¶¶134-138, 158-160, 168-169, 177-182). Moreover, Kratochwil is an "empiric dose escalation" to find the "maximum tolerable dose", not the effective amount for treatment, which is a different question. (*Id.* ¶¶117, 175-176; Ex. 1031.001)

Jurcic, asserted only against Claim 9, combined ^{225}Ac -lintuzumab with

standard leukemia treatment without comparing that treatment alone, providing no guidance on effective ^{225}Ac -lintuzumab dosing. Lintuzumab, an antibody binding CD33 on leukemia cells, cannot offer insight into PSMA-targeting-molecule dosing. (Ex. 2138 ¶¶164-174).

Curium's references and arguments provide no basis for combining parts of very different molecules into the claimed invention, and Weineisen 2015 shows such modifications produce unpredictable results. The Petition does not establish that teachings concerning different radionuclides, ligands, targets, and cancer types would have given a POSA a reasonable expectation of success for the claimed methods. Curium's references prove otherwise. (*Id.* ¶¶174, 203-230).

B. Procedural Background

Curium challenges Claims 1, 2, and 4-13 of the '901 Patent based on the molecule ^{225}Ac -PSMA-I&T, contending that 1) claims 1, 2, 4-8, and 10-13 are obvious over Weineisen 2015 and Kratochwil; 2) claim 9 is obvious over Weineisen 2015, Kratochwil, and Jurcic; and 3) Kratochwil 2016 anticipates the invention. (Petition, p. 5).

II. THE '901 PATENT AND RELEVANT TECHNOLOGY

A. Challenged Claims and Claim Construction

POs believe no construction beyond the claims' plain and ordinary meaning is necessary. However, POs reserve the right to respond to any express or implicit claim construction Petitioner advances.

Claim 1 recites a method for treating PSMA-expressing cancers comprising

administering a specified “effective amount” (25 kBq to 400 kBq/kg of body weight or a unitary dosage of 3 MBq to 30 MBq) of a ^{225}Ac -radiopharmaceutical from a Markush group (A through E) of ligands chelating ^{225}Ac . (Ex. 1001, 18:13-20:37). The dependent claims narrow the ligands (claim 2), specific cancers (claims 4-7), effective dosages (*Id.*, claims 8-11), and dosing regimens (claims 12-13).

B. Level of Skill in the Art: the '901 Patent's Clinical Treatment Method Require a POSA with Relevant Clinical Experience

Because the '901 Patent concerns treatment of “PSMA expressing cancers,” a clinical compound, particular dosages, and treatment responses (*see* Ex. 1001 Claim 1), a clinician is best suited to opine on this clinical product's obviousness and how a POSA would have understood the field. Therefore, a POSA would have (1) clinical experience with radiopharmaceuticals, (2) an understanding of radiopharmaceuticals dosimetry in human subjects, (3) knowledge of the radiobiology of radiopharmaceuticals, (4) an understanding of the design and conduct of clinical dose-finding studies, and (5) clinical experience in the management of prostate cancer or other PSMA-expressing cancers. (Ex. 2138 ¶¶27-34). Dr. Michael Gorin, who provides a Declaration (Ex. 2138) supporting this Response, meets these requirements. He is a practicing physician with over fifteen years' experience in urology and urologic oncology and over a decade in molecular imaging research. He is currently an Associate Professor in the Milton and Carroll Petrie Department of Urology at the Icahn School of Medicine at Mount Sinai. (*Id.* ¶¶3-14).

Dr. Gorin satisfies both POs' and Petitioner's proposed level of ordinary skill. POs' arguments do not depend on resolving the parties' dispute regarding the level skill, because the claimed invention would not have been obvious under either standard.

POs further disagree that Petitioner's expert satisfies the appropriate level of ordinary skill. Unlike Dr. Gorin, Dr. Zalutsky is not a medical doctor and lacks clinical experience treating patients with prostate cancer or other PSMA-expressing cancers. Dr. Zalutsky cannot properly opine on the relationship between MTD and effective dose (Ex. 2139, at 21:19-22:9) or whether a POSA would have found the clinical results surprising or qualitatively different from the prior art.

C. Technology Background and Overview of Patent

While radiopharmaceuticals are increasingly accepted in cancer treatment, selecting their components remains a technical and clinical challenge. Radiopharmaceuticals typically comprise: (1) a targeting moiety (ligand) specific to target markers predominantly expressed by target cells, (2) a chelating moiety, (3) a linker between them, and (4) a radionuclide chelated (bound) to the chelating moiety. This combination binds targets on cells to destroy them or nearby cells, such as cancer cells. (Ex. 1001, 1:20-55). Each component contributes to a radiotherapeutic's function in treating a specific cancer, and modifying any one can have surprising effects on performance. (Ex. 2138 ¶35-36).

The '901 Patent claims methods of treating PSMA (*Prostate Specific Membrane Antigen*)-expressing cancers using the radiometal ^{225}Ac linked to a PSMA-targeting molecule. PSMA-expressing cancers rank among the most frequent. (Ex. 1001, 1:66 – 2:5). Prostate cancer is a leading cause of cancer death in men. Localized prostate cancer has high survival rates, but metastatic disease worsens prognosis and limits treatment options. (Ex. 2185.001).

In this context, the '901 Patent describes the surprising discovery that a low dosage of specific ^{225}Ac -radiopharmaceuticals can produce an unexpectedly strong anticancer effect, including remission, with limited hematotoxicity in patients with PSMA-expressing cancers.

This result was surprising in multiple ways. First, an unusually low 6-10 MBq dose provided effective treatment. Second, the results went beyond treatment: complete remission of prostate cancer, with PSA below detectable levels after only 3-4 treatments. (Ex. 1001, 13:65-14:2; 14:10-13; 17:53-61). Third, no significant hematotoxicity was found. These last two points were most remarkable because radiopharmaceutical efficacy usually correlates directly with toxicity, forcing clinicians to use high dosages with greatly increased toxicity risk to achieve the complete remission seen in the '901 Patent. (Ex. 2138 ¶¶39-45; 85-88, 119).

These results were also surprising given the widely recognized problem of

alpha-emitter release from the chelator, allowing radionuclides to redistribute and cause damage. (*Id.* ¶60-67).

As Petitioner's references show (Figure 8, below), beta-decaying radionuclides like gallium-68 (“ ^{68}Ga ”) and lutetium-177 (“ ^{177}Lu ”), which emit electron-sized beta particles, were preferred for their stability.

Figure 8 (Ex. 1032.2.0011).

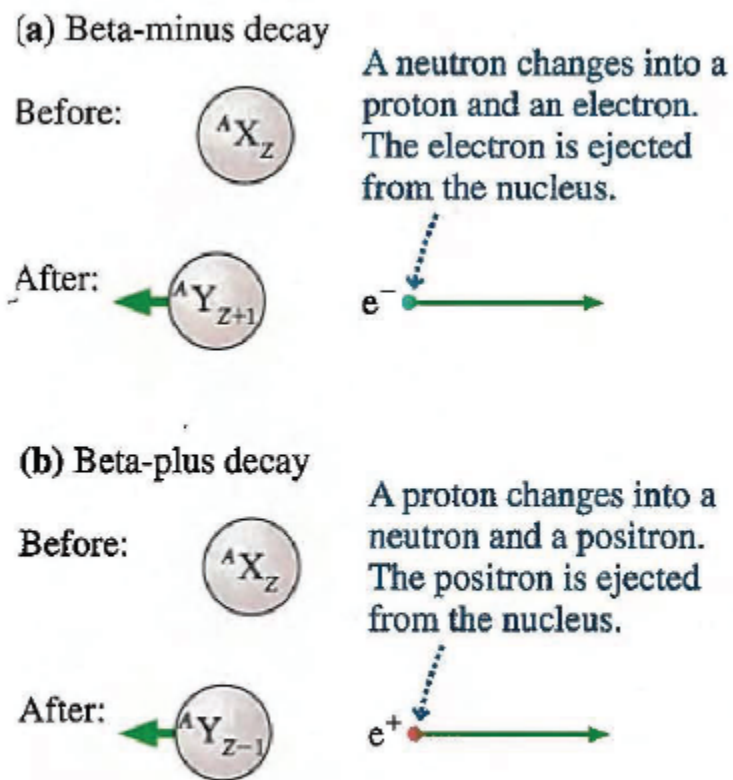
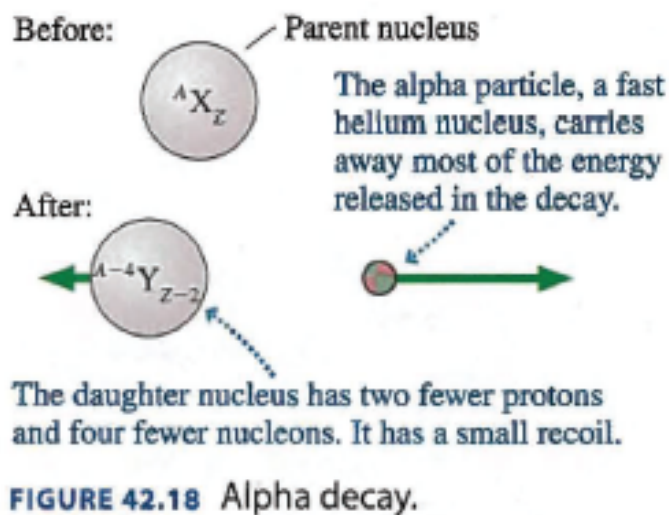
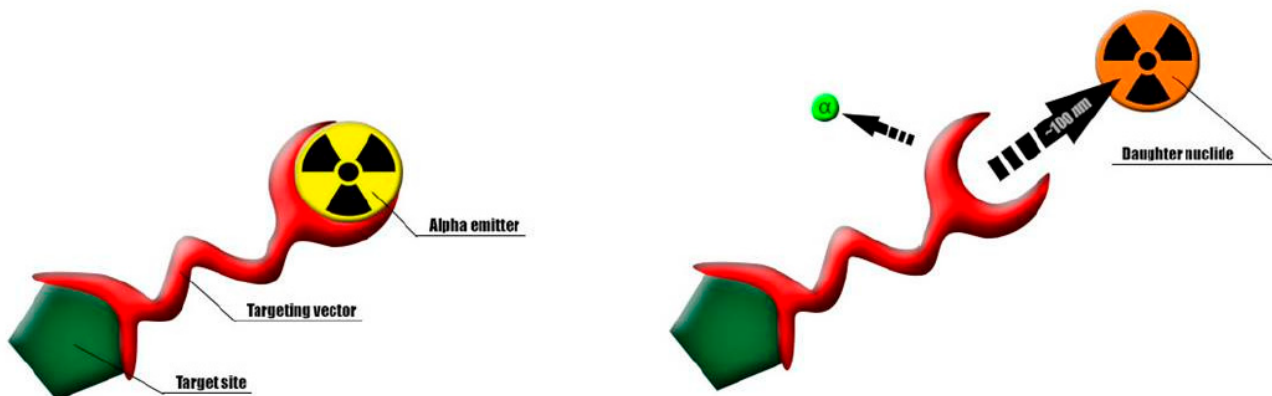


FIGURE 42.20 Beta decay.

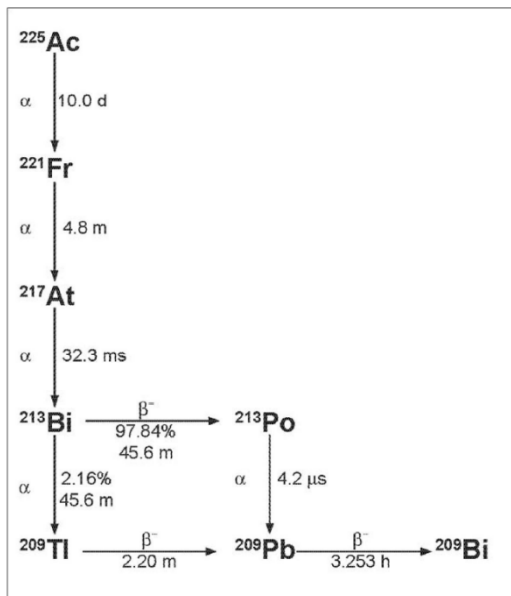
Alpha-emitting radionuclide particles are ~7300x bigger and expelled with greater force. The alpha-emitter decays into a “daughter” nuclide, releasing its particle forcefully enough to create recoil. Figure 9.

Figure 9 (Ex. 1032.2.0010).

As Figure 10 illustrates, alpha-emitters' heavy particles impart ~100 keV of recoil energy, far exceeding chemical bond strengths, causing bond rupture and daughter release. (Exs. 1043.003). The daughter travels ~100 μm – far beyond a typical carrier molecule's (e.g., chelator) size, allowing it to roam freely. (Exs. 1043.002, 2138 ¶60).

Figure 10 (Ex. 1043.004).**Figure 1.** Schematic representation of a recoiling daughter radionuclide detaching from a targeting agent as a consequence of alpha decay.

Escaping alpha-emitters posed a widely recognized problem. ^{225}Ac 's six-daughter decay chain, emitting three alpha and two beta particles before becoming stably nonradioactive (see Figure 11), was widely recognized as particularly problematic. (Ex. 2138 ¶¶60-69; 154-155).

Figure 11 (1022.025)

Miederer (Ex. 1015), noted in a 2008 review 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.” (Ex. 1015.002). Actinium-225’s “3 α-emitting daughter elements generated have the potential for significant toxicity” after release. (Ex. 2072.001). The “release of the daughters from ²²⁵Ac” was a “key drawback” because “such daughters may not be retained in tumor tissue,” increasing the chances of side effects. (Ex. 2072.002). Miederer cites examples in which ²²⁵Ac and daughters were “distributed to liver and bone and the subsequent release of its daughters contributed to acute radiotoxicity.” (Ex. 1030.003). Miederer acknowledged that the α-emitting daughter nuclides remain “capable of relocating within the organism and accumulation of ²¹³Bi originating from the bloodstream into the kidneys with

subsequent radiation damage has been shown in nonhuman primates.” (1015.002).

