

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' BRIEF REQUESTING
DISCRETIONARY DENIAL OF INSTITUTION**

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I. INTRODUCTION

Pursuant to the Director’s March 26, 2025, Memorandum on Interim Processes for PTAB Workload Management, Patent Owners, The European Atomic Energy Community and Universität Heidelberg (jointly “Patent Owner” or “PO”), request discretionary denial of Curium US, LLC’s (“Curium” or “Petitioner”) petition for *inter partes* review (“Petition” or “Pet.”) challenging claims 1-2, 4-13 of U.S. Patent No. 10,980,901 (“the ’901 Patent”).

The USPTO should not waste its resources on Curium’s Petition. *First*, Curium’s Petition rehashes prior art and cumulative references already considered by the Examiner. Kratochwil, Kratochwil 2016, and patents to which Weineisen 2015 is cumulative were previously before the Examiner and overcome due to their lack of specificity, missing limitations, and the ’901 Patent’s surprising results.¹ Curium hopes to piggyback on a previously instituted petition (*Fusion Pharm. v. Universität Heidelberg et al.* IPR2023-00551 (“*Fusion*”)) by lifting its arguments and prior art wholesale and falsely implying that institution shifts the burden to PO. But that institution was in error, under a different standard, and Curium fails to rebut PO’s Response arguments. *Third*, the substantial time, money, and resources

¹ Insofar as Curium argues surprising results supporting validity must be claimed, it is just wrong. *Application of Merch.*, 575 F.2d 865, 869 (C.C.P.A. 1978).

spent on this invention and its commercialization establish settled expectations.

A. Background: The Intersection of Unpredictable Sciences

The '901 Patent provides a phenomenally successful strategy for the treatment of cancers expressing prostate-specific membrane antigen ("PSMA") using a radioligand with the radioactive atom (radionuclide) ^{225}Ac . Such cancers are amongst the most common types, with prostate cancer being one of the leading causes of cancer death in men. Exs. 1001, 1:66-2:5; 2001.001. While radiation therapy had previously been a common cancer treatment strategy, it damages healthy and cancerous tissues alike. Direct injection or targeted exposure of radionuclides to the tumor target the radiation at the tumor, but this is ineffective for metastasized tumors. Exs. 2071.001; 1043.001. Metastasis considerably decreases survival prognosis and limits treatment availability. Ex. 2071.001.

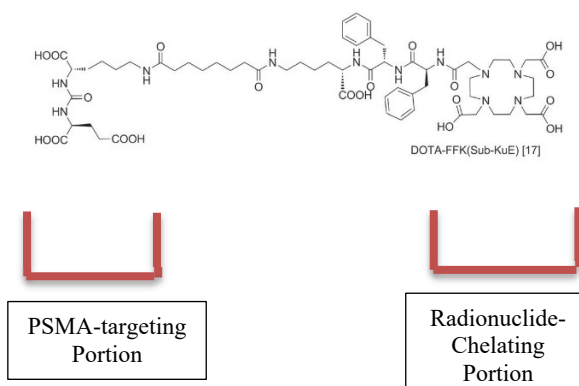
Despite considerable efforts spent on various approaches during the previous decades, a reliable and effective therapy for PSMA-expressing cancers was elusive until the '901 Patent. The '901 Patent uses a combination of: **(1)** a targeting moiety (ligand) specific to the PSMA molecule, **(2)** a chelating moiety able to chelate (bind) the ^{225}Ac radionuclide, and **(3)** a linker between the two. Ex. 1001, 1:20-55. Before the '901 Patent, the design and use of such radioligands were complicated by (1) the unpredictable stereochemistry of the molecules, affecting their function, (2) the inability of the carrier molecule to retain alpha-emitters like ^{225}Ac , and (3)

the unpredictability of the radioligand's binding to the target molecules and its cellular uptake. Modification of any part of the radioligand, its binding region, chelator domain, or radionuclide, could have unpredictable effects on its function. As Curium's expert admits: "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." Ex. 1002 at ¶27.

