

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. IPR2025-00808
U.S. Patent No. 11,938,201**

PETITION FOR INTER PARTES REVIEW

TABLE OF CONTENTS

I.	Introduction	5
II.	Compliance with IPR Requirements	11
A.	Certification of Standing	11
B.	Mandatory Notices.....	11
1.	<i>Real Party-in-Interest</i>	<i>11</i>
2.	<i>Related Proceedings</i>	<i>11</i>
3.	<i>Counsel and Service Information</i>	<i>11</i>
III.	Grounds.....	11
IV.	Background on the Patent.....	12
A.	Knowledge in the Field of the Patent	12
1.	<i>Radiolabeling and Linker Components of Modular Radiopharmaceuticals Were Well-Known.....</i>	<i>12</i>
(a)	Targeting Moieties	13
(b)	Radiolabeling Groups.....	14
(c)	Linkers.....	16
2.	<i>Radionuclides</i>	<i>17</i>
3.	<i>Fibroblast Activation Protein (FAP)</i>	<i>18</i>
B.	Person of Ordinary Skill in the Art.....	20
C.	Prosecution History	20
D.	The Challenged Claims.....	21
E.	Claim Scope and Construction of Terms.....	22
1.	<i>Radiolabeling Moiety (“B”) and Linker (“L”) Components Are Defined in Functional Terms</i>	<i>23</i>
2.	<i>“Low Molecular Weight” Need Not Be Construed</i>	<i>25</i>
3.	<i>Low Molecular Weight Refers to a Magnitude of Weight</i>	<i>26</i>
V.	Ground 1: Claims 1-3 Are Obvious Based on US-633, Meletta and Jansen	30

A.	Teachings of the Prior Art	32
1.	<i>US-633</i>	<i>32</i>
	(a) Modular Three-Component Radiopharmaceuticals	32
	(b) Imaging Platforms and Radionuclides	34
	(c) Chelator and Prosthetic Group Radiolabeling Moieties.....	34
	(d) Linkers (“Tethers”).....	39
	(e) Boronic Acid Pyrrolidine Targeting Moiety	44
	(f) US-633 Identifies Examples of Compounds Based on its Targeting Moieties	45
2.	<i>Meletta (EX1008)</i>	<i>49</i>
3.	<i>Jansen (EX1006).....</i>	<i>53</i>
	(a) Jansen Highlights Interest in FAP as a Drug Target	53
	(b) Jansen Described a Need for Improved FAP-Targeting Moieties that It Solved with Compound 60	54
	(c) Jansen Identifies Compound 60 as Its Most Promising FAP Inhibitor.....	56
	(d) Additional In Vitro and In Vivo Testing Identifies Appealing Attributes of Compound 60	61
B.	Differences Between the Claims and the Prior Art.....	63
C.	A Skilled Artisan Would Have Considered US-633 with Both Meletta and Jansen	65
D.	A Skilled Artisan Would Have Been Motivated to Use Compound 60 as the Targeting Moiety of FAP-Targeting Radiotracers	67
E.	Compound 60 Meets Every Requirement of the “A” Moiety of the Claimed Compounds	72
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	74
1.	<i>A Modular Three Component Design Would Be Used.....</i>	<i>74</i>
2.	<i>Choices for the Radiolabeling Moiety</i>	<i>74</i>
3.	<i>Choices for the Linker</i>	<i>76</i>

4.	<i>Construction of Compound 60- Linker-Radiolabeling Moiety Compounds</i>	79
G.	Examples of Compounds Suggested by US-633, Meletta and Jansen Satisfy Claims 1-3	81
1.	<i>A PET Radiotracer Based on ⁶⁸Ga, DOTA and PEG Satisfies Claims 1-3 (Compound A1)</i>	82
2.	<i>A SPECT Radiotracer Based on ⁶⁸Ga, DPA and PEG Satisfies Claims 1-3 (Compound A2)</i>	84
3.	<i>A PET Radiotracer Based on ¹⁸F, a Prosthetic Group and PEG Satisfies Claims 1-3 (Compound A3)</i>	86
4.	<i>A SPECT Radiotracer Based on ¹²³I, a Prosthetic Group and PEG Satisfies Claims 1-3 (Compound A4)</i>	87
H.	Claims 1-3 Would Have Been Obvious	89
VI.	Ground 2: Claims 1-3 Are Obvious Based on US-121 (EX1005) and Jansen (EX1006)	90
A.	Teachings of US-121	90
B.	A Skilled Artisan Would Have Considered US-121 with Jansen	95
C.	A Skilled Artisan Would Have Modified the US-121 Radiotracers to Use Compound 60 to Target FAP	97
D.	Compounds Made Obvious by US-121 and Jansen Meet All Requirements of the Claims	106
VII.	No Secondary Indicia Exist or Are Relevant	109
VIII.	Discretionary Denial Is Not Warranted	110
A.	§ 325(d) Denial Not Warranted	110
1.	<i>The Examination Record</i>	111
2.	<i>The First Inquiry Supports Institution</i>	113
3.	<i>The Second Inquiry Supports Institution</i>	114
B.	Discretionary Denial Based on an Unrelated PGR Is Not Warranted	115
IX.	CONCLUSION	116

TABLE OF AUTHORITIES**Page(s)****Cases**

<i>Advanced Bionics, LLC v. MED0EL Elektromedizinische Geräte GmbH,</i> IPR2019-01469, Paper 6 (PTAB Dec. 13, 2020)	109, 110
<i>Apple Inc. v. Fintiv, Inc.,</i> IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020)	109
<i>Becton, Dickinson & Co. v. B. Braun Melsungen AG,</i> IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017)	109, 110
<i>Gen. Plastic Indus. Co., Ltd. v. Canon Kabushiki Kaisha,</i> IPR2016- 01357, Paper 19 (PTAB Sept. 6, 2017)	115
<i>ITM Isotope Techs. Munich SE v. The Johns Hopkins Univ.,</i> PGR2025-00012 (PTAB Dec. 24, 2024)	114, 115
<i>KSR Intern. Co. v. Teleflex Inc.,</i> 550 U.S. 398 (2007)	30

Statutes

35 U.S.C. § 103	12, 29
35 U.S.C. § 325(d)	109, 110, 113

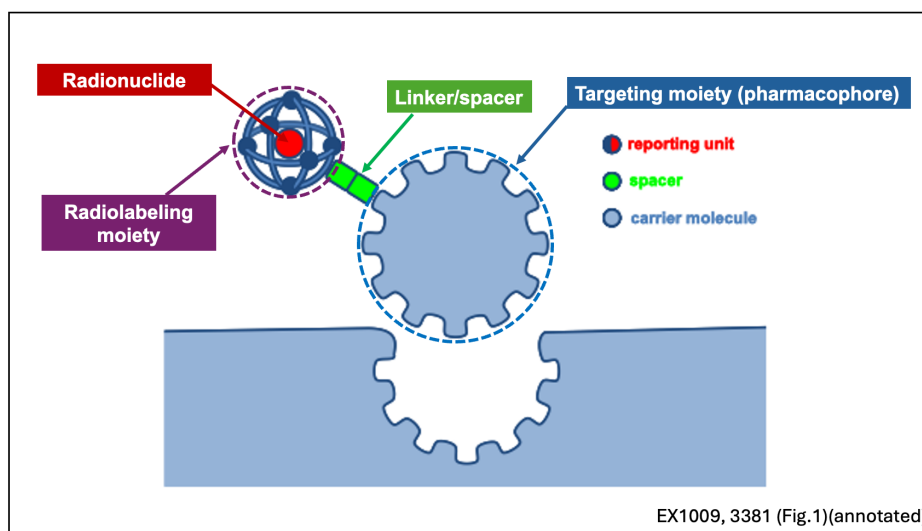
I. Introduction

Radiopharmaceuticals are drugs that selectively target particular cells and contain a radioactive isotope. They are used to treat and diagnose diseases; in both applications, after the radiopharmaceutical is administered to a patient, it selectively accumulates in tissues containing the cells targeted by the drug. In radiotherapy, radiation emitted by the accumulated radiopharmaceuticals in the tissue kills the targeted cells. In diagnosis, the accumulated radiopharmaceuticals (called “radiotracers”) emit radiation that is measured by a scanner and used to generate an image of the tissues or organs where the target cells reside. In both applications, selectivity for the target cells is critical—if the radiopharmaceutical binds to normal cells, it can harm healthy tissue or lead to false results.

A common modular design used in radiopharmaceutical compounds combines three components (illustrated below):¹

- (i) a “radiolabeling moiety” attached to a radionuclide;
- (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.

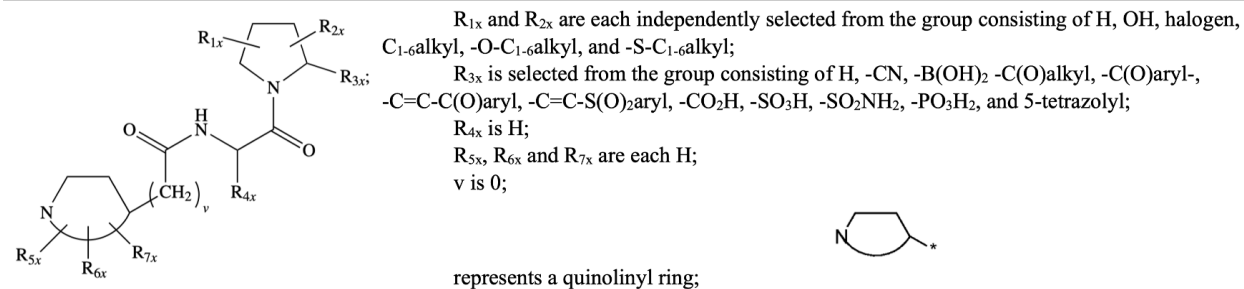
¹ EX1003, ¶¶ 27-28; EX1009, 3380 (annotated).



U.S. Patent No. 11,938,201 (the '201 Patent)(EX1001) broadly claims radiopharmaceuticals with this modular, three-component design: “low molecular weight compounds comprising components B-L-A.”

The claims define “B” and “L in functional terms, causing them to capture “*any* ...radiolabeling moiety... suitable for” Positron Emission Tomography (PET) or Single Photon Emission Computed Tomography (SPECT) imaging and *any* linker “having bi-functionalization adapted to form a chemical bond with B and A”, respectively.

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

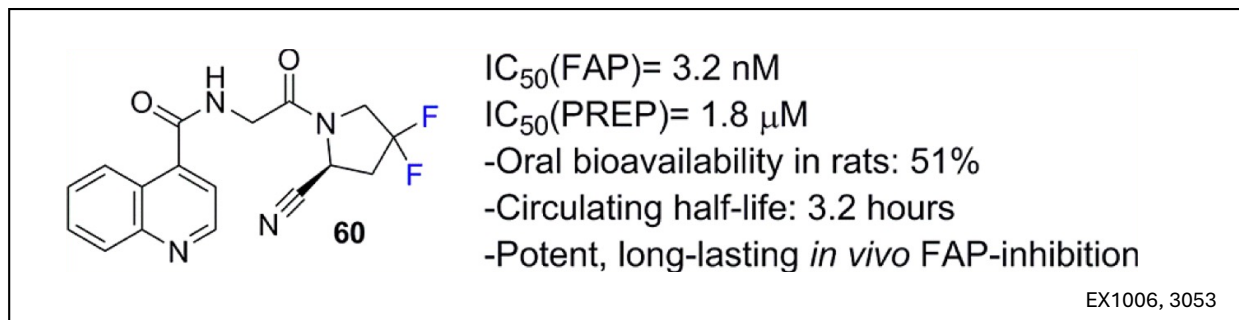


Before 2017, two different published applications—US-633 (EX1004) and US-121 (EX1005)—described low molecular weight radiotracers useful for PET or SPECT imaging sharing this modular three-component design. Both described incorporating small molecule targeting moieties for proteins selectively expressed 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 that was not disclosed in these publications is a small molecule, highly selective FAP-inhibitor within the structural genus of the “A” component of the claims.

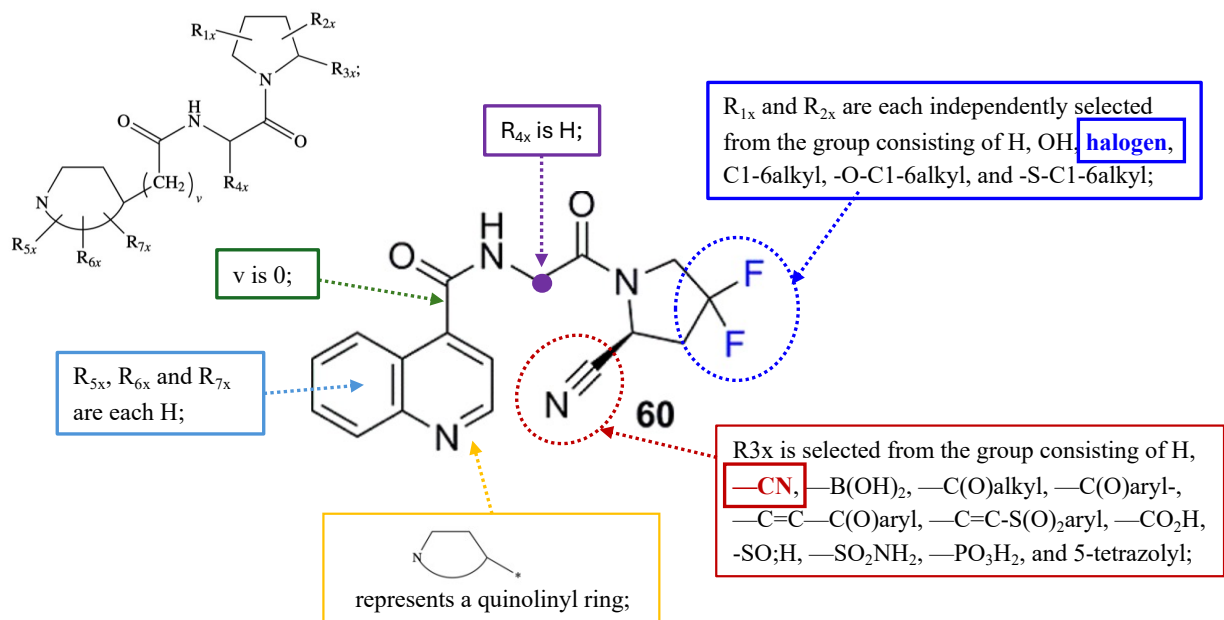
But Jansen (EX1006) did. It showcased “compound 60” in its abstract, identifying it as a potent, highly-selective FAP inhibitor. And it highlighted attributes of compound 60 that signaled to the skilled artisan it would be an excellent FAP-targeting moiety for a radiotracer, including its high oral

² EX1004 (US2010/0098633); EX1005 (US2012/0009121).

bioavailability and its “potent, long lasting *in vivo* FAP-inhibition.”



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



Claims 1 to 3 are unpatentable because they capture compound 60-based FAP-targeting radiotracers that would have been obvious over the prior art. Two independent grounds support this conclusion.

First, US-633 described “low molecular weight” FAP-targeting radiopharmaceuticals, including radiotracers useful for tumor imaging with PET or

SPECT nuclear imaging devices. These compounds share the modular three-component design of the claims: (i) a small molecule, boronic acid pyrrolidine targeting moiety for FAP, (ii) known radiolabeling/radionuclide structures and (iii) linkers (“tethers”). The FAP-targeting moiety of the US-633 radiotracers, however, does not fall within the structural genus “A” of the claims.

But in 2015, Meletta (EX1008)—after citing US-633—reported that its boronic acid pyrrolidine targeting moiety was insufficiently selective for FAP, rendering it unsuitable for use in FAP-targeting radiotracers. Meletta, critically, also identified the need for more selective FAP inhibitors, stating: “[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. That would have led those artisans to Jansen’s highly FAP-selective compound 60. And, as explained below, the collective teachings of US-633, Meletta and Jansen would have made obvious particular compound 60-based PET and SPECT radiotracers that meet every requirement of claims 1-3. Consequently, US-633, Meletta and Jansen render claims 1-3 unpatentable.

Second, a skilled artisan would have found the radiopharmaceuticals of

³ EX1008, 2089-90.

claims 1-3 obvious based on US-121 (EX1005)⁴ with Jansen (EX1006). US-121 describes low molecular weight radiotracers targeting PSMA for use in PET and SPECT imaging. They employ the three-component design specified in claims 1-3, use comparable prior art linkers and radiolabeling moieties, but again use a different targeting moiety (a urea-based structure).

By 2017, skilled artisans viewed FAP as an appealing target for radiopharmaceuticals, as it is expressed at elevated levels in >90% of epithelial cancers but not in normal tissue. Such persons would thus have been motivated to adapt the proven PSMA-targeting radiotracers described in US-121 to make them suitable for use in a wider array of tumors by using a suitable targeting moiety for FAP. That would have led the skilled artisan to Jansen's compound 60, not only because of its highly selective, potent inhibition of FAP and its favorable characteristics (above), but because it has a comparable size to the small molecule targeting moiety used in the US-121 compounds. Again, this would have led a skilled artisan to particular compounds that meet every requirement of claims 1-3.

Because each ground demonstrates that radiotracers within the scope of claims 1-3 of the '201 Patent would have been obvious, each claim is unpatentable. The Board should institute trial.

⁴ U.S. Publication No. 2012/009121.

II. Compliance with IPR Requirements

A. Certification of Standing

Petitioner certifies this Petition for *inter partes* review is filed more than 9 months after issuance of the '201 Patent. Petitioner also certifies it is not barred or estopped from requesting this IPR. Petitioner and its privies have not filed a civil action challenging the validity of any claim of the '201 Patent.

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

There are no related proceedings.

3. Counsel and Service Information

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III. Grounds

The grounds advanced in this Petition are:

- (1) Claims 1-3 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 1-3 would have been obvious under 35 U.S.C. § 103 based on US-112 (EX1005) in view of Jansen (EX1006).

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

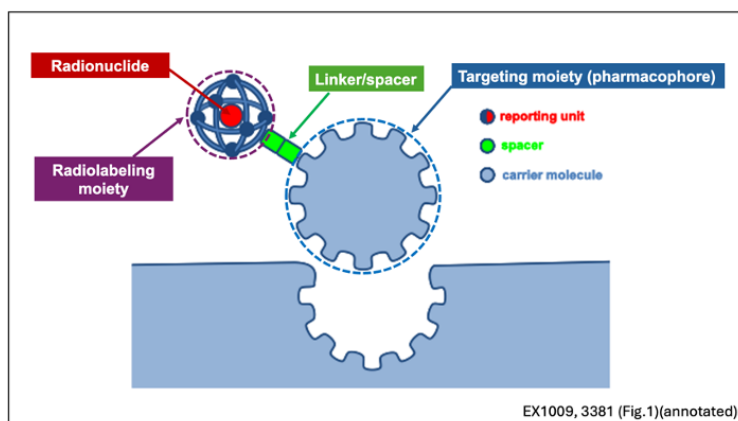
A. Knowledge in the Field of the Patent

The field of radiopharmaceutical development was advanced by October 2017. The information below describes what would have been known by skilled artisans by October 2017.

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

As explained in § I, radiopharmaceuticals that used the modular, three component design illustrated in Jamous were well-known (below, annotated).⁵

⁵ EX1003, ¶¶ 27-28.



The modular three-component radiopharmaceutical design provides practical benefits, such as being able to readily alter the structure and characteristics of the radiopharmaceutical by choosing or replacing different chemical moieties for the individual components of the compound.⁶

(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.⁷ Targeting moieties can be small molecules, peptides or antibodies, but small molecules are most

⁶ EX1003, ¶ 28.

⁷ EX1003, ¶ 29.

commonly used in radiotracers, as they can more quickly penetrate tissues and are quickly cleared due to their rapid pharmacokinetic profiles.⁸

(b) Radiolabeling Groups

The radiolabeling moiety associates a radionuclide (a radioactive form of a metal or halogen) with a radiopharmaceutical, and consists of a chemical structure and the radionuclide. Two general classes of radiolabeling moieties were well-known: (i) chelators used with radiometals (*e.g.*, ⁶⁸Ga, ^{99m}Tc), and (ii) prosthetic groups labeled with radiohalogens (*e.g.*, ¹⁸F, ¹²³I).⁹ The purpose of both is to ensure the radionuclide does not dissociate from the radiopharmaceutical before it reaches and accumulates in tissues containing the targeted cells.¹⁰

Chelators are selected based on the particular radiometal being used—the chelator molecule must form a stable coordination complex with the selected radiometal, and suitable chelators for each radiometal were known.¹¹ For example, chelators that had proven suitable for ⁶⁸Ga included NOTA, DOTA, HBED,

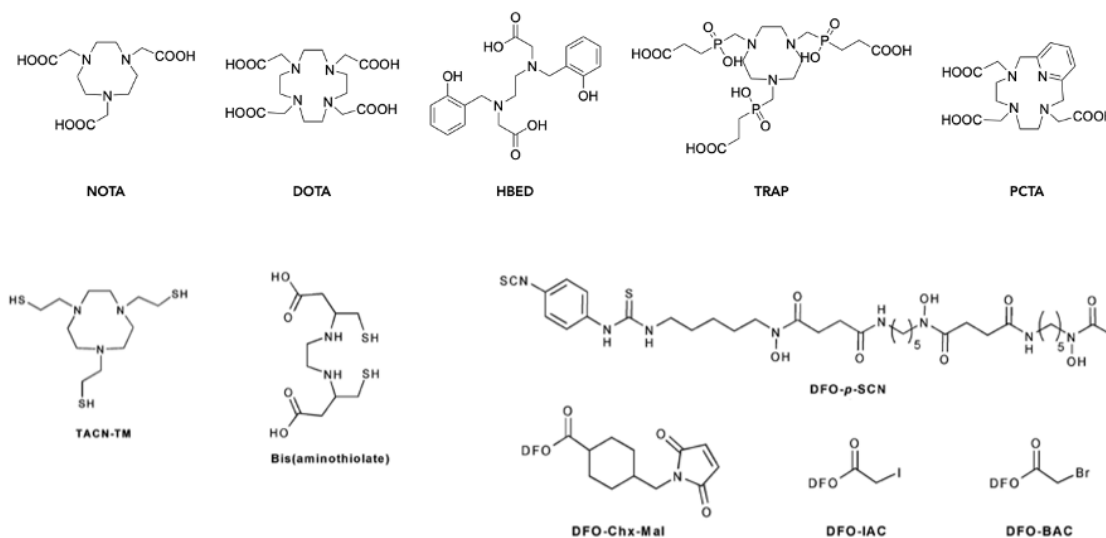
⁸ EX1003, ¶ 30; EX1010, 1-3; EX1012, 2859.

