

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

**GE Healthcare Ltd.,
Petitioner**

v.

**Johns Hopkins University,
Patent Owner**

**Case No. PGR2025-00059
U.S. Patent No. 12,115,233**

PETITION FOR POST GRANT REVIEW

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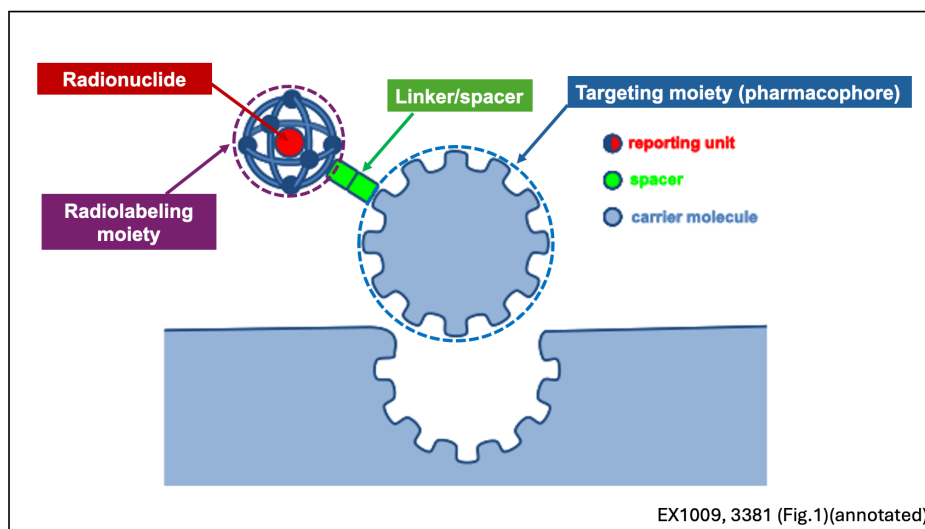
I. Introduction

Radiopharmaceuticals and optical imaging agents work by selectively accumulating in tissues or organs containing cells targeted by the agent. In radiotherapy, radiation emitted by the accumulated radiopharmaceuticals in the tissue kills the targeted cells. In diagnosis, devices are used to locate and image tissues or organs in which the agent has accumulated. In each application, selectivity of the agent for the target cells is critical—if it binds to normal cells, it can produce inaccurate diagnoses, and in radiotherapy, can harm healthy tissue.

A common modular design used in radiopharmaceuticals and optical imaging agents combines three components (illustrated below):¹

- (i) a “reporter moiety—either a “radiolabeling moiety” attached to a radionuclide or a light-absorbing or -emitting molecule;
- (ii) a “targeting moiety” that binds to a structure selectively expressed by the targeted cells; and
- (iv) a “linker” that connects the targeting and radiolabeling moieties.

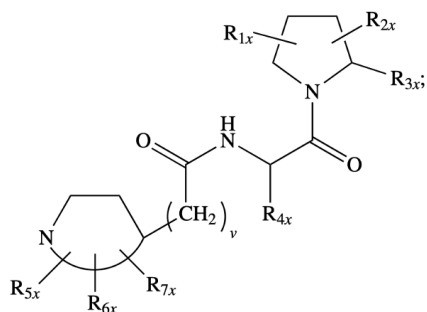
¹ EX1003, ¶¶ 27-28; EX1009, 3380 (annotated).



U.S. Patent No. 12,115,233 (the '233 Patent)(EX1001) broadly claims optical imaging and radiopharmaceutical agents with this modular, three-component design: “low molecular weight” compounds with the formula “B-L-A.” The claims define the “B” and “L” components in functional terms: (i) “B” is “any ...optical or radiolabeled functional group... *suitable for*” optical imaging, Positron Emission Tomography (PET) imaging, Single Photon Emission Computed Tomography (SPECT) imaging or radiotherapy, while “L” is a linker “having bi-functionalization *adapted to form* a chemical bond with B and A.”

The claims define the third component “A” as “a targeting moiety for FAP- α ” (“A”), which is any compound within a structurally defined genus (below):

A is a targeting moiety for FAP- α , wherein A has the structure of:



(X)

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

R_{3x} is selected from the group consisting of H, $-CN$, $-B(OH)_2-C(O)$ alkyl, $-C(O)$ aryl-, $-C-C-C(O)$ aryl, $-C-C-S(O)_2$ aryl, $-CO_2H$, $-SO_3H$, $-SO_2NH_2$, $-PO_3H_2$, and 5-tetrazolyl;

R_{4x} is H;

R_{5x} , R_{6x} and R_{7x} are H;

v is 0; and



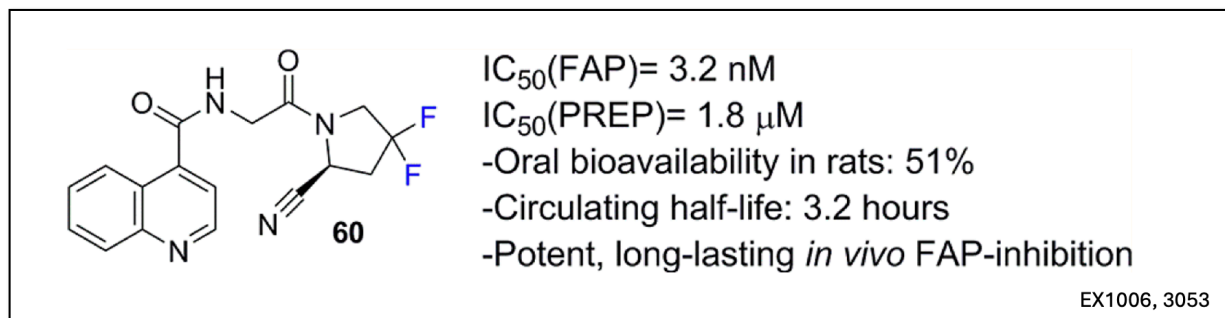
represents a quinolinyl ring having a point of attachment to a remainder of the FAP binding moiety at the 4-position of the quinolinyl ring;

Before 2017, two different published applications—US-633 (EX1004) and US-121 (EX1005)—described low molecular weight radiotracers useful for PET or SPECT tumor imaging employing this modular, three-component design. Both used small molecule targeting moieties for proteins selectively expressed on cells in tumors: (i) US-633 described radiotracers targeting fibroblast activation protein- α (FAP- α , seprase)(“FAP”), while (ii) US-121 targeted the prostate-specific membrane antigen (PSMA).² The only component of the claimed compounds not disclosed in these publications was a FAP-targeting compound within the structural genus of the “A” component of the claims.

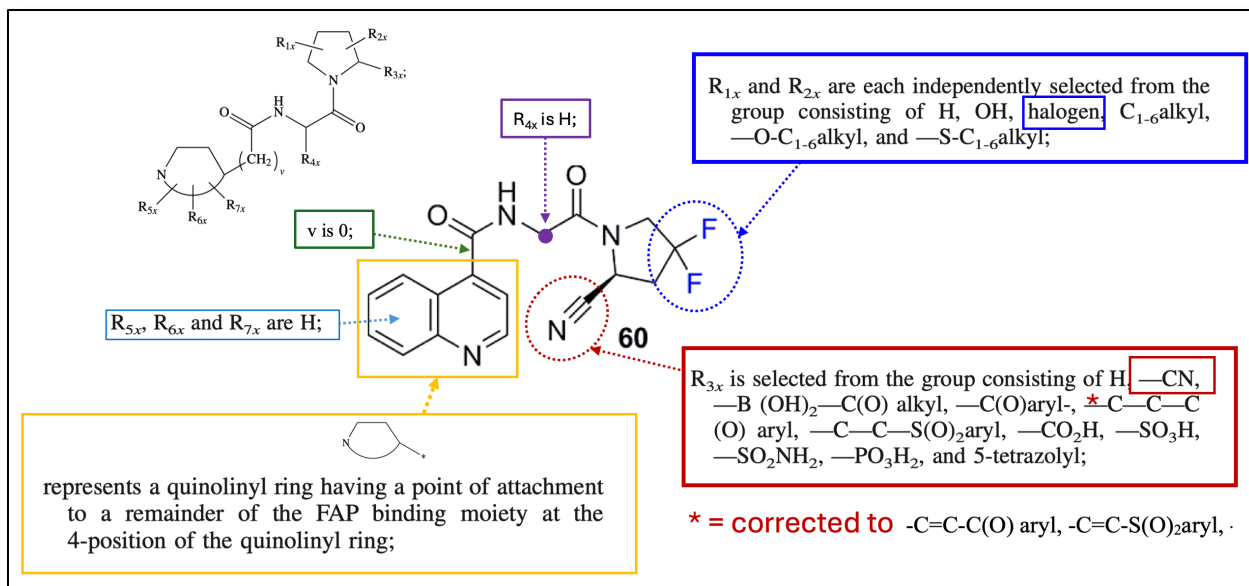
But Jansen (EX1006) did. It showcased “compound 60” in its abstract, identifying it as a potent, highly-selective FAP inhibitor (below). And it

² EX1004 (US-633); EX1005 (US2-121).

highlighted attributes of compound 60 that signaled to the skilled artisan it would be an excellent FAP-targeting moiety for a radiotracer, including its high oral bioavailability and its “potent, long lasting *in vivo* FAP-inhibition.”



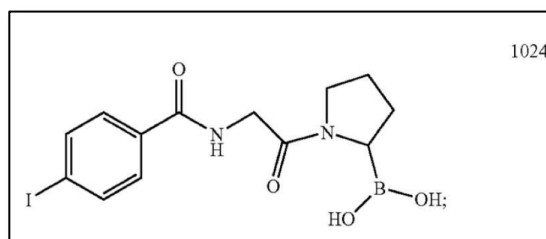
Compound 60 meets *every* requirement of the targeting moiety (“A”) of the claimed compounds (below):



Claims 1 to 4 are unpatentable because they capture compound 60-based FAP-targeting radiotracers that would have been obvious over the prior art.

First, the sole distinction between the claimed compounds and the low-

molecular weight radiopharmaceuticals taught by US-633 is the latter's targeting moiety, which a boronic acid pyrrolidine structure not within the structural genus "A" of the claims (*e.g.*, compound 1024)(below):



In 2015, Meletta (EX1008), after citing US-633, reported that a radiotracer based on compound 1024 was insufficiently selective for FAP, rendering it unsuitable for use in FAP-targeting radiotracers. Meletta also explained that "[f]or future studies *more selective inhibitors are needed* to reduce non-specific tissue accumulation."³ Meletta thus provided a specific motivation for skilled artisans to improve the US-633's radiotracers by finding and using more selective FAP-targeting moieties. So motivated, skilled artisans would have found Jansen's highly FAP-selective Compound 60 and used it to improve the US-633 radiotracers. Claims 1 to 4 are unpatentable because those obvious radiotracers meet every requirement of those claims.

Second, a skilled artisan would have found the radiopharmaceuticals of claims 1-4 obvious based on US-121 (EX1005) with Jansen (EX1006). US-121

³ EX1008, 2089-90.

describes low molecular weight radiotracers targeting PSMA for use in PET and SPECT imaging that employ the same three-component design in claims 1-4, use comparable prior art linkers and radiolabeling moieties, but again have a different targeting moiety (a urea-based structure). By 2017, skilled artisans considered FAP an appealing target for radiopharmaceuticals due to its elevated expression in >90% of epithelial cancers but not normal tissue, which would have motivated skilled persons to adapt proven radiotracer designs (*e.g.*, those in US-121) to produce FAP-targeting radiopharmaceuticals. Such persons, so motivated, would have considered Jansen, and its highly selective, potent FAP-inhibitor compound 60, which also has comparable size to the targeting moiety in the US-121 radiopharmaceuticals. Adapting the US-121 compounds to use compound 60 as its targeting moiety yields compounds meeting every requirement of claims 1-4.

Third, in addition to capturing obvious radiotracers, claims 1 to 4 are neither supported by an adequate written description nor are enabled by the '233 patent disclosure. The narrowest claim captures *more than* 10^{27} distinct “B-L-A” compounds. The specification describes *only two*. Instead of describing other “B-L-A” species to demonstrate possession of the claimed genera, the specification presents laundry lists of options for “B” and “L” moieties that *might be* combined with “A” moieties to yield B-L-A compounds. Those are not descriptions of claimed species. And the disclosure omits many other known B and L moieties

captured by the *functional* definitions used for each.

Certainly, not every possible combination of B, L and A options permitted by the claims will possess the diagnostic or therapeutic utility the patent identifies for the claimed compounds. Because the disclosure does not identify a common structure of the unknown number that do, and does not describe actual B-L-A species representative of the immense structural diversity of the claimed genera, it does not demonstrate possession of the claimed genera.

The disclosure also provides very little guidance to navigate the unpredictable process of determining which B-L-A compounds being claimed have the diagnostic or therapeutic utilities specified by the patent. Consequently, to practice the full scope of the claimed genera, a skilled artisan would need to make and test an immense number of B-L-A compounds, a scale of experimentation is not only undue, it is impossible.

Because each ground demonstrates that claims 1-4 of the '233 Patent are unpatentable, the Board should institute trial.

II. Compliance with PGR Requirements

A. Certification of Standing

Petitioner certifies this Petition for *inter partes* review is filed less than 9 months after issuance of the '233 Patent. Petitioner also certifies it is not barred or estopped from requesting this PGR. Petitioner and its privies have not filed a civil

action challenging the validity of any claim of the '233 Patent. The '233 Patent also is governed by the AIA: its earliest priority date is after March 16, 2013.

B. Mandatory Notices

1. Real Party-in-Interest

GE Healthcare Ltd. (“GE Healthcare”) and Sofie Biosciences, Inc. are the real-parties-in-interest for this Petition.

2. Related Proceedings

IPR2025-00808 and PGR2025-00012 are related proceedings involving U.S. Patent No. 11,938,201, which claims priority and benefit to the same applications to which the '233 patent claims priority and benefit.

3. Counsel and Service Information

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Petitioner consents to service via e-mail at the email addresses listed above.

III. Grounds

The grounds advanced in this Petition are:

- (1) Claims 1-4 would have been obvious under 35 U.S.C. § 103 based on US-633 (EX1004) in view of Jansen (EX1006) and Meletta

(EX1008).

- (2) Claims 1-4 would have been obvious under 35 U.S.C. § 103 based on US-112 (EX1005) in view of Jansen (EX1006).
- (3) Claims 1-4 are unpatentable under 35 U.S.C. § 112(a) as lacking adequate written description.
- (4) Claims 1-4 are unpatentable under 35 U.S.C. § 112(a) as not being enabled.

The grounds are supported by the evidence advanced with this petition, including, *inter alia*, the declaration of Dr. Brian Zeglis (EX1003).

IV. Background on the Patent

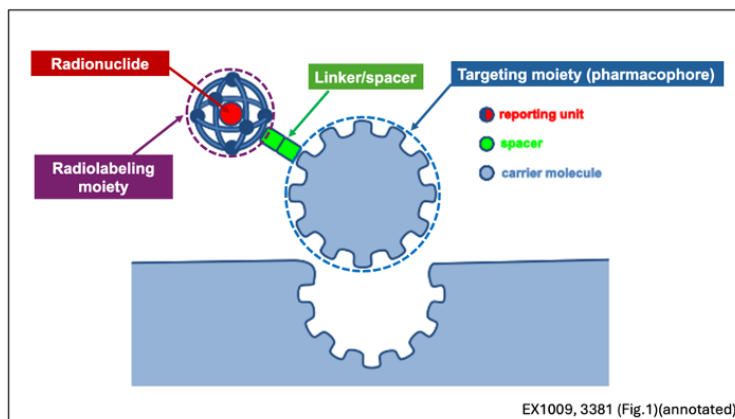
A. Knowledge in the Field of the Patent

The fields of molecular imaging and radiotherapy were advanced by October of 2017. The information below would have been known by skilled artisans before October 2017, and, unless noted otherwise, also as of October of 2018.

1. Radiolabeling and Linker Components of Modular Radiopharmaceuticals Were Well-Known

Radiopharmaceuticals and optical imaging agents that used the modular, three component design in Jamous were well-known by 2017 (below, annotated).⁴

⁴ EX1003, ¶¶ 37-38.



The modular three-component design provides practical benefits, such as being able to readily alter the structure and characteristics of the agent by choosing or replacing different chemical moieties for the individual components.⁵

(a) Targeting Moieties

The targeting moiety facilitates delivery of a radiopharmaceutical to particular cells (target cells) in the patient by binding to a chemical structure on the surface of those cells—selective binding to target cells (instead of normal cells) is critical to ensure accurate delivery of the radiopharmaceutical.⁶ Targeting moieties can be small molecules, peptides or antibodies, but small molecules are most commonly used in radiotracers, as they can more quickly penetrate tissues and are quickly cleared due to their rapid pharmacokinetic profiles.⁷

⁵ EX1003, ¶ 38.

⁶ EX1003, ¶ 39.

⁷ EX1003, ¶ 40; EX1010, 1-3; EX1012, 2859.

(b) *Reporter Moieties*

Reporter moieties enable detection of the agent after it is administered to a patient. For example, a radiolabeling moiety associates a radionuclide (a radioactive form of a metal or halogen) with the agent. Two general classes of radiolabeling moieties were well-known: (i) chelators used with radiometals (*e.g.*, ^{68}Ga , $^{99\text{m}}\text{Tc}$), and (ii) prosthetic groups labeled with radiohalogens (*e.g.*, ^{18}F , ^{123}I).⁸ The purpose of each is to ensure the radionuclide does not dissociate from the radiopharmaceutical before it reaches and accumulates in tissues containing the targeted cells.⁹

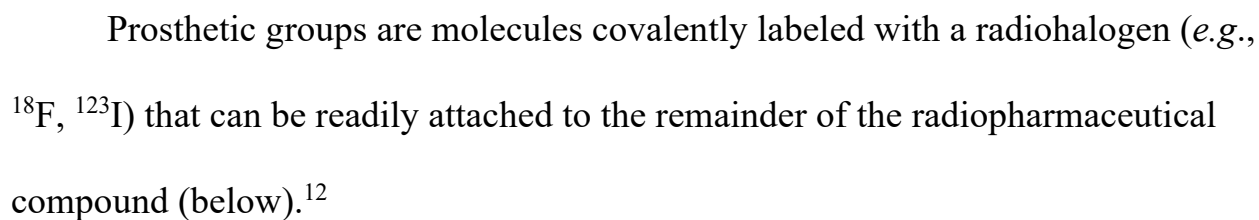
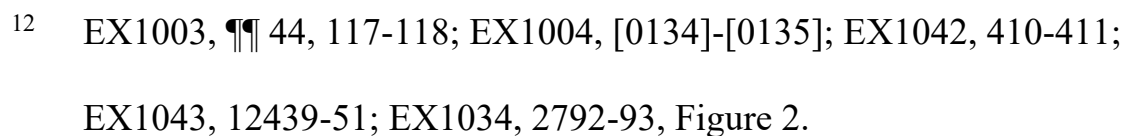
Chelators are molecules that form a stable coordination complex with a selected radiometal; suitable chelators for each radiometal were known.¹⁰ For example, chelators suitable for ^{68}Ga included NOTA, DOTA, HBED, TRAP, PCTA, TACN-TM and DFO (below).¹¹

⁸ EX1003, ¶ 42.

⁹ EX1003, ¶ 41.

¹⁰ EX1003, ¶¶ 42-43; EX1011, 1882; EX1012, 2865, 2869; EX1013, 260-262, 266-269.

¹¹ EX1003, ¶ 116; EX1011, 1882-1883, 1887-1888; EX1013, 267, 272, 275, 276.



(c) *Linkers*

A linker is a chemical moiety that connects the reporter moiety to the targeting moiety. Linkers serve three purposes: (i) they spatially separate the targeting and reporter moieties to avoid impairing the selective binding of the former, (ii) they facilitate the efficient assembly of the agent, and (iii) they can enhance the stability, solubility and other characteristics of the agent.¹³ Linkers use functional groups at either of their termini to form covalent bonds with corresponding functional groups on the targeting and reporter moieties.¹⁴

2. Radionuclides

Radiopharmaceuticals deliver a radioactive element (a radionuclide) to targeted cells, either to kill the cells (therapy) or to enable their detection (nuclear imaging). The particular radionuclide used is dictated by the purpose of the radiopharmaceutical.¹⁵ For radiotracers (radiopharmaceuticals used in nuclear imaging), the radionuclide must (i) work with the imaging device (*e.g.*, a PET or SPECT scanner) and (ii) have a half-life compatible with the half-life of the

¹³ EX1003, ¶¶ 45-46.

¹⁴ EX1003, ¶ 47.

¹⁵ EX1003, ¶ 48.

radiopharmaceutical in the body.¹⁶ Common radionuclides used in PET and SPECT imaging are shown below, along with their half-lives.¹⁷

	Isotope	Type	Emission	Half-Life
S P E C T	^{99m} Tc	Metal	Gamma	6.0 h
	¹⁸⁸ Re	Metal	Gamma	16.9 h
	¹²³ I	Halogen	Gamma	13.2 h
	¹¹¹ In	Metal	Gamma	67.2 h
	⁶⁷ Ga	Metal	Gamma	78.3 h
P E T	⁶⁸ Ga	Metal	Positron	1.1 h
	¹⁸ F	Halogen	Positron	109 min
	⁶⁴ Cu	Metal	Positron	12.7 h
	⁸⁶ Y	Metal	Positron	14.7 h
	⁸⁹ Zr	Metal	Positron	78.4 h
	¹²⁴ I	Halogen	Positron	100.3 h

3. Fibroblast Activation Protein (FAP)

FAP is a member of a family of enzymes called prolyl oligopeptidases (below), which selectively cleave peptide bonds after proline residues.¹⁸

¹⁶ EX1003, ¶¶ 49-51.

¹⁷ EX1003, ¶ 49; EX1010, 3, Table 2 (⁶⁸Ga and ⁸⁹Zr), Table 1 (¹⁸F and ¹²⁴I); EX1034, 2795 (^{99m}Tc); EX1012, 2860, Table 2 (⁶⁴Cu), Table 1 (⁶⁷Ga); EX1013, 262, Table 1 (¹¹¹In).

¹⁸ EX1003, ¶¶ 66-67; EX1006, 3053; EX1016, 259 (Table 1); EX1024, 454.

Table 1. Characteristics of known post-prolyl peptidases

Prolyl peptidase	Enzymatic activity	Cellular localization	References
DPPIV	Dipeptidase	Membrane	(25, 36–38)
FAP	Dipeptidase/endopeptidase	Membrane	(25, 36, 38)
DPP6	Inactive	Membrane (K_v^+ channel)	(25, 37)
DPP8	Dipeptidase	Cytoplasm	(25, 37, 38)
DPP9	Dipeptidase	Cytoplasm	(25, 37, 38)
DPP10	Inactive	Membrane (K_v^+ channel)	(25, 37)
AAP	Acylpeptide hydrolase	Cytoplasm	(38, 39)
POP	Prolyl oligopeptidase	Cytoplasm	(38)
DPPII (DPP7)	Dipeptidase	Intracellular vesicles	(37, 38)
PCP	Prolyl carboxypeptidase	Lysosome	(38)

Unlike other members of this protein family (*e.g.*, PREP/POP), FAP expression is limited in normal cells but elevated in cancer associated fibroblasts (CAFs) and certain diseases associated with activated stroma.¹⁹ “FAP is [] highly expressed on activated fibroblasts in over 90% of common human epithelial tumors” and has been linked to a variety of cancers.²⁰

Before 2017, several publications had identified FAP as a compelling target for radiopharmaceuticals, particularly radiotracers used in nuclear imaging of tumors.²¹ A 2011 publication observed:

Due to the highly restricted and specific expression of FAP, particularly within tumor stroma, FAP is *clinically interesting as a*

¹⁹ EX1003, ¶ 68; EX1022, 124; EX1024, 456; EX1023, 288; EX1041, 2

²⁰ EX1006, 3053; EX1022, 124; EX1024, 456; EX1016, 260.

²¹ EX1003, ¶ 69; EX1046, 26. *Also* EX1024, 454, 455; EX1022, 124; EX1045, 2427; EX1016, 264.

target for immunotherapy in the treatment of cancer and *non-invasive bio-imaging*. ... It appears that *FAP shows more promise as a biomarker and target for non-invasive imaging of tumours* or for use as site-directed targeted cancer radiotherapy.²²

FAP's unique profile also induced skilled artisans to discover small molecules that selectively inhibited the enzymatic activity of FAP ("FAP inhibitors"), including one designated "compound 60" reported in Jansen (EX1006).²³

B. Person of Ordinary Skill in the Art

A person of ordinary skill in the art ("a skilled artisan") would have had (i) an undergraduate and Ph.D. degrees in chemistry, biochemistry, medicinal chemistry or comparable fields and (ii) familiarity with chemical synthesis methods (including organic synthesis, radiometal chelation and radiohalogen labeling of prosthetic groups), assessment of cellular targets for radiopharmaceuticals, and other techniques relevant to the design, development, testing and/or evaluation of radiopharmaceuticals. The person would also be familiar with how radiopharmaceuticals are distributed and used in patients to perform therapy or imaging of diseases, including cancer.²⁴

²² EX1046, 26.

²³ EX1003, ¶ 71, 144-146; EX1006, 3053.

²⁴ EX1003, ¶¶ 12-14-15.

C. Prosecution History

The '233 Patent was issued without no rejections. The Examiner credited the high FAP-specificity of the compounds in her reasons for allowance.²⁵

D. The Challenged Claims

The '233 Patent has four claims (below).²⁶

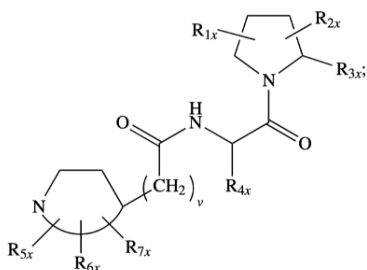
1. A low molecular weight compound of Formula (I):

B-L-A

(I)

wherein:

A is a targeting moiety for FAP- α , wherein A has the structure of:



(X)

wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

R_{3x} is selected from the group consisting of H, $-CN$, $-B(OH)_2-C(O)$ alkyl, $-C(O)$ aryl-, $-C-C-C(O)$ aryl, $-C-C-S(O)_2$ aryl, $-CO_2H$, $-SO_3H$, $-SO_2NH_2$, $-PO_3H_2$, and 5-tetrazolyl;

R_{4x} is H;

R_{5x} , R_{6x} and R_{7x} are H;

v is 0; and



represents a quinolinyne ring having a point of attachment to a remainder of the FAP binding moiety at the 4-position of the quinolinyne ring;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.

2. The compound of claim 1, wherein R_{1x} and R_{2x} are each independently selected from the group consisting of H and F.

3. The compound of claim 2, wherein R_{3x} is $-CN$.

4. The compound of claim 3, wherein B comprises a chelating agent.

²⁵ EX1002, 213.

²⁶ EX1001 contains the certificate of correction with corrected claim 1.

EX1002, 502-504.

E. Claim Scope and Construction of Terms

The terms in the claims generally employ objective language that requires no special construction. Two terms (*i.e.*, components “B” and “L”) warrant observations to illustrate their breadth. Also, while the phrase “low molecular weight compound” may be disputed, it is inconsequential to the grounds, which show (i) radiopharmaceuticals with a comparable size to those exemplified in the disclosure would have been obvious over the prior art, and (ii) the term does not alter the scale of the genera being claimed. Petitioner nonetheless addresses the meaning of this term that is conveyed by the intrinsic evidence.

1. Radiolabeling Moiety (“B”) and Linker (“L”) Components Are Defined in Functional Terms

Claims 1 to 4 use functional language (below) to define the “B” and “L” components of the claimed compounds.²⁷

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

Each identifies only the *purpose* of the component in the compound:

- The “B” component (*i.e.*, the radiolabeling moiety) is “any optical or

²⁷ EX1001, 64:48-53.

radiolabeled functional group *suitable for optical imaging, ... (PET) imaging, ... (SPECT) imaging, or radiotherapy.*”

- The “L” component (*i.e.*, the linker) must have “bi-functionalization adapted *to form a chemical bond with B and A.*”

The unambiguous claim language precludes limiting the “B” or “L” components to any particular chemical structures for each component.

The specification reinforces this conclusion. Regarding radiolabeling moieties (“B”), it reiterates the functional definition in the claims,²⁸ and then identifies three broad classes of “B” compounds: (i) “radiolabeled prosthetic groups comprising a radioisotope” (*e.g.*, ¹⁸F, ¹²³I), (ii) “chelating agent[s]” and (iii) an “optical dye.”²⁹ The specification illustrates each class with (known) examples, but repeatedly emphasizes B compounds “*are not limited to*” to those examples.³⁰

Regarding linkers (“L”), the specification repeats the “bi-functionalization” attribute from the claims,³¹ but does not define linkers as requiring use of any structural attributes (*i.e.*, there are no minimum or maximum size parameters, or

²⁸ EX1001, 1:65-2:5.

²⁹ EX1001, 17:55-18:34, 18:35-19:7, 25:18-29:52.

³⁰ EX1001, 17:57-59, 19:8-11, 26:25; EX1003, ¶ 75.

³¹ EX1001, 2:3-5, 8:24-25.

restrictions/requirements on the makeup of the chemical moiety). And while the specification states that “[s]uitable linkers are disclosed in” two published U.S. applications (including US-121), neither identifies any required *structural* attributes of linkers.³² There was no substantive prosecution history, and thus no basis for altering the definitions in the claim language and specification.

2. “Low Molecular Weight”

While it is theoretically possible the phrase “low molecular weight” might exclude some combination of a targeting moiety (“A”), radiolabeling moiety (“B”) and a linker (“L”), that theoretical possibility is irrelevant to the present grounds.

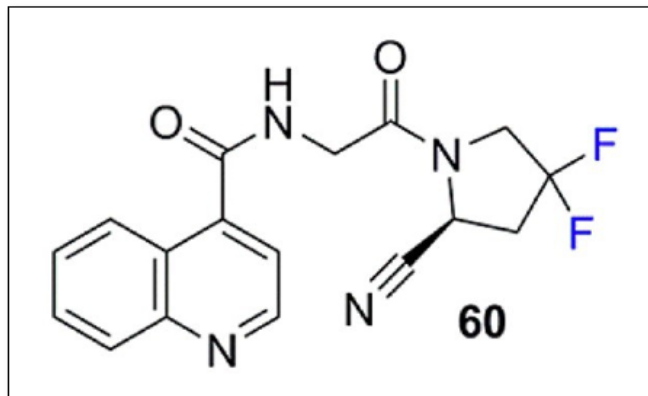
First, the obviousness grounds demonstrate that particular radiopharmaceutical compounds with the FAP-targeting small molecule designated “compound 60” in Jansen (EX1006) would have been obvious. Compound 60 (below, left) is *identical* to one of the “A” structures exemplified in the specification (below, right).³³ The illustrative obvious compounds used in the grounds are “low molecular weight” compounds for the same reasons the examples in the ’233 Patent are, and have molecular weights below or near 1500 Da,³⁴ the

³² EX1001, 17:46-54 (citing US2011/0064657) and US-121(EX1005)).

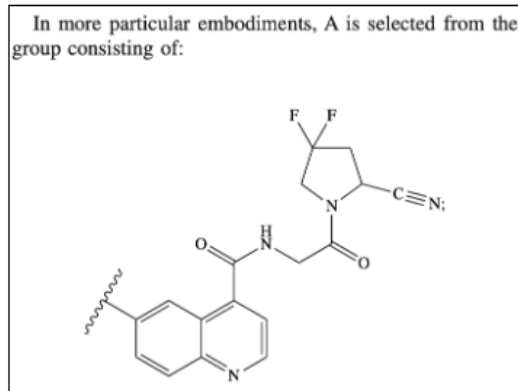
³³ EX1006, 3053; EX1001, 13:33-14:16.

³⁴ See §§ V.G, VI.D.

(arbitrary) weight limit chosen by Dr. Pomper (an inventor) in a declaration he submitted during examination.³⁵



EX1006 (Jansen), 3053



EX1001, 13:33-49

Second, the § 112(a) grounds rest on the pronounced discrepancy between the extreme breadth of the claims and the paucity of the disclosure, which is unaffected by the construction of “low molecular weight.”

If the Board finds it necessary to construe “low molecular weight,” Petitioner submits the intrinsic evidence demonstrates it means “*having a molecular weight at least an order of magnitude less than an antibody-based radiopharmaceutical.*”

Only one phrase in the specification informs the meaning of “low molecular

³⁵ EX1002, 169 (¶17).

weight.”³⁶ In it, “low molecular weight (LMW) agents” are distinguished from anti-FAP antibodies based on their behavior *in vivo*, ease of synthesis and ability to get approved by the FDA (below).³⁷

man, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date,

Named inventor Dr. Pomper cited some of these factors when he distinguished “low molecular weight” compounds from antibodies (~150,000 Da) and anti-FAP “iBody”-HMPA compound of comparable size (~149,000 Da) (below):³⁸

³⁶ The second passage (EX1001, 7:46-54) observes that “low-molecular-weight ligands of FAP- α ” can be conjugated to other components of radiopharmaceuticals and used for *in vivo* imaging.

³⁷ EX1001, 1:53-61.

³⁸ EX1002, 167-168 (¶¶ 10, 13-14).