The alpha-emitting ^{223}Ra product, Xofigo (Petition, p. 14), did not allay these concerns. (Ex. 2138 ¶73-74). Unlike ^{225}Ac in the '901 Patent, ^{223}Ra inherently “mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases,” rapidly integrating into metastasized bone without targeting molecules. (Ex. 1046.009). Ten minutes after injection, 88% of ^{223}Ra is cleared from blood, and 94% within an hour. (Ex. 2112.005). This is not true of ^{225}Ac . Unlike ^{223}Ra , ^{225}Ac -radiopharmaceuticals administered under the claimed methods do not inherently localize to their target but rely on a chelator and targeting molecule for selective delivery.

After most of the ^{223}Ra stably integrates into bone like calcium and recoils from its first alpha emission, its next two alpha-emitting daughters have half-lives of 4 seconds and 2 milliseconds. Thus, the first three alpha particles are limited in range and likely released near the target site. (Ex. 2113.002; 2138 ¶74).

By comparison, ^{225}Ac must rely on the '901 Patent's compound's PSMA-targeting moiety and chelator to deliver it to tumor and keep it there. Once ^{225}Ac experiences recoil, its first and third daughter isotopes have half-lives of five and forty-five minutes, respectively (Ex. 1022.025), enough time to pass through the body several times. (Ex. 2138 ¶74). A POSA would not have viewed ^{223}Ra , with its automatic, self-targeting approach, as providing relevant guidance for the claimed ^{225}Ac PSMA-targeted treatment methods. (*Id.*)

One reviewer concluded: “by and large we find that in most studies

concerning long-lived alpha-emitters, recoiling daughter atoms pose a serious problem. If the distribution of recoiled atoms is not controlled, toxic effects due to the recoiling daughters will be present.” (Ex. 1043.011). Before the ’901 Patent, researchers suggested abandoning the chelator-radiometal complex altogether for alpha-emitters and using nano-carriers (*Id.*) or switching to more stable radiohalogens. (Ex. 2140.001).

III. CURIUM’S PRIOR ART REFERENCES FAIL TO SHOW OBVIOUSNESS

Curium’s obviousness arguments rely on hindsight to combine unrelated prior art in an unpredictable field despite the prior art’s teaching away. Combined, Petitioner’s three references, Weineisen 2015 (Ex. 1028), Kratochwil (Ex. 1031), and Jurcic (Ex. 1011), still fail to include an effective ^{225}Ac -PSMA-I&T dosage. (Ex. 2138 ¶¶, 152, 164-182).

First, the prior art fails to teach the ’901 Patent’s effective ^{225}Ac -PSMA-I&T dosage. Although Petitioner and Dr. Zalutsky assert that the claims “do not require ... any clinical endpoint for the treatment” (Pet. 29; Ex. 1002 ¶83), the claims require “an effective amount” be administered and specify narrow, low-dosage ranges as the effective amount. (Exs. 1001 18:14-19, 20:31-37; 2138 ¶¶75-79).

Weineisen 2015 teaches ^{177}Lu doses 1000x higher than those claimed in the ’901 Patent, providing no guidance for ^{225}Ac dosing. Kratochwil determines MTD, unrelated to the effective dose, which could be much lower or higher. Jurcic masks any ^{225}Ac treatment effect by combining it with standard leukemia treatment. None

of these references teach or suggest the claimed effective dose for small-molecule ^{225}Ac -PSMA-targeting treatment.

Second, with nothing linking the asserted prior art, Petitioner relies on an obvious-to-try argument to combine PSMA-I&T and ^{225}Ac in an inherently unpredictable field. Radiotherapeutic effectiveness depends on the targeting moiety, linker, radionuclide, chelator, cancer type, binding, affinity, internalization rates, number of targets, and more. These variables cause therapeutics to act differently and unpredictably toward a patient's tumor, especially *in vivo*. As Weineisen 2014 and 2015 show (Ex. 1027, 1028), modifying the ligand or radionuclide can unpredictably change attributes. (Ex. 2138 ¶¶56-59, 129-151, 197, 237).

Third, Petitioner ignores the field's concern about ^{225}Ac 's invariable ejection from chelators upon release of its first alpha particle. (*Id.* ¶¶60-69). Every discussion or review of ^{225}Ac warned that its wandering daughter nuclides will release three more alpha and two beta particles (*Id.* ¶¶154, 60-66) and are known to pool in the liver, kidney, and bone, causing radiotoxicity. (Exs. 1030.004; 2138 ¶¶48, 95, 61-65, 163, 194, 205). This counters Petitioner's assumption that tightly retainable ^{177}Lu and unfailingly escaping ^{225}Ac are interchangeable on PSMA-I&T. Actinium-225's dangerous decay pathway also contradicts Petitioner's contention that other, safer alpha-emitters would have informed expectations regarding the claimed methods or ^{225}Ac efficacy.

Recoil shifts the focus from Petitioner's argument that the chelator merely holds the radionuclide (which it ultimately cannot if it is ^{225}Ac) to the uncertainty of

whether the radiopharmaceutical can reach its intended *in vivo* target, be taken up by tumor cells before daughter nuclides are released and retain those daughters at the tumor site.

Fourth, as Dr. Gorin explains, a POSA would not have been motivated to combine the asserted prior art because a POSA would not have relied on one drug's recommended dose to select a dose for a completely different drug, particularly unrelated pharmaceuticals involving different ligands, targets, and diseases. An effective dose is highly sensitive to cancer-cell characteristics, none of which Petitioner has shown were known or predictable for ^{225}Ac -PSMA-I&T. (*See* III.A.1.b). These unknowns prevent one pharmaceutical's administrative dose (the amount given to a patient) from predicting another's absorbed tumor dose (the amount taken into the tumor, which controls therapeutic effectiveness). (Exs. 2138 ¶¶35-37, 42-45, 177-182, 198-202, 212-213, 223-225; 2080, 167:7-168:7).

Petitioner's combined prior art does not result in the claimed invention. Even assuming references from unrelated therapies disclosed individual claim elements, Petitioner has not identified a record-based reason to combine them as claimed, much less in a way that would give a POSA a reasonable expectation of success. Petitioner's hindsight-based obvious-to-try arguments are countered by unpredictable chemistry and biotechnology and the considerable praise the invention's surprising results garnered, including from Petitioner and its expert.

A. Ground 1: The Combination of Weineisen 2015 and Kratochwil

Cannot Render '901 Patent Claims 1, 2, 4-8, 10-13 Obvious

1. Weineisen 2015 and Kratochwil Do Not Teach an Effective Dose of ^{225}Ac -PSMA-I&T Individually or Together.

The challenged claims require administering “an effective amount” of the ^{225}Ac -radiopharmaceutical within specified low-dosage ranges (25 kBq to 400 kBq/kg, or 3 MBq to 30 MBq). (Ex. 1001, 18:13–20:37). But no Petitioner reference, alone or combined, teaches or implies a ^{225}Ac -PSMA-I&T effective dose – the critical claim limitation.

a) Weineisen 2015 Does Not Teach An Effective Dose of ^{225}Ac -PSMA-I&T.

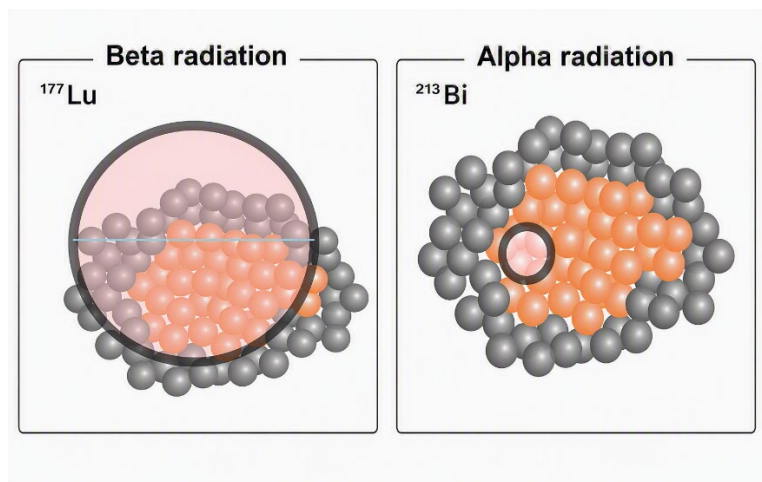
Weineisen 2015 teaches ^{68}Ga for imaging and ^{177}Lu for therapy, not ^{225}Ac -PSMA-I&T or its effective dose. Its two therapeutic patients received ^{177}Lu -PSMA-I&T at doses of 5.7 GBq and 8.0 GBq—orders of magnitude above the '901 Patent's claimed MBq-level ^{225}Ac doses. (Ex. 1028.003, .006). Nothing in Petitioner's prior art supports extrapolating from GBq-level ^{177}Lu doses to the claimed 1000-fold lower MBq-level ^{225}Ac doses. (Ex. 2138 ¶53, 148-152.).

Petitioner and its expert glossed over this issue, asserting a POSA would have understood that lower ^{225}Ac doses would be effective because alpha particles are more potent than ^{177}Lu 's beta particles. (Pet. 16; Ex. 1002 at ¶32). But this begs the questions: *how much* lower the dose should be, where efficacy would begin, and

when organ toxicity would become limiting. Petitioner points to nothing in Weineisen 2015 or other prior art providing a scientifically grounded motivation to deviate from its GBq-level ^{177}Lu administrations to the claimed 1/1000th lower MBq-level effective amounts.

Petitioner cannot provide a conversion factor from ^{177}Lu -radiopharmaceutical to ^{225}Ac -pharmaceutical dosage because effective dosage depends on too many factors beyond the radionuclide (Section III.A.2). (Ex. 2138 ¶¶197-202, 148-152). As Petitioner explains, the tradeoff for alpha particles' power is their short range (Petition 30), so efficacy depends on successful delivery. Dr. Zalutsky admits an alpha particle's range is only "a few cell diameters" while a beta particle's is "a few hundred." (Ex. 1002 ¶32) As Figure 12 puts in perspective, a beta-emitter need only reach a tumor's *vicinity*, while an alpha-emitter must be on the spot. (Ex. 2138 ¶153).

Figure 12



Therefore, Weineisen 2015's ^{177}Lu -PSMA-I&T prostate treatment results cannot predict the claimed ^{225}Ac -PSMA-I&T effective dose, because ^{177}Lu -PSMA-I&T could miss the tumor and still be effective, while misdirected ^{225}Ac -PSMA-I&T would fail. Weineisen 2015 cannot predict ^{225}Ac -PSMA-I&T's effectiveness or that its claimed low radiation dose would provide complete remission in patients resistant to ^{177}Lu -PSMA-targeting molecules. (III.D.2)

Weineisen 2015's cell studies showing internalization and affinity also provide no data on *in vivo* effectiveness because the environments are incomparable. In cell culture, radiopharmaceuticals have unrestricted access to targets. But *in vivo*, the target may be buried, limiting access; be more abundant on healthy tissue, sequestering the administered dose; or have a different conformation due to the microenvironment. (Ex. 2138 ¶46-48, 141).

Petitioner's reference to the ^{177}Lu -Lutathera Product (Pet. 36) does not resolve this question. Like Weineisen 2015, ^{177}Lu -Lutathera teaches doses 1000X higher than claimed. Petitioner has not shown how that dosing would teach an effective ^{225}Ac -PSMA-I&T dose or that a POSA would view a 1000-fold reduction as routine optimization rather than a clinical dose-finding experiment requiring compound-specific evidence.

b) **Kratochwil Does Not Teach An Effective Dose of ²²⁵Ac-PSMA-I&T.**

Kratochwil is an abstract demonstrating “an empiric dose escalation to find the maximum tolerable dose (MDT),” for ²²⁵Ac-DOTATOC targeting somatostatin receptors (“SSTR”) in patients with neuroendocrine tumors (“NET”). (Ex. 1031.001). Petitioner’s assertion that Kratochwil teaches an effective ²²⁵Ac-PSMA-I&T dose fails because it conflates MTD with effective dose and administered activity with absorbed dose.