⁹ EX1003, ¶ 32.

¹⁰ EX1003, ¶ 31.

¹¹ EX1003, ¶¶ 32-33; EX1011, 1882; EX1012, 2865, 2869; EX1013, 260-262, 266-269.

TRAP, PCTA, TACN-TM and DFO (below).¹²

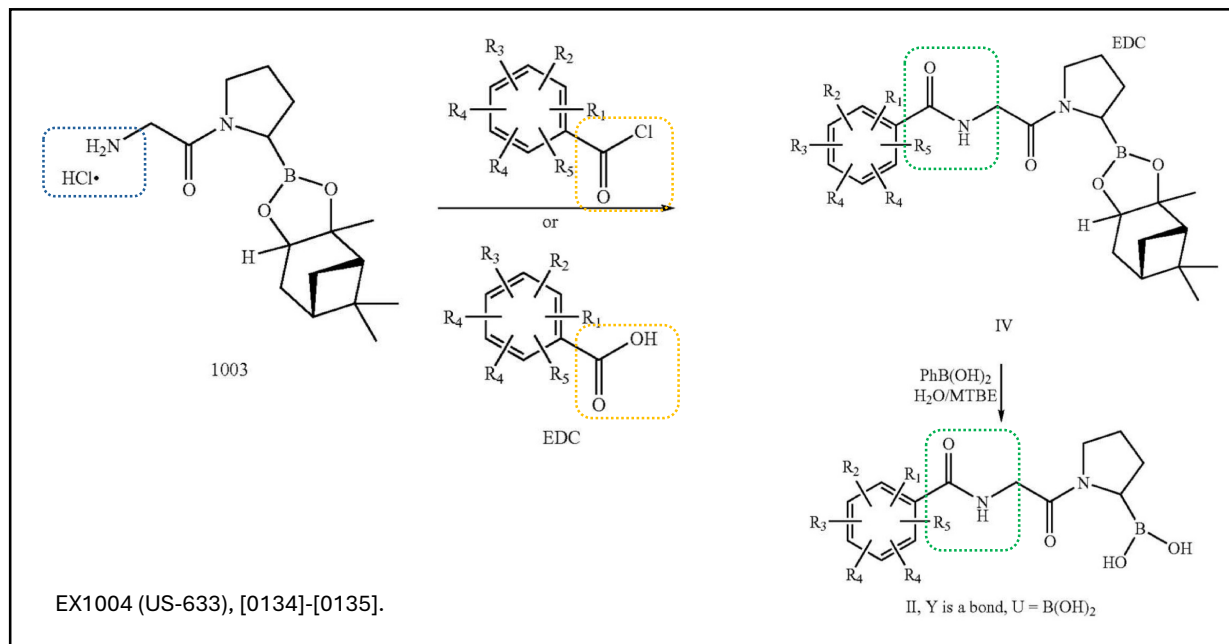


Prosthetic groups are chemical moieties that are covalently labeled with a radiohalogen (*e.g.*, ^{18}F , ^{123}I).¹³ Once radiolabeled, they can be easily attached to the remainder of the radiopharmaceutical compound (illustrated below).¹⁴

¹² EX1003, ¶ 82; EX1011, 1882-1883, 1887-1888; EX1013, 267, 272, 275, 276.

¹³ EX1003, ¶¶ 34, 83, 85; EX1042, 410-411; EX1043, 12439-51; EX1034, 2792-93, Figure 2.

¹⁴ EX1004, [0134]-[0135]; EX1003, ¶ 84.



(c) Linkers

A linker is a chemical moiety that connects the radiolabeling moiety to the targeting moiety. Linkers serve three purposes: (i) they spatially separate the targeting and radiolabeling moieties to avoid impairing the selective binding of the radiopharmaceutical, (ii) they facilitate the efficient assembly of the radiopharmaceutical, and (iii) they can enhance the stability, solubility and other characteristics of the radiopharmaceutical compound.¹⁵ Linkers use functional groups at either of their termini to form covalent bonds with corresponding functional groups on the targeting and radiolabeling moieties.¹⁶

¹⁵ EX1003, ¶¶ 35-36.

¹⁶ EX1003, ¶ 37.

2. Radionuclides

Radiopharmaceuticals deliver a radioactive element (a radionuclide) to targeted cells, either to kill the cells (therapy) or to enable imaging of tissues containing them (nuclear imaging). The particular radionuclide used is dictated by the purpose of the radiopharmaceutical.¹⁷ 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 radiopharmaceutical in the body.¹⁸ Common radionuclides used in PET and SPECT imaging are shown below, along with their half-lives.¹⁹

¹⁷ EX1003, ¶ 38.

¹⁸ EX1003, ¶¶ 39-41.

¹⁹ EX1003, ¶ 39; 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).

	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.²⁰

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)

²⁰ EX1003, ¶¶ 56-57; EX1006, 3053; EX1016, 259 (Table 1); EX1024, 454.

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.²¹ More significantly, “FAP is [] highly expressed on activated fibroblasts in over 90% of common human epithelial tumors” and has been linked to a variety of cancers.²²

Before 2017, a number of publications had identified FAP as being a compelling target for radiopharmaceuticals, and particularly radiotracers used in nuclear imaging of tumors.²³ As one 2011 publication observed:

Due to the highly restricted and specific expression of FAP, particularly within tumor stroma, FAP is *clinically interesting as a 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.²⁴

²¹ EX1003, ¶ 58; EX1022, 124; EX1024, 456; EX1023, 288; EX1041, 2

²² EX1006, 3053; EX1022, 124; EX1024, 456; EX1016, 260.

²³ EX1003, ¶ 59; EX1046, 26. *Also* EX1024, 454, 455; EX1022, 124; EX1045, 2427; EX1016, 264.

²⁴ EX1046, 26.

Before 2017, FAP's unique profile induced skilled artisans to discover small molecule compounds that selectively bound to and inhibited the enzymatic activity of FAP ("FAP inhibitors"), including one designated "compound 60" reported in Jansen (EX1006).²⁵

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 degree and a Ph.D. in chemistry, biochemistry, medicinal chemistry or a comparable field, and (ii) experience with and/or knowledge of 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 nuclear imaging of diseases, including cancer.²⁶

C. Prosecution History

The prosecution history of the '201 Patent is described in § VII, below.

²⁵ EX1003, ¶ 61; EX1006, 3053.

²⁶ EX1003, ¶¶ 12-14.

D. The Challenged Claims

The '201 Patent has three claims.²⁷ Claims 1 and 3 differ slightly in the preamble: in relation to the phrase “B-L-A”, claim 1 recites “of” while claim 3 (below) recites “consisting essentially of.” As such, the genus of claim 1 is fully encompassed within the genus of claim 3. Claim 2 limits the B component to “any radiolabeled functional group suitable for” PET or SPECT imaging.

²⁷ EX1001 contains the certificate of correction with corrected claims 1 and 3. EX1002, 502-504.

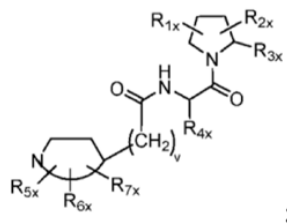
Claim 1, Column 64, Lines 47-67, Column 65, Lines 1-62 should read:

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:



wherein:

R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

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)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

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

v is 0;



represents a quinolinyl 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.

E. Claim Scope and Construction of Terms

The terms in the claims employ objective language that requires no special construction. Two (*i.e.*, components “B” and “L”) warrant observations to illustrate their breadth.

Petitioner anticipates Patentee may contend the phrase “low molecular weight compound” requires a special construction. It does not—the grounds show that radiopharmaceuticals with a comparable size to those in the disclosure would have been obvious over the prior art. 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 3 use functional language (below) to define the “B” and “L” components of the claimed compounds.

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) can be “any optical or radiolabeled functional group *suitable for*” optical, PET or SPECT imaging, or for radiotherapy.
- Likewise, the “**L**” component (*i.e.*, the linker) simply requires “having bi-functionalization adapted *to form a chemical bond with B and A.*”

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

The specification reinforces this conclusion. Regarding radiolabeling

moieties (“B”), it reiterates the functional definition in the claims,²⁸ and then identifies two broad classes of “B” compounds. One consists of “radiolabeled prosthetic groups comprising a radioisotope” (*e.g.*, ¹⁸F, ¹²³I), and the other are “chelating agent[s]”.²⁹ The specification illustrates each class with (known) examples, but then states such B compounds “are not limited to” to those examples.³⁰ Regarding linkers (“L”), it repeats the “bi-functionalization” attribute of linkers from the claims.³¹ It does not, however, define linkers as requiring use of any structural attributes (*i.e.*, there are no minimum or maximum size parameters, or 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

Nothing in the prosecution history concerned the chemical structures that can be “B” or “L” components. Rather, claim amendments addressed the size of

²⁸ EX1001, 2:3-12.

²⁹ EX1001, 17:55-18:45, 18:46-20:9.

³⁰ EX1001, 17:57-59, 20:9-11.

³¹ EX1001, 2:10-12, 8:24-25.

³² EX1001, 17:45-53 (citing US2011/0064657) and US-121(EX1005)).

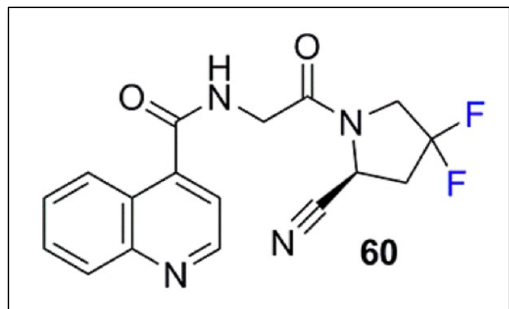
the compounds as a whole (“low molecular weight” compounds) and the structure of the targeting moiety.³³ The claim language and the specification thus foreclose interpreting the terms “B” and “L” in the claims as requiring or excluding any particular radiolabeling or linker structures, respectively, for the B and L components of the claimed compounds.

2. “Low Molecular Weight” Need Not Be Construed

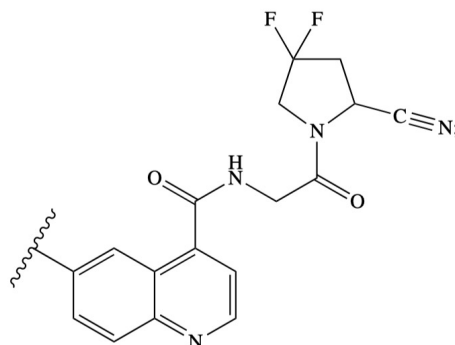
It is theoretically possible that the phrase “low molecular weight” might exclude some combination of a targeting moiety (“A”), radiolabeling moiety (“B”) and a linker (“L”). That theoretical possibility is irrelevant to the present grounds, which are based on obvious radiopharmaceutical compounds containing the FAP-targeting small molecule designated “compound 60” in Jansen (EX1006). Compound 60 is *identical* to one of the “A” structures exemplified in the specification (below, right).³⁴ Compounds containing compound 60 and conventional, known “B” and “L” components, thus, are “low molecular weight” compounds for the same reasons this example in the ’201 Patent is.

³³ EX1002, 415-420, 400.

³⁴ EX1006, 3053; EX1001, 13:34-14:16.



In more particular embodiments, A is selected from the group consisting of:



Moreover, the grounds rely on illustrative compounds that are obvious from the prior art that have molecular weights below or near 1500 Da,³⁵ the (arbitrary) upper weight limit chosen by Dr. Pomper (an inventor) in a declaration submitted during examination.³⁶ The Board thus need not determine the precise meaning of the “low molecular weight” term, as the grounds involve compounds that meet even Patentee’s arbitrary boundary.

3. Low Molecular Weight Refers to a Magnitude of 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.*”

³⁵ See §§ V.G, VI.D.

³⁶ EX1002, 358-360.

Two phrases in the specification use “low molecular weight” but only one informs its meaning.³⁷ In it, “low molecular weight (LMW) agents” are distinguished from anti-FAP antibodies based on their (i) behavior *in vivo*, (ii) ability to be synthesized and (iii) ability to get approved by the FDA (below).³⁸

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,

Patentee and named inventor Dr. Pomper cited some of these factors when they distinguished “low molecular weight” compounds from antibodies (~150,000 Da) as well as an anti-FAP “iBody”-HMPA compound having a comparable size (~149,000 Da) (below):³⁹

³⁷ The second passage (EX1001, 7:46-53) simply observes that “low-molecular-weight ligands of FAP- α ” can be conjugated to other components of radiopharmaceuticals and used for *in vivo* imaging.

³⁸ EX1001, 1:54-67.

³⁹ EX1002, 358 (¶ 10).

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 thus distinguishes “low molecular weight” compounds from antibodies and similar compounds by their attributes, not by a precise molecular weight boundary.

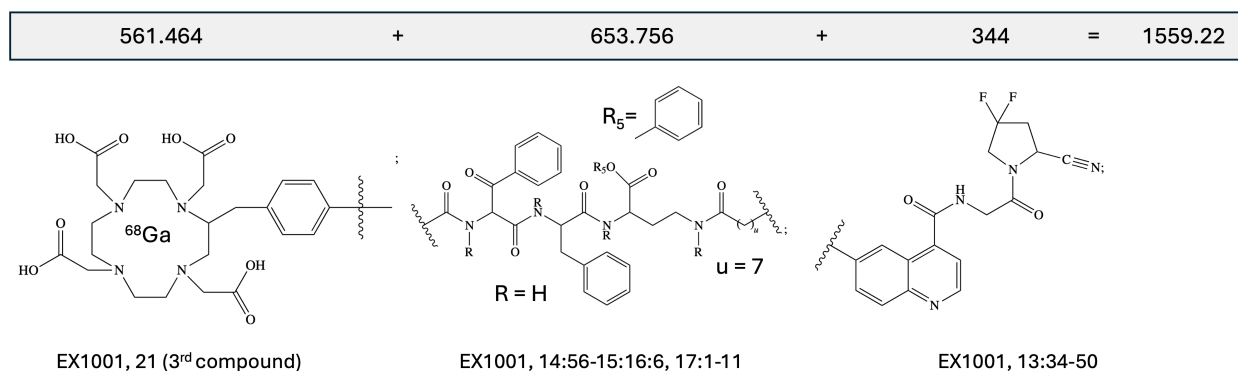
Despite this, Dr. Pomper and Patentee contended that the meaning of “low molecular weight compound” was “well accepted in the chemical arts” and was “a molecular weight from about 50 Daltons to about 1,500 Daltons.”⁴⁰ But the basis of this opinion was *not* the specification—it was *extrinsic* evidence (*i.e.*, certain scientific publications).⁴¹ Yet, other literature attributes the same benefits the

⁴⁰ EX1002, 360 (¶ 17)

⁴¹ *Id.*

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—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



⁴² EX1052, 59-60; EX1003, ¶ 172.

⁴³ EX1002, 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, 13:34-50, 14:56-15:16:6, 17:1-11.

Small molecule compounds with molecular weights above 1500 Da (*e.g.*, 1,700 Da) would also “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 larger, antibody-sized compounds. If the Board finds a construction is necessary, it should find that “low molecular weight” means “*having a molecular weight at least an order of magnitude less than an antibody-based radiopharmaceutical.*”

V. Ground 1: Claims 1-3 Are Obvious Based on US-633, Meletta and Jansen

Claims 1 to 3 of the '201 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 targeting moieties and linkers, including those in the compounds in US-633.

A finding of obviousness under § 103 requires an articulated reasoning with a rational underpinning as to why the claimed invention would have been

⁴⁵ EX1001, 1:60-65; EX1003, ¶¶ 130, 174.

obvious.⁴⁶ Here that reason would not only be evident to a skilled artisan—it 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) not only reported that the boronic acid pyrrolidine targeting moiety in the compounds disclosed in US-633 was insufficiently selective for FAP, it identified a need for more selective targeting moieties to be used in FAP-targeting radiopharmaceuticals.⁴⁷

Prompted by those observations and the general motivation a skilled artisan would have had to discover and use more selective FAP inhibitors in radiotracers, a skilled artisan would have discovered Jansen (EX1006), which showcases a highly selective FAP inhibitor—compound 60—that solves the problem Meletta identified with the US-633 radiopharmaceuticals.

Consequently, this case presents two straightforward inquiries: (i) would a skilled artisan have had a reason to modify the targeting moiety of the US-633 radiopharmaceuticals, and (ii) would that have led that person to replace the targeting moiety of radiopharmaceuticals taught by US-633 with compound 60

⁴⁶ *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 418.

⁴⁷ EX1008, 2089, 2090 (“For future studies more selective inhibitors are needed to reduce non-specific tissue accumulation.”)

from Jansen? Because the evidence demonstrates the answer to both questions is “yes,” claims 1 to 3 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 of tumors and tissues that express FAP and in radiotherapy of tumors:⁴⁸

[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.

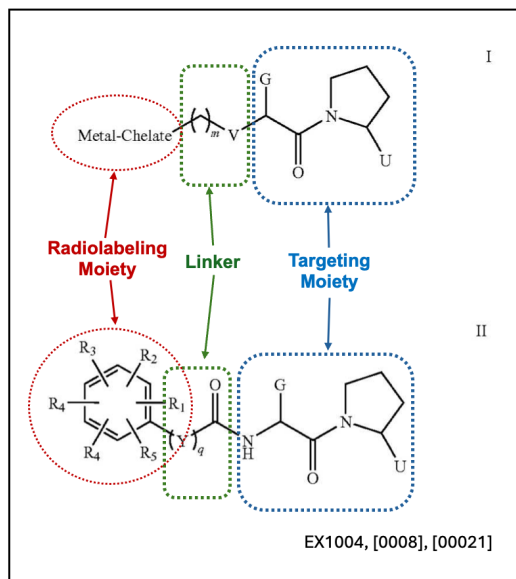
[0007] Small molecule inhibitors of seprase are provided for use as therapeutic medicines or as radiopharmaceuticals useful in diagnostic imaging and in the therapeutic treatment of diseases characterized by overexpression of seprase. The radiopharmaceuticals include complexes or compounds that

(a) Modular Three-Component Radiopharmaceuticals

US-633 describes two types of FAP-targeting radiopharmaceuticals, each

⁴⁸ EX1004, [0002], [0007].

employing the same modular, three-component design as the claims: (i) a targeting moiety connected via (ii) a “tether” (a linker) to (iii) a radiolabeling moiety (illustrated below).⁴⁹ One class uses a chelator as the radiolabeling group (Formula I), while 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 moieties could be used as the radiolabeling moiety, linker and targeting moiety.⁵⁰ Consistent with this, US-633 illustrates several different options for each of the radiolabeling moiety and linker components of Formulas I and II.

⁴⁹ EX1004, [0008], [0021]; EX1003, ¶¶ 71-72.

⁵⁰ EX1003, ¶ 28.

(b) *Imaging Platforms and Radionuclides*

US-633 indicates that the radionuclides that can be used with its radiotracers 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).”⁵¹ It lists many radionuclides, including radiometals (*e.g.*, ^{68}Ga , $^{99\text{m}}\text{Tc}$) and radiohalogens (*e.g.*, ^{18}F , ^{123}I).⁵² A skilled artisan would have known that particular radionuclides must be used with particular imaging devices: PET scanners require a positron-emitting radionuclide (*e.g.*, ^{68}Ga or ^{18}F), while SPECT scanners require a gamma-emitting radionuclide (*e.g.*, $^{99\text{m}}\text{Tc}$, ^{123}I).⁵³

(c) *Chelator and Prosthetic Group Radiolabeling Moieties*

US-633 describes radiolabeling moieties that form a complex between one of two types of chemical structures and a radionuclide suitable for either PET or SPECT imaging (below).⁵⁴ Formula I compounds use chelator groups while

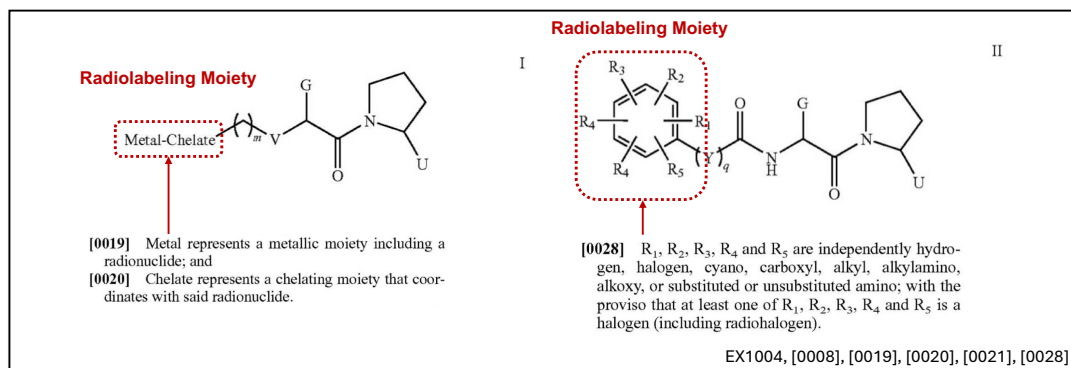
⁵¹ EX1004, [0049].