10. Claim 29 is amended and further defines the compound of formula (I) as being “low molecular weight” (“LMW”). I distinguish the LMW compound of the pending claims from large molecule imaging agents containing anti-FAP moieties. In particular, I characterize large molecule imaging agents as having numerous disadvantages, including pharmacokinetic limitations, including slow blood and non-target tissue clearance and non-specific organ uptake. Page 1, lines 28-34; page 2, lines 1-7. In contrast, the LMW imaging agents of the instant application possess numerous advantages compared with the large molecule imaging agents. *Id.* Specifically, LMW imaging agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. *Id.* They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval.

11. I distinguish between the LMW compounds of the pending claims and larger biologic compounds such as antibodies and high relative molecule mass polymers, as cited below.

The specification and file history thus distinguish “low molecular weight” compounds from antibodies and similarly-sized compounds by their attributes associated with their pronounced size compared to small molecule agents, not with a precise molecular weight boundary.³⁹

Despite this, Dr. Pomper contended the meaning of “low molecular weight compound” was “well accepted in the chemical arts” and was “a molecular weight from about 50 Daltons to about 1,500 Daltons.”⁴⁰ But the basis of this opinion was

³⁹ EX1003, ¶¶80-81, 83.

⁴⁰ EX1002, 169 (¶ 17)

not the specification—it was *extrinsic* evidence (*i.e.*, scientific publications).⁴¹

Other literature attributes the same benefits the specification associates with “low molecular weight” compounds to peptide-based radiotracers up to **3500** Da.⁴² A precise molecular weight boundary also was unnecessary to overcome rejections in a related patent—it was the selectivity of targeting moiety, which the Examiner did not appreciate was already known in the prior art.⁴³

Under established principles of claim construction, extrinsic evidence cannot displace the meaning of a term conveyed by the specification. Here, nothing in the specification supports construing “low molecular weight” to mean *only* compounds weighing between 50 Da and 1500 Da. In fact, picking allowed components per the parameters of the disclosure yields “B-L-A” compounds above 1500 Da.⁴⁴

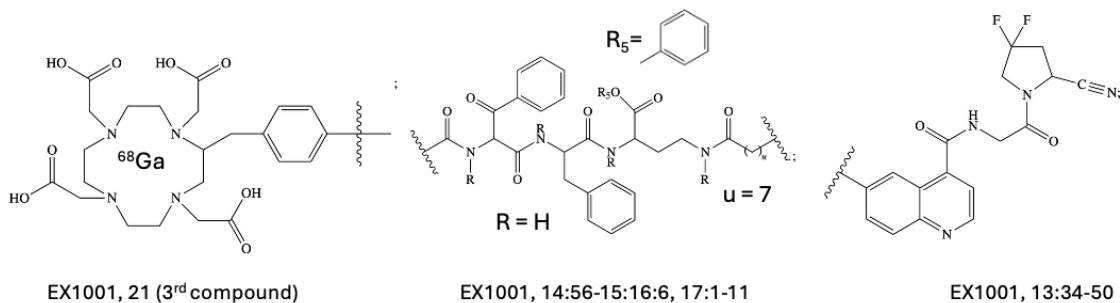
⁴¹ *Id.*

⁴² EX1052, 59-60; EX1003, ¶ 81.

⁴³ EX1002, 171 (¶ 27); EX1054, 442 (suggesting “quinolinyl compounds of the instant claims” have much higher selectivity than “other small molecule FAP inhibitors found in the prior art.”).

⁴⁴ EX1001, 13:33-50, 14:56-16:14, 17:9-20.

561.464	+	653.756	+	344	=	1559.22
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Likewise, small molecule compounds with molecular weights above 1500 Da (*e.g.*, 1,700 Da) can “demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration” and “can be synthesized in radiolabeled form more easily.”⁴⁵

The intrinsic evidence thus does nothing more than distinguish the *magnitude* of the molecular weight of “low-molecular-weight” compounds relative to antibody-sized compounds that are orders of magnitude larger.⁴⁶

V. Ground 1: Claims 1-4 Are Obvious Based on US-633, Meletta and Jansen

Claims 1 to 4 of the '233 Patent differ from US-633 in only one respect: the identity of the targeting moiety (“A”). The other two components of the claimed compounds—“B” and “L”—are defined functionally, and as such, capture prior art

⁴⁵ EX1001, 1:54-59; EX1003, ¶¶ 164, 83.

⁴⁶ EX1003, ¶ 83.

targeting moieties and linkers, including those that US-633 teaches use of in FAP-targeting radiopharmaceuticals.

A finding of obviousness under § 103 requires an articulated reasoning with a rational underpinning as to why the claimed invention would have been obvious.⁴⁷ Here that reason is documented in the literature, and concerns the sole distinction between the claims and US-633 (*i.e.*, the targeting moiety of the US-633 FAP-targeting radiopharmaceuticals). Specifically, Meletta (EX1008) reported that the boronic acid pyrrolidine targeting moiety in compounds disclosed in US-633 was insufficiently selective for FAP, and identified a need for more selective targeting moieties for FAP-targeting radiopharmaceuticals.⁴⁸

Prompted by Meletta and a general motivation to discover and use more selective FAP inhibitors in radiotracers than those used in US-633, a skilled artisan would have found Jansen (EX1006). The collective teachings of US-633, Meletta and Jansen, in turn, would have made it obvious to improve the radiopharmaceuticals taught in US-633 by incorporating Jansen's highly selective FAP inhibitor (compound 60) as the targeting moiety, thus solving the problem

⁴⁷ *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 418.

⁴⁸ EX1008, 2089, 2090 (“For future studies more selective inhibitors are needed to reduce non-specific tissue accumulation.”)

Meletta identified. Before October of 2017, Claims 1 to 4 would have been obvious over US-633, Jansen and Meletta, and are unpatentable.

A. Teachings of the Prior Art

1. US-633

US-633 is a published U.S. application dated April 22, 2010. It describes a class of small molecule radiopharmaceuticals that target “seprase” (FAP), and explains they can be used in diagnostic imaging and radiotherapy of tumors and tissues that express FAP.⁴⁹

[0002] This invention relates in general to small molecule inhibitors of seprase that can be used as therapeutic agents through inhibition of seprase’s enzymatic activity, or as radiopharmaceuticals that bind to seprase and therefore enable imaging of tissues that express seprase or for delivering radiotherapy to tumor tissues that express seprase.

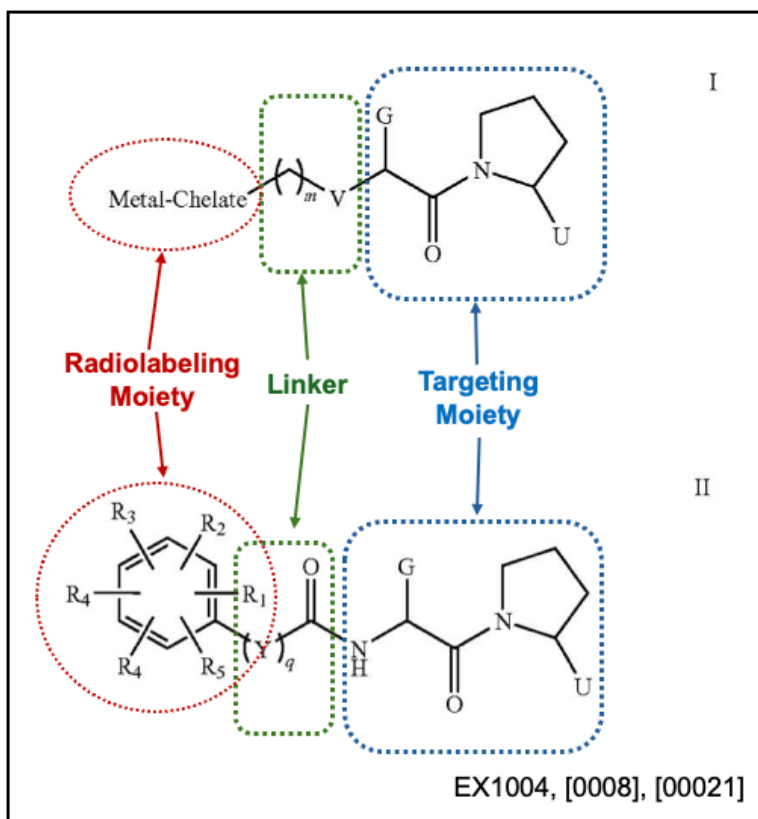
[0007] Small molecule inhibitors of seprase are provided for use as therapeutic medicines or as radiopharmaceuticals useful in diagnostic imaging and in the therapeutic treatment of diseases characterized by overexpression of seprase. The radiopharmaceuticals include complexes or compounds that

(a) Modular Three-Component Radiopharmaceuticals

US-633 describes two types of FAP-targeting radiopharmaceuticals, each employing the same modular, three-component design as the claimed compounds:

⁴⁹ EX1004, [0002], [0007].

(i) a targeting moiety connected via (ii) a “tether” (a linker) to (iii) a radiolabeling moiety (below).⁵⁰ One uses a chelator as the radiolabeling group (Formula I); the other uses a prosthetic group (Formula II).



The skilled artisan would have recognized that because Formulas I and II employ a modular design, different linkers, targeting and radiolabeling moieties could be used in the compounds.⁵¹ US-633 also illustrates several options for the radiolabeling moiety and linker components in each of Formulas I and II.

⁵⁰ EX1004, [0008], [0021]; EX1003, ¶¶ 105-106.

⁵¹ EX1003, ¶ 38, 105, 124.

(b) *Imaging Platforms and Radionuclides*

US-633 describes use of radionuclides with its radiotracers that are “capable of generating a detectable image that can be detected either by the naked eye or using an appropriate instrument, *e.g.* positron emission tomography (PET) and single photon emission computed tomography (SPECT).”⁵² It lists several radiometals (*e.g.*, ⁶⁸Ga, ^{99m}Tc) and radiohalogens (*e.g.*, ¹⁸F, ¹²³I).⁵³ A skilled artisan would have known that PET scanners require a positron-emitting radionuclide (*e.g.*, ⁶⁸Ga or ¹⁸F), while SPECT scanners require a gamma-emitting radionuclide (*e.g.*, ^{99m}Tc, ¹²³I).⁵⁴

(c) *Chelator and Prosthetic Group Radiolabeling Moieties*

US-633 describes using radiolabeling moieties with two alternative chemical structures with radionuclides suitable for either PET or SPECT imaging (below).⁵⁵ Formula I compounds use chelators while Formula II compounds use prosthetic

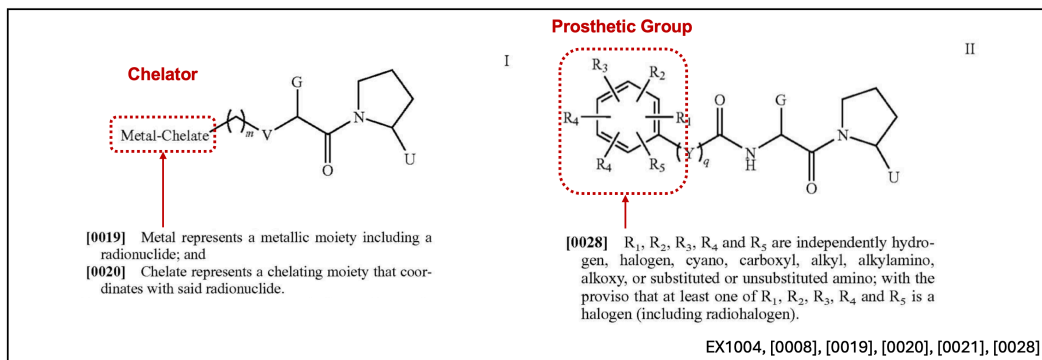
⁵² EX1004, [0049].

⁵³ *Id.*

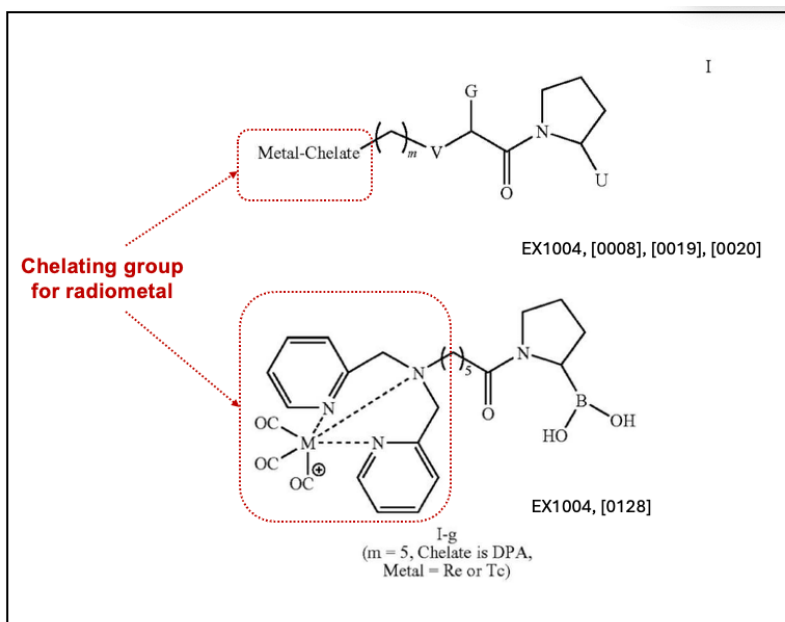
⁵⁴ EX1003, ¶ 49; EX1010, 1, 4; EX1012, 2859; EX1013, 260.

⁵⁵ EX1004, [0008], [0019]-[0020] (chelator), [0021],[0028] (prosthetic group), [0049].

groups.⁵⁶



US-633 describes examples of chelators (illustrated below), which form stable coordinated complexes with a radiometal.⁵⁷



⁵⁶ EX1003, ¶¶ 111, 117; EX1004, [0008], [0019], [0020], [0021], [0111], [0128], [0175]; EX1003, ¶ 116.

⁵⁷ EX1004, [0008], [0019], [0020], [0128]; *also id.*, [0087], [0097], [0098], [0101]-[0110]; EX1003, ¶¶ 117, 65.

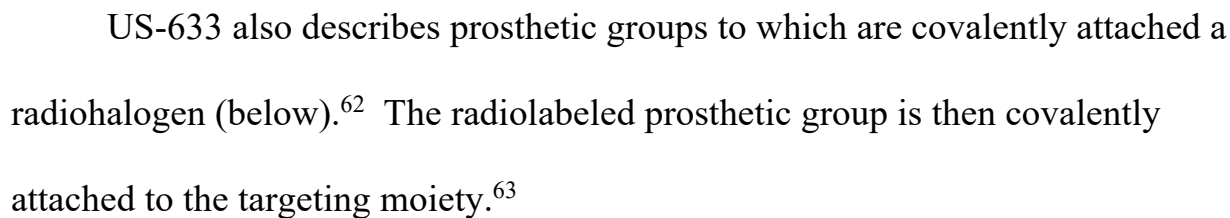
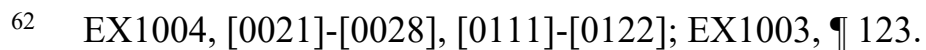
Numerous examples of each type of radiolabeling moiety are taught by US-633. For example, US-633 lists several classes and examples of metal chelators, including DOTA, DPA, DTPA, PAMA.⁵⁸ US-633 also explains that “[a]ny suitable chelating moiety may be used to provide a covalent or other association with a radionuclide.”⁵⁹ A skilled artisan would have understood this to mean that any known chelator could be used if it was suitable for the particular radionuclide being used with the radiotracer.⁶⁰ By 2017, a skilled artisan would have known that DOTA, NOTA, HBED, TRAP, PCTA, TACN-TM and DFO (below) had been successfully used to form stable coordination complexes with ⁶⁸Ga.⁶¹

⁵⁸ EX1004, [0048], [0100]-[0110], Table 4.

⁵⁹ EX1004, [0100], Tables 3, 4.

⁶⁰ EX1003, ¶ 115.

⁶¹ EX1003, ¶¶ 116, 42; EX1011, 1882-83, 1887-88; EX1013, 267, 272, 275, 276.

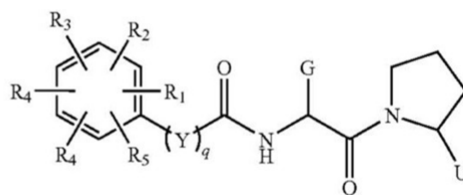


⁶³ EX1003, ¶ 124; EX1004 (US-633), [0134]-[0135].

US-633 also describes covalently attaching radiohalogens at various positions on a phenyl ring included in the radiotracer.⁶⁴

[0021] In another aspect, a compound of general Formula II, its enantiomer, stereoisomer, racemate or pharmaceutically acceptable salt is provided:

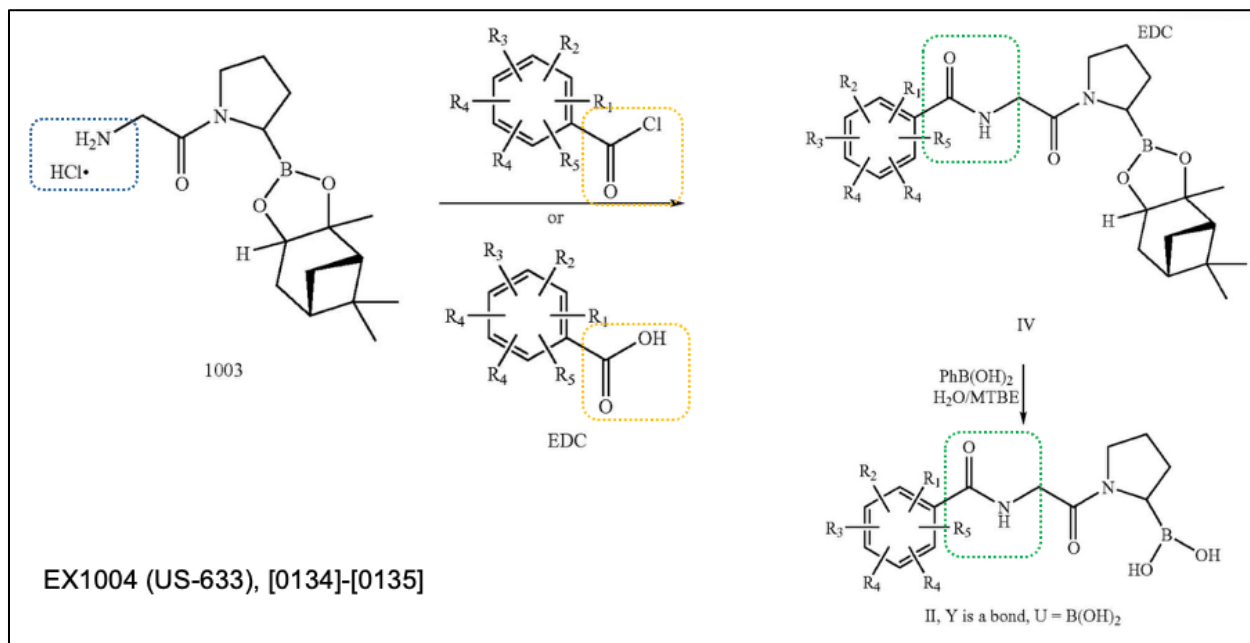
[0028] R_1 , R_2 , R_3 , R_4 and R_5 are independently hydrogen, halogen, cyano, carboxyl, alkyl, alkylamino, alkoxy, or substituted or unsubstituted amino; with the proviso that at least one of R_1 , R_2 , R_3 , R_4 and R_5 is a halogen (including radiohalogen).



II

EX1004, [0021]-[0028]

It also illustrates conventional synthetic schemes for attaching a radiolabeled prosthetic group to the remainder of the radiotracer. In it, a radiolabeled benzoic acid is reacted with a functionalized targeting moiety to form an amide bond.⁶⁵



⁶⁴ EX1004, [0021]-[0028], [0111]-[0123], [0173]-[0176].

⁶⁵ EX1004, [0135]; EX1003, ¶ 118.

By 2017, a skilled artisan would have known of other prosthetic groups that could be radiolabeled with ^{18}F or ^{123}I and included in radiotracers being described in US-633.⁶⁶ That person also would have been familiar with efficient techniques for incorporating the radionuclide into the prosthetic group (*e.g.*, “click chemistry” techniques).⁶⁷

A skilled artisan would have known to select a chelating structure that is suitable for the particular radiometal (*e.g.*, ^{68}Ga or $^{99\text{m}}\text{Tc}$), or to use a prosthetic group that can be labeled with an appropriate radiohalogen (*e.g.*, ^{18}F or ^{123}I).⁶⁸

Any of the chelator or prosthetic groups described in US-633, when complexed with or covalently attached to a suitable radiometal or radionuclide, respectively, satisfy the “radiolabeled functional group...” element (“B”) of the claims. Likewise, any of the chelators or prosthetic groups known by 2017, when combined with a particular radionuclide for which it was known to be suitable, would meet the “B” element of the claims.

(d) Linkers (“Tethers”)

US-633 describes using a “tether” (a linker) to connect the “functionalized

⁶⁶ EX1003, ¶ 119; EX1034, 2792-95; EX1019, 475-476.

⁶⁷ EX1003, ¶¶ 63-64; EX1015, 202-3; EX1021, 1-2, 6-12.

⁶⁸ EX1003, ¶¶ 43-44, 115, 119.

proline” targeting moiety to a radiolabeling moiety.⁶⁹ It explains that attributes of “tethers” can be altered to vary the distance between the targeting moiety and the radiolabeling moiety and/or alter the pharmacokinetic characteristics of the radiopharmaceutical.⁷⁰ For example it teaches incorporation of heteroatoms to influence the pharmacokinetics of the overall compound.

[0101] The distance between the Metal-Chelate moiety and the pyrrolidine moiety of the complex represented by Formula I can be varied by altering the tether and/or expanding the length of the tether between them to modify the affinity and selectivity of the complex for seprase. The pharmacokinetic properties of the complex may also be modified by incorporating heteroatoms into the tethers. The following structures represented by Formulas I-a to I-k are some exemplary embodiments with different tethers and/or the length of tethers. To facilitate description, the complexes are described below with embodiments where the Metal-Chelate moiety has the following structure:

US-633 also describes a variety of examples of tethers, or components of tethers. It lists, for example, representative chemical moieties, including simple alkyl chains, polyethylene glycol (“PEG”) and polyethylamine oligomers, terminal alkanolic acids, including amino-PEG and carboxylic acid PEG moieties, and amino acids (*e.g.*, glycine and lysine), being used in tethers.⁷¹

⁶⁹ EX1004, [0005], [0051]; EX1003, ¶¶ 120.

⁷⁰ EX1004, [0101], [0133]; EX1003, ¶ 121.

⁷¹ EX1004, [0130], [0131].

[0130] Scheme 3 can be utilized to synthesize functionalized proline- $M^+(CO)_3$ complexes to explore the effect of more significant variations of the distance of the metal chelator from the proline moiety by incorporating a tether into these structures. The tether may comprise a simple alkyl chain as shown, a PEG $(CH_2CH_2O)_n$, a polyethylene amine $((CH_2CH_2NH)_n)$, or the like. Terminal aminoalkanoic acids (such as β -alanine, 4-aminobutanoic acid, 5-aminopentanoic acid, 6-aminohexanoic acid and the 8-aminooctanoic acid) or amino-PEG-acids $(NH_2-(CH_2CH_2O)_n-CH_2-COOH)$, e.g. 2-(2-(3-aminopropoxy)ethoxy)acetic acid) may be utilized as tethers, according to some embodiments.

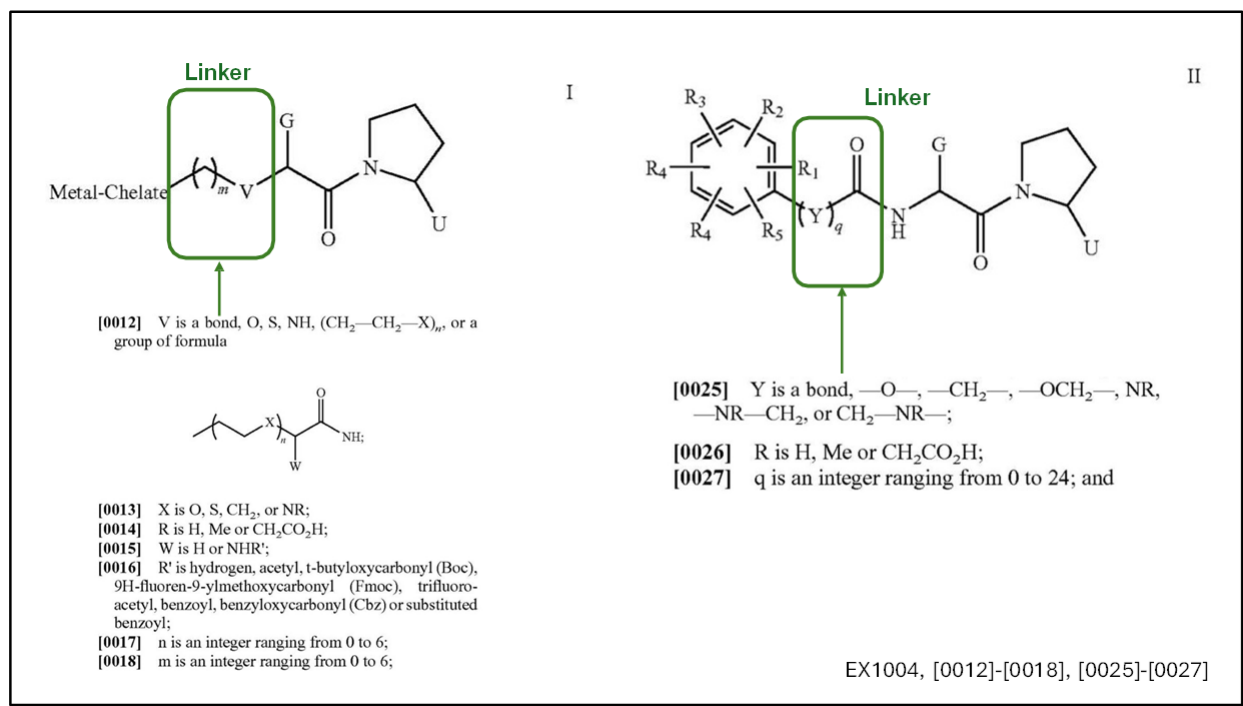
US-633 explains that commercially available polyethylene glycol compounds (*e.g.*, PEG-diamines) “can be readily incorporated” into radiotracer compounds.⁷² It identifies practical benefits of using PEG compounds, which were commercially available in varying lengths and characteristics (*e.g.*, different functionalization of the termini of the PEG oligomer).⁷³

[0133] The above reaction scheme is applicable to any modification of the tether by incorporation of heteroatoms into the tether chain. This may have additional benefits on the affinity as well as the selectivity for seprase. Incorporation of heteroatoms into the tether such as oxygen can take advantage of the commercial availability of a variety of short polyethylene glycol (PEG) diamines that can be readily incorporated into the complexes. One of ordinary skilled in the art would also readily apply other chelates to prepare functionalized proline- $M^+(CO)_3$ complexes.

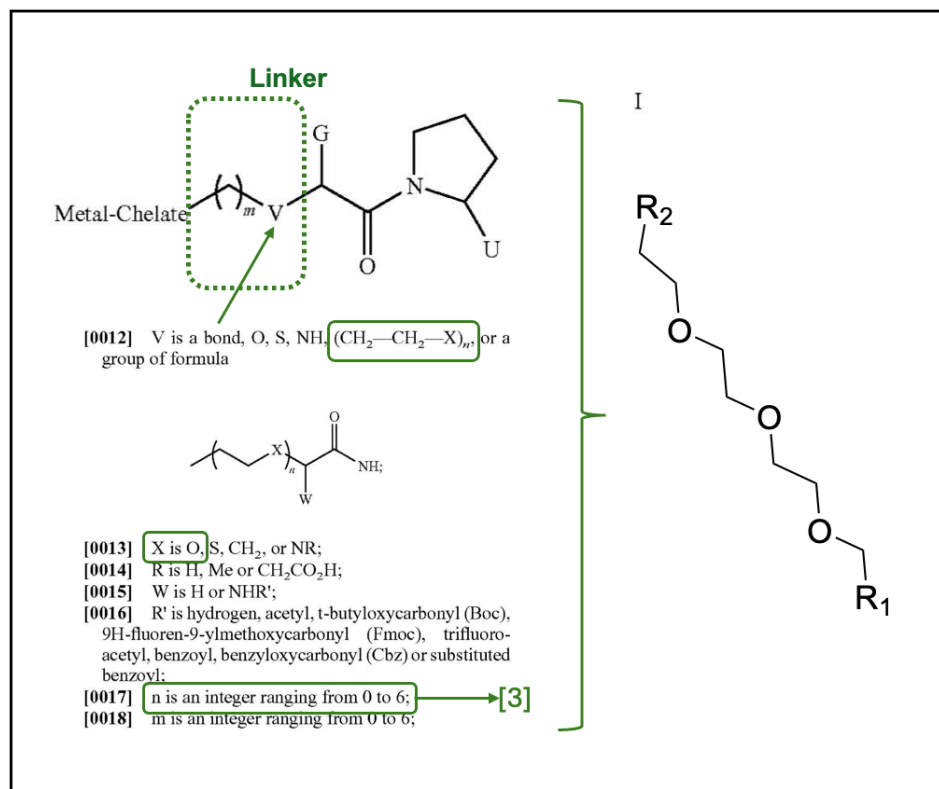
⁷² EX1004, [0133]; EX1003, ¶ 122.

⁷³ EX1003, ¶¶ 128, 186.

US-633 describes via formulae of radiopharmaceuticals with tethers positioned between the chelator/prosthetic and targeting moieties, as well as tethers with varying chemical characteristics pursuant to the parameters of formulae, one of which is a 3-monomer PEG linker (*i.e.*, “V”=“CH₂—CH₂—X), X=“O” and “n”=3, R₁ and R₂ representing functional groups)(annotated figures below).⁷⁴



⁷⁴ EX1003, ¶ 185-186.



US-633 also describes tethers that have formed one chemical bond with a radiolabeling moiety and a second chemical bond with a targeting moiety—these tethers have “bi-functionalization” as both of their termini have groups (*e.g.*, -OH, -CO₂H, -NH₂, -SH) that enable formation of covalent bonds with each of the targeting and radiolabeling moieties.⁷⁵

Before 2017, a skilled artisan would have understood from the guidance in US-633 about tethers, and from their own knowledge and experience, that there are practical benefits of using PEG-based “tethers” in radiotracers, such as that many

⁷⁵ EX1004, [0128], [0130], [0132]-[0133]; EX1003, ¶¶ 126-127.

different PEG compounds of varying length and having different types of functionalization at their termini could be purchased.⁷⁶ That person likewise would have been familiar with the chemical attributes, selection and use of “tethers” (linkers) that are illustrated and exemplified throughout US-633 and would know how to use different linkers to form the types of radiotracer compounds being described in US-633.⁷⁷

The linkers described and suggested by US-633 are examples of “L” components in the claimed compounds.

(e) Boronic Acid Pyrrolidine Targeting Moiety

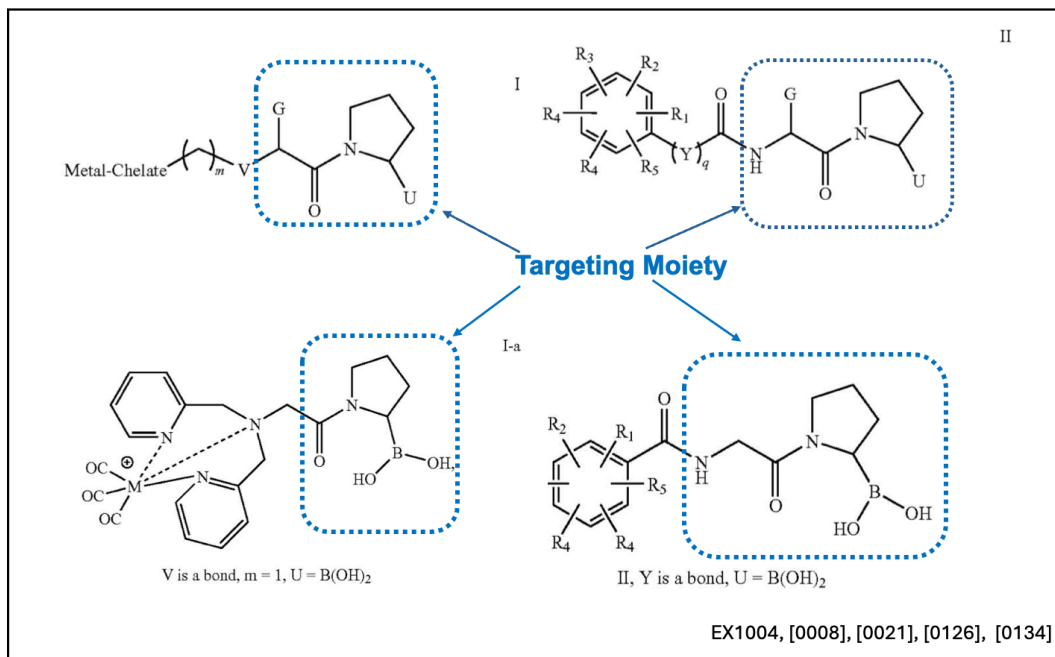
Both Formulae in US-633 use as their targeting moiety a “functionalized proline moiety capable of selectively inhibiting seprase” (*i.e.*, FAP).⁷⁸ US-633 illustrates use of a particular boronic acid pyrrolidine moiety as the FAP-targeting moiety in most of its examples (*i.e.*, where “U” is boronic acid (below)).⁷⁹

⁷⁶ EX1003, ¶¶ 128, 192.