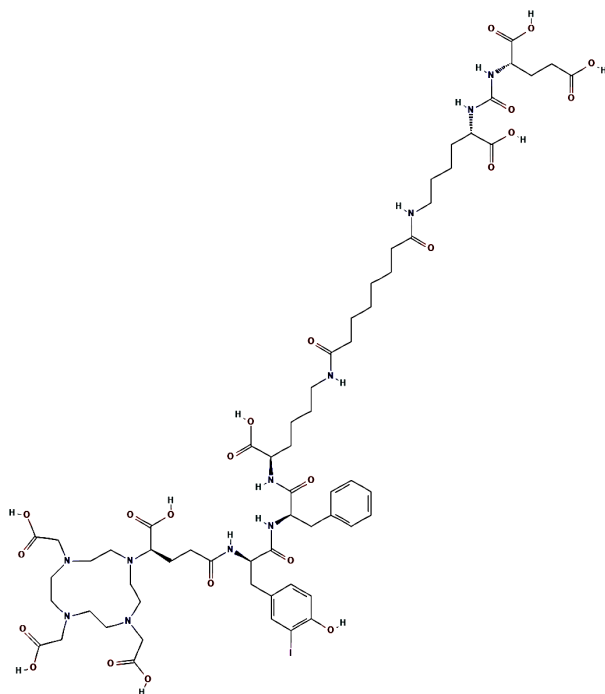
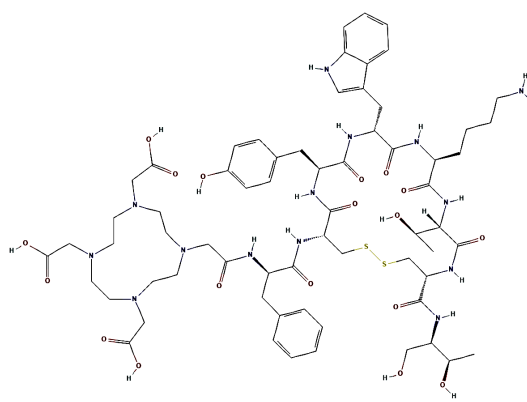
First, Kratochwil studies only MTD which is distinct from efficacy. (*Id.*; Ex. 2138 ¶¶175-177, 36-41) Kratochwil’s reported single-cycle MTD of 40 MBq, cumulative MTD of 75 MBq, and fractional 25 and 18.5 MBq doses (Ex. 1031.001–.002) relate only to *tolerable* doses. They provide no guidance on the *effective* dosage level, which both Drs. Zalutsky and Gorin understand could be far removed from the MTD. (Ex. 2139, 87:17-89:11; Ex. 2138 ¶¶36-41, 175-177).

Even if Petitioner argues that Kratochwil implied efficacy from the tolerability study, efficacy need not have occurred below or at the MTD. In determining when toxicity became unacceptable, Kratochwil would have *exceeded* the reported MTDs. (Ex. 2138 ¶176). Efficacy could, therefore, have occurred at higher doses. Kratochwil is silent, leaving a POSA to guess.

Second, administered activity does not equal absorbed dose, and DOTATOC and PSMA-I&T are entirely different molecules. (*Id.* ¶¶35-36, 178-182). Although Petitioner acknowledged that dosage amounts would be based “on the amount of the radionuclide that needs to be *delivered* to the target site to achieve the *therapeutic effect*,” ((Pet. 36) (emphasis added)), it mistakenly treats Kratochwil’s and Jurcic’s *administered activities* of ^{225}Ac as effective amounts for all ^{225}Ac molecules. “Administered activity” is the amount of radiation given to a patient; “absorbed dose” is the amount of radiation delivered to the tumor or tissue, which drives effectiveness. (*Id.* ¶¶35-42, 197-199; 2139, 28:18-29:4). Because absorption is complex – varying between molecules, depending on, *e.g.*, receptor affinity, residence time/clearance, stability and radiopharmaceutical uptake – administered activity does not equal a tumor’s absorbed dose. (Ex. 2138 ¶¶35-38, 148-179). Dr. Zalutsky agreed that one “could administer the same activity with two different molecules but get different absorbed doses at a particular tissue.” (Ex. 2139, 29:10-17; 30:14-21; 30:23-31:3). One radiopharmaceutical’s effective administered activity will not necessarily be another’s because different characteristics produce different absorbed doses. (Ex. 2138 ¶¶36-45, 129-152).

^{225}Ac -DOTATOC and ^{225}Ac -PSMA-I&T would have unrelated absorbed and effective doses because, as Figure 13 shows, their structures differ substantially. (*Id.*

¶177-181, 231-235)

Figure 13 (Exs. 2141.002; 2142.003).**PSMA-I&T****DOTATOC**

Dr. Zalutsky explained: “Selection of each of the radionuclide, chelator, linker, and targeting moiety is key to ensure the radiopharmaceutical is effective in the treatment of the particular cancer a patient may have;” changing any of these elements could change the radiopharmaceutical’s functioning. (Exs. 1002 ¶27; 2139, 110:7-23). DOTATOC and PSMA-I&T are different molecules, with different chelators, linkers, and targeting moieties, resulting in unrelated absorbances and pharmacokinetics. Thus, one’s effective dose cannot be determined from the other’s

administered dose.

Third, Kratochwil's administered activity cannot be extrapolated to ^{225}Ac -PSMA-I&T because the agents bind different targets expressed at different densities across tissues. (Ex. 2138 ¶¶178-183).

The MIRD Pamphlet, Petitioner's own dosimetry authority (Pet. 37), makes target properties, not the radionuclide, the controlling variables. Cell killing is highly sensitive to cancer-cell characteristics (e.g., cell geometry, nuclear size, DNA distribution, and spatial arrangement of target to the nuclei (Ex. 1017.004)) and specific ligand and target features (e.g., cellular targeting kinetics, binding site distribution per cell, ligand affinity, and internalization (Ex. 1017.013)). MIRD accordingly prescribes a target-driven program starting with determining the "number of sites per cell and fraction of cells expressing target", "distribution of binding sites per cell", affinity, internalization, and "median lethal dose in targeted versus nontargeted cells" before progressing to human studies. (Ex. 1017.013). Kratochwil determined MTD for ^{225}Ac -DOTATOC, not MTD or effectiveness for unrelated, targets. (Ex. 2138 ¶¶175-182).

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

adrenals, and kidney but primarily spleen. (Ex. 2143.005). ^{68}Ga -PSMA I&T shows low uptake in liver, spleen and small intestine but high uptake in kidney and salivary glands. (Ex. 1028.005-006).

Different target densities result in different percentages of administered activity reaching dose-limiting organs, different MTDs, and different efficacies between SSTR-directed peptides versus PSMA-directed ligands. For example, the dose-limiting toxicity for ^{225}Ac -PSMA-617 and ^{225}Ac -PSMA-I&T is xerostomia (dry mouth), with salivary glands as the dose-limiting organ. (Exs. 1001, 15:55-56; 16:35-36; Ex. 2096.026, Table 5; 1045.002). But Kratochwil mentions only chronic kidney toxicity because DOTATOC, an SSTR-targeting ligand, has qualitative and quantitative effects different from a PSMA-targeting ligand. (Exs. 1031.001; 2138 ¶161-162, 178-182). Just as Kratochwil could not indicate xerostomia's importance to the patented PSMA-based invention, it offers no guidance on effective dose.

Petitioner's own references show extrapolation fails even *within* the somatostatin class. Changing DOTATOC to DOTANOC shifted SSTR subtype affinity and produced "higher uptake in normal tissues," increasing whole-body dose. (Ex. 1038.020). If structural changes within one receptor family prevent dose extrapolation, Petitioner cannot bridge SSTR to PSMA. (Ex. 2138 ¶178-182).

Kratochwil provides no guidance on ^{225}Ac -PSMA-I&T's effective amount

because (1) it studied tolerability, not efficacy; (2) any implied efficacy implications is at unknown dosages; and (3) DOTATOC binds a different target expressed at different densities in different tissues in a different cancer, precluding dose extrapolation. (Ex. 1017.004, .013).

c) **Weineisen 2015 and Kratochwil Together Do Not
Render the Claimed Effective Dose of ²²⁵Ac-PSMA-
I&T Obvious.**

Even if Wineisen 2015 and Kratochwil together provided ²²⁵Ac-PSMA-I&T's components, they cannot teach its effective dose. Wineisen 2015's doses are 1000x higher (*see* III.A.1) than claimed, while Kratochwil's tolerable doses concern DOTATOC, a different molecule (*see* III.A.1.b). Because Kratochwil's (or Jurcic's) dosages concern unrelated molecules, Petitioner has not shown a POSA could determine ²²⁵Ac-PSMA-I&T's effective dose with a reasonable expectation of success.

Petitioner wrongly treats any overlapping numerical range as presumptively obvious. (Pet. 44-45). Overlapping numerical activity ranges do not establish obviousness here because the cited ranges concern different radiopharmaceuticals, targets, and diseases, and Petitioner has not shown that the same variable(s) were being modified for the same purpose. (Ex. 2138 ¶¶212-215). "[A] presumption of

obviousness may be invoked when the *only difference* from the prior art is a difference in the range or value of a particular variable.” *Pharmacyclics LLC v. Alvogen, Inc.*, No. 2021-2270, 2022 WL 16943006, at *9 (Fed. Cir. Nov. 15, 2022) (internal quotes removed, emphasis added) citing *In re Kumar*, 418 F.3d 1361, 1366 (Fed. Cir. 2005). In *Pharmacyclics*, the Federal Circuit found this presumption did not apply because the prior art did not teach that the claimed compound was effective against a particular disease. *Id.* The overlapping range presumption is inapplicable here for the same reason: Kratochwil studied an SSTR-directed ligand, whose absorbed doses depend on SSTR density and distribution; the claims recite doses for PSMA-directed ligands depending on PSMA density and distribution—different molecules, disease settings, and dosing considerations. These are neither the same variable nor the same purpose. (*See* III.A.1.b) (Ex. 2138 ¶¶212-215, 179-182)

That Kratochwil and the '901 Patent's invention both use ^{225}Ac , or that administrations are measured in radioactivity, does not make their ranges overlap because they are dosing *molecules*, not ^{225}Ac alone, and *effective* dose depends on delivery to, absorption in, and efficacy against the tumor, which varies by molecule, among other factors. (*see* III.A.1.b and c). (Ex. 2138 ¶¶213-224). The '901 Patent is not “merely select[ing] a dose amount from within the purported ‘ranges’” to optimize a workable ^{225}Ac radionuclide range from Kratochwil because neither

administers ²²⁵Ac alone. See *Westminster Pharms. v. LPRI France*, No. IPR2022-00677, 2022 WL 3649220, at *7 (P.T.A.B. Aug. 24, 2022). The obviousness-range assumption therefore does not apply to the dosage ranges reported for such different radiopharmaceuticals.

Petitioner's reliance on *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775 (Fed. Cir. 1985) and *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996 (Fed. Cir. 2018) is misplaced because both cases assume the prior art shares all other claimed parameters. They do not establish that a claim becomes obvious merely because one claimed parameter overlaps a prior-art range while other material limitations remain absent or different. Even if the presumption applied, it is rebutted by teaching away from ²²⁵Ac and unexpected and widely lauded complete remission of prostate cancer discussed below. *E.I. DuPont*, 904 F.3d at 1008 citing *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013).

Petitioner's argument that awareness of ²²⁵Ac made it obvious to try with PSMA-I&T using Kratochwil's administered activity fares no better. That theory fails in unpredictable fields like chemistry, biotechnology, and cancer treatment, all of which apply here (see III.A.2). *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008); *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1377-78 (Fed. Cir. 2019). While Petitioner points to the field's awareness and

experimentation with ^{225}Ac , background knowledge alone does not render an invention obvious-to-try without considering the nature of the science or technology, particularly when that background teaches away as here (see III.A.3). *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013). An obvious-to-try theory cannot stand where the prior art does not provide the POSA information on what dose or concentration would produce a therapeutically effective formulation. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012).

Petitioner identifies no reason, because there was none, for a POSA to choose PSMA-I&T from the wide field of PSMA-targeting scaffolds or ^{225}Ac among the 24 beta- and 8 alpha-emitting radionuclides actively being investigated. (Ex. 1038.004). Dr. Zalutsky described other scaffolds, including “thiols, carbamates, phosphoramidates, phosphinic acids, and ureas,” being explored then (Ex. 2140.001; Ex. 2139, 34:22-35:7), and Petitioner’s references describe alternative PSMA-targeting small molecules, many tested in people and animals:

- DOTA-FFK; DOTAGA-FFK; DOTAGA-ffk (Ex. 1027).
- HBED-CC (Ex. 1007).
- DCMI; DCIT (Ex. 1008).
- MIP-1072; MIP1375 (Ex. 1009).

- MIP-1095; MIP-1466. (Ex. 1010).

(Ex. 2138 ¶¶184-1288) Other alpha-emitters were being pursued, including ^{223}Ra , ^{213}Bi , ^{211}At , ^{227}Th , ^{149}Tb , ^{203}Pb , and ^{212}Pb . (*Id.* ¶¶67-68, 123-125; Ex. 1017.002). Petitioner provides no reason to select PSMA-I&T and ^{225}Ac over them.

Petitioner's argument that others would have used ^{225}Ac but for its rarity is legally, logically, and factually incorrect. First, it violates 35 U.S.C. §103's admonition that "[p]atentability shall not be negated by the manner in which the invention was made." Petitioner assumes others would have made ^{225}Ac -PSMA-I&T *but for* the inventor's special access, basing its argument on the inventor's actions rather than what a POSA would have done. Second, it assumes access rather than considering the non-obviousness of pursuing a problematic resource. Third, Dr. Zalutsky testified that availability of other alpha-emitters "at that point in time ... was not great" (Ex. 2139 84:7-20), so ^{225}Ac 's rarity was comparable to other alpha-emitters.

Petitioner's reliance on MIRD (Pet. 37) for dosing is misplaced. Dr. Gorin explains, MIRD supplies no dose, only target- and compound-specific inputs needed to derive one. (see III.A.1.b). (Ex. 1017.009, .013). Because the asserted prior art provides none of this information for ^{225}Ac -PSMA-I&T, MIRD gives no insights into effective amounts or doses. (Ex. 2138 ¶¶42-45, , 199-201).

In 2022, Petitioner acknowledged dosimetry's unpredictability in its own patent application after reviewing public ^{225}Ac -PSMA-targeted studies:

“The clinical **dosimetry for ^{225}Ac is cumbersome . . .** Even though dosimetry . . . is mandatory . . . **there are no tools available** for clinical practice.”

(Ex. 2096.030 [0120] (emphasis added)). Curium instead used the '901 Patent inventors' ^{225}Ac -PSMA-617 data from a 2017 paper as Figure 16 in its application to determine its own dosing. (*Id.*, Fig 16; Ex. 2101.006). Now, Petitioner claims that the determination it could not do in 2022 was obvious in 2016.