⁵² EX1004, [0049].

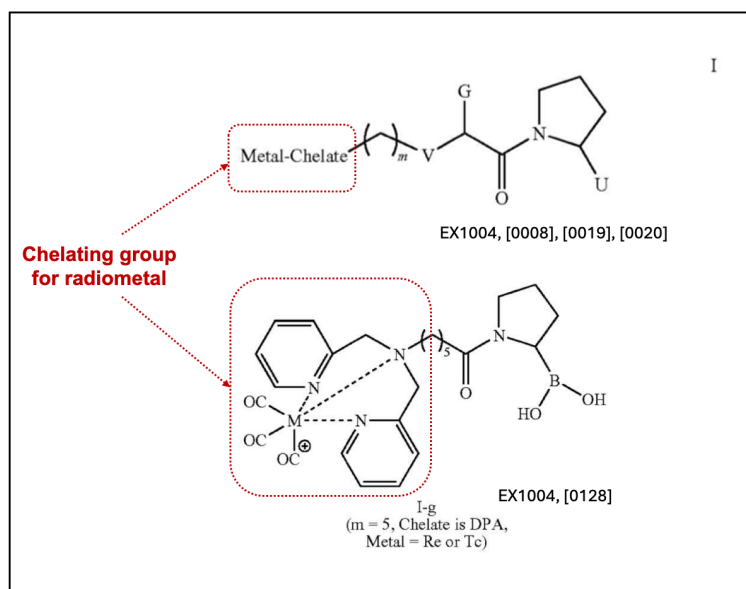
⁵³ EX1003, ¶¶ 39, 129; EX1010, 1, 4; EX1012, 2859; EX1013, 260.

⁵⁴ EX1004, [0008], [0019]-[0020] (chelator), [0021],[0028] (prosthetic group), [0049].

Formula II compounds use prosthetic groups.⁵⁵



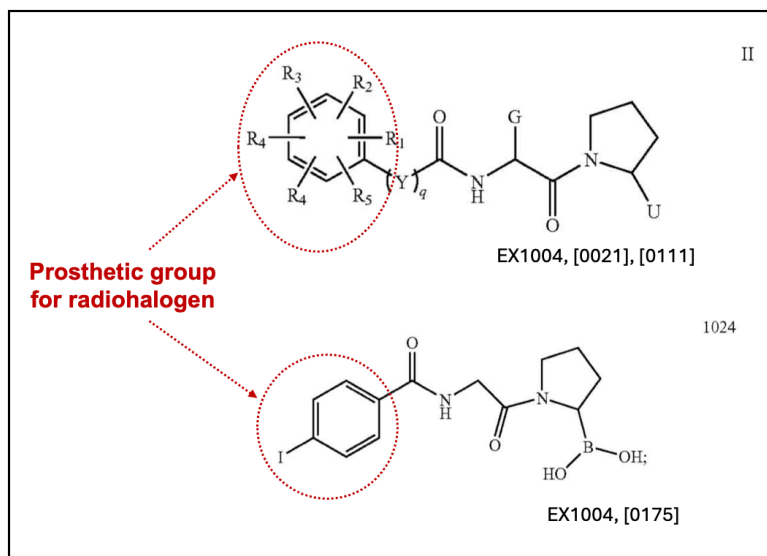
US-633 describes examples of chelators (illustrated below) that form a stable coordinated complex with a radiometal.⁵⁶



⁵⁵ EX1003, ¶¶ 77, 83; EX1004, [0008], [0019], [0020], [0021], [0111], [0128], [0175].

⁵⁶ EX1004, [0008], [0019], [0020], [0128]; *also id.*, [0087], [0097], [0098], [0101]-[0110]; EX1003, ¶¶ 55, 77-78.

US-633 also describes prosthetic groups to which are covalently attached a radiohalogen (*e.g.*, at the para position of the phenyl group below).⁵⁷ The radiolabeled prosthetic group is then covalently attached to the targeting moiety.⁵⁸



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 a radiohalogen (*e.g.*, ^{18}F or ^{123}I).⁵⁹

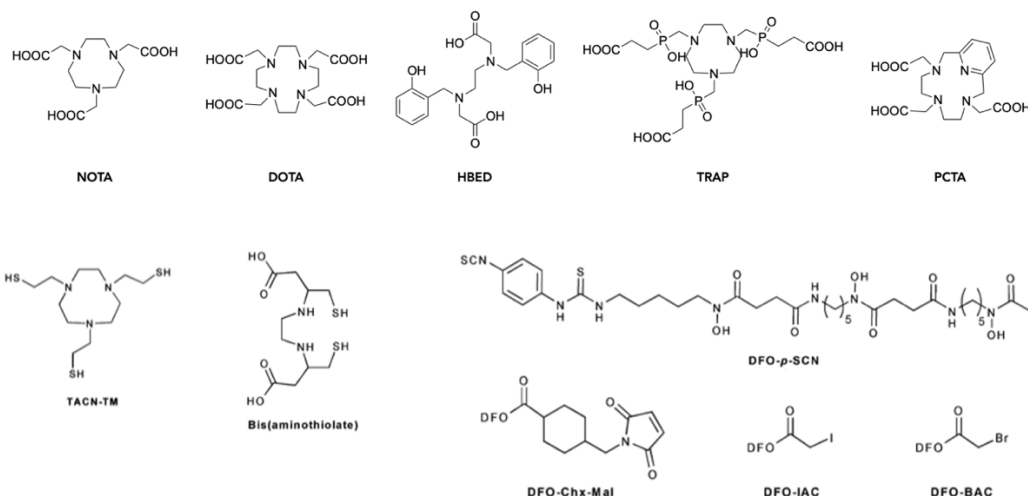
Numerous examples of each type of radiolabeling moiety are taught by US-633. For example, US-633 lists several classes and examples of metal chelators,

⁵⁷ EX1004, [0021]-[0028], [0111]-[0122]; EX1003, ¶ 83.

⁵⁸ EX1003, ¶ 84; EX1004 (US-633), [0134]-[0135].

⁵⁹ EX1003, ¶¶ 33-34.

including DOTA, DPA, DTPA, PAMA.⁶⁰ US-633 also explains that “[a]ny suitable chelating moiety may be used to provide a covalent or other association with a radionuclide.”⁶¹ 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.⁶² By 2017, a skilled artisan would have known the following chelators were suitable for ⁶⁸Ga-based radiotracers, as each was known to form stable coordination complexes with ⁶⁸Ga: DOTA, NOTA, HBED, TRAP, PCTA, TACN-TM and DFO (below).⁶³



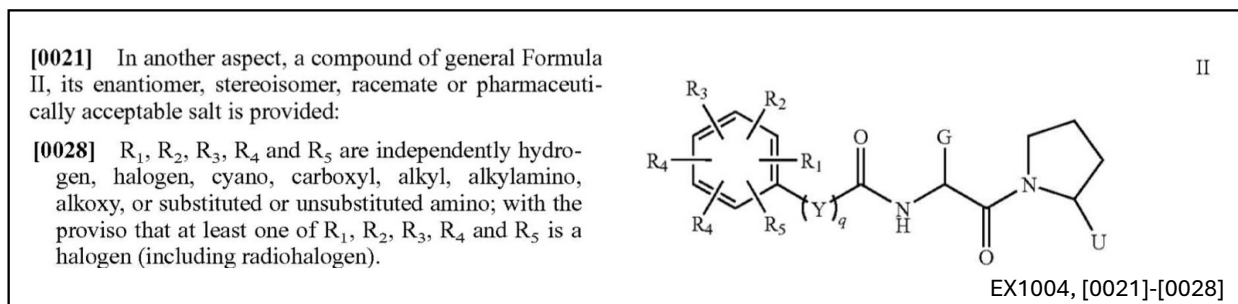
⁶⁰ EX1004, [0048], [0100]-[0110], Table 4.

⁶¹ EX1004, [0100], Tables 3, 4.

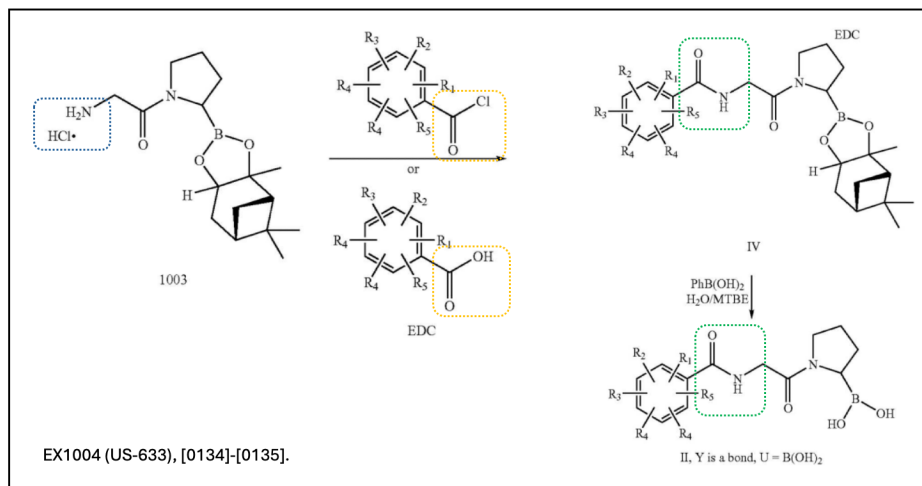
⁶² EX1003, ¶ 81.

⁶³ EX1003, ¶¶ 32, 82; EX1011, 1882-83, 1887-88; EX1013, 267, 272, 275, 276.

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



US-633 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 structure to form an amide bond.⁶⁵



By 2017, a skilled artisan would have known of other prosthetic groups

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

⁶⁵ EX1004, [0135]; EX1003, ¶ 84.

suitable for ^{18}F or ^{123}I that could be radiolabeled and included in the 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

Any of the chelator or prosthetic groups described in US-633, when complexed with or covalently attached to a suitable radiometal or radionuclide, respectively, meets 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 proline” targeting moiety to a radiolabeling moiety.⁶⁸ 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

⁶⁶ EX1003, ¶ 85; EX1034, 2792-95; EX1019, 475-476.

⁶⁷ EX1003, ¶¶ 53-54; EX1015, 202-3; EX1021, 1-2, 6-12.

⁶⁸ EX1004, [0005], [0051]; EX1003, ¶¶ 86-88.

radiopharmaceutical:⁶⁹ 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 use of a variety of examples of tethers, or components of tethers. It lists, for example, representative chemical moieties, including simple alkyl chains, and polyethylene glycol (“PEG”) and polyethylamine oligomers, terminal alkanoic acids, including amino-PEG and carboxylic acid PEG moieties, and amino acids (*e.g.*, glycine and lysine), being used in tethers.⁷⁰

⁶⁹ EX1004, [0101]. *Also, id.* at [0133]; EX1003, ¶ 87.

⁷⁰ EX1004, [0130], [0131].

[0130] Scheme 3 can be utilized to synthesize functionalized proline- $M^+(\text{CO})_3$ 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 $(\text{CH}_2\text{CH}_2\text{O})_n$, a polyethylene amine $((\text{CH}_2\text{CH}_2\text{NH})_n)$, or the like. Terminal aminoalkanoic acids (such as β -alanine, 4-aminobutanoic acid, 5-aminopentanoic acid, 6-aminohexanoic acid and the 8-aminooctanoic acid) or amino-PEG-acids $(\text{NH}_2-(\text{CH}_2\text{CH}_2\text{O})_n-\text{CH}_2-\text{COOH})$, e.g. 2-(2-(3-aminopropoxy)ethoxy)acetic acid) may be utilized as tethers, according to some embodiments.

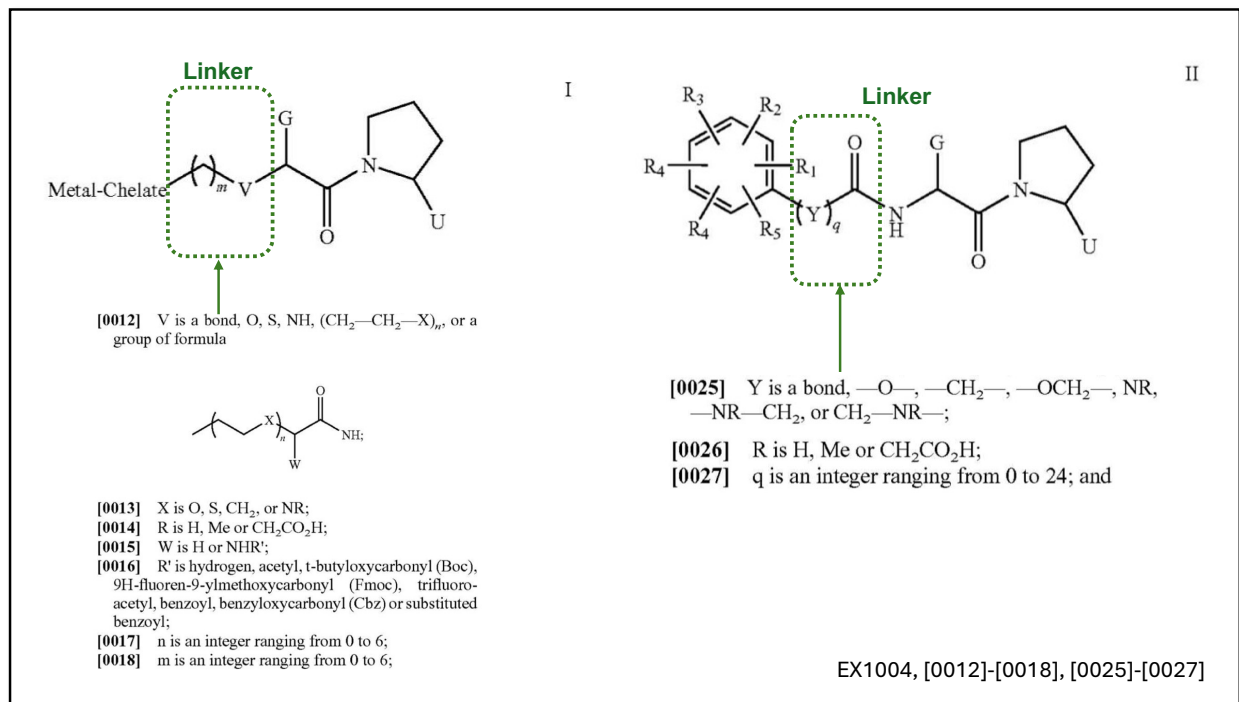
US-633 also describes using commercially available polyethylene glycol compounds (*e.g.*, PEG-diamines) that “can be readily incorporated” into radiotracer compounds.⁷¹ It explains this provides practical benefits, as PEG compounds with varying lengths and other characteristics (*e.g.*, functionalization of the termini of the PEG oligomer) can be purchased.⁷²

[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- $M^+(\text{CO})_3$ complexes.

⁷¹ EX1004, [0133].

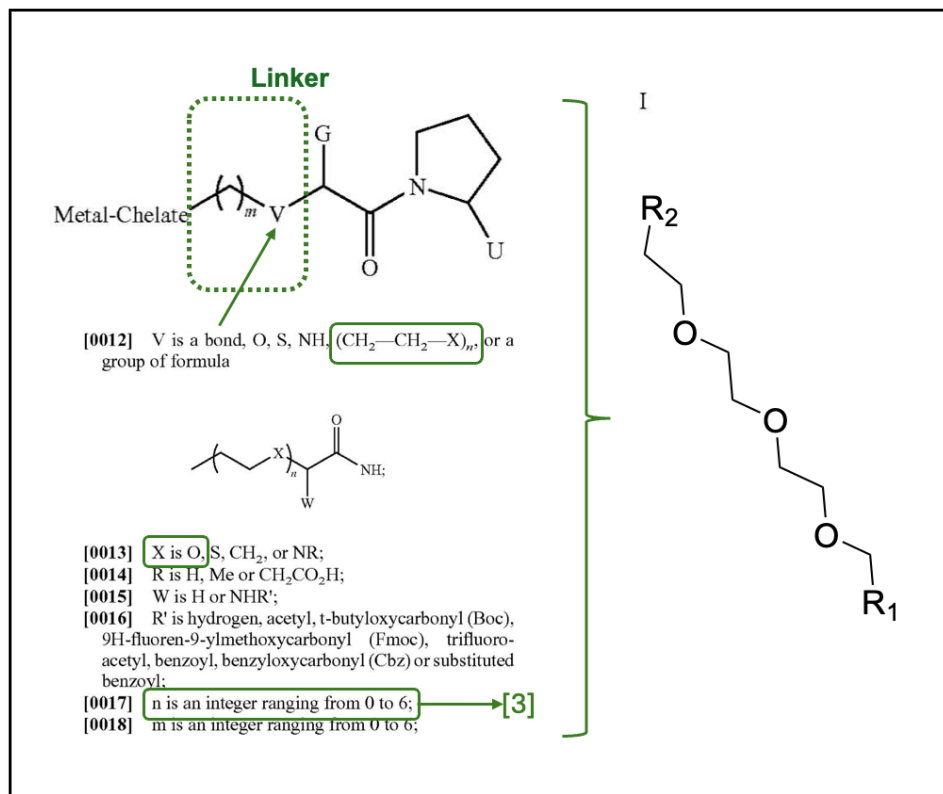
⁷² EX1003, ¶ 88.

US-633 also describes via its two formulas for radiopharmaceuticals that tethers are positioned between the chelator/prosthetic and targeting moieties, and then describes varying chemical characteristics of tethers pursuant to the parameters for these formulae (below):⁷³



For example, one of the tethers taught by formula I is a 3-monomer PEG linker (*i.e.*, “V”=“CH₂—CH₂—X), X=“O” and “n”=3). (below, with R₁ and R₂ representing functional groups):

⁷³ EX1003, ¶ 149.



US-633 also describes tethers that have formed one chemical bond with a radiolabeling moiety and a second chemical bond with a targeting moiety.⁷⁴ Such tethers have “bi-functionalization,” as both of their termini had groups (*e.g.*, -OH, -CO₂H, -NH₂, -SH) that enabled formation of covalent bonds with each of two different 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

⁷⁴ EX1004, [0157].

⁷⁵ EX1004, [0157]; EX1003, ¶ 88.

practical benefits of using PEG-based “tethers” in radiotracers, such as that many 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

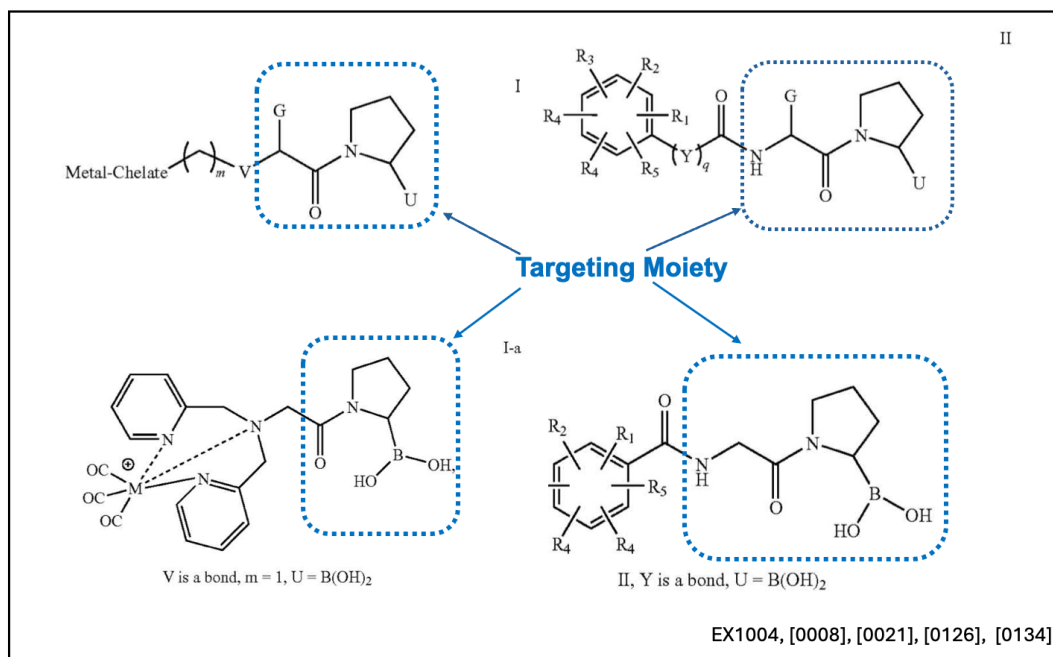
Both Formulas in US-633 use as their targeting moiety a “functionalized proline moiety capable of selectively inhibiting seprase” (*i.e.*, FAP).⁷⁸ US-633 illustrates use of a particular boronic acid pyrrolidine moiety as the FAP-targeting moiety in most of its examples (*i.e.*, where “U” is boronic acid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

⁷⁶ EX1003, ¶¶ 88, 150.