Curium's reference, Weineisen 2014, showed different radionuclides bound to a molecule's chelator portion differently impaired the PSMA-binding region despite being on the opposite end of the molecule. Ex. 1027.003, .010. The DOTA-FFK(Sub-KuE) molecule showed a third of the affinity once gallium was chelated and a sixth of the affinity with lutetium. See annotated below. *Id.* at Table 1, Fig 2.

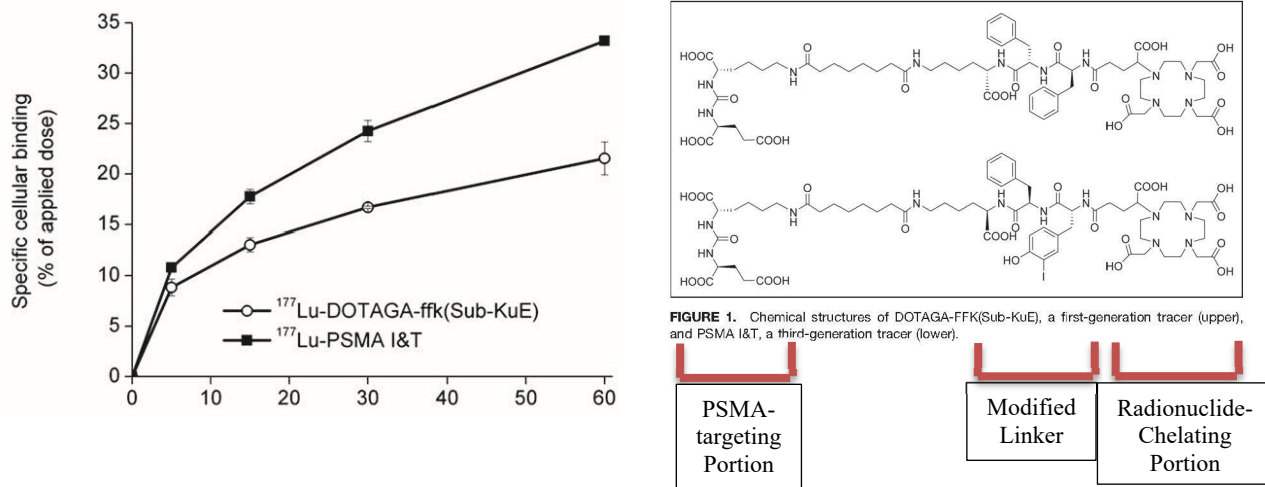
Table 1 PSMA affinities (IC₅₀) of the compounds investigated

Ligand		IC ₅₀ [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



Weineisen later found that modifying only the linker between the chelator and PSMA-binding sites gave very different binding. Ex. 1028.002, .004. So, the research in targeting radionuclides was complicated by the unpredictable effects of

structure on function. See annotated below. *Id.* at Figs. 1 and 2.



This was further complicated by the few safely usable radionuclides. Most research focused on beta-emitting nuclides, like ¹⁷⁷Lu and ⁶⁸Ga, that release electron-sized particles requiring very little energy to expel. But alpha-emitting radionuclides, like ²¹³Bi and ²²⁵Ac, expelled particles thousands of times bigger with proportional increases in force. This extra force unfailingly ejected the daughter radionuclide (the atom lower on the periodic table into which the alpha-emitter converted) from the chelator, releasing it to deliver damaging radiation elsewhere in the body. Ex. 1044.026; Ex. 1043.004. Such free-floating radioactive daughters were a “key drawback” to alpha emitters (Ex. 2072.002) because they would be “distributed to liver and bone” and “contribut[e] to acute radiotoxicity.” Ex. 1030.003. Liver damage after distribution has been shown in nonhuman primates. Ex. 1015.002. ²²⁵Ac was the riskier emitter because ²¹³Bi’s daughter atoms release *one* more high-energy alpha and two low-energy beta particles,

whereas ^{225}Ac 's release *three* more alphas and two betas. Exs. 1044.028; 1022.025.

The safety and efficacy of ^{225}Ac -PSMA-targeted molecules were previously unknown. It depended on various factors, such as the diffusion time, the affinity for PSMA, the degree of uptake, and daughter radionuclide distribution.