A POSA would not have reasonably expected success by extrapolating the claimed PSMA-I&T dosing regimen from Kratochwil's DOTATOC MTD study. Weineisen 2015's ^{177}Lu -PSMA-I&T doses are 1000x greater than claimed, and Kratochwil provides no therapeutic efficacy data.

2. The Unpredictability of the Field Would have Prevented a Reasonable Expectation of Success

a) The Asserted Prior Art Demonstrates the Unpredictability in the Field

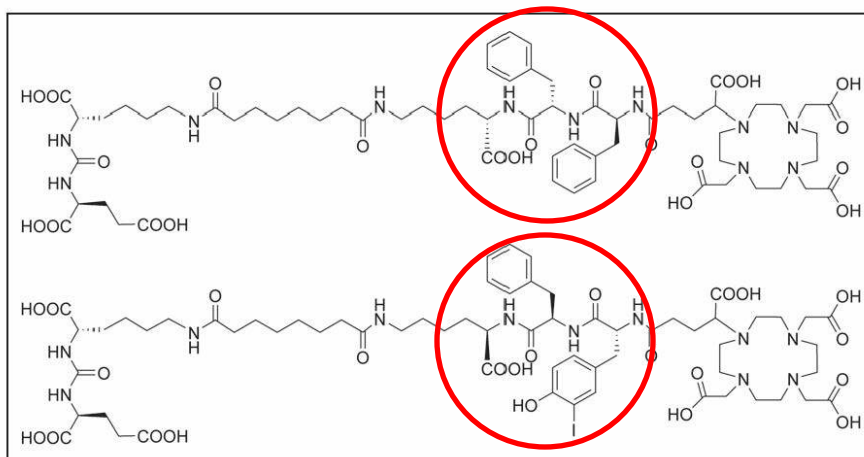
The cited references would not give a POSA reason to combine ^{225}Ac with PSMA-I&T, let alone a reasonable expectation of success, given the chemistry and pharmacology fields' inherent complexity and unpredictability. Because Petitioner provides no motivation to choose these components from many possible molecules and radionuclides, it relies on an obvious-to-try argument, which has no place in such an unpredictable field. *Eisai*, 533 F.3d at 1359 (Fed. Cir. 2008) (“to the extent an art is unpredictable, as the chemical arts often are,” *KSR*'s focus on these

“identified, predictable solutions” presents a difficult hurdle because potential solutions are less likely to be genuinely predictable.), citing, *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 402-403 (2007).

Weineisen 2014 and 2015 demonstrate that, rather than leading a POSA to combine PSMA-I&T with untested ^{225}Ac , changing radionuclides, linkers, and chelators can produce unpredictable, materially different affinity and uptake results, defeating a reasonable expectation of success. (Ex. 2138 ¶129-152).

Weineisen 2015 compared ^{177}Lu -Dotaga-ffk(Sub-KuE) and ^{177}Lu -PSMA-I&T, differing only in the linker between chelator and targeting moiety (circled in Figure 14 below). (Ex. 1028.003).

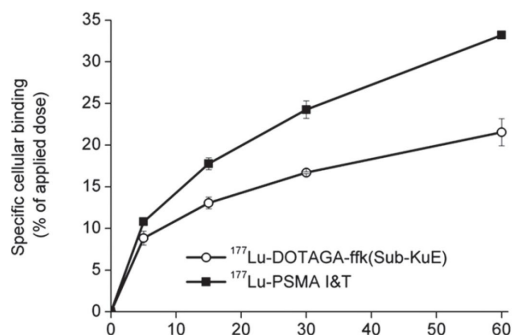
Figure 14 (Ex. 1028.002, Fig. 1).



Although the small change was outside the binding region, IC_{50} values shifted from 13.1 ± 2.2 nM for metal-free DOTAGA-ffk(Sub-KuE) to 7.9 ± 2.4 nM for

^{nat}Lu -PSMA-I&T,¹ while PSMA-mediated internalization increased from $44\% \pm 2\%$ to $76\% \pm 2\%$ for ^{177}Lu -labeled compounds. (Ex. 1028.002-004).

Figure 15 (Ex. 1028.004, Fig. 2).



Thus, minor modifications can dramatically affect ligand binding affinity and biodistribution. (Exs. 2138 ¶143-144; 1028.003).

Weineisen 2015 also reported that changing ^{68}Ga to ^{177}Lu in the *same ligand*, *PSMA-I&T*, produced “marginally” different affinity for PSMA but significantly different uptake profiles in mouse organs, with higher PSMA-mediated internalization for ^{177}Lu -PSMA-I&T than ^{68}Ga -PSMA-I&T in the spleen, kidney, and tumor. (*Id.* ¶145; 1028.004-005, .007, Table 2).

¹ IC_{50} is the unlabeled ligand concentration required to halve ^{125}I -BA]KuE binding; lower IC_{50} means stronger binding.

Table 1 (Ex. 1028.004, Table 2).

Dual-Tracer Biodistribution (%ID/g) in LNCaP Tumor-Bearing CD-1 *nu/nu* Mice at 1 Hour After Injection ($n = 4$)

Organ	^{68}Ga -PSMA I&T	^{177}Lu -PSMA I&T
Blood	0.45 ± 0.23	0.44 ± 0.19
Heart	0.26 ± 0.08	0.29 ± 0.08
Lung	1.49 ± 0.38	1.65 ± 0.56
Liver	1.00 ± 0.39	1.10 ± 0.41
Spleen	3.88 ± 1.46	5.85 ± 2.26
Pancreas	0.54 ± 0.15	0.57 ± 0.24
Stomach	0.42 ± 0.10	0.42 ± 0.14
Intestine	0.27 ± 0.07	0.69 ± 0.14
Kidney	53.26 ± 9.02	107.24 ± 15.61
Muscle	0.35 ± 0.08	0.56 ± 0.36
Brain	0.03 ± 0.02	0.04 ± 0.03
Bone	0.27 ± 0.08	0.22 ± 0.05
Tumor	4.95 ± 1.57	7.96 ± 1.76

%ID/g = percentage injected dose per gram.

Although Weineisen 2015 attributed the difference to enhanced ^{177}Lu -PSMA-I&T uptake (presumably through steric interaction), Petitioner's expert attributed the $^{68}\text{Ga}/^{177}\text{Lu}$ differences to reduced ^{68}Ga signaling because the chelator failed to hold smaller gallium. (Exs. 1028.004; 2136;67:13-69:12, 70:1-71:10; 2138 ¶¶146-149),). This contradicts Price's Table 2 showing ^{68}Ga and ^{177}Lu with comparable thermodynamic affinities for DOTA: 21.3 and 21.6-23.5, respectively. (Ex. 1041.008). *In vivo* instability from size differences sufficient to halve the signal

would be remarkable, if true, and underscores the challenge of predicting radiopharmaceutical behavior from thermodynamic affinity data alone.

Although available data do not identify whether the $^{68}\text{Ga}/^{177}\text{Lu}$ -PSMA-I&T difference reflects bound-nuclide steric effects or lower *in vivo* ^{68}Ga stability, this uncertainty is consistent with the field's unpredictability. Because ^{225}Ac is ~30% bigger than ^{177}Lu , its size could uniquely affect binding or steric interactions. A POSA would not know the cause or effect.

Weineisen 2014 likewise showed that metal identity and ligand design unpredictably affected PSMA affinity, internalization, pharmacokinetics, and biodistribution. It created PSMA-targeting radionuclide carriers with the same PSMA-targeting moiety. Although the chelator was structurally distant from the targeting moiety, binding different nuclides produced different PSMA affinity.

Table 2 (Ex. 1027.010).

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

For example, Weineisen 2014's Table 1 above, shows the IC₅₀ of Ga-bound DOTA-FFK(Sub-KuE) (29.5 nM) was more than double, and Lu-bound DOTA-FFK(Sub-KuE) (54.7 nM) more than quadruple, that of unbound DOTA-FFK(Sub-KuE) (13.1 nM) (red-boxed). (*Id.*).

Weineisen 2014 also found that changing radionuclides affected ligand internalization: ¹⁷⁷Lu-bound ligands showed a higher rate than ⁶⁸Ga-bound ligands (red-boxed in Table 3, below).

Table 3 (Ex. 1027.011).

Ligand		Internalization (1 h) in % of (^{125}I)-BA)KuE
^{68}Ga]HBED-CC-Ahx-KuE		91.1 ± 1.7
^{68}Ga]DOTA-FFK(Sub-KuE)	(^{68}Ga -10)	14.6 ± 0.8
^{177}Lu]DOTA-FFK(Sub-KuE)	(^{177}Lu -10)	19.3 ± 0.9
^{68}Ga]DOTAGA-FFK(Sub-KuE)	(^{68}Ga -11)	28.4 ± 0.7
^{177}Lu]DOTAGA-FFK(Sub-KuE)	(^{177}Lu -11)	36.1 ± 1.1
^{68}Ga]DOTAGA-ffk(Sub-KuE)	(^{68}Ga -12)	42.5 ± 1.7
^{177}Lu]DOTAGA-ffk(Sub-KuE)	(^{177}Lu -12)	44.4 ± 1.8

The Weineisen articles taught a POSA that modifying ligand structure or changing radionuclides in identical ligands unpredictably alters radiopharmaceutical binding, affinity, internalization, and efficacy. (Ex. 2138, ¶129-152). One radionuclide's benefits, *e.g.* ^{68}Ga or ^{177}Lu , would not predict ^{225}Ac 's performance in PSMA-I&T. If small ligand changes can have unpredictable effects, switching entirely from DOTATOC to PSMA-I&T would be more unpredictable, preventing any reasonable expectation of success.

Because they studied only ^{177}Lu and ^{68}Ga , they taught POSAs nothing about an effective ^{225}Ac cancer-treatment dose or its effects on ligands. A POSA could not infer from Weineisen's ^{177}Lu and ^{68}Ga data that the claimed ^{225}Ac -PSMA-I&T dosing methods would be effective. (*Id.* ¶134-138).

Miederer likewise found that using ^{225}Ac in two molecules, DOTA-biotin and DOTATOC (Ex. 1030.008) produced divergent toxicity. Lethal toxicity occurred at 60 kBq after 180 days with ^{225}Ac -DOTATOC but only at 740 kBq after 110 days with ^{225}Ac -DOTA-Biotin. (Ex. 1030.008). Miederer thus taught a POSA that

findings for one ^{225}Ac -labeled molecule (DOTATOC) could not be extrapolated to another.

Petitioner also overstates its claim, based on Price (Ex. 1041), that PSMA-I&T's DOTAGA was an obvious chelator for ^{225}Ac . (Pet. at 17). Price's Table 2 shows no stability data for DOTA with ^{225}Ac and calls ^{225}Ac coordination "uncertain" (note "?" in Table 2). (Ex. 1041.008-009). Petitioner misrepresents Price as lumping DOTA and DOTAGA as "gold standard." But Price only gave DOTA the gold standard label, not DOTAGA, because no one had yet tried DOTAGA with ^{225}Ac . (Ex. 1041.008-009). Even if DOTA use with ^{225}Ac was taught, there was none for DOTAGA, the chelator used in PSMA-I&T. (Ex. 1028.002; 2138 ¶¶69-72).

Even assuming DOTAGA bound ^{225}Ac , chelators do more than carry radiometals; they also influence targeting-molecule properties through unpredictable steric or charge-related effects. Dr. Zalutsky testified he switched from DOTA to DOTAGA on his own investigative molecules not to bind ^{211}At , which was covalently bound, but for its functional effect on the molecule. (Ex. 2139 41:24-42:18). This increased PSMA affinity by 50% and quadrupled cellular uptake (Ex. 2108.012-13); however, a year later he still did not know whether the DOTAGA effect stemmed from steric hindrance or molecular charge (Ex. 2145.010). Petitioner cannot establish DOTAGA was obvious based only on its chelating ability because

it has broader effects on the ligand.

b) **Petitioner's Mouse and Cellular Data do Not Establish Reasonable Expectations of Success for the Claimed Human Dosing Methods.**

Petitioner's reliance on mouse data to support ^{225}Ac is misplaced. At the time of the invention, POSAs knew mice were limited models for predicting human outcomes because laboratory mice and xenografts lack genetic diversity. (Exs. 2138 ¶¶49-55, 156-157, 141; 2121). Real-world cancers are heterogeneous, varying across and within patients because of mutations. (*Id.* ¶49). This helps explain why many cancer cures appear promising in mice but, as Dr. Zalutsky admitted, fail in humans. (*Id.* ¶49-53; 2139 135:18-136:13; Ex. 2111.001-2;).

Dr. Zalutsky demonstrated the PSMA-cancer model was inherently flawed because the human-PSMA xenograft differs from mouse PSMA. Kidney accumulation varied based on whether ligands preferred mouse or human PSMA. Ex. 2145.008. Some mouse studies predicted large tumor/kidney ratio differences that shrank 15x in humans. (Ex. 2145.004). He found mouse models overestimated PSMA-I&T kidney uptake, noting that it is "difficult and perhaps misleading to compare biodistribution data" across PSMA-targeted agents. (Ex. 2108.015). Dr. Zalutsky concluded that biodistribution and therapy results with PSMA-targeted

agents in mice may “be misleading due to differences in PSMA expression in mice and humans.” (Ex. 2145.010). He agreed his research called the reliability of mouse studies into question. (Ex. 2139 133:15-134:7).

