UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ITM Isotope Technologies Munich SE
Petitioner

v.

The Johns Hopkins University
Patent Owner

Case PGR2025-00012
Patent No. 11,938,201

PETITION FOR POST GRANT REVIEW

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1004	Prosecution History for U.S. Patent No. 11,938,201 (downloaded from USPTO Patent Center)
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1007	U.S. Patent No. 9,346,814 to Jansen et al., issued May 24, 2016 ("Jansen I")

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1015	Ronnie C. Mease et al., *N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-[18F]fluorobenzyl-L-cysteine, [18F]DCFBC: A new Imaging probe for prostate cancer*, 14 CLIN CANCER RES 3036-43 (2008)
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1021	Anne Hellebust et al., *Advances in molecular imaging: Targeted Optical Contrast Agents For Cancer Diagnostics*, 7 NANOMEDICINE 429-45 (2012)
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I. PRELIMINARY STATEMENT

This claimed subject matter of U.S. Patent No. 11,938,201 ("the '201 patent") is nothing more than the obvious combination of known elements used in diagnostic imaging and radiotherapeutics targeting fibroblast-activation protein-α ("FAP-α") for cancer screening and detection. The '201 patent broadly claims "low molecular weight" compounds having the formula B-L-A, wherein 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"; A is a targeting moiety for FAP-α having a structure falling within the genus described in the claims, and L is "a linker having bi-functionalization adapted to form a chemical bond with B and A." As Patent Owner Johns Hopkins University ("Patent Owner") readily concedes in the specification of the '201 patent, the genus of targeting moieties for FAP-α, A, was already disclosed in references like Jansen I and Jansen II, while components meeting the broad functional language specified for B and L were also disclosed in references like Zimmerman and Pomper.

During prosecution, the Examiner recognized these teachings in the prior art and rejected the claims as obvious. In response, Patent Owner submitted a declaration from one of the '201 patent's co-inventors, Dr. Pomper, asserting that the claimed compounds demonstrate allegedly unexpectedly promising imaging

properties compared to other small molecule FAP inhibitors. But Dr. Pomper's assertion of unexpected results is based on only 11 examples, and is certainly insufficient to represent the thousands, if not millions or more, of possible FAP inhibitors, linkers, optical dyes, radiolabeling groups, and combinations thereof encompassed by the broad language used in the claims. These alleged unexpected results were the sole basis given by the Examiner for allowing the *prima facie* obvious claimed invention over the applied prior art. EX1004 at 1308 (Notice of Allowance). That was legally improper, for Dr. Pomper's presented evidence of alleged unexpected results was not even remotely commensurate with the extremely broad scope of the claims, and the claimed invention remains obvious in light of that applied art.

Moreover, during prosecution, the Examiner rejected the sole pending claim as anticipated by Dvořáková. In response, Patent Owner amended the claim to add the indefinite phrase "low molecular weight." But other references, including Dr. Pomper's own prior art Pomper reference cited by the '201 patent, taught that low molecular weight inhibitors may have better access to tumors than larger antibodies and that low molecular weight agents had shown promise in pre-clinical imaging studies. The art would have taught and motivated a POSA to design and prepare a low molecular weight compound with high affinity and selectivity for FAP that would serve as an imaging or therapeutic agent, and the art would have further

motivated a POSA to combine these known features into the compounds recited in the claims of the ’201 patent with a reasonable expectation that such compounds would work for their desired purpose, thus rendering the ’201 patent claims obvious.

Not only is the subject matter of ’201 patent claims obvious, but also the ’201 patent claims fail to comply with § 112’s requirement of a fully and clearly described invention. 35 U.S.C. § 112 requires a patent application to contain a full and clear description of the invention to ensure that the public is adequately compensated for the exclusionary rights granted to an inventor. Here, Patent Owner submitted broad genus claims containing functional language of the exact type that has been invalidated by the Supreme Court in cases like *Amgen Inc. v. Sanofi*, 598 U.S. 594 (2023) and the Federal Circuit in cases like *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc) for failing to satisfy § 112’s enablement and written description requirements. The Patent Owner also introduced the relative and undefined phrase “low molecular weight” into the claims, in violation of § 112’s requirement to inform those skilled in the art about the scope of the invention with reasonable certainty. Nevertheless, the Examiner allowed Patent Owner’s U.S. Patent No. 11,938,201 (“the ’201 patent”) without a single rejection based on § 112.