B. The '901 Patent Invention: A Surprising Leap Ahead

In this context, the '901 Patent describes the surprising discovery that treating PSMA-expressing cancer patients with a low dosage of the claimed ^{225}Ac radiopharmaceutical compounds with a PSMA-targeting moiety and a chelating moiety results in *complete remission* of the cancer with low hematotoxicity.

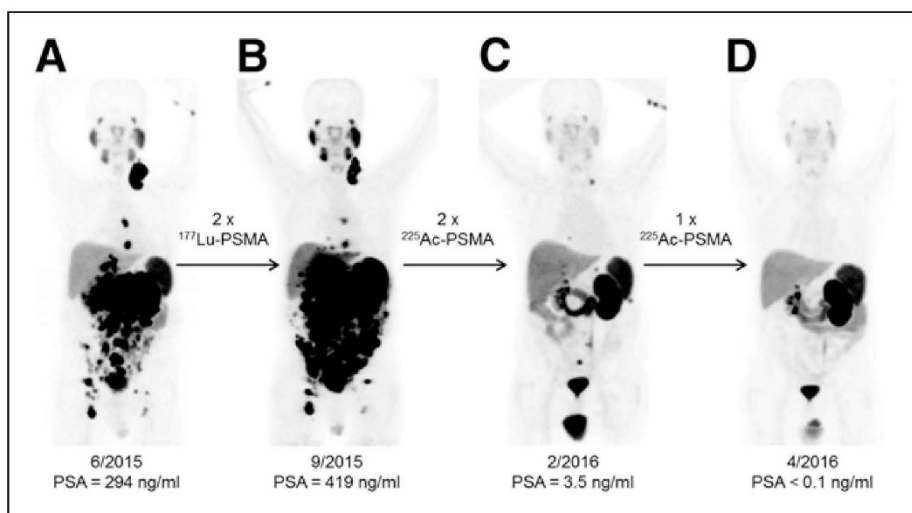


FIGURE 3. ^{68}Ga -PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β -emitting ^{177}Lu -PSMA-617 presented progression (B). In contrast, restaging after second (C) and third (D) cycles of α -emitting ^{225}Ac -PSMA-617 presented impressive response.

Ex. 1001, Fig. 14, 17:32-56. The '901 Patent's Fig 14 data appeared in a corresponding article as Figure 3 (above) comparing the patent embodiment, ^{225}Ac -PSMA-617, against its closest prior art, the beta-emitting ^{177}Lu -PSMA-617. Ex.

1045.003. While ^{177}Lu allowed continued prostate cancer progression ($A \rightarrow B$), the patent embodiment produced “complete remission” ($B \rightarrow C/D$). *Id.* This result was so startling that the president of the Prostate Cancer Foundation called it one of the field’s “most potentially important original papers in the last 20 years” and Figure 3 was on the *Journal of Nuclear Medicine*’s cover. Exs. 2073 at ¶24; 1045; 2074.

The results were surprising because (1) an unusually low dose of 6-10 MBq provided an effective treatment, (2) radionuclide release from recoiling did not cause cytotoxicity, (3) while previous treatments merely mitigated metastasis, this one drove complete remission of prostate cancer, including its primary marker Prostate-Specific Antigen (“PSA”) after only 3-4 treatments, and (4) there was no significant hematotoxicity of the platelets, white blood cells, or hemoglobin. Ex. 1001, 13:65-14:2; 14:10-13; 17:53-61. These last two points were the most remarkable because the kind of complete remission seen in the patient usually requires a very high dosage, which also increases the toxicity. Ex. 1044.017.

