

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FUSION PHARMACEUTICALS, INC.,
Petitioner,

v.

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

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

**PATENT OWNERS' PRELIMINARY RESPONSE
PURSUANT TO 37 C.F.R. §42.107**

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EXHIBIT LIST

Exhibit No.	Description
2001	National Institutes of Health Cancer Registration & Surveillance Modules Cancer Classification, https://training.seer.cancer.gov/disease/categories/classification.html (“NIH”)
2002	B. Zielinska, et al., “ <i>An Improved Method for the Production of Ac225/Bi-213 from Th-229 for Targeted Alpha Therapy</i> ”, Solvent Extraction and Ion Exchange, 2007;25(3):339-49 (“Zielinska”)
2003	Christos Apostolidis, et al., “ <i>Production of Ac-225 from Th-229 for targeted alpha therapy</i> ”, Analytical Chemistry, 2005;77(19):6288-91 (“Apostolidis”)
2004	Cytarabine Injection U.S. Food and Drug Administration Label, Hospira, Inc. (2020) https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/071868s032lbl.pdf (“Cytarabine FDA”)
2005	Thomas Langbein, et al., “ <i>Future of Theranostics: An Outlook on Precision Oncology in Nuclear Medicine</i> ”, Journal of Nuclear Medicine, Sep. 2019, Vol. 60, No. 9 (Supplement 2) 13S-19S (“Langbein”)
2006	Rodrigo Bovolín de Medeiros, et al., “ <i>Metastatic castration-resistant prostate cancer (mCRPC) treated with 225Ac-PSMA-617. Case report</i> ”, Brazilian Journal Of Oncology (2019) (“de Medeiros”)

I. INTRODUCTION

Pursuant to 37 C.F.R. §42.107, Patent Owners Universität Heidelberg (“UH”) and The European Atomic Energy Community (EURATOM), Represented by The European Commission (“EURATOM”), (collectively, “Patent Owners”), submit their Preliminary Response to the Petition (Paper No. 2, “Pet.”) for *Inter Partes* Review (“IPR”) of U.S. Patent No. 10,980,901 (the “’901 Patent”) filed by Fusion Pharmaceuticals, Inc. (“Fusion” or “Petitioner”). This submission is timely as it is within three months of the February 17, 2023, mailing date of the Notice of Filing Date Accorded to Petition (Paper No. 3).

II. OVERVIEW

Fusion requests institution of an IPR of the ‘901 Patent, challenging claims 1, 2 and 4-13 . (Pet., p.1). Fusion asserts two grounds for institution: 1) obviousness of claims 1, 2, 4-8, and 10-13 over Weineisen 2015 and Kratochwil; and 2) obviousness of claim 9 over Weineisen 2015, Kratochwil and Jurcic. (Pet., p.5).

This Petition should be denied. Two of the three references relied upon by Fusion are the same as or cumulative of those considered during the examination of the ‘901 Patent, and the third is directed to the treatment of a substantially different cancer that is far afield from the subject of the challenged claims.

Within the ‘901 Patent and during its examination, Patent Owners repeatedly emphasized the surprising results embodied in the challenged claims. Yet, Fusion’s expert failed to explicitly address them, instead stating that she is “not aware of any secondary considerations that show the challenged claims to be non-obvious.” (Ex. 1002, ¶107). And even if Fusion argues its expert impliedly addressed them, she fails to adequately address the key differences and missing disclosures among the relied upon references. For example, Fusion’s expert ignores copious evidence in the literature she relies upon that dosage and efficacy is inextricably linked not only to the radionuclide, but also to the specific structure of the ligand and to the particular type of cancer to be treated, which is the gravamen of the combination recited in the challenged claims.

The PTO did not commit material error in its original examination. Fusion’s challenge is at best based on arguments upon which reasonable minds can differ. Such arguments are insufficient to compel the Board to institute IPR. Patent Owners disagree with Fusion that the challenged claims are obvious, and responds to Fusion’s allegations and arguments in turn. Additionally, Fusion confusingly presents a number of additional references not asserted in the Grounds for institution. This seems to be a tactic to improperly minimize the number of references actually relied upon by Fusion to cobble together its obviousness grounds.

III. LEVEL OF SKILL IN THE ART

For the purposes of this Preliminary Response, Patent Owners do not challenge Fusion’s description of a person of ordinary skill in the art (“POSITA”).

IV. THE ‘901 PATENT

Among cancers, PSMA (*Prostate Specific Membrane Antigen*) expressing cancers – notably prostate and breast cancers – indubitably rank among the most frequent cancers. (Ex. 1001, 1:66 – 2:5). However, in spite of considerable efforts spent on various approaches during the last decades, these PSMA expressing cancers are still among those for which a reliable and efficient therapy remained elusive. The ‘901 Patent describes a breakthrough method for treating PSMA expressing cancers that allows for efficient treatment with as few side-effects as possible. (Ex. 1001, 2:9-14).

According to the Background section of the ‘901 Patent, radiopharmaceuticals are particularly interesting for treating various cancers. Radiopharmaceuticals typically comprise a combination of: **(1)** a targeting moiety (ligand) and **(2)** a chelating moiety. The targeting moiety **(1)** is specific to certain target markers (predominantly) expressed by target cells, and the chelating moiety **(2)** is able to chelate (bind) a radionuclide. The radiopharmaceutical (*i.e.*, the combination of the targeting and chelating moieties) is thus able to target and bind to the desired site of

such cells to destroy the cell it's bound to or nearby cells, such as cancer cells. (Ex. 1001, 1:2-55).

There are numerous different cancers and even more potentially useful different targeting sites for appropriately conceived radiopharmaceuticals. (Ex. 1001, 2:56-60). For any given cancer type of this multitude, a number of different targeting sites may be considered and may (or may not) be of use for the docking of radiopharmaceuticals. Choosing an appropriate targeting site and developing an appropriate targeting moiety combined with identifying an appropriate chelating unit with an appropriate radionuclide to develop a working radiopharmaceutical for a particular cancer is a challenging, yet promising way to manage tumors. (Ex. 1001, 1:61-65).

Notably, Fusion's expert corroborates and reinforces the '901 Patent's characterization of the background art and its many challenges. (Ex. 1002). In her Declaration, she explicitly states that:

1. in radiopharmaceuticals, **“the challenge lies in the ability to selectively target the desired tissue/cells;”** (Ex. 1002.-13, ¶25)
2. **“[t]he targeting moiety is used to direct the rest of the molecule to a particular part of the body;”** and

3. **“[s]election of each of the radionuclide, chelator, linker and targeting moiety is key to ensure the radiopharmaceutical is effective in the treatment of the particular cancer a patient may have.”** (Ex. 1002.015, ¶27) (*emphasis added*).

As such, **the specific combination** of a radionuclide, chelator, and targeting moiety represents **a key challenge for an efficient treatment of a particular cancer in a patient, while having as few side-effects as possible**. And the specific selection of **each portion** of the radiopharmaceutical affects the dosage effective to treat the particular cancer.

Within this context, the ‘901 Patent describes the surprising discovery that treating patients having PSMA expressing cancers with an unexpectedly low dosage of one or more specific Ac-225-radiopharmaceuticals (i.e., with alpha-emitting Ac-225 radionuclide compounds having a specific targeting moiety and a chelating moiety, that is administered in the specific claimed effective amount), allows for a particularly strong anticancer effect with low hematotoxicity. These remarkable results were achieved despite using an exponentially lower dosage than Lu-177 counterparts that Fusion relies upon – which even at such higher dosages could not even come close to the “absolutely impressive and unprecedented” results achieved by the claimed dosages of the claimed, specific Ac-225 radiopharmaceuticals.

V. CLAIM CONSTRUCTION

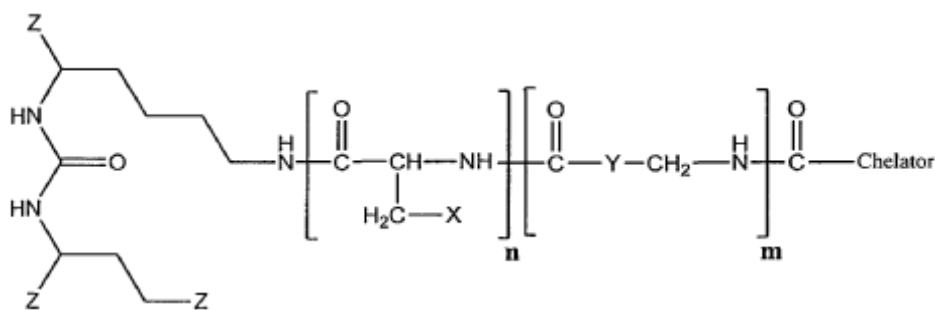
Petitioner's proposed combinations fail to show the challenged claims would have been obvious even under the plain and ordinary meaning of their terms. Thus, it is not necessary to construe any claim term at this stage. *See Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999); *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).

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

Claim 1 states:

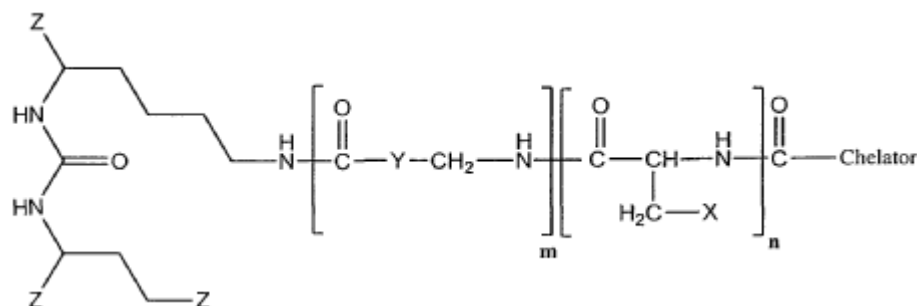
A method for treating PSMA expressing cancers, wherein the method comprises administering to a patient in need thereof an effective amount of one or more Ac-225-radiopharmaceuticals, said one or more Ac-225-radiopharmaceuticals comprising Ac-225 chelated with a targeting compound of Formula (A), (B),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

Formula (A)



or

Formula (B)



with:

- n:** 0,1
- m:** 1,2,3,4
- Z:** -CO₂H, -SO₂H, -SO₃H, -SO₄H, -PO₂H, -PO₃H, -PO₄H₂
- X:** naphthyl, phenyl, biphenyl, indolyl (=2,3-benzopyrrolyl), benzothiazolyl
- Y:** aryl, alkylaryl, cyclopentyl, cyclohexyl, cycloheptyl
- Chelator:** 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), N,N''-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-

N,N''-diacetic acid (HBED-CC),
 1,4,7-triazacyclononane-1,4,7-triacetic
 acid (= NOTA),
 2-(4,7-bis(carboxymethyl)-1,4,7-
 triazonan-1-yl)pentanedioic acid
 (NODAGA),
 2-(4,7,10-tris(carboxymethyl)-
 1,4,7,10-tetraazacyclododecan-1-
 yl)pentanedioic acid (DOTAGA),
 1,4,7-triazacyclononane phosphinic
 acid (TRAP),
 1,4,7-triazacyclononane-1 -[methyl(2-
 carboxyethyl)phosphinic acid]-4,7-
 bis[methyl(2-
 hydroxymethyl)phosphinic acid]
 (NOPO),
 3,6,9,15-
 tetraazabicyclo[9.3.1.]pentadeca-
 1(15),11,13-triene-3,6,9-triacetic acid
 (PCTA),
 N'-{5-[Acetyl(hydroxy)amino]pentyl}-
 N-[5-({4-[(5-aminopentyl)-
 (hydroxy)amino]-4-
 oxobutanoyl} amino)pentyl]-N-
 hydroxysuccinamide (DFO),

diethylenetriaminepentaacetic acid
(DTPA),

Trans-cyclohexyl-
diethylenetriaminepentaacetic acid
(CHX-DTPA),

1-oxa-4,7,10-triazacyclododecane-
4,7,10-triacetic acid (oxo-Do3A) p-
isothiocyanatobenzyl-DTPA (SCN-Bz-
DTPA),