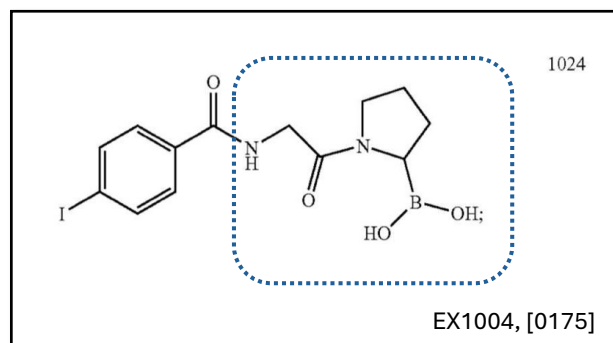
⁷⁷ EX1003, ¶¶ 35-37, 89.

⁷⁸ EX1004, [0007].

⁷⁹ EX1004, [0134]. Scheme 5.



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 Identifies 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

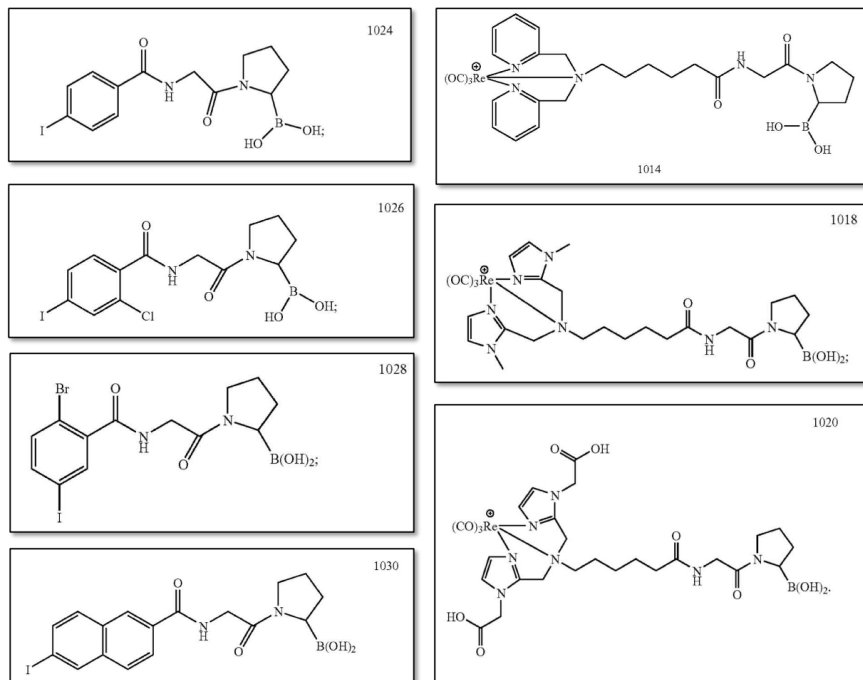
radiolabeling groups.⁸⁰ The various combinations of linkers and radiolabeling groups in these examples are illustrative of what a skilled artisan would have contemplated as possible radiopharmaceutical structures that could be developed once a suitable targeting moiety had been identified.⁸¹

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 had IC₅₀ values between 2 and 5 nM, with compound 1014 at 21 nM (some compounds shown below).

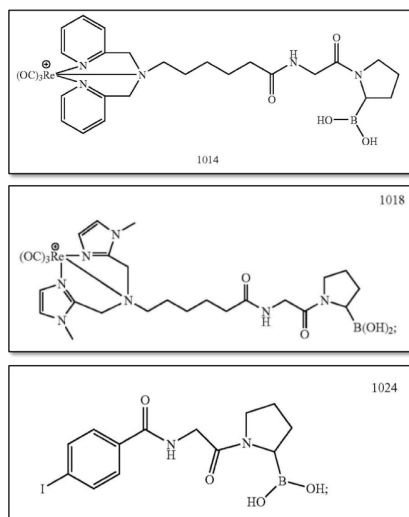
⁸⁰ EX1004, [0151](1006), [0157] (1010), [0159] (1011), [0160] (1014), [0161] (1016), [0162] (1016), [0164] (1020), [0175] (1023-1036), [0176] (1039), [0179] (1039), [0180] (1040-1050).

⁸¹ EX1003, ¶¶ 49, 71, 74, 90.

⁸² EX1004, [0185], Table 2.



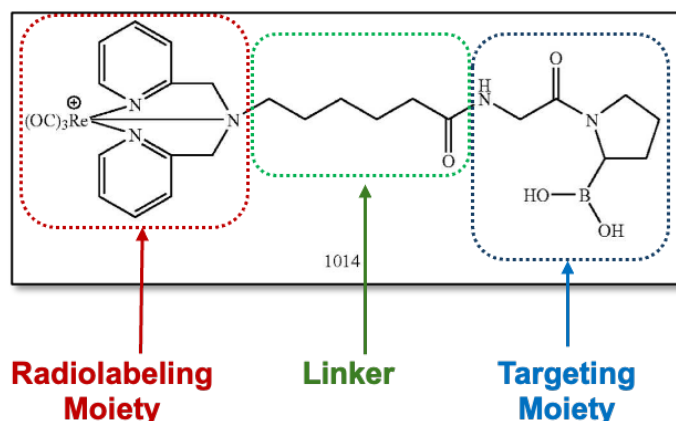
US-633 reported results from additional testing of compounds 1014/1109, 1018/1110 and 1024 (below).⁸³



A skilled artisan would have viewed any of these compounds to be a FAP-

⁸³ EX1004, [0189]-[0192].

targeting radiotracer with a three-component (“B-L-A”) design specified in the patent claims (compound 1014 illustrated below).⁸⁴ These examples, however, have a targeting moiety that does not satisfy the requirements of component A.



Importantly, 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.⁸⁵ 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.⁸⁶

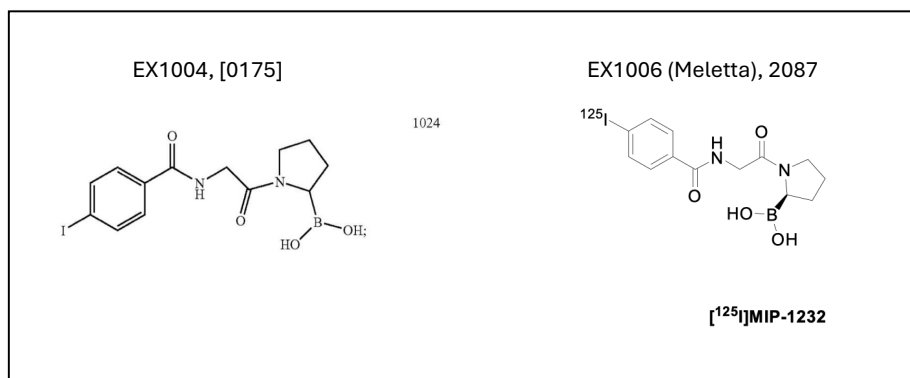
⁸⁴ EX1003, ¶¶ 90, 93.

⁸⁵ EX1003, ¶¶ 45, 47-48, 60; EX1004, [0003], [0005].

⁸⁶ EX1003, ¶ 91.

2. Meletta (EX1008)

Meletta is a 2015 publication. It reports experimental results from testing an ^{125}I -labeled form of compound 1024 (designated MIP-1232) in US-633. Meletta specifically cites to US-633.⁸⁷



Meletta investigated the ability of compound 1024/MIP-1232 to be used as a radiotracer for atherosclerosis imaging.⁸⁸ 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.⁸⁹

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

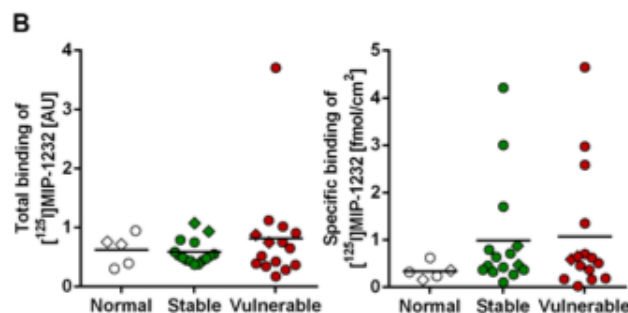
⁸⁷ EX1008, 2087, 2098 (FN31). *See* § V.C.

⁸⁸ EX1008, 2083.

⁸⁹ EX1008, 2083; *also id.* 2081-2, 2089.

for compound 1024/MIP-1232 for FAP and PREP.⁹⁰ Meletta thus provides information on the selectivity of compound 1024 that was not in US-633.

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).⁹¹



⁹⁰ EX1008, 2083; EX1035 (“The IC₅₀ values of ... MIP-1232...for POP [PREP] were ... 19... nM, respectively, with POP[PREP]/FAP ratios of ... 32 ..., respectively.”) EX1003, ¶ 97.

⁹¹ 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*).

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 [¹²⁵I]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 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 μM. ... 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*.⁹²

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

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. *For future studies more selective inhibitors are needed* to reduce

⁹² EX1008, 2089-90 (*emphases added*); EX1003, ¶¶ 99-100.

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* [].⁹³

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 identification of FAP-positive tumors sensitive to a FAP-targeted radiotherapy with existing antibodies.”⁹⁴

Patentee and Dr. Pomper reached the same conclusion from Meletta. Dr. Pomper, for example, portrayed Meletta as demonstrating that MIP-1232/compound 1024 was “determined as not suitable for the [radiotracer] application” and that was because of the “low selectivity” of the compound for FAP.⁹⁵

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-

⁹³ EX1008, 2089-90 (*emphases added*); EX1003, ¶¶ 100-101.

⁹⁴ EX1008, 2090; EX1003, ¶ 101.

⁹⁵ EX1002, 363-365 (¶¶ 32-37); EX1003, ¶ 102.

inhibitor compounds to use in FAP-targeting radiotracers.⁹⁶

3. Jansen (EX1006)

Jansen (EX1006) is a scientific paper 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.”⁹⁷ It showcases one compound in particular—“compound 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 particular compounds.⁹⁸

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

Jansen’s introduction provides an overview of past efforts to develop FAP-selective compounds. It starts by explaining why FAP has been an appealing

⁹⁶ EX1003, ¶¶ 101, 103-104.

⁹⁷ EX1006, 3053.

⁹⁸ EX1003, ¶ 128.

target for pharmaceutical development, including 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 ...⁹⁹

That perspective was widely shared in the field before 2017, as explained in §IV.A.3.¹⁰⁰

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

Jansen recounts challenges of finding small molecules that exhibit sufficient FAP-selectivity to serve as a drug targeting moiety, particularly the selectivity of each compound for FAP over PREP (below).¹⁰¹

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

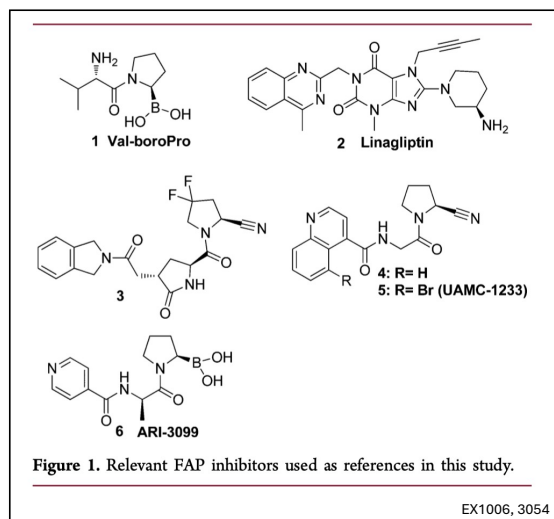
⁹⁹ EX1006, 3053 (*emphasis added*).

¹⁰⁰ EX1003, ¶¶ 58-59, 61-62, 128.

¹⁰¹ EX1006, 3053; EX1003, ¶¶ 107, 109 (*emphasis added*).

with respect to PREP.[.]

Jansen surveyed six, pre-2014 compounds as potential FAP inhibitors (below), and identified shortcomings for each compound.¹⁰²



- 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.¹⁰³
- 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*).¹⁰⁴

¹⁰² EX1006, 3054, Fig. 1; EX1003, ¶¶ 108-109.

¹⁰³ EX1003, ¶ 109(a)-(b).

¹⁰⁴ EX1003, ¶ 109(c).

- Compound #6 shared a pyrrolidine-2-boronic acid structure with 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.¹⁰⁵

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), described around 60 such inhibitors and provided data from testing them for affinity and selectivity to FAP and other prolyl-specific peptidases.¹⁰⁶

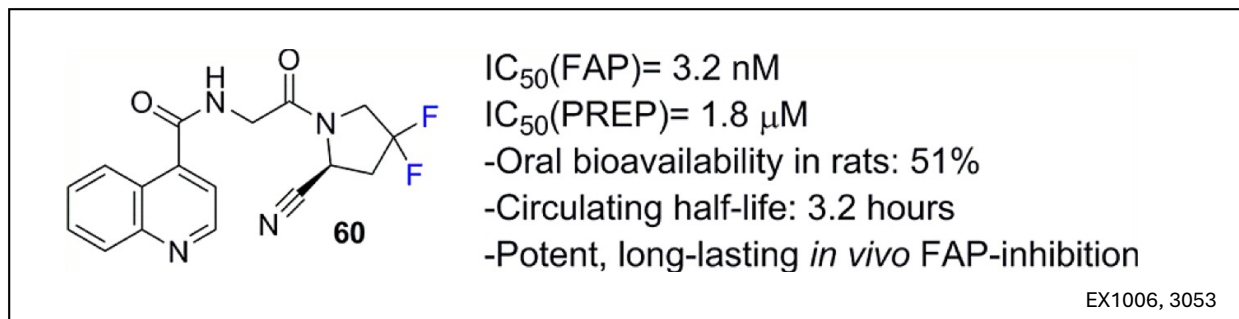
(c) Jansen Identifies Compound 60 as Its Most Promising FAP Inhibitor

Jansen showcases compound 60 as its most promising FAP inhibitor. In fact, it included the structure of compound 60 in its abstract, along with an array of properties that a skilled artisan would have recognized to be favorable characteristics of a targeting moiety for a FAP-targeting radiotracer.¹⁰⁷

¹⁰⁵ EX1003, ¶ 109(d).

¹⁰⁶ EX1006, 3054, Tables 1-6.

¹⁰⁷ EX1006, 3053; EX1003, ¶¶ 110-111.



The data reported by Jansen reinforces this conclusion about Compound 60. Tables 1 to 6 show potency values of each compound for inhibition of the activity of FAP and other prolyl-specific peptidases (*i.e.*, an IC₅₀ concentration). Jansen also reports a “selectivity index” for each compound calculated by dividing its IC₅₀ value for PREP by its IC₅₀ value for FAP.¹⁰⁸ 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 (*i.e.*, compounds 4, 5, 60 and 61):

Taking into account the number of low nanomolar FAP inhibitors with high FAP/PREP selectivity that we had discovered as part of this and the foregoing study, ***four of the most promising compounds were then selected*** for which *in vitro* pharmacokinetic parameters were determined (log D_{7.4}, kinetic solubility, stabilities in mouse, rat, and/or human plasma) (Table 7).¹⁰⁹

¹⁰⁸ *E.g.*, EX1006, 3054, Table 1.

¹⁰⁹ EX1006, 3063 (*emphasis added*).

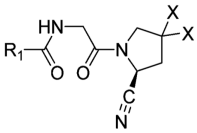
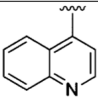
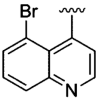
Jansen reported IC₅₀ and selectivity values for the four compounds (below).¹¹⁰

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

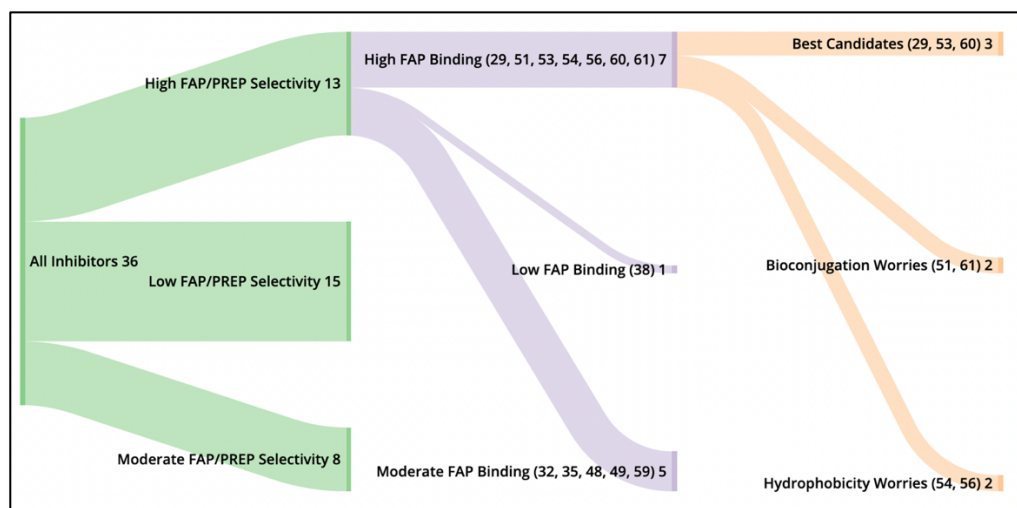
									
Nr	R ₁	X	IC ₅₀ (μM)					SI (FAP/PREP) ^a	
			FAP	PREP	DPPIV	DPP9	DPP2		
60		F,F	0.0032±0.0004	>1.8 ± 0.2	>100	>12.5	>100	562.5	
62		F,F	9.0 ± 0.5	9.3 ± 0.4	>100	≥25	>50	1.0	

EX1006, 3062

A skilled artisan also would have concluded that compound 60 was one of the most promising FAP inhibitors in Jansen based on the selectivity/affinity data

¹¹⁰ EX1006, Table 1 (compounds 4, 5), Table 5 (compounds 60, 61). Compound 60 is identical to Compound 1 in Example 1 of US-650. EX1044, [0317], Table 4.

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 characteristic is high selectivity for FAP over PREP.¹¹¹ 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.¹¹²

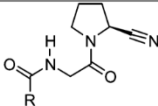
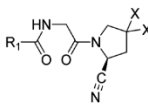
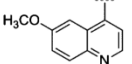


The binding characteristics and structures of compounds 29, 53 and 60 are

¹¹¹ EX1003, ¶ 117; EX1006, 3053 (“FAP over PREP selectivity could nonetheless be an important feature for inhibitors.”)

¹¹² EX1003, ¶¶ 119-121.

shown below. As can be seen, compound 60 had the highest affinity for FAP (lowest IC₅₀), and the second highest selectivity rating relative to PREP.¹¹³

								
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 being one of its most promising FAP inhibitors, it would have been recognized as such by a skilled artisan based on its affinity and selectivity characteristics before 2017.¹¹⁴

¹¹³ EX1006, 3059-60 (29,53), 3062 (60, 61).

¹¹⁴ EX1006, 3064; EX1003, ¶¶ 111-113, 115-116.

(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. The results of those experiments are reported in Table 7 (below).

Table 7. In Vitro Pharmacokinetic Properties of Selected FAP Inhibitors^a

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.¹¹⁵

Jansen subjected three of the compounds (5, 60 and 61) to *in vivo* testing in rats.¹¹⁶ It reported that while compounds 5, 60 and 61 each “displayed significant,

¹¹⁵ EX1006, 3063 (“In general, no large differences between individual inhibitors were observed for the evaluated parameters.”) Table 7 appears to contain a typographical error in referencing a “compound 68.”

¹¹⁶ 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”

roughly comparable oral bioavailabilities (50-79%) and reasonable elimination half-lives (1.5–3 h),” compound 60 exhibited superior *in vivo* characteristics.¹¹⁷ 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.¹¹⁸

A skilled artisan would have concluded that compound 60’s favorable FAP to PREP selectivity, high affinity, stability, pharmacokinetics, long half-life and *in vivo* potency in inhibiting FAP made it one of the best small-molecule FAP inhibitors available before 2017.¹¹⁹ Thus, as Jansen 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 its continuing validation as a drug target.¹²⁰

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

EX1003, ¶¶ 114, 125.

¹¹⁷ EX1006, 3064; EX1003, ¶¶ 125-126.

¹¹⁸ EX1006, 3064; EX1003, ¶ 126.

¹¹⁹ EX1003, ¶¶ 111-112, 115-116, 127.

¹²⁰ EX1006, 3065.

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.¹²¹

B. Differences Between the Claims and the Prior Art

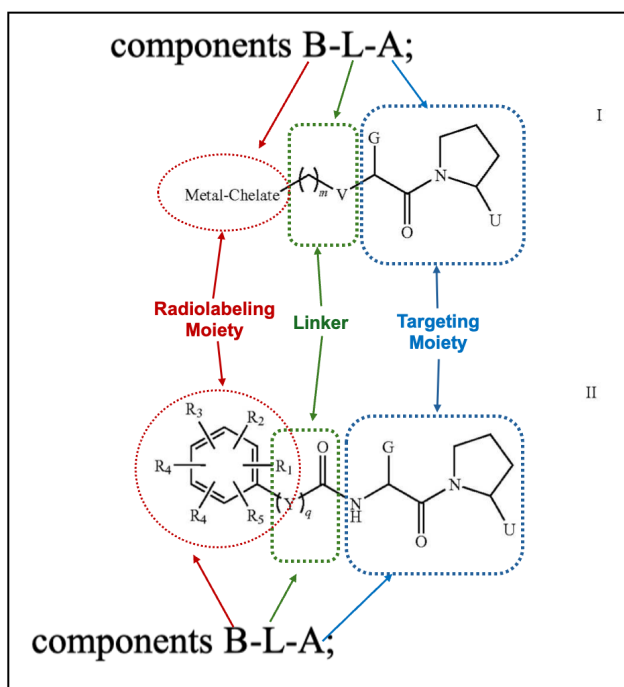
As explained in § V.A.1(a), US-633 describes radiopharmaceutical compounds having a modular design with three components:

- (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.