C. Prosecution History: Overcoming ^{177}Lu -PSMA Radioligands

The ’901 Patent’s application (the “Application”) claimed priority to PCT/EP2016/081313 filed Dec. 15, 2016. In the First Office Action, the Examiner made a double patenting rejection based on molecules claimed in U.S. Patent Nos. 10,471,160 (the “’160 Patent”) and 10,398,791 (the “’791 Patent,”) (together the “Eder Patents”), a patent family sharing a specification. Ex. 1004.400-401. The

Examiner asserted that the Application's claims were not patentably distinct from the Eder Patents' carrier molecules, anticipating or rendering obvious the overlapping molecules in the Application's Claim 1 Markush group. *Id.*

Comparing the Application's Markush group compounds to those in the '791 Patent and '160 Patent, the Examiner stated that the '791 Patent compounds complexed to ^{177}Lu were, like the Application's, "used in method[s] of treating cancer and/or a metastasis thereof" (*Id.* at 404) and that the '160 Patent compound claims were directed to a "method of their use in treating prostate cancer and/or metastasis thereof" (*Id.* at 406-408) – concluding the differences between the Application and the Eder Patents were "in scope only." *Id.* at 404, 406-408.

The patentee overcame the Examiner's double patenting, anticipation, and obviousness rejections, but not by denying the similarity of the carrier molecules. *Id.* at 381. Instead, the patentee *first* pointed out that the Eder Patents together claimed 14 possible radionuclides and named 28 illustrative radionuclides without distinguishing ^{225}Ac . *Id.* at 382.

Second, the patentee argued that the Eder Patents offered no ^{225}Ac *treatment* dosage. They mentioned that 1.0 to 100 millicuries (37 MBq to 3.7 GBq) should be sufficient for *imaging* and used 3.3 GBq of ^{177}Lu -labeled chelator for metastasized prostate cancer treatment. *Id.* at 382 citing '791 Patent, 22:39-40, 5:27-28; '160 Patent, 21:24-25; 5:28-57. But the Application claimed an effective dose range of

3-30 MBq -- 100 times less than the Eder Patents' ^{177}Lu compound dose -- and even less than the Eder Patents used for imaging. *Id.* at 383. The patentee explained that a POSA would have to specifically pick ^{225}Ac out of the Eder Patent radionuclides and choose "a dose that is **significantly lower** than the broadest range suggested in the '791 and '160 patents." *Id.* (emphasis in original).

Third, the patentee pointed to the surprising results far exceeding the Eder Patents, captured by the now iconic Figure 14. *Id.* at 383-384, citing Application ¶0094, Fig. 14. In Figure 14, a patient had only partial response to 7.4 GBq of the ^{177}Lu -PSMA-617 (twice the dose of the Eder Patents), while 1000 times less of the claimed ^{225}Ac -PSMA-617 induced complete remission. *Id.* at 384. A POSA would not have expected such a strong response at such low doses. *Id.* at 383-84.

The Examiner issued an allowance soon after. In the Statement of Allowance, the Examiner recognized that U.S. Patent No. 8,926,944, which the examiner considered the closest prior art, would not render the '901 Patent obvious because the differences between the claimed molecules' chemical structures, even those distant from the binding region, can result in different binding. *Id.* at 033.

II. ARGUMENT

A. Discretionary Denial under 35 U.S.C. § 325 is Appropriate Because Curium Relies on Repeated and Cumulative References

Curium's references, Kratochwil and Kratochwil 2016, were both before the Examiner at the time of the '901 Patent's prosecution. Ex. 1001, Refs. Cited.

Additionally, Weineisen 2015, which Curium relies on for teaching molecules that fall under the range of radioligand molecules claimed by the '901 Patent, in particular PSMA I&T, is cumulative of the Eder Patents cited by the Examiner.

Curium hopes to coast into an institution of its Petition by copying an earlier instituted petition practically verbatim. But following that roadmap is a mistake because the Board in 2023 failed to properly apply 35 U.S.C. § 325(d) to that earlier petition. Curium's attempts to cover the earlier petition's holes constitute only conclusory handwaving without overcoming PO's arguments.