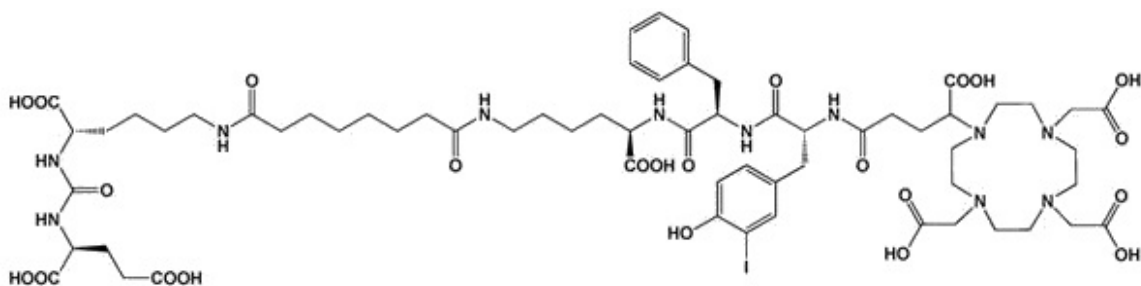
1-(p-isothiocyanatobenzyl)-3-methyl-
DTPA (1B3M),

2-(p-isothiocyanatobenzyl)-4-methyl-
DTPA (1M3B), or

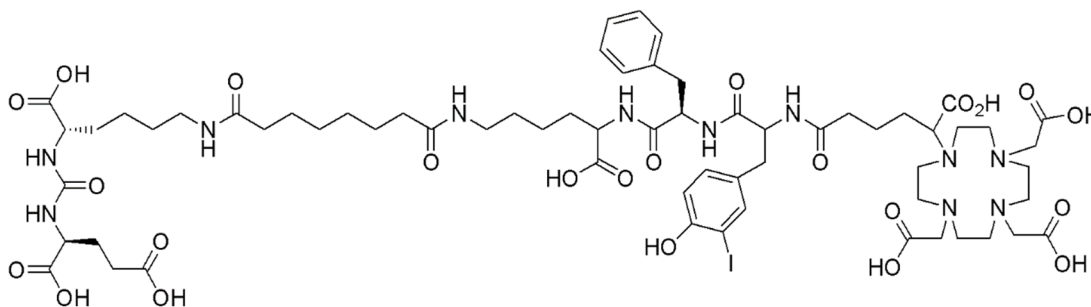
1-(2)-methyl-4-isocyanatobenzyl-
DTPA (MX-DTPA)

or

Formula (C)



or

Formula (D)

,

or

Formula (E)

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

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

As will be readily appreciated, the claims plainly recite a narrow specific class of ligands in combination with a specific radionuclide applied at specific low dosages to target a specific class of cancer. The dependent claims go further, reciting specific cancers (claims 2, 4-8, 10-14) and an even more narrow effective dosage (claim 9).

VI. THE BOARD SHOULD EXERCISE ITS DISCRETION TO DENY INSTITUTION

The Board has discretion under 35 U.S.C. § 325(d) whether to institute an IPR proceeding. *See* 35 U.S.C. § 325(d); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (stating that “the PTO is permitted, but never compelled, to institute an IPR proceeding”). 35 U.S.C. § 325(d) establishes that “[i]n determining whether to institute or order” an IPR proceeding, “the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” To determine whether to exercise this discretion, the Board uses the following two-part framework:

1. “whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office;” and

2. “if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of [the] challenged claims.”

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6, *8 (Feb. 13, 2020) (precedential). The Board also relies upon *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, *17-

18 (Dec. 15, 2017) (precedential as to section III.C.5, first paragraph), which establishes non-exclusive factors that provide “useful insight” into the application of the two-part framework under 35 U.S.C. § 325(d).

If the first prong is satisfied, the Board “generally will exercise discretion not to institute *inter partes* review” unless the petitioner makes a sufficient showing of material error. *Advanced Bionics, LLC*, *9. To demonstrate material error, the petitioner must advance more than an argument regarding patentability as to which reasonable minds may differ. “If 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.*

A. The Cited References Were Either Considered By Or Are Cumulative Of Other References Considered By The Examiner

Both of Fusion’s proffered Grounds rely on the combination of Weinesen 2015 and Kratochwil. (Pet., p.5). In its first Ground, Fusion asserts that claims 1, 2, 4-8 and 10-13 are obvious over Weineisen 2015 in combination with Kratochwil. In its second Ground, Fusion asserts that claim 9 is obvious over Weineisen 2015 in combination with both Kratochwil and Jurcic. (Pet., p.5). Of these identified references – Weineisen 2015, Kratochwil, and Jurcic – the Examiner considered Kratochwil (as admitted by Fusion), and considered and applied references substantially similar to or cumulative of Weineisen 2015.

1. Kratochwil Was Considered and is Cumulative of Other Considered and Applied References

As admitted by Fusion, Kratochwil was considered by the Examiner during examination of the ‘901 Patent. (Pet., p.52). Therefore, Kratochwil is the “same or substantially the same art” that was “previously presented to the Office.” *Advanced Bionics*, *8 .

Additionally, Kratochwil is cumulative of Eder ‘791 and ‘160, both of which were applied in a rejection during prosecution of the ‘901 patent. And Kratochwil is cumulative of statements made by Patent Owners in response to the Office action dated June 24, 2020. Specifically, Patent Owners specifically argued to the Office that “[t]he [Eder] ‘791 and ‘160 patents focus on the provision of a **targeted chelator** to which **multiple different radionuclides can be complexed.**” (Ex. 1004.382). Patent Owners further noted that “[t]he [Eder] ‘160 patent claims a metal complex including ‘a radionuclide,’ and in separate claims list **14 different illustrative radionuclides,**” and that “these patents disclose **twenty eight illustrative radionuclides,** eleven of which are presented separately,” and explicitly stated that “[t]hese lists with various radionuclides **include Ac-225.**” (Ex. 1004.382). Not only did the considered and applied Eder ‘791 and ‘160 patents already disclose the same Ac-225 radionuclide for which Fusion cites Kratochwil, but Patent Owners explicitly called out those sections of Eder ‘791 and ‘160 to the

Examiner's particular attention. Accordingly, Kratochwil's disclosure of Ac-225 provides no new information.

Further, as discussed in detail in Sections VI(A)(2), VI(B) and VII(A), *supra*, Kratochwil discloses treatment of a very different cancer with a different ligand that is not covered by the '901 patent claims. And as Fusion's expert admits, the specific selection of a radionuclide paired with a specific ligand to target specific cells to treat a specific cancer is a "key challenge." *See* (Ex. 1002.015, ¶27). The Examiner was acutely aware of different effects caused by structural differences in the ligands, as his reasons for allowance pointed to structural differences in the ligands of another considered prior art reference as one reason for finding allowability of the '901 Patent claims. (Ex. 1004.033; Section VI(B)). Given these significant structural differences in Kratochwil's ligand, and Kratochwil's treatment of a completely different cancer, Kratochwil's dosage disclosure is not relevant to the patentability inquiry. Accordingly, the disclosure in Kratochwil of a completely different – unclaimed – ligand for targeting completely different cells to treat a completely different cancer (neuroendocrine tumors (NETs)) renders Kratochwil's additional disclosure of a dosage irrelevant to the patentability of a treatment for PSMA-expressing cancers using a very different compound.

2. Weineisen 2015 Is Cumulative of Eder ‘791 and Eder ‘160, Both of Which Were Considered

Fusion relies on Weineisen 2015 as disclosing PSMA I&T as a PSMA targeting ligand that can be chelated to a radionuclide to produce a radiopharmaceutical. (Pet., pp. 21-23, 29-30). Fusion notes that “PSMA I&T comprises a chelating moiety (DOTAGA), a linker, and a PSMA-targeting moiety (Sub-KuE).” (Pet., p.22).

Fusion also points to other prior art references (not relied on in the grounds for institution) also disclosing ligands having a chelating moiety, linker, and PSMA-targeting moiety. For instance, Fusion points to Weineisen 2014 as disclosing a “Compound 12” ligand which has the same chelating moiety (DOTAGA), a “structurally similar” linker, and the same targeting moiety (Sub-KuE). (Pet., pp.20-22). Additionally, Fusion points to Kratochwil as disclosing DOTATOC (which is not a PSMA-targeting ligand), which Fusion also states is a “radiopharmaceutical ligand comprising a chelating moiety, a linker, and a peptide-based targeting moiety.” (Pet., pp.24, 26).

The challenged claims each recite a Markush group covering the general structure of a number of PSMA-targeting ligands. Fusion fails to mention that several other PSMA-targeting ligands covered by the challenged claims – as well as ligands with similar structures (though not PSMA-targeting) – were disclosed in the

prior art considered by the Examiner. Indeed, the DOTATOC ligand (which is **not** PSMA-targeting) is disclosed in Kratochwil which Fusion admits was already considered. (Ex. 1031, ¶1, 3, 4). And Eder '791 and Eder '761 – considered and applied by the Examiner – disclose many PSMA-targeting ligands having the same general targeting structure identified by Fusion, all of which are also recited in the claims of the '901 Patent. (Ex. 1026, 6:10-65, 7:43-64, 11:17-19:28, 32:25-33:50, 36:66-43:30, claims 1, 7, 12, 16, 21, 27; Ex. 1025, 6:7-56, 7:25-47, 11:1-18:27, 32:8-33:7, 36:31-43:30, claims 1, 3, 28).

Notably, the Office previously considered numerous PSMA-targeting ligands having the general structure – chelating moiety-linker-targeting moiety – noted by Fusion and used for PSMA-targeting for the treatment of prostate cancer. Many of these ligands – e.g., those identified in Eder '791 and Eder '160 – are recited in the Markush group of the claims of the '901 Patent. Consequently, the Examiner has already considered the issue of whether the claims of the '901 Patent distinguish over prior art disclosing the same ligands recited in the claims – including prior art disclosing many PSMA-targeting ligands having the chelating moiety-linker-targeting moiety structure asserted by Fusion.

The PSMA I&T ligand is not specifically disclosed in the references previously before the Office, but that is immaterial. In examining the '901 Patent,

the Examiner considered the patentability of the claims in light of the claimed Markush group of PSMA-targeting ligands. This is evidenced by the Examiner's issuance of a double patenting rejection over Eder '791 and '160, both of which recite and disclose many ligands falling within the claimed Markush group. (Ex. 1004.400-.410). Having considered multiple prior art references disclosing several different PSMA-targeting ligands of the Markush group – the addition of yet another reference pointing to yet another recited member of the Markush group does not add anything new to the examination calculus. Weineisen 2015, therefore, does nothing more than duplicate the analysis and examination already conducted.

Moreover, Weineisen 2015 is less relevant and material than the other references already considered by the Examiner. For instance, the Examiner explicitly considered – and issued rejections over – both Eder '791 and Eder '160, which collectively disclose Formula A and Formula B recited in claim 1 of the '901 Patent, and all but the PSMA I&T compound recited in claim 2 of the '901 Patent. (Ex. 1026, 6:10-65, 7:43-64, 11:17-19:28, 32:25-33:50, 36:66-43:30, claims 1, 7, 12, 16, 21, 27; Ex. 1025, 6:7-56, 7:25-47, 11:1-18:27, 32:8-33:7, 36:31-43:30, claims 1, 3, 28)). Indeed, the specific PSMA-targeting ligand recited in the claims of Eder '791 is listed in claim 2 in the same Markush group as the PSMA I&T highlighted by Fusion. (Ex. 1001, claim 2). Similarly, both Formula Ia and Ib disclosed and

recited in Eder '160 are also listed in that same Markush group. *Id.* And unlike Weineisen 2015 – which Fusion acknowledges does not disclose chelation to ^{225}Ac – both Eder '791 and Eder '160 explicitly disclose chelation of the disclosed PSMA-targeting ligands to a variety of radionuclides, including ^{225}Ac . (Pet., p. 30, noting that Weineisen 2015 discloses using PSMA I&T with beta-emitting radionuclides ^{68}Ga and ^{177}Lu ; Ex. 1026, 21:65-22:7; Ex. 1025, 20:46-55). In fact, Fusion admits that Eder '791 and '160 include this disclosure in attempting to argue that the Examiner “improperly ignored the teachings in the '791 and '160 patents that the claimed targeting molecule could be used with ^{225}Ac .” (Pet., p.53).