These three components are components “B”, “L” and “A” within the meaning of the ’201 Patent claims (below).¹²²

¹²¹ EX1003, ¶ 127.

¹²² EX1003, ¶ 71.



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.”¹²³

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.”¹²⁴ In particular, each of the molecules contains chemical bonds between a linker and each of the

¹²³ EX1001, 2:8-10.

¹²⁴ 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 together with each of 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.¹²⁵

Second, all three discuss small molecule FAP inhibitors that can be used in radiotracers and other radiopharmaceuticals. More directly, each describes FAP

¹²⁵ 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, ¶ 128(a).

inhibitor compounds within the same structural class (*i.e.*, each contains a substituted pyrrolidine structure) and provides similar types of data characterizing the affinity of such compounds for FAP and other prolyl oligopeptidases.¹²⁶ For example, Jansen discusses work on boronic acid pyrrolidine FAP inhibitors that were the subject of US-633 and Meletta,¹²⁷ while US-633 reports on 2-cyano-pyrrolidine structures that are the focus of Jansen.¹²⁸

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 [^{125} 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.

A skilled artisan thus would have considered the collective teachings of US-633, Meletta and Jansen.¹²⁹

¹²⁶ EX1003, ¶ 128(b).

¹²⁷ EX1006, 3054, 3055, 3063.

¹²⁸ EX1004, [0169]-[0170], [0178]-[0180], [0185].

¹²⁹ EX1003, ¶ 128.

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

Before 2027, the prior art indicated, and a skilled artisan would have believed, that FAP was an appealing drug target for therapeutic and diagnostic radiopharmaceuticals.¹³⁰ 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:¹³¹

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

¹³⁰ EX1003, ¶¶ 58-59, 61-62, 67, 69-70, 106.

¹³¹ EX1004, [0005], [0007] (*emphases added*).

them *focusing on applications in the oncology domain* (vide infra).¹³²

Other publications from before 2017 reinforce this conclusion.¹³³

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.¹³⁴ 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.¹³⁵

Before 2017, however, the boronic acid pyrrolidine targeting moiety used in the radiotracers described in US-633 was shown to be insufficiently selective for

¹³² EX1006, 3053 (*emphases added*).

¹³³ See § IV.A.3; EX1003, ¶ 59; EX1046, 26; EX1026, 1, 8; EX1022, 123, 125; EX1024, 454, 455.

¹³⁴ See §§ V.A.1(a); EX1003, ¶¶ 71, 27-28.

¹³⁵ See §§ V.A.1(c), V.A.1(d); EX1003, §§ III.A.4, III.A.5.

FAP, effectively terminating interest in developing radiotracers based on the boronic acid pyrrolidine targeting moiety used in the US-633 radiotracers.¹³⁶

Consistent with the view of skilled artisans, Meletta did not propose giving up on FAP as a target for radiotracers—it instead identified a need for *more selective* FAP targeting moieties (including small molecules) (below).¹³⁷

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 radiotracers in US-633 and following the recommendation in Meletta, skilled artisans would have looked for alternative small molecule compounds that were highly selective for

¹³⁶ EX1008, 2089-90 (“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*.”); EX1002, 363-365 (¶¶ 32-37); EX1003, ¶¶ 99-100, 102.

¹³⁷ EX1008, 2090 (*emphases added*); EX1003, ¶¶ 101, 103-104; *also id.* ¶¶ 59, 61-62.

FAP and could serve as a targeting moiety for a FAP-targeting radiotracer, which would have led such artisans to Jansen and compound 60.¹³⁸

Initially, a skilled artisan would have read Jansen as identifying 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.¹³⁹

A skilled artisan would have found compound 60 to be an excellent candidate for the targeting moiety of a small molecule FAP-targeting radiotracer, as it has an array of attributes that make it ideal for that role:

- 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));¹⁴⁰
- it is stable in human plasma, was not subject to oxidative metabolism, exhibits *in vitro* half-life exceeding 6 hours and exhibited no signs of cellular toxicity;¹⁴¹

¹³⁸ EX1003, ¶¶ 133-134.

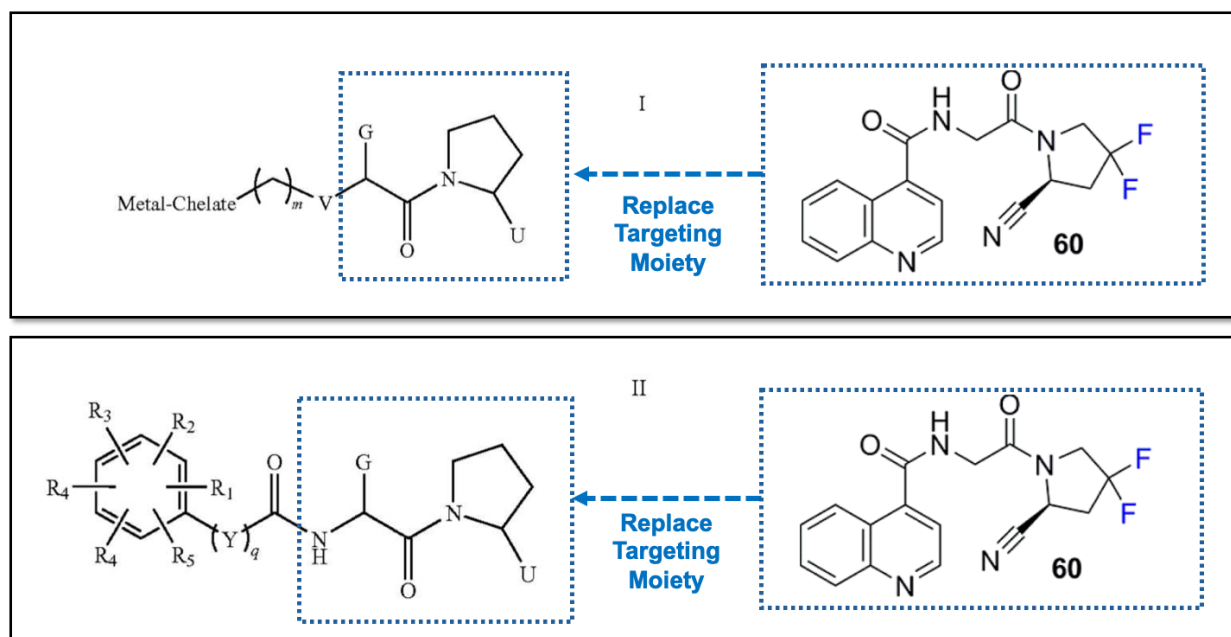
¹³⁹ EX1006, 3053, 3064, 3065; EX1003, ¶¶ 134-135, *also* ¶¶ 110-115, 120-127.

¹⁴⁰ EX1006, 3062 (Table 5); EX1003, ¶¶ 112, 115, 122.

¹⁴¹ EX1006, 3063; EX1003, ¶¶ 112, 114, 123-124.

- *in vivo*, it showed good oral bioavailability and elimination half-lives;¹⁴² 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.¹⁴³

Consequently, a skilled artisan would have been motivated to replace the boronic acid pyrrolidine targeting moiety of the radiotracers described in US-633 with more selective compound 60 of Jansen (below).¹⁴⁴

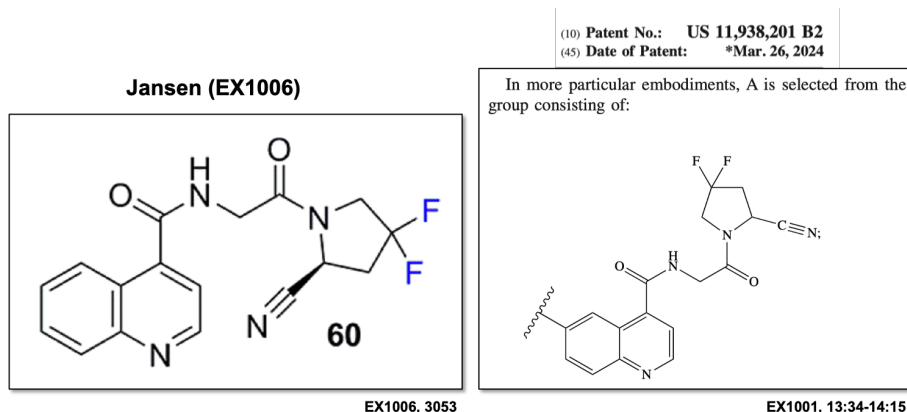


¹⁴² EX1006, 3064; EX1003, ¶¶ 113, 125.

¹⁴³ EX1006, 3064; EX1003, ¶¶ 125-126.

¹⁴⁴ EX1003, ¶¶ 134-135, 146.

Notably, in late 2017, the '201 Patent itself portrayed compound 60—a compound that was published in the scientific literature before then—as a small molecule targeting moiety suitable for a FAP-targeting radiotracer, labeling it a “particular embodiment” of its “A” component (below right).¹⁴⁵



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

In addition to matching a structure that the '201 Patent portrays as a “particular embodiment” of an “A” moiety in its claimed compounds, compound 60 unquestionably meets every requirement of that “A” component in the claims.

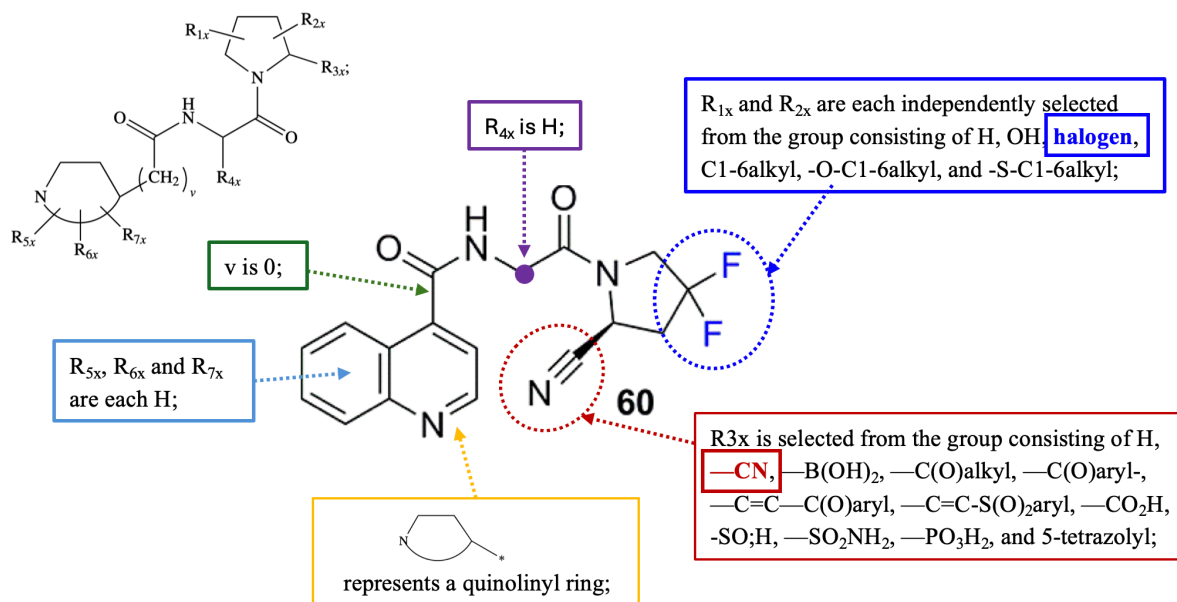
First, Jansen describes compound 60 as a highly selective FAP inhibitor (e.g., it has a selectivity index of >560 for binding to FAP relative to PREP, and a high affinity (*i.e.*, an IC₅₀ of 3.2 nM)).¹⁴⁶ A skilled artisan would conclude that,

¹⁴⁵ EX1001, 13:34-14:15; Jansen, 3053.

¹⁴⁶ EX1006, 3053.

when incorporated in a radiotracer, compound 60 is “a targeting moiety for FAP- α ” within the meaning of the claims.¹⁴⁷

Second, compound 60 meets the structural requirements of the “A” component in the claimed “Formula (I)” of “B-L-A” based on its structure. As shown below, compound 60 has attributes at positions in the “A” generic structure that match parameters in the claims for those positions:¹⁴⁸



Also, the claims’ options for the left side of the quinolinyl ring require 3 of the 4 available positions to be hydrogen, which allows one (*e.g.*, position C⁶ or C⁷) to be functionalized to be the site of the linker attachment.

¹⁴⁷ EX1003, ¶ 168.

¹⁴⁸ EX1001, Claim 1 (corrected).

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

To integrate compound 60 into radiotracer structures suggested by US-633, a skilled artisan would have made decisions regarding the radionuclide to use, the type and identity of the radiolabeling moiety and linkers to use in the compounds. In making these choices, the skilled artisan would draw 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

Initially, a skilled artisan would have used the modular three-component design for a radiotracer based on the guidance in US-633, the structure of compound 60 and guidance in Jansen and related literature regarding modifications to compound 60 that can influence its selectivity and affinity.¹⁴⁹

2. Choices for the Radiolabeling Moiety

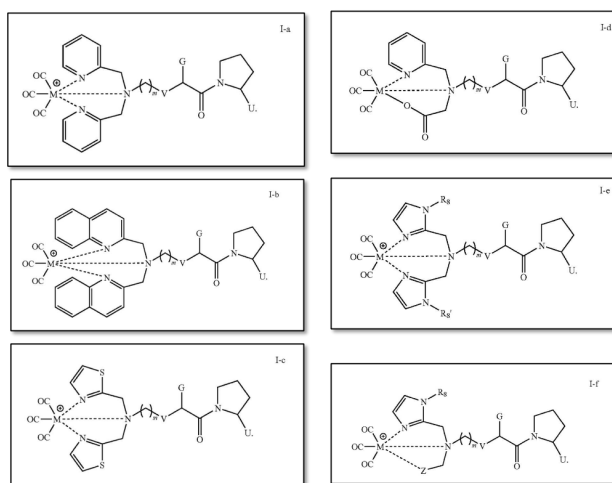
As Dr. Zeglis explains, a skilled artisan would select a radionuclide based on the imaging platform to be used (*i.e.*, PET or SPECT) and by matching its radioactive half-life to the pharmacokinetic half-life of the radiotracer carrying it.¹⁵⁰ A skilled artisan would have believed a radiotracer based on compound 60 would have a short pharmacokinetic half-life, and as such, would have considered

¹⁴⁹ EX1003, ¶¶ 71, 139, 142; EX1006, 3062 (Table 5); EX1007, 493.

¹⁵⁰ EX1003, ¶¶ 39-41, 129-130.

certain radionuclides appropriate: (i) ^{68}Ga and ^{18}F for PET imaging, and (ii) $^{99\text{m}}\text{Tc}$ and ^{123}I for SPECT imaging.¹⁵¹

As US-633 explains, “[a]ny suitable chelating moiety may be used to provide a covalent or other association with a radionuclide.”¹⁵² Skilled artisans would have selected a chelator that was known to be suitable for the particular radiometal chosen.¹⁵³ US-633 lists DOTA as one chelator option, which was known to be suitable for ^{68}Ga .¹⁵⁴ US-633 also describes several chelators that were known to be suitable for $^{99\text{m}}\text{Tc}$ (below), including DPA (“1-a”).¹⁵⁵



¹⁵¹ EX1004, [0049]; EX1003, ¶¶ 39, 42, 43, 132.

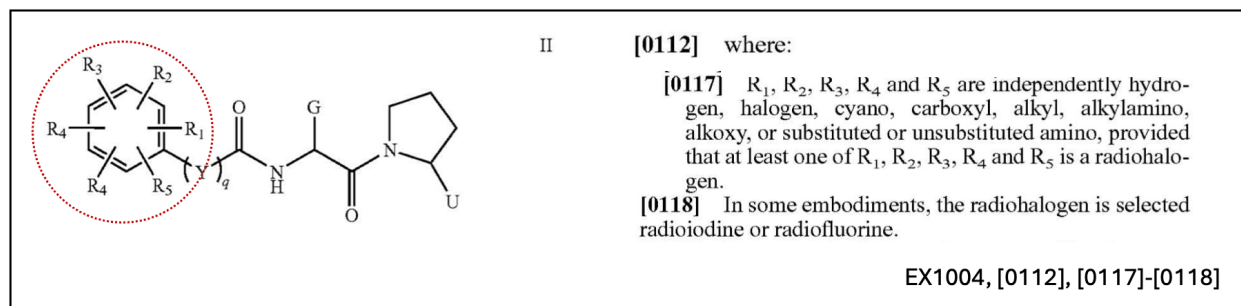
¹⁵² EX1004, [0100].

¹⁵³ EX1003, ¶¶ 32-33, 81, 147.

¹⁵⁴ EX1004, [0100] (DOTA); EX1003, ¶¶ 78, 82; *also id.* ¶ 33.

¹⁵⁵ EX1003, ¶¶ 78-80, 148.

US-633 teaches use of prosthetic groups in radiotracers based on radiohalogens (*i.e.*, ^{18}F , ^{123}I). It illustrates use of a prosthetic group in Formula II, teaching covalently attaching radioiodine (^{123}I) or radiofluorine (^{18}F) to a position on the phenyl ring (below):¹⁵⁶



A skilled artisan would have considered the prosthetic groups illustrated in US-633 to be suitable options for a compound 60-based radiotracer based on ^{18}F or ^{123}I .¹⁵⁷

3. Choices for the Linker

A skilled artisan would have been familiar with linkers used commonly in the construction of radiotracers.¹⁵⁸ 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,

¹⁵⁶ EX1004, [0117]-[0118].

¹⁵⁷ EX1003, ¶¶ 83-85, 157, 161; *also id.* ¶ 34.

¹⁵⁸ EX1003, ¶¶ 35-36, 88-89.

inter alia, simple alkyl chains or PEG.¹⁵⁹ US-633 also explains (as would be known by the skilled artisan) that the size of the linker can be adjusted to ensure the radiolabeling moiety is sufficiently far from the targeting moiety.¹⁶⁰

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

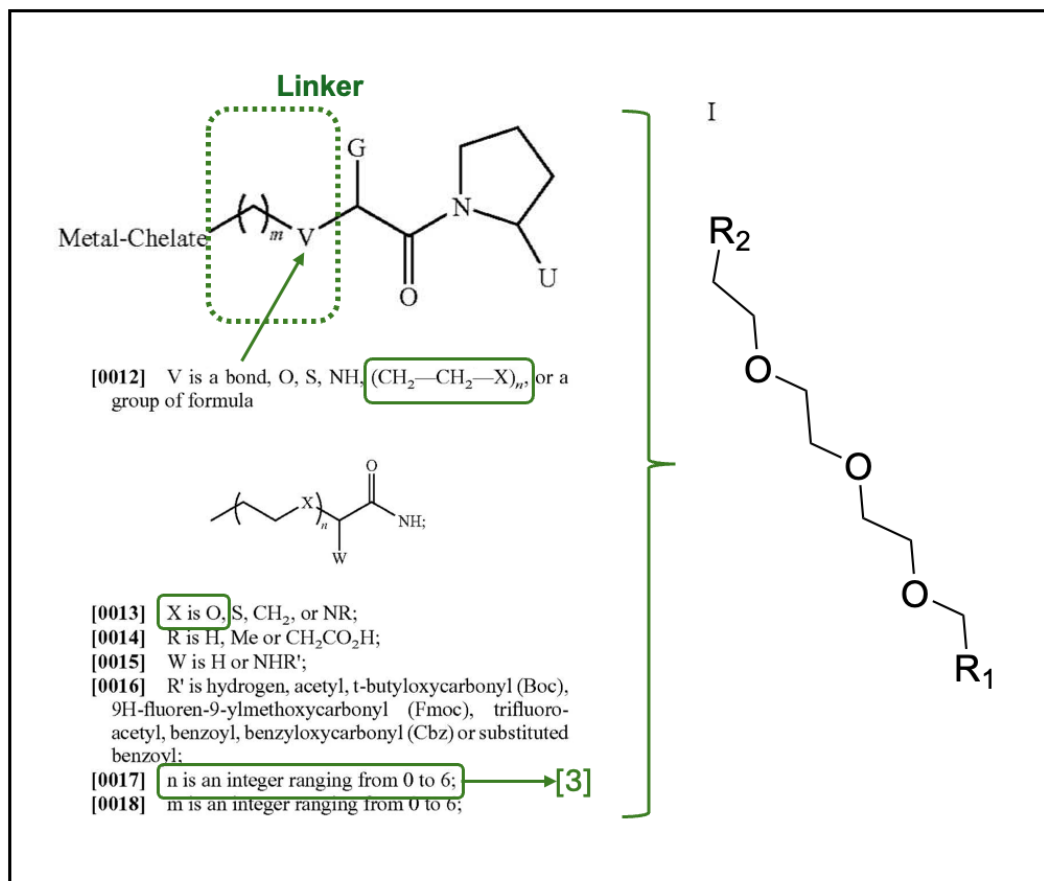
[0133] The above reaction scheme is applicable to any modification of the tether by incorporation of heteroatoms into the tether chain. This may have additional benefits on the affinity as well as the selectivity for seprase. Incorporation of heteroatoms into the tether such as oxygen can take advantage 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). As shown below, in Formula I, selecting “V” as “(CH₂—CH₂—X)_n,” X as “O” and “n” as 3 yields a 3 monomer unit PEG oligomer (below).¹⁶¹

¹⁵⁹ EX1004, [0130] (“The tether may comprise a simple alkyl chain as shown, a PEG (CH₂CH₂O)_n, a polyethylene amine ((CH₂CH₂NH)_n), or the like.”)