POSAs would have known mice were poor models for predicting human toxicity because some toxic effects, like dry mouth, are not reportable in mice and toxicity is often too delayed (*e.g.*, kidney) to appear in mouse time courses. (Ex. 2138 ¶¶49-55, 157).

Determining a drug’s therapeutic window from mice was impossible because of therapeutic overdosing, target overexpression in xenografts, and unclear conversion factors. (*Id.*). For example, assuming an ~85-kg human and ~25-gram mice, Chatalic’s 5 MBq ²¹³Bi-PSMA-I&T injection would convert to $(85/.025 \times 5)=17,000$ MBq in humans, exponentially higher than the ’901 Patent’s claimed dosage of 3–30 MBq (Ex. 1001.019) and twice Weineisen 2015’s beta-emitter activity (5,700 and 8,000 MBq of ¹⁷⁷Lu). Miederer’s 20kBq MTD converts to 68 MBq for humans. (Ex. 2138 ¶¶53, 155-157). Neither teaches the ’901 Patent’s claimed dosage.

Because Chatalic and Miederer use different radionuclides and/or ligands at ranges well above the ’901 Patent’s effective dose, a POSA would not have expected the claimed human ²²⁵Ac-PSMA-I&T dosages to be safe and effective, and

Petitioner has not shown otherwise. (*Id.*)

Chatalic's dangerously high dose is especially problematic. If mouse experiments were predictive, Chatalic would teach that excessive, dangerous radiation levels were required, teaching away from alpha-emitters. If mice are not valid models, Chatalic and Miederer offer no guidance. As POSAs would have known at the time of the invention and Dr. Zalutsky's data showed for PSMA, data from Chatalic or Miederer based on xenografted mice have questionable relevance to the '901 Patent's human treatments.

Weineisen 2015's cellular data is also unreliable because affinity and internalization in unrestricted, homogeneous cell lines cannot replicate human body conditions. *In vivo*, the target may be hidden in a tumor mass, which would be more detrimental to short-ranged alpha-emitters than long-ranged beta-emitters. Target-expressing, nonspecific sites or other nonspecific binding could capture the radiopharmaceutical, decreasing effectiveness. And radiopharmaceuticals or targets could have different conformations *in vivo* due to, *e.g.*, differences in pH or ionic strength.

3. The Prior Art Teaches Away from Using ^{225}Ac Due to Risk of Cell Damage.

The prior art affirmatively taught away from using ^{225}Ac in targeting

radiopharmaceuticals because recoil could release daughter nuclides that damage kidneys. As Section II.C explains, unlike beta-emitters like ^{177}Lu , which emit low-mass electrons and remain stably chelator-bound, alpha-emitters release heavy particles forcefully enough to consistently eject the nuclide from its chelator – known as the “recoil effect.” (Exs. 2138 ¶¶60-67; 1043.004). This could release ^{225}Ac from the targeting molecule (*e.g.*, PSMA-I&T) before reaching its target, with daughter nuclides releasing their particles, three more alphas and two betas, anywhere in the body and damaging healthy tissue. Fig. 11. (*Id.* ¶¶60-67, 154). The first daughter’s 4.8-minute half-life is long enough to reach healthy tissue before releasing particles and preferentially pool in and damage the kidney, spleen, liver, and bone. (*Id.* ¶74; Ex. 1043.006,).

The recoil issue undermines Petitioner’s assumption that ^{177}Lu and ^{225}Ac are interchangeable. ^{225}Ac ’s recoil and subsequent daughters posed a qualitatively different risk to patients that did not exist with stably-bound ^{177}Lu and its daughters. (Ex. 1043.003-4, .006). Lutetium-177’s safer stability made it preferable for small-molecule therapies and could not predict ^{225}Ac ’s safety profile. (Exs. 1027; 1028). As Dr. Zalutsky explains, human studies like Weineisen 2015 are “reserved for only the safest and most promising therapies.” (Ex. 1002, ¶81, copying Ex. 1040, ¶77). The “safest and most promising” therapy in that case was not just PSMA-I&T—it

was ¹⁷⁷Lu-PSMA-I&T, teaching that ¹⁷⁷Lu was the safe choice. That safety rationale did not automatically carry over to ²²⁵Ac-based radiopharmaceuticals because of recoil and daughter-nuclide risks.

The inventors could only try their ²²⁵Ac-PSMA-617 as compassionate care under the Declaration of Helsinki's "Unproven Intervention in Clinical Practice." (Ex. 2076 ¶26). Under this program, compounds may be used only with patients near death after other treatments failed. (*Id.*) Thus, the '901 Patent patients had extensive metastasis and PSA levels in the 2900 and 400 ng/ml range. (*See* Ex. 1001 Figs 12 & 14). The asserted references did not establish ²²⁵Ac-PSMA treatments' safety and efficacy at the time, particularly at the claimed dosages.

Concern over ²²⁵Ac-daughter-mediated nephrotoxicity and recoil was so prevalent that no ²²⁵Ac article was complete without it. Miederer (Ex. 1015.002) repeatedly warned that ²²⁵Ac's daughters were a "key drawback," threatening "significant toxicity" to the liver and bone, deterring a POSA from using it. (Ex. 2072.001-2). Miederer explains that "due to the high toxicity of ²²⁵Ac and its daughter nuclides,... unwanted side effects are to be expected" (Ex. 1015.005) and recommends "renal protection from the accumulation of ²²⁵Ac daughter nuclides," using scavengers such as chelating agents or promoting diuresis to push the radioligand through the system. (Ex. 1015.006).

In Weineisen 2014, ^{68}Ga -PSMA-targeting compounds' biodistribution in mice was higher in kidney and spleen than tumor. (Ex. 1027.012). In Weineisen 2015, ^{68}Ga -PSMA I&T kidney uptake was >10-fold higher than tumor uptake and ^{177}Lu -PSMA I&T's >13-fold higher, with splenic uptake approximately equal to tumor uptake. Ex. 1028.004. Weineisen 2015 estimated the highest absorbed radiation doses in humans would be to the kidneys, adrenals, uterus, spleen, and pancreas. Ex. 1028.005.

Jurcic reinforces concern about kidney damage by prescribing furosemide during two ^{225}Ac -lintuzumab treatments and spironolactone for a year afterward to prevent "radiation-induced nephrotoxicity." (Ex. 1011.002). This undermines Petitioner's assertion that Miederer or Jurcic supplied motivation or a reasonable expectation of success for the claimed ^{225}Ac -PSMA-I&T methods.

Kratochwil's MTD study on ^{225}Ac -DOTATOC focused on "chronic kidney toxicity." (Ex. 1031.001). A POSA reading Kratochwil would have recognized that ^{225}Ac carried substantial, unpredictable toxicity risks. Miederer's, Jurcic's, and Kratochwil's concerns over ^{225}Ac -induced nephrotoxicity would have countered any motivation to use ^{225}Ac in the '901 Patent compounds or combine Weineisen, Jurcic, and Kratochwil because of safety concerns.

Petitioner misinterprets Chatalic's (Ex. 1006) use of ^{213}Bi as endorsing the

safety of all alpha-emitters, including ^{225}Ac . But Figure 11 shows that ^{213}Bi is downstream of ^{225}Ac , emitting only one alpha particle. A POSA would view Chatalic's selection of ^{213}Bi -PSMA-I&T as avoiding ^{225}Ac 's five additional daughter emissions. In fact, Dr. Zalutsky has promoted short-lived, single-alpha-emitting nuclides for decades. (See III.A.3.a).

Attempting to minimize the field's recognition of ^{225}Ac 's dangers, Petitioner and its expert misread de Kruijff (Ex. 1043) as saying it "largely indicates that safe and effective treatments may be reasonably achieved." (Pet. 13). But after reviewing the alpha-emitter literature, de Kruijff concludes the opposite:

"[B]y and large we find that in most studies concerning long-lived alpha-emitters, recoiling daughter atoms pose a serious problem. If the distribution of recoiled atoms is not controlled, toxic effects due to the recoiling daughters will be present. At higher injected radionuclide activities, this could induce significant damage to healthy tissue."

(Ex. 1043.011).

Petitioner cherry picks language from de Kruijff to infer a ≤ 0.1 MBq/kg of ^{225}Ac -labeled Humanized Anti-CD33 Monoclonal Antibody HuM195 as "safe." (Petition pp. 13-14, 34). But Petitioner ignores de Kruijff's follow-up studies' description with the compound in which "no complete remissions have been

reported” and patients suffered thrombocytopenia and febrile neutropenia. (Ex. 1043.003).

Petitioner also mischaracterizes de Kruijff’s reporting of animal studies using J591 and B4 conjugates to DOTA. Focusing on the *initial* lack of toxicity at “low administered activities,” Petitioner ignores the subsequent statement that “at cumulative doses of 215 to 370 kBq severe toxic effects become apparent,” attributed to ^{225}Ac ’s released daughters, “ ^{221}Fr and ^{213}Bi , which are expected to accumulate in the kidneys.” (Ex. 1043.009-10) . When confronted with this language, Dr. Zalutsky acknowledged the discrepancy between his claim of “clear benefit[s]” and the report of later toxicity. (Ex. 2139 116:6-13).

a) **Dr. Zalutsky Taught Away From ^{225}Ac**

While Petitioner refers to ^{225}Ac as the “common-sense” choice (Pet. 14; Ex. 1002 at ¶30), Dr. Zalutsky’s decades of published work state the opposite. Before and after the ’901 Patent, he identified ^{225}Ac as powerful but problematic. Instead, he promoted alpha-emitting radiohalogens, especially ^{211}At , based on features opposite ^{225}Ac ’s:

- ^{211}At ’s 7.2-hour short half-life vs ^{225}Ac ’s 10-day half-life;
- ^{211}At ’s single α particle emission vs ^{225}Ac ’s six particles;

- ^{211}At being a radiohalogen for covalent bonding vs ^{225}Ac 's escapable chelation;
- ^{211}At 's emitting X-rays for tracking vs ^{225}Ac 's indirect measurements.

(2146.002). This contradicts his current testimony that a POSA would have been motivated to select ^{225}Ac for PSMA-targeted alpha therapy with a reasonable expectation of success.

Before the '901 Patent, Dr. Zalutsky described radiohalogens as the “first line of pursuit” for easier synthesis and lack of substantial steric perturbations (Ex. 2140.001), and ^{211}At was “probably the most promising” among emitters (including ^{225}Ac) (Ex. 2146.002-3). He explained ^{211}At lacks ^{225}Ac 's “ α -particle-emitting daughters, which can lead to excessive radiation doses to normal tissues when released from the parent molecule.” (Ex. 2140.005). And its problems with radioactivity were

“much less severe than that associated with the much longer half life α -particle emitting radioactive daughters of ^{225}Ac because the half life of the ^{211}Po intermediate is only 520 msec, limiting its diffusion distance prior to emission of its α -particle.”

(Ex. 2134.002). He also praised ^{211}At 's 7.2-hour half-life as better for cell-specific targeting agents and short-lived small-molecule biologics (like PSMA-I&T) (Exs.

2134.002; 2146.002-3), unlike ^{225}Ac 's 10-day half-life. He said ^{211}At 's X-ray emissions, which ^{225}Ac lacks, benefited tracking. (*Id.*; *see also* Ex. 2146.002). He noted important halogen properties allowing covalent bonding of ^{211}At to targeting molecules, which would be more stable than chelator-bound ^{225}Ac . (Ex. 2148.002).

Even after Kratochwil 2016 and the filing of the '901 Patent's application, Dr. Zalutsky continued to express skepticism over ^{225}Ac in favor of ^{211}At while noting ^{225}Ac -PSMA-617's success. In 2022, he noted that ^{225}Ac produces multiple α -emitting daughters, each imparting "nuclear recoil effect [] orders of magnitude greater than chemical bonds," leading to "unintended irradiation of nontarget tissues," while ^{211}At has single α -particle decay and quick daughter decay, so that " ^{211}At remains the best option for α -therapy." (Ex. 2147.001).

After years of emphasizing radiometals', including ^{225}Ac 's, challenges, Dr. Zalutsky now says, as this case's expert, that ^{225}Ac would have been the "common-sense solution."

4. A POSA Would Not Have Been Motivated to Combine Weineisen 2015 and Kratochwil

Obviousness claims based on combined references require an articulated 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). Such reasons must exceed "mere conclusory

statements” but “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). 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).

Petitioner’s proposed combination of Weineisen 2015, Kratochwil, and Jurcic fails this standard. As the diagram below summarizes, these references address different subject matter across every relevant dimension: chelator, targeting molecule, target molecule, disease, and particle emission.

Table 4

Attribute	Exhibit 1011 (Jurcic et al.)	Exhibit 1028 (Weineisen et al.)	Exhibit 1031 (Kratochwil et al.)
Chelator Used	p-SCN-Bn-DOTA (Ex. 2149)	DOTAGA (1,4,7,10-tetraazacyclododecane-1-(glutamic acid)-4,7,10-triacetic acid)	DOTA (1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid, as part of DOTATOC)
Disease Treated	Acute myeloid leukemia (AML)	Metastatic castration-resistant prostate cancer (mCRPC)	Progressive neuroendocrine tumors (NET)
Targeting Molecule Type	Humanized monoclonal antibody (lintuzumab)	Small-molecule urea-based PSMA inhibitor (PSMA-I&T)	Somatostatin analog peptide (octreotide/TOC)
Molecule	CD33 (on AML	PSMA (prostate-	Somatostatin receptors

Targeted	cells)	specific membrane antigen)	(on NET cells)
Particle Emitted	Alpha particles (from Ac-225)	Beta particles (from Lu-177)	Alpha particles (from Ac-225)

Petitioner claims that a POSA would have looked to “structurally similar ^{225}Ac ” radiopharmaceuticals to determine dosing. (Pet. 37). But Weineisen 2015 and Kratochwil share nothing in common, which Dr. Zalutsky confirmed when asked about their differences. (Ex. 2139 78:22-80:12).