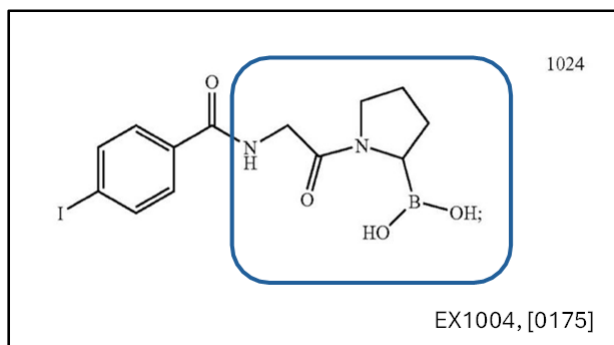
⁷⁷ EX1003, ¶¶ 45-47, 122-123, 185.

⁷⁸ EX1004, [0007].

⁷⁹ EX1004, [0008], [0021], [0126], [0134].



This targeting moiety is also used in compound 1024 (below).



While the targeting moieties used in US-633 are “a targeting moiety for FAP- α ,” they do not meet the structural requirements for the “A” component of the claimed compounds.

(f) US-633 Describes Examples of Compounds Based on its Targeting Moieties

US-633 describes examples of compounds that combine a boronic acid pyrrolidine FAP-targeting moiety with different combinations of linkers and

radiolabeling groups.⁸⁰ The various combinations of linkers and radiolabeling groups in these examples illustrate what a skilled artisan would have contemplated as possible radiopharmaceutical designs that could be used once a suitable targeting moiety had been identified.⁸¹

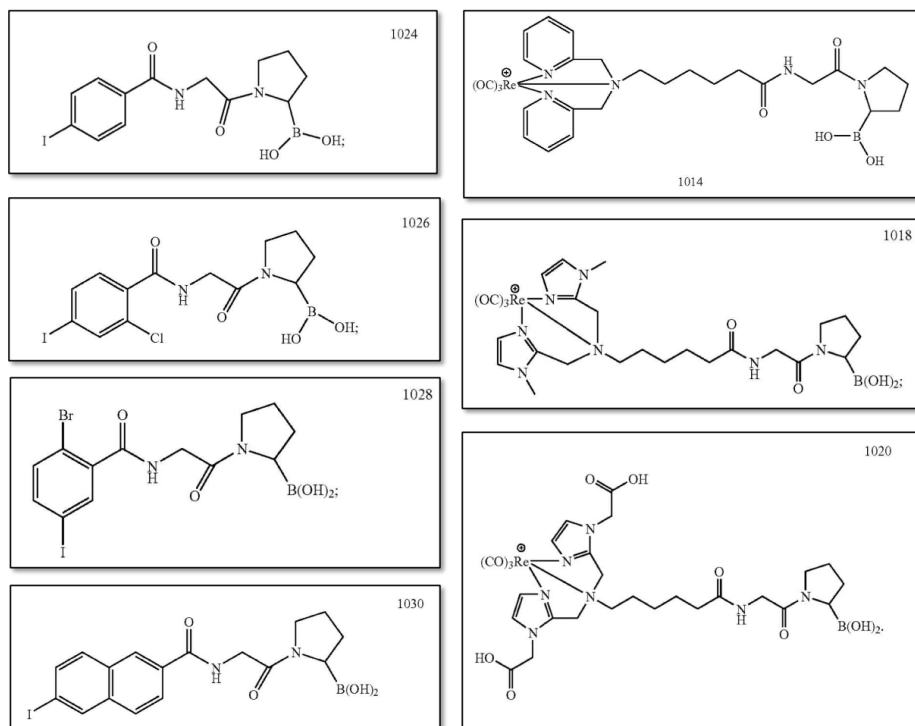
US-633 reports in Table 2 the potency of each example compound's inhibition of FAP (*i.e.*, “*in vitro* data of exemplary compounds against seprase (fibroblast activation protein, FAP)...”), with an IC₅₀ value for each (*i.e.*, “how much of a particular compound is needed to inhibit seprase by half.”).⁸² Compounds 1018, 1020, 1024, 1025, 1026, 1027, 1028, 1030 and 1040 (below) had IC₅₀ values between 2 and 5 nM.⁸³

⁸⁰ EX1004, [0151](1006), [0157] (1010), [0159] (1011), [0160] (1014), [0161] (1016), [0162] (1016), [0164] (1020), [0175] (1023-1036), [0176] (1039), [0179] (1039), [0180] (1040-1050).

⁸¹ EX1003, ¶¶ 59, 105, 108, 124.

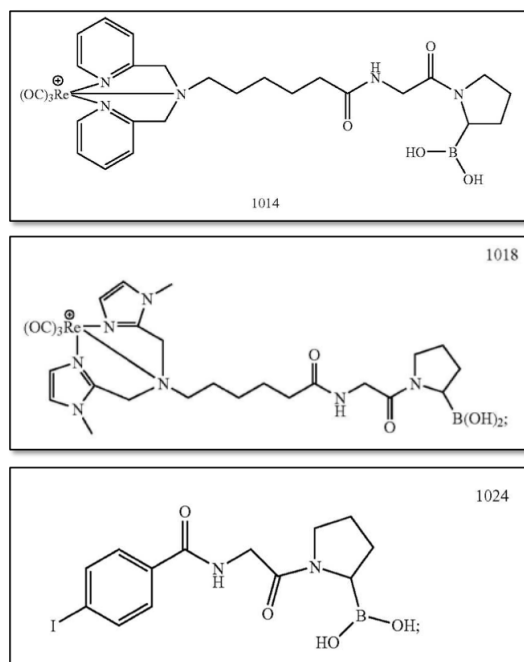
⁸² EX1004, [0185], Table 2.

⁸³ *Id.*

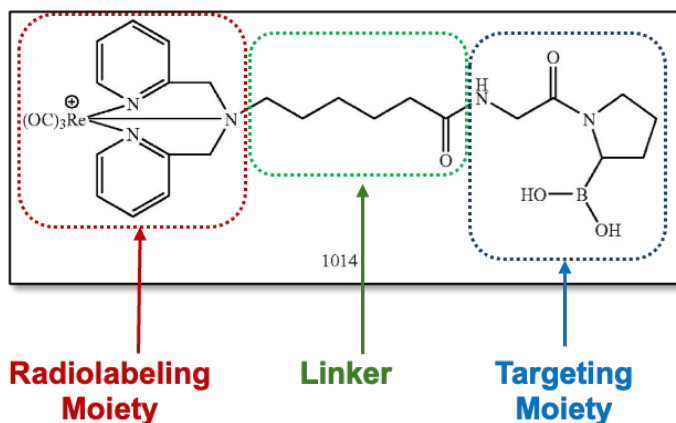


US-633 reported results from additional testing of compounds 1014/1109, 1018/1110 and 1024 (below).⁸⁴

⁸⁴ EX1004, [0189]-[0192].



A skilled artisan would have viewed any of these compounds to be a FAP-targeting radiotracer with a three-component (“B-L-A”) design specified in the patent claims (below).⁸⁵ These examples, however, have a targeting moiety that does not satisfy the requirements of component A.

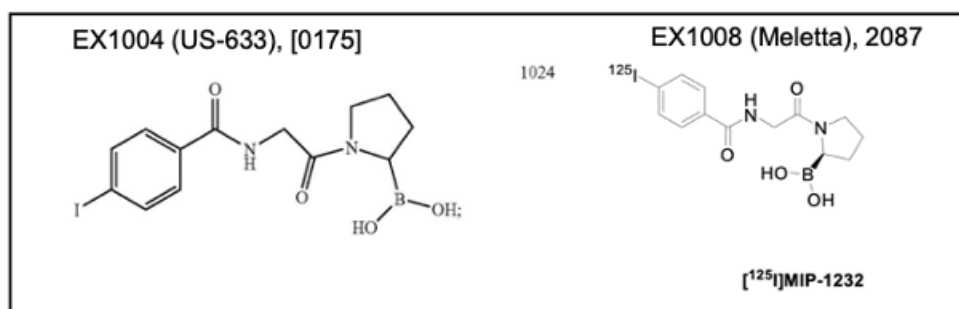


⁸⁵ EX1003, ¶¶ 126-127.

US-633 provides no information on selectivity of any of its compounds for FAP relative to PREP or other prolyl oligopeptidases. Such data is important to differentiate compounds that merely exhibit high affinity for FAP from compounds that can *selectively* bind cells in tissues that express elevated levels of FAP but not prolyl oligopeptidases.⁸⁶ A skilled artisan, thus, would have considered publications further characterizing the boronic acid pyrrolidone compounds described in US-633 to assess their feasibility for being used as the targeting moiety of a FAP-targeting radiotracer.⁸⁷

2. Meletta (EX1008)

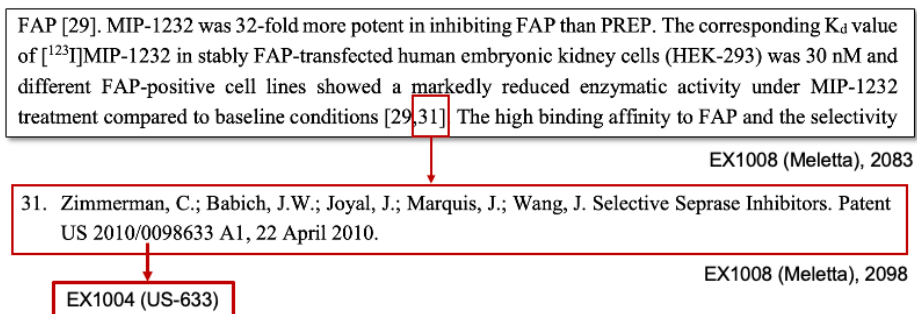
Meletta is a 2015 publication. It reports experimental results from testing a compound designated MIP-1232, an ¹²⁵I-labeled form of compound 1024 in US-633.



⁸⁶ EX1003, ¶¶ 39, 55, 57-58, 70-71; EX1004, [0003], [0005].

⁸⁷ EX1003, ¶ 162.

Meletta specifically cites US-633 (below).⁸⁸



Meletta investigated the ability of compound 1024/MIP-1232 to be used as a radiotracer for atherosclerosis imaging.⁸⁹ It explains that studies had shown that FAP expression is elevated in atherosclerotic plaques, and that a FAP-selective radiotracer could be useful in non-invasive atherosclerotic plaque imaging.⁹⁰

Meletta reports that compound 1024/MIP-1232 was 32-fold more potent in inhibiting FAP than PREP, citing an abstract that reported measured IC_{50} values for compound 1024/MIP-1232 for FAP and PREP—FAP selectivity information that was not provided in US-633.⁹¹

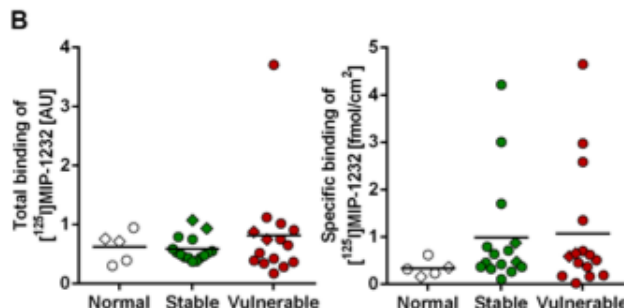
⁸⁸ EX1008, 2087, 2098 (FN31). *See* § V.C.

⁸⁹ EX1008, 2083.

⁹⁰ EX1008, 2083; *also id.* 2081-2, 2089.

⁹¹ EX1008, 2083; EX1035 (“The IC_{50} values of ... MIP-1232...for POP [PREP] were ... 19... nM, respectively, with POP[PREP]/FAP ratios of ... 32 ..., respectively.”) EX1003, ¶ 132.

Meletta reported that while compound 1024/MIP-1232 exhibited binding that “was higher in atherosclerotic plaques than normal arteries,” “after correction for the size of the tissue samples, average total binding was similar for the three categories,” citing Figure 3B (below).⁹²



Based on its experimental results, Meletta portrayed compound 1024/MIP-1232 as *not being sufficiently selective for FAP*:

Based on our data *we cannot conclude on the selectivity of $[^{125}\text{I}]\text{MIP-1232}$ for FAP*. In the absence of a known selective inhibitor, we investigated specificity by blocking with the unlabeled compound itself. The relatively high amount of remaining

⁹² EX1008, 2084-85 (reporting FAP expression levels in Figs. 1, 2), 2087-88 (in vitro imaging of three types of tissue with compound 1024/MIP-1232); 2089 (... we found a pronounced binding to carotid plaques, however with *no difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries*, after correction for the size of the tissue samples”)(*emphasis added*).

radiotracer after blocking ***must, therefore, accumulate with low affinity***. ... The ***non-specific accumulation*** may result from interactions with highly abundant hydrolases or other proteins with affinities in the high micromolar range, considering that our blocker concentration was 100 μ M. ... A conclusive evaluation of the binding affinity to dipeptidyl peptidases such as DPP-2, DPP-4, DPP-8 and DPP-9 would be required, irrespective of the fact that DPPs display in general low affinities for N blocked peptides []. As [¹²⁵I]MIP-1232 did not selectively accumulate in the atherosclerotic tissue and ***as its low FAP/PREP affinity ratio is already known we did not further investigate its selectivity profile***.⁹³

Due to the insufficient selectivity of compound 1024/MIP-1232 for FAP, Meletta explained that new, more FAP-selective targeting moieties were needed:

For future studies more selective inhibitors are needed to reduce non-specific tissue accumulation. ***To overcome limitations in specificity, novel lead structures*** and the use of antibodies and fusion proteins was proposed ***to minimize off-target effects*** [].⁹⁴

Despite the failure of compound 1024/MIP-1232, Meletta indicated that there was continuing interest in targeting FAP for diagnostic imaging, explaining that its "...findings with the tumor xenografts are of interest in oncology" and explained that "FAP imaging with a selective ligand would enable the

⁹³ EX1008, 2089-90 (*emphases added*); EX1003, ¶¶ 133-134.

⁹⁴ EX1008, 2089-90 (*emphases added*); EX1003, ¶¶ 134-135.

identification of FAP-positive tumors sensitive to a FAP-targeted radiotherapy with existing antibodies.”⁹⁵

Dr. Pomper reached the same conclusion from Meletta, which he portrays as demonstrating that MIP-1232/compound 1024 was a “documented failure” and “determined as not suitable for the [radiotracer] application” and that was because of the “low selectivity” of the compound for FAP.⁹⁶

A skilled artisan would have read Meletta as indicating there was a need for new compounds exhibiting greater selectivity for FAP and would have been motivated by it to search for other, more FAP-selective small molecule FAP-inhibitor compounds to use in FAP-targeting radiotracers.⁹⁷

3. Jansen (EX1006)

Jansen (EX1006) was published in 2014. It reports on the development and characterization of a number of FAP inhibitors based on an “N-4-quinolinoyl-Gly-(2S)-cyanoPro scaffold.”⁹⁸ It showcases one compound in particular—“compound

⁹⁵ EX1008, 2090; EX1003, ¶ 135.

⁹⁶ EX1002, 172-173 (¶¶ 32-37); EX1003, ¶ 136.

⁹⁷ EX1003, ¶¶ 134-135, 137-138.

⁹⁸ EX1006, 3053.

60”—as being a highly selective FAP-inhibitor with characteristics that make it a desirable candidate to use as a FAP-targeting moiety in a radiotracer.

A skilled artisan interested in developing FAP-targeting small molecule radiopharmaceuticals would have found and evaluated Jansen, as it describes not only important considerations for developing highly selective small molecule FAP-targeting moieties but provides numerous examples and experimental data on those compounds.⁹⁹

(a) Jansen Highlights Interest in FAP as a Drug Target

Jansen explains why FAP was recognized as an appealing target for pharmaceutical development—its selective expression on human epithelial tumors and role in promoting tumor growth:

These appealing characteristics of FAP account for its ongoing evaluation as a drug target. Both immunotherapy and small-molecule based approaches have so far been reported, most of them focusing on applications in the oncology domain ...¹⁰⁰

That perspective was widely shared in the field before 2017. *See* § IV.A.3.¹⁰¹

⁹⁹ EX1003, ¶ 141, 144, 146.

¹⁰⁰ EX1006, 3053 (*emphasis added*).

¹⁰¹ EX1003, ¶¶ 68-69, 71-72, 162.

(b) *Jansen Described a Need for Improved FAP-Targeting Moieties that It Solved with Compound 60*

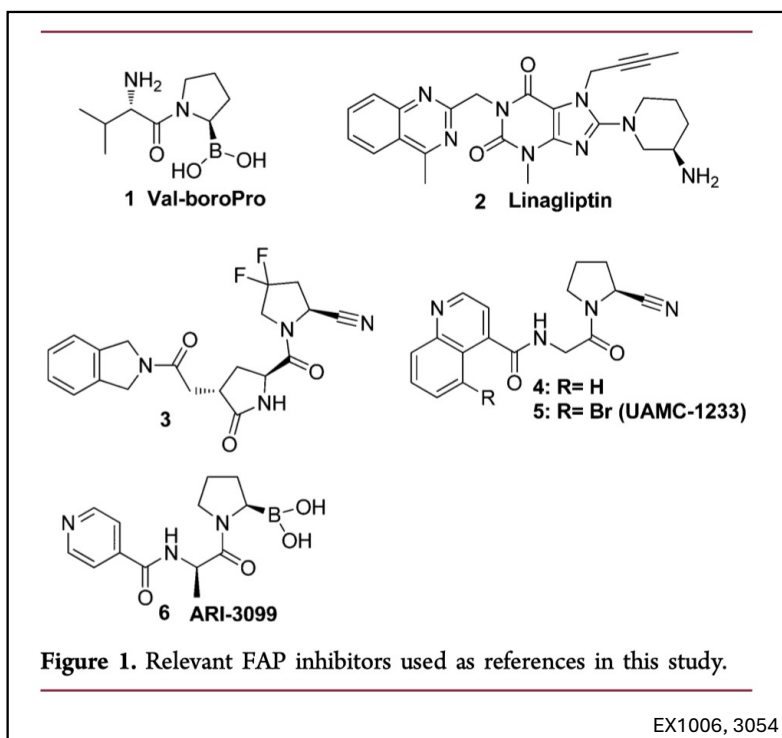
Jansen recounts the challenges of finding small molecules that exhibit sufficient FAP-selectivity to serve as a drug candidate, particularly the selectivity of compounds for FAP over PREP (below).¹⁰²

While designing out DPP affinity in FAP inhibitors is relatively straightforward, ***obtaining inhibitors possessing selectivity for FAP over PREP is considered to be far more challenging.*** This is, among others, illustrated by the significant overlap between in vitro processable substrate sequences for FAP and PREP and the fact that numerous reported FAP inhibitors have limited or no selectivity with respect to PREP.[]

Jansen surveyed six pre-2014 compounds as potential FAP inhibitors (below), and identified shortcomings for each.¹⁰³

¹⁰² EX1006, 3053; EX1003, ¶¶ 141, 143 (*emphasis added*).

¹⁰³ EX1006, 3054, Fig. 1; EX1003, ¶¶ 142-143.



- Val-boroPro (1) was a “non-selective boronic acid inhibitor” that was withdrawn after initial clinical testing, while linagliptin (2) was not selective for FAP—it also inhibited DPPIV.¹⁰⁴
- Compound #3 had good FAP/PREP selectivity but exhibited poor pharmacokinetics, while compounds 4 and 5 exhibited overall properties that were not as favorable as compound 60 (discussed *infra*).¹⁰⁵
- Compound #6 shared a pyrrolidine-2-boronic acid structure with

¹⁰⁴ EX1003, ¶ 143(a)-(b).

¹⁰⁵ EX1003, ¶ 143(c).

compound 1024 in US-633, and while Jansen reports it showing high selectivity for FAP over PREP, it also noted a lack of pharmacokinetic data for it.¹⁰⁶

Jansen explains that it explored modifications to positions on the quinolinyl-ring structures shared by compounds 4 and 5 to deduce structure-activity relationships (SAR), and provided data from testing around sixty compounds for their FAP-binding affinity and selectivity.¹⁰⁷

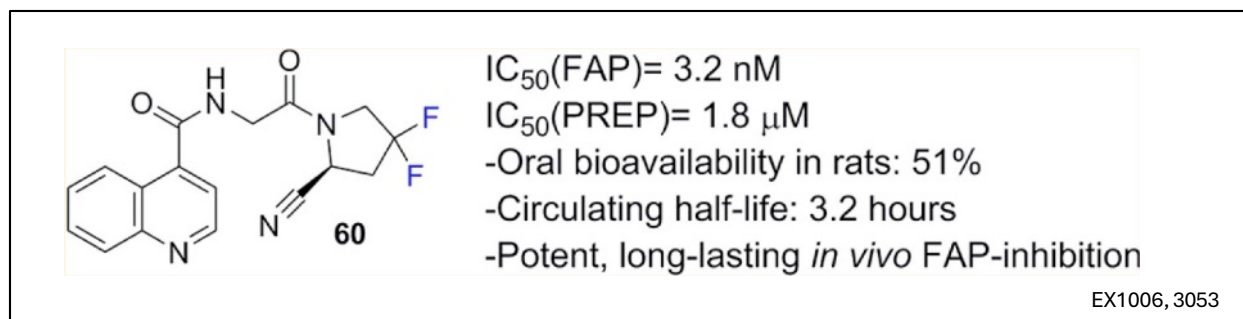
(c) Jansen Identifies Compound 60 as Its Most Promising FAP Inhibitor

Jansen showcases compound 60 as its most promising FAP inhibitor—its abstract displays compound 60 and reports it having an array of properties that a skilled artisan would have recognized render it a favorable FAP-targeting moiety for a FAP-targeting radiotracer.¹⁰⁸

¹⁰⁶ EX1003, ¶ 143(d).

¹⁰⁷ EX1006, 3054, Tables 1-6.

¹⁰⁸ EX1006, 3053; EX1003, ¶¶ 146-147, 149.



The data in Jansen reinforces this conclusion about Compound 60. Tables 1 to 6 shows the potency of each compound's inhibition of the activity of FAP and other prolyl-specific peptidases.¹¹⁰ Jansen also reports a “selectivity index” for each compound calculated by dividing its IC_{50} value for PREP by its IC_{50} value for FAP.¹¹¹ After assessing the compounds for potency and FAP/PREP selectivity, Jansen reported that compound 60 was one of the “four most promising compounds” selected for additional testing based on selectivity/affinity and stability (*i.e.*, compounds 4, 5, 60 and 61) (Table 7) (below).¹¹²

¹¹⁰ EX1006, 3057-3062 (Tables 2 to 5).

¹¹¹ EX1006, 3054, Table 1, FN b.

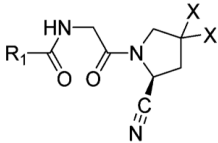
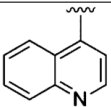
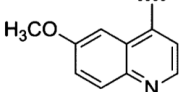
¹¹² EX1006, 3063, Table 1 (compounds 4, 5), Table 5 (compounds 60, 61); EX1003, ¶ 156. Compound 60 is identical to Compound 1 in Example 1 of US-650. EX1044, [0317], Table 4.

Table 1. IC₅₀ of Reference FAP Inhibitors

compd	IC ₅₀ (μM) ^a					SI (FAP/PREP) ^b
	FAP	PREP	DPPIV	DPP9	DPP2	
1	0.066 ± 0.011	0.98 ± 0.06	0.022 ± 0.001	ND ^c	0.086 ± 0.007	14.8
2	0.37 ± 0.002	>100	0.0020 ± 0.0002	>100	>100	>250
3	0.017 ± 0.001	>100	>100	>100	>100	5882.4
4	0.0103 ± 0.0004	0.86 ± 0.07	>100	>100	>100	83.5
5	0.011 ± 0.0004	>50	>100	>100	>100	>4500
6	0.025 ± 0.001	0.99 ± 0.04	>100	>50	>100	39.6

^aDetermined under our own assay conditions. ^bSI stands for "selectivity Index" (calculated as [IC₅₀(PREP)/IC₅₀(FAP)]). ^cND stands for "not determined".

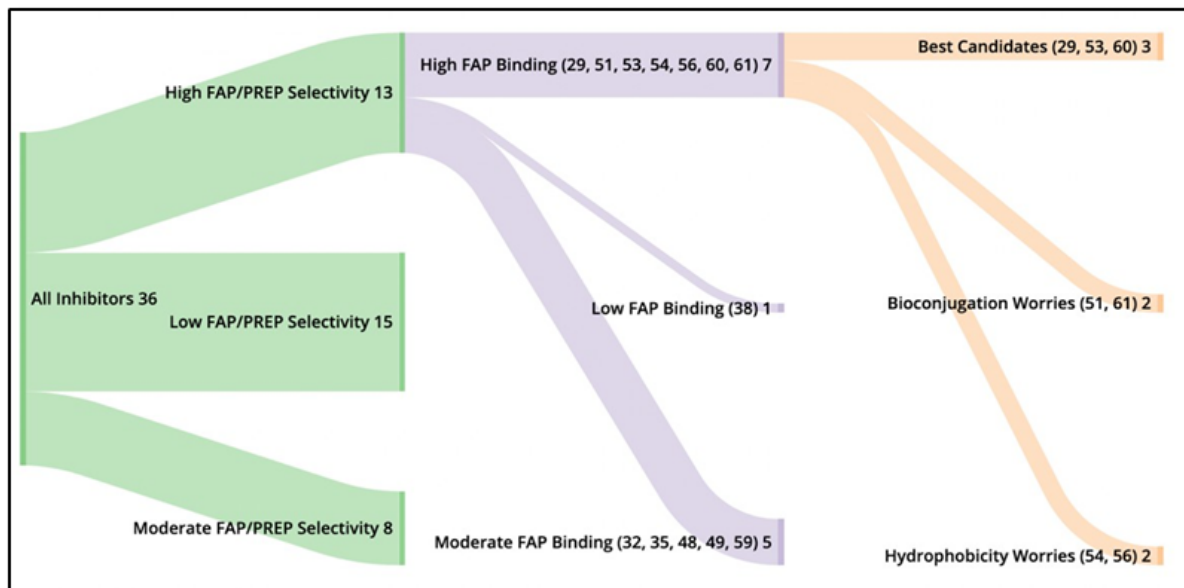
EX1006, 3054

								
Nr	R ₁	X	IC ₅₀ (μM)					SI (FAP/PREP) ^a
			FAP	PREP	DPPIV	DPP9	DPP2	
60		F,F	0.0032±0.0004	>1.8 ± 0.2	>100	>12.5	>100	562.5
61		F,F	0.0085±0.0009	8.3 ± 0.7	19±1.3	27.2±0.8	>100	976.4

EX1006, 3062 (60, 61)

A skilled artisan would have concluded that compound 60 was one of the most promising FAP inhibitors in Jansen based on the selectivity/affinity data in the paper. As Dr. Zeglis explains, a skilled artisan would have ranked the Jansen compounds using a sequence of classification steps, the first and most important of

which is high selectivity for FAP over PREP.¹¹³ Next, compounds exhibiting high FAP-vs-PREP selectivity would be ranked based on potency (*i.e.*, lower IC₅₀ values better). Finally, the compounds would be classified based on their susceptibility to degradation, hydrophobic character (which can influence pharmacokinetics), and ability to be incorporated into a radiopharmaceutical. Using this methodology, Dr. Zeglis identified compounds 29, 53 and 60 as the most promising FAP inhibitors in Jansen.¹¹⁴

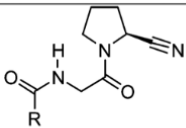
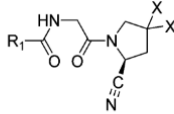
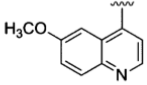


The binding characteristics and structures of compounds 29, 53 and 60 are shown below. As can be seen, compound 60 had the highest affinity for FAP

¹¹³ EX1003, ¶¶ 151-152; EX1006, 3053 (“FAP over PREP selectivity could nonetheless be an important feature for inhibitors.”)

¹¹⁴ EX1003, ¶¶ 153-155.

(lowest IC₅₀), and the second highest selectivity rating relative to PREP.¹¹⁵

								
Nr	R =	IC ₅₀ (μM)					SI (FAP/PREP) ^a	
		FAP	PREP	DPPIV	DPP9	DPPII		
29		0.063± 0.003	11.3 ± 1.2	>100	>100	>100	179.4	
53		0.0043± 0.0001	9.1 ± 0.6	>100	>50	>100	2116.3	
								
Nr	R ₁	X	IC ₅₀ (μM)					SI (FAP/PREP) ^a
			FAP	PREP	DPPIV	DPP9	DPP2	
60		F,F	0.0032± 0.0004	>1.8 ± 0.2	>100	>12.5	>100	562.5
61		F,F	0.0085± 0.0009	8.3 ± 0.7	19±1.3	27.2±0.8	>100	976.4

EX1006, 3059-60 (29,53), 3062 (60, 61)

Compound 60, thus, was not only portrayed by Jansen as one of its most promising FAP inhibitors, a skilled artisan would have recognized it as such based on its affinity and selectivity characteristics before 2017.¹¹⁶

¹¹⁵ EX1006, 3059-60 (29,53), 3062 (60, 61).

¹¹⁶ EX1006, 3064; EX1003, ¶¶ 145-147, 149-151, 154-155.

(d) *Additional In Vitro and In Vivo Testing Identifies Appealing Attributes of Compound 60*

Jansen subjected four compounds (4, 5, 60 and 61) to a series of *in vitro* tests, including stability of the compounds in plasma.¹¹⁷ The results of those experiments are reported in Table 7 (below).

parameter	4	5	68	60	61
kinetic solubility (μ M)	>200	>200	>200	>200	>200
log <i>D</i>	0.5	0.7	0.8	1	nd
plasma stability (% unchanged at 6 h) (mouse/rat/human)	100/90/nd	90/nd/100	nd/100/80	85/95/nd	nd
microsomal stability (% unchanged at 6 h) (mouse/rat)	nd	75/nd	90/nd	90/94/nd	nd
cytotoxicity (MRC-5 cells) (μ M)	>64	>64	>64	>64	>64

^and stands for “not determined”.

Jansen reported no significant differences between the compounds from these *in vitro* tests, observing that compound 60, like the other tested compounds, was stable in human, mouse and rat plasma, showed an acceptable *in vitro* half-life (> 6 hours), and none of the compounds showed cytotoxicity in a cellular assay.¹¹⁸

Jansen subjected compounds 5, 60 and 61 to *in vivo* testing in rats.¹¹⁹ It

¹¹⁷ EX1006, 3063 (indicating four “most promising compounds” tested *in vitro*).

Table 7 appears to have an error, as there is no “compound 68.”

¹¹⁸ EX1006, 3063 (“In general, no large differences between individual inhibitors were observed for the evaluated parameters.”)

¹¹⁹ EX1006, 3064. Jansen omitted compound 4 after questions were raised due to its toxicity in rats: “all rats treated with this compound died within 6 hours”

reported that while compounds 5, 60 and 61 each “displayed significant, roughly comparable oral bioavailabilities (50-79%) and reasonable elimination half-lives (1.5–3 h),” compound 60 exhibited superior *in vivo* characteristics.¹²⁰ Specifically, Jansen reported that when administered intravenously (as opposed to orally), compound 60 caused a more extensive inhibition of FAP activity (>85% at all time points) for a longer period than compounds 5 and 61 (~50% after 24 hours) (below), which Jansen attributed the compound 60’s longer *in vivo* half-life.¹²¹

From compound 60’s favorable FAP to PREP selectivity, high affinity, stability, pharmacokinetics, long half-life and *in vivo* potency of inhibition of FAP, a skilled artisan would have found that it was one of the best small-molecule FAP inhibitors available before 2017.¹²² Jansen likewise reports:

We believe that our selective, *in vivo* active inhibitors are currently best placed among all published compounds to help elucidate the function of FAP in different animal models of disease and to allow

while rats given compounds 5, 60 and 61 “did not show signs of toxicity.”

EX1003, ¶¶ 148, 159.

¹²⁰ EX1006, 3064; EX1003, ¶¶ 159-160.

¹²¹ EX1006, 3064; EX1003, ¶ 160.