As can be seen from this, all of Eder '791, Eder '160 and Weineisen 2015 disclose a PSMA-targeting ligand listed in the same Markush group recited in the '901 Patent claims. However, while Eder '791 and Eder '160 note the potential of these ligands to chelate ^{225}Ac , Weineisen does not. Accordingly, the Examiner has already considered closer references – Eder '791 and Eder '160 – and Weineisen 2015 does not add anything new to the obviousness equation. Therefore, Weineisen 2015 cumulative or duplicative of art that was previously presented to and considered by the Office. See *R.J. Reynolds Vapor Co. v. Fontem Holdings I B.V.*, IPR2017-01642, Paper 10, *11 (Jan. 16, 2018) (finding the content of previously considered art to be “the same in all material respects” to art cited by the petitioner).

3. None of Weineisen 2015, Kratochwil and Jurcic Provide New, Relevant Information to the Patentability Inquiry

With respect to Ground 2 for invalidity of claim 9, Fusion adds Jurcic solely for the particularly recited dosage range. (Pet., pp.2, 27-28, 37-38, 49-50). But as discussed in Section VII(A)(6), *infra*, Jurcic does not relate to PSMA-targeting ligands having the general structure asserted by Fusion and allegedly disclosed in Weineisen 2015. Instead, Jurcic discloses ^{225}Ac linked to a “humanized anti-CD33 monoclonal antibody,” namely lintuzumab, which is completely different than the PSMA-targeting ligands covered by the challenged claims. (Ex. 1011.001-.003).

Additionally, Jurcic discusses a potential treatment for Acute Myeloid Leukemia – a completely different cancer and cancer classification than the prostate cancer discussed in Weineisen 2015 and the '901 Patent, and neuroendocrine tumors (NETs) disclosed in Kratochwil. (*See* Ex. 2001, defining the six major categories of cancer). Neither Fusion nor Fusion’s expert provide an opinion or explanation as to why a POSITA would have combined Jurcic’s dosage for treating a leukemia with Weineisen 2015’s treatment for prostate cancer or Kratochwil’s treatment for NETs.

Further, in addition to describing a different radiopharmaceuticals than Weineisen 2015 and Kratochwil, Jurcic also discloses a very different treatment protocol. Specifically, Jurcic discloses a combination therapy including the co-

administration of the 225Ac-lintuzumab compound with low-dose cytarabine (LDAC) – a drug only indicated for the treatment of leukemia. (Ex. 1011.001-.003; Ex. 2001). Again, neither Fusion nor Fusion’s expert provide an opinion, analysis, or explanation as to why a POSITA would have selected the dosage of **one part of a two-part combination therapy** to use in the methods of Weineisen and/or Kratochwil, which disclose monotherapies for treating entirely different diseases with very different compounds.

Neither the POSITA nor the Examiner, therefore, would have found any information in Jurcic relevant to the obviousness inquiry of claims directed to the treatment of PSMA expressing cancers or cancer cells.

Neither Fusion nor Fusion’s expert appreciate or meaningfully acknowledge these differences in either the petition or the Expert Declaration. Nor do they provide any explanation as to why a POSITA would have used the dosage of a different compound used for a different purpose in the Weineisen 2015 or Kratochwil treatment protocol, or why that POSITA would have used the dosage from a **combination** therapy – unchanged – in the **solo** therapies of Weineisen 2015 and Kratochwil for a different disease. Even considering that the ‘901 Patent claims cover combination therapies using the claimed PSMA targeting compounds as one part of the combination, Jurcic fails to provide meaningful or useful instruction to

the POSITA regarding dosages for the treatment of PSMA expressing cancers or cancer cells. Therefore, Jurcic – disclosing a **combination** therapy for **leukemia** – does not appear to provide relevant additional information to the patentability inquiry of a claim reciting a radiopharmaceutical therapy – solo or combination – for **PSMA expressing cancers or cancer cells**.

In summary, Kratochwil was previously considered by the Office or is cumulative to Eder ‘791 and ‘160, Weineisen 2015 is merely cumulative of Eder ‘791 and Eder ‘160, both of which were previously considered by the Office, and Jurcic does not provide any new, **relevant** information to the patentability inquiry. Accordingly, the art and arguments Fusion relies on in Grounds 1 and 2 is either not relevant, or is the same or substantially the same art and arguments that were “previously presented to the Office.” *Advanced Bionics*, *8.

B. Fusion Omits Material Disclosure in Previously Considered References and in the Prosecution History to Allege Material Error by the Examiner

Fusion advances a number of arguments in an effort to convince the Board not to exercise its discretion to deny this petition. First, Fusion argues “the prior art relied on in this petition is not the same or substantially the same as that considered during prosecution.” (Pet., p.51). However, as discussed at Section VI(A), *supra*, Kratochwil was indeed considered by the Examiner – which Fusion admits – or is

cumulative or irrelevant. (Pet., pp.49, 52) And Weineisen 2015 is cumulative of Eder ‘791 and Eder ‘160, both of which were considered by the Examiner and the subject of a rejection during prosecution. Fusion, in fact, acknowledges some of these substantial similarities , noting that Eder ‘791 and ‘106 “are similar in scope to Weineisen 2015—i.e., they disclose a PSMA-targeting radiopharmaceutical complexed with ^{177}Lu .” (Pet., p.52).

Second, Fusion argues “the challenged claims are unpatentable as obvious based on Weineisen 2015 in light of prior art that was not presented to the Office or considered during prosecution.” (Pet., p.52). Specifically, Fusion argues the allegedly missing prior art discloses that “(1) chelator targeting compounds could be easily used with a variety of radionuclides; (2) alpha emitters would have been preferred over beta emitters; and (3) alpha emitters like ^{225}Ac were known to be more potent than beta emitters like ^{177}Lu , such that lower dosages of alpha emitters would be required.” (Pet., p.52). Contrary to Fusion’s assertions, however, the information alleged to be missing can be found in the prosecution history and in the prior art presented to and considered by the Examiner.

For example, the prosecution history contradicts Fusion’s first assertion that art establishing that “chelator targeting compounds could be easily used with a variety of radionuclides” was not presented to the Office or addressed during

prosecution. (Pet., p.52). Specifically, in response to the Office action dated June 24, 2020, Patent Owners specifically stated that “[t]he [Eder] ‘791 and ‘160 patents focus on the provision of a **targeted chelator** to which **multiple different radionuclides can be complexed**.” (Ex. 1004.382). Patent Owners further noted “[t]he [Eder] ‘160 patent claims a metal complex including ‘a radionuclide,’ and in separate claims list **14 different illustrative radionuclides**.” (Ex. 1004.382). Patent Owners also pointed out that “these patents disclose **twenty eight illustrative radionuclides**, eleven of which are presented separately,” and explicitly stated “[t]hese lists with various radionuclides **include Ac-225**.” (Ex. 1004.382). As can be seen from this, Patent Owners expressly stated to the Examiner that the targeted chelators in Eder ‘791 and ‘160 could be “used with a variety of radionuclides,” and specifically pointed to disclosure regarding Ac-225. This completely contradicts Fusion’s first assertion of material error.

Additionally, multiple prior art references considered by the Examiner establish that “alpha emitters would have been preferred over beta emitters,” and “alpha emitters like ^{225}Ac were known to be more potent than beta emitters like ^{177}Lu .” (Pet., p.52). For example, Zielinska was considered by the Office, and states that “[t]argeted alpha therapy (TAT) is a novel and promising treatment strategy for the therapy of a variety of cancers and infectious diseases.” (Ex. 2002.001).

Zielinska goes on to explain that “[d]ue to the high linear energy transfer (LET $\approx$ 100 keV/ μ m) of alpha particles and their short path length in human tissue (40-90 μ m) such radio-immuno-conjugates have the potential of delivering a highly cytotoxic radiation dose to the tumor cells while sparing normal body tissues.” (Ex. 2002.002). Zielinska also explicitly discusses Ac-225 as a particularly “promising” “ α -emitting radioisotope” for targeted alpha therapy. (Ex. 2002.002, noting Ac-225 is the mother nuclide of ^{213}Bi which is “presently the most promising”).

Similarly, Apostolidis – also considered by the Office – states:

The principle of **targeted α therapy (TAT)** of cancer is based on the coupling of α -particle emitting radionuclides to tumor selective carrier molecules, e.g., monoclonal antibodies or peptides, serving as vehicles for the specific targeting of cancer cells. **Due to the high linear energy transfer of α particles and, consequently, their short path length in human tissue (<100 μ m), a highly cytotoxic radiation dose can be delivered to targeted cancer cells, while damage to surrounding healthy tissue is limited.** As a consequence of the short range of α particles in human tissue, TAT is particularly promising for the treatment of single-cell cancers, small-cell clusters, and minimal residual disease following surgery or chemotherapy. The potential of TAT for the treatment of a variety of cancer types has been shown in several preclinical and clinical studies...and has recently been demonstrated also for therapy of infectious diseases.

(Ex. 2003.001). Apostolidis goes on to state “[s]everal α -emitting nuclides are under consideration for TAT, including Ac-225...” (Ex. 2003.001).

As demonstrated, Zielinska and Apostolidis – previously considered by the Office – establish the novelty and promise of targeted alpha therapy, and specifically delineate certain advantages of that therapy. Specifically, both Zielinska and Apostolidis point out that α particles have the advantage of high linear energy transfer and shorter path lengths in human tissue, enabling the delivery of highly cytotoxic radiation doses to targeted cancer cells while minimizing damage to surrounding healthy tissue. (Ex. 2002.002; Ex. 2003.001). This fully contradicts Fusion’s second and third assertions of material error.

Fusion’s three assertions supporting the conclusion that “the challenged claims are unpatentable as obvious based on Weineisen 2015 in light of prior art not presented to the Office or considered during prosecution” are erroneous and contrary to the prosecution history. Accordingly, Fusion’s first effort to convince the Board not to exercise its discretion to deny institution must fail.

In its second effort to convince the Board not to exercise its discretion to deny this petition, Fusion argues that even if “the arguments considered by the Examiner are substantially the same as arguments presented in this petition, the Examiner erred in [the] analysis.” (Pet., p.53). Here, Fusion contends the Office made two material

errors. The first alleged error is that “the Examiner seems to have improperly ignored the teachings in the ‘791 and ‘160 patents that the claimed targeting molecule could be used with ^{225}Ac .” (Pet., p.53). However, as discussed in this Section, *supra*, Patent Owners specifically pointed the Examiner’s attention to the very same claims and passages in the Eder ‘791 and ‘160 patents that Fusion relies on here in asserting error. Indeed, Fusion lists claim 7 (column 51, lines 5-7) in Eder ‘160, and the passage at column 21, lines 65 through column 22, line 7 of Eder ‘791 as the disclosure that “the Examiner seems to have improperly ignored.” (Pet., pp.53-54). But as discussed in more detail in this Section, *supra*, in response to the June 24, 2020 Office action, Patent Owners cited “[Eder] ‘160 patent, claims 6, 7, 17 and 18,” and “column 20, lines 49-55” as well as “[Eder] ‘791 patent, claims 12, 16 and 27” and “**column 22, lines 1-7.**” (Ex. 1004.382).

In connection with these arguments, Patent Owners made only one minor, non-substantive amendment to claim 13 (later issued as claim 1) to correct “administering to patient” to “administering to a patient.” (Ex. 1004.386). As such, the arguments were the only response to the Examiner’s substantive double patenting rejection over Eder ‘791 and ‘160. Given that only arguments were provided in response to the Examiner’s rejection, it is untenable to conclude that the Examiner “improperly ignored” those arguments.