¹⁶⁰ EX1003, ¶ 151.

¹⁶¹ EX1004, [0012]-[0018].

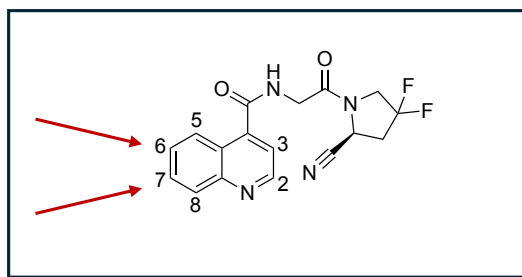


While the “tether” is illustrated with a chelator group, a skilled artisan would have found this guidance useful for compounds incorporating prosthetic groups. Specifically, the skilled artisan would recognize that the compound 60 moiety should be separated by a sufficient distance (*e.g.*, 10 to 20 bonds) to avoid interacting with the prosthetic group, which would be achieved by using a 3-monomer PEG linker.¹⁶²

¹⁶² EX1003, ¶¶ 35, 151; EX1004, [0101], [0130].

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.¹⁶³ He also explained that, after determining which part of compound 60 is responsible for its binding to FAP¹⁶⁴ 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 (below), as modifications to those positions did not affect the selectivity or affinity of the compound.¹⁶⁵

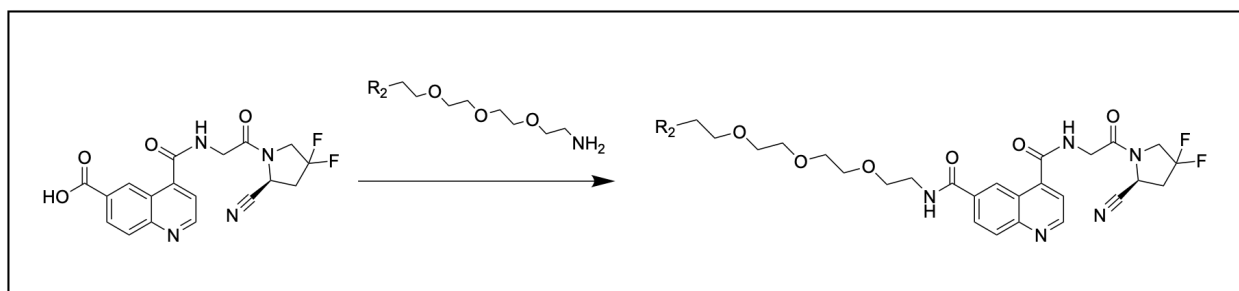


¹⁶³ EX1003, ¶ 139.

¹⁶⁴ EX1003, ¶ 140.

¹⁶⁵ EX1003, ¶ 142.

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. The skilled artisan, for example, 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).¹⁶⁶



A skilled artisan would also have functionalized the R₂ terminus in the above exemplary PEG linker to enable formation of a second covalent bond with either a chelating or prosthetic structure. For example, if the R₂ group were also an amine (*e.g.*, a “diamine PEG” linker discussed in US-633),¹⁶⁷ it would enable formation of an amide bond with a free carboxylic acid on a DOTA chelator.¹⁶⁸ Of course, other synthetic routes could be taken (*e.g.*, forming the DOTA-linker

¹⁶⁶ EX1003, ¶¶ 143, 151.

¹⁶⁷ EX1004, [0133].

¹⁶⁸ EX1003, ¶ 152.

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 in 2007.¹⁶⁹

G. Examples of Compounds Suggested by US-633, Meletta and Jansen Satisfy Claims 1-3

A skilled artisan would have found particular compounds to have been an obvious application of the teachings of US-633, Meletta and Jansen, in view of their training and experience as of early 2017. In particular, the skilled artisan would have found it obvious from those teachings 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);
- (ii) select a radionuclide and its suitable chelator or prosthetic group for a desired imaging platform (PET or SPECT) pursuant to US-633 and knowledge they possessed in 2017 (*see* § V.F.2);
- (iii) 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) (*see* § V.F.3); and

¹⁶⁹ EX1003, ¶ 154.

- (iv) 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 reflecting these choices suggested by the prior art are illustrated below and meet every requirement of claims 1-3 of the '201 Patent.

1. A PET Radiotracer Based on ⁶⁸Ga, DOTA and PEG Satisfies Claims 1-3 (Compound A1)

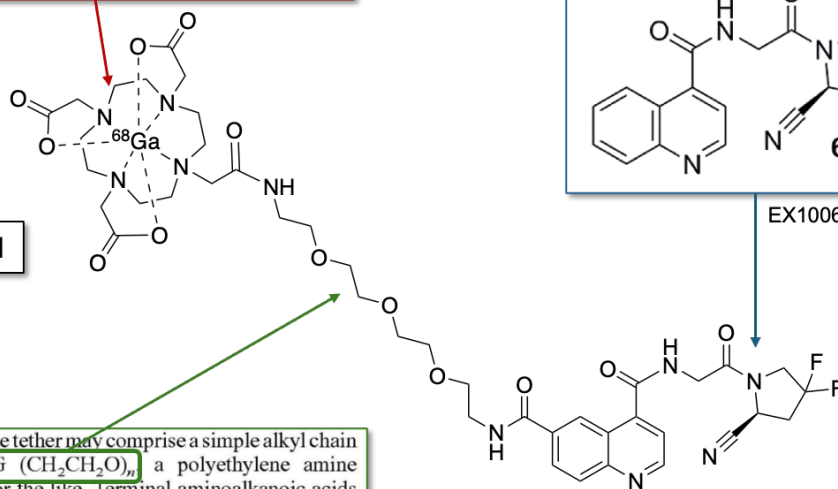
Below is illustrated Compound A1 that incorporates (i) Jansen's compound 60 functionalized to contain a carboxylic group at position C⁶, (ii) a DOTA chelator suitable for ⁶⁸Ga, and (iii) a 3-monomer PEG functionalized to contain terminal amine groups. Some of the support within US-633 and Jansen for these component selections is also shown.¹⁷⁰

¹⁷⁰ EX1003, ¶¶ 149-153; 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 A1



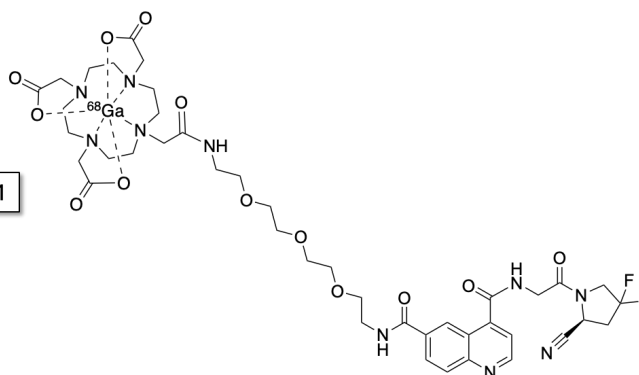
EX1006, 3053, 3062

these structures. The tether may comprise a simple alkyl chain as shown, a PEG (CH₂CH₂O)_n, a polyethylene amine ((CH₂CH₂NH)_n), or the like. Terminal aminoalkanoic acids

EX1004, [0130]

Chemical Formula: C₄₂H₅₅F₂⁶⁸GaN₁₀O₁₃
Molecular Weight: 1013.88

Compound A1



Chemical Formula: C₄₂H₅₅F₂⁶⁸GaN₁₀O₁₃
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.¹⁷¹ With its stably coordinated

¹⁷¹ EX1003, ¶ 176.

complex with ^{68}Ga , the Compound A1 compound would be suitable for use as a radiotracer for PET imaging.¹⁷² Compound A1 renders claims 1-3 obvious.

2. A SPECT Radiotracer Based on ^{68}Ga , DPA and PEG Satisfies Claims 1-3 (Compound A2)

Below is illustrated Compound A2 incorporating (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.¹⁷³ Some of the support within US-633 and Jansen for these component selections being included is also shown.¹⁷⁴

¹⁷² EX1003, ¶ 177.

¹⁷³ EX1003, ¶ 154.

¹⁷⁴ 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

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

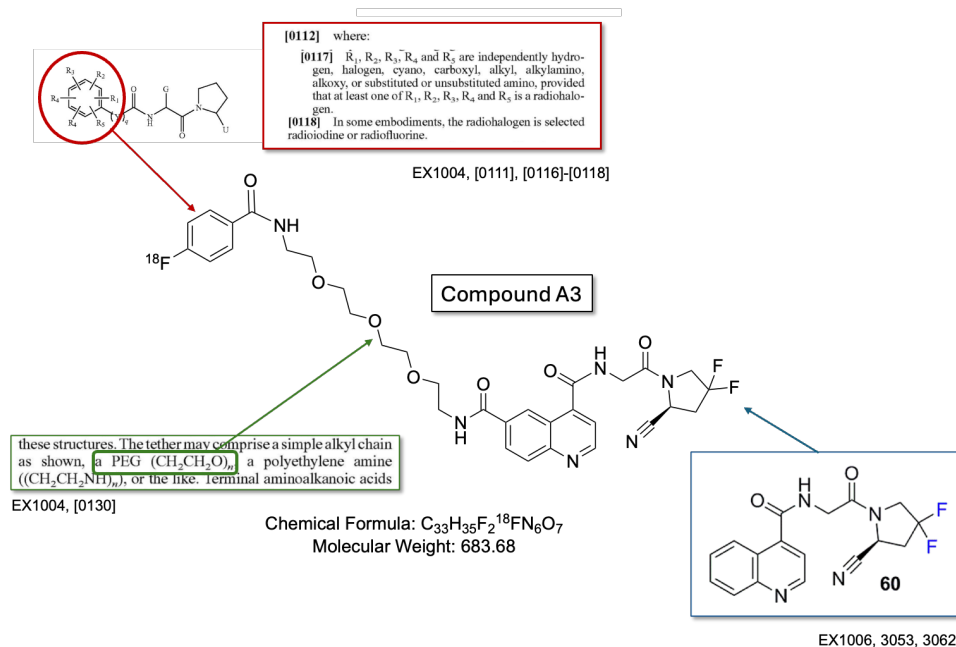
Compound A2 is a “low molecular weight” compound in the meaning of the claims as it has a molecular weight of ~928 Da, which is orders of magnitude smaller than an antibody, and below 1500 Da.¹⁷⁵ With its stably coordinated

¹⁷⁵ EX1003, ¶ 176.

complex with ^{99m}Tc , the Compound A2 radiotracer would be suitable for use in SPECT imaging.¹⁷⁶ Compound A2 renders claims 1-3 obvious.

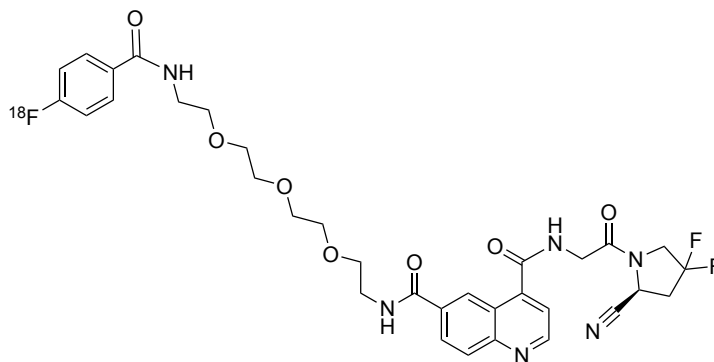
3. A PET Radiotracer Based on ^{18}F , a Prosthetic Group and PEG Satisfies Claims 1-3 (Compound A3)

Below is illustrated Compound A3 incorporating (i) compound 60 functionalized to contain a carboxylic group at position C⁶, (ii) a prosthetic group labeled with ^{18}F at the para position of the phenyl group, and (iii) a 3-monomer PEG functionalized to contain terminal amine groups. Some of the support within US-633 and Jansen for these component selections being included is also shown.¹⁷⁷



¹⁷⁶ EX1003, ¶ 177.

¹⁷⁷ EX1003, ¶¶ 156-161; EX1004, [0021], [0028], [0049], [0111], [0116]-[0118], [0133]; EX1006, 3053, 3061, 3062.



Chemical Formula: C₃₃H₃₅F₂¹⁸FN₆O₇
Molecular Weight: 683.68

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 ¹⁸F radionuclide, the Compound A3 radiotracer would be suitable for use in PET imaging.¹⁷⁹ Compound A3 renders claims 1-3 obvious.

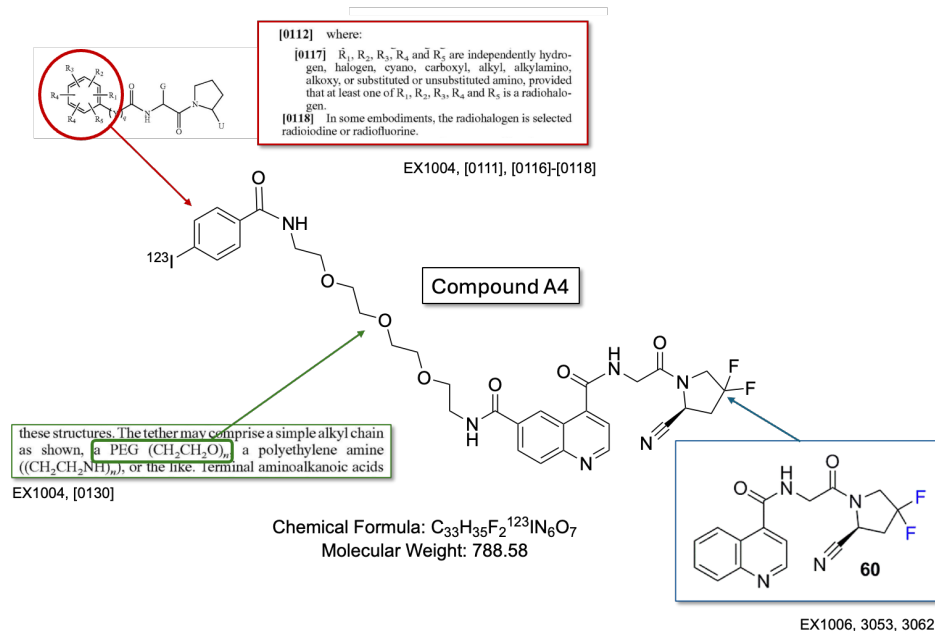
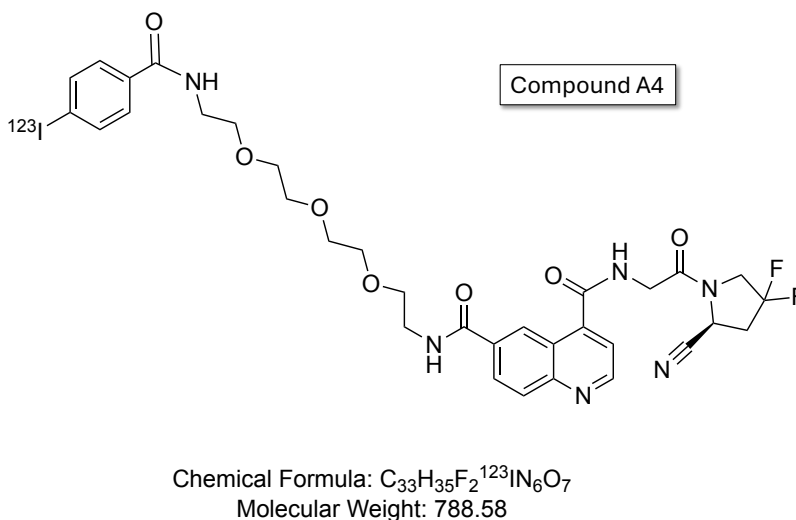
4. A SPECT Radiotracer Based on ¹²³I, a Prosthetic Group and PEG Satisfies Claims 1-3 (Compound A4)

Below is illustrated Compound A4 incorporating (i) compound 60 functionalized to contain a carboxylic group at position C⁶, (ii) a prosthetic group labeled with ¹²³I at the para position of the phenyl group, and (iii) a 3-monomer

¹⁷⁸ EX1003, ¶ 176.

¹⁷⁹ EX1003, ¶ 177.

PEG functionalized to contain terminal amine groups. Some of the support within US-633 and Jansen for these component selections is also shown.¹⁸⁰



¹⁸⁰ EX1003, ¶¶ 156-161; 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.¹⁸¹ With its covalently attached ¹²³I radionuclide, the Compound A4 radiotracer would be suitable for use in SPECT imaging.¹⁸² Compound A4 renders claims 1-3 obvious.

H. Claims 1-3 Would Have Been Obvious

As explained in § V.G, a skilled artisan would have found particular radiotracer compounds meeting every requirement of claims 1-3 obvious before 2017 based on the combined teachings of US-633, Meletta and Jansen.

A skilled artisan would have reasonably expected compounds such as A1-A4 to retain the selectivity and affinity of compound 60, and thus render them viable radiotracers.¹⁸³ The illustrated PEG linker included in these compounds separates the radiolabeling moiety in each compound from the compound 60 targeting moiety by 12+ bonds.¹⁸⁴ In addition, a skilled artisan would expect that

¹⁸¹ EX1003, ¶ 176.

¹⁸² EX1003, ¶ 177.

¹⁸³ EX1003, ¶ 177.

¹⁸⁴ EX1003, ¶¶ 151, 165; EX1004, [0101], [0130], [0131].

attaching the linker at position C⁶ of the quinolinyl ring of compound 60 would not disturb its selectivity and affinity for FAP.¹⁸⁵

VI. Ground 2: Claims 1-3 Are Obvious Based on US-121 (EX1005) and Jansen (EX1006)

Claims 1-3 also would have been obvious from the combined teachings of US-121 and Jansen.

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

A. Teachings of US-121

US-121 published in 2012 and is owned by the assignee of the '201 Patent that also names Dr. Pomper as an inventor.

US-121 describes “low molecular weight” compounds used as radiotracers and therapeutic radiopharmaceuticals.¹⁸⁶ 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,”¹⁸⁷ and (ii) provide better

¹⁸⁵ EX1003, ¶ 177.

¹⁸⁶ EX1005, [0012].

¹⁸⁷ EX1005, [0012].

tumor penetration.¹⁸⁸ These advantages are similar to the ones identified in the '201 Patent (below).¹⁸⁹

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):¹⁹⁰

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.¹⁹¹

¹⁸⁸ EX1005, [0012] (“greater cellular retention”), [0008]-[0009], [0188] (longer tumor residence).

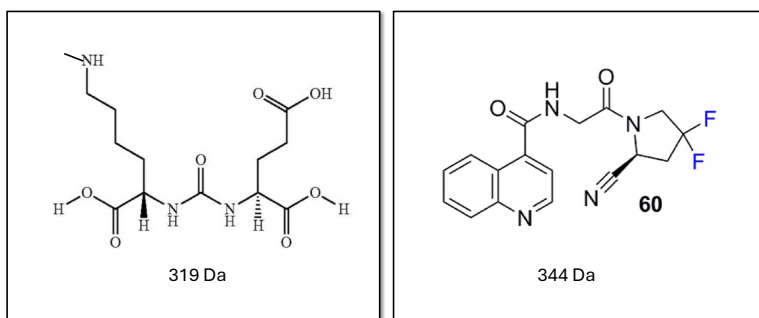
¹⁸⁹ Compare EX1005, [0008]-[0009]; EX1001, 1:49-67. See EX1003, ¶ 183.

¹⁹⁰ EX1005, [0007].

¹⁹¹ See § IV.A.3; EX1004, [0003].

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.”¹⁹² That need certainly persisted past 2012 and was not limited to PSMA-targeting radiotracers.

The radiotracers described in US-121 use as their targeting moiety a small molecule lysine-urea-glutamic acid moiety (below, left).¹⁹³ It has a comparable molecular weight to Jansen’s compound 60 (*i.e.*, 319 Da vs. 344 Da) (below right).¹⁹⁴



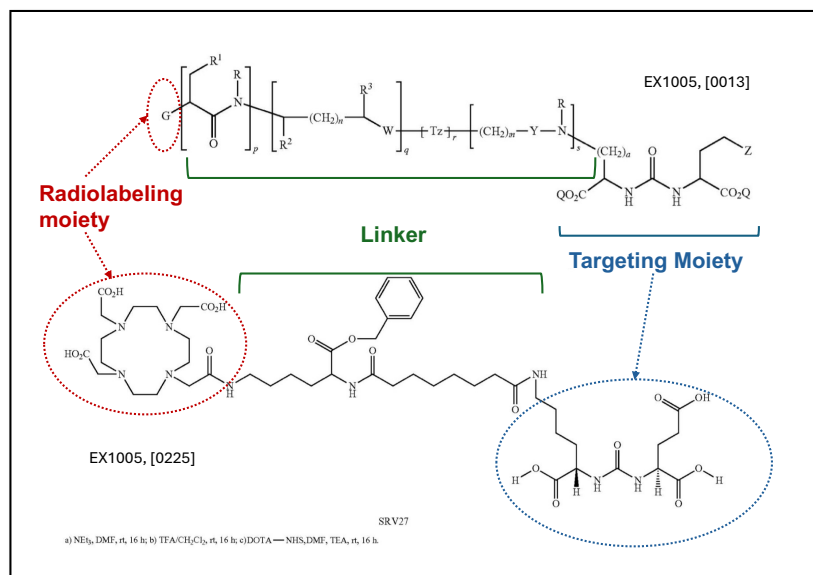
The radiotracers described in US-121 join a urea-based targeting moiety to a chelator using a variety of linkers. These radiotracers share the same modular, three-component design as the claimed radiotracers (illustrated below using

¹⁹² EX1005, [0012].