Petitioner ITM Isotope Technologies Munich SE (“Petitioner”) respectfully submits that this PGR should be instituted and all claims held unpatentable.

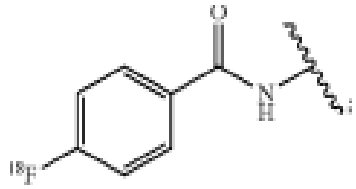
II. THE '201 PATENT

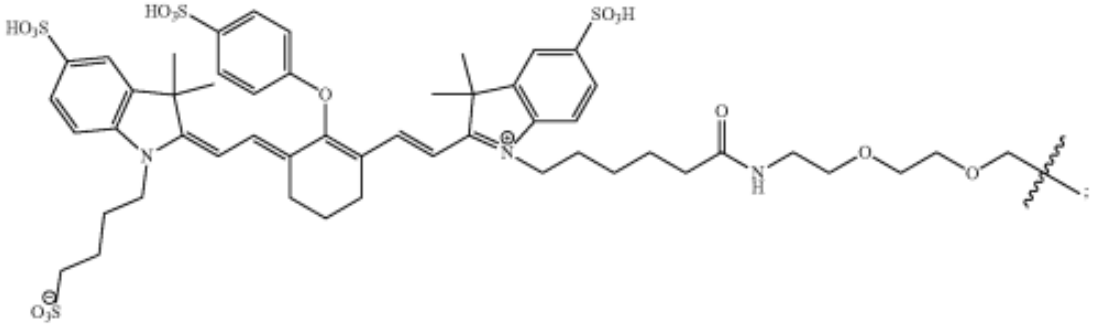
A. Specification

The '201 patent (EX1001) describes certain imaging and radiotherapeutics agents targeting a specific protein, namely, fibroblast-activation protein-α (FAP-α), and "their use in imaging and treating FAP-α related diseases and disorders . . . ." EX1001 at Abstract; EX1002 at ¶ 69. FAP-α is a well-studied member of the prolyl oligopeptidase family, known for its ability to cleave certain peptide bonds and play a role in cancer by modifying bioactive signaling peptides through such enzymatic activity. EX1001 at 6:64-7:2; *see also* EX1002 at ¶¶ 32-37. Since FAP-α expression has been detected on the surface of fibroblasts in the stroma of a vast majority of epithelial cancers, with nearly no expression in healthy tissues, the disclosure explains the clinical importance of imaging and radiotherapeutic agents specifically targeting FAP-α. EX1001 at 7:3-10; *see also* EX1002 at ¶¶ 39-48.

The '201 patent discloses and claims compounds having a Formula (I) of B-L-A, wherein B is any optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging, or radiotherapy; L is a linker having bi-functionalization adapted to form a chemical bond with B and A; and A is a targeting moiety for FAP-α. EX1001 at 2:3-12, 8:13-25, 64:46-65, 65:1-63, 66:1-67, 67:1-4; EX1002 at ¶ 69.

Moiety B is described throughout the '201 patent as any optical or radiolabeled functional group "suitable for" optical imaging, PET imaging, SPECT imaging, or radiotherapy. EX1001 at 2:4-10, 8:19-23, 15:40-44, 65:54-58, 66:64-67; EX1002 at ¶ 70. While some non-limiting examples of moiety B are provided in columns 17-32, the specification does not provide any additional guidance describing which specific structural features would result in compounds "suitable for" optical imaging, PET imaging, SPECT imaging, or radiotherapy. EX1002 at ¶ 70. Moreover, the structural variations present in the examples that are described suggests that considerable experimentation would be needed to determine the boundaries of moiety B. *Id.* For example, the non-limiting examples of moiety B include a broad range of radiolabeled prosthetic groups, chelating agents, and optical dyes, such as the following:



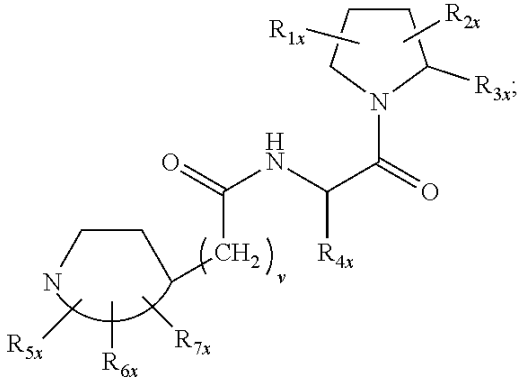


EX1001 at 18:60-66, 27:1-10; EX1002 at ¶ 70.