Further, the Examiner cited only two references in rejections during the prosecution of the '901 Patent (i.e., Eder '791 and '160), and addressed one additional reference in the Notice of Allowance (i.e., U.S. Patent No. 8,26,944). (Ex. 1004.398-.413; Ex. 1004.027-.037). The relatively few references cited in rejections during prosecution of the '901 Patent suggests the Examiner did meaningfully consider those references, including the claims and passages specifically listing alpha-emitters and Ac-225 specifically. Indeed, the Examiner considered eleven references in allowing the '901 Patent, eight of which were cited by Patent Owners. (Ex. 1001.001). Thus, the Examiner's search apparently revealed only three new references, two of which were Eder '791 and '160, which were the subject of substantive rejections. This strongly suggests that the Examiner meaningfully considered both Eder '791 and '160. *See Alarm.com Inc. v. Vivint, Inc.*, IPR2015-01967, Paper 12, *21 (Mar. 30, 2016) (stating that "we are unwilling to assume that, after having uncovered a very limited amount of relevant art, the Examiner failed to consider at least that art....").

Perhaps even more notably, each of the '901 Patent, Eder '791 and Eder '160 were examined by the same Examiner, i.e., Jagadishwar R. Samala. (Ex. 1001.001; Ex. 1025.001; Ex. 1026.001). As the same Examiner examined all three of these patents, it is unreasonable to conclude that the Examiner was unaware of the contents

of Eder '791 and '160 when examining the '901 Patent, or that the Examiner would have “improperly ignored” any disclosure in Eder '791 and '160. On the contrary, it is far more likely that the Examiner was more intimately aware and cognizant of the disclosure, claims and teachings of Eder '791 and '160 than any other Examiner would have been.

The second material error alleged by Fusion is that “the Examiner only considered the claimed dosage ranges in light of prior art disclosing dosage ranges for a different radionuclide (^{177}Lu).” (Pet., p.54). However, Fusion itself contradicts this statement. Specifically, Fusion itself relies on Kratochwil to provide the claimed dosage ranges, and Kratochwil was previously considered by the Office – as admitted by Fusion. (Pet., p.52). Kratochwil discloses an “**Ac-225** radionuclide therapy,” and thus any dosages discussed in Kratochwil must, *inter alia*, relate to the Ac-225 radionuclide – not ^{177}Lu . (Ex. 1031.001).

Also, the DOTATOC ligand disclosed in Kratochwil is significantly different than those recited in the '901 Patent claims. As discussed in Section VII(A), *infra*, the POSITA would not believe that dose is only linked to the radionuclide, but would consider it to be at least linked to the ligand as well. For example, the POSITA would consider that there would also be an impact of target binding, amount of target expressed on the tumor, amount of target expressed on non-target tissue (and causing

toxicity) and the tumor type itself. Therefore, it is just as likely – or even more likely – that the Examiner considered the dosages allegedly described in Kratochwil for the Ac-225 radionuclide but discounted that disclosure due to the significantly different ligand used in that reference.

Indeed, the Examiner was acutely aware of different effects caused by structural differences in the ligands. In his Reasons for Allowance, Examiner Samala pointed to structural differences in the ligands of another considered prior art reference as one reason for finding allowability of the ‘901 Patent claims. (Ex. 1004.033). And given the significant structural differences in Kratochwil’s ligand, and Kratochwil’s treatment of a completely different cancer, as discussed in Section VI(A)(1), *supra*, Kratochwil’s dosage disclosure is not relevant to the patentability inquiry. As “reasonable minds can disagree” on the treatment of the dosages in Kratochwil by the Examiner, “it cannot be said that the Office erred in a manner material to patentability.” *See Advanced Bionics*, *9 (stating that “[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”).

C. Fusion’s Expert Declaration Fails to Meaningfully Add to the Prosecution History and Previously Considered Prior Art

In her Declaration, Fusion’s expert makes several assertions intended to explain why she believes the Examiner committed material error. First, she states

that prior art was not presented “demonstrating the known benefits of using ^{225}Ac and other alpha emitters in radiotherapies” including that “alpha emitters were known to have higher potency than beta emitters like ^{177}Lu , leading to lower doses needed for alpha emitters” and that “alpha emitters can only travel limited distances, and therefore cause less damage to cells surrounding the target cells.” (Ex. 1002.024, ¶47). From this, Fusion’s expert concludes the POSITA would have been motivated to combine PSMA I&T with ^{225}Ac based on Weinesen 2015 and Kratochwil. (Ex. 1002.043-.044, ¶¶85-86, noting that “[a]lpha emission is higher in energy than beta emission, therefore alpha particles can do more damage to cells within the body than beta particles” and that “their size prevents alpha particles from traveling long distances within the body, reducing the damage caused to healthy cells in the vicinity”).

However, as discussed in Section VI(B), *supra*, Patent Owners did indeed present prior art relating directly to the information Fusion’s expert alleges was not provided to the Examiner. For example, in response to the Office action dated June 24, 2020, Patent Owners explicitly directed the Examiner’s attention to multiple passages and claims in Eder ‘791 and ‘160 that discussed chelation of targeted chelators to multiple different radionuclides, and specifically noted that these radionuclides can include ^{225}Ac . (Ex. 1004.382). Further, multiple additional prior

art references considered by the Examiner – including Zielinska and Apostolidis – establish the “benefits of using ^{225}Ac and other alpha emitters in radiotherapies” including that “alpha emitters were known to have higher potency than beta emitters like ^{177}Lu ” and that “alpha emitters can only travel limited distances, and therefore cause less damage to cells surrounding the target cells.” *See* Section VI(B), *supra*; (Ex. 1002.024, ¶47).

Further, the specification of the ‘901 Patent itself provides this information – which Fusion’s expert admits. In particular, Fusion’s expert states:

The specification acknowledges some of the known benefits of using alpha emitters like ^{225}Ac in radiopharmaceuticals. For example, the specification discloses that the ‘the very efficient and specific targeting of the Ac-225-radiopharmaceuticals to PSMA combined [with] the short range (<100 micrometers) action of the Ac-225 alpha emitter allows for very good results of destruction of cancer cells without notable damage to non-target tissues.’

(Ex. 1002.020-.021, ¶38, citing Ex. 1001, 12:19–23). In light of this admission, as well as the discussions in Zielinska and Apostolidis of the benefits of alpha-emitters, Fusion’s expert’s conclusion that the Examiner was not made aware of this information is baffling. Indeed, given this admission, taken together with the disclosure of ^{225}Ac in Eder ‘791 and ‘160, and the discussion of the benefits of alpha-

emitters and targeted alpha therapy in Zielinska and Apostolidis, Fusion's expert fails to provide any new information missing from the examination of the '901 Patent.

Second, Fusion's Expert "disagrees" that the stated differences in efficacy of the claimed dosages of the claimed Ac-225 radiopharmaceuticals over Lu-177 counterparts would have been surprising or unexpected. (Ex. 1002.024, ¶46). Interestingly, in reaching this conclusion, Fusion's expert does not appear to actually consider or analyze the data and results pointed to by Patent Owners in asserting that the recited dosages exhibit surprising and unexpected results. Instead, Fusion's expert apparently relies on Miederer 2008a and Jurcic to establish that the use of the claimed compounds at the claimed dosages do not exhibit unexpected and surprising results in the treatment of prostate cancer. (See Ex. 1002.034-.035, .043, .046, .050, .052-.053, .054). For example, Fusion's expert relies on Miederer 2008a – which again is not used in either of Fusion's Grounds for institution – to show that ²²⁵Ac-DOTATOC exhibited "improved efficacy compared with ¹⁷⁷Lu-DOTATOC." (Ex. 1002.034-.035, ¶65). In discussing Miederer 2008a, however, Fusion's expert does not address the applicability of this reference to the specific dosages claimed in the '901 Patent. *Id.* This may be because Miederer 2008a discloses significantly different dosages in a mouse study. (Ex. 1015.001-.006).

Further, as discussed in Section VI(B), *supra*, the DOTATOC ligand is not claimed in the '901 Patent, and is rather different than the ligands that are claimed. And as discussed in Section VII(A), *infra*, differences in the ligands can lead to differences in dosage and the efficacy of those dosages. As Miederer 2008a does not provide any insight regarding the comparative efficacy of ^{225}Ac -DOTATOC and ^{177}Lu -DOTATOC at the dosage ranges actually claimed in the '901 Patent, and as Miederer 2008a compares ligands that do not fall within the claims of the '901 Patent, Fusion's expert's reliance on Miederer 2008a in this context is misplaced.

Perhaps because Miederer 2008a does not provide a useful comparison of ^{225}Ac -DOTATOC and ^{177}Lu -DOTATOC at the claimed ranges, Fusion's expert points to Jurcic as establishing the efficacy of another ^{225}Ac therapeutic at lower dosages. (Ex. 1002.046, ¶91). However, as discussed in Sections VI(A)(3), *supra*, and VII(A)(6), *infra*, Jurcic discloses a different compound having an antibody-based ligand, a different treatment protocol including a combination therapy, and the treatment of a completely different disease – leukemia, not prostate cancer. (Section VI(A)(3), *supra*; Section VII(A)(6), *infra*; Ex. 1011.001-.003). And Fusion's expert does not explain or provide any opinion as to how these significant differences would affect an assessment of efficacy of a different compound, used in a different treatment protocol to treat a different disease. In addition, Jurcic does not provide

any comparison of the ²²⁵Ac-lintuzumab compound to a counterpart compound using ¹⁷⁷Lu or another beta-emitting radionuclide. (*See* Ex. 1015.001-.003). As such, Jurcic does not provide any meaningful or useful information to the inquiry of whether Patent Owner's data and results were surprising or unexpected.

As such, neither Miederer 2008a nor Jurcic, even if considered together, provides support for Fusion's expert's conclusory statements regarding Patent Owners' unexpected results. And as Fusion's expert herself does not appear to have actually reviewed and assessed Patent Owner's data, or even addressed that data in her Declaration, Fusion's expert's conclusory "disagree[ment]" that those are unexpected can carry no weight. Given this, Fusion's expert's discussion of the unexpected results issue shows nothing more than a disagreement between her and the Examiner on the treatment of the proffered evidence, which cannot support a finding of material error. *See Advanced Bionics*, *9 (stating there can be no material error "[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments").

Third, Fusion's expert states that "[t]he Examiner allowed the claims without addressing applicant's nonstatutory double patenting remarks." (Ex. 1002.024, ¶48). However, she provides no credible support for this assertion. (*See* Ex. 1002.024-.025, ¶48). Instead, Fusion's expert appears to base this conclusion on the

mere fact that the Examiner did not specifically and comprehensively respond to Patent Owners' arguments either before issuing the Notice of Allowance or in stating the reasons for allowance. *See Id.* Such a lack of written remarks is hardly an indication of a failure to address or consider the arguments. Quite to the contrary, this is common practice at the Office. In fact, providing a statement of reasons for allowance is only warranted in instances in which "the record of the prosecution as a whole does not make clear [the] reasons for allowing a claim or claims." (37 CFR § 1.104(e)).

Also, as discussed in Section VI(B), *supra*, Patent Owners' remarks rebutting the double patenting rejection are the only substantive response given to the only substantive rejection made by the Examiner in the June 24, 2020 Office action. As the next communication from the Office was the Notice of Allowance, it is entirely reasonable to assume – indeed, it's extremely likely – the Examiner carefully considered the arguments, and determined they were sufficient to overcome the rejection. Had they not been sufficient, the next communication from the Office would have been another Office action – not a Notice of Allowance. Accordingly, the Examiner did address Patent Owners' remarks regarding the double patenting rejection. Therefore, at best, Fusion's expert's assertions amount to nothing more than a disagreement as to the treatment of these arguments, which is not sufficient

to establish material error. *See Advanced Bionics*, *9 (stating there can be no material error “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments”).