¹⁹³ EX1005, [0166], [0169]; EX1003, ¶¶ 183, 205.

¹⁹⁴ EX1003, ¶ 205.

generic structure and exemplified compound SRV27)(below).¹⁹⁵



US-121 identifies advantages of this modular design, including that it allows one to easily optimize the pharmacokinetics of the radiotracer.¹⁹⁶ US-121 provides several other examples of radiotracer compounds that embody this modular three-component structure of the '201 Patent claims.¹⁹⁷

US-121 explains that its radiotracers can be used with both PET and SPECT devices.¹⁹⁸ It identifies advantages of using PET with ⁶⁸Ga-labeled radiotracers,¹⁹⁹

¹⁹⁵ EX1003, ¶ 183.

¹⁹⁶ EX1003, ¶ 184; EX1005, [0279](YC27 pharmacokinetics).

¹⁹⁷ EX1005, [0103], [0207], [0214], [0225], [0244], [0249]-[0250].

¹⁹⁸ EX1005, [0184]; EX1003, ¶ 184.

¹⁹⁹ EX1005, [0242], [0011]; EX1003, ¶ 188.

but also describes examples of ^{99m}Tc -based radiotracers being used with SPECT imaging.²⁰⁰ It also explains that “[n]umerous metal chelating moieties are known in the art” and lists several pages of them (*e.g.*, DOTA, DTPA, NOTA),²⁰¹ 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), explaining that one is more lipophilic “which is reasonable in

²⁰⁰ EX1005, [0027], [0214]; EX1003, ¶¶ 189, 197.

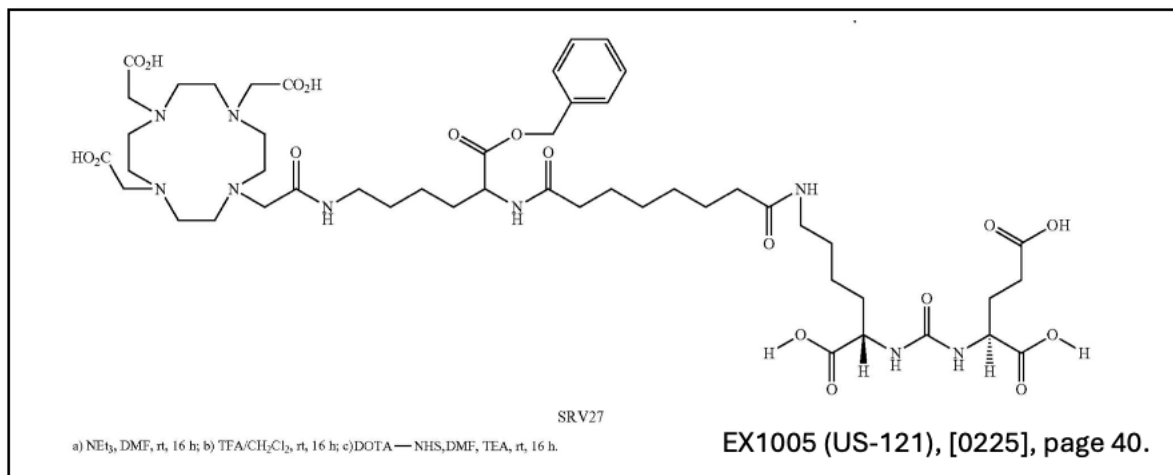
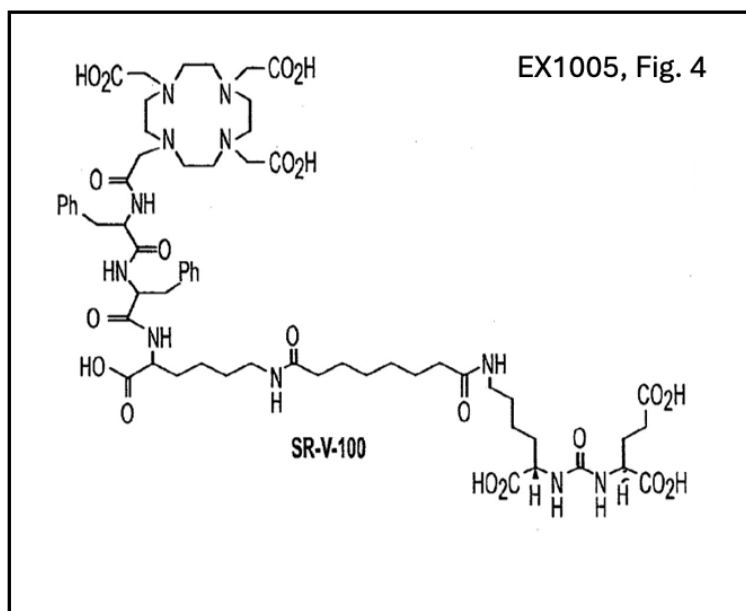
²⁰¹ EX1005, [0102].

²⁰² EX1005, [0102].

²⁰³ EX1005, [0102].

²⁰⁴ EX1005, [0187], [0012]; EX1003, ¶¶ 193, 207.

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



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

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

²⁰⁵ EX1005, [0231]; Fig. 4.

before 2017.

First, both report developments in the same scientific field—small-molecule inhibitors of enzymes (*i.e.*, PSMA and FAP) that are selectively expressed on the surface of epithelial cells and that were recognized as being appealing targets for imaging and therapy.²⁰⁶ For example, 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 publications highlight the importance of selectivity of the small molecule for its targeted cell-surface enzyme.²⁰⁹

Third, a skilled artisan would have recognized that the compounds identified in US-121 and Jansen are not only both small molecule inhibitors of their enzyme targets (PSMA and FAP, respectively), but that they have approximately the same

²⁰⁶ EX1003, ¶¶ 179, 199, 201; 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).

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 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 useful for tumor imaging to accelerate development of radiotracers adapted to use compound 60 as the targeting moiety.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 described 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%

²¹⁰ EX1003, ¶ 205.

²¹¹ EX1006, 3053, 3065; EX1003, ¶¶ 200, 202-203.

²¹² EX1003, ¶¶ 199, 204, 206.

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

Second, a skilled artisan would have understood from the guidance in 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 modify those individual components of its exemplified radiotracers, 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

²¹³ EX1003, ¶¶ 202-203, 58.

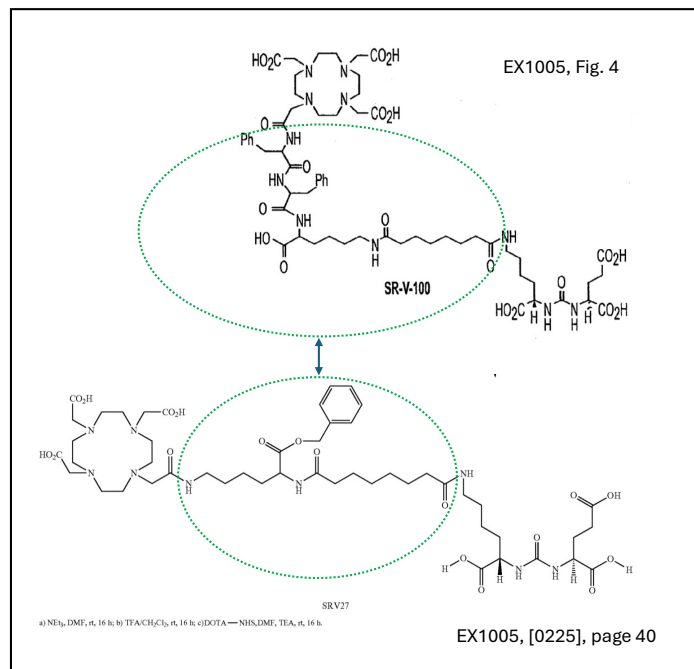
²¹⁴ EX1003, ¶¶ 58-59, 208.

²¹⁵ EX1003, ¶¶ 205-206.

²¹⁶ EX1003, ¶¶ 184, 203.

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

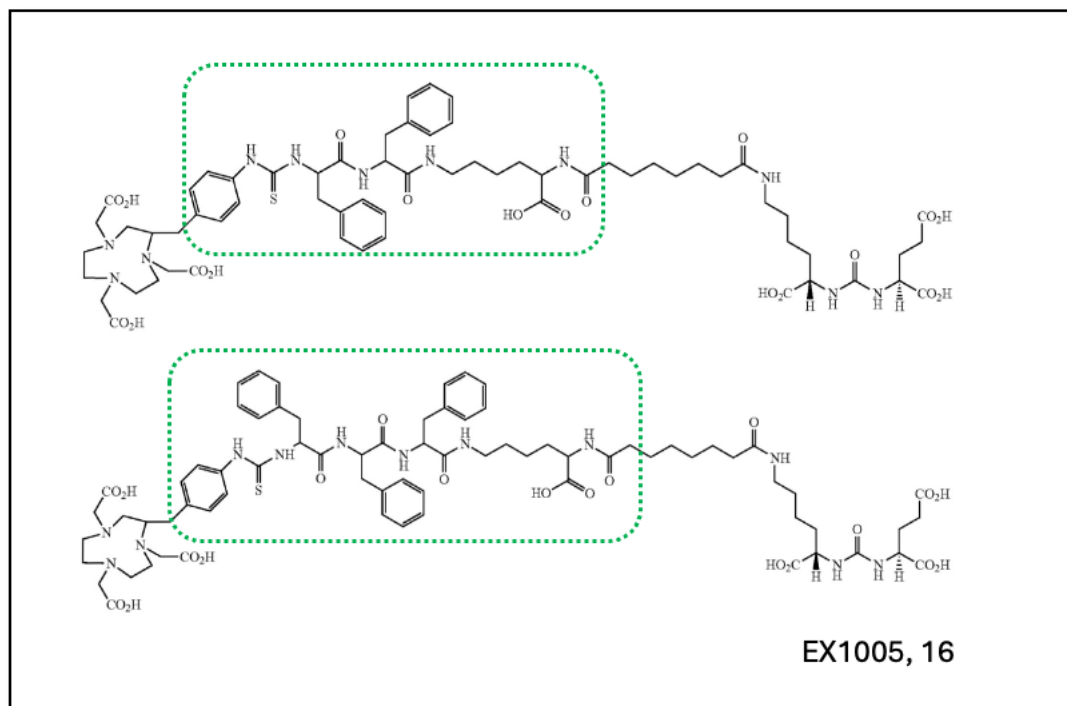
For example, US-121 shows compounds SR-V-100 and SRV27, which share the same targeting and radiolabeling moieties, but use different linkers (below).



Third, US-121 credits the use of particular linkers in radiotracers that had proven successful in imaging 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 series of linkers having varying numbers of pendent benzyl groups to influence their hydrophobic character (below).²¹⁹

²¹⁸ EX1005, [0187]; EX1003, ¶¶ 193, 207.

²¹⁹ EX1005, [0103], page 16, *also* 14, 47; EX1003, ¶¶ 206, 36.



The emphasis in US-121 of using particular linkers within radiotracers to achieve benefits in tumor imaging would have motivated a skilled artisan to use the particular combinations of linkers and chelators found in examples of radiotracers in US-121 to produce FAP-targeting radiotracers that use compound 60 as their targeting moiety.²²⁰

Fourth, the skilled artisan would have recognized that compound 60 has a comparable size as the urea-based PSMA targeting moiety (*i.e.*, 344 Da vs. 319 Da). Likewise, the skilled artisan would recognize that compound 60 could be functionalized to enable its attachment to particular linker-chelator structures

²²⁰ EX1003, ¶¶ 206-208.

described in US-121 via an amide bond with the same orientation with which the PSMA targeting moiety is attached.²²¹

Fifth, a skilled artisan would have recognized that small molecule radiotracers have relatively short pharmacokinetic half-lives.²²² Following the established design principle that the radiotracer's half-life should match the half-life of the radionuclide, a skilled artisan would have selected ⁶⁸Ga and ^{99m}Tc as the radionuclide to use in a compound 60-based radiotracer based on examples in US-121.²²³ US-121 also emphasizes use of radiometals in its radiotracers, particularly ⁶⁸Ga and ^{99m}Tc.²²⁴ The skilled artisan consequently would have focused on radiotracers in US-121 that include chelators suitable to use with ⁶⁸Ga or ^{99m}Tc.²²⁵ Dr. Zeglis illustrates modifications to four examples of such radiotracers that use compound 60 as the targeting moiety (below).²²⁶

²²¹ EX1003, ¶ 209.

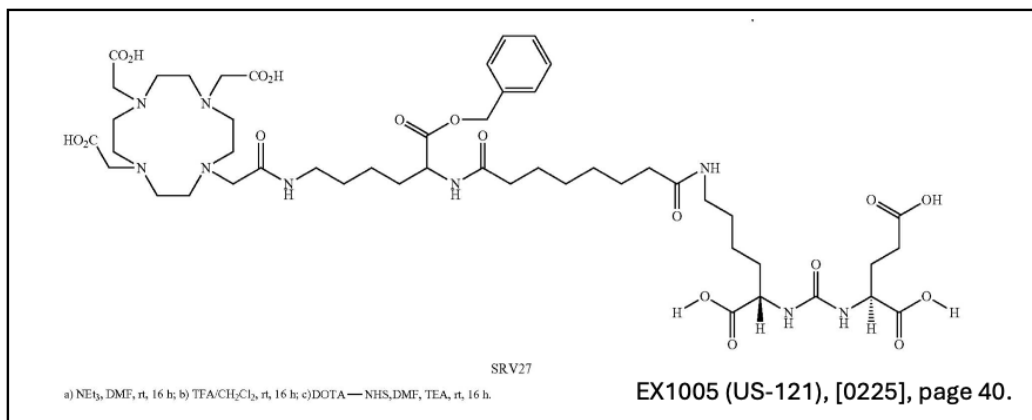
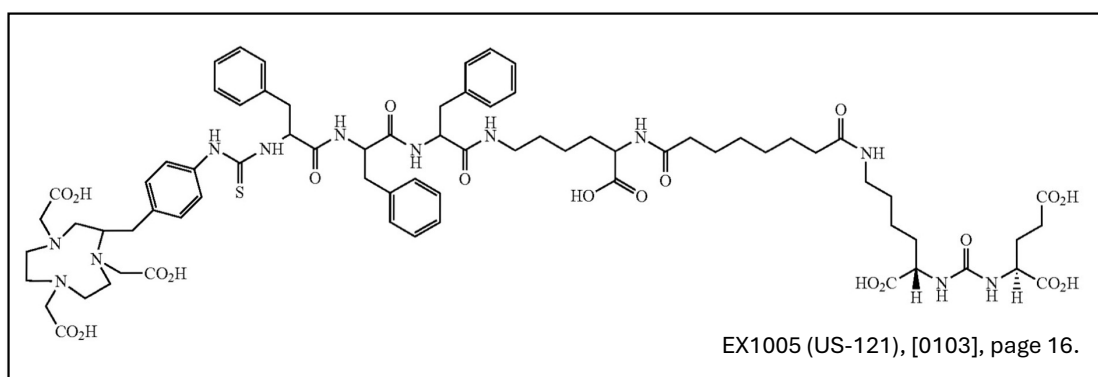
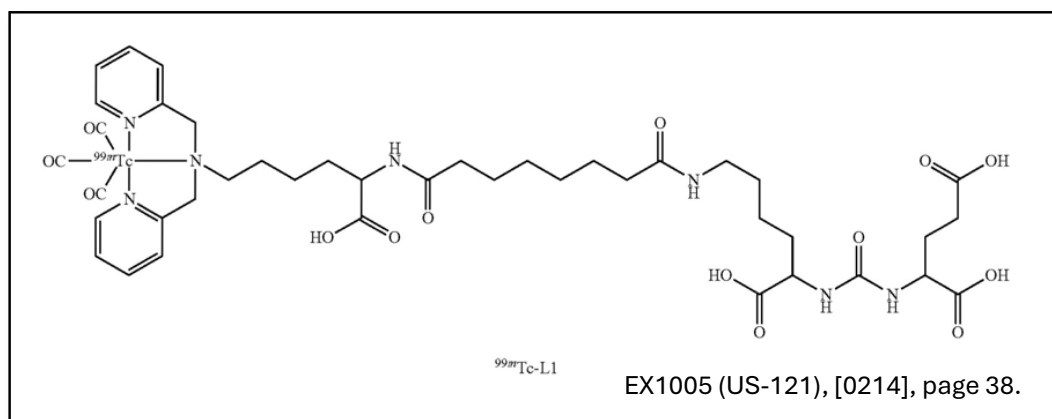
²²² EX1003, ¶ 30.

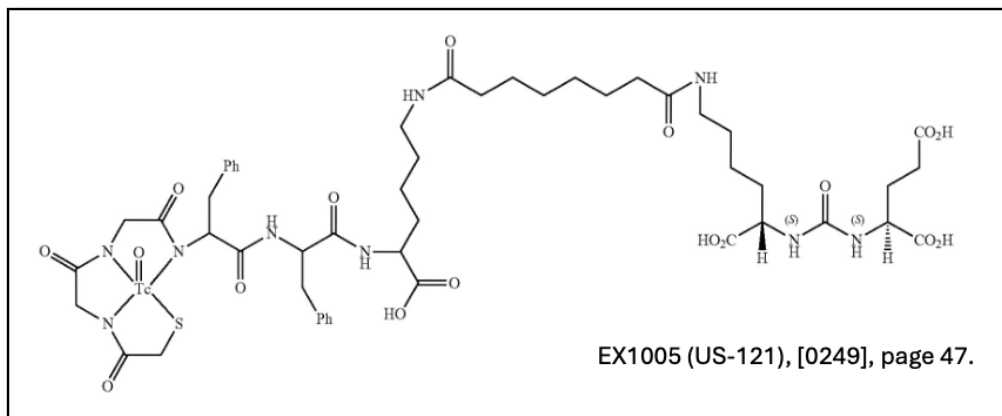
²²³ EX1003, ¶¶ 40-41, 188(c).

²²⁴ EX1005, [0011], [0242]; EX1003, ¶¶ 187-188, 197, 204.

²²⁵ EX1003, ¶¶ 189, 195-199.

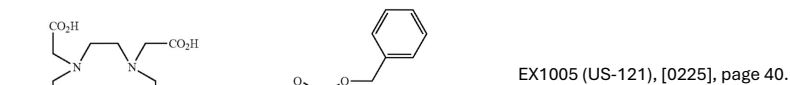
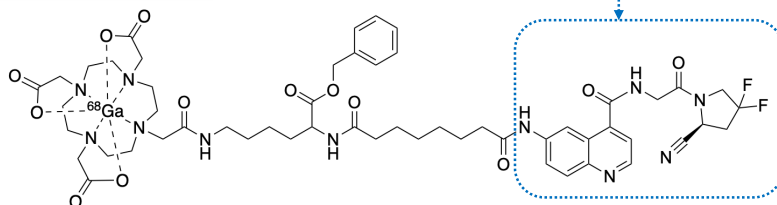
²²⁶ EX1003, ¶¶ 210-211.