¹²² EX1003, ¶¶ 149, 150, 154, 156, 160-161.

its continuing validation as a drug target.¹²³

A skilled artisan thus would have seen compound 60 as an excellent targeting moiety for a FAP-targeting radiopharmaceutical to be used in nuclear imaging or therapy of cancer.¹²⁴

B. Differences Between the Claims and the Prior Art

As explained in § V.A.1(a), US-633 describes radiopharmaceutical compounds having a modular design with three components:

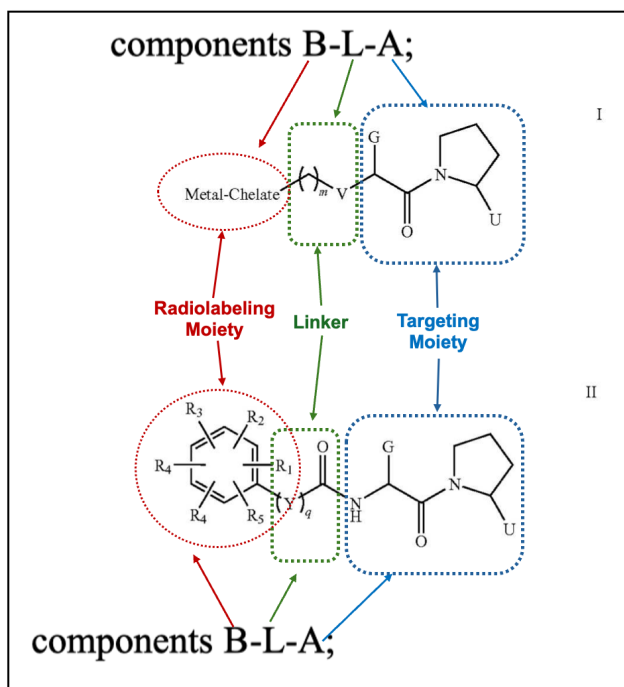
- (i) a radiolabeling moiety containing a radionuclide (*e.g.*, a radiometal such as ⁶⁸Ga or ^{99m}Tc complexed with a chelator, or a radiohalogen such as ¹⁸F or ¹²³I attached to a prosthetic group),
- (ii) a “tether” (linker) and
- (iii) a FAP- α targeting moiety.

The compounds disclosed in US-633 share the “B-L-A” design of the claimed compounds (below), use moieties that satisfy the “B” and “L” requirements, and use a targeting moiety that has the same purpose of the “A” component of the claimed compounds (*i.e.*, “a targeting moiety for FAP- α ”).¹²⁵

¹²³ EX1006, 3065.

¹²⁴ EX1003, ¶ 161.

¹²⁵ EX1003, ¶ 105.



As explained above (§ V.A.1(b)-V.A.1(b)), US-633 describes compounds comprising radiolabeling moieties and a radionuclide that together meet the requirements of “B” as each is a “... radiolabeled functional group suitable for ... positron-emission tomography (PET), single-photon emission computed tomography (SPECT) or radiotherapy.”¹²⁶

As explained above (§ V.A.1(d)), US-633 describes compounds that contain “tethers” (linkers) that meet the requirements of “L” as each has “bi-functionalization adapted to form a chemical bond with B and A.”¹²⁷ In particular, each of the molecules contains chemical bonds between a linker and each of the

¹²⁶ EX1001, 2:1-3.

¹²⁷ EX1004, [0051], [0101].

radiolabeling group and the targeting moiety.

While the targeting moiety in the US-633 molecules is “a targeting moiety for FAP- α ,” its structure does not meet the parameters of “A.” This is *the only difference* between the claimed compounds and the FAP-targeting radiopharmaceuticals described in US-633.

C. A Skilled Artisan Would Have Considered US-633 with Both Meletta and Jansen

A skilled artisan would have considered US-633 with Meletta and Jansen.

First, all three concern scientific developments in the same field—targeting FAP in cancer diagnosis and treatment due to its prevalent and selective expression in tumors.¹²⁸

Second, all three discuss small molecule FAP inhibitors that can be used in radiotracers and other radiopharmaceuticals. More directly, each describes FAP inhibitor compounds within the same structural class (*i.e.*, each contains a

¹²⁸ EX1004, [0004] (“The expression of seprase [FAP] on tumors makes it an attractive target to exploit for noninvasive imaging as well as targeted radiotherapy.”); EX1006, 3053 (“These appealing characteristics of FAP account for its ongoing evaluation as a drug target.”); EX1008, 2082 (FAP expression pattern and role in tumor environment indicated it “may serve as a therapy target in oncology [].”); EX1003, ¶ 162(a).

substituted pyrrolidine structure) and provides similar types of data characterizing the affinity of such compounds for FAP and other prolyl oligopeptidases.¹²⁹ For example, Jansen discusses work on boronic acid pyrrolidine FAP inhibitors that were the subject of US-633 and Meletta,¹³⁰ while US-633 reports on 2-cyano-pyrrolidine structures that are the focus of Jansen.¹³¹

Third, Meletta cites US-633 (below) and describes experimental investigations of one of the US-633 compounds (*i.e.*, compound 1024). This demonstrates that skilled artisans actually did consider the collective teachings of these two publications before 2017.

FAP [29]. MIP-1232 was 32-fold more potent in inhibiting FAP than PREP. The corresponding K_d value of [^{123} I]MIP-1232 in stably FAP-transfected human embryonic kidney cells (HEK-293) was 30 nM and different FAP-positive cell lines showed a markedly reduced enzymatic activity under MIP-1232 treatment compared to baseline conditions [29,31] The high binding affinity to FAP and the selectivity

31. Zimmerman, C.; Babich, J.W.; Joyal, J.; Marquis, J.; Wang, J. Selective Seprase Inhibitors. Patent US 2010/0098633 A1, 22 April 2010.

D. A Skilled Artisan Would Have Been Motivated to Use Compound 60 as the Targeting Moiety of FAP-Targeting Radiotracers

Before 2017, the prior art indicated, and a skilled artisan would have believed, that FAP was an appealing drug target for therapeutic and diagnostic

¹²⁹ EX1003, ¶ 162(b).

¹³⁰ EX1006, 3054, 3055, 3063.

¹³¹ EX1004, [0169]-[0170], [0178]-[0180], [0185].

radiopharmaceuticals.¹³² One reason was its elevated expression on >90% of human epithelial tumors and its effective absence of expression in normal adult tissues and non-malignant tumors. A second was that small molecule compounds existed that were selective inhibitors of FAP. For example, US-633 states:¹³³

The expression of seprase [FAP] on tumors makes it *an attractive target* to exploit *for noninvasive imaging* as well as *targeted radiotherapy*.

Small molecule inhibitors of seprase [FAP] are provided for use as therapeutic medicines or as *radiopharmaceuticals useful in diagnostic imaging* and in the therapeutic treatment of diseases characterized by overexpression of seprase.

Jansen similarly identified the appeal of selectively targeting FAP as a drug target with small molecule compounds:

These appealing characteristics of FAP account for its *ongoing evaluation as a drug target*. Both immunotherapy and *small-molecule based approaches* have so far been reported, most of them *focusing on applications in the oncology domain* (vide infra).¹³⁴

¹³² EX1003, ¶¶ 68-69, 71-72, 101, 103-104, 140.

¹³³ EX1004, [0005], [0007] (*emphases added*).

¹³⁴ EX1006, 3053 (*emphases added*).

Other publications from before 2017 reinforce this conclusion.¹³⁵

US-633 attempted to realize the goal of producing small-molecule FAP-targeting radiotracers, and described modular, three-component FAP-targeting radiotracers which enable the facile replacement of one or more of its components.¹³⁶ US-633 also provided extensive guidance on varying the chelating and linker components of its radiotracers, listing many options and variables for each that were well known to those skilled in the art.¹³⁷

Before 2017, however, the boronic acid pyrrolidine targeting moiety used in the radiotracers described in US-633 was shown to be insufficiently selective for FAP, effectively terminating interest in developing radiotracers based on the boronic acid pyrrolidine targeting moiety used in the US-633 radiotracers.¹³⁸

¹³⁵ See § IV.A.3; EX1003, ¶ 69; EX1046, 26; EX1026, 1, 8; EX1022, 123, 125; EX1024, 454, 455.

¹³⁶ See §§ V.A.1(a); EX1003, ¶¶ 105.

¹³⁷ See §§ V.A.1(c), V.A.1(d); EX1003, §§ IV.A.4, IV.A.5.

¹³⁸ EX1008, 2089-90; EX1002, 172-173 (¶¶ 32-37); EX1003, ¶¶ 132-134.

Consistent with the view of skilled artisans, Meletta did not propose abandoning FAP as a target for radiotracers—it identified a need for *more selective* FAP targeting moieties (including small molecules) (below).¹³⁹

For *future studies more selective inhibitors are needed to reduce non-specific tissue accumulation*. To overcome limitations in specificity, *novel lead structures* and the use of antibodies and fusion proteins was proposed to minimize off-target effects [].

Prompted by the failure of the boronic acid pyrrolidine-based targeting moiety in US-633 and Meletta's observations, skilled artisans would have looked for alternative small molecule compounds that were highly selective for FAP and could serve as a targeting moiety for a FAP-targeting radiotracer, which would have led such artisans to Jansen and compound 60.¹⁴⁰

A skilled artisan would have read Jansen as portraying compound 60 as its most promising FAP inhibitor—it showcases that compound in its abstract, and portrays it as having the best combination of selectivity, affinity, *in vitro* and *in vivo* characteristics of the compounds tested.¹⁴¹

¹³⁹ EX1008, 2090 (*emphases added*); EX1003, ¶¶ 135, 137-138.

¹⁴⁰ EX1003, ¶¶ 167-168.

¹⁴¹ EX1006, 3053, 3064, 3065; EX1003, ¶¶ 168-169, *also* ¶¶ 144-147, 149.

A skilled artisan also would have found compound 60 to be an excellent and appealing candidate for a FAP-targeting radiopharmaceutical because it has an array of favorable characteristics:

- it is highly selective for FAP relative to PREP (*i.e.*, a FAP IC₅₀ more than 562 times more potent than its IC₅₀ for PREP), and has very high affinity for FAP (*i.e.*, IC₅₀ of 3.2 nanomolar (0.0032 μM));¹⁴²
- it is stable in human plasma, not subject to oxidative metabolism, and exhibits *in vitro* half-life exceeding 6 hours and no signs of cellular toxicity;¹⁴³
- *in vivo*, it showed good oral bioavailability;¹⁴⁴ and
- it caused “the most extensive and prolonged inhibition of FAP in the pK studies” due to its “longer in vivo half-life” relative to other tested compounds.¹⁴⁵

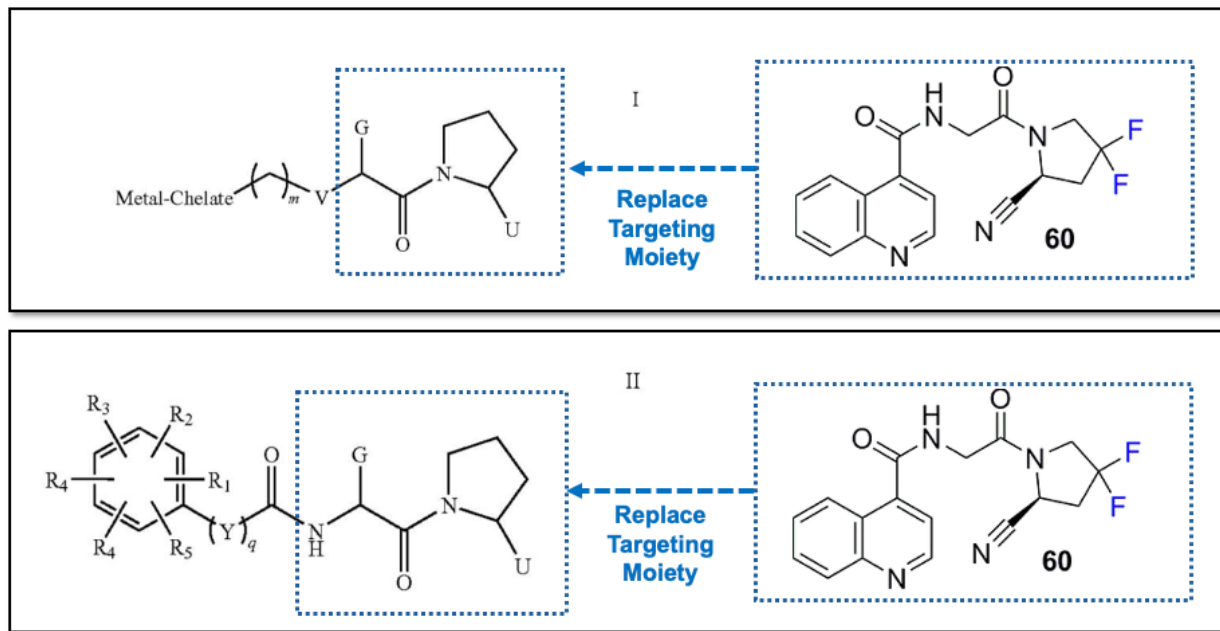
¹⁴² EX1006, 3062 (Table 5); EX1003, ¶¶ 146, 149, 156.

¹⁴³ EX1006, 3063; EX1003, ¶¶ 146, 148, 157-158.

¹⁴⁴ EX1006, 3064; EX1003, ¶¶ 147, 159.

¹⁴⁵ EX1006, 3064; EX1003, ¶¶ 159-160.

Consequently, a skilled artisan would have been motivated to replace the targeting moiety of the radiotracers described in US-633 with the more selective compound 60 of Jansen (below).¹⁴⁶



E. Compound 60 Meets Every Requirement of the “A” Moiety of the Claimed Compounds

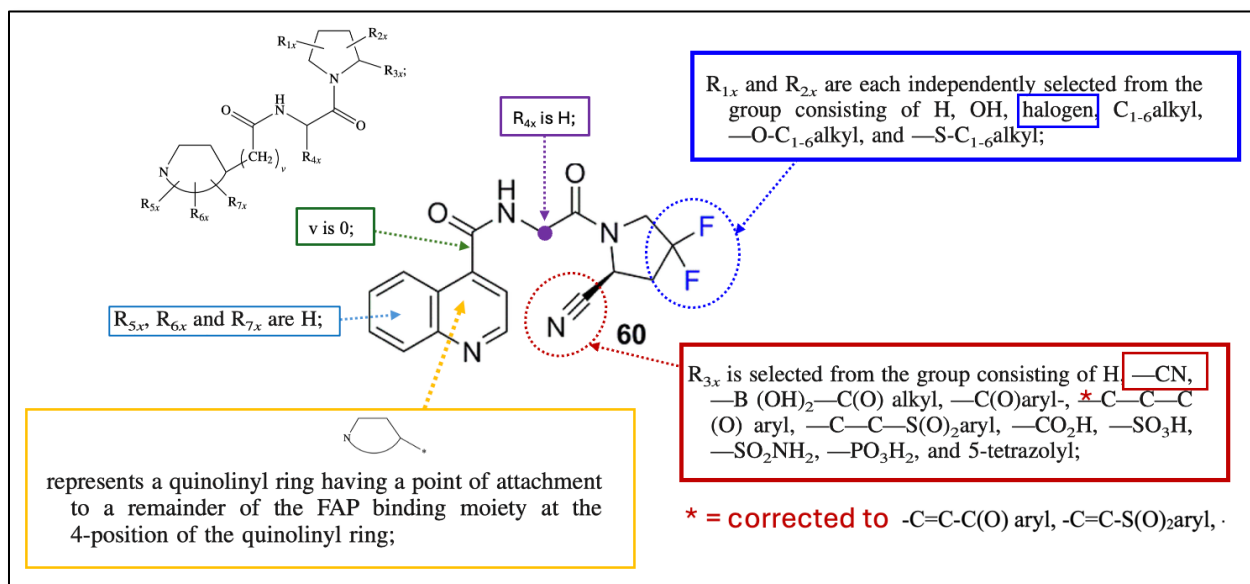
In addition to matching a structure that the '233 Patent portrays as a “particular embodiment” of an “A” moiety in its claimed compounds, compound 60 unquestionably meets every requirement of the “A” component of the claims.

First, Jansen describes compound 60 as a highly selective FAP inhibitor (*e.g.*, it has a selectivity index of >560 for binding to FAP relative to PREP, and

¹⁴⁶ EX1003, ¶¶ 168-169, 182, 194.

high affinity (*i.e.*, an IC_{50} of 3.2 nM)).¹⁴⁷ A skilled artisan would conclude that, when incorporated in a radiotracer, compound 60 would be “a targeting moiety for FAP- α ” within the meaning of the claims.¹⁴⁸

Second, compound 60 meets the structural requirements of the “A” component in the claimed “Formula (I)” of “B-L-A.” As shown below, compound 60 has attributes at positions in the “A” generic structure that match parameters in the claims for those positions:¹⁴⁹ Also, the remainder of the FAP-targeting moiety is attached via position 4 of the quinolinyl ring in compound 60.



The claims require 3 of 4 positions on the left side of the quinolinyl ring to

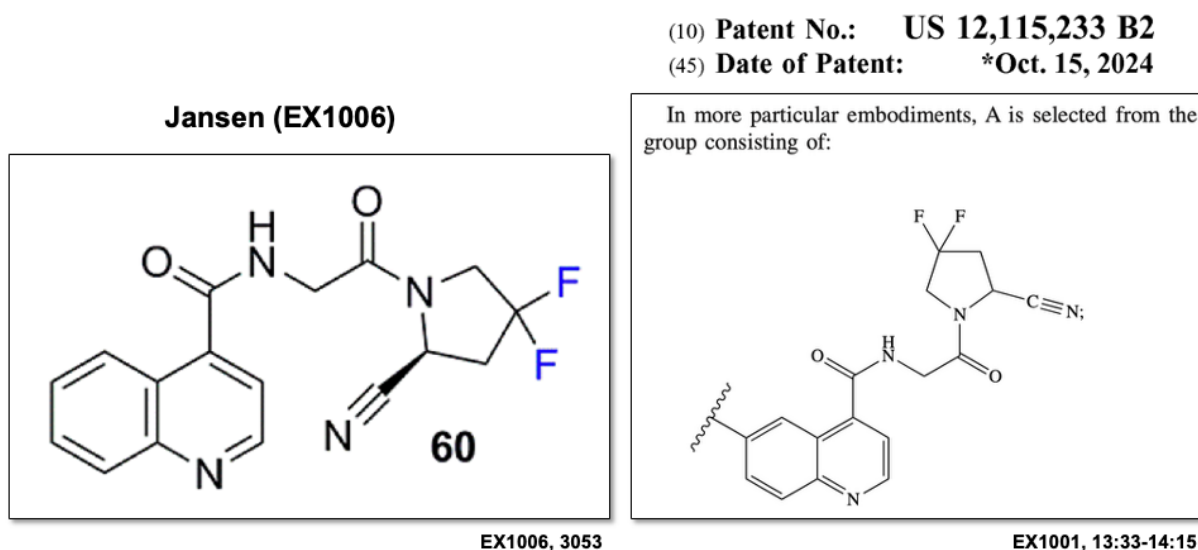
¹⁴⁷ EX1006, 3053.

¹⁴⁸ EX1003, ¶ 202.

¹⁴⁹ EX1001, Claim 1.

be hydrogen, which allows any of the four positions in that ring to be the site of linker attachment (among other positions elsewhere in compound 60).

The ‘233 Patent also portrays compound 60—which had been published in the scientific literature years before—to be a small molecule targeting moiety suitable for a FAP-targeting radiotracer, labeling it a “particular embodiment” of its “A” component (below right).¹⁵⁰



F. A Skilled Artisan Would Have Found It Obvious to Combine Compound 60 with Conventional Radiolabeling Groups and Linkers Suggested by US-633 to Yield Specific Radiotracers

The prior art would have not only motivated a skilled artisan to develop compound 60-based radiopharmaceuticals (§ V.D), it would have directed them produce particular compounds, such as those that integrate compound 60 into

¹⁵⁰ EX1001, 13:33-14:15; EX1006, 3053.

radiotracer structures taught by US-633. In doing so, skilled artisans would have drawn on the guidance in US-633 as well as their own education, training and experience as of early 2017.

1. A Modular Three Component Design Would Be Used

A skilled artisan would have used the modular three-component design known in the art and taught by taught by US-633 for a radiopharmaceutical based on compound 60.¹⁵¹ A skilled artisan also would have used a linker to connect it to a radiolabeling moiety (*e.g.*, to avoid adverse effects observed from attaching halogens to the quinoliny ring).¹⁵²

2. Choices for the Radiolabeling Moiety

As Dr. Zeglis explains, a skilled artisan would select a radionuclide based on the imaging platform to be used (*i.e.*, PET or SPECT) and by matching its radioactive half-life to the pharmacokinetic half-life of the radiotracer.¹⁵³ Given the short pharmacokinetic half-life of compound 60, skilled artisans would have

¹⁵¹ EX1001, [0008], [0021], [0101]; EX1003, ¶¶ 33-38, 105-106, 127, 167.

¹⁵² EX1003, ¶ 175.

¹⁵³ EX1003, ¶¶ 49-51, 163-164.

considered the following radionuclides appropriate: (i) ^{68}Ga and ^{18}F for PET imaging, and (ii) $^{99\text{m}}\text{Tc}$ and ^{123}I for SPECT imaging.¹⁵⁴

As US-633 explains, “[a]ny suitable chelating moiety may be used to provide a covalent or other association with a radionuclide.”¹⁵⁵ Skilled artisans would have known how to select a chelator that was suitable for a particular chosen radiometal.¹⁵⁶ They would have recognized that US-633 teaches chelators suitable for ^{68}Ga , such as DOTA,¹⁵⁷ as well as ones suitable for $^{99\text{m}}\text{Tc}$ (below), including DPA (“1-a”).¹⁵⁸ US-633 thus suggested particular chelators for ^{68}Ga and $^{99\text{m}}\text{Tc}$ radionuclides used in PET or SPECT imaging.

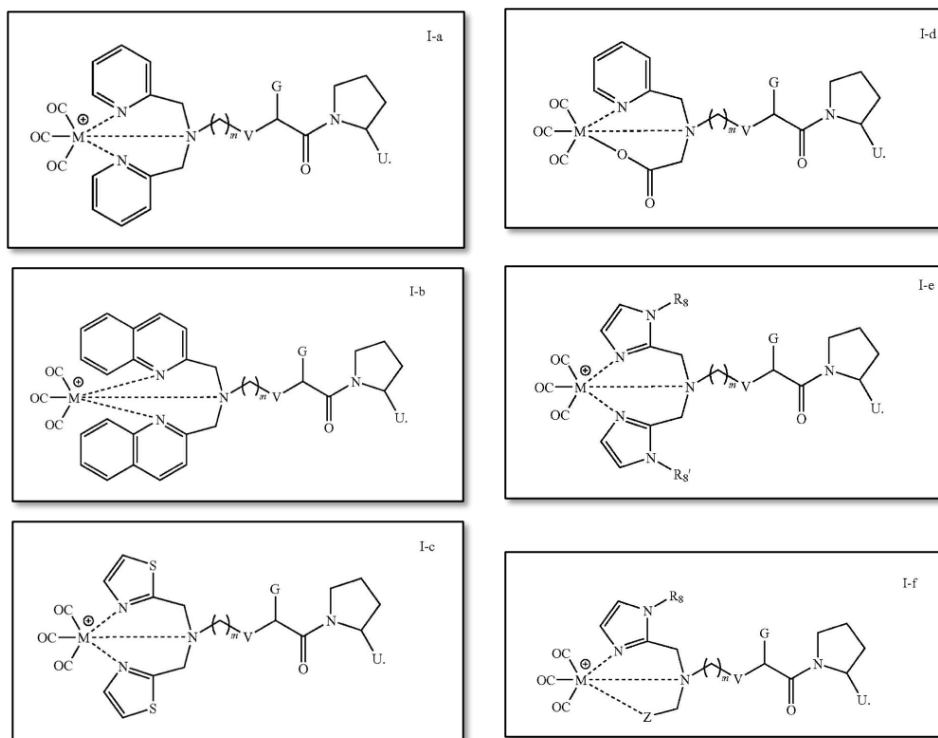
¹⁵⁴ EX1004, [0049]; EX1003, ¶¶ 49, 52, 53, 166.

¹⁵⁵ EX1004, [0100].

¹⁵⁶ EX1003, ¶¶ 42-43, 115, 183.

¹⁵⁷ EX1004, [0100] (DOTA); EX1003, ¶¶ 112, 116.

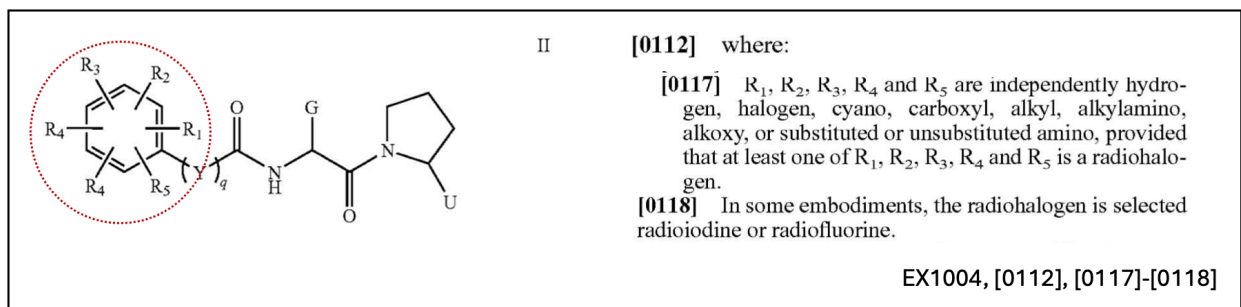
¹⁵⁸ EX1003, ¶¶ 112-114, 184.



US-633 also teaches using prosthetic groups in radiotracers based on ^{18}F and ^{123}I (*e.g.*, Formula II with radioiodine (^{123}I) or radiofluorine (^{18}F) covalently attached to the phenyl ring (below).¹⁵⁹ A skilled artisan would have considered the prosthetic group options illustrated in US-633 to be suitable for a compound 60-based radiotracer based on ^{18}F or ^{123}I .¹⁶⁰

¹⁵⁹ EX1004, [0117]-[0118]; EX1003, ¶¶ 117, 192-193.

¹⁶⁰ EX1003, ¶¶ 117-119, 192-193, 197.



3. Choices for the Linker

A skilled artisan would have been familiar with linkers used commonly in the construction of radiotracers.¹⁶¹ US-633 also provides guidance regarding linkers (“tethers”) suitable to use in the modular radiotracer compounds it describes. *See* § V.A.1(d). For example, US-633 proposes use of linkers that are, *inter alia*, simple alkyl chains or PEG.¹⁶² US-633 also explains (as a skilled artisan would know) that the size of the linker can be adjusted to ensure the radiolabeling moiety is sufficiently separated from the targeting moiety.¹⁶³

US-633 also explains that PEG-based linkers can be readily incorporated into radiotracers by skilled artisans:

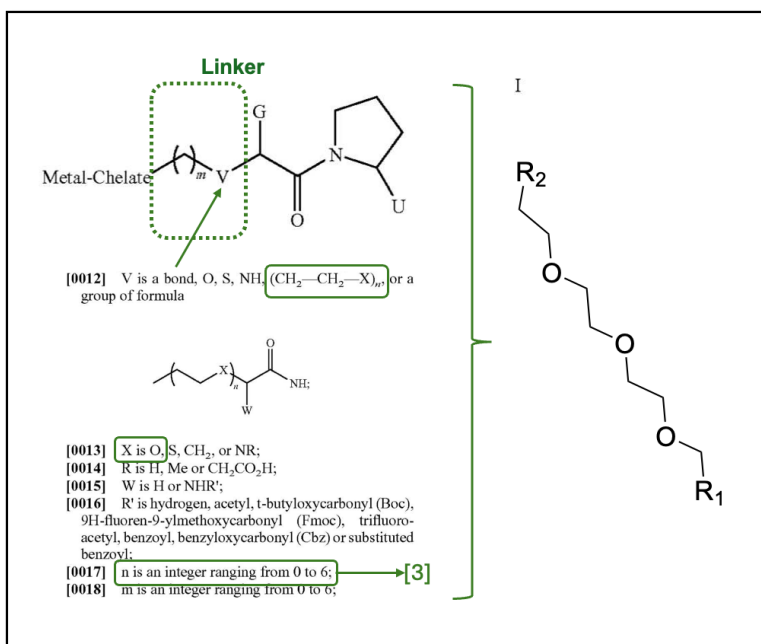
¹⁶¹ EX1003, ¶¶ 45-46, 122-123.

¹⁶² EX1004, [0130] (“The tether may comprise a simple alkyl chain as shown, a PEG $(CH_2CH_2O)_n$, a polyethylene amine $((CH_2CH_2NH)_n)$, or the like.”)

¹⁶³ EX1003, ¶¶ 187, 195.

[0133] The above reaction scheme is applicable to any modification of the tether by incorporation of heteroatoms into the tether chain. This may have additional benefits on the affinity as well as the selectivity for seprase. Incorporation of heteroatoms into the tether such as oxygen can take advantage of the commercial availability of a variety of short polyethylene glycol (PEG) diamines that can be readily incorporated into the complexes. One of ordinary skilled in the art would also readily apply other chelates to prepare functionalized proline- $M^+(CO)_3$ complexes.

US-633 also teaches, via options it sets forth in its structural description of its radiotracers, use of short PEG oligomers (*e.g.*, 3 units). Below, selecting “V” as “ $(CH_2—CH_2—X)_n$,” X as “O” and “n” as 3 yields a 3 monomer PEG oligomer (below).¹⁶⁴



While US-633 illustrates the “tether” with a chelator group, skilled artisans would

¹⁶⁴ EX1004, [0012]-[0018].

have found this guidance useful for prosthetic groups, as they would appreciate that the targeting moiety (compound 60) should be separated by a sufficient distance (*e.g.*, 10 to 20 bonds) from the prosthetic group, which would be achieved using a 3-monomer PEG linker.¹⁶⁵

4. Construction of Compound 60-Linker-Radiolabeling Moiety Compounds

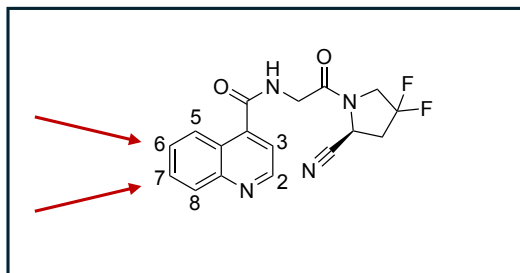
Compound 60 has a structure amenable to being integrated into a radiotracer. As Dr. Zeglis explains, a skilled artisan would have used a linker to connect compound 60 to a radiolabeling moiety in order to avoid causing steric or chemical interference between the radiolabeling and targeting moieties.¹⁶⁶ He also explained that, after determining which part of compound 60 is responsible for its binding to FAP¹⁶⁷ and studying the effects on selectivity and affinity from substitutions at various positions in quinolinyl-glycyl(2-cyanopyrrolidine) FAP inhibitors, a skilled artisan would have considered positions C⁶ or C⁷ on the quinolinyl ring of compound 60 to be the most suitable positions to attach a linker

¹⁶⁵ EX1003, ¶¶ 45, 105, 187; EX1004, [0101], [0130].

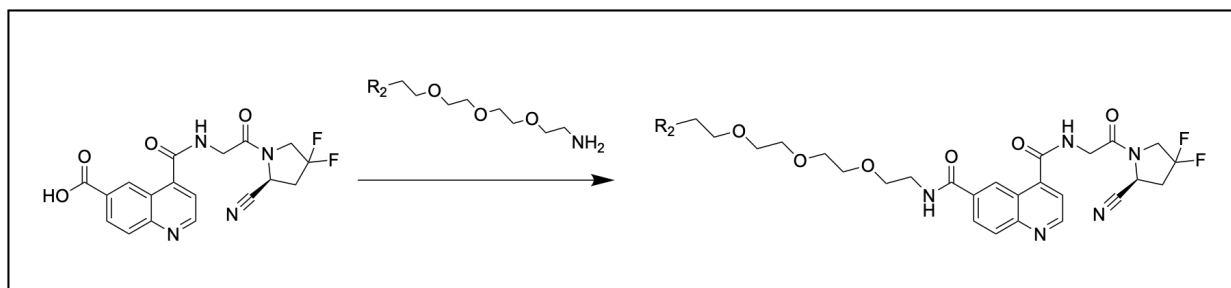
¹⁶⁶ EX1003, ¶¶ 174-175.

¹⁶⁷ EX1003, ¶ 176.

(below), as modifications to those positions did not affect the selectivity or affinity of the compound.¹⁶⁸



A skilled artisan would have recognized that positions C⁶ or C⁷ would need to be functionalized to enable formation of a covalent bond to the linker, and to do so would have found it obvious to incorporate a carboxyl group at positions C⁶ (illustrated) or C⁷ that could be exploited to form an amide bond with an amine-terminated PEG oligomer (such as the one discussed above), thereby yielding the following linker-compound 60 construct (below).¹⁶⁹



¹⁶⁸ EX1003, ¶ 178.

¹⁶⁹ EX1003, ¶¶ 179, 187.

A skilled artisan would also have functionalized the R₂ terminus in the PEG linker above to enable formation of a second covalent bond with either a chelating or prosthetic structure—using a “diamine PEG” linker discussed in US-633 (R₂=amine) enables formation of an amide bond with a free carboxylic acid on a DOTA chelator.¹⁷⁰ Of course, other synthetic routes could be taken (*e.g.*, forming the DOTA-linker construct first, and then attaching it to a functionalized compound 60). These are routine synthetic chemistry steps that would be familiar to a skilled artisan before 2017.¹⁷¹

G. Examples of Compounds Suggested by US-633, Meletta and Jansen Satisfy Claims 1-4

From the collective guidance in US-633, Meletta and Jansen, by early 2017 a skilled artisan would have found it obvious to:

- (i) use the modular, three-component design for radiotracers described in US-633 (*see* § V.F.1);
- (i) replace the boronic acid pyrrolidine targeting moiety of the radiotracers in US-633 with compound 60 from Jansen (*see* § V.D);
- (iii) select a radionuclide and its suitable chelator or prosthetic group for a desired imaging platform (PET or SPECT) pursuant to US-633 and

¹⁷⁰ EX1004, [0133], EX1003, ¶ 188.