Dr. Zalutsky asserts that selecting a radionuclide, chelator, linker, and targeting moiety is key to treating a particular cancer. (Ex. 1002 ¶27) He agreed that a successful radiotherapeutic considers these four components and modifying any one could change its function. (Ex. 2139 110:7-23). But Jurcic and Kratochwil differ from Weineisen 2015 in all four components and from each other in three. These differences would have deterred a POSA from combining the references in an attempt to reach the claimed invention.

A POSA would not base treatment of one disease on a molecule for a different disease with a different targeting strategy. There would be no reason to expect one disease’s dosing to succeed in another. (Ex. 2138 ¶178-182, 197-203, 210-215, 223-230).

Yet, Petitioner forces the combination by focusing on one component, the ^{225}Ac radionuclide, misframing the references as “doses of ^{225}Ac ” (*see e.g.*, Petition pp. 35, 36, 38, 44, 47, 51) rather than doses of distinct ^{225}Ac -labeled molecules (e.g., DOTATOC, lintuzumab, or PSMA-I&T). This overlooks their different affinities, uptakes, solubilities, targets, and diseases, which a POSA would have considered.

Petitioner’s only motivation to combine is the general desire to “improve on the radiopharmaceuticals,” in the prior art (Pet. 30-32) or use the presumptively improved ^{225}Ac -PSMA-I&T (Pet. 34, 40-43). But motivation to improve the field is too vague to support improving the technology in the manner claimed in the ’901 Patent, with the results in the ’901 Patent, over all other possible combinations of PSMA-targeting molecules and radionuclides (III.A.1.c). (Ex. 2138 ¶¶125, 184--197). Petitioner’s assumption that a POSA would have combined ^{225}Ac with PSMA-I&T because it was a possible improvement overlooks the POSA’s knowledge that replacing ^{177}Lu with ^{225}Ac would have unpredictable effects on safety, efficacy, and dosing (*see* III.A.2) other than the certainty of recoil, uncontrolled daughter nuclides, and liver, kidney, and bone toxicity (*See* III.A.3). This combination would not have been obvious to try because a POSA would not have had a reasonable expectation of success.

In fact, Dr. Zalutsky could reach a Kratochwil/Weineisen 2015 combination only through the hindsight assumption that: “you’d have to want to use actinium-225.” (Ex. 2139 83:8-13). This explanation presupposes the proposition Curium

must prove – the desired combination of ^{225}Ac and PSMA-I&T at specific effective doses – in a case of hindsight.

Discussing Jurcic, he likewise assumed the hypothetical POSA already “wanted to develop” an actinium-PSMA compound:

“I think that a person of ordinary skill who wanted to develop a, for example, actinium PSMA targeted compound would read everything they can get their hands on about actinium and everything they can get their hands on about PSMA and look for the best way of combining all of that information.”

(*Id.* 96:25-97:11). That reasoning starts with the claimed objective and works backward rather than identifying a prior-art reason to select ^{225}Ac for Weineisen 2015’s PSMA-I&T construct among all possible radionuclides.

Because Weineisen 2015 never mentions ^{225}Ac , Petitioner relies on hindsight, seeking motivation from other references. Petitioner relies primarily on a passing mention of ^{225}Ac in a different paper, Weineisen 2014. But this fails because, although it shares authors with Weineisen 2015, it uses different targeting molecules. Weineisen 2014 described complexation of M^{3+} radiometals with its ligands, mentioning “therapeutic M^{3+} -radiometals, e.g. ^{177}Lu , ^{90}Y or ^{225}Ac .” (Ex. 1027.011) Actinium-225 appears only in passing, with no suggestion to combine it with PSMA-

I&T, which did not exist then. The radiometals for complexation with the Weineisen 2014 ligands encompass a broad list: ^{177}Lu , ^{90}Y , ^{68}Ga , ^{47}Sc , ^{149}Tb , ^{161}Tb , ^{111}In , ^{153}Sm , ^{166}Ho , ^{165}Dy , ^{169}Er . (Ex. 2138 ¶125, 139-140, 196). Nothing in Weineisen 2014 identifies ^{225}Ac as the best or preferred choice; it was only an example of M3+ radiometals alongside ^{90}Y and ^{177}Lu , which Weineisen 2014 preferred since DOTA forms “stable complexes with a broad range of radiometals, for therapy most importantly ^{90}Y and ^{177}Lu .” (Ex. 1027.002). Petitioner’s assertion that this passing reference supplied motivation for the specific, claimed combination reads more into Weineisen 2014 than the reference provides.

If a POSA noticed Weineisen 2014’s mention of ^{225}Ac , its absence from Weineisen 2015 would signal that Weineisen preferred other radiometals and undercut Petitioner’s assertion that Weineisen 2014 provided specific motivation to use ^{225}Ac . (Ex. 2138 ¶151-152). Although Petitioner contends combining ^{225}Ac with PSMA-I&T would have been obvious, it apparently did not occur to Weineisen despite previously mentioning it. Instead, Weineisen 2015 targeted ^{177}Lu , a safer alternative.

Miederer and Chatalic also cannot motivate the combination because neither teaches that ^{225}Ac is safe or effective. First, as explained above (III.A.2.b), Chatalic’s use of ^{213}Bi -PSMA-I&T would be interpreted as avoiding ^{225}Ac because it is lower

on ^{225}Ac 's decay chain. Dr. Zalutsky's argument that nuclides with shorter half-lives and one alpha emission are superior (III.A.2.b) applies to ^{213}Bi .

Second, Chatalic does not preferentially teach alpha-emitters because, as shown in Figure 11, *supra*, ^{213}Bi releases two betas per alpha, with beta emissions first 97% of the time. This creates uncertainty about alpha-particle efficacy apart from ^{213}Bi 's beta particles.

Third, as explained above, Chatalic's high dose raises doubt about alpha-emitter effectiveness (III.A.2.b). A POSA would presume this amount was required to achieve results while requiring 2-PMPA or gelofusin "for renal protection" (Ex. 1006.001). This raises concerns about alpha-particle toxicity from ^{225}Ac 's recoiling daughters and human safety and efficacy. Chatalic would make a POSA less likely to risk ^{225}Ac .

Miederer, which uses DOTATOC like Kratochwil, no more justifies combining ^{225}Ac with PSMA-I&T than Kratochwil does (*see* III.A.1b), and its dose also exceeds the '901 Patent's. Even Miederer's lower mouse dosage range of 12–20 kBq converts to 40–68 MBq for humans (III.A.2.b), above the '901 Patent's effective dose.

Nothing recommends to a POSA the combining Kratochwil with Weineisen 2015 to create ^{225}Ac -PSMA-I&T. (Ex. ¶¶231-238). Curium never explained why a

POSA would combine these divergent references except to match the '901 Patent's claim features, confirming the combination is pure hindsight.

5. Weineisen 2015 and Kratochwil do Not Render Dependent Claims 2, 4-8, and 10-13 Obvious.

Claim 2 narrows the formulae to PSMA I&T. Because the discussion of Claim 1 focused on ^{225}Ac -PSMA-I&T, its nonobviousness explanation applies to Claim 2.

Claims 4-7 narrow the cancers to a list in Claim 4, disseminated cancers in Claim 5, prostate cancer in claim 6, and breast cancer in claim 7. Claim 1's nonobviousness explanation, incorporated herein, applies to these Claims. Neither *Weineisen 2015* nor *Kratochwil* describes treating breast cancer.

Claims 8, 10-13 narrow the dosages or divide them over time. Claim 1's nonobviousness explanation, incorporated herein, applies to Claims 8, 11-13. As explained above (III.A.1.c; III.A.4), a POSA would not base one pharmaceutical's dose on another's when their designs, targets, and diseases differ. Therefore, the POSA would not use the doses allegedly described in *Kratochwil* (Ex. 1031) for the PSMA I&T construct described in *Weineisen 2015* (Ex. 1028).

B. Ground 2: Claim 9 is Not Obvious in Light of Jurcic, *Weineisen 2015*, and *Kratochwil*

Curium adds *Jurcic* for its narrower dosage range. The technology's unpredictability (III.A.2), teaching away from ^{225}Ac (III.A.3), incompatibility with the other asserted prior art (III.A.1.c & b), and lack of motivation to combine

(III.A.4) discussed above apply equally here and are incorporated into this section. Jurcic’s spironolactone treatment for a year to prevent “radiation-induced nephrotoxicity” after only two ^{225}Ac -lintuzumab treatments highlights concerns over ^{225}Ac -induced kidney damage. (Ex. 1011.002). As explained below (III.B.1), ^{225}Ac -lintuzumab appeared to provide no treatment benefit. These safety concerns without demonstrated benefit would reduce any incentive to pursue Jurcic’s ^{225}Ac -lintuzumab approach or rely on Jurcic to support the claimed ^{225}Ac -PSMA-I&T methods.

1. Jurcic Does Not Teach an Effective Dose

Jurcic does not teach or suggest the claimed effective dose for the challenged ^{225}Ac -PSMA-I&T methods. Jurcic uses ^{225}Ac -lintuzumab, an antibody binding CD33 to treat Acute Myeloid Leukemia (“AML”), so its doses provide no guidance for a small molecule like PSMA-I&T. (Exs. 2138 ¶¶164-174; 1011.001). A POSA would not have relied on Jurcic’s treatment concerning a specific molecule, target, and disease to guide treatment with different molecules, targets, and diseases, and Petitioner has not shown otherwise.

Jurcic does not allow a POSA to determine what contribution, if any, ^{225}Ac -lintuzumab made to reported outcomes. Jurcic combines standard AML treatment—low-dose (20 mg) cytarabine (“LDAC”) twice daily for 10 days, followed by two fractions of ^{225}Ac -lintuzumab one week apart, then additional LDAC—all without a negative control for ^{225}Ac -lintuzumab. (Ex. 1011.002). Jurcic found 11% of patients reached complete remission. (*Id.*) But because LDAC is already standard leukemia

care, patients are expected to benefit without ^{225}Ac -lintuzumab. Without a negative control, POSAs could not determine whether benefits came from LDAC or ^{225}Ac -lintuzumab, providing no efficacy information. (Ex. 1011.001–1011.002).

Dr. Zalutsky suggested that a POSA could examine studies using LDAC alone to assess whether ^{225}Ac -lintuzumab had any effect. (Ex. 2139 100:25-102:2; 104:5-17; 105:11-19). If LDAC alone achieved similar or better results, a POSA could conclude that ^{225}Ac -lintuzumab was ineffective. *Id.*

Burnett used Jurcic's LDAC protocol without ^{225}Ac -lintuzumab, reporting an 18% complete-remission rate. Burnett also cited papers reporting 9–50% complete-remission rates with LDAC (cytosine arabinoside) alone (summarized in Table 5 below). (Ex. 2116):

Table 5

References	LDAC Dosing	Reported CR
Ex. 1011. Jurcic, JG, et al.	20 mg x 2/day	11%
Ex. 2116. Burnett, AK, et al.	20 mg x 2/day	18%
Ex. 2117. Winter, JN, et al.	10 mg/m ² (~17-20 mg) x 2/day	9%
Ex. 2118 Tilly, H, et al.	10 mg/m ² (~17-20 mg) x 2/day	50%
Ex. 2119. Cheson, BD, et al.	5-20 mg/m ² (~8.5-40 mg) /day	16-32% (summarizing articles)

A POSA would have understood that Jurcic's results were due to the established leukemia drug cytarabine. (Ex. 2138 ¶¶165-174). Because ^{225}Ac -

lintuzumab showed no improvement – and a lower success rate – over reported LDAC alone outcomes, a POSA would have deemed it an ineffective or dilatory unnecessary, and dangerous radiation exposure. A POSA could not have determined any effective dosage from Jurcic, much less one for ^{225}Ac -PSMA-I&T. (*Id.*).

2. There Was No Motivation to Combine Jurcic with Weineisen 2015 and/or Kratochwil

A POSA would not have been motivated to combine Weineisen 2015, Kratochwil, and Jurcic because they involve different cancers, targets, and molecule types, with Jurcic furthest afield: a CD33-targeting antibody for leukemia, a liquid cancer. (*See* Table 3). Lintuzumab, with its slower clearance (Zalutsky Decl. Ex. 1002, ¶88), would have slower pharmacokinetics, providing no treatment or dosage guidance for the more quickly cleared PSMA-I&T.

Jurcic also administered ^{225}Ac -lintuzumab with LDAC rather than as the monotherapy used in Weineisen 2015 or Kratochwil. (Ex. 1011.001-.003). Petitioner never explains why a POSA would extract one component of Jurcic’s two-part leukemia regimen for use in unrelated monotherapies – especially when Jurcic provides no evidence ^{225}Ac -lintuzumab was effective (*see* III.B.1).

C. Ground 3: Kratochwil 2016 is Not Prior Art Under 102(a) or (e) Because it was Not Invented by Another

Kratochwil 2016 describes the novel ^{225}Ac -PSMA-617 molecule and dosage determinations in the ’901 Patent but is not prior art under 35 U.S.C §102(b)(1) because the inventors published it less than a year before the patent’s filing. (Ex.