The linker, L, is also broadly defined as only requiring "bi-functionalization adapted to form a chemical bond with B and A." EX1001 at 2:10-12, 8:24-25, 15:40-44, 65:58-60, 66:67, 67:1-2; EX1002 at ¶ 71. The specification does not provide any additional guidance describing which specific structural features would result in compounds having "bi-functionalization," instead relying on specific, earlier patent applications that are incorporated into the instant specification by reference. EX1001 at 17:45-54 (citing U.S. Patent Publication No. 2011/0064657 ("US '657"; EX1005) and U.S. Patent Publication No. 2012/0009121 ("Pomper"; EX1006)); EX1002 at ¶ 71. These references do not explain what is meant by "bi-functionalization" and do little to limit the universe of linkers. EX1002 at ¶ 71. For example, US '657 merely provides general statements, such that various linkers can be used, that the length of the linker can be varied, that longer linkers can be accommodated, and that lipophilicity can be altered by varying the position of certain moieties on the linker. EX1005 at Abstract, ¶¶ 306, 316; EX1002 at ¶ 71. Similarly, Pomper explains that, "[f]or instance linking groups having alkyl, aryl, combination of alkyl and aryl, or alkyl and aryl groups having heteroatoms," are suitable. EX1006 at ¶¶ 0102, 0129; EX1002 at ¶ 71.

Regarding the FAP-α targeting moiety, A, the '201 patent readily concedes that the claimed genus of compounds is not new. EX1002 at ¶ 72. Indeed, the '201

patent explains that FAP-α inhibitors having the following Formula are disclosed in U.S. Patent No. 9,346,814 to Jansen et al. ("Jansen I"; EX1007):



wherein:

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

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

R_{4x} is H;

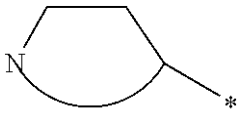
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, — C_{1-6} alkyl, —O—C_{1-6} alkyl, —S—C_{1-6} alkyl, —$NR_{8x}R_{9x}$, —OR_{12x}, —Het_2 and —Ar_2 each of C_{1-6} alkyl being optionally substituted with from 1 to 3 substituents selected from —OH and halogen;

R_{8x}, R_{9x}, and R_{12x} are each independently selected from the group consisting of H, —OH, halo, —C_{1-6}alkyl, —O—C_{1-6}alkyl, —S—C_{1-6}alkyl, and —Ar_3;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, —OH, halogen, —C_{1-6}alkyl, —O—C_{1-6}alkyl, and —S—C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted 10 with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, — C_{1-6}alkyl, —O—C_{1-6}alkyl, and —S— C_{1-6}alkyl;