¹⁷¹ EX1003, ¶ 190.

knowledge they possessed in 2017 (*see* § V.F.2);

- (iv) select a linker pursuant to the guidance in US-633 to connect compound 60 to the radiolabeling moiety (*e.g.*, a 3-monomer functionalized PEG) so as to separate the reporter and targeting moieties by ~10-20 bonds (*see* § V.F.3); and
- (v) construct the compound by conventional synthetic steps (*e.g.*, functionalize compound 60 at position C⁶ with a carboxylic group, attach PEG linker via amide bond, attach chelator/prosthetic group via amide bond) (*see* § V.F.4).

Compounds A1 to A4 result from these choices suggested by the prior art (illustrated below) and meet every requirement of claims 1-4 of the '233 Patent.

1. A PET Radiotracer Based on ⁶⁸Ga, DOTA and PEG Satisfies Claims 1-4 (Compound A1)

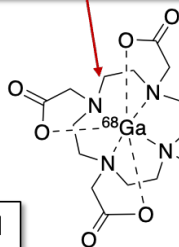
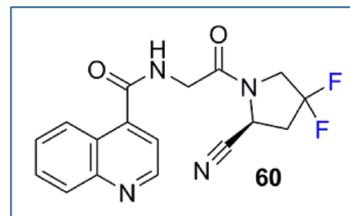
Compound A1 (below) incorporates (i) Jansen's compound 60 functionalized to contain a carboxylic group at position C⁶, (ii) a DOTA chelator suitable for ⁶⁸Ga, and (iii) a 3-monomer PEG functionalized to contain terminal amine groups.¹⁷²

¹⁷² EX1003, ¶¶ 185-189; 201-202; EX1004, [0008], [0019], [0020], [0048], [0049], [0100], [0130]; EX1006, 3053, 3062.

stituted or unsubstituted cyclopentadienyl. By way of example, suitable chelating agents include tetra-azacyclododecanetetra-acetic acid (DOTA), diethylenetriamine-pentaacetic acid (DTPA), bis(pyridin-2-ylmethyl)amine (DPA), quinolinemethylamino acetic acid, 2,2'-azanediyldi-

EX1004, [0100]

Compound A1



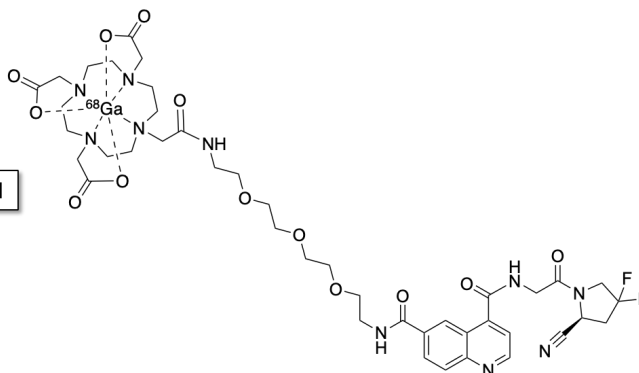
EX1006, 3053, 3062

these structures. The tether may comprise a simple alkyl chain as shown, a PEG $(\text{CH}_2\text{CH}_2\text{O})_n$, a polyethylene amine $((\text{CH}_2\text{CH}_2\text{NH})_n)$, or the like. Terminal aminoalkanoic acids

EX1004, [0130]

Chemical Formula: $\text{C}_{42}\text{H}_{55}\text{F}_2^{68}\text{GaN}_{10}\text{O}_{13}$
Molecular Weight: 1013.88

Compound A1



Chemical Formula: $\text{C}_{42}\text{H}_{55}\text{F}_2^{68}\text{GaN}_{10}\text{O}_{13}$
Molecular Weight: 1013.88

Compound A1 is a “low molecular weight” compound in the meaning of the claims as it has a molecular weight of ~1014 Da, which is orders of magnitude smaller than an antibody, and below 1500 Da.¹⁷³ When stably complexed with

¹⁷³ EX1003, ¶¶ 171, 204.

^{68}Ga , Compound A1 is a radiotracer suitable for PET imaging.¹⁷⁴ Compound A1 renders claims 1-4 obvious.

2. A SPECT Radiotracer Based on ^{68}Ga , DPA and PEG Satisfies Claims 1-4 (Compound A2)

Compound A2 (below) incorporates (i) compound 60 functionalized to contain a carboxylic group at position C⁶, (ii) a DPA chelator suitable for $^{99\text{m}}\text{Tc}$, and (iii) a 3-monomer PEG functionalized to contain terminal groups that enable formation of the compound. Because the DPA chelator has an accessible nitrogen, a skilled artisan could use a PEG where one end is a protected amine (*e.g.*, NH-Boc), and the other terminates with a chlorine group. The first step would create the DPA-PEG-NH-Boc, and then in a second step, it would be attached to the carboxyl group functionalized compound 60, yielding Compound A2 below.¹⁷⁵

¹⁷⁴ EX1003, ¶¶ 198-199, 202.

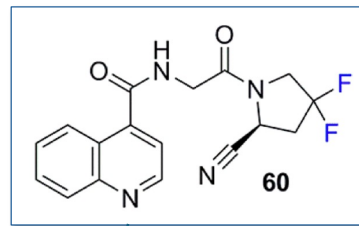
¹⁷⁵ EX1003, ¶ 185-86, 190, 201-202; EX1004, [0008], [0019], [0020], [0048], [0049], [0100], [0130]; EX1006, 3053, 3062.

stituted or unsubstituted cyclopentadienyl. By way of example, suitable chelating agents include tetra-azacyclododecanetetra-acetic acid (DOTA), diethylenetriamine-pentaacetic acid (DTPA), bis(pyridin-2-ylmethyl)amine (DPA), quinolinemethylamino acetic acid, 2,2'-azanediyl-

EX1004, [0100]

Compound A2

these structures. The tether may comprise a simple alkyl chain as shown, a PEG ($(\text{CH}_2\text{CH}_2\text{O})_n$), a polyethylene amine $((\text{CH}_2\text{CH}_2\text{NH})_n)$, or the like. Terminal aminoalkanoic acids



EX1006, 3053, 3062

EX1004, [0130]
Chemical Formula: $\text{C}_{41}\text{H}_{42}\text{F}_2\text{N}_8\text{O}_9^{99}\text{Tc}$
Molecular Weight: 927.74

Compound A2

Chemical Formula: $\text{C}_{41}\text{H}_{42}\text{F}_2\text{N}_8\text{O}_9^{99}\text{Tc}$
Molecular Weight: 927.74

Compound A2 is a “low molecular weight” compound: it has a molecular weight of ~928 Da, which is orders of magnitude smaller than an antibody, and

below 1500 Da.¹⁷⁶ When stably complexed with ^{99m}Tc, Compound A2 is a radiotracer suitable for use in SPECT imaging.¹⁷⁷ Compound A2 renders claims 1-4 obvious.

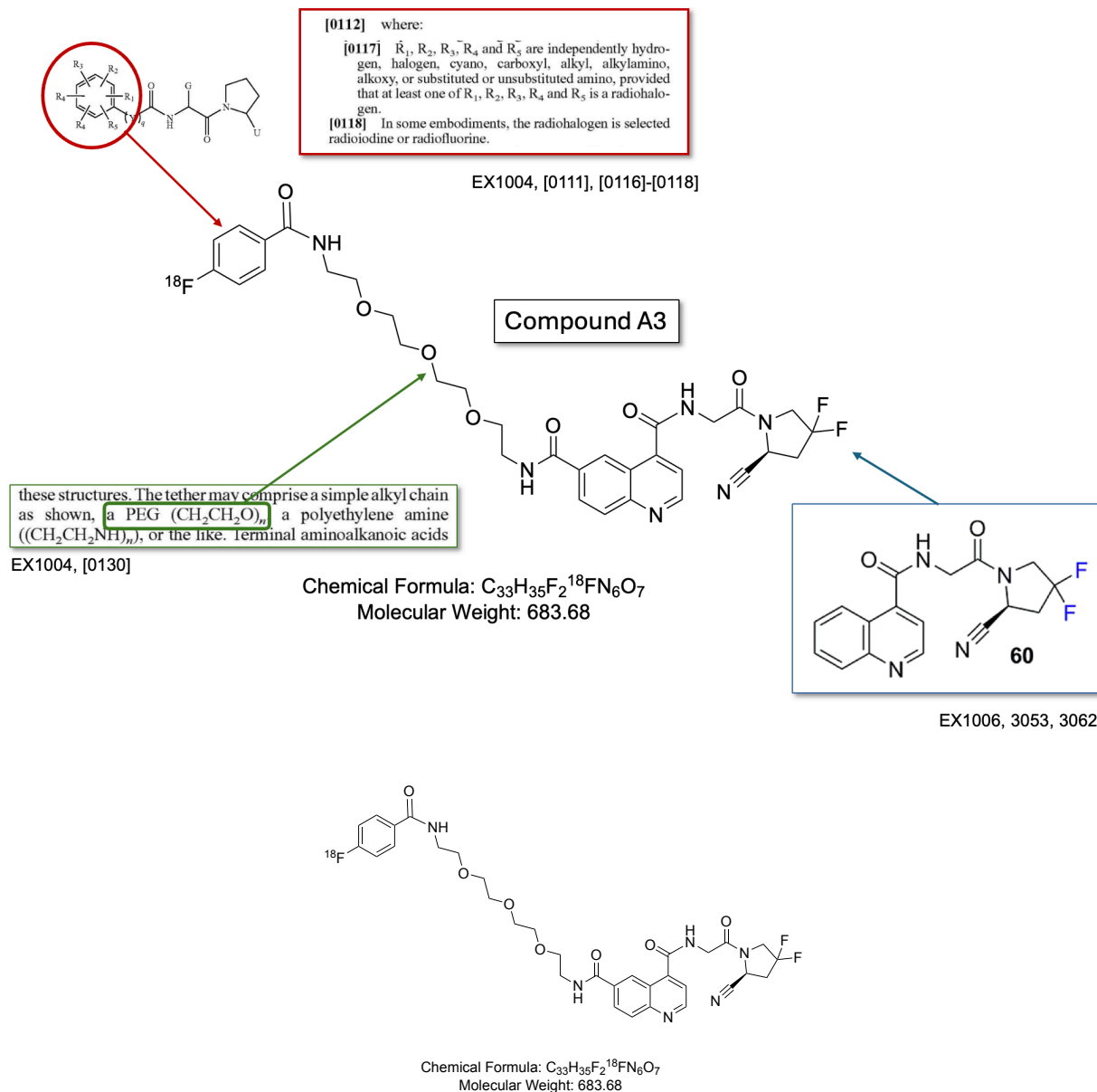
3. A PET Radiotracer Based on ¹⁸F, a Prosthetic Group and PEG Satisfies Claims 1-3 (Compound A3)

Compound A3 (below) incorporates (i) compound 60 functionalized to contain a carboxylic group at position C⁶, (ii) a prosthetic group labeled with ¹⁸F at the para position of the phenyl group, and (iii) a 3-monomer PEG functionalized to contain terminal amine groups.¹⁷⁸

¹⁷⁶ EX1003, ¶¶ 171, 204.

¹⁷⁷ EX1003, ¶¶ 198-199, 202.

¹⁷⁸ EX1003, ¶¶ 192-197; EX1004, [0021], [0028], [0049], [0111], [0116]-[0118], [0133]; EX1006, 3053, 3061, 3062.



Compound A3 is a “low molecular weight” compound in the meaning of the claims as it has a molecular weight of ~683 Da, which is orders of magnitude smaller than an antibody, and below 1500 Da.¹⁷⁸ With its covalently attached ^{18}F

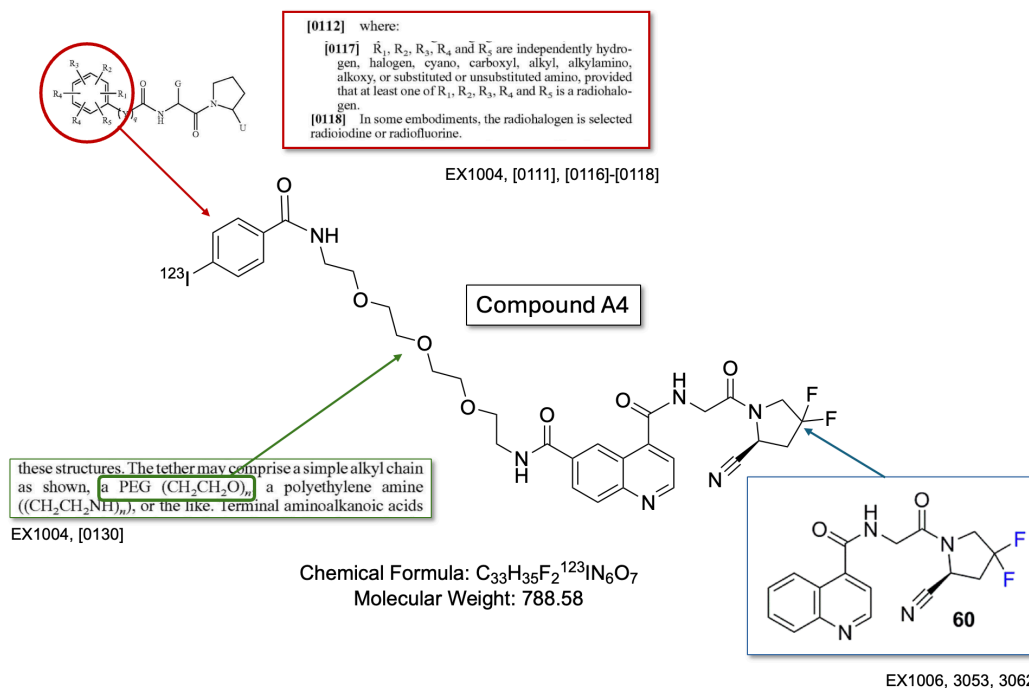
¹⁷⁸ EX1003, ¶¶ 171, 204.

radionuclide, Compound A3 is a radiotracer suitable for use in PET imaging.¹⁷⁹

Compound A3 renders claims 1-3 obvious.

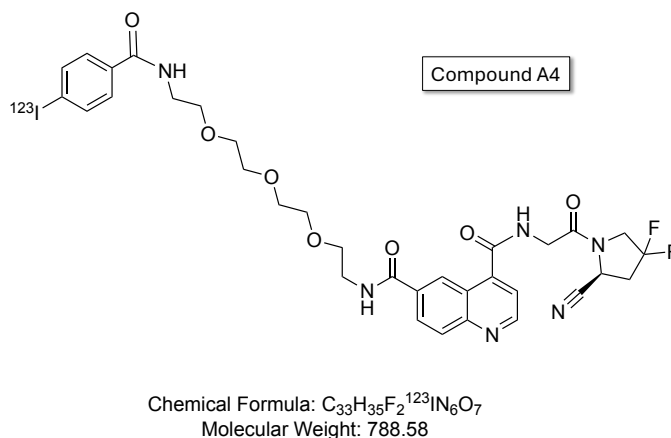
4. A SPECT Radiotracer Based on ^{123}I , a Prosthetic Group and PEG Satisfies Claims 1-3 (Compound A4)

Compound A4 (below) incorporates (i) compound 60 functionalized to contain a carboxylic group at position C⁶, (ii) a prosthetic group labeled with ^{123}I at the para position of the phenyl group, and (iii) a 3-monomer PEG functionalized to contain terminal amine groups.¹⁸⁰



¹⁷⁹ EX1003, ¶¶ 198-199, 202.

¹⁸⁰ EX1003, ¶¶ 192-197; EX1004, [0021], [0028], [0049], [0111], [0116]-[0118], [0133]; EX1006, 3053, 3061, 3062.



Compound A4 is a “low molecular weight” compound in the meaning of the claims as it has a molecular weight of ~791 Da, which is orders of magnitude smaller than an antibody, and below 1500 Da.¹⁸² With its covalently attached ^{123}I radionuclide, Compound A4 is a radiotracer suitable for use in SPECT imaging.¹⁸³ Compound A4 renders claims 1-3 obvious.

H. Claims 1-4 Would Have Been Obvious

As explained in § V.G, a skilled artisan would have found compounds A1-A4 to have been obvious from US-633, Meletta and Jansen before October 2017.

A skilled artisan also would have reasonably expected compounds A1 to A4 to be viable nuclear imaging agents, as they would be expected to retain the selectivity and affinity of compound 60.¹⁸⁴ Data published in Jansen showed that

¹⁸² EX1003, ¶¶ 171, 204.

¹⁸³ EX1003, ¶¶ 198-199, 202.

¹⁸⁴ EX1003, ¶ 205.

substituents at positions C⁶ and C⁷ of the quinolinyl ring in (4-quinolinoyl)glycyl-2-cyanopyrrolidine compounds did not significantly impair the selectivity or affinity the compound, which would have led a skilled artisan to reasonably expect that attaching the PEG linkers in Compounds A1-A4 at position C⁶ of the quinolinyl ring of compound 60 to not disturb its selectivity and affinity for FAP.¹⁸⁵ DOTA and PEG linkers have been used successfully in radiotracer compounds, and the illustrated PEG linker included in compounds A1 to A4 separates the radiolabeling moiety in each compound from the compound 60 targeting moiety by 12+ bonds.¹⁸⁶

Because compounds A1-A4 meet every requirement of claims 1-4 and would have been obvious, claims 1-4 are unpatentable.

VI. Ground 2: Claims 1-4 Are Obvious Based on US-121 (EX1005) and Jansen (EX1006)

Claims 1-4 also would have been obvious from the combined teachings of US-121 and Jansen.

A. Teachings of the Prior Art (US-121)

The teachings of Jansen (EX1006) are summarized in § V.A.3.

¹⁸⁵ EX1003, ¶ 178; EX1006, 3061-2 (Tables 4-5), 3081-82; EX1044, [0633]; EX1007, 492-494.

¹⁸⁶ EX1003, ¶¶ 187, 211, 213; EX1004, [0101], [0130], [0131].

US-121 published in 2012, is owned by the assignee of the '233 Patent and names Dr. Pomper as an inventor.

US-121 describes “low molecular weight” compounds used as radiotracers and therapeutic radiopharmaceuticals.¹⁸⁷ It identifies several advantages of such agents over antibody-based imaging agents, including that they (i) “offer better contrast between target tissues and non-target tissues,”¹⁸⁸ and (ii) provide better tumor penetration.¹⁸⁹ The ‘233 Patent echoes these points.¹⁹⁰

US-121 provides examples of radiotracer designs that target a protein called prostate-specific membrane antigen (PSMA), which US-121 describes as “an excellent target for imaging ...” of tumors and prostate cancer because it is an enzyme with an extracellular site (below):¹⁹¹

¹⁸⁷ EX1005, [0012].

¹⁸⁸ EX1005, [0012].

¹⁸⁹ EX1005, [0012] (“greater cellular retention”), [0008]-[0009], [0188] (longer tumor residence).

¹⁹⁰ *Compare* EX1005, [0008]-[0009]; EX1001, 1:44-61. *See* EX1003, ¶ 214.

¹⁹¹ EX1005, [0007].

renal lesion, did not express PSMA. As an enzyme with an extracellular active site, PSMA represents an excellent target for imaging and therapy directed toward solid tumor neovasculature in addition to prostate cancer itself. PSMA-based agents can report on the presence of this marker, which is increasingly recognized as an important prognostic determinate in PCa (Murphy et al., *Urology*, vol. 51, pp. 89-97, 1998). It is also the target for a variety of new PCa therapies (Galsky et al., *J Clin Oncol*, vol. 26, pp. 2147-2154, 2008).

EX1005, [0007]

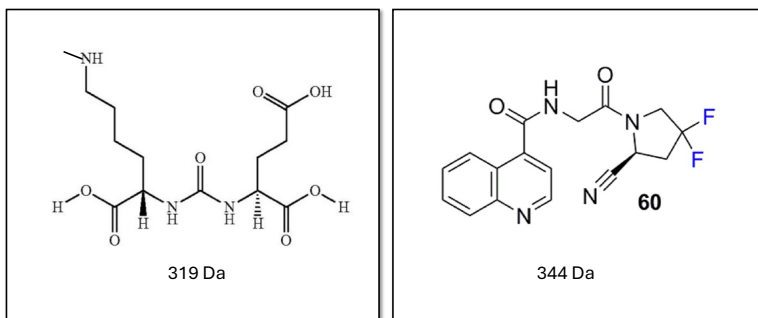
Like PSMA, FAP is a transmembrane (cell-surface) enzyme with an extracellular active site that is selectively expressed in epithelial cancers.¹⁹²

US-121 describes its compounds as responding to “the long standing and unmet need for new imaging and therapeutic compounds for targeting prostate cancer and cancer angiogenesis.”¹⁹³ That need certainly persisted past 2012 and was not limited to PSMA-targeting radiotracers.

¹⁹² See § IV.A.3; EX1004, [0003].

¹⁹³ EX1005, [0012].

The US-121 radiotracers use as their targeting moiety a small molecule lysine-urea-glutamic acid moiety (below, left).¹⁹⁴ It has a comparable molecular weight to Jansen's compound 60 (*i.e.*, 319 Da vs. 344 Da) (below right).¹⁹⁵

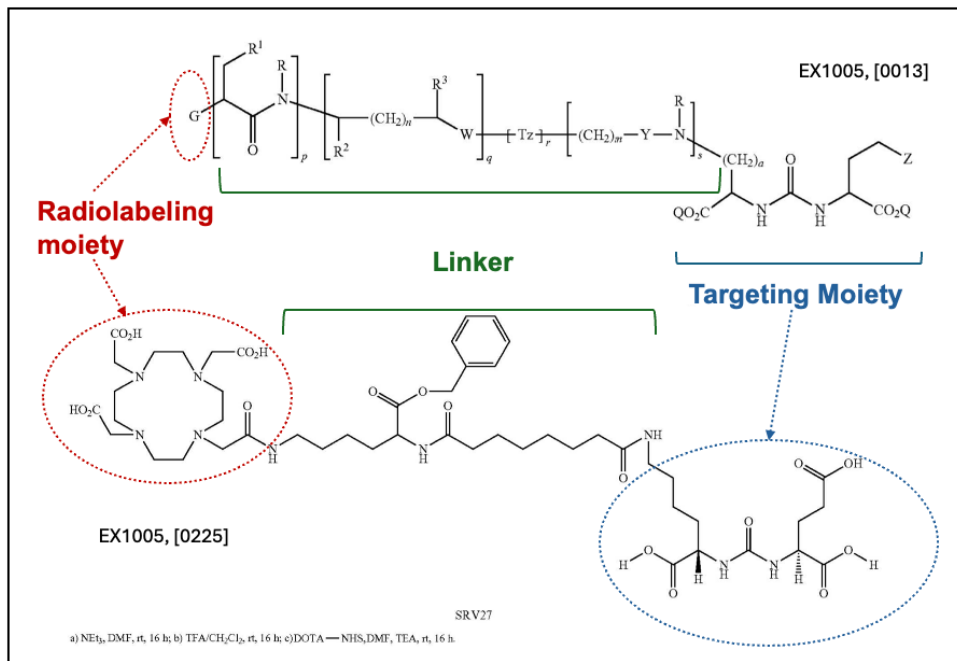


The radiotracers described in US-121 join the urea-based targeting moiety to a chelator using a variety of linkers, and share the same modular, three-component design as the claimed radiotracers (illustrated below).¹⁹⁶

¹⁹⁴ EX1005, [0166], [0169]; EX1003, ¶ 233.

¹⁹⁵ EX1003, ¶ 233.

¹⁹⁶ EX1003, ¶ 211.



US-121 identifies advantages of this modular design, including that it allows one to improve pharmacokinetics “by optimization of the linker-chelate complex.”¹⁹⁷ US-121 provides several other examples of radiotracer compounds that embody this modular three-component structure of the '233 Patent claims.¹⁹⁸

US-121 explains that its radiotracers can be used with both PET and SPECT devices.¹⁹⁹ It identifies advantages of using PET with ⁶⁸Ga-labeled radiotracers,²⁰⁰ but also describes examples of ^{99m}Tc-based radiotracers being used with SPECT

¹⁹⁷ EX1003, ¶ 212; EX1005, [0279].

¹⁹⁸ EX1005, [0103], [0207], [0214], [0225], [0244], [0249]-[0250].

¹⁹⁹ EX1005, [0184]; EX1003, ¶ 212, 215.

²⁰⁰ EX1005, [0242], [0011]; EX1003, ¶ 216.

imaging.²⁰¹ It observes that “[n]umerous metal chelating moieties are known in the art,” lists several pages of them (*e.g.*, DOTA, DTPA, NOTA), and explains that “[a]ny acceptable chelator can be used with the present invention as long as compatible and capable of chelating a desired metal.”²⁰²

US-121 explains that linkers “attach the metal chelating moiety to the rest of the compound” and that the linker group may comprise “alkyl, aryl, combination of alkyl and aryl, or alkyl and aryl groups having heteroatoms....”²⁰³ US-121 also explains that linkers (or their constituents) can be selected to make a radiotracer compound more hydrophobic, and that such radiotracers “may have longer circulation times, thereby providing more prolonged supply of tracer to bind to cells.”²⁰⁴ For example, US-121 compares two examples of radiotracers (SRV27, SRV100)(below), with one more lipophilic “which is reasonable in light of the presence of two phenylalanine residues in the long linker of SRV100, while SRV27 has only one lysine residue protected as the benzyl ester.”²⁰⁵

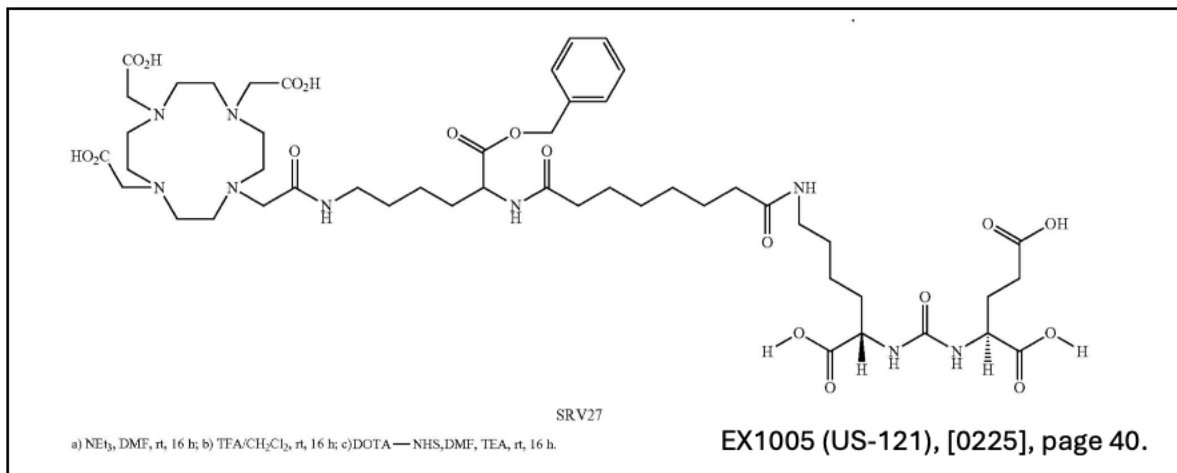
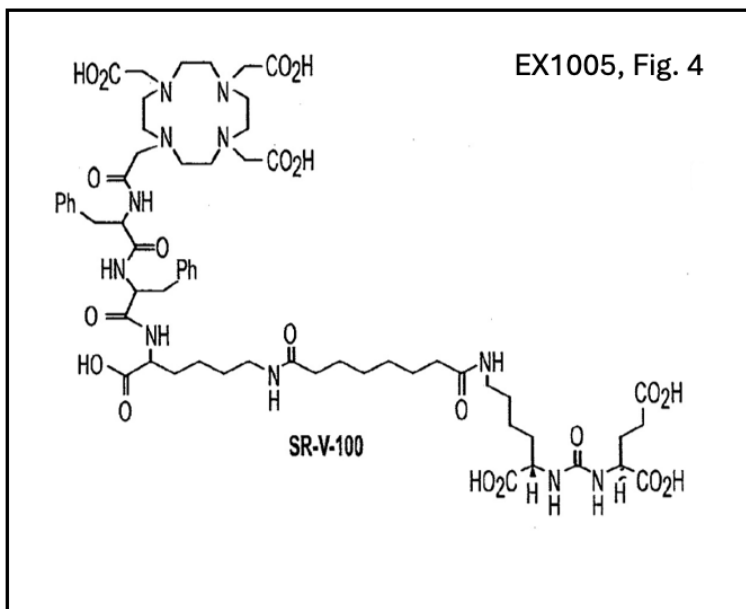
²⁰¹ EX1005, [0027], [0214]; EX1003, ¶¶ 217, 225-226.

²⁰² EX1005, [0102].

²⁰³ EX1005, [0102].

²⁰⁴ EX1005, [0187], [0012]; EX1003, ¶¶ 221, 235.

²⁰⁵ EX1005, [0231]; Fig. 4.



B. A Skilled Artisan Would Have Considered US-121 with Jansen

US-121 and Jansen would have been considered together by a skilled artisan before 2017.

First, both report developments in the same scientific field—small-molecule inhibitors of enzymes (*i.e.*, PSMA and FAP) selectively expressed on the surface of tumors of epithelial cell origin and recognized as appealing targets for imaging

and therapy.²⁰⁶ US-121 reports that PSMA is “expressed in prostate tumor epithelium” and “in the neovasculature of many solid tumors.”²⁰⁷ Similarly, Jansen explains that “FAP is highly expressed on activated fibroblasts in over 90% of common human epithelial tumors” and that is one of “appealing characteristics of FAP ... for its ongoing evaluation as a drug target.”²⁰⁸

Second, both highlight the importance of selectivity of the small molecule for its targeted cell-surface enzyme.²⁰⁹

Third, a skilled artisan would have recognized the compounds identified in US-121 and Jansen are not only both small molecule inhibitors of their enzyme targets (PSMA and FAP, respectively), but have approximately the same size (*i.e.*, 319 Da vs. 344 Da).²¹⁰

Finally, a skilled artisan would be prompted to consider development of compound 60-based radiopharmaceuticals based on Jansen’s observations about

²⁰⁶ EX1003, ¶¶ 207, 227, 229; EX1036, 226-27; § IV.A.3.

²⁰⁷ EX1005, [0007].

²⁰⁸ EX1006, 3053.

²⁰⁹ EX1005, [0240] (selectivity key to accurate imaging); EX1006, 3053 (FAP-PREP selectivity), 3065 (selectivity key attribute).

²¹⁰ EX1003, ¶ 233.

the potential of its compounds to selectively target FAP as a drug target.²¹¹ Such persons would have found the guidance in US-121 helpful, as it provides examples of particular radiotracer designs demonstrated to be useful in tumor imaging that would accelerate development of compound 60-based radiotracers.²¹²

C. A Skilled Artisan Would Have Modified the US-121 Radiotracers to Use Compound 60 to Target FAP

A skilled artisan, starting with the exemplified radiotracers in US-121, would have found it obvious to replace the urea-based targeting moiety in them with Compound 60 of Jansen.

First, a skilled artisan would have recognized that a compound 60-based radiotracer could be used for imaging a wider range of tumors than the PSMA-targeting radiotracers, given that FAP was expressed at elevated levels in over 90% of epithelial tumors.²¹³ More generally, FAP was seen as a particularly promising target for nuclear imaging, which would have encouraged skilled artisans to find radiotracer designs that had proven successful in tumor imaging, such as those in US-121.²¹⁴ This would have motivated the skilled artisan to adapt the PSMA-

²¹¹ EX1006, 3053, 3065; EX1003, ¶¶ 228, 230-231.

²¹² EX1003, ¶¶ 227, 232, 234.

²¹³ EX1003, ¶¶ 230-231, 68.

²¹⁴ EX1003, ¶¶ 68-69, 236.

targeting radiotracers in US-121 to use a FAP targeting moiety, particularly compound 60.²¹⁵

Second, a skilled artisan would have understood from US-121 that *any* individual components of the modular, three-component radiotracers being described in US-121 could be altered—including the targeting moiety.²¹⁶ Indeed, US-121 invites skilled artisans to do so, stating:

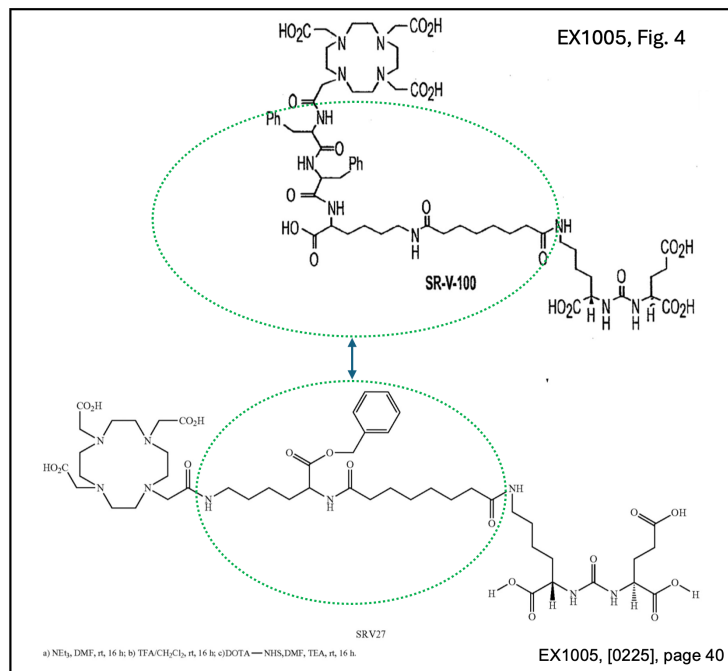
A person skilled in the relevant art will recognize that *other equivalent components can be employed* and other methods developed without departing from the broad concepts of the current invention.²¹⁷

For example, US-121 shows compounds SR-V-100 and SRV27, which share the same targeting and radiolabeling moieties, but use different linkers (below).