1045). Curium’s argument that the reference qualifies as prior art because of four non-inventor co-authors – Mirjam Weis, Frederik Verburg, Felix Mottaghy, and Klaus Kopka – fails because co-authorship does not indicate co-inventorship; the standards differ. *In re Katz*, 687 F.2d 450, 455 (C.C.P.A. 1982); *Ruling Meng v. Ching-Wu Paul Chu*, 643 F. App’x 990, 996 (Fed. Cir. 2016). Co-authors who obtained the invention’s subject matter from a disclosure by the named inventors do not convert a publication into prior art. *Katz*, 687 F.2d at 455. The sworn declarations by all four non-inventor co-authors and two inventors show that conception and reduction to practice of the ’901 Patent invention resided exclusively with the named inventors. (Ex. 2076, ¶17).

The named inventors conceived and began testing the invention in March 2014 (*Id.*, ¶20), long before non-inventor co-authors became involved in the publication’s subject matter. The non-inventors uniformly state that they do not believe they are inventors on the ’901 Patent (Exs. 2150 ¶12; 2152 ¶10; 2151 ¶10; 2077 ¶11) and that their information about the invention originated from the named inventors. (Exs. 2150 ¶12; 2152 ¶10; 2151 ¶10; 2077 ¶11).

At the time of the invention, Mirjam Weis was a Technical Assistant in Professor Morgenstern’s laboratory at the European Commission’s Joint Research Centre in Karlsruhe, Germany (Ex. 2150, ¶3), performing cell culture, experiments, and lab maintenance. (*Id.* ¶7). Any experiments were designed and supervised by Professor Morgenstern. (*Id.* ¶8). She provided no data to the ’901 Patent or Kratochwil 2016, “was not involved in the creation or design of the ²²⁵Ac-PSMA-

617 compound,” and “did not know anything about the dosing or methodology of using ^{225}Ac -PSMA-617 for any treatments” (*Id.* ¶¶9–12).

The inventors confirm Ms. Weis “did not create any of the molecules used in the study or suggest any dosages, radionuclides, treatment strategies, or otherwise contribute to the invention” or “generate any of the data that appears in Kratochwil 2016 or the ’901 Patent.” (Ex. 2073, ¶27). She was included as co-author to acknowledge her lab support. (*Id.*).

At the time of the invention, Frederik Verburg and Felix Mottaghy were at RWTH University Hospital in Aachen, Germany. Their only contribution was referring a patient and providing diagnostic imaging (Kratochwil 2016’s Figure 3) before and after treatment as standard care, separate from treatment. (Exs. 2151, ¶15, ¶8; 2152, ¶8). They did not have “any control over or input in the study and the elements of the invention, such as the molecule and the dosage, which had been determined before they were involved.” (Ex. 2076, ¶24.) They “did not administer the therapeutic agent, did not participate in discussions regarding the dosing regimen, and played no role in designing or deciding any aspects of the use of ^{225}Ac -PSMA-617.” (*Id.* ¶22).

The patient Drs. Verburg and Mottaghy asked Dr. Kratochwil to include in the experimental clinical treatment in December 2014, nine months into the ^{225}Ac -PSMA-617 study, was the twenty-second study patient. (Exs. 2076, ¶¶17, 21-24; 2073, ¶26). When they contacted Dr. Kratochwil, the named inventors “had already conceived and created the radiotherapeutic molecule and were determining the

dosage based on work with the patients.” (Ex. 2076, ¶22).

When they referred their patient, they “did not know what results Drs. Kratochwil and Haberkorn were getting at that point or the details of the treatment.” (Ex. 2151, ¶14). The patient going “from having extensive, life-threatening metastasis to in essence complete remission” surprised them, and they wanted to publish. (Exs. 2151, ¶16; 2152, ¶15).

Dr. Kratochwil confirms he was already “obtaining unexpectedly good results,” prompting him to include these unbiased physicians from another renowned university hospital as co-authors to lend credibility to the results. (Ex. 2076, ¶24).

Dr. Kopka, a co-inventor on the related but separate PSMA-617 carrier molecule, was included as a co-author “because [the inventors] had a friendly and collaborative relationship and as a recognition of Dr. Kopka being one of the co-inventors of the PSMA-617 molecule.” (Exs. 2077, ¶¶11; 2076, ¶20; 2073, ¶28). Dr. Kopka confirms that developing ²²⁵Ac-PSMA-617 was “a separate and distinct project.” (Ex. 2077, ¶11). He played no role in creating the molecule or determining dosages and learned of the results afterward from the named inventors. (Exs. 2077, ¶¶14-15; 2073, ¶¶11, 28; 2076, ¶20).

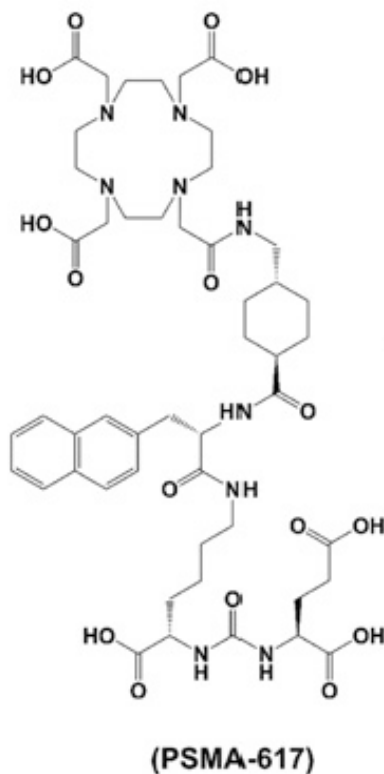
These testimonies confirm that the non-inventor co-authors on Kratochwil 2016 were not involved in conceiving the claimed invention and learned of the results only after the relevant work occurred.

D. Objective Evidence Confirms Nonobviousness

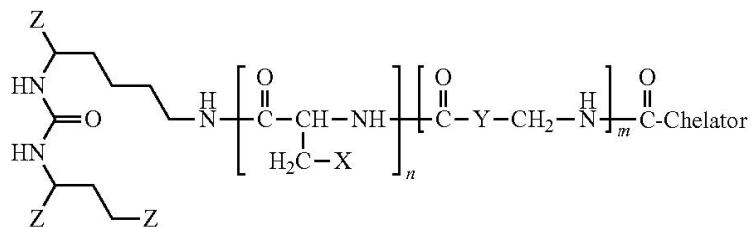
The claimed invention’s nonobviousness is supported by objective indicia

with a nexus to the claimed invention, including resounding praise from the scientific community. Petitioner contradictorily claims Kratochwil 2016 is anticipatory prior art (Petition 51), laying out the nexus evidence POs provided in their 2023 Response (Petition 53-56 citing Ex. 1044, pp. 37-41), while simultaneously claiming no nexus between the article and patent claims (Petition 56) without explaining what is missing. Petitioner is wrong on both counts.

The experts agree that Kratochwil 2016 embodies the '901 Patent claims. (Exs. 2139 170:18-171:18; 2138 ¶¶80-95, 101-103). Dr. Gorin explains that it meets Claims 1-2, 4-5, and 8-13 by administering the ^{225}Ac -PSMA-617 radiopharmaceutical to patients for cancer treatment at 9-10 MBq or 6.4 MBq (within the claimed range) every two months. (Exs. 2138 ¶¶80-100; 1045.002-3; 1001, 18:14-20:37). These doses are demonstrably effective against PSMA-related prostate cancer because the patients' complete remission was detected through ^{68}Ga -PSMA PET/CT scans appearing in both Kratochwil 2016 and the '901 Patent (see Figs. 1-5, *supra*). (Ex. 1045.002-3). Kratochwil 2016's PSMA-617 was originally described in Benesova et al. (Exs. 1045.001; 2078) and has the following structure:

Figure 16 (Ex. 2078.002, excerpt of Fig. 1)

Dr. Gorin testified that PSMA-617 falls within the Markush Formula A (Exs. 1001, 18:20-30; 2138 ¶80-95):

Figure 17 (Ex. 1001, Claim 1, Formula A).

The novel combination of ^{225}Ac with the chelator, linker, and PSMA-targeting moieties directs the alpha-emitter to PSMA cancer cells, producing surprisingly

complete remission over the closest prior art ^{177}Lu -PSMA-617. Dr. Gorin explains that complete remission with ^{225}Ac -PSMA-617, but not ^{177}Lu -PSMA-617, demonstrates the improvement resulted from combining ^{225}Ac and the PSMA-617 targeting molecule at that dose, establishing a nexus between the patent's claimed treatment combinations and Kratochwil 2016's results. (Ex. 2138 ¶¶80-95; 121, 243-244). Praise for these results also creates a nexus between them.

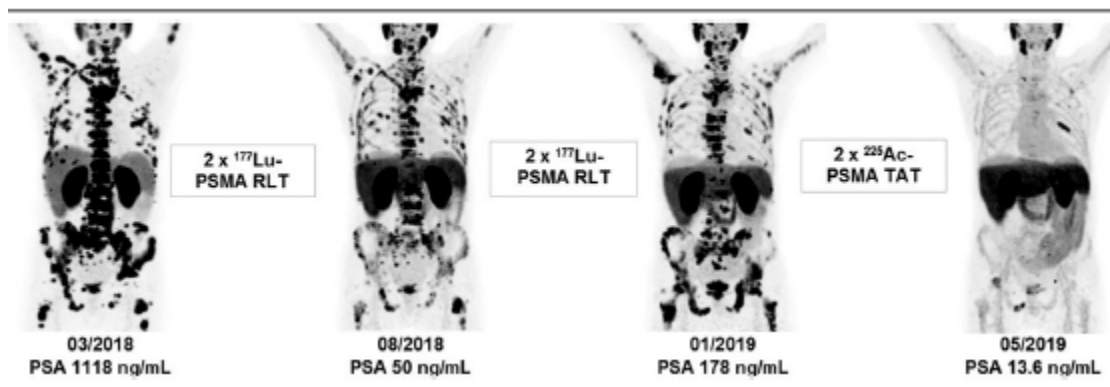
Petitioner contends that praise and unexpected results matter only when every embodiment is equally praised and surprising, and evidence is traceable to a single claim limitation, even arguing every dose in a claimed range must be tested for every PSMA-related cancer to support secondary considerations. (Petition, 56-58). This overstates the law.

In re Huai-Hung Kao (“Kao”) only requires evidence of secondary considerations “be *reasonably commensurate* with the scope of the claims.” 639 F.3d 1057, 1068 (Fed. Cir. 2011) (emphasis added). This “does not mean that an applicant is required to test every embodiment within the scope of his or her claims.” *Id.* POs “need not sell every conceivable embodiment of the claims in order to rely upon evidence of commercial success, so long as what was sold was within the scope of the claims.” *Id.* at 1069 citing *In re DBC*, 545 F.3d 1373, 1384 (Fed. Cir. 2008). Similarly, it would be oppressive to require an academic to clinically test every claim embodiment to show surprising results and praise of a patent embodiment. *See Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (“we do not require a patentee to produce objective evidence of nonobviousness for every potential

embodiment of the claim.”).

The patentee need only provide “an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner” to establish evidence commensurate with the claims’ scope. *Kao*, 639 F.3d at 1068. Petitioner misconstrues *Allergan, Inc. v. Apotex Inc.* 754 F.3d 952, 963 (Fed. Cir. 2014). *Allergan* requires that “other embodiments,” not *all* embodiments, “behave in the ‘same manner’.” *Id.* Petitioner has already acknowledged that ^{225}Ac -PSMA-I&T produced comparable outcomes to Kratochwil 2016’s ^{225}Ac -PSMA-617.

In 2021, five years after Kratochwil 2016 and the ’901 Patent’s filing, Dr. Harun Ilhan’s lab (the “Ilhan group”) evaluated the claimed treatment using ^{225}Ac -PSMA-I&T—the compound Petitioner claims invalidates the patent. (Ex. 2122). The Ilhan group used a similar treatment design, showing failure of four prior ^{177}Lu -PSMA-I&T treatments followed by nearly complete remission of metastasized prostate cancer and 92% PSA reduction after two treatments with 100 kBq/kg ^{225}Ac -PSMA-I&T:

Figure 18 (Ex. 2122.003, Fig. 2)

The Ilhan group concluded that their data “indicat[ed] comparable results for ²²⁵Ac-labeled PSMA-617 and PSMA-I&T after failure of ¹⁷⁷Lu-PSMA RLT” (Ex. 2122.004) and “²²⁵Ac-PSMA-I&T TAT showed promising antitumor effects comparable to ²²⁵Ac-PSMA-617” (Ex. 2122.006). Two concordant clinical studies by different groups using the '901 Patent's Claim 1 strategy of ²²⁵Ac with chelator, PSMA-targeting molecule, and linker demonstrate that the reported cancer remissions are reasonably commensurate with the claims' scope, as the '901 Patent's Markush formulations Petitioner challenges, Formulas C and D, (Petition, 43, 45-46), and Formula A used in Kratochwil 2016 have demonstrated surprising results.

Petitioner also confirmed the embodiments' commensurate scope in its own 2022 U.S. patent application, cataloging studies with ²²⁵Ac-PSMA-617 and ²²⁵Ac-PSMA-I&T at dosages within Claim 1's ranges. (Ex. 2096 at Table 5 and [0088]-[0101]). Petitioner's own application concluded that “using ²²⁵Ac-PSMA-I&T showed *highly comparable biochemical responses* as after ²²⁵Ac-PSMA-617 TAT.” (*Id.* [0099] (emphasis added)). Petitioner's application then claims a ²²⁵Ac-PSMA-

I&T composition based on the clinical results the '901 Patent inventors obtained with ^{225}Ac -PSMA-617. Petitioner directly copies from the '901 Patent inventors' publications on its embodiments. (*See* Ex. 2096 Figs 3-5, 7, 10-12, 14-16 *reproducing* 2097.006; 2098.004; 2099.002; 2100.003, 005; 2101.002, 004, 006). After relying on the comparable efficacy of ^{225}Ac -PSMA-617 and ^{225}Ac -PSMA-I&T, Petitioner cannot deny that they represent the commensurate scope of the '901 Patent invention's surprising results.