In addition to these assertions of error, and similar to Fusion’s arguments presented in the petition, Fusion’s expert argues in her Declaration that the POSITA would have been “motivated to administer ²²⁵Ac PSMA I&T at the doses shown to be safe and effective in Jurcic.” (Ex. 1002.046, ¶91). In reaching this conclusion, however, Fusion’s expert fails to explain why the POSITA would have used the same dosage as a compound having a significantly different ligand (i.e., an antibody in place of a small molecule) to treat a completely different disease (i.e., a leukemia in place of a carcinoma or NET). *See* Section VI(A)(3), *supra*. And Fusion’s expert also fails to provide any opinion or explanation as to why the POSITA would have adopted the dosage of only one part of a two-part combination therapy without any modification to account for the use of two different therapeutics in the Jurcic study. *See* Section VI(A)(3), *supra*. Having failed to provide these missing links in her obviousness analysis, Fusion’s expert fails to provide any meaningful addition to the art and arguments previously considered by the Examiner on the issue of the recited dosage.

The three main assertions of error rely on Fusion's expert's opinion that the Examiner was not made aware of prior art establishing the benefits of alpha emission, her "disagreement" with the Examiner's assessment of unexpected results, and her belief that the claims were allowed without consideration of Patent Owners' arguments regarding Eder '791 and '160. However, the Examiner was plainly made aware of prior art establishing the benefits of alpha emission – including explicitly in the specification of the '901 Patent. Further, as the double patenting rejection over Eder '791 and '160 was the only substantive rejection, it is untenable for Fusion's expert to assume that those arguments were not considered or "addressed." And while Fusion's expert "disagrees" with the Examiner's assessment of unexpected results, she does not appear to assert that the Examiner did not properly assess them – and as such, her "disagree[ment]" with the Examiner does not amount to material error. *See Advanced Bionics*, *9 (stating there is no material error "[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments").

Finally, as Fusion's expert fails to provide the missing link between the Jurcic study and Weineisen 2015 and Kratochwil, she has again not provided any meaningful addition to the analysis and examination already conducted by the

Examiner on the issue of dosage. Accordingly, Fusion’s expert does not meaningfully supplement the prosecution history or the prior art.

VII. FUSION HAS NO REASONABLE LIKELIHOOD OF SUCCESS

Fusion, as the petitioner, “has the burden from the onset to show with particularity” why the ‘901 Patent is unpatentable. *Samsung Electronics Co., Ltd. v. LED Wafer Solutions, LLC*, IPR2021-01554, Paper 10, *7 (Apr. 12, 2022) (quoting *Harmonic Inc. v. Avid Tech. Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3))) (internal quotations omitted). To that end, Fusion “must ‘specify where each element of the claim is found in the [relied upon] prior art patents.’” *In-Depth Geophysical, Inc. v. ConocoPhillips Co.*, IPR2019-00850, Paper 56, *27 (Sept. 3, 2020) (quoting 37 C.F.R. § 42.104(b)(4)). And when, as here, the grounds of unpatentability involve a combination of teachings, there must have been “‘an apparent reason to combine the known elements in the fashion claimed by the patent at issue.’” *Id.* (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)). 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).

Therefore, to set forth a proper ground of unpatentability based on obviousness, Fusion “must identify *both* the specific teaching in each prior art reference that it relies upon with respect to each claim limitation, *and* a rationale for why one of ordinary skill in the art would have combined those specific teachings in the specific manner claimed.” *In-Depth Geophysical, Inc.*, IPR2019-00850, Paper 56, *27 (Sept. 3, 2020) (emphasis in original). Fusion cannot satisfy this burden with “mere conclusory statements.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1376, 1380 (Fed. Cir. 2016).

Fusion has failed to demonstrate a reasonable likelihood that even one challenged claim is unpatentable. Indeed, at critical junctures in both Grounds 1 and 2, Fusion fails to provide analysis sufficient to satisfy its burden. *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (quoting 35 U.S.C. § 316(e)) (stating that “the burden of persuasion is on the petitioner to prove ‘unpatentability by a preponderance of the evidence’ ... and that burden never shifts to the patentee”).

A. Fusion Fails to Establish that Weineisen 2015, Kratochwil and/or Jurcic Render Claims 1, 2 and 4-13 Obvious

Fusion argues that claim 1 of the ‘901 Patent is unpatentable as obvious in light of Weineisen 2015 in combination with Kratochwil. (*See* Pet., p. 28). Patent

Owners respectfully disagree, and submit that claim 1 is not obvious over Weineisen 2015 and Kratochwil, and claim 1 is therefore patentable.

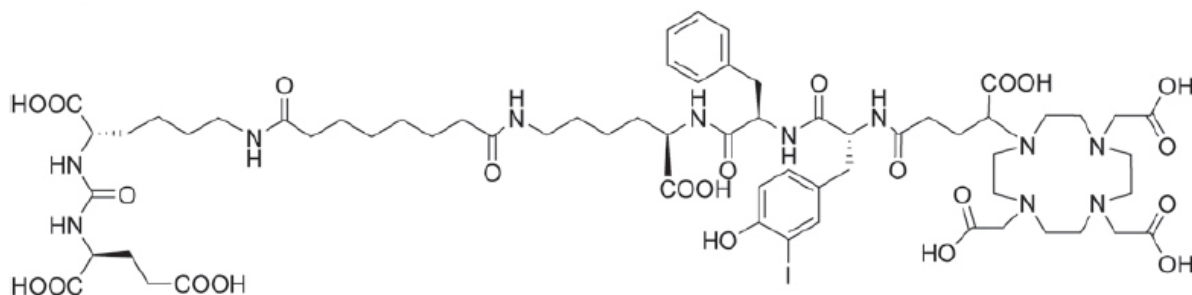
1. Weineisen 2015 Discusses the Importance of Disease-Specific Targets, and is Specific to Metastatic Castration Resistant Prostate Cancer

Weineisen 2015 describes a PSMA inhibitor for imaging and therapy (PSMA I&T) for ^{177}Lu -based endoradiotherapeutic treatment in patients with metastatic castration-resistant prostate cancer (mCRPC). (Ex. 1028.001, Abstract). Weineisen 2015 discloses that “approaches focusing on disease-specific targets are increasingly important for cancer diagnosis and treatment with radiopharmaceuticals.” (Ex. 1028.001). In particular, Weineisen 2015 notes that “[o]n prostate cancer cells, the cell surface enzyme prostate-specific membrane antigen (PSMA)...is highly upregulated, whereas it shows low or no expression in the normal prostate,” and that “PSMA expression correlates with the malignancy of the disease, being further increased in metastatic and hormone-refractory patients.” (Ex. 1028.001). Weineisen further states that “[a]s a consequence, PSMA has attracted attention as a target for molecular imaging and for targeted radioligand therapy, especially in [mCRPC].” (Ex. 1028.001).

Within this context, Weineisen 2015 discloses the development and *in vitro* and *in vivo* evaluation of ^{177}Lu -PSMA I&T. (Ex. 1029.002-.008). As depicted in

FIGURE 1 of Weineisen, the chemical structure of PSMA I&T is:

PSMA I&T



(Ex. 1028.002, Figure 1).

Weineisen describes certain endoradiotherapy experiments, in which two patients with mCRPC, and multiple metastases in bone and lymph nodes, were assessed before ^{177}Lu -PSMA I&T therapy by ^{68}Ga -PSMA-HBED-CC PET/CT imaging. (Ex. 1028.003). Both patients with progressive mCRPC separately underwent therapy with **5.7 and 8.0 GBq of ^{177}Lu -PSMA I&T**, respectively, administered intravenously over 15 min. (Ex. 1028.003).

2. The POSITA Must Make Numerous Mental Leaps to Bridge the Differences Between Weineisen 2015 and the Claims of the '901 Patent

Fusion argues that the POSITA would have been motivated to use the Lu-177-PSMA I&T disclosed in Weineisen 2015 as a basis for an improved PSMA expressing cancer therapy. (Pet., p.30). As follows from Fusion's statements in the

petition itself, various steps are required to progress from Weineisen 2015 to the subject-matter of the claims. These include at least:

1. a motivation to use an alpha-emitter instead of Weineisen 2015's beta-emitter (*See Pet.*, p.31);
2. the specific selection of Ac-225 from various alpha-emitters (*See Pet.*, p.32);
3. a reasonable expectation of success in making Ac-225-PSMA I&T (*See Pet.*, p.34);
4. a motivation to use Ac-225-PSMA I&T at the doses recited in the '901 Patent claims (*See Pet.*, p.35);
5. a motivation to use Ac-225-PSMA I&T in repeat doses (*See Pet.*, p.38);
and
6. a motivation to use Ac-225-PSMA I&T to treat PSMA expressing cancers (*See Pet.*, p.39).

These various steps would not have been at all obvious. Indeed, in order to move along the required modifications, Fusion must rely on impermissible hindsight and must provide essential missing elements from Fusion's expert declaration.

While Patent Owners maintain their rights to address any other issues during possible further proceedings, this Preliminary Response particularly addresses two

points making it clear that there is no reasonable likelihood that Fusion would prevail with respect to at least one challenged claim. In particular:

1. the POSITA would not have been motivated to combine Weineisen 2015 with Kratochwil; and
2. the POSITA would not have been motivated to use the repeat dosages of Kratochwil for a hypothesized Ac-225-PSMA I&T, and would not have had a reasonable expectation of success for such dosages.

3. The POSITA Would Not Have Been Motivated to Combine Weineisen 2015 with Kratochwil

Kratochwil, contrary to Fusion's arguments, is primarily, and in fact only, concerned with tolerability, and in particular, tolerability of Ac-225-DOTATOC, and fails to provide substantial indications of effectiveness.

Regarding the tolerability of the single tested compound Ac-225-DOTATOC, Kratochwil references a dose escalation study including “46 treatment cycles in 34 patients with progressive [NETs].” (Ex. 1031.001). After each treatment cycle, acute toxicity was documented. (Ex. 1031.001). Kratochwil concludes that the maximum tolerable dose of a single cycle of Ac-225-DOTATOC was 40 MBq, and that “[m]ultiple fractions were tolerated with 25 MBq every four months or 18.5 MBq every two months.” (Ex. 1031.002). Despite Kratochwil being overwhelmingly concerned with tolerability, Fusion appears to

hone in on only the very brief discussion in Kratochwil that “[t]he radiologic treatment response that was observed in some patients is without clear preference of a particular fractionation concept until now,” and the conclusion that a “well tolerable treatment protocol for [targeted alpha-therapy (TAT)] with Ac-225-DOTATOC in [patients with NETs] that also demonstrated promising treatment efficacy in various patients.” (Ex. 1031.002). Notably, however, Kratochwil also states that whether “[targeted alpha-therapy] provides general advantages in comparison to beta emitter based radionuclide therapy cannot be derived from the available data.” (Ex. 1031.002).

Therefore, contrary to Fusion’s arguments, Kratochwil provides no motivation to specifically select and use the disclosed lower doses of Ac-225-DOTATOC for radionuclide therapy (i.e., 18.5 MBq and 25 MBq) instead of the 40 MBq dose determined to be the maximum tolerable dose. Quite to the contrary, even if a POSITA looking at Kratochwil in its entirety would have been motivated to actually use one of the explicitly disclosed doses – which Patent Owners do not concede and expressly contest – that POSITA more likely would have used the reported highest tolerable dose (i.e., 40 MBq) since that dose is described as corresponding to the maximum tolerable dose of a single cycle of Ac-225-DOTATOC. (Ex. 1031.002). Indeed, Kratochwil itself teaches that “radiological

treatment response that was observed in some patients was without clear preference of a particular fractionation concept until now.” (Ex. 1031.002). If there is no effect in using fractionation (i.e., lower repeat doses) versus a single higher dose for treatment response and toxicity, the POSITA would have selected the simpler single administration of 40 MBq, and would have found no motivation to select the more burdensome 18.5 MBq and 25 MBq repeat doses.