²¹⁵ EX1003, ¶¶ 233-234.

²¹⁶ EX1003, ¶¶ 212, 231.

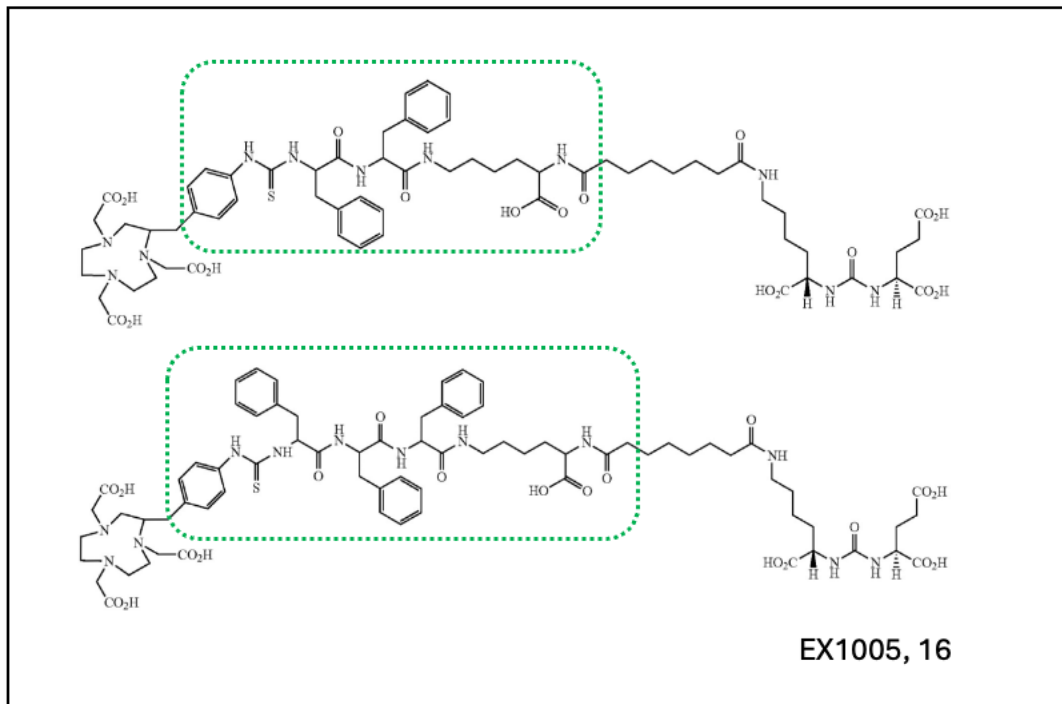
²¹⁷ EX1005, [0060] (*emphasis added*).



Third, US-121 credits the use of particular linkers in radiotracers to improve imaging of tumors: “compounds with increased hydrophobicity, such as compounds having hydrophobic linkers, may have longer circulation times, thereby providing more prolonged supply of tracer to bind to cells.”²¹⁸ US-121 also describes linkers with varying numbers of pendent benzyl groups to influence their hydrophobic character (below).²¹⁹

²¹⁸ EX1005, [0187]; EX1003, ¶¶ 221, 235.

²¹⁹ EX1005, [0103], page 16, *also* 14, 47; EX1003, ¶¶ 234, 46.



The emphasis in US-121 of using particular linkers to improve the performance of radiotracers in tumor imaging would have motivated a skilled artisan to use the particular combinations of linkers and chelators in examples of radiotracers in US-121 to produce FAP-targeting radiotracers based on compound 60.²²⁰

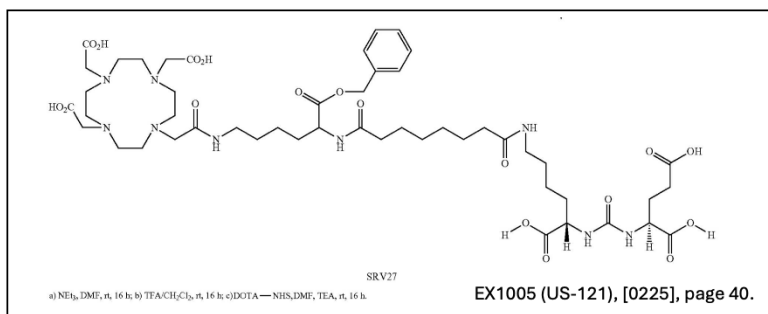
Fourth, the skilled artisan would have viewed the substitution of compound 60 for the urea-based PSMA targeting moiety to be straightforward due to their comparable size (*i.e.*, 344 Da vs. 319 Da),²²¹ and because compound 60 could be functionalized to enable its attachment to particular linker-chelator structures in

²²⁰ EX1003, ¶¶ 234-236.

²²¹ EX1003, ¶ 233.

US-121 via an amide bond similarly to how the PSMA targeting moiety is attached.²²²

Fifth, a skilled artisan would have recognized that small molecule radiotracers have relatively short pharmacokinetic half-lives.²²³ Following the design principle that the radiotracer's half-life should match the half-life of its radionuclide, a skilled artisan would have selected ^{68}Ga and $^{99\text{m}}\text{Tc}$ as radionuclides to use in a compound 60-based radiotracer.²²⁴ US-121 also highlights the use of ^{68}Ga and $^{99\text{m}}\text{Tc}$ in its radiotracers.²²⁵ The skilled artisan consequently would have focused on radiotracers in US-121 with chelators suitable for ^{68}Ga or $^{99\text{m}}\text{Tc}$.²²⁶ (below)



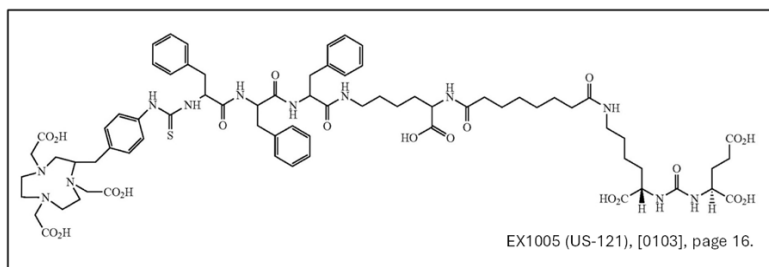
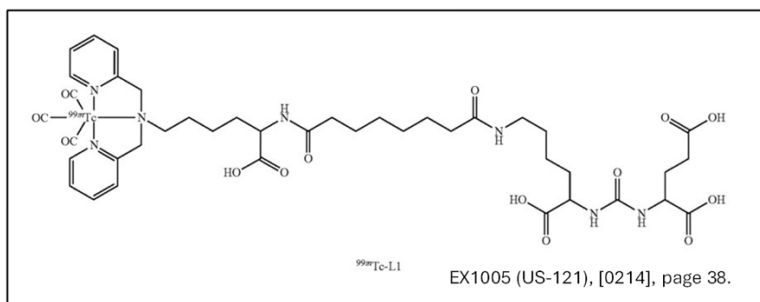
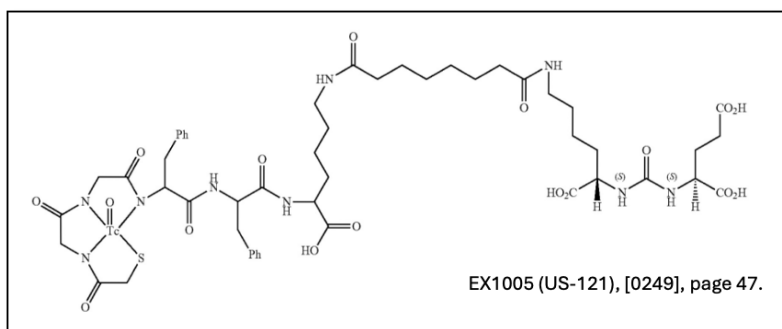
²²² EX1003, ¶ 237.

²²³ EX1003, ¶ 40.

²²⁴ EX1003, ¶¶ 50-51, 216(c).

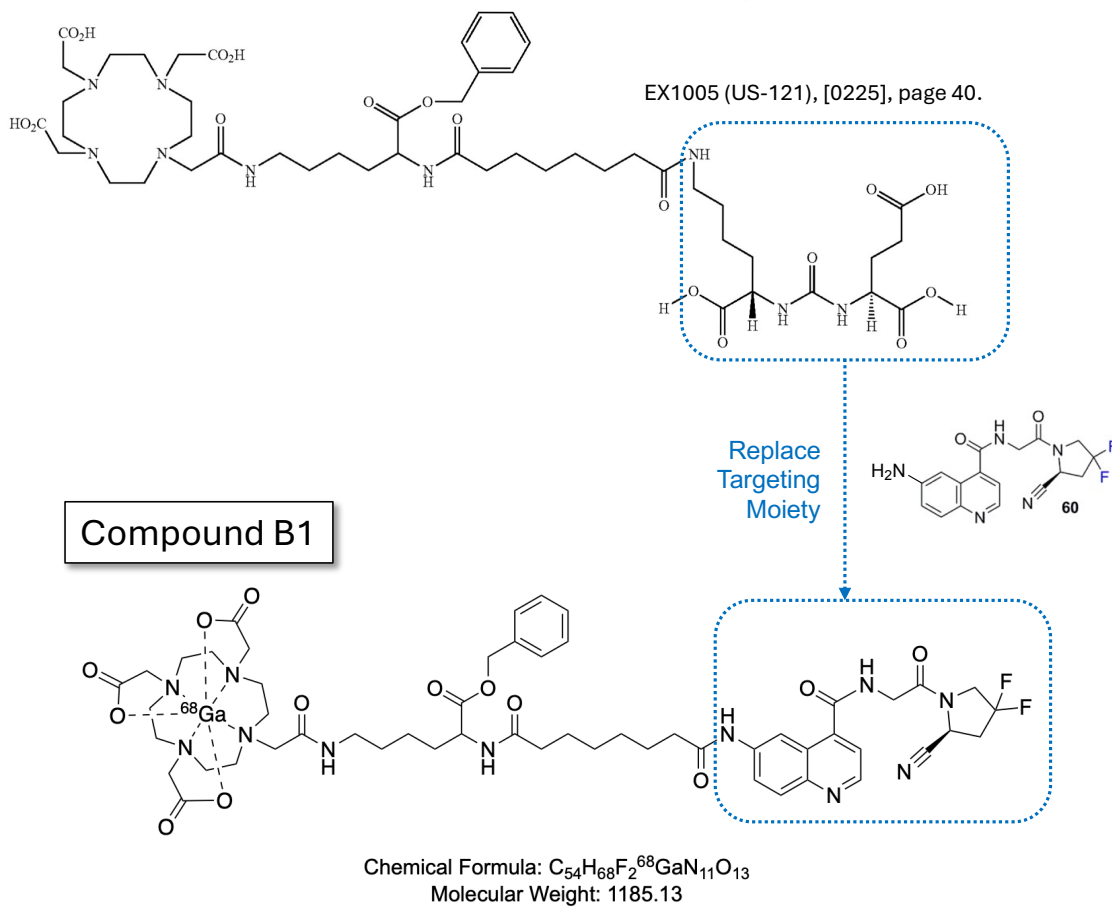
²²⁵ EX1005, [0011], [0242]; EX1003, ¶¶ 215-216, 225, 232.

²²⁶ EX1003, ¶¶ 217, 232, 237.



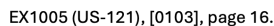
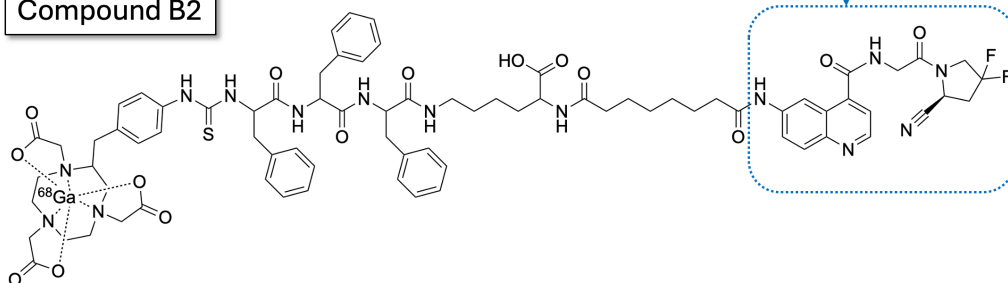
For the reasons provided above, a skilled artisan would have considered it obvious before 2017 to modify the four radiotracers described above (which are depicted in US-121) by replacing the urea-based targeting moiety with compound 60 of Jansen. This could be achieved using a functionalized form of compound 60 having an amine group at position C⁶ (illustrated) or C⁷ which would preserve the orientation of the amide bond in the starting compounds relative to the urea-based

targeting moiety.²²⁷ Dr. Zeglis illustrates modifications that yield compound 60-based variants of these exemplary radiotracers (below).²²⁸

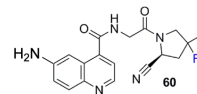
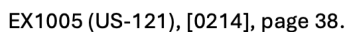
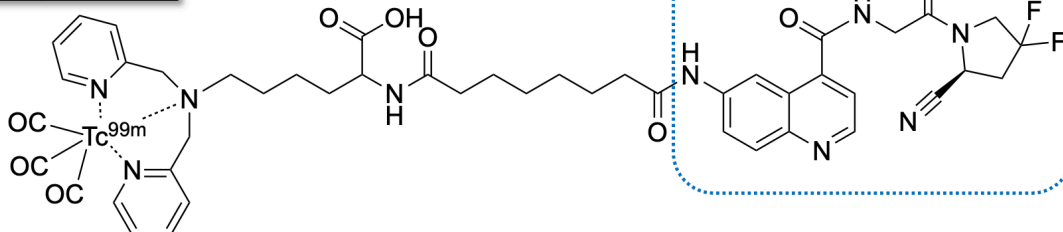


²²⁷ EX1003, ¶¶ 237-239.

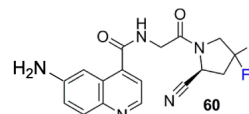
²²⁸ EX1003, ¶¶ 223-226.

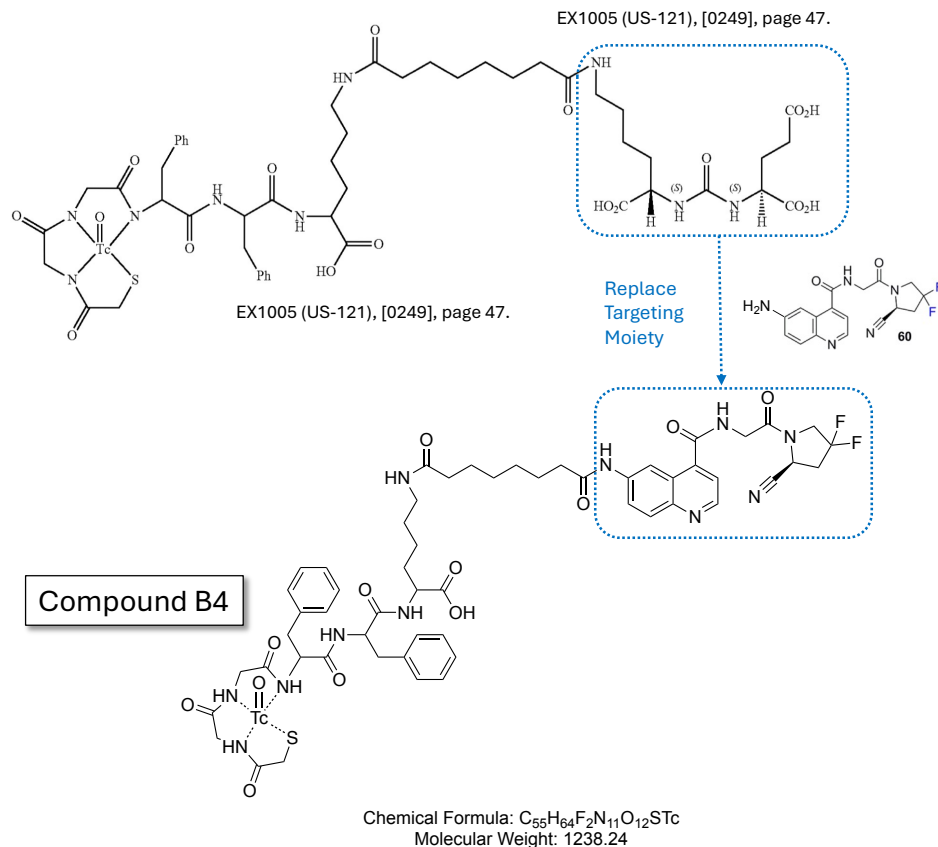


Replace Targeting Moiety



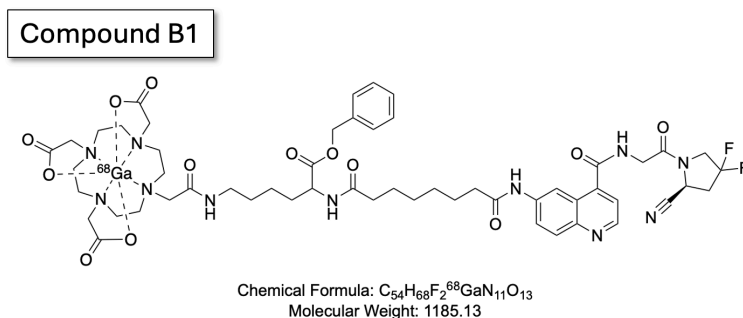
Replace Targeting Moiety



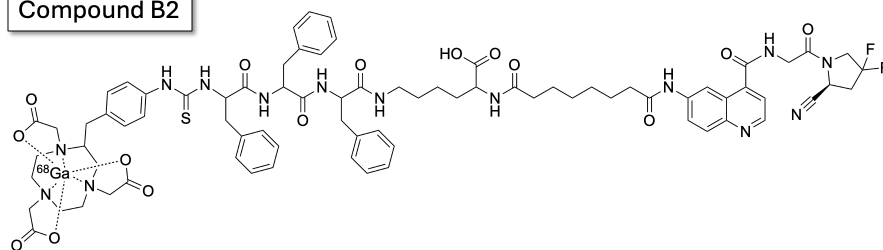


D. Compounds Made Obvious by US-121 and Jansen Meet All Requirements of the Claims

Following the straightforward logic and methodology in § VI.C, a skilled artisan would have produced particular radiotracers that incorporate compound 60 but retain the particular chelator and linker combinations in examples of US-121 (*i.e.*, compounds B1 to B4, below).

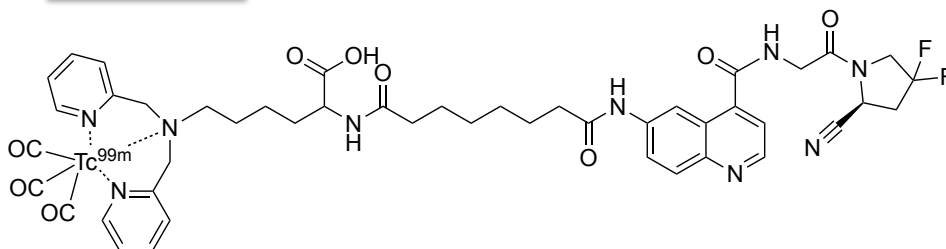


Compound B2



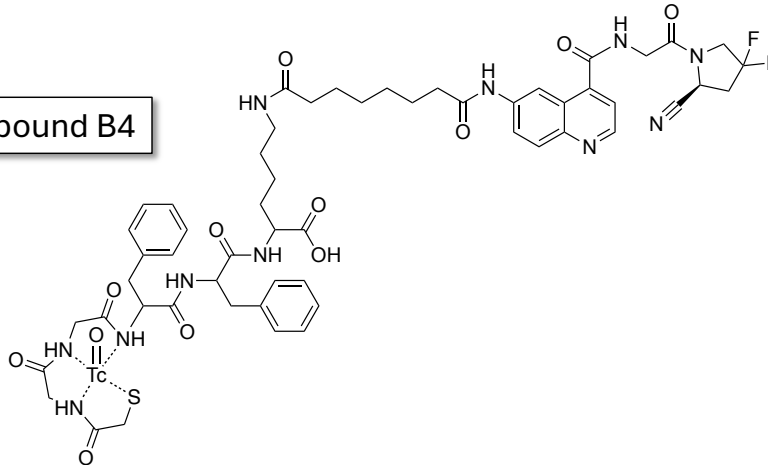
Chemical Formula: $C_{78}H_{89}F_2^{68}GaN_{14}O_{15}S$
Molecular Weight: 1600.64

Compound B3



Chemical Formula: $C_{46}H_{49}F_2N_9O_9^{99m}Tc$
Molecular Weight: 1008.86

Compound B4



Chemical Formula: $C_{55}H_{64}F_2N_{11}O_{12}S^{99m}Tc$
Molecular Weight: 1238.24

Each of compounds B1 to B4 falls within the scope of claims 1 to 4 of the '233 Patent.

First, each is a "low molecular weight compound" as each has a molecular

weight orders of magnitude below an antibody and are near or below 1500 Da.²²⁹

Second, each contains a chelator complexed with either ^{68}Ga or $^{99\text{m}}\text{Tc}$, which in each instance is a “radiolabeled functional group suitable for ...” PET or SPECT imaging that satisfies the “B” component.²³⁰

Third, each contains a chemical structure that forms distinct chemical bonds with both the radiolabeling moiety (“B”) and compound 60 FAP-targeting moiety (“A”) components of the compound, and thus is a “linker having bi-functionalization adapted to form a chemical bond with B and A.”²³¹

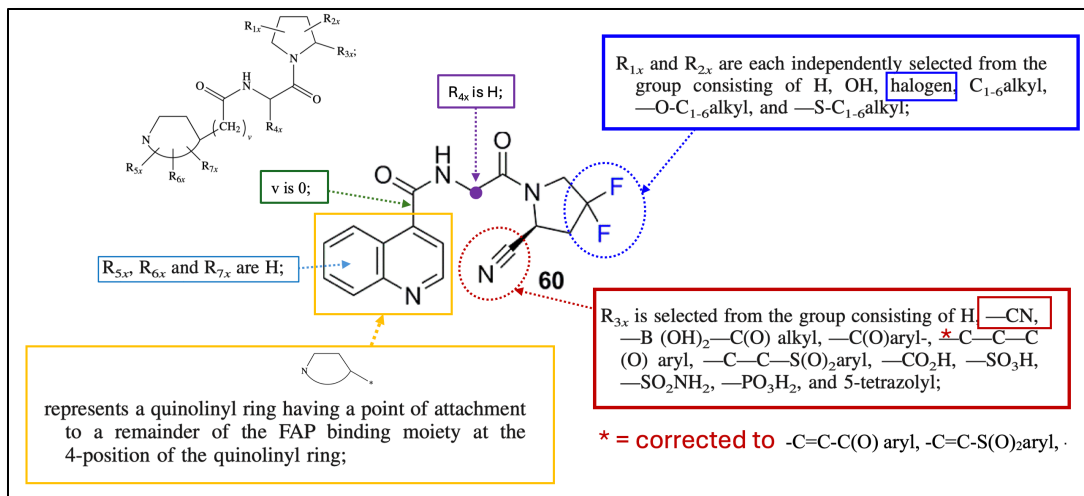
Finally, each contains compound 60, which is a “targeting moiety for FAP- α ” because of its high selectivity and binding affinity for FAP, and which thus meets the requirements of the “A” element of the claims (below).²³²

²²⁹ EX1003, ¶ 245.

²³⁰ EX1003, ¶ 242.

²³¹ EX1003, ¶ 243.

²³² EX1003, ¶ 202.



Skilled artisans would have reasonably expected that compounds B1-B4 would retain the selectivity and affinity of compound 60 because: (i) the size of the linker used would position the radiolabeling moiety to avoid it affecting the characteristics of the targeting moiety²³³ and (ii) based on experimentation by Jansen, attaching the linker at position C⁶ of the quinolinyl ring would not be expected to affect the selectivity and affinity for FAP of compound 60.²³⁴ And each of compounds B1 to B4 could be synthesized using straightforward synthetic procedures based on the descriptions in US-121.

Because compounds B1 to B4 each are obvious and within the scope of claims 1-4, each of those claims is unpatentable.

²³³ EX1003, ¶ 246.

²³⁴ EX1003, ¶ 178.

VII. No Secondary Indicia Exist or Are Relevant

Patentee may contend that compounds within the scope of claims 1-4 possess unexpected benefits or other secondary indicia of non-obviousness. Such an assertion has no legal merit. For claims to benefit from secondary considerations evidence, there must be a nexus between the evidence and the claims. Here, the claims capture any possible “B” and “L” component while the “A” component captures prior art compound 60 (along with its attributes). Any secondary considerations thus would be associated with prior art elements, not the claims. To the extent Patentee alleges secondary considerations exist, Petitioner respectfully submits such issues should be addressed after institution.

VIII. Grounds 3 & 4: All Challenged Claims are Unpatentable Under § 112(a)

Claims 1-4 are unpatentable because each claims immense genera of low molecular weight FAP-targeting compounds that lack written description in and were not enabled by the patent disclosure.

The claimed genera include any “low molecular weight” FAP-targeting compound that combines (i) a targeting moiety within the structural parameters of “A”, (ii) *any* “B” functional group suitable for optical imaging, PET or SPECT imaging, or radiotherapy, and (iii) *any* linker (“L”) having bi-functionalization adapted to form a chemical bond with “A” and “B.” The B-L components also can

be attached at **any** of 11 positions on “A” compounds.²³⁵ These claim parameters capture substantially more than 9.41×10^{27} (claim 4) and 1.08×10^{36} (claim 1) distinct B-L-A compounds reflecting immense structural diversity, particularly in B and L components.

But the specification *describes only two examples* of FAP-targeting compounds meeting the “B-L-A” definition. Instead of describing *species of B-L-A compounds* that demonstrate possession of the claimed genera, the disclosure provides lists of *optional components* that might be combined—disparate chelators, optical imaging and prosthetic groups, formula-based options for bifunctional linkers, with no restrictions on how to attach the B-L segment to the targeting moiety “A.” Which of these $10^{27}+$ possible combinations yield useful “B-L-A” compounds is unknown and is certainly not described.

The disclosure also fails to guide skilled artisans in the selection of B, L and A components, and equally important, how to arrange them, to yield compounds with the diagnostic or therapeutic utilities identified in the specification. Instead, it simply lists the A, B and L options, and permits the B-L moiety to be attached at any available position on the targeting moiety A. But, in the words of Dr. Pomper

²³⁵ EX1003, ¶ 94.

(an inventor), “developing a medical imaging agent is highly unpredictable.”²³⁶

Indeed, the diversity of characteristics of possible linkers and imaging moieties and their point of attachment on “A” can unpredictability affect whether a B-L-A compound will be a useful imaging or therapeutic agent. The absence of meaningful guidance in selecting and arranging the B, L and A options means that skilled artisans must make and test at least a fraction of the claimed genera of compounds to overcome this admitted unpredictability. Even if only one in a million compounds had to be tested, that would require synthesizing and testing more than *~9 sextillion compounds!* Such experimentation is far more than undue.

Consequently, the '233 Patent does not demonstrate possession of the vast remainder of compounds being claimed, and does not enable a skilled artisan to practice the full scope of the claimed genera without undue experimentation.

A. A Massive Number of FAP-Targeting Compounds Are Claimed

The claims capture an immense number and variety of B-L-A compounds reflecting innumerable combinations of targeting moieties, linkers and imaging moieties. Considering only the options from the various formulae and laundry lists in the specification, there are:

²³⁶ EX1002, 172 ¶¶ 30-32.

- (i) between 44 (claims 3/4) and **31,752** (claim 1) options for “A”;²³⁷
- (ii) between 33 (claim 4) to **5,225,957** options for “B”²³⁸ and
- (iii) more than **5.89 x 10²³** options for “L.”²³⁹

For example, all that is required of the “L” moiety is “bi-functionalization adapted to form a bond with A and B.” Few discrete linkers are actually described—instead, the specification provides formulae with numerous options for substituents at numerous positions.²⁴⁰ For example, in the linker formula below: (i) *every* segment is optional and can be arranged “in any order,” (ii) “R” groups can be entire classes of chemical substituents (“alkyl, substituted alkyl, cycloalkyl, ...”) and (iii) alkyl segments can have 1 to 8 repeats (below).²⁴¹

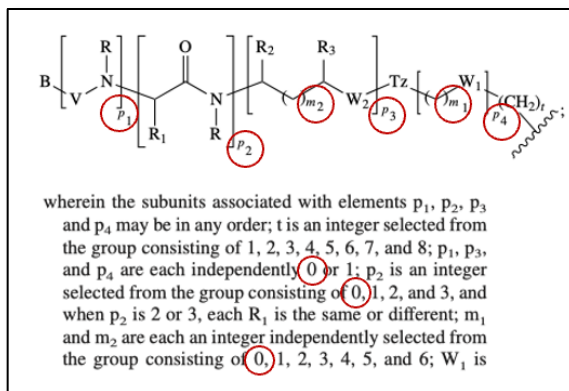
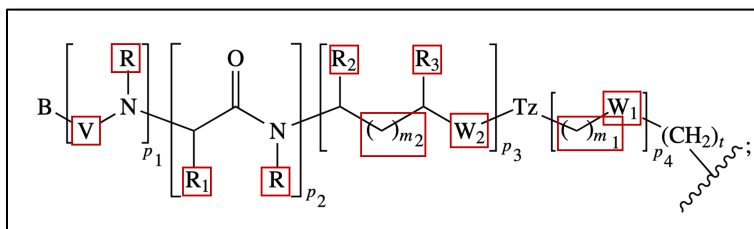
²³⁷ EX1003, ¶¶ 91-92.

²³⁸ EX1003, ¶¶ 88-89, Appendix B.

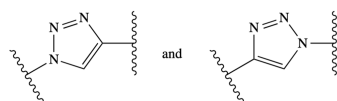
²³⁹ EX1003, ¶¶ 85-87; Appendix A.

²⁴⁰ EX1001, 14:57-15:48, 15:49-17:54; EX1003, Appendix B.

²⁴¹ EX1001, 14:57-15:48 ; EX1003, ¶ 85-86.



the group consisting of 0, 1, 2, 3, 4, 5, and 6; W_1 is selected from the group consisting of a bond, $-S-$, $-C(=O)-NR-$, and $-NR-C(=O)-$; W_2 is selected from the group consisting of a bond, $-S-$, $-CH_2-C(=O)-NR-$, $-C(O)-$, $-NRC(O)-$, $-NR'C(O)NR-$, $-NRC(S)NR_2-$, $-NRC(O)O-$, $-OC(O)NR-$, $-OC(O)-$, $-C(O)NR-$, $-NR-C(O)-$, $-C(O)O-$, $-(O-CH_2-CH_2)_q-$ and $-(CH_2-CH_2-O)_q-$, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-OR_4$, wherein R_4 is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove; Tz is a triazole group that can be present or absent and, if present, is selected from the group consisting of



each R_1 is independently H, C_1-C_6 alkyl, C_3-C_{12} aryl, $-(CH_2)_q-C_3-C_{12}$ aryl, $-C_4-C_{16}$ alkylaryl, or $-(CH_2)_q-C_4-C_{16}$ alkylaryl; R_2 and R_3 are each independently H and $-CO_2R_5$, wherein R_5 is selected from the group consisting of H, C_1-C_6 alkyl, C_3-C_{12} aryl, and C_4-C_{16} alkylaryl, wherein when one of R_2 or R_3 is CO_2R_5 , then the other is H; V is selected from the group consisting of $-C(O)-$, $-C(S)-$, $-NRC(O)-$, $-NRC(S)-$, and $-OC(O)-$; B is any optical

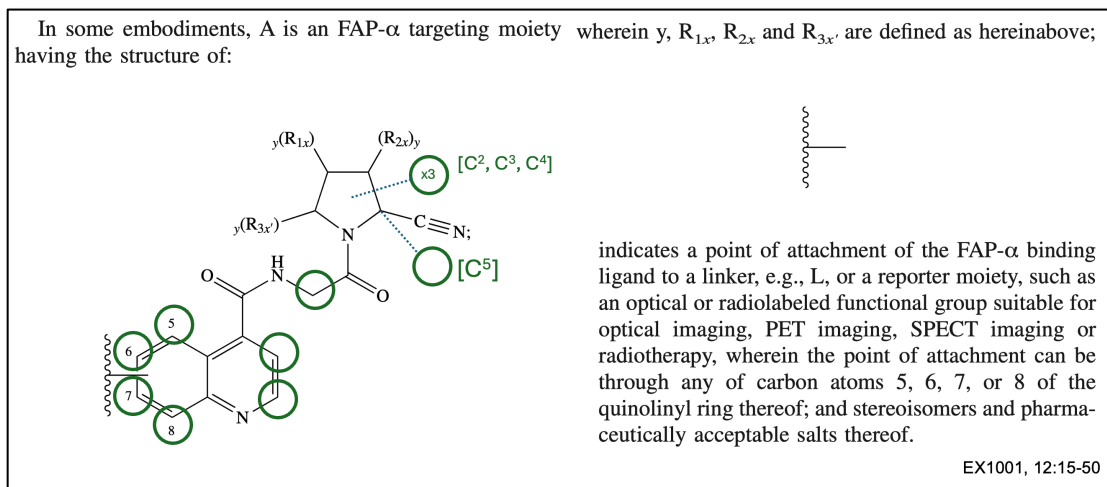
Even with simplifications (e.g., counting “alkyl” groups as only one option), these options yield $\sim 5.89 \times 10^{23}$ possible linker structures.²⁴²

The B options are more limited: 33 chelators, 6 prosthetic group formulae, and 10 prosthetic group-radionuclide examples. However, one prosthetic group

²⁴² EX1003, ¶ 86.

formula captures 5.2 million options.²⁴³

There also are **eleven** possible points of attachment for the B-L- moiety on the “A” moiety (below).²⁴⁴



The number of distinct B-L-A structures being claimed is calculated by multiplying the number of options for each of A, B and L and the 11 points of attachment, which yields the following numbers for the four claims.²⁴⁵

²⁴³ EX1001, 15:18-28; EX1003, ¶ 89, Appendix B.