1. Weineisen and the Eder Patents are Substantially the Same Prior Art for the Same Argument

The first step for a § 325(d) analysis under *Adv. Bionics, LLC v. Med El Elektromedizinische Geräte GmbH*, is determining whether “the same or substantially the same art” or “the same or substantially the same arguments” were previously presented. IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020); *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17 (PTAB Dec. 15, 2017). Here, the Examiner previously argued that the Eder Patents described molecules within the '901 Patent's Markush group of PSMA-targeting molecules with radionuclides. Ex. 1004.400-401. The patentee did not deny this. Instead, the patentee argued that the prior art did not sufficiently narrow the range of radionuclides, it did not teach the dosage claimed by the Application, and the results from the claimed treatment were striking and surprising. *Id.* at 382-84. The

specific species of the Markush group was immaterial to the Examiner's rejection and the patentee's response. Had the Examiner instead relied on PSMA I&T, the objections, arguments, response, and decision to issue would have been the same.

Weineisen 2015 and the Eder Patents are "substantially the same" prior art by both teaching PSMA-targeting molecules that fall within the '901 Patent's Markush group of molecules but carrying the radionuclides ^{177}Lu and ^{68}Ga (not ^{225}Ac). Petitioner offers "the same argument": the '901 Patent is allegedly invalid because Wineisen 2015 teaches molecules within its Markush group of PSMA-targeting molecules bearing radionuclides. Curium merely substitutes the Eder Patents' Markush group member for Wineisen 2015's while offering nothing to surmount the inventive features used to overcome the Eder Patents. While the Eder Patents at least discussed and claimed ^{225}Ac use, Wineisen does not even mention it. Neither teaches the claimed treatment dosage nor rebuts the unexpected results.

Just as the '901 Patent's claimed compounds' efficacy far surpassed the Eder Patents' compounds, it also exceeded the similar dose used in Wineisen 2015. Wineisen 2015 used 5.7 and 8.0 GBq of ^{177}Lu -PSMA-targeting compounds. Ex. 1028.006. The Eder Patents used 3.3 GBq of the Lu-PSMA-targeting compounds. Ex. 1004.382. The '901 Patent compared a 7.4 GBq of ^{177}Lu -PSMA-targeting compound (similar to Wineisen 2015) treatment with 6.4 MBq of ^{225}Ac -PSMA-617. Exs. 1004.384; 1001, 15:65-16:2. But where Wineisen and Eder saw *double-*

digit PSA levels drop to around single digits (40.2 ng/ml to 0.7 ng/ml in Weineisen and 38 ng/ml to 8 ng/ml in Eder) (Exs. 1028.006; 2075 5:28-59), the '901 Patent decreased PSA levels from *three- and four-digit* levels to undetectability (2923 ng/ml and 419 ng/ml to <0.1 ng/ml in Figs. 12 and 14, respectively). Ex. 1001, Figs. 12, 14, 17:44-54, 16:62-17:8. Weineisen's report of only "partial remission" (Ex. 1028.006) and the Eder Patent's "significant impact," (Ex 2006 5:62-67) could not predict the '901 Patent's "complete remission." Ex. 1001, 17:50-53.

The Examiner's rejections based on the Eder Patents were overcome by their failure to describe a species (the ^{225}Ac) from the array of possible radionuclides; include a limitation (the effective dosage amount for ^{225}Ac , much less the ^{225}Ac -PSMA-targeting molecule); and explain the surprising results ("complete remission" of prostate cancer). Ex. 1004.382-84. Because the points that overcame the Eder patent molecule equally apply to Weineisen 2015's molecule, its use of PSMA I&T is cumulative to the Eder Patents. Its use of a different species, even if it were slightly improved, is moot. It would be a waste of the Board's resources to review this patent again based on essentially the same or cumulative prior art and arguments that the Examiner withdrew. After removing the two previously considered Kratochwil references and Weineisen 2015, Curium is left with Jurcic, whose antibody-based molecule against a non-PSMA cancer cannot fill the gap.

2. Prior Institution Was in Error by Misapplying § 325(d) Standard

Curium mimics the *Fusion* petition hoping the Director will just follow the Board's lead.² But the PTAB's previous institution erred by misapplying § 325(d). The PTAB improperly concluded that Weineisen 2015 was not "substantially the same" and cumulative to the Eder Patents because the Eder Patents did not disclose "all the members of the [Application's] Markush group" and "the species disclosed in the Weineisen 2015 reference is not present in the Eder '160 patent claims." *Fusion*, Paper 8 at 13 (emphasis in original). But the PTAB's exact species identity requirement was not the "substantially the same" standard required under § 325(d). There are no "material differences" between the two references because of the exact "overlap between the arguments" concerning the molecules during petition and prosecution. *Becton*, IPR2017-01586, Paper 8 at 17, 23-24.