Petitioner's argument that a single element must be linked to the secondary factor is also wrong. "[P]roof of nexus is not limited to only when objective evidence is tied to the supposedly 'new' feature(s)." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330 (Fed. Cir. 2016). The "claimed combination as a whole" can "serve[] as a nexus for the objective evidence." *Id.* The combination of ^{225}Ac with PSMA-targeting molecules together produced the claimed invention's unexpected results.

1. The '901 Patent Embodiment in Kratochwil 2016 Has Received Considerable Praise

a) The Community Praised the '901 Patent Embodiment

Evidence that industry praised a claimed invention or product embodying patent claims weighs against obviousness. *WBIP*, 829 F.3d at 1334. Because Drs. Gorin and Zalutsky agree Kratochwil 2016 embodies the '901 Patent (Exs. 1045; 2138, ¶¶80-95, 101), the praise and attention it garnered reflect on the '901 Patent.

Kratochwil 2016's Figures 1 and 3 (corresponding to the '901 Patent's Figures 12 and 14, respectively) quickly became iconic in oncology and radiology, cited in

numerous publications and presentations.

The month it was published in the *Journal of Nuclear Medicine*, Kratochwil 2016 was honored with its Figure 3 on the cover.

Figure 19



(Ex. 2074, Fig. 3).

Shortly after, Dr. Simons, president of the Prostate Cancer Foundation, emailed the inventors, calling Kratochwil 2016 “one of the most potentially important original papers in the last 20 years in our field of experimental therapeutics.” He later travelled to University Hospital Heidelberg to meet them. (Ex. 2073, ¶24).

Praise and attention for the unexpected result continued for years. In 2017, “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 where Dr. Kratochwil presented the data that the Journal called a “promising compound” (Ex. 2123.012). The work also received the 2017 **EANM Marie Curie Award**, among EANM’s highest honors. (Exs. 2123; 2138 ¶106-107).

The Kratochwil 2016 results impressed Dr. Gorin and the field, as shown by various independent assessments:

- “About TAT-targeting PSMA, the **surprising therapeutic effects** of [²²⁵Ac]Ac-PSMA-617 were reported in clinical studies in 2016 (Fig. 11).” (Ex. 2130.010).
- “Compared to initial tumor spread (A), restaging after two cycles of β -emitting ¹⁷⁷Lu-PSMA-617 presented progression (B). In contrast, restaging after the second (C) and third (D) cycles of α -emitting ²²⁵Ac-

PSMA-617 gave an **impressive response**.” (Ex. 2126.006, Fig 2).

- “Kratochwil et al. first described a **remarkable therapeutic effect** of 225Ac-PSMA-617 in patients with late-stage prostate cancer (Fig. 3).” (Ex. 2127.003)
- “Notably, the first patient exhibited the **disappearance of PSMA-positive lesions** on PSMA PET/CT and a **remarkable decline in PSA** levels from over 3,000 ng/mL to 0.26 ng/mL within two months of treatment of [225Ac]Ac-PSMA-617.” (Ex. 2071.008).
- “Since the **seminal** paper by Kratochwil *et al.* establishing its feasibility, 225Ac-labeled PSMA ligands have gained momentum.” (Ex. 2128.003).

(emphasis added to all) (Ex. 2138 ¶126, 104-107, 240-241).

Experts agree that citations objectively measure a paper’s importance because influential papers are cited more frequently. (*Id.* ¶108-118). As the Table 6 shows, Kratochwil 2016’s citations far outstrip those for, *e.g.*, Weineisen 2015, which came out a year and a half earlier.

Table 6

Source	Weineisen 2015 Citations	Kratochwil 2016 Citations
PubMed	224	419
Google Scholar	643	1224

(Exs. 2131; 2094; 2132; 2133). In the twelve weeks surrounding publication,

Kratochwil 2016 is in the 96th percentile of citations and 98th percentile of all tracked articles. (Ex. 2095). It is the fifty-seventh most cited article among *all* of Journal of Nuclear Medicine’s tracked publications. (*Id.*). These metrics objectively demonstrate scientific attention and recognition for the claimed invention.

b) **Dr. Zalutsky and Petitioner Praised the ’901 Patent Embodiment**

Dr. Zalutsky also praised the claimed invention. In 2024, he praised the Kratochwil 2016 results as “dramatic” and “demonstrated significant responses, even in individuals nonresponsive to prior β -emitter therapy.” (Ex. 2108.003).

In 2021, he wrote that the inventor’s work on ^{225}Ac -PSMA-617 “reported significant responses even in patients that did not respond to its ^{177}Lu -labeled analogue” demonstrating “the promise of targeted α -particle therapy (TAT) in combination with a low-molecular-weight PSMA inhibitor” (Ex. 2153.003). He admitted the molecule had “excellent therapeutic effectiveness.” (*Id.*003-4).

In 2022, he noted “the α -emitter ^{225}Ac -PSMA-617 have been encouraging, even in late-stage disease” with “PSA declines of at least 90% in roughly half of patients [] and overall survival of more than 15 mo ... exceed those of new chemo- or hormonal therapies.” (Ex. 2147.006).

He also praised the Ilhan Group’s copying of the ’901 Patent with ^{225}Ac -PSMA-I&T as “even more promising” “with an ^{225}Ac -labeled agent producing a

significant tumor response in patients who were unresponsive to prior b-emitter therapy.” *Id* at 001. In 2023, he described the Kratochwil 2016 results as “superior clinical results.” (Ex. 2144.002). He acknowledged that since the Kratochwil 2016 paper, “*a*-emitters have been attracting increased interest due to their higher therapeutic efficacy” *Id*.

Before being paid as an expert in this proceeding, Dr. Zalutsky acknowledged that the '901 Patent invention outshined previous treatments and prompted additional work in the field. Regardless of how he recharacterizes his past statements now that he works for Curium, his previous objective opinion was that the invention described in Kratochwil 2016 was dramatic, superior, and generated significant interest.

Petitioner also praised the invention when lifting data from the inventors' publication (Ex. 2101) for its 2022 patent application, noting that with ²²⁵Ac-PSMA-617 “Remarkable antitumor activity by means of objective radiologic response or tumor marker decline was observed in 9 of 11 evaluable patients.” (Ex. 2096.030 [0116-0118]).

2. The Patent Invention Embodiment Produced Unexpected Results

Such praise stems from surprisingly superior results exceeding a POSA's

reasonable expectations. Kratochwil 2016 showed metastasized cancer completely disappearing after three treatments over six months (see Figures 1-5, above). (Ex. 1001, Figs. 12, 14). The treatment succeeded completely after ^{177}Lu -PSMA-617 failed, allowing further metastasis. (Ex. 1001, Fig 14, 17:42-57). Petitioner provides nothing predicting this level of success.

These results were unexpected given the conventional wisdom discussed above regarding ^{225}Ac 's recoil, daughter-nuclide release, and redistribution causing normal-organ toxicity. (See Section II.C). Yet the patients experienced striking tumor responses without reductions in white blood cells, platelets, or hemoglobin after months of treatment. (Ex. 1001, Figs. 11, 13, 15).

To establish unexpected results, “a patent owner need not demonstrate that one of ordinary skill would have expected *failure*,” only that “the results would have been *unexpected* to one of ordinary skill at the time of invention, or ‘much greater than would have been predicted.’” *Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1356 (Fed. Cir. 2017) (emphasis in original) citing *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). “[T]he results must be shown to be unexpected compared with the closest prior art.” *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991). Accordingly, the ’901 Patent and Kratochwil 2016 show the closest prior art, ^{177}Lu -PSMA-617, failing to remove the metastasized cancer while the claimed ^{225}Ac -PSMA-617 produced complete remission. (Exs. 1001, Fig. 14; 1045.003; 1004.383). Complete remission is not merely a change in degrees but a qualitative improvement over the prior art.

Even if alpha-emitters were expected to be better, nothing predicted this level of improvement.

Curium misstates Kratochwil 2016's observation that ^{225}Ac -PSMA-617 matches the "theoretic *considerations*" of alpha-emitter treatments as "theoretic *outcomes*," suggesting the clinical outcome was predictable. (Petition 62) Kratochwil 2016 instead reported achieving *all* factors important to a therapy, *i.e.*, a Wishlist, that had merely been theoretical before. (Ex. 2154 ¶16, 24-25) Kratochwil's discussion of previous research shows other attempts met *one* element but failed others. While Kratochwil's previous work had shown "α-therapy can break radioresistance to β-radiation" with ^{213}Bi -DOTATOC, it had to do so in the range of 3.3-10.5 Gbq, 1000x times the claimed dosages, to get partial responses. (*Id.* ¶17-18; Ex. 2155.003). Internalization and retention of daughters after internalization had only been shown *in vitro*, not *in vivo*, which is more complex, and only with either unrelated molecules (antibody) or radionuclides (^{177}Lu).² (Exs. 1045.003; 1013; 2154 ¶22-23).

Everyone involved was surprised by the results and described the clinical outcomes as unexpected. (*See* Exs. 2077, ¶15; 2151, ¶16; 2152, ¶15). Drs. Verburg

² Benešová's (Ex. 2009) internalization speed ("54% and 75% ... after 1 h and 3 h") is not published. Dr. Kratochwil knew this because he is an author on the paper.

and Mottaghy were so impressed by their patient's unexpected complete remission that they asked to publish it immediately as a case report (now the famous Kratochwil 2016). (Ex. 2076, ¶24). Dr. Kratochwil agreed to publish with these independent physicians from another renowned university hospital to lend credence to unbelievably good results. (*Id.* ¶29).

Dr. Morgenstern considered their earlier clinical results with ^{225}Ac -DOTATOC for treating NET, at best, a marginal improvement over ^{177}Lu . (Ex. 2073, ¶12). He described Kratochwil 2016's outcomes as unexpected. (*Id.* ¶22).

Even independent observer Dr. Kopka, a co-inventor of ^{177}Lu -PSMA-617 (Ex. 2076, ¶20), found the ^{225}Ac -PSMA-617 results "very surprising." (Ex. 2077, ¶15).

Others in the field described the results as "surprising," "impressive," and "remarkable." (*See* Exs. 2130.010; 2126.006; 2127.003). The President of the Prostate Cancer Foundation had to read the paper multiple times, take a break, and read it again to believe the results. (Ex. 2073 ¶24).

Petitioner points to no prior art suggesting POSAs would reasonably expect the claimed molecule to achieve complete cancer remission.

3. Experts Were Skeptical

Significant skepticism surrounded whether alpha-emitters, particularly ^{225}Ac , would provide clinical benefits given their risks. In 2011, Dr. Zalutsky argued that, compared with other alpha-emitters, ^{225}Ac had a more severe problem with diffusion of escaped daughter nuclides from uptake sites because of its longer half-life. (Ex. 2134.002). (*See also* Section III.A.3.a).

Dr. Morgenstern's colleagues and superiors told him ^{225}Ac would never be useful, was a dead end, and a waste of time and resources. (Ex. 2073, ¶19). Without ^{225}Ac -PSMA-617's surprising results, he likely would have been forced to abandon ^{225}Ac . (*Id.*).

Current interest in ^{225}Ac radioligand therapy should not be conflated with interest at the time of invention. As Dr. Zalutsky observed, interest in ^{225}Ac increased *after* Kratochwil 2016's publication. (Ex. 2144.002; Ex. 2073, ¶18).

4. The Patent Resolved a Long-felt Unmet Need

Dr. Zalutsky agrees prostate cancer long needed better treatments. Before 2014, prostate cancer therapies emphasized androgen-deprivation therapy and chemotherapy, which, like most cancer treatments, had considerable and damaging side effects. (Exs. 1002 at ¶38, copying 1040 at ¶35). The field needed more effective, faster treatment with fewer side effects. Despite awareness of ^{225}Ac for at least 15 years before the '901 Patent (*see* Ex. 1013), no prior study reported successful clinical use before the '901 Patent's filing and Kratochwil 2016's publication, showing that the patent fulfilled a long-felt need others had not met despite an interest in doing so.

Petitioner mistakenly argues that the long-felt need must be for the invention's specific "method of using ^{225}Ac radiopharmaceuticals to treat cancer" or "the problem of limited availability of ^{225}Ac ." (Petition, 63). But defining long-felt need by the invention's method of meeting it is effectively hindsight. A long-felt need is defined more generally, such as avoiding CO poisoning (*WBIP*, 829 F.3d at 1332)

or avoiding needle breakage (*Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998)). The long-felt need for a better mousetrap is defined by the problem, not the solution. Here, patients suffered failed treatments and significant side effects. The '901 Patent reported complete remissions in heavily pretreated patients with limited side effects (primarily dry mouth (xerostomia)).

IV. CONCLUSION

For these reasons, the Petition fails to demonstrate that the '901 Patent is obvious or anticipated; the Board should confirm the challenged claims.

DATED: August 24, 2026,

Respectfully submitted,
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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. §42.24(d), the undersigned hereby certifies that this paper contains 13,986 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.

The undersigned further certifies that this paper complies with the typeface requirements of 37 C.F.R. §42.6(a)(2)(ii) and formatting requirements of 37 C.F.R. §42.6(a)(2)(iii). This paper has been prepared in 14-point, Times New Roman proportional font with normal spacing.

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CERTIFICATE OF SERVICE

I hereby certify that on August 24, 2026, a copy of this **PATENT OWNERS' RESPONSE PURSUANT TO 37 C.F.R. §42.120** and all previously unserved supporting materials (Exs. 2135 - 2185), 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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