²⁴⁴ EX1003, ¶ 93.

²⁴⁵ EX1003, ¶ 94.

	<i>B</i>	<i>L</i>	<i>A</i>	#	<i>Total</i>
<i>Claim 1</i>	5,225,956	5.89×10^{23}	31,752	11	1.08×10^{36}
<i>Claim 2</i>	5,225,956	5.89×10^{23}	528	11	1.79×10^{34}
<i>Claim 3</i>	5,225,956	5.89×10^{23}	44	11	1.49×10^{33}
<i>Claim 4</i>	33	5.89×10^{23}	44	11	9.41×10^{27}

The actual sizes of each claimed genera, however, are several orders of magnitude larger—the numbers above do not include: (i) options for “B” and “L” not described in the disclosure, (ii) combinations with different radionuclides, (iii) stereoisomers, tautomers, racemates, salts, and solvates.²⁴⁶

B. The Diversity of Choices Permitted by the Claims Renders the Properties of Many Claimed B-L-A Compounds Unpredictable

The diversity of substituent choices and points of attachment creates substantial uncertainty about the properties of the B-L-A compounds being claimed.

As Dr. Zeglis explains, even slight modifications to the structure of the FAP-targeting moiety can unpredictably impact its affinity and selectivity for its molecular target, making many such modifications a “tricky endeavor.”²⁴⁷ Dr.

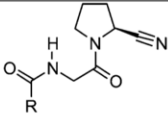
²⁴⁶ EX1003, ¶¶ 95-96.

²⁴⁷ EX1003 ¶ 59(b).

Pomper likewise portrays producing imaging agents as “highly unpredictable.”²⁴⁸

And as shown in Jansen and other prior art, substitutions in the pyrrolidine ring, at the glycine α -carbon, or at different positions on the quinolinyl ring can significantly and adversely impact affinity and selectivity for FAP.²⁴⁹

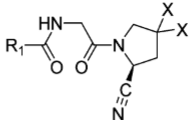
For example, a methyl group at the C⁵ of the quinolinyl ring (compound 53) exhibited high affinity and selectivity for FAP, but methoxy (#57, C⁵-OMe), bromine (#62, C⁵-Br) and cyano (#63, C⁵-CN) groups at C⁵ significantly reduced FAP affinity and selectivity (below).²⁵⁰

							
		IC ₅₀ (μM)					SI (FAP/PREP) ^a
Nr.	R	FAP	PREP	DPPIV	DPP9	DPPII	
53		0.0043± 0.0001	9.1 ± 0.6	>100	>50	>100	2116.3
57		16.6 ± 0.6	1.28 ± 0.06	>100	>100	>100	0.08

²⁴⁸ EX1002, 172 ¶¶ 30-32.

²⁴⁹ EX1003, ¶ 174, 178.

²⁵⁰ EX1003, ¶ 178; EX1006 (Jansen), 3061-3062.

									
Nr	R ₁	X	IC ₅₀ (μM)					SI (FAP/PREP) ^a	
			FAP	PREP	DPPIV	DPP9	DPP2		
60		F,F	0.0032± 0.0004	>1.8 ± 0.2	>100	>12.5	>100	562.5	
62		F,F	9.0 ± 0.5	9.3 ± 0.4	>100	≥25	>50	1.0	
63		F,F	7.2 ± 0.3	16.8 ± 0.7	>100	>25	>50	2.3	

Similarly, introducing a methyl group at the glycine α -carbon substantially reduced or even abolished FAP inhibition.²⁵¹ A skilled artisan also would have been concerned that attaching the linker to the pyrrolidine group or the C² or C³ positions in the quinolinyl ring would cause steric interference that affects the ability of the “A” moiety to interact with its target, FAP.²⁵²

The individual moieties chosen for B, L and A—and how they are attached to the A moiety—can cause unpredictable effects within B-L-A compounds. As

²⁵¹ EX1006 (Jansen), 3056 (D-Ala in place of glycine reduced FAP affinities of compounds 11 and 12 by 600- and 300-fold, while L-Ala and 1-amino-1-carboxycyclopropane abolished FAP inhibition).

²⁵² EX1003, ¶¶ 178, 276, 297; EX1006, 3061-62.

the '233 Patent recognizes, a key question that must be answered is whether the starting FAP-binding “A” moieties “can be modified, e.g., conjugated with labeling groups *without significantly losing their potency*.”²⁵³ Preserving the potent and selective binding to FAP of the starting “A” moiety is important because (per the specification) “[t]he highly potent and specific binding moiety targeting FAP- α enables its use in nuclear imaging and radiotherapy.”²⁵⁴ In addition, the B-L-A compound must be stable in bodily fluids and *in vivo*²⁵⁵ and must have sufficient bioavailability—these three characteristics of a B-L-A compound are essential to viable molecular imaging or therapeutic agents.²⁵⁶

Dr. Pomper recognized this unpredictability. As he testified in a § 1.132 declaration submitted during examination, the “art of developing a medical

²⁵³ EX1001, 7:46-56 (emphasis added); 34:63-35:52.

²⁵⁴ EX1001, 7:41-43.

²⁵⁵ EX1001, 38:65-39:9 (must avoid structures yielding “inherently unstable compounds”), 35:42-46 (stability against metabolism *in vivo* before excretion important to molecular imaging); 35:47-52 (stability in bodily fluids important for *in vitro* applications); EX1003, ¶ 59.

²⁵⁶ EX1003, ¶¶ 59, 133, 275, 277.

imaging agent” was “highly unpredictable” (below).²⁵⁷

30. Further, due to the high unpredictability of the medical imaging art, I believe one of ordinary skill in the art would not reasonably expected success in modifying the cited prior art to arrive at the compounds of the pending claims for medical imaging applications.

31. There are numerous important parameters which need to be taken into consideration for successfully developing a FAP imaging agent. Those parameters include, for example, affinity for FAP, selectivity (specificity) for FAP, ease of synthesis, and biodistribution, and the like. It is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with a medical condition. The high specificity allows the imaging agent to bind selectively to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein. The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

32. The unpredictability of the art is clearly manifested by the documented failure of a compound disclosed in Zimmerman.

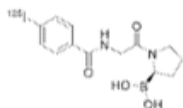
He also testified this unpredictability can result in “failure” of a potential imaging candidate, citing Meletta.²⁵⁸ But the unpredictability he references for *one* compound relative to prior art is dwarfed by the present claims—one cannot predict from the guidance in the ’233 Patent which of the myriad possible combinations will be a successful candidate for medical imaging. It identifies only *two* but but claims more than 10²⁷.

²⁵⁷ EX1002, 172 ¶¶ 30-32.

²⁵⁸ EX1002, 172-173, ¶¶ 32-37, Meletta (EX1008), 2089, 2095; *see* § V.A.2.

32. The unpredictability of the art is clearly manifested by the documented failure of a compound disclosed in Zimmerman.

33. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for atherosclerotic



[¹²⁵I]MIP-1232

plaque, and was determined as not suitable for the application. See Meletta et al., *Molecules*, 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta").

34. As provided on page 2089 of Meletta, while pronounced binding of [¹²⁵I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Based on these data, Meletta could not conclude on the selectivity of [¹²⁵I]MIP-1232 for FAP.

35. Accordingly, because of the low specificity MIP-1232 displayed in the testing, Meletta concluded that MIP-1232 was not suitable for the medical imaging application for the particular medical condition being tested in Meletta. *Id.* at 2095.

36. Based on my review, I am not aware of any other compounds disclosed in Zimmerman that fared better than MIP-1232 and that was developed successfully as a medical imaging agent.

37. The failure of investigations with MIP-1232, which is a compound disclosed in the cited prior art, is especially telling as it demonstrates the high unpredictability of the art and lack of reasonable expectation of success by combining the prior art to arrive at the compounds of the pending claims for medical imaging applications.

The set of choices for B, L and A reflected in each B-L-A compound directly implicates whether that compound will be useful in diagnostic or therapeutic applications—the sole utility identified by the patent.²⁵⁹ Yet, a skilled artisan could not have predicted from the structure of many of the claimed B-L-A compound alone whether they possess the necessary characteristics of a viable imaging or radiotherapy candidate.²⁶⁰ Instead, she would have to synthesize and

²⁵⁹ EX1001, 4:27-51 (describing uses of B-L-A compounds).

²⁶⁰ EX1003, ¶¶ 275-277.

test such compounds to determine if any (i) retained high affinity and selectivity for FAP, (ii) was stable, and (iii) had adequate bioavailability.²⁶¹

C. All Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure.²⁶² “To fulfill the written description requirement, a patent owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and demonstrate that by disclosure in the specification of the patent.”²⁶³

Claims to genera of chemical compounds require “a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other

²⁶¹ EX1003, ¶ 277.

²⁶² *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

²⁶³ *Idenix Pharm., LLC v. Gilead Scis., Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019) (quoting *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991))(internal quotes omitted).

materials.”²⁶⁴ “[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.”²⁶⁵ As the Federal Circuit has explained:

... just because a moiety is listed as one possible choice for one position does not mean there is *ipsis verbis* support for every species or sub-genus that chooses that moiety. Were this the case, a “laundry list” disclosure of every possible moiety for every possible position would constitute a written description of every species in the genus. This cannot be because such a disclosure would not “reasonably lead” those skilled in the art to any particular species.²⁶⁶

The written description thus must “show that one has truly invented the genus..., [o]therwise, one has only a research plan, leaving it to others to explore the

²⁶⁴ *Ariad*, 598 F.3d at 1350 (quoting *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993)).

²⁶⁵ *Ariad*, 598 F.3d at 1350.

²⁶⁶ *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571 (Fed. Cir. 1996); accord *Regents of Univ. of Minn. v. Gilead Sciences, Inc.*, 61 F. 4th 1350, 1357 (Fed. Cir. 2023).

unknown contours of the claimed genus.”²⁶⁷

“[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of ordinary skill in the art can visualize or recognize the members of the genus.”²⁶⁸ “One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent...[I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus.”²⁶⁹ A disclosure that fails to “provide sufficient blaze marks to direct a POSA to the specific subset” of a genus with the claimed function or characteristic will not satisfy § 112(a).²⁷⁰

²⁶⁷ *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

²⁶⁸ *Idenix*, 941 F.3d at 1164 (quoting *Ariad*, 598 F.3d at 1350 (internal quotation marks omitted)).

²⁶⁹ *AbbVie*, 759 F.3d at 1299-1300.

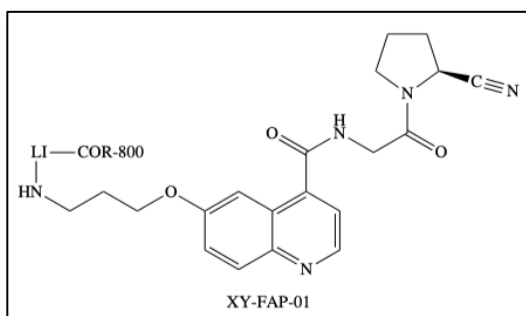
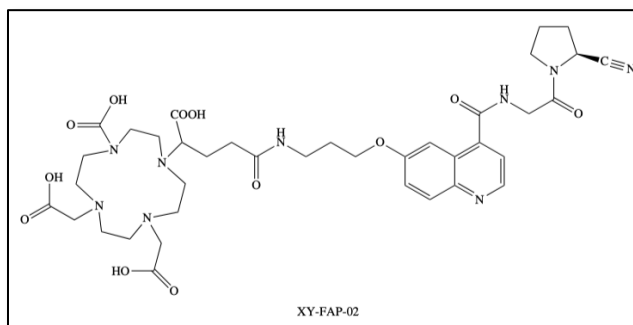
²⁷⁰ *Idenix*, 941 F.3d at 1164.

1. The Written Description Does Not Describe a Representative Number of Species of the Immense Genera of B-L-A Compounds Being Claimed

The '233 Patent disclosure *describes only two examples* of FAP-targeting B-L-A compounds (*i.e.*, one optical imaging agent and one SPECT imaging agent). Given the admitted unpredictability of combining different B and L moieties in varying ways with an “A” moiety (*see* § VIII.B), simply listing large numbers of possible choices for A, B and L components does not constitute a description of species sufficient to demonstrate possession of the claimed genera.

(a) The Specification Identifies Only Two B-L-A Compounds that Are Not Representative of the Claimed Genera of B-L-A Compounds

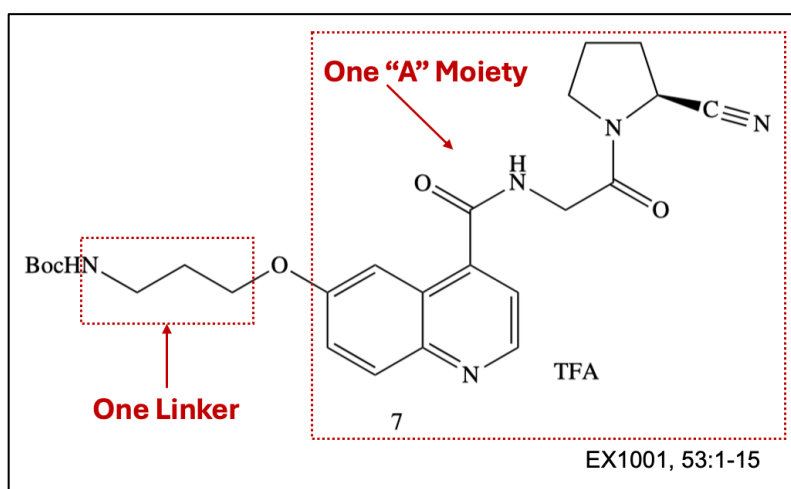
The two complete B-L-A structures of FAP-targeting molecular imaging agents within the scope of claim 1 depicted in the '233 Patent disclosure are: (i) an optical imaging agent designated XY-FAP-01 and (ii) a SPECT imaging radiopharmaceutical designated XY-FAP-02-[In] (below).²⁷¹



²⁷¹ EX1003, ¶ 249.

These two examples plainly are not representative of the immense diversity of B-L-A compounds within the claimed genera. In fact, because the two compounds derive from a single intermediate (compound 7), they illustrate two B-L-A compounds having:

- (i) **one** “A” FAP-targeting moiety,
- (ii) **one** straight-chain alkyl (propyl) “L” linker (below),²⁷²



- (iii) **one** optical (*i.e.*, the fluorophore IRDye-800CW) and **one** chelator (*i.e.*, a DOTA chelator with ¹¹¹In), and
- (iv) **one** point of and manner of attachment of the B-L component to the “A” moiety (*i.e.*, an ether linkage at C⁶ of the quinolinyl ring).

²⁷² EX1001, 53:53-5:60 (intermediate compound 7 was used to make both examples); EX1003, ¶ 250.

The two examples provide no insights on every variable influencing how B, L and A moieties might be selected and combined to yield B-L-A compounds.

Importantly, there are **zero** examples (prophetic or actual) of assembled B-L-A compounds (*i.e.*, what the claims require) that:

- (i) incorporate **any** radiolabeled prosthetic group;²⁷³
- (ii) incorporate **any** chelator-radionuclide combinations “suitable for” PET imaging;²⁷⁴
- (iii) incorporate linkers with **more complex** structures (*e.g.*, those conferring hydrophobic characteristics, having a larger size, greater rigidity, etc.), or
- (iv) **attach** the B-L structure to any of **other 10 positions** in the “A” moiety, despite the demonstrated unpredictability of doing so.²⁷⁵

The description thus describes **zero** “species” within nearly every distinct sub-category (“sub-genera”) of B-L-A compounds being claimed.²⁷⁶ The two described examples (XY-FAP-01 and XY-FAP-02) plainly are not representative

²⁷³ EX1003, ¶¶ 252-253.

²⁷⁴ EX1003, ¶ 261.

²⁷⁵ EX1003, ¶ 93, 178.

²⁷⁶ EX1003, ¶¶ 250, 251.

of the broad and diverse genera of $10^{27}+$ to $10^{36}+$ distinct FAP-targeting B-L-A compounds being claimed.

(b) *The Laundry Lists and Formulae for B and L Moieties Do Not Describe Useful Species of the Claimed B-L-A Compounds and Even Ignore Known Options*

An adequate description of a genus of chemical compounds requires a “precise definition, such as by structure, formula ... of *species falling with the genus* sufficient to distinguish the genus from other materials.”²⁷⁷ Here, that requires identification of the structures of *species of B-L-A compounds* with the diagnostic or therapeutic utility identified in the specification.²⁷⁸ Listing possible options of components that *may* be combined to yield the hypothetical B-L-A compounds does not demonstrate possession of the claimed genera of B-L-A compounds.²⁷⁹

That is particularly true here, where not every one of the $10^{27}+$ possible

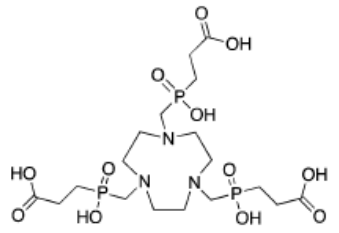
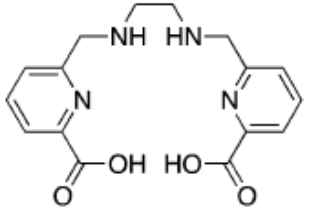
²⁷⁷ *Ariad*, 598 F.3d at 1350 (emphasis added) (quoting *Fiers*, 984 F.2d at 1171).

²⁷⁸ EX1001, 4:27-51, 7:41-43 (“The highly potent and specific binding moiety targeting FAP- α enables its use in nuclear imaging and radiotherapy”); 7:46-56 (compounds are “potent and selective” and “can be modified ... without significantly losing their potency”); 34:63-35:52.

²⁷⁹ *Fujikawa*, 93 F.3d at 1571, *Regents*, 61 F. 4th at 1357.

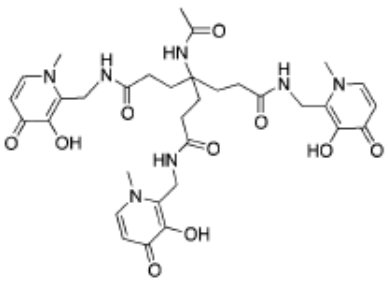
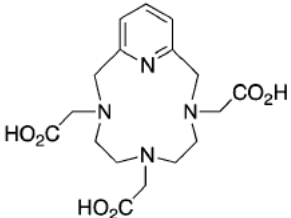
combinations of A, L and B moieties will yield B-L-A compounds that can be used in imaging or radiotherapy. The '233 Patent thus provides no “blaze marks” that identify patent-eligible species and instead provides only “a research plan leaving others to explore the unknown contours of the claimed genus.”²⁸⁰

Notably, while the specification lists many possible choices for chelators and prosthetic groups via its formulae and laundry lists, it omits many well-known before 2017. For example, Dr. Zeglis identified several chelators known to be suitable for ⁶⁸Ga before 2017 that were not identified in the specification.²⁸¹

TRAP	 <p>TRAP (PRP9, TRAP-Pr), 1,4,7-triazacyclononane-1,4,7-tris[methyl(2-carboxyethyl)phosphinic acid], N₃O₃ CN = 6 (+ distal carboxylates CN = 9?)</p>	EX1013 (Price), 274-80; EX1011 (Zeglis 2013), 1887-88.
H ₂ dedpa	 <p>H₂dedpa, 1,2-[[6-(carboxy)-pyridin-2-yl]-methylamino]ethane, N₄O₂ CN = 6</p>	EX1013 (Price), 279; EX1011 (Zeglis 2013), 1888.

²⁸⁰ *Fujikawa*, 93 F.3d at 1571; *AbbVie*, 759 F.3d at 1300.

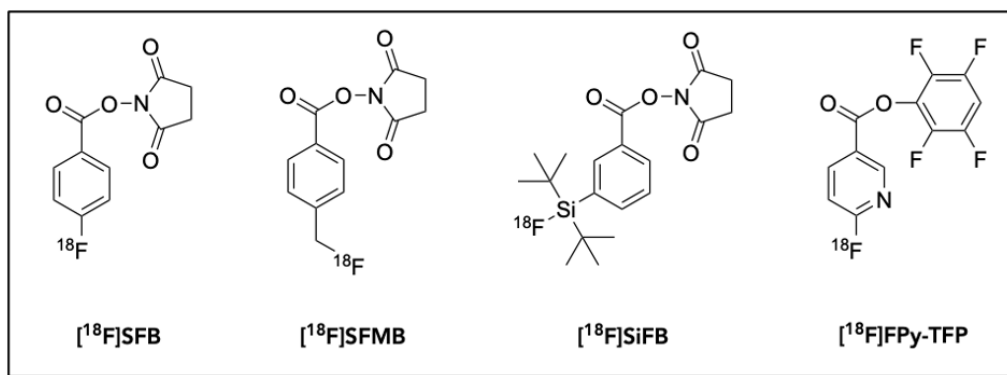
²⁸¹ EX1003, ¶ 266.

CP256	 <p>CP256, O₆ CN = 6</p>	EX1013 (Price), 278.
PCTA	 <p>PCTA, 3,6,9,15-tetraazabicyclo[9.3.1]- pentadeca-1(15),11,13-triene-3,6,9,- triacetic acid, N₄O₃ CN = 7</p>	EX1013 (Price), 279.

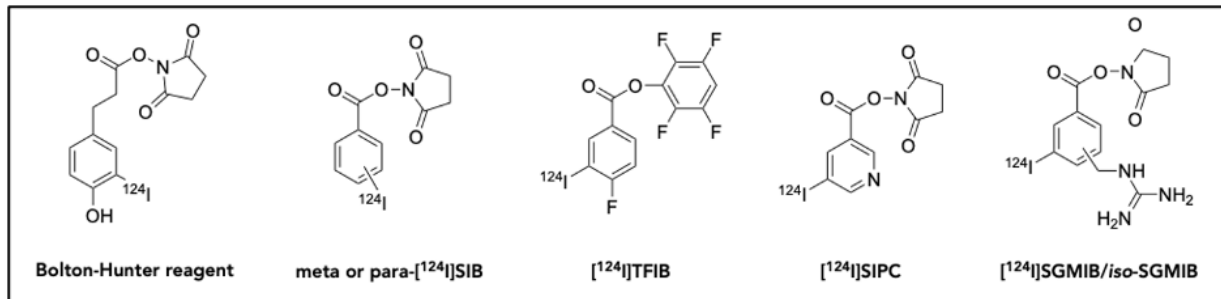
Likewise, he identified several prosthetic groups well-known before 2017 that were not be identified,²⁸² including:

- [¹⁸F]SFB, [¹⁸F]SFMB, [¹⁸F]SiFB, and [¹⁸F]FP_y-TFP;

²⁸² EX1003, ¶¶ 254-257; EX1019, 479-81.



- Bolton-Hunter reagent, $[^{124}\text{I}]\text{SIB}$, $[^{124}\text{I}]\text{TFIB}$, $[^{124}\text{I}]\text{SIPC}$, and $[^{124}\text{I}]\text{SGMIB}$:



In *Idenix*, the Federal Circuit affirmed a finding of no written description because the specification “provides no indication that any nucleosides *outside of those disclosed in its formulas could be effective* to treat HCV—much less any indication as to *which* of those undisclosed nucleosides would be effective.”²⁸³ Likewise here, there is no disclosure of B-L-A compounds that incorporate known but not described chelators and prosthetic groups and no indication *which* of them (or any others beside the two examples XY-FAP-01 and XY-FAP-02) have the

²⁸³ *Idenix*, 941 F.3d at 1164.

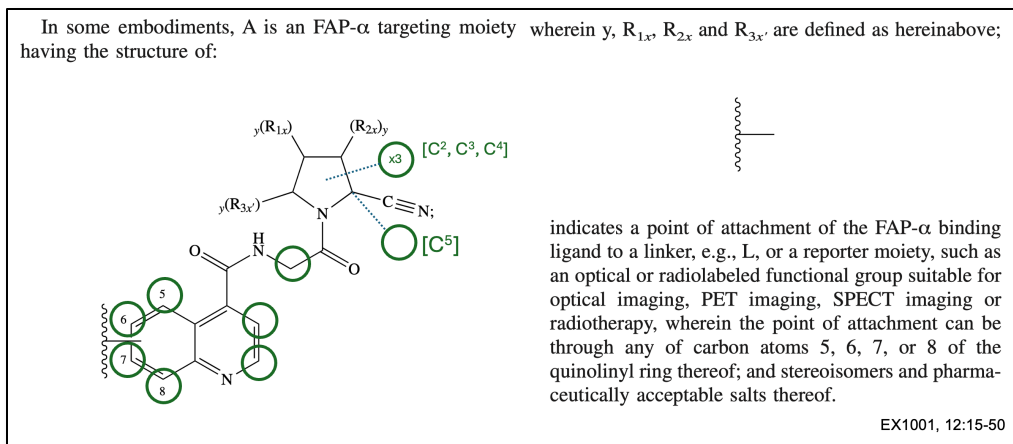
characteristics necessary for diagnostic or therapeutic utility.

2. The '233 Patent Disclosure Does Not Identify a Structure-Function Relationship for FAP-Targeting Compounds

As explained in § VIII.A, claim 1 captures *all* low molecular weight FAP-targeting compounds with the structure B-L-A that are useful for optical imaging, PET or SPECT imaging, or radiotherapy. There are more than 10^{24} compounds being claimed, spanning those incorporating any optical dye, chelator, prosthetic group, radiometal, radiohalogen or linker structure.

There is immense structural diversity in the claimed genera. For example, the claimed B-L-A compounds can attach the B-L moiety to any of 11 positions on the “A” moiety, but a skilled artisan, based on prior art and their knowledge, would have expected that doing so at many of those positions art would cause unpredictable effects on the binding and selectivity of the “A” targeting moiety (e.g., positions C², C³ and C⁵ of the quinolinyl ring, on the glycine α -carbon or at positions C², C³ or C⁴ of the pyrrolidine ring)(below).²⁸⁴

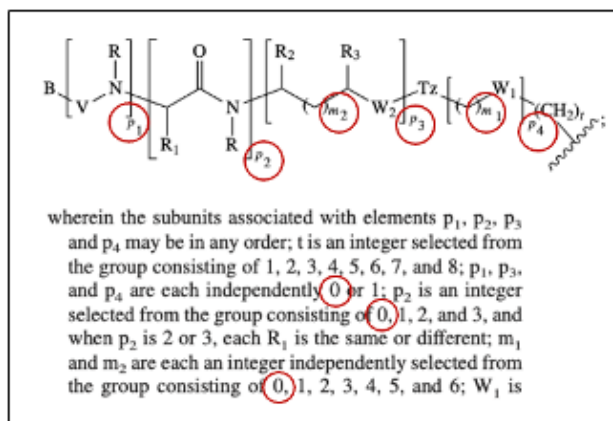
²⁸⁴ EX1003, ¶¶ 93, 178.



Similarly, the claims capture B-L-A compounds with immensely diverse linker structures, including those within highly variable formulae. For example, one linker formula specifies an array of 5 subunits that “may be in any order” and where one, several or all subunits can be omitted (1944 distinct arrangements) (below).²⁸⁵ That “linker” can even be a single methylene group, which if used to link a large chelator or optical dye structure and an “A” targeting moiety would raise substantial questions about whether steric or chemical interference would affect FAP binding by the targeting moiety.²⁸⁶

²⁸⁵ EX1001, 14:57-65, 15:1-6, 26-27.

286 EX1003, ¶ 85(b).



The patent's linker formulae also capture highly heterogenous linker structures.

For example, choices for R , R_1 , R_2 , R_3 , and T_z include aryl, substituted aryl,

heteroaryl and alkylaryl substituents (below).²⁸⁷ But incorporating multiple large,

aromatic substituents within the linker moiety would introduce significant size and

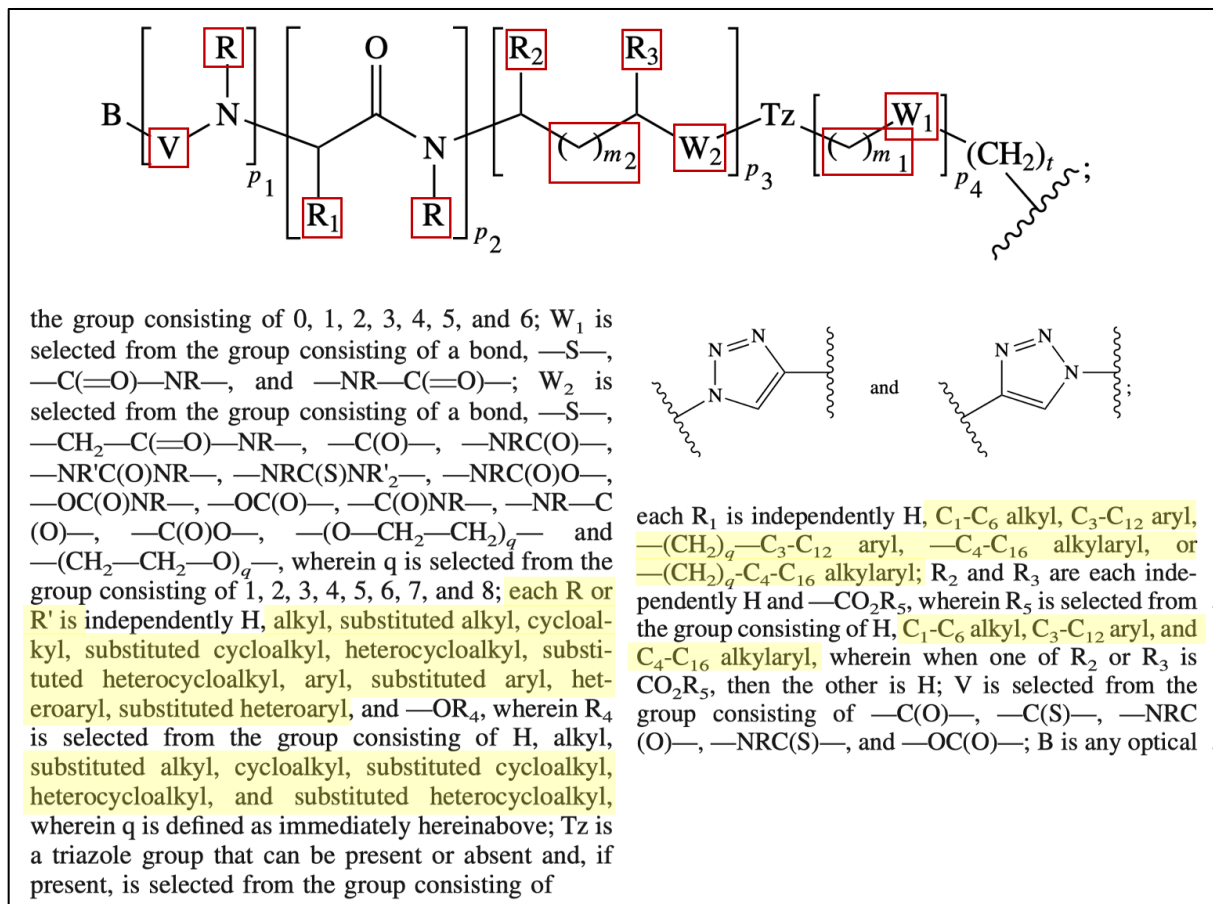
hydrophobic character into B-L-A structure, which could adversely affect the

bioavailability, affinity and selectivity of the B-L-A compound, which would not

be true for B-L-A compounds without those substituents.²⁸⁸

²⁸⁷ EX1001, 14:57-15:48.

²⁸⁸ EX1003, ¶ 270.



Consequently, the '233 Patent disclosure does not identify to a skilled artisan *a common structural feature* shared by all low molecular weight FAP-targeting compounds being claimed by claims 1-4 that have the disclosed diagnostic or therapeutic utility.²⁸⁹

3. Dependent Claims 2-4 Lack Written Description

Dependent claims 2-4 depend from claim 1 and do not alter significantly the size or character of the claimed "B-L-A" compounds. These claims instead specify

²⁸⁹ EX1003, ¶ 253, 248, *see also* ¶¶ 251, 270.

certain selections for R_{1x} and R_{2x} (claim 2), R_{3x} (claim 3), and the “B” component (claim 4). They lack written description for the same reasons explained above (§§ VIII.C.1, VIII.C.2).