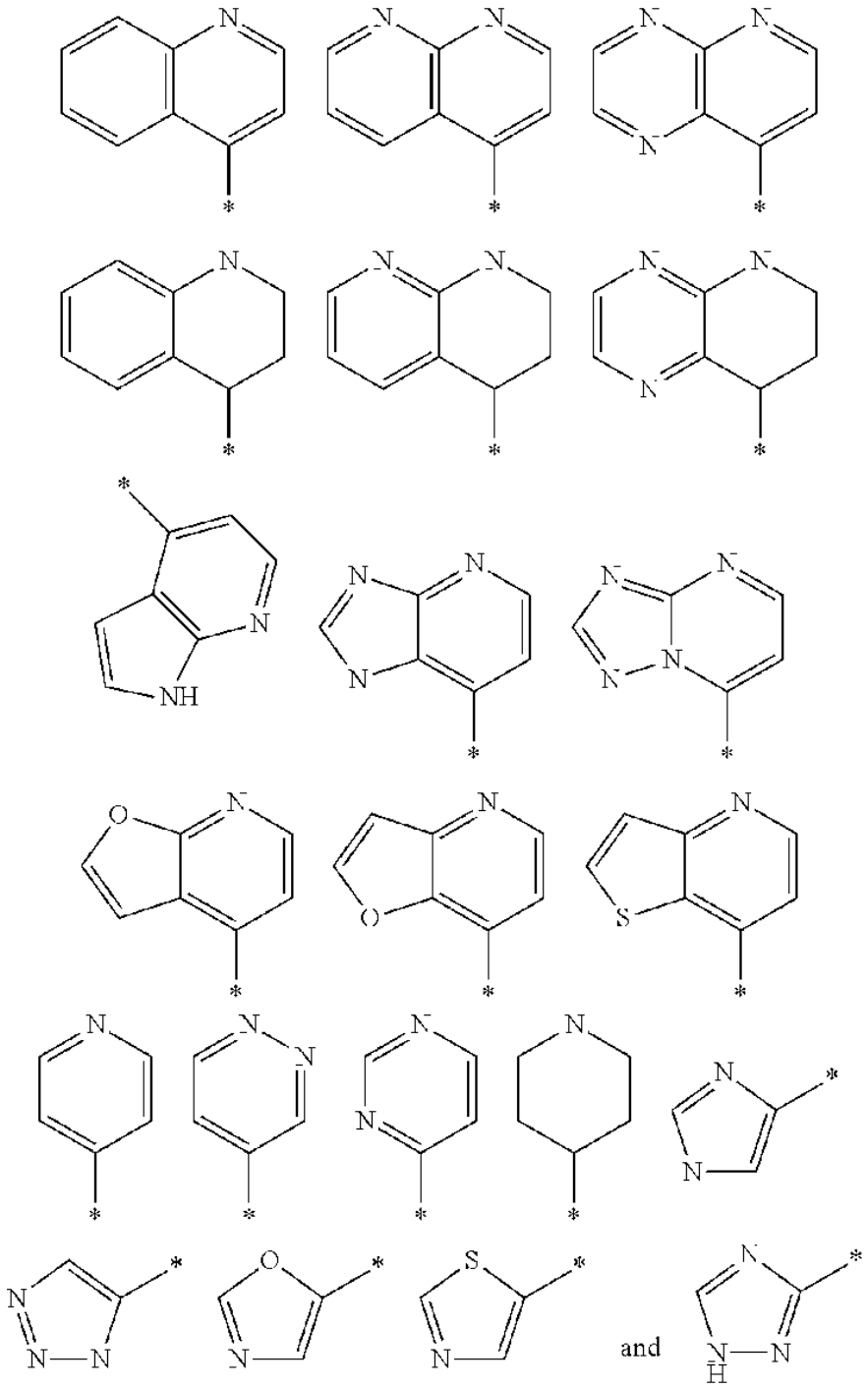
Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from —$NR_{13x}R_{14x}$, —C_{1-6}alkyl, —O—C_{1-6}alkyl, and —S—C_{1-6}alkyl;

v is 0, 1, 2, or 3; and

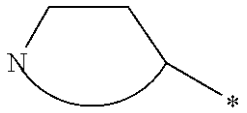


represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S. EX1001 at 8:33-9:28 (citing EX1007).

The ’201 patent specification also describes many of the same exact embodiments taught in Jansen I, including the identical options around the ring structure as present in the same Markush-type manner, such as:



Compare EX1001 at 9:30-10:10, 11:30-12:14 *with* EX1007 at claims 1-8, 24:26-54, 25:1-10; EX1002 at ¶ 73. Notably, the A moiety recited in the claims of the '201 patent is this same genus disclosed in Jansen I, wherein R_{5x}, R_{6x}, and R_{7x} are each H; v is 0; and

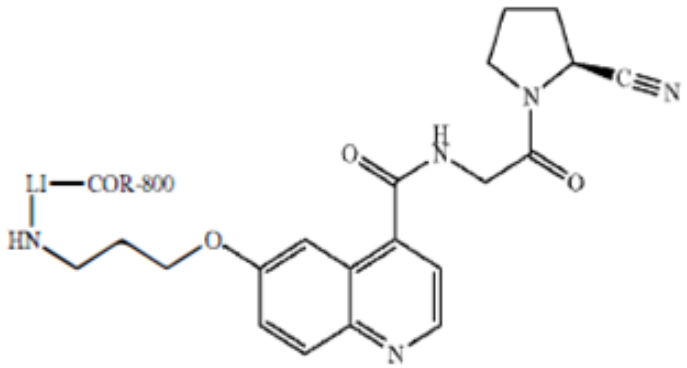


is a quinolinyl ring. EX1001, Certificate of Correction, at claims 1, 3; EX1002 at ¶ 74.