Section 325(d) does not require *identical* prior art. It requires "the same or substantially the same prior art or arguments." As explained above, Weineisen 2015 simply replaces another molecule for those in the Eder Patents to attack the '901 Patent's Markush with the "same argument." But, like the Eder Patents, it still teaches ¹⁷⁷Lu and ⁶⁸Ga instead of ²²⁵Ac and does not answer any of the points that

² In Curium's Petition, pp. 39-50 are wholly from *Fusion*, Paper 2; pp. 1-38 include ~16 new paragraphs; only pp. 51-63 offer new material. Curium's expert only adds eight paragraphs to the previous expert's opinion. *Compare* Exs. 1002 *with* 1040.

were used to overcome the Eder Patents. Weineisen 2015 provides substantially the same prior art for the exact same argument. Patentee's points overcoming the Eder Patent molecules at prosecution equally overcome Weineisen 2015's, making it cumulative and duplicative. The PTAB erred by requiring that Weineisen 2015 and the Eder Patents have identical species to apply § 325(d).

The PTAB also erred by ignoring PO's evidence of the unexpected result of obtaining complete remission with such a low dose. *Fusion*, Paper 8 at 22-24. Instead, it relied on groundless assertions by the petitioner and its expert (which Curium and its expert parrot) that improvement with ²²⁵Ac was expected, falsely concluding (*see supra* p. 3) that all radionuclides were interchangeable in carrier molecules. *Id.* It ironically noted that "when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *Id.* at 25 (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007)). But complete cancer remission, when the closest prior art failed utterly, is not predictable. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (finding evidence and statement of substantially improved results establish unexpected results). The PTAB erred by not properly considering PO's secondary factors. *Apple Inc. v. Int'l Trade Comm'n*, 725 F.3d 1356, 1365–66 (Fed. Cir. 2013).

3. No Material Error: Prior Art Properly Considered

If previous prior art or arguments are the same or substantially the same as those presented, as they are here, § 325(d) analysis then asks if there was examiner error. *See Adv. Bionics*, Paper 6 at 8. Curium cites no error. It instead asks that examiner-deference be ignored based on its own disagreement as to what a POSA would have expected from the '901 Patent invention. But “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at 9.

To the extent Petitioner claims that it was Examiner error to not consider Kratochwil 2016 as prior art, it would be Curium in error. It is not prior art. It was published by the inventors less than a year before the '901 Patent's filing (Ex. 1045) and its co-authorship is not indicative of co-inventorship because the two standards are very different. *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).

Under AIA 35 U.S.C. § 102(b), Kratochwil 2016 is not prior art if the non-inventor authors obtained the invention's subject matter from a disclosure by the named inventors. This can be demonstrated by inventor declarations provided under 37 U.S.C. § 1.130 once the prior art is asserted (see MPEP §2155) – not proactively – explaining the role of the reference co-authors (*Katz*, 687 F.2d at 455 (explanation by named inventor that co-authors were students supervised by him was sufficient)). If the explanation is consistent “with the content of the article”

and “the nature of the publication” then further speculation as to the co-author’s views is “clear error” (*Id.*), because instituting review for a fishing expedition to challenge the inventor’s declarations nullifies the point of § 1.130.

These inventors’ declarations explain the non-inventor’s roles. Therapeutic studies of the claimed molecules and doses were well underway when Drs. Verburg and Mottaghy asked that one of their patients be included. Exs. 2076 at ¶¶17, 21-24, 2073 at ¶26. Their PET/CT scans of their patient confirmed the inventors’ own findings but did not contribute to conception. Dr. Morgenstern supervised Mirjam Weis in administering radioactive material transfers and basic lab tasks but she did not contribute to the conception of any claim. Ex. 2073 at ¶27.