While Kratochwil indicates that treatment response was observed in some patients, it does not disclose whether this is significant within the tested patient population and/or which doses would have provided a response. (See Ex. 1031.001-.002). Given that Weineisen 2015 claims to have observed an impressive molecular treatment response for its Lu-177-PSMA I&T compound (Exhibit 1028.007), the POSITA would not have been motivated to apply the teaching of Kratochwil – which only observes a treatment response in some patients and acknowledges that there are no established dosimetry tools to predict toxicity of targeted alpha-therapy yet. (Ex. 1031.001-.002). The POSITA would not have been motivated to modify a treatment that already shows an impressive response based on a reference that discloses a response in only some patients and teaches that toxicity would be unpredictable.

Finally, Kratochwil is incompatible with Fusion’s obviousness challenge. Among the various steps required to move from Weineisen 2015 to the ‘901 Patent

claims, Fusion acknowledges that there must be a motivation to use an alpha-emitter instead of the beta-emitter of Weineisen 2015. (*See* Pet., p.31). Assuming *arguendo* (and without concession) that such a motivation did exist, the POSITA would then allegedly have been prompted by Kratochwil to replace the beta-emitter, Lu-177, with the alpha-emitter, Ac-225. However, Kratochwil concludes by stating that “[whether targeted alpha-therapy] provides general advantages in comparison to beta emitter based radionuclide therapy **cannot be derived from the available data, yet.**” (Ex. 1031.002). Thus, Kratochwil does not provide the requisite motivation to replace the beta-emitter Lu-177 with an alpha-emitter such as Ac-225. Instead, even in light of Weineisen 2015, Kratochwil would – at best – have taught the POSITA three things: 1) there are no established dosimetry tools for alpha-emitter therapy, which would make the POSITA particularly cautious to enter this field; 2) treatment response was seen only in **some** patients, without providing any more detail, while the POSITA would have seen that Weineisen 2015 observed an impressive molecular treatment response; and 3) the data do **not** support a conclusion that Ac-225 alpha-emitter therapy has general advantages over beta-emitter therapy. Faced with these realities, the POSITA would not have combined Kratochwil with Weineisen 2015 as suggested by Fusion. On the contrary, these

teachings by Kratochwil would lead the POSITA away from any desire to replace Weineisen's beta-emitter Lu-177 with Kratochwil's Ac-225 alpha-emitter.

4. The POSITA Would Not Have Been Motivated to Use the (Repeat) Dosages of Kratochwil for a Hypothesized Ac-225-PSMA I&T and Would Not Have Had a Reasonable Expectation of Success for Such Dosages

Perhaps the most obvious missing element in Fusion's analysis is any argument as to why the POSITA, when replacing Lu-177 from Weineisen 2015 with Ac-225 from Kratochwil, would also adopt the dose disclosed in Kratochwil. Fusion's analysis seems to overlook that the ligands disclosed in Weineisen 2015 and Kratochwil (i) bind completely different targets on cancer cells, and (ii) are used in completely different cancers.

The POSITA would not have believed or technically understood that an effective dose for administration of a radiopharmaceutical would only be dependent on the chemical nature of the radionuclide itself. Indeed, the POSITA would readily comprehend that there would also have been a huge impact on the effective and tolerable dose due to target binding affinity and specificity, amount of the target expressed on the tumor, amount of the target expressed on nontargeted tissue thereby causing the risk of side-effects and toxicity, and the tumor type itself. This is already pointed out in the '901 Patent, which states that "choosing an appropriate targeting site and developing an appropriate targeting moiety combined to the identification

of an appropriate chelating unit with an appropriate radionuclide to a working radiopharmaceutical is a challenging, yet promising way to be able to manage tumors.” (Ex. 1001.010, 1:61-65).

As it is generally known in the field of targeted radiotherapy that dosimetry depends on target binding affinity and specificity, amount of the target expressed on the tumor, amount of the target expressed on nontargeted tissue thereby causing the risk of side-effects and toxicity, and the tumor type itself, it is no surprise that evidence of this is also present in Fusion’s Exhibits and Expert Declaration.

a) Fusion’s Expert Acknowledges that the Individual Selection of the Different Moieties is Key in Designing an Effective Dose of a Radiopharmaceutical

In her Declaration, Fusion’s expert expressly states that in radiopharmaceuticals, “the challenge lies in the ability to selectively target the desired tissue/cells,” that “[t]he targeting moiety is used to direct the rest of the molecule to a particular part of the body,” that “the targeting moiety might be an antibody known to bind to a protein on the surface of a specific type of tumor cell or a small molecule that binds to proteins only found on cancer cells,” and that “[s]election of each of the radionuclide, chelator, linker and targeting moiety is key

to ensure the radiopharmaceutical is effective in the treatment of the particular cancer a patient may have.” (Ex. 1002.013-.015, ¶25-27).

b) Sgourous – Relied on by Fusion’s Expert – Evidences that Dosage is Linked to Factors Other than the Radionuclide Itself

Sgourous is particularly relevant as it is a pamphlet for dosimetry of alpha-emitting targeted radionuclide therapy and is relied on by Fusion as allegedly providing guidance for the relative biological effectiveness considerations impacting dosimetry for alpha-emitters. (Pet., p.35; Ex. 1017.001). Sgourous provides recommendations for dosimetry which specify that one must first determine the cellular targeting kinetics and properties. (Ex. 1017.012-.013). And Sgourous identifies seven elements for making such determinations, which include the number of sites per cell and fraction of cells that express the target, distribution of binding sites per cell among the targeted cells, binding and dissociation constants for cell targeting, internalization rate, and lethal dose in targeted and nontargeted cells. *Id.*

c) Miederer 2008b – Relied on by Fusion’s Expert – Evidences Significant Differences in Toxicity Using the Same Radionuclide but Different Ligands

In Miederer 2008b, the toxicity of Ac-225-DOTA-biotin and Ac-225-DOTATOC was determined clinically and by weight measurement in BALB/c mice.

(Ex. 1030.0008, section 4.3.2). Specifically, “lethal toxicity was not observed until 60 kBq [²²⁵Ac]DOTATOC at 180 days (n=5) and until 740 kBq [²²⁵Ac]DOTA-Biotin at 110 days (n=3),” and “[w]eight loss was predominant in the first 20 days and for animals injected with [²²⁵Ac]DOTA-Biotin, weight recovery was remarkably better than for animals injected with [²²⁵Ac]DOTATOC.” *Id.* Thus, although the same alpha-emitting radionuclide was used in these toxicity experiments (i.e., Ac-225), and only the ligand was somewhat different, significant differences were observed in toxicity, thereby emphasizing the importance of the targeting moiety. *See Id.* Accordingly, Miederer 2008b, provided by Fusion, directly contradicts Fusion’s arguments both that the POSITA would have been motivated to simply swap Lu-177 with Ac-225, and that the ‘901 Patent claims do not exhibit unexpected and surprising results.

d) Banerjee – Relied on by Fusion’s Expert – Evidences the Importance of the Targeting Moiety Independent of the Radionuclide

Banerjee discloses that the success of a therapeutic modality “depend[s] on the principal interdependent factors such as the specificity and affinity of the antibody, the antigen concentration in the tumor, and the radiotoxicity of the radionuclide.” (Ex. 1038.013). Although this statement pertains to antibodies as a targeting moiety, it also relays the understanding of the POSITA that the

specificity/affinity of the ligand is a **principal factor** to be considered for radionuclide therapy using radiopharmaceuticals, as well as the receptor concentration in the tumor.

And Banerjee's disclosure is entirely in line with the description of radiopharmaceuticals in paragraphs 25-27 of Fusion's Expert Declaration, as discussed in Sections V and VI(A)(5), *supra*. In addition, Banerjee discloses that the DOTATOC (i.e. [DOTA,Tyr³]octreotide) and DOTANOC ([DOTA,1-Nal³]octreotide) ligands are structurally similar somatostatin analog peptides for targeting somatostatin receptors (sstrs) having only a single L-Tyrosine amino acid residue change towards an L-3-(1-naphthyl)alanine amino acid residue. (Ex. 1038.020). In Banerjee, although both DOTATOC and DOTANOC ligands demonstrate affinity to sstr3 and sstr5 and hence bind to the same (sub)type of somatostatin receptors, ¹⁷⁷Lu-DOTANOC showed a higher uptake in normal tissues which resulted in an increase in the whole-body dose. *Id.*

Even more telling, Banerjee discloses the unlabeled [DOTA⁰,Tyr³]**octreotate** peptide has 8–9-fold higher affinity for sstr2 subtype receptors as compared to [DOTA⁰,Tyr³]**octreotide**. (Ex. 1038.032). And the [DOTA⁰,Tyr³]**octreotide** cyclic peptide ligand and the [DOTA⁰,Tyr³]**octreotate** cyclic peptide ligand are structurally similar, and both cyclic peptide octreotide analogue ligands target sstrs

– i.e., said ligands only chemically differ from each other via the substitution/exchange of the L-Threonine-ol amino alcohol residue or L-Threoninol in the 8 position in [DOTA⁰,Tyr³]octreotide with a L-Threonine amino acid residue in [DOTA⁰,Tyr³]octreotate. *Id.* Banerjee found that the uptake of ¹⁷⁷Lu–[DOTA⁰,Tyr³]octreotate was 2.1-fold higher compared to ¹⁷⁷Lu–[DOTA⁰,Tyr³]octreotide in patient studies. *Id.* This property has made ¹⁷⁷Lu–octreotate potentially more useful for therapy, as higher tumor-absorbed radiation doses can be delivered. Thus, Banerjee also shows the importance of the targeting moiety independent of the radionuclide.

e) Dosage is Therefore Not Only Linked to the Radionuclide, But Especially to the Ligand

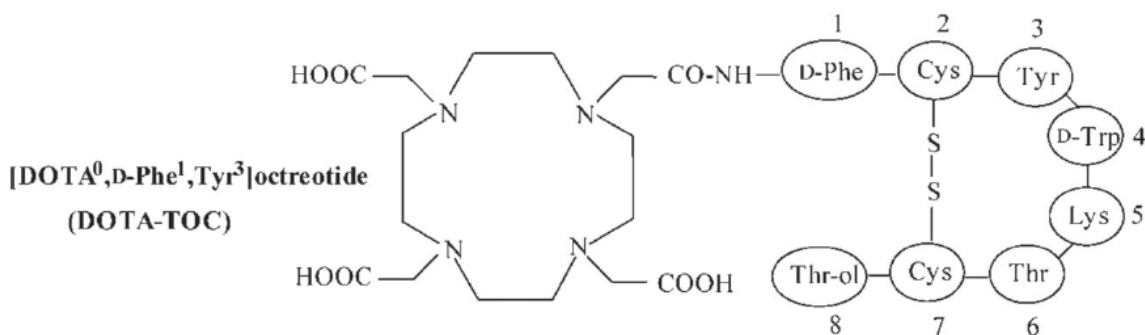
The determination of an effective dose for administration of a radiopharmaceutical is certainly not only dependent on and linked to the chemical nature of the radionuclide itself. On the contrary, as evidenced by the above references – provided by Fusion, and relied on by Fusion’s expert – a POSITA would have immediately understood that the nature of the ligand also has a principal effect on the dosage requirement – in particular, target binding (affinity and specificity), amount of the target expressed on the tumor, amount of the target expressed on nontargeted tissue, thereby causing side-effects and toxicity, and the tumor type itself.

The '901 Patent Examiner understood this. In his Reasons for Allowance, the Examiner stated that the compounds recited in the '901 Patent claims differed from the closest prior art reference in the “chemical structure of the variable linker,” and that “[t]he proposed changes in [the] chemical structure of the linker results in change[s] of lipophilic interactions in the linker regions, as well as binding affinity to prostate-specific membrane antigen (PSMA) protein.” (Ex. 1004.033) Thus, the Examiner correctly understood that the chemical structure of the linker, and therefore the binding affinity of said linker to the (PSMA) target expressing cancer or cancer cells, also plays an essential role in determining an effective dose for the administration of a radiopharmaceutical to a patient in need thereof.