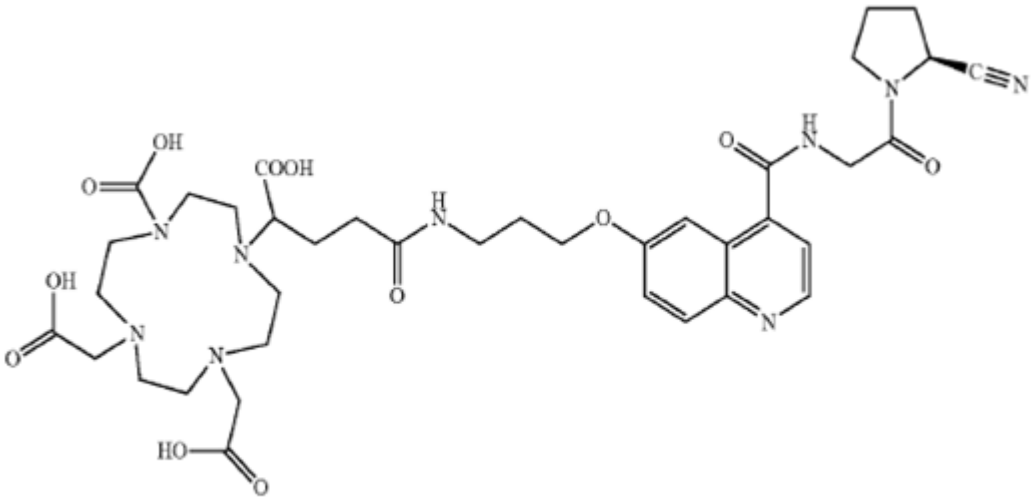
The majority of the '201 patent's specification then continues with disclosures related to standard or dictionary-sourced definitions of pharmaceutical preparations, radiolabeled components, imaging agents and standard chemical preparations (FN) (EX1001 at 32:1-50:54) before eventually reaching the Examples section. EX1002 at ¶ 75.

Throughout the entirety of the specification, largely devoted to subject matter belonging to other parties' patents and a multitude of standard definitions spread across boilerplate provisions, the '201 patent provides only ***two*** working examples purportedly supporting the claimed genus: XY-FAP-01 and XY-FAP-02. EX1001 at Examples 1.1-1.2; EX1002 at ¶ 76. XY-FAP-01 and XY-FAP-02 are generally prepared using the same materials and include the same A and L, while only varying

the B moiety, where XY-FAP-01 has a LICOR-800CW dye and XY-FAP-02 has DOTA chelator group:



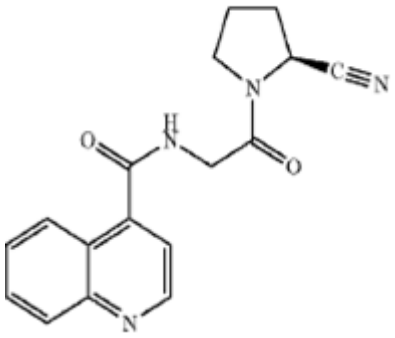
XY-FAP-01



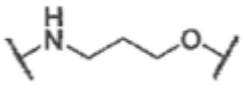
XY-FAP-02

EX1001 at 54-55; EX1002 at ¶ 76.

To conclude, the specification supports at most two compounds under the broad formula (B-L-A), as follows: both compounds have the same A



both compounds have the same linker and it is ***only*** ever disclosed as attached at the same position to A (6-position of the quinolinyl moiety):



and only one embodiment of each of the radiolabeled functional group (DOTA) and an optical functional group (LICOR-800CW) are exemplified under the (B) element. EX1002 at ¶ 77.

Further, the ’201 patent states that because “[l]ow molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal [than anti-FAP antibodies] within clinically convenient times after administration,” it allegedly would be desirable to use a “low molecular weight” ligand “with ideal properties for nuclear imaging of FAP-α.” EX1001 at 1:60-67. Despite identifying “low molecular weight” ligands or agents as allegedly having improved properties over anti-FAP antibodies, the ’201 patent never defines the term “low molecular weight” or provides any guidance as to its boundaries. EX1002 at ¶ 78. For example, the only

other mention of "low molecular weight" states that "in some embodiments, the presently disclosed subject matter provides potent and selective low-molecular-weight (LMW) ligands of FAP-α, i.e., an FAP-α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable in vivo optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α." EX1001 at 7:44-54; EX1002 at ¶ 78. Accordingly, the numerical range for the term "low molecular weight" is not defined in the '201 patent.