Since Curium specifically cites Dr. Kopka’s authorship (Pet. at 52-53), he provided a declaration asserting he is not an inventor, did not help to make the ²²⁵Ac molecule or determine dosage, and had no involvement in the invention, which was a distinct project from his. Ex. 2077 at ¶11. He had not considered using ²²⁵Ac with PSMA-617 and only learned of the project, whose results he found very surprising, *after* it had begun. Exs. 2076 at ¶20, 2077 at ¶14-15. The Declarations demonstrate that the inventors conceived of all the ’901 Patent limitations and the Kratochwil 2016 co-authors had no role in the invention.

Curium’s contention that Dr. Kopka deserves credit for Kratochwil 2016’s inclusion of the PSMA-617 molecule lacks merit because, by the time of

Kratochwil 2016, PSMA-617 had already been disclosed though Dr. Kopka's 2015 publication (2078.004) and his 2013 '791 Patent application (2077 at ¶8, 12; 2079, 1:10-17). It could have been relied upon by the inventors like any other prior art technology. And even if the PSMA-617 in Kratochwil 2016 were from Dr. Kopka, Kratochwil 2016 would only be prior art for that one non-inventor contribution, making his alleged PSMA-617 contribution cumulative to the Eder Patents that the PO already overcame. *See Incyte Corp. v. Concert Pharma., Inc.*, PGR2021-00006, Paper 68 at 40 (PTAB May 11, 2022) citing MPEP § 717.01(b)(2))

B. The Merits Were Weak Then and Are Weak Now Because the References Lack Crucial Elements

Curium's references from the prior petition still do not teach the effective dose of "25 kBq to 400 kBq/kg of body weight" or "3 MBq to 30 MBq" claimed by the '901 Patent. Weineisen 2015 teaches ¹⁷⁷Lu compound doses 1,000 times higher than those claimed. Ex. 1028.006. Kratochwil only teaches a "maximum tolerable dosage" for ²²⁵Ac-DOTATOC (i.e., how much treatment a patient can take before it is unbearable) of 40 MBq, which teaches nothing as to the *effective* dose for cancer *treatment*. Exs. 1031.001; 1044.070-071. PO's previous expert, Dr. Hope, explained that tolerability and efficacy are unrelated (Ex. 1044.070-71), and Dr. Abergel, *the previous petitioner's expert*, agreed:

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

A. That's correct.

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

A. That's correct.

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

A. That's correct.

Ex. 2080, Abergel Tr. 169:23-170:17. The *effective* dose for the '901 Patent compounds could have been exponentially more or less than the *tolerable* dose taught in Kratochwil. Even if Kratochwil suggested a ^{225}Ac -DOTATOC treatment dose, there was no motivation to use it with the entirely different compounds in the '901 Patent for this new therapeutic area of an unpredictable field. *See In re Soni*, 54 F.3d at 750 (noting chemistry is an unpredictable field because "minor changes in a product or process may yield substantially different results"). Juncic is no better. Its antibodies used to treat the non-PSMA cancer, leukemia, are dissimilar to the '901 Patent compounds. The Director recently confirmed that petitioners may no longer rely on general understandings in the field but must identify each element of the claim in the prior art. *Memo. on Enforcement and Non-Waiver of 37 C.F.R. § 42.104(B)(4)* (July 31, 2025). Therefore, any presumption of institution based on misreadings of prior institution as gap-filling, merit determinations improperly displaces this Office's independent judgment and must be rejected.

Curium hopes that the previous institution based on these references will carry the day. But the PTAB never found any of these references teach the '901 Patent's claimed effective dose, instead relying on Petitioner and expert arguments that Curium now echoes. According to the PTAB, Kratochwil does *not* teach an effective dosage for treating cancer but only "reasonably suggests that the alpha emitter ²²⁵Ac may be administered at doses of 40 MBq[.]" *Fusion*, Paper 8 at 24. Ignoring that this is higher than the 3-30 MBq dose claimed by the '901 Patent, institution based on obviousness should not rely on mere suggestion, but on the presence of the limitations within the prior art. *See iRhythm Techs., Inc. v. Welch Allyn, Inc.*, IPR2025-00363, Paper 10 at 2-3 (PTAB June 6, 2025) (filling gaps with expert testimony favors denial); Patent FAQ 22. The prior institution overlooked the absence of a key limitation, the unpredictability of the field, and the unexpected results. Curium should not benefit from a laxer standard.