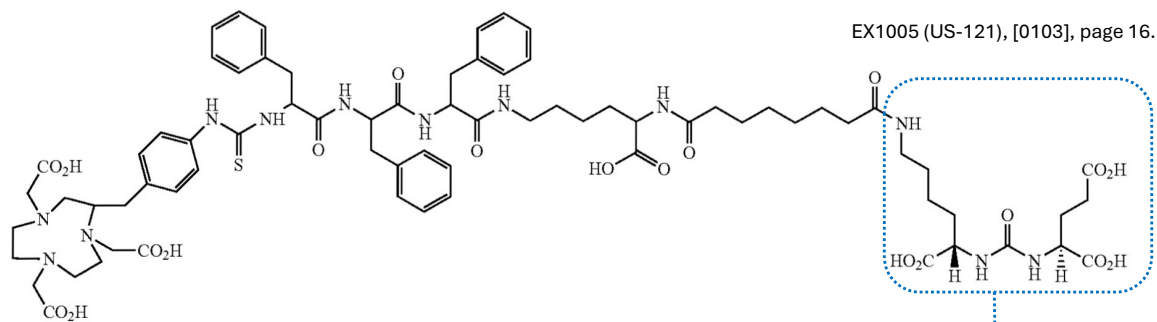
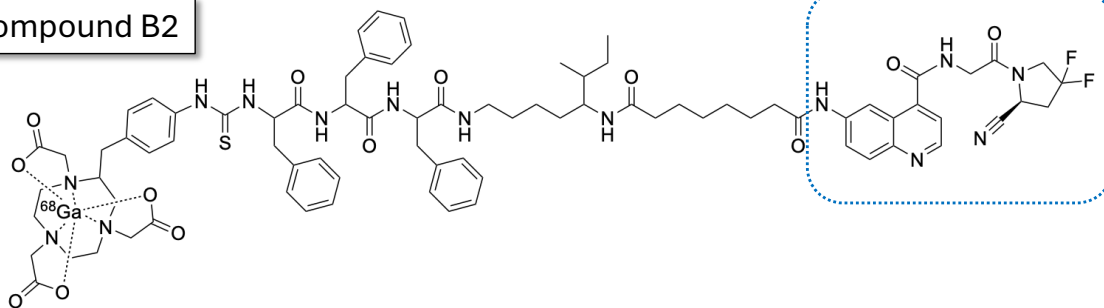


For the reasons provided above, a skilled artisan would have considered it obvious before 2017 to modify the four radiotracers described above (which are depicted in US-121) by replacing the urea-based targeting moiety with compound 60 of Jansen. This could be achieved using a functionalized form of 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

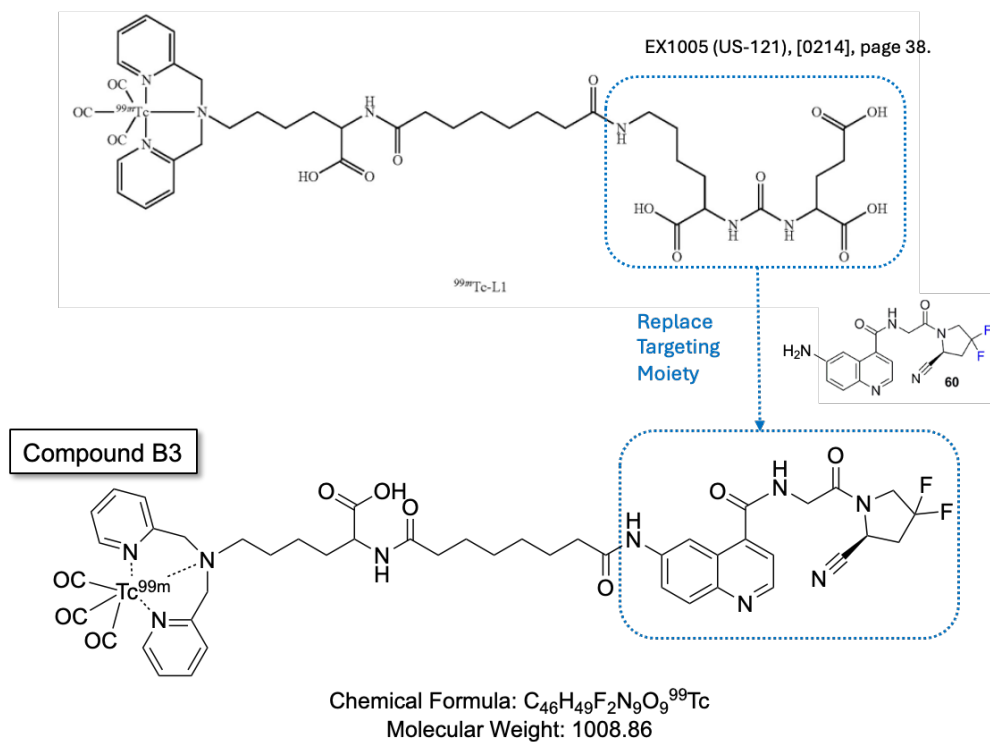
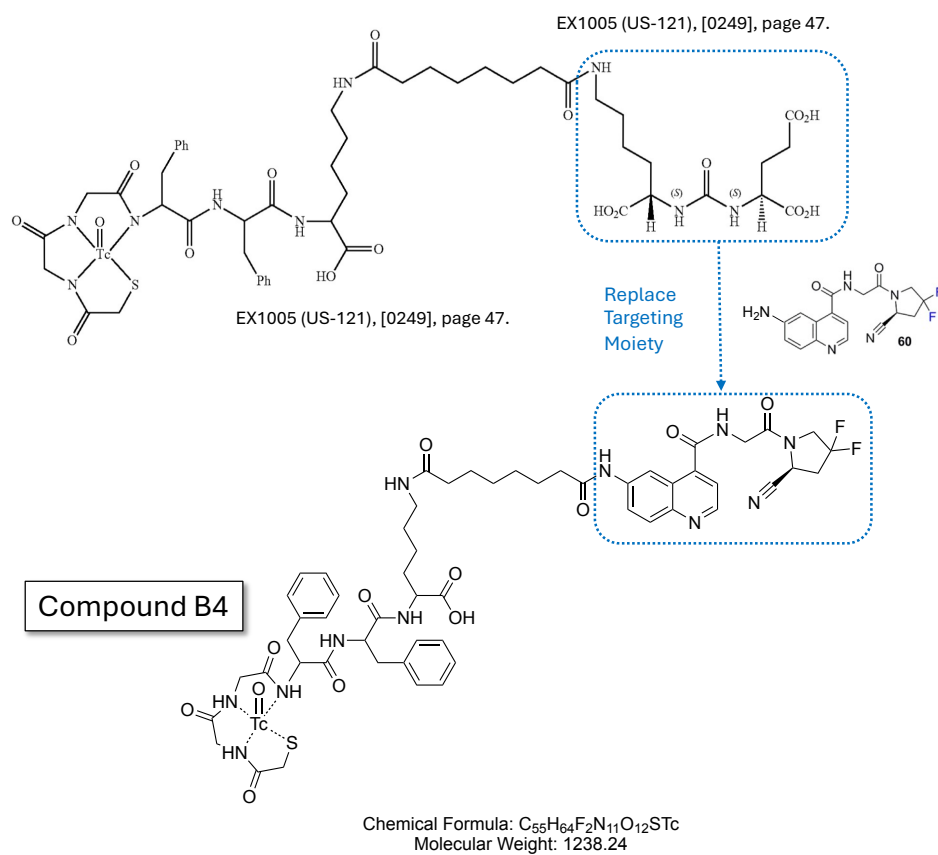
²²⁷ EX1003, ¶ 209.

**Compound B1**

Chemical Formula: $C_{54}H_{68}F_2^{68}GaN_{11}O_{13}$
Molecular Weight: 1185.13

**Compound B2**

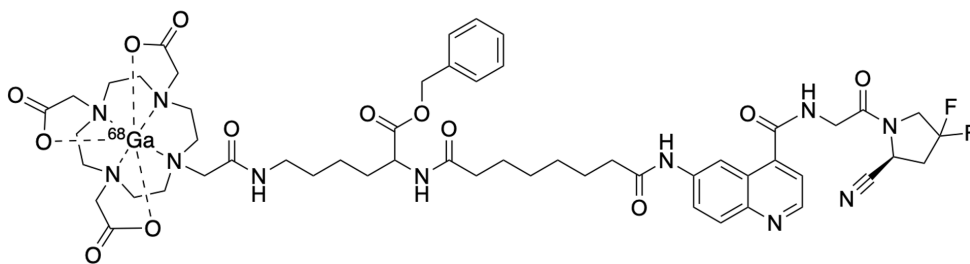
Chemical Formula: $C_{81}H_{97}F_2^{68}GaN_{14}O_{13}S$
Molecular Weight: 1612.74



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

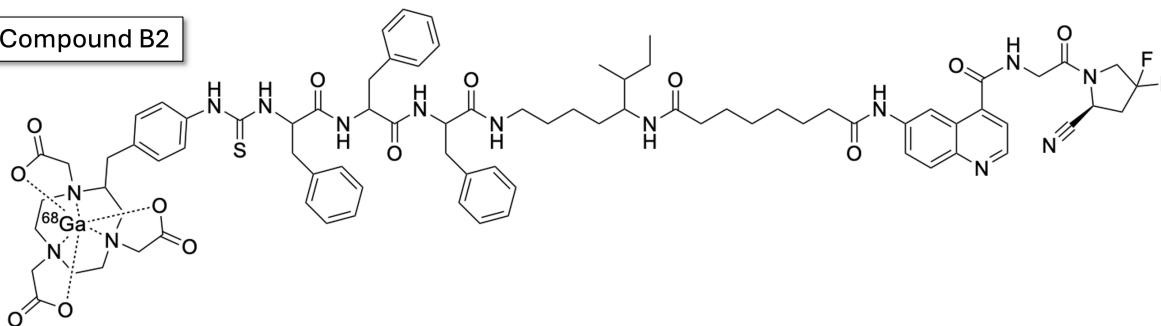
Following the straightforward logic and methodology described in § VI.C, a skilled artisan would have arrived at particular radiotracer compounds that incorporate compound 60 into radiotracer compounds having particular chelator and linker combinations shown in examples of US-121 (*i.e.*, compounds B1 to B4, below).

Compound B1



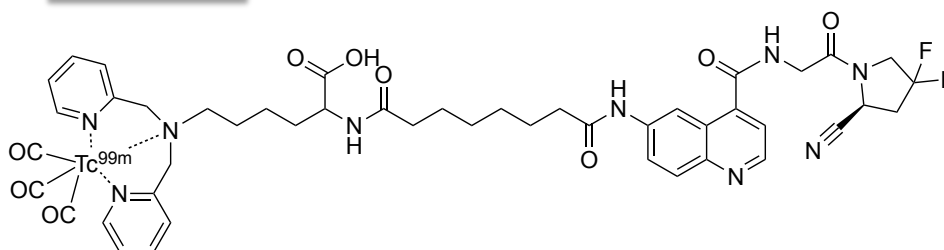
Chemical Formula: C₅₄H₆₈F₂⁶⁸GaN₁₁O₁₃
Molecular Weight: 1185.13

Compound B2



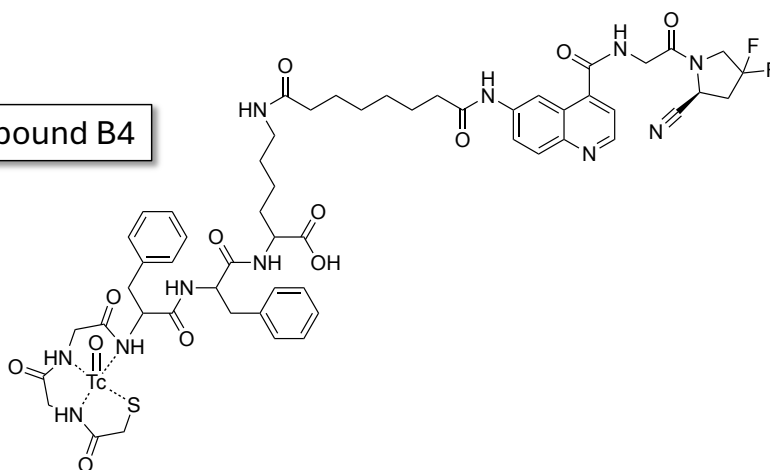
Chemical Formula: C₈₁H₉₇F₂⁶⁸GaN₁₄O₁₃S
Molecular Weight: 1612.74

Compound B3



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

Compound B4



Chemical Formula: $C_{55}H_{64}F_2N_{11}O_{12}STc$
Molecular Weight: 1238.24

Each of compounds B1 to B4 falls within the scope of claims 1 to 3 of the '201 Patent.

First, each is a “low molecular weight compound” as each has a molecular weight near or below 1500 Da, which is orders of magnitude smaller than an antibody.²²⁸

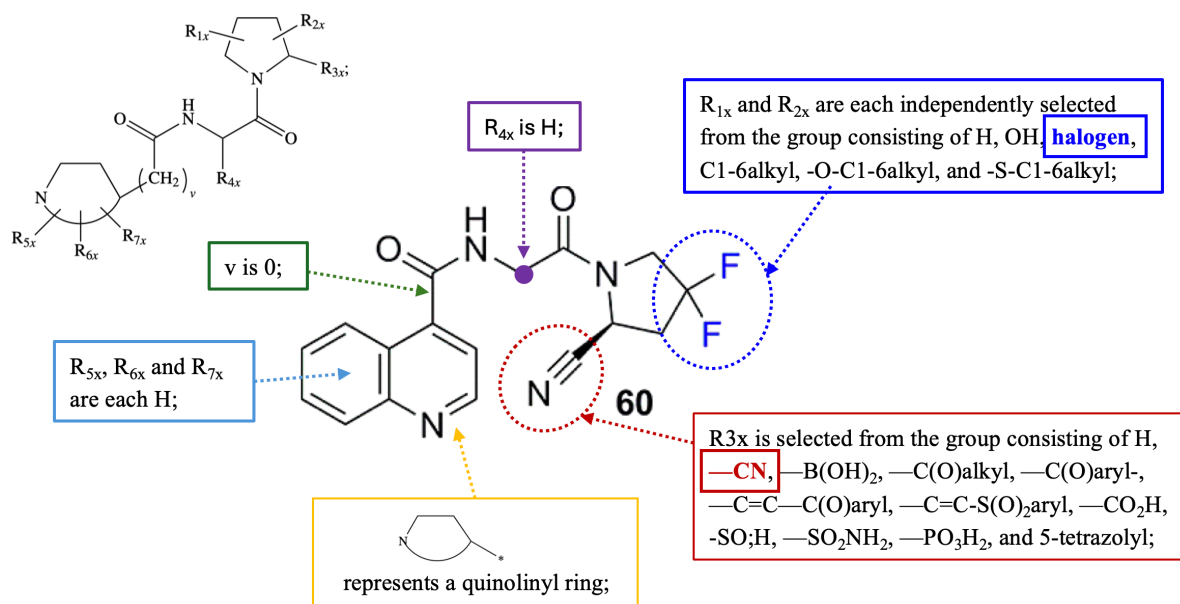
Second, each contains a chelator complexed with either ^{68}Ga or ^{99m}Tc , which

²²⁸ EX1003, ¶ 217.

is in each instance a “radiolabeled functional group suitable for ...” PET or SPECT imaging that satisfies the “B” component.²²⁹

Third, each contains chemical structure that forms distinct chemical bonds with each the radiolabeling moiety (“B”) and compound 60 FAP-targeting moiety (“A”) components of the compound, and as such, is a “linker having bi-functionalization adapted to form a chemical bond with B and A.”²³⁰

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).



²²⁹ EX1003, ¶ 214.

²³⁰ See § V.E.

Skilled artisans would have reasonably expected that compounds B1-B4 would retain the selectivity and affinity of compound 60 because they would have believed: (i) the size of the linker used would position the radiolabeling moiety so as to avoid it affecting the characteristics of the targeting moiety²³¹ and (ii) based on experimentation by Jansen, attaching the linker at position C⁶ of the quinolinyl ring would not alter the characteristics of compound 60 in a way that would affect its selectivity and affinity for FAP.²³²

Finally, 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 1-3, each of those claims is unpatentable.

VII. No Secondary Indicia Exist or Are Relevant

Patentee may contend that compounds within the scope of claims 1-3 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

²³¹ EX1003, ¶ 218.

²³² EX1003, ¶ 142.

“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. Discretionary Denial Is Not Warranted

No litigation involving the '201 Patent is pending, making discretionary denial unwarranted under *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11, 5-6 (P.T.A.B. Mar. 20, 2020).

A. § 325(d) Denial Not Warranted

Based on the grounds and the record of examination, the Board should not exercise its discretion under 35 U.S.C. § 325(d).²³³

The Board's § 325(d) assessment of the grounds focuses on two inquiries:

- (1) were the same or substantially the same art or arguments presented to the Office, and
- (2) if either occurred, did the petitioner demonstrate that the Office erred

²³³ *Advanced Bionics, LLC v. MED0EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (PTAB 12/13/2020) (“*Advanced Bionics*”); *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB 12/15/2017) (“*Becton*”).

in a manner material to the patentability of challenged claims.²³⁴

In answering these questions, Board considers six factors summarized in *Becton*.²³⁵

Under this framework, the Board should not exercise § 325(d) discretion.

1. The Examination Record

An obviousness rejection cited US-633 but none of the other references used in the grounds (*i.e.*, US-121 (EX1005), Jansen (EX1006) and Meletta (EX1008)).²³⁶ US-633 was combined with two earlier Jansen publications (*i.e.*, EX1044 (US-650) and EX1007 (Jansen-2013)), by the following steps:²³⁷

- (a) Select FAP compounds within certain formulas (US-650),
- (b) add a C₁₋₆ alkyl and a radiohalogen to the heterocycle moiety of the compounds (per US-650),
- (c) Per Jansen-2013 modify this structure to:
 - (i) “substitute the FAP inhibitors” with those having a quinolinyl ring because such compounds had ~ 60 times FAP affinity of the N-(1-naphthoyl) FAP inhibitors, and

²³⁴ *Advanced Bionics*, 8.

²³⁵ *Becton*, 17-18.

²³⁶ Jansen and Meletta were cited, as was the PCT of US-121 (EX1053).

²³⁷ EX1002, 360.

- (ii) halogenate the quinolinyl group with, *e.g.*, trifluoromethoxy.

Patentee responded by disputing the Examiner's lead compound selection, and every chemical modification the Examiner found necessary to yield a FAP inhibitor with a fluorinated quinolinyl ring.²³⁸ Patentee contended there was no "reasonable expectation of success in *modifying and making the structural changes to* the compounds of [US-650] and [Jansen-2013] *to arrive at the compounds of the pending claims*"—especially those with "high specificity" (selectivity) for FAP (which the FAP inhibitor confers).²³⁹ Again emphasizing "specificity" (selectivity), Patentee argued the claimed compounds had unexpected properties relative those in US-650 and Jansen-2013 (but not compound 1 of US-650, which is *identical* to compound 60 of Jansen-2014 (EX1006)).²⁴⁰

Two things are clear from this record:

- ***First***, the Examiner believed the prior art did not describe a FAP inhibitor ***within*** the scope of the "A" component of the claims, which explains why he thought it necessary to modify the Jansen I compounds.

²³⁸ EX1002, 404-406.

²³⁹ EX1002, 407 (*emphases added*).

²⁴⁰ See § V.E; EX1044, [0317], Table 4.

- ***Second***, the obviousness question was argued and decided under the legal standards governing ***chemical obviousness***, and particularly whether particular changes needed to yield an “A” compound were obvious.

2. The First Inquiry Supports Institution

The examination record favors institution because the grounds use different art with materially different teachings than those used during examination, and present materially different questions of obviousness.

In Ground 1, Jansen (EX1006) and Meletta are used—neither was used in any rejection during examination. Meletta provides a specific motivation to alter US-633’s FAP-targeting radiotracers to use a more selective FAP inhibitor. Jansen describes compound 60, which is not a “lead compound” that must be chemically modified to satisfy the “A” component of the claims but meets it unchanged. Jansen also discloses *in vivo* and *in vitro* data about compound 60 not in US-650 or Jansen-2013, and which provides additional reasons (beyond selectivity) to select compound 60 as a FAP-targeting moiety.

In Ground 2, US-121 and Jansen-2014 are used, neither of which was part of any rejection during examination. This ground presents a materially different obviousness issue—that it was obvious to modify radiotracers targeting PMSA to use compound 60 instead, yielding FAP-targeting radiotracers of the claims. This

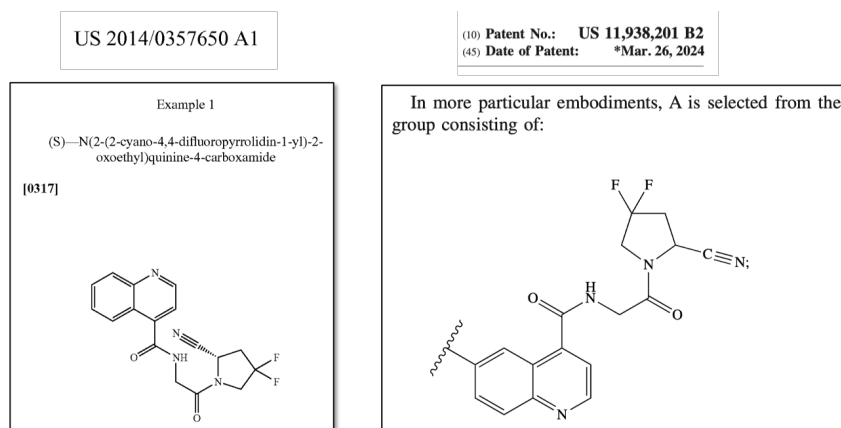
ground also does not require chemical modifications to meet the “A” component of the claims.

Consequently, neither ground presents the same or substantially similar prior art or arguments as those considered during examination. Either ground, thus, warrants the Board not exercising its § 325(d) discretion.

3. The Second Inquiry Supports Institution

The record does not necessitate reaching the second inquiry. Regardless, it justifies the Board not exercising § 325(d) discretion due to significant and clear errors by the Examiner.

Most notably, the Examiner erred by not recognizing that Jansen I (US-650) disclosed compound 1 (Example 1), which is identical to an “A” structure in the ’201 specification (below).²⁴¹



This error led the Examiner to believe that changes to prior art compounds in

²⁴¹ EX1044, [0317]; EX1001, 13:34-14:15.

US-650 molecules were necessary to meet the claimed “A” requirement. Worse, the examiner was persuaded by Patentee’s arguments that contended the prior art did not disclose a FAP inhibitor that met the requirements of “A.” The Examiner also incorrectly accepted Patentee’s assertion that the claimed compounds “surprisingly have a specificity (PREP/FAP ratio) for FAP that is several orders of magnitude higher than *other small molecule FAP inhibitors found in the prior art.*”²⁴² Had the Examiner recognized that compound 60 was *identical* to the patent’s exemplified A compounds, he would not have been persuaded by Patentee’s incorrect statements.

B. Discretionary Denial Based on an Unrelated PGR Is Not Warranted

The Board should not deny institution based on PGR2025-00012 (PTAB Dec. 24, 2024).

First, this petition presents materially different grounds resting on different prior art (Jansen-2014, Meletta) than the grounds in PGR2025-00012.

Second, this petition is filed as an IPR, rather than a PGR, and was promptly filed after expiration of the PGR deadline in late December. It also is filed prior to the deadline for filing of a Patent Owner Preliminary Response in PGR2025-00012.

²⁴² EX1002, 442.

Third, there is no relationship between the real parties of interest of this petition and the Petitioner of PGR2025-00012, and Petitioner only learned of PGR2025-00012 when it became publicly available on the PTACTS website.

As none of the *General Plastic* Factors are present, the Board should not exercise its discretion under § 314(a).

IX. CONCLUSION

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

Dated: March 28, 2025

Respectfully Submitted,

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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 13,949 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: March 28, 2025

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I hereby certify that on this 28th day of March, 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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Dated: March 28, 2025

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