The POSITA would not have been motivated to merely swap the ^{177}Lu radionuclide in the most promising radiopharmaceutical disclosed in Weineisen 2015 for targeting PSMA expressing cancers (^{177}Lu -PSMA I&T) with an ^{225}Ac radionuclide, **and at the same time not only** significantly lower the administered activities disclosed in Weineisen 2015, **but also** specifically select and use the **lower** doses disclosed in Kratochwil related to Ac-225-DOTATOC with any reasonable expectation of success. In fact, the POSITA would have instead **refrained from** combining the teachings of Weineisen 2015 and Kratochwil since both prior art references are **incompatible** with one another, as discussed in Section VI(A)(3), *supra*.

As also mentioned in Section VI(A)(3), *supra*, Kratochwil describes an empiric dose escalation study conducted to find the maximum tolerable dose of single cycle and fractionation concepts for Ac-225-DOTATOC radionuclide therapy. (Ex. 1031.001). The chemical structure of DOTATOC, taken from Banerjee, is depicted below. (Ex. 1038.019, Figure 16).

DOTATOC



(Ex. 1038.019, Figure 16). It is immediately evident that DOTATOC is structurally very distinct from the targeting compounds of **Formula (A), (B), (C), (D) or (E)** according to '901 Patent claim 1 and from Weineisen 2015's PSMA I&T . DOTATOC is a **cyclic somatostatin analog peptide**, i.e. [DOTA⁰,Tyr³]octreotide, which specifically displays binding affinity to the somatostatin receptors (sstrs). (See Ex. 1038). As discussed in Banerjee, the most widely employed modality of peptide receptor radionuclide therapy uses somatostatin analogues for targeting somatostatin receptors, which are overexpressed in neuroendocrine cancer. (Ex. 1038.018, section 7.2). Hence, somatostatin analogues are by far the most exhaustively studied therapeutic peptides in nuclear medicine using peptide receptor radionuclide therapy. (Ex. 1038.019). The POSITA would have been fully aware

that DOTATOC – as a cyclic peptide analogue of octreotide – specifically binds to and targets sstrs. This is, for instance, evidenced in Miederer 2008b, which states that [^{225}Ac]DOTATOC might be usable for somatostatin receptor radionuclide therapy (Ex. 1030.008, section 4.3.2), as well as in Banerjee as discussed above. (Ex. 1038.020 and .032).

Thus, Kratochwil specifically uses Ac-255-DOTATOC for radionuclide targeting of somatostatin receptors, which are overexpressed in neuroendocrine tumors and cancers (as evidenced by Banerjee (Ex. 1038.018, section 7.2)), while on the other hand, Weineisen 2015 uses ^{177}Lu -PSMA I&T for targeting PSMA in the endoradiotherapeutic treatment of mCRPC. (*See* Exs. 1028 and 1031).

The POSITA would have known, or at least expected that:

1. Target binding (affinity and specificity) will be different for Ac-255-DOTATOC on sstrs versus ^{177}Lu -PSMA I&T on PSMA;
2. The amount of sstrs expressed on NET tumor cells will be different from the amount of PSMA expressed on metastatic prostate tumor cells;
3. The amount of sstrs expressed on non-tumor cells will be different from the amount of PSMA expressed on non-tumor cells;
4. NETs behave differently from metastatic prostate cancer.

The POSITA would not have had any reasonable expectation of success in selecting and applying the lower doses described in Kratochwil for binding the

DOTATOC ligand to sstrs in NETs to the rather different PSMA-binding ligand PSMA I&T of Weineisen 2015 for targeting PSMA on mCRPC because the POSITA would have known that the nature of the ligand is tied to the dose. Fusion's position seems to be that the POSITA would have plucked any radionuclide from nearly any ligand and plug it into another ligand and simply adopted the dose, regardless of targeting moiety structure, intended target, or treated disease. More than that, Fusion would have us believe that the POSITA would simply have expected this scheme to work despite the different ligands, targets and cancers. As detailed above, such assumptions are incorrect. The POSITA would have known that the **principal determinants in producing an effective dose of an effective radiopharmaceutical** include not only the radionuclide, but also ligand binding affinity and specificity, target expression on cancer and non-cancer cells, etc. Accordingly, Fusion's position can only be reached by using impermissible hindsight.

Specifically, Fusion's arguments amount to picking-and-choosing from among selected disclosures in the prior art using the patented claims as a blueprint, which amounts to impermissible hindsight, and cannot sustain an obviousness rationale. *See Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985) (stating "[t]he invention must be viewed not with the blueprint drawn by the

inventor, but in the state of the art that existed at the time”); *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (stating “it is impermissible to use the claimed invention as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is rendered obvious,” and “[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention”). For example, Fusion “picks” the PSMA I&T ligand from Weineisen 2015, and the ^{225}Ac radionuclide from Kratochwil while ignoring the fact that it is disclosed with a specific, and chemically different ligand. And Fusion self-servingly “chooses” the lower fractionated doses from Kratochwil despite that reference also disclosing a much larger maximum tolerable dose that the POSITA would have been far more motivated to select. As the POSITA would not have arrived at such a cobbled-together radiopharmaceutical and treatment for PSMA-expressing cancers without the direction given by the claims of the ‘901 Patent, Fusion’s picking-and-choosing amounts to impermissible hindsight, and thus Fusion’s obviousness rationale must fail.

5. The Treatments Recited in the ‘901 Patent Claims Exhibit Unexpected and Surprising Results Unrebutted By Fusion

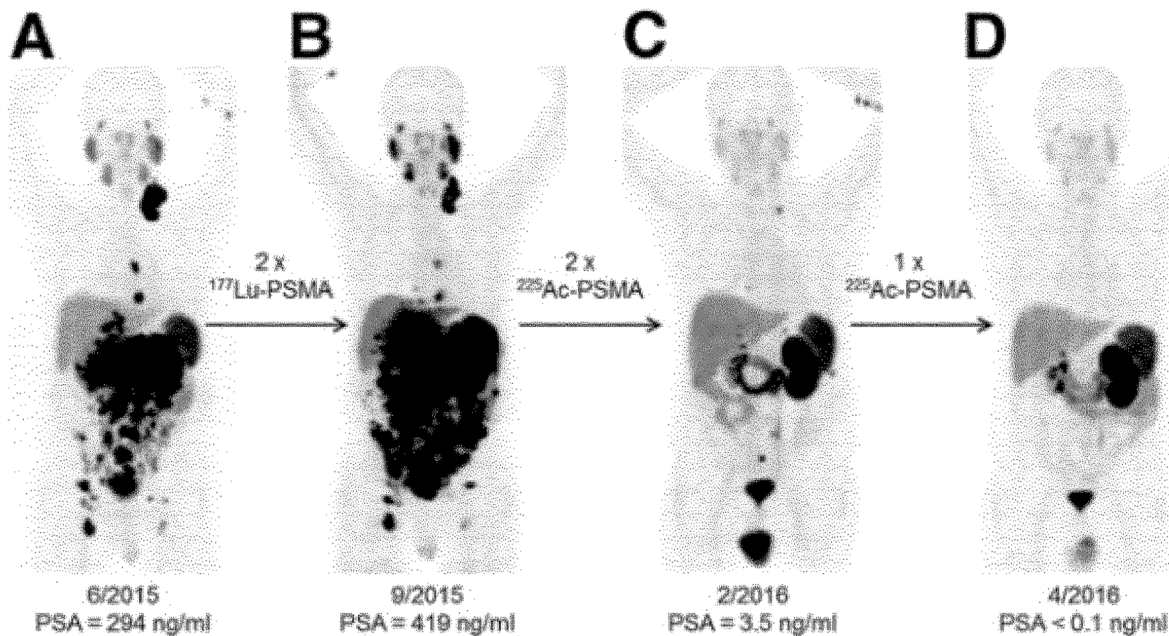
In addition, the methods of treating PSMA expressing cancers claimed in the ‘901 Patent exhibit surprising and unexpected results. As demonstrated in the experimental section of the ‘901 Patent, the very efficient and specific targeting of

the Ac-225-radiopharmaceuticals to PSMA combined to the short-range action of the Ac-225 alpha-emitter remarkably and unexpectedly allows for very good results of destruction of cancer cells without notable damage to nontarget tissues. For example, the '901 Patent presents experiments and data comparing Ac-225-PSMA-617 with Lu-177-PSMA-617. (Ex. 1001, 16:10-18:10). In particular, the '901 Patent presents detailed experimental evidence that the group treated with Ac-225-PSMA-617 – i.e., an Ac-225-radiopharmaceutical according to claim 1 – had a significantly higher response rate in comparison to the group treated with Lu-117-PSMA-617. *Id.* The treatment analysis revealed that 15/28 patients (54% of patients) treated with Ac-225-PSMA-617 were in PSA response at week-24 upon comparison with only 9/30 patients (30% of patients) treated with Lu-117-PSMA-617. (Ex. 1001, 16:10-31). These experimental results prove a remarkable difference, particularly considering similar hematological toxicity.

Even more remarkably, while Example B2 showed progression upon treatment of patient B with Lu-117-PSMA-617, **an unexpected but impressive response** was clearly demonstrated in patient B after switching from treatment with Lu-117-PSMA-617 to treatment with Ac-225-PSMA-617 at the low dosages recited in the '901 Patent claims. (Ex. 1001, 17:31-61). This observation is clearly demonstrated in Fig. 14 of the '901 Patent (reproduced below), which pictures the

only partial response of patient B to treatment with **7.4 GBq of Lu-117-PSMA-617**, but the **subsequent remission** after treatment with **6.4 MBq (100 kBq per kg body weight) of Ac-225-PSMA-617**. (Ex. 1001, 17:31-61, Figure 14). It is immediately evident from the 68-Ga-PSMA-11 PET/CT scans of patient B shown in Fig. 14 that a strong and increased response after initial staging (A in Figure 14) was obtained in patient B after switching from treatment with a much higher dose of Lu-117-PSMA-617 (B in Figure 14) to treatment with an exponentially lower dose of Ac-225-PSMA-617 (C, D in Figure 14). *Id.*

Figure 14 of the '901 Patent



That these results are surprising and unexpected is corroborated by literature published after the filing of the '901 Patent. For example, Langbein notes “Kratochwil et al. used a fixed-dose regimen of 100 kBq/kg of body weight in a larger cohort of patients and found ²²⁵Ac-PSMA-617 to have remarkable antitumor activity.” (Ex. 2005.003). Langbein also states “[o]ne case series also reported on the use of ²²⁵Ac-PSMA-617 radioligand therapy in chemotherapy-naïve patients with advanced metastatic prostate carcinoma,” and “[i]n this earlier state of prostate cancer, a PSA decline of at least 90% was observed in 82% of patients, including 41% of patients with undetectable serum PSA, who remained in remission for 12 mo after therapy.” *Id.* Langbein concludes “[t]he remarkable therapeutic efficacy reported in this study could be achieved with reduced toxicity to the salivary glands due to de-escalation of administered activities in subsequent treatment cycles.” *Id.*

Additionally, de Medeiros report on a patient in Brazil diagnosed with prostate cancer in 2007 and, after distinct treatment regimes, received external beam radiotherapy in 2013. (Ex. 2006.002). Successive progressions were seen over the following months and palliative care included several lines of treatment. (Ex. 2006.003). de Medeiros state they “became aware of articles from Heidelberg University reporting impressive responses to ²²⁵Ac-PSMA therapy,” and

submitted the patient to that university. (Ex. 2010.003). The patient underwent treatment with doses of 8 MBq and 6 MBq ^{225}Ac -PSMA-617 and the remarkable PET/CT Scan results are shown in Figure 4 of de Medeiros. (Ex. 2010.003-.004). de Medeiros note in the Discussion section that “**[t]he initial results are extremely encouraging**, and phase 2 trials are ongoing with **great preliminary data**,” and that “[s]ome reports indicate 95% objective response rates and up to 20% complete tumor response in imaging assessments, **which is absolutely impressive and unprecedented**.” (Ex. 2006.008).