C. Inventor and Licensee Extraordinary Investments Show Settled Expectations

The '901 Patent has been in force only since 2021, nearly five years, but the inventors and licensees have expended significant time, money, and resources in the development and commercialization of the invention, creating settled expectations. *See Amgen, Inc. v. BMS*, IPR2025-00601, Paper 9 at 2 (PTAB July 24, 2025) ("an extraordinary amount of investment, time, and resources dedicated to research, development, trials, and regulatory approval correlates to settled

expectations”). The inventors treated 233 patients in a decade-long clinical study on the ’901 Patent’s compounds’ dosages, efficacy, and safety—evidenced by their eighteen publications on the invention from 2016 to 2024. Ex. 2076 at ¶¶26-30.

The patent licensees, Novartis Pharmaceuticals and Fusion Pharmaceuticals, have also committed to expensive clinical studies based on their settled expectations that the ’901 Patent is valid. Novartis has independently sponsored three clinical studies (NCT04597411, NCT06855277, and NCT06780670) and is collaborating on two more studies with U.S. universities (NCT07054346 and NCT07150715)—two Phase I, a Phase II, a Phase III, and a Phase II/III—using patented compounds. Exs. 2081-2085. Fusion Pharmaceuticals is recruiting for, or is currently running, three Phase II clinical studies (NCT06909825, NCT06402331, and NCT05219500). Exs. 2086-2088. The inventors have another Phase I study (NCT05902247) in the recruiting phase. Ex. 2089.

These clinical studies represent significant investments. Phase I trials average \$4-5.26 million each. Ex. 2090.003. Phase II trials average \$7-20 million each and Phase III \$20-100+ million each, with some estimates as high as \$500 million. *Id.*; Ex. 2092.001-002. Oncology studies with radioligands fall in the upper ranges due to the costs of radiation safety management. Exs. 2092.005; 2093. The exact amounts spent are confidential and this Office has recognized that precise figures are not required to find expenditures noteworthy. *See Empower Clin. Servs.*

LLC v. Eli Lilly & Co., IPR2025-01024, Paper 15 at 2 citing Paper 6, at 1-2, 15-16.

These extraordinary investments of time, money, and resources began before the '901 Patent's issuance, were initiated and committed to before the previous institution against it, and continue up to this day. Indeed, the inventors' extensive research, Novartis's licensing, and the clinical studies early in the patent's life and before the previous institution, display strong settled expectations even then.

Curium's failure to previously challenge a patent that it must have known about also created settled expectations. First, Kratochwil 2016 was widely lauded in the field. It was *Journal of Nuclear Medicine*'s cover story and is one of its most cited articles (1000+ times). Exs. 2074, 2094, 2095. Second, ten of seventeen of Curium's 2021 U.S. Patent Application figures are from the *inventors'* publications on the '901 Patent embodiment. *See* Ex. 2096 Figs 3-5, 7, 10-12, 14-16 *reproducing* Exs. 2097.006; 2098.004; 2099.002; 2100.003, 005; 2101.002, 004, 006. Two of the articles Curium cites notify the public of the '901 Patent and its application. *See* Exs. 2096.026; 2099.002; 2102.008. It is inexplicable that Curium—part of a sophisticated, international organization (Ex. 2103.008)—did not know of the '901 Patent, which published internationally in 2018 and issued in 2021 (Ex. 1001.001), and could not have challenged it earlier.

III. CONCLUSION

Institution should be denied under 35 U.S.C. § 325(d), and/or § 314(a).

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on March 5, 2026, a copy of this PATENT OWNERS' BRIEF REQUESTING DISCRETIONARY DENIAL OF INSTITUTION, was served by E-MAIL on the following correspondence address of record for Petitioner, pursuant to 37 C.F.R. § 42.6(e):

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