D. All Challenged Claims Are Not Enabled

All challenged claims are unpatentable for lack of enablement.

The enablement requirement provides a “simple statutory command”—“[i]f a patent claims an entire class of processes, machines, manufactures, or compositions of matter the patent’s specification *must enable a person skilled in the art to make and use the entire class*.”²⁹⁰ “In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable.”²⁹¹ “Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.”²⁹² The enablement requirement only allows for a specification to “call for a reasonable amount of experimentation

²⁹⁰ *Amgen v. Sanofi*, 598 U.S. 594, 610 (2023) (emphasis added).

²⁹¹ *Id.*

²⁹² *Wyeth & Cordis Corp. v. Abbott Laboratories*, 720 F.3d 1380, 1383-84 (Fed. Cir. 2013).

to make and use a claimed invention.”²⁹³ “[A] patentee ‘cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification.’”²⁹⁴

Although not required, enablement may be assessed using the *Wands* factors, which consider: “(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention.”²⁹⁵

Where the scope of the claims is large, few working examples are disclosed, and the only guidance to practice “the full scope of the invention [is] to use trial and error to narrow down the potential candidates...the asserted claims are not

²⁹³ *Amgen*, 598 U.S. at 612.

²⁹⁴ *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019) (quoting *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010)).

²⁹⁵ *Idenix*, 941 F.3d at 1156 (citing *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)).

enabled.”²⁹⁶

When a claim covers functional material, and a disclosure provides numerous variables, “the specification’s guidance as to how such variables would or would not impact the functionality of the claimed” technology is relevant.²⁹⁷

“Given the unpredictability of the art at the time and the serious doubts held by those of skill in the art...merely stating” a technology will work “is not sufficient to enable one of skill in the art that it would indeed function” as intended.²⁹⁸

“It is well established that the enablement requirement of § 112 incorporates the utility requirement of § 101.”²⁹⁹ A claimed invention must be *presently useful*—stating a hypothesis and proposing testing to determine its accuracy is insufficient.³⁰⁰ Further, if a claim encompasses significant numbers of inoperative

²⁹⁶ *Baxalta, Inc. v. Genentech, Inc.*, 579 F.Supp.3d 595, 615-16 (D. Del. 2022).

²⁹⁷ *Enzo*, 928 F.3d at 1347.

²⁹⁸ *Id.*

²⁹⁹ *In re Fisher*, 421 F.3d 1365, 1378 (Fed. Cir. 2005).

³⁰⁰ *In re ’318 Pat. Infringement Litig.*, 583 F.3d 1317, 1327 (Fed. Cir. 2009); *In re Kirk*, 376 F.2d, 936, 942 (C.C.P.A. 1967).

embodiments, and a skilled artisan must engage in undue experimentation to identify the operative ones, that renders the claims non-enabled.³⁰¹

1. Independent Claim 1 is Not Enabled

The '233 Patent does not enable the vast genus of FAP-targeting compounds being claimed— more than 10^{27} (claim 4) to 10^{36} (claim 1) distinct “B-L-A” compounds pieced together from laundry lists of possible linkers, chelators, and prosthetic groups. But to determine which of these possess the requisite characteristics of a viable molecular imaging or radiotherapeutic agent—“very potent and specific binding” to FAP, along with stability and sufficient bioavailability—would require an impossible scale of experimentation.³⁰² The full scope of the claims is thus not enabled.

(a) Immense and Diverse Genera of B-L-A Compounds Are Claimed

As explained in § VIII.A, the scope of the claims is enormous: between 1.08×10^{36} (claim 1) and 9.41×10^{27} (claim 4) distinct B-L-A compounds are claimed. The B-L-A compounds in each genera also have tremendous structural variability

³⁰¹ *Crown Operations Int’l Ltd v. Solutia Inc.*, 289 F.3d 1367, 1380, n.8 (Fed. Cir. 2002); *Atlas Powder Co. v. E.I. Dupont De Nemours*, 750 F.2d 1569, 1577 (Fed. Cir. 1984).

³⁰² EX1001, 7:41-56; EX1003, ¶¶ 275, 278.

due to the innumerable combinations of B and L structures they may contain.

(b) *Producing Viable B-L-A Radiopharmaceutical or Imaging Agents Was Unpredictable and the Patent and Prior Art Provides No Guidance to Navigate that Uncertainty*

As Dr. Pomper—a named inventor—testified, : “... the art of developing a medical imaging agent is **highly unpredictable** as it involves optimizing numerous parameters including the specificity of the compound.”³⁰³ His admission explains **why** the present claims are not enabled—the ’233 Patent simply lists options for B, L and A components and leaves to the skilled artisan the entirety of the task of selecting between $\sim 10^{27}$ and $\sim 10^{36}$ possible combinations of those components to yield B-L-A compounds that possess the necessary affinity, selectivity, stability and bioavailability to have utility as molecular imaging or therapeutic agents.³⁰⁴

Dr. Pomper’s testimony underscores the challenges in overcoming the unpredictability of developing radiopharmaceutical and molecular imaging agents. US-633 reported that a boronic acid targeting moiety (Compound 1024) had high

³⁰³ EX1002, 172 ¶¶ 31; *also* ¶¶ 30 (“due to the high unpredictability of the medical imaging art”), 32, 37 (failure of MIP-1232 “demonstrates the high unpredictability of the art”), 43 (differences in B-L-A compounds attributable to use of particular linkers “are surprising and unexpected”).

³⁰⁴ EX1003, ¶ 275.

affinity for FAP (IC₅₀ of 3 nM), suggesting it would be a promising candidate for a FAP-targeting radiopharmaceutical. Meletta, however, demonstrated that this targeting moiety, when incorporated into a radiopharmaceutical ([¹²⁵I]MIP-1232), lacked sufficient selectivity for FAP.³⁰⁵ As Dr. Pomper testified, “[t]he unpredictability of the art is clearly manifested *by the documented failure*” of the [¹²⁵I]MIP-1232 compound.³⁰⁶ Notably, claim 1 captures boronic acid FAP-targeting moieties, but the specification provides no guidance to overcome this “documented failure.”

As explained in § VIII.B, a skilled artisan would not have been able to predict the effects of many combinations of B, L and A moieties permitted by the claims (as well as where the B-L moieties is attached on the “A” moiety). For example, the data reported in Jansen and other prior art showed widely varying effects on FAP affinity and selectivity from substitutions at different positions in FAP-targeting compounds meeting the claim parameters.³⁰⁷ The prior art thus

³⁰⁵ EX1003, ¶ 132; EX1004 (US-633), [0185] (Table 2) (showing the IC₅₀ value for compound 1024); EX1008 (Meletta), 2089-2090.

³⁰⁶ EX1002, 172 (¶ 32).

³⁰⁷ EX1006, 3057-58 (Table 2), 3059-60 (Table 3), 3061-62 (Table 4, 5); EX1003, ¶ 178.

documents, rather than resolves, the unpredictability of making modifications to “A” targeting moieties, which occurs when attaching them to B-L moieties.

The ‘233 Patent specification also does not guide the selection of combinations of B, L and A components to overcome this unpredictability—it instead strains to avoid favoring any particular B or L moieties. Other than two examples that share the same combination of targeting moiety and linker, it provides no guidance about *particular combinations* of B, L and A components. Its formulae permit with enormous variation in possible linker structures,³⁰⁸ and simply *lists* examples of B and L components, portraying them as “some” or “particular” examples, and emphasizing they are only “representative” and that chelators/prosthetic groups/dyes that can be used “are not limited to” these examples.³⁰⁹ Yet, the claims indiscriminately claim *any and all* possible combinations.

The unpredictability associated with the myriad possible combinations within by the immense genera of each claim is not answered by the teachings in the patent disclosure or knowledge in the prior art. Consequently, a skilled artisan would need to draw upon their own training and judgment to select combinations

³⁰⁸ EX1001, 14:60-15:48, 15:49-16:8, 16:15-17:45, 17:58-18:34.

³⁰⁹ EX1001, 17:56-60, 19:8-10, 26:25.

of A, B and L moieties, and for many of them, would need to synthesize sufficient quantities of each hypothetical B-L-A compound and perform experiments to determine its characteristics.³¹⁰

(c) Undue Experimentation Would Be Required to Practice the Full Scope of Claimed B-L-A Compounds

A skilled artisan attempting to practice the full scope of the claims would need to engage in far more than undue experimentation—it requires an impossible scale of experimentation.

As Dr. Zeglis explains, skilled artisans would have expected that many compounds could be designed that fall within the scope of the claims and would have properties that render them viable molecular imaging or radiopharmaceutical agents.³¹¹ However, many combinations of A, B and L moieties will yield B-L-A compounds that a skilled artisan would doubt will possess those requisite characteristics, including compounds that:

- incorporate linkers containing highly hydrophobic or large, bulky pendant groups;
- attach the linker-imaging moiety at positions on the targeting moiety that adversely affect its binding affinity and selectivity for FAP;

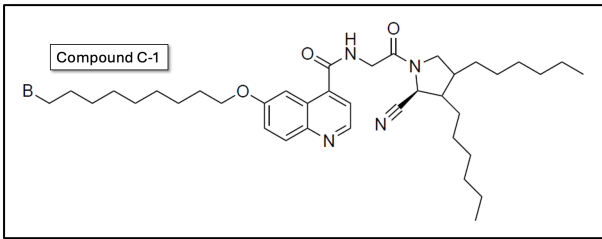
³¹⁰ EX1003, ¶ 277.

³¹¹ EX1003, ¶ 276.

- incorporate bonds or moieties that render the compound unstable within the physiological environment; and
- incorporate linker or imaging moieties in a way that that causes steric or other effects that adversely affect delivery of the radionuclide to the target tissue within its radioactive half-life.³¹²

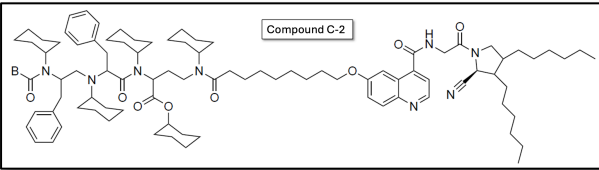
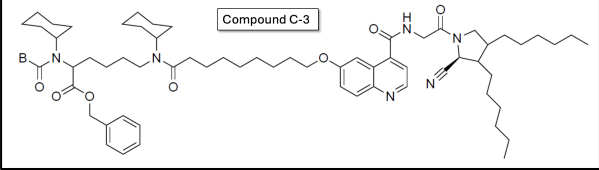
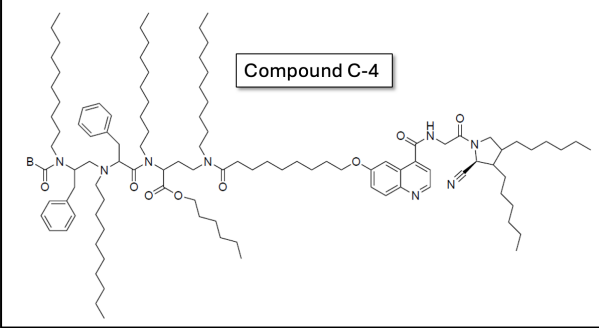
Dr. Zeglis devised a series of examples of compounds with particular linkers to illustrate these types of problems. Each has a structure that a skilled artisan could not have predicted would retain high affinity and selectivity for FAP, was stable under physiological conditions (*e.g.*, in plasma), and had adequate bioavailability.³¹³

(i) Hydrophobic Structures

<i>Compound</i>	<i>Issues</i>
 <p>Chemical structure of Compound C-1 is shown. It features a long aliphatic linker (B) connected to a targeting moiety. The targeting moiety includes a pyridine ring and a complex amide/ester structure with two 6-carbon alkyl chains, making it highly hydrophobic.</p>	<p>Highly hydrophobic structure due to aliphatic linker and two 6-carbon alkyl chains on targeting moiety. EX1003, ¶¶ 281-282.</p>

³¹² EX1003, ¶ 276.

³¹³ EX1003, ¶ 279.

 <p>Chemical structure of Compound C-2, showing a highly hydrophobic molecule with multiple cyclohexyl groups on the linker and two 6-carbon alkyl chains on the targeting moiety.</p>	<p>Highly hydrophobic structure due to cyclohexyl groups on linker and two 6-carbon alkyl chains on targeting moiety. EX1003, ¶ 283.</p>
 <p>Chemical structure of Compound C-3, showing a less hydrophobic structure than C-2, but still likely to cause problems, which may increase if large fluorophore (e.g., IR800CW) used.</p>	<p>Less hydrophobic structure than C-2, but still likely to cause problems, which may increase if large fluorophore (e.g., IR800CW) used. EX1003, ¶ 284.</p>
 <p>Chemical structure of Compound C-4, showing a highly hydrophobic molecule due to the presence of multiple 10-carbon chains and 6-carbon chains on the targeting moiety.</p>	<p>Highly hydrophobic due to presence of multiple, 10-carbon chains, plus 6-carbon chains on targeting moiety. EX1003, ¶ 286.</p>

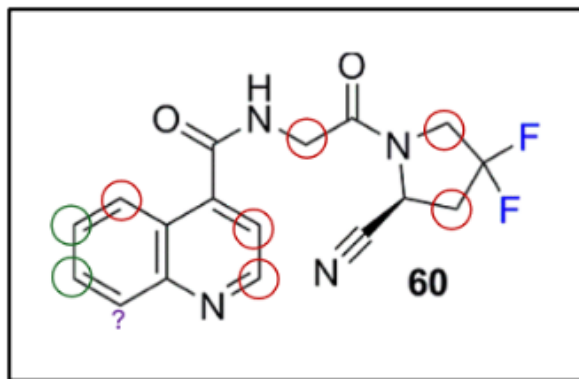
The guidance in the specification about options for linkers permit even more hydrophobic linkers to be used in the claimed B-L-A compounds.³¹⁴

(ii) Compounds with Selectivity/Affinity Problems

The data in Jansen shows that certain positions on its compound 60 structure are less tolerant to substitutions—particularly, the C², C³, C⁵ positions on the

³¹⁴ EX1003, ¶ 285.

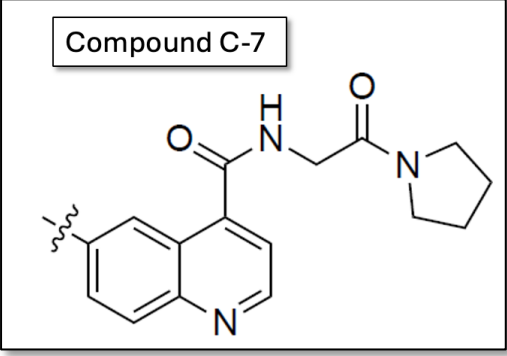
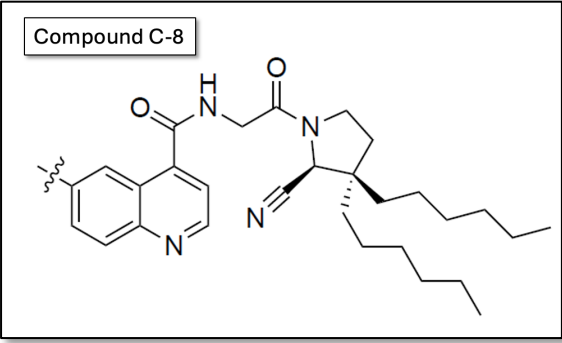
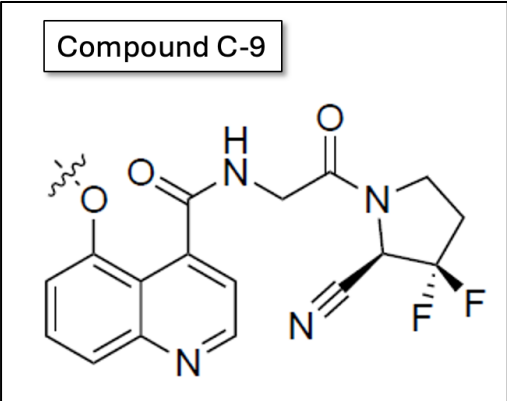
quinolinyl ring, the glycine α -carbon and the open positions on the pyrrolidine ring (below).³¹⁵



Some examples of compounds that would raise questions about their affinity and/or selectivity are shown below.

<i>Compound</i>	<i>Issues</i>
<div data-bbox="212 1079 716 1451"> <div data-bbox="240 1100 480 1146">Compound C-6</div> </div>	<p>Compound 66 in Jansen, which has very high affinity but poor FAP/PREP selectivity (3.0). EX1003, ¶¶ 292-293. Also has boronic acid pyrrolidine structure Pomper describes as a failure.</p>

³¹⁵ EX1003, ¶ 290.

<p>Compound C-7</p> 	<p>Compound 64 in Jansen, which has poor affinity, but higher selectivity (>10). EX1003, ¶¶ 294-295.</p>
<p>Compound C-8</p> 	<p>Presence of bulky and hydrophobic 6-carbon chains adjacent to cyano group on pyrrolidine would raise questions of effect on affinity and selectivity. EX1003, ¶ 297.</p>
<p>Compound C-9</p> 	<p>Similar to compound 60, but with di-fluoro substitution, would be expected to increase affinity/selectivity. Presence of substituent at C⁵ of quinolinyl ring reduced affinity/selectivity. Not possible to resolve conflicting characteristics. EX1003, ¶ 298.</p>

A skilled artisan would not have believed that testing was necessary for every B-L-A compound—those incorporating linker and chelator/prosthetic groups with an established track record would be more likely to be viewed as viable

without testing.³¹⁶ However, for innumerable compounds within the claimed genera that have the types of issues noted above (and others), a skilled artisan could not have reasonably predicted from the structure of the compound alone whether it was a viable molecular imaging or radiopharmaceutical agents.³¹⁷ Skilled artisans would need to synthesize and test each such compound to determine if it retained high affinity and selectivity for FAP, was stable in the physiological environment and had adequate bioavailability.³¹⁸

The percentage of compounds that a skilled artisan could not assess without experimental characterization is unknown. Even if was very small (*e.g.*, 1 out of 1,000,000 compounds, or 0.0001%), it would entail synthesizing and testing ~**9 sextillion** (10^{21}) compounds for the smallest genus claimed (claim 4, at least 9.41×10^{27} compounds). By comparison, the Jansen lab produced and tested ~95 compounds for affinity and selectivity over a roughly 2-year period, as reflected in their 2013 and 2014 papers, and further characterized only 6 with stability and bioavailability testing.³¹⁹

³¹⁶ EX1003, ¶ 278.

³¹⁷ EX1003, ¶¶ 275-277.

³¹⁸ EX1003, ¶ 277.

³¹⁹ EX1003, ¶ 278; EX1006, 3054-55, 3063-64; EX1007, 493-94.

Given the admitted unpredictability of producing viable compounds, a skilled artisan would have considered this scale of experimentation to require an unreasonable scale of time, effort and money to perform (even if were possible); it is plainly undue experimentation (if not impossible).³²⁰

Claims with comparable breadth have been routinely found to be non-enabled. In *Amgen*, the invalid claims covered “at least millions of candidates.”³²¹ Similarly, *Enzo* likewise held that a genus of nucleotides with a scale “of at least ‘tens of thousands’” were not enabled, even if one example was tested.³²²

Here, the immense number of possible B-L-A compounds (more than $\sim 10^{27}$ to $\sim 10^{36}$), coupled with the unpredictable effect of combinations of moieties, prevents a skilled artisan from being able to determine which B-L-A compounds possess the attributes required for a viable FAP-targeting optical imaging or radiopharmaceutical agent without undue experimentation.

(d) Limited Working Examples

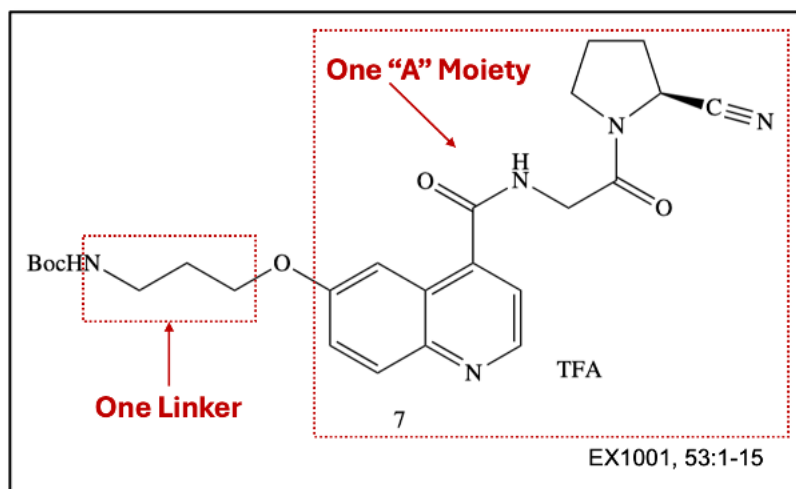
The disclosure provides only two working examples for its immensely large number of possibilities (XY-FAP-01, XY-FAP-02). Those two compounds

³²⁰ EX1003, ¶ 278.

³²¹ *Amgen*, 598 U.S. at 613.

³²² *Enzo*, 928 F.3d at 1348-1349.

illustrate one combination of one FAP-targeting moiety with one linker (below), plus either an optical dye or a DOTA-based chelator with ^{111}In . *See* § VIII.C.1(a). These examples provide no guidance regarding selection of the more than 10^{27} to $\sim 10^{36}$ combinations of *other* linkers, imaging moieties (*e.g.*, chelators, prosthetic groups, optical dyes) and FAP-targeting moieties being claimed.



(e) *Other Wands Factors and Conclusion*

The remaining *Wands* factors either support the conclusion that practicing the full scope of the claims would require undue experimentation or are neutral.

For example, while a skilled artisan in this field is highly skilled (*see* § IV.B), the field of radiopharmaceutical design is admittedly unpredictable (*see* § VIII.B).

* * * * *

For the reasons presented above, claim 1 is not enabled, as it would require the skilled artisan to engage in undue experimentation to practice its full scope.

2. Dependent Claims 2-4 Are Not Enabled

Claims 2-4 all depend from claim 1. While they narrow the genera relative to claim 1, the claimed genera remain massive on the scale of claim 1. As such, none of claims 2-4 materially alter the nature of their enablement deficiencies. Claims 1-4 are also not enabled.

E. '233 Patent's Priority Application

The reasons why the '233 Patent does not adequately describe or enable claim 1-4 apply with greater force to its priority application, which omits Example 2 and other information added in the '233 Patent.³²³

IX. DISCRETIONARY DENIAL NOT WARRANTED

Should Patentee allege there is a basis for discretionary denial, Petitioner reserves the right to respond pursuant to the Acting Director's March 26, 2025, Memorandum.

X. CONCLUSION

For the foregoing reasons, the Board should institute trial in this proceeding and cancel the challenged claims.

Dated: July 14, 2025

Respectfully Submitted,

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³²³ Compare EX1049, 43:15-49:10 to EX1001, 60:25-61:23.

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CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24, because it contains 18,397 words (as determined by the Microsoft Word word-processing system used to prepare the brief), excluding the parts of the brief exempted by 37 C.F.R. § 42.24.

Dated: July 14, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 14th day of July 2025, I caused to be served a true and correct copy of the foregoing and any accompanying exhibits by FedEx on the following counsel:

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EXHIBIT LIST

No.	Exhibit Description	Short Name
1001	U.S. Patent No. 12,115,233	US-233
1002	File History of U.S. Patent No. 12,115,233	US-233 FW
1003	Declaration of Dr. Brian Zeglis	Zeglis Dec.
1004	U.S. Patent Publication 2010/0098633	US-633
1005	U.S. Patent Publication 2012/0009121	US-121
1006	Jansen et al., “Extended Structure–Activity Relationship and Pharmacokinetic Investigation of (4-Quinolinoyl)glycyl-2-cyanopyrrolidine Inhibitors of Fibroblast Activation Protein (FAP),” J. Med. Chem, 57:3053–3074 (2014)	Jansen
1007	Jansen et al., “Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold,” ACS Med. Chem. Lett., 4:491–496 (2013)	Jansen 2013
1008	Meletta et al., “Evaluation of the Radiolabeled Boronic Acid-Based FAP Inhibitor MIP-1232 for Atherosclerotic Plaque Imaging,” Molecules, 20:2081–2099 (2015)	Meletta
1009	Jamous et al., “Synthesis of Peptide Radiopharmaceuticals for the Therapy and Diagnosis of Tumor Diseases,” Molecules, 18:3379–3409 (2013)	Jamous
1010	Zeglis et al., “A practical guide to the construction of radiometallated bioconjugates for positron emission tomography,” Dalton Trans., 40(23):6168–6195 (2011)	Zeglis 2011
1011	Zeglis et al., “Underscoring the Influence of Inorganic Chemistry on Nuclear Imaging with Radiometals,” Inorg. Chem., 53:1880–1889 (2013)	Zeglis 2013

No.	Exhibit Description	Short Name
1012	Wadas et al., “Coordinating Radiometals of Copper, Gallium, Indium, Yttrium, and Zirconium for PET and SPECT Imaging of Disease,” <i>Chem. Rev.</i> , 110(5):2858–2902 (2010)	Wadas
1013	Price et al., “Matching chelators to radiometals for radiopharmaceuticals,” <i>Chem. Soc. Rev.</i> , 43:260–290 (2014)	Price
1014	Riondato et al., “Radiopharmaceuticals,” Chapter 4, 31-57, in <i>PET-CT and PET-MRI in Neurology</i> (Ciarmiello and Mansi, editors), Springer, Int. Publ., (2016)	Riondato
1015	Ross, “The Click Chemistry Approach Applied to Fluorine-18,” <i>Current Radiopharmaceuticals</i> , 3:202–223 (2010)	Ross
1016	Brennen et al., “Rationale Behind Targeting Fibroblast Activation Protein–Expressing Carcinoma-Associated Fibroblasts as a Novel Chemotherapeutic Strategy,” <i>Mol. Cancer Ther.</i> , 11(2):257–266 (2012)	Brennen 2012
1017	Sarko et al., “Bifunctional Chelators in the Design and Application of Radiopharmaceuticals for Oncological Diseases,” <i>Current Medicinal Chem.</i> , 19:2667–2688 (2012)	Sarko
1018	Fichna et al., “Synthesis of Target-Specific Radiolabeled Peptides for Diagnostic Imaging,” <i>Bioconjugate Chem.</i> , 14:3–17 (2003)	Fichna
1019	Schirrmacher et al., “Small Prosthetic Groups in ^{18}F -Radiochemistry: Useful Auxiliaries for the Design of ^{18}F -PET Tracers,” <i>Semin. Nucl. Med.</i> , 47(5):474–492 (August 2017)	Schirrmacher
1020	Saha et al., “Synthesis of PET Radiopharmaceuticals,” Chapter 8, 161-168, in <i>Basics of PET Imaging</i> (Saha, editor), Springer Int. Publ., (2010)	Saha

No.	Exhibit Description	Short Name
1021	Kettenbach et al., “ ¹⁸ F-Labeling Using Click Cycloadditions,” BioMed Research International, 2014:1–16 (2014)	Kettenbach
1022	Liu et al., “Fibroblast activation protein, A potential therapeutic target in cancer,” Cancer Biology & Ther., 13(3):123–129 (2012)	Liu
1023	DiMagno et al., “Advanced Fibroblast Activation Protein-Ligand Developments, FAP Imaging Agents: A Review of the Structural Requirements,” PET Clin., 18:287–294 (2023)	DiMagno
1024	Hamson et al., “Understanding fibroblast activation protein (FAP): Substrates, activities, expression and targeting for cancer therapy,” Proteomics Clin. Appl., 8:454–463 (2014)	Hamson
1025	O’Brien et al., “Seprase: An overview of an important matrix serine protease,” Biochimica et Biophysica Acta, 1784:1130–1145 (2008)	O’Brien
1026	Jia et al., “FAP- α (Fibroblast activation protein- α) is involved in the control of human breast cancer cell line growth and motility via the FAK pathway,” BMC Cell Biology, 15(16): 1–14 (2014)	Jia
1027	Agdeppa et al., “A Review of Imaging Agent Development,” The American Association of Pharmaceutical Scientists (AAPS) J., 11(2):286–299 (2009)	Agdeppa
1028	Mankoff et al., “Tumor Receptor Imaging,” J. Nucl. Med., 49:149S–163S (2008)	Mankoff
1029	Ryabtsova et al., “Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity,” Bioorganic & Medicinal Chemistry Letters, 22(10):3412–3417 (2012)	Ryabtsova

No.	Exhibit Description	Short Name
1030	Eder et al., “ ⁶⁸ Ga-Complex Lipophilicity and the Targeting Property of a Urea-Based PSMA Inhibitor for PET Imaging,” <i>Bioconjugate Chem.</i> , 23:688–697 (2012)	Eder
1031	File History of U.S. Patent No. 11,938,201	US-201 FW
1032	Fani et al., “Radiolabeled Peptides: Valuable Tools for the Detection and Treatment of Cancer,” <i>Theranostics</i> , 2(5):481–501 (2012)	Fani
1033	Mach et al., “Challenges for Developing PET Tracers: Isotopes, Chemistry, and Regulatory Aspects,” 5(2): 131–153 (2010)	Mach
1034	Meyer et al., “Click Chemistry and Radiochemistry: The First 10 Years,” <i>Bioconjugate Chem.</i> , 27:2791–2807 (2016)	Meyer 2016
1035	Marquis et al., “Abstract #4467: Targeting tumor microenvironment with radiolabeled inhibitors of seprase (FAP#945;),” <i>Cancer Chem.</i> , 69:4467 (2009)	Marquis
1036	Maurer et al., “Current use of PSMA-PET in prostate cancer management,” <i>Nature Reviews: Urology</i> , 13:226–235 (2016)	Maurer
1037	Karakatsanis et al., “Dosage optimization in positron emission tomography: state-of-the-art methods and future prospects,” <i>Am. J. Nucl. Med. Mol. Imaging</i> , 5(5):527–547 (2015)	Karakatsanis
1038	LeBeau et al., “Targeting the cancer stroma with a fibroblast activation protein-activated promelittin protoxin,” <i>Mol. Cancer Ther.</i> 8(5):1378–1386 (2009)	LeBeau
1039	Nelson et al., “Good practices for ⁶⁸ Ga radiopharmaceutical production,” <i>EJNMMI Radiopharmacy and Chem.</i> , 7(1):1–26 (2022)	Nelson

No.	Exhibit Description	Short Name
1040	Meyer et al., “Exploring Structural Parameters for Pretargeting Radioligand Optimization,” J. Med. Chem., 60:8201–8217 (2017)	Meyer 2017
1041	Gorrell, “Dipeptidyl peptidase IV and related enzymes in cell biology and liver disorders,” Clinical Science, 108:1–16 (2005)	Gorrell
1042	Kiesewetter et al., “Automated radiochemical synthesis of [¹⁸ F]FBEM: A thiol reactive synthon for radiofluorination of peptides and proteins,” Appl. Radiation and Isotopes, 69(2): 410–414 (2011)	Kiesewetter
1043	Chansaenpak et al., “[¹⁸ F]-NHC-BF ₃ adducts as water stable radio-prosthetic groups for PET imaging,” Chem. Commun., 51(62):12439–12442 (2015)	Chansaenpak
1044	U.S. Patent Publication 2014/0357650	US-650
1045	Ji et al., “Tumor fibroblast specific activation of a hybrid ferritin nanocage-based optical probe for tumor microenvironment imaging,” Small J., 9(14):2427–2431 (2013)	Ji
1046	Wilson et al., “Chapter 1, Dipeptidyl Peptidases: Substrates and Therapeutic Targeting in Human Health and Disease,” Royal Society of Chemistry, (2012)	Wilson
1047	Tsai et al., “Substituted 4-carboxymethylpyroglutamic Acid Diamides as Potent and Selective Inhibitors of Fibroblast Activation Protein,” J. Med. Chem. 53(18):6572–6583 (2010)	Tsai
1048	International Publication 2010/108125	US-121 PCT
1049	US 12,115,233 Provisional application No. 62/575,607	US-607
1050	Billaud et al., “Development and Preliminary Evaluation of TFIB, a New Bimodal	Billaud

No.	Exhibit Description	Short Name
	Prosthetic Group for Bioactive Molecule Labeling,” ACS Med. Chem. Lett. 6(2):168–172 (2015)	
1051	Harris et al., “Impact of 2-Deoxy-2[F-18]Fluoro-D-Glucose Positron Emission Tomography on the Management of Patients with Advanced Melanoma,” Mol. Imaging Biol., 7(4):304–308 (2005)	Harris
1052	Zhou et al., “Radiolabeled Cyclic RGD Peptides as Radiotracers for Imaging Tumors and Thrombosis by SPECT,” Theranostics, 1:58–82 (2011)	Zhou
1053	U.S. Patent Publication 2011/0064657	US-657
1054	Kim et al., “Synthesis and the structure of mixed carboxylatoplatinum(IV) complexes involving one trifluoroacetate ligand,” Inorganica Chimica Acta, 358(2):415–418 (2005)	Kim
1055	Pruszyński et al., “Improved Tumor Targeting of Anti-HER2 Nanobody Through N-Succinimidyl 4-Guanidinomethyl-3-Iodobenzoate Radiolabeling,” Journal of Nuclear Medicine, 55(4):650–656 (2014)	Pruszyński
1056	Declaration of Jeffrey P. Kushan	Kushan Dec.