These attestations of “absolutely impressive and unprecedented” results, “extremely encouraging preliminary data,” “great preliminary data,” “remarkable antitumor activity,” and “remarkable therapeutic efficacy” directly contradict Fusion’s expert’s “disagreement” that the results are surprising or unexpected. And in the face of these attestations from multiple artisans in the relevant field, Fusion’s expert’s conclusion that Patent Owners’ results are not in fact unexpected – especially without her detailed review of the data presented in the ‘901 Patent – is in direct contrast to the findings of de Medeiros and Langbein and provides little to no probative value. Her failure to carefully address the substantial evidence of unexpected results is fatal to Fusion’s case.

Hence, even assuming *arguendo* (and without concession) that the POSITA would consider **i)** swapping the ^{177}Lu radionuclide in the most promising radiopharmaceutical of Weineisen 2015 with Kratochwil's ^{225}Ac radionuclide for a very different ligand and for treating a very different cancer, **and ii)** adopting certain specific doses disclosed in Kratochwil, it would have been entirely unexpected that the results obtained from the treatment would improve to the significant extent demonstrated in the '901 Patent, and that patients non-responsive to a high dose of ^{177}Lu would respond to an exponentially lower dose of ^{225}Ac . As such, these unexpected and surprising results – which were presented and argued to the Examiner and plainly embodied in the challenged claims – are sufficient to overcome any *prima facie* case of obviousness.

6. The POSITA Would not Have Combined Jurcic with Weineisen 2015 and Kratochwil

Fusion relies on Jurcic in addition to Weineisen 2015 and Kratochwil to advance a theory of obviousness for claim 9 of the '901 Patent. (Pet., pp.2, 27-28, 37-38, 49-50). Claim 9 depends from claim 1, but recites a dosage of 50 kBq to 200 kBq/kg of body weight. (Ex. 1001, claim 9). However, as discussed in Section VI(A)(3), *supra*, Jurcic does not relate to PSMA-targeting ligands having the general structure asserted by Fusion and allegedly disclosed in Weineisen 2015. Instead, Jurcic discloses ^{225}Ac linked to a “humanized anti-CD33 monoclonal antibody,”

namely lintuzumab, which is completely different than the PSMA-targeting ligands covered by the challenged claims. (Ex. 1011.001-.003). Thus, Jurcic discloses Ac-225 conjugated to yet another ligand (lintuzumab) that binds yet another target (CD33) expressed in yet another cancer (acute myeloid leukemia).

As noted by Fusion’s own expert, “[w]hile the literature disclosed using both antibodies and oligonucleotides as targeting moieties, a [POSITA] would have understood that an oligonucleotide targeting portion would be preferred” because “oligonucleotide/small molecule-based conjugates have shorter half-lives in serum, leading to a substantially decreased risk in non-specific toxic interactions of the radiotherapeutic with other parts of the body.” (Ex. 1002.0038, ¶1074). Therefore, Fusion’s own expert admits that the POSITA would have recognized a difference in efficacy and “non-specific toxic interactions” between antibody and oligonucleotide targeting moieties. It follows that such differences would also indicate a potential difference in dosage, such that the POSITA would not have applied Jurcic’s dosage of an antibody-based compound to Weineisen 2015’s and Kratochwil’s small molecule-based compounds.

Additionally, Jurcic discusses a potential treatment for Acute Myeloid Leukemia – a completely different cancer and cancer classification than the prostate cancer of Weineisen 2015 and the NETs of Kratochwil. (*See* Ex. 2001, noting the

six major categories of cancer). Indeed, as discussed in NIH, prostate cancer is classified as a carcinoma – which is “a malignant neoplasm of epithelial origin or cancer of the internal or external lining of the body” – while leukemia is in a class of its own and is a blood cancer. (Ex. 2001).

Adding Jurcic to the already improper combination of Weineisen 2015 and Kratochwil would mean that a POSITA would have had to select the ligand in Weineisen 2015 disclosed for use against prostate cancer, combine that prostate cancer-specific ligand to the radionuclide disclosed in Kratochwil for use against NETs, and then also select the dose described in Jurcic for use against a completely different class of cancer – leukemia. In this scheme, the POSITA must cobble together three structurally different compounds, all disclosed for use against three very different cancers, and somehow Frankenstein a method of treating prostate cancer from that. This strains reason.

Neither Fusion nor Fusion’s expert provide an opinion or explanation as to why a POSITA would have combined Jurcic’s dosage for treating a **leukemia** with Weineisen 2015’s treatment for **prostate cancer**, and Kratochwil’s treatment for **NETs**. In fact, neither Fusion nor Fusions’ expert addresses the discrepancy in treated diseases at all. Instead, both Fusion and Fusion’s expert simply state – in a conclusory manner without analysis of the differences in ligands and treated diseases

– that the POSITA would have been “motivated to administer ^{225}Ac PSMA I&T at the doses shown to be safe and effective in Jurcic.” (Ex. 1002.046, ¶¶91). But Jurcic discloses a treatment for leukemia, and a very different ligand than that disclosed in both Wieneisen 2015 and Kratochwil, and neither Fusion nor Fusion’s expert explains the significance of these differences.

Further, Jurcic also discloses a very different treatment protocol than either Weineisen 2015 or Kratochwil – i.e., a combination therapy including the co-administration of ^{225}Ac -lintuzumab with low-dose cytarabine (LDAC). (Ex. 1011.001-.003). Again, neither Fusion nor Fusion’s expert provide an opinion, any analysis, or any explanation as to why a POSITA would have selected the dosage of one part of a two-part combination therapy to use in either Weineisen 2015’s or Kratochwil’s method of treating an entirely different disease with a very different compound. Instead, the only mentions Fusion makes regarding Jurcic’s use of ^{225}Ac -lintuzumab in combination with LDAC is in the formal citations of the reference. (Pet., p.vi, Exhibit list, and p.27, footnote simply providing the Jurcic citation). And the only mentions Fusion’s expert makes regarding Jurcic’s use of the combination therapy is again in the formal citation of the reference, and in a one-line summary statement of Jurcic’s alleged disclosure. (Ex. 1002.035, ¶¶66 and 67). While that one line notes “Jurcic discloses the doses and dosing frequency used in a phase I

clinical trial for ^{225}Ac -Lintuzumab, a radiolabeled antibody and low-dose cytarabine,” Fusion’s expert provides no further analysis as to, for example, whether the POSITA would have used a higher dosage of ^{225}Ac -Lintuzumab in the absence of LDAC co-administration. (Ex. 1002.035, ¶67).

Additionally, cytarabine is only indicated by the FDA for use in treating certain leukemias. (Ex. 2004.003). The POSITA would not have found Jurcic instructive as to dosing since the second part of the combination therapy – cytarabine – cannot be used to treat PSMA expressing cancers or cancer cells or NETs. *Id.* The POSITA, therefore, would not have found any motivation to randomly pluck the dose from Jurcic for the treatment of leukemia and use it in the treatment of prostate cancer (as disclosed in Weineisen 2015) or NETs (as disclosed in Kratochwil).

Accordingly, Jurcic concerns a rather different radiolabeled compound, and the treatment of a very different disease than disclosed in both Weineisen 2015 and Kratochwil. Jurcic also discloses a different treatment protocol than either Weineisen 2015 or Kratochwil – i.e., where Weineisen 2015 and Kratochwil disclose the solo administration of a radiopharmaceutical, Jurcic discloses the co-administration of a different radiolabeled compound with LDAC. (Exs. 1028, 1031, 1011). Neither Fusion nor Fusion’s expert seem to appreciate or meaningfully acknowledge these differences in either the petition or the expert declaration. And

neither Fusion nor Fusion's expert provide any explanation as to why a POSITA would have used the dosage of a different compound used for a different purpose in the Weineisen 2015 or Kratochwil treatment protocol, or why that POSITA would have used the dosage from a combination therapy for leukemia – unchanged – in a therapy for PSMA expressing cancers or cancer cells, wherein part of that combination therapy cannot be used.

Accordingly, adding Jurcic to the obviousness inquiry provides nothing more than additional impermissible hindsight. For example, as discussed in Section VII(A)(6), *supra*, Fusion's arguments again amount to "picking" the PSMA I&T ligand from Weineisen 2015, and the ^{225}Ac radionuclide from Kratochwil while ignoring the fact that it is disclosed with a specific, and chemically different ligand. And adding Jurcic to this mix is simply Fusion again self-servingly "choosing" a random dosage from Jurcic despite that reference disclosing a completely different ligand than both Weineisen 2015 and Kratochwil, as well as Jurcic disclosing treatment of a completely different cancer. As this combination would mean that the POSITA would now have to cobble together three distinct aspects of three structurally different compounds and ignore the fact that all three references teach the treatment of three very different cancers, the POSITA would not have arrived at such a hodge-podge radiopharmaceutical and treatment for PSMA-expressing

cancers without the direction given by the '901 Patent claims. Fusion's picking-and-choosing amounts to impermissible hindsight, and thus Fusion's obviousness rationale against claim 9 must also fail.

VIII. FUSION'S EXPERT DECLARATION IS CONCLUSORY

Fusion's expert provides merely conclusory arguments supporting alleged obviousness. For example, while Fusion's expert states that the POSITA would have found it obvious to combine the radionuclide discussed in Kratochwil with the different compounds of Weineisen 2015 for the treatment of a different cancer, she fails to adequately address the differences in ligand structure, binding affinity and specificity, and different targets due to the design for the treatment of different cancers.

This failure is compounded in Fusion's expert's arguments for obviousness over Jurcic. Adding Jurcic to the obviousness equation means that the POSITA looking at Weineisen 2015, Kratochwil and Jurcic would have to cobble together three structurally different compounds, all disclosed for use against three very different cancers, and somehow Frankenstein a method of treating PSMA expressing cancers from that. Such an expectation of the POSITA strains the bounds of reason, and Fusion's expert fails to adequately address either how the POSITA would approach this problem or begin to address the obstacles, for example of different

binding affinities and specificities, different targets, and treatment of different cancers or cancer cells.

Fusion's only evidence as to the missing link between Weineisen 2015, Kratochwil and Jurcic is the expert declaration. But that declaration fails to explain why the POSITA would have combined the treatment for NETs of Kratochwil with the treatment for prostate cancer of Weineisen 2015 and the treatment for leukemia of Jurcic. The "[d]etermination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534,546 (Fed. Cir. 1998).

And as discussed in Section VII, *supra*, while Fusion's expert introduces certain references in an attempt to support her conclusions -- which in and of itself is improper as those references are not recited in the Grounds -- she ignores or neglects to address disclosures in those references that contradict her conclusions. It is improper to "stitch together an obviousness finding from discrete portions of prior art references without considering the references as a whole." *In re Enhanced Security Research, LLC*, 739 F.3d 1347, 1355 (Fed. Cir. 2014). Accordingly, Fusion's expert declaration is entitled to little weight. *Xerox Corp. v. Bytemark, Inc.*, IPR2022-00624, Paper No. 9 (Aug 24, 2022) (designated precedential Feb. 10,

2023); *See also Monsanto Co. v. Pioneer Hi-Bred Int'l, Inc.*, No. IPR2013-00022, at 6 (P.T.A.B. Apr. 11, 2013), Paper No. 43 (expert failed to provide sufficient underlying data such that the POSITA would have a reasonable basis to believe that his calculations and conclusions were correct); *Fidelity Nat'l Info. Serv., Inc. v. Datatransury Corp.*, IPR2014-00491, Paper 9 (August 13, 2014)(denying an IPR Petition that cited primarily to an expert declaration as failing to contain a “full statement of the reasons for the relief requested, including a detailed explanation of the significance of the evidence” as required under 37 C.F.R. § 42.22(a)(2)).

IX. CONCLUSION

In view of the foregoing, claims 1, 2 and 4-13 are patentable, and Fusion has not met its burden to prove otherwise. Accordingly, Patent Owners request the Petition be denied.

DATED: May 17, 2023

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 13,997 words, excluding the portions exempted under 37 C.F.R. §42.24(a)(1), according to the word count feature of the word-processing system used to prepare this paper.

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CERTIFICATE OF SERVICE

I hereby certify that on May 17, 2023, a copy of this **PATENT OWNERS’ PRELIMINARY RESPONSE PURSUANT TO 37 C.F.R. §42.107**, 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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