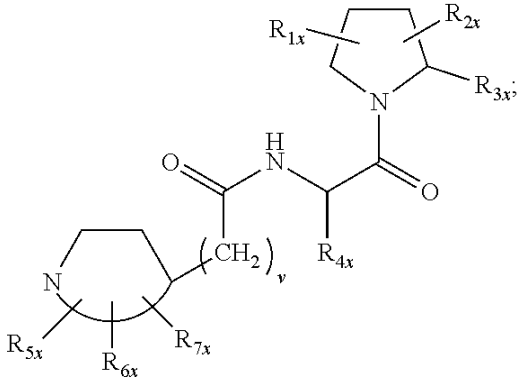
B. Prosecution History

The application for the '201 patent, filed on July 18, 2023, is a continuation of U.S. Patent Application No. 16/758,182, filed on April 22, 2020. U.S. Patent Application No. 16/758,182 is itself a National Stage Entry of PCT/US18/57086, which was filed on October 23, 2018 and claims priority to U.S. Provisional Application No. 62/575,607, filed on October 23, 2017. EX1001 at Cover. A terminal disclaimer was filed over U.S. Patent Application No. 16/758,182. EX1004 at 1226.

Following a preliminary amendment ("Preliminary Amendment"; EX1004 at 128-36) submitted soon after filing, the only pending claim (29) was as follows:

29. "A 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, C_{1-6} alkyl, -O-C_{1-6} alkyl, and -S-C_{1-6} alkyl;

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

R_{4x} is H;

R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6} alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

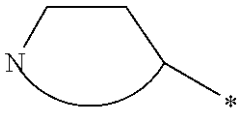
R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C_{1-6} alkyl, -O-C_{1-6} alkyl, -S-C_{1-6} alkyl, and -Ar_3;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6} alkyl, -O-C_{1-6} alkyl, and -S-C_{1-6} alkyl; Ar_1, Ar_2

and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from $-NR_{10x}R_{11x}$, $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}$ alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

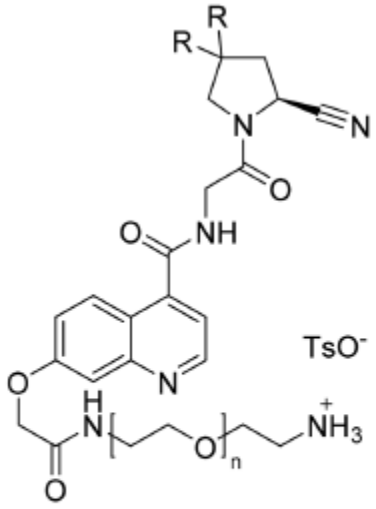
v is 0, 1, 2, or 3; and



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S; 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." EX1004 at 134-35 (Preliminary Amendment).

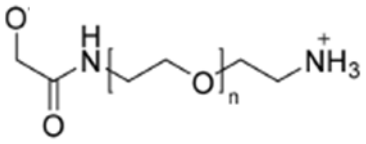
A non-final rejection ("Office Action"; EX1004 at 1175-84) was issued on September 26, 2023, which included rejections of the only pending claim under 35 U.S.C. § 102(a)(1) as anticipated by Petra Dvořáková at al., *Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein*, 60 JOURNAL OF MEDICINAL CHEMISTRY 8385-8394 (2017) ("Dvořáková"; EX1008) and under 35 U.S.C. § 103 as obvious over Jansen I in view of U.S. Patent Publication No. 2010/0098633 to Zimmerman et al. ("Zimmerman"; EX1009) and Keon Jansen et al., *Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold*, 2013(4) ACS MEDICINAL CHEMISTRY, 491-96 (2013) ("Jansen II"; EX1010). EX1004 at 1177-82 (Office Action).

With respect to the anticipation rejection under § 102, the Office stated that Dvořáková discloses "anti-FAP iBody FAP inhibitors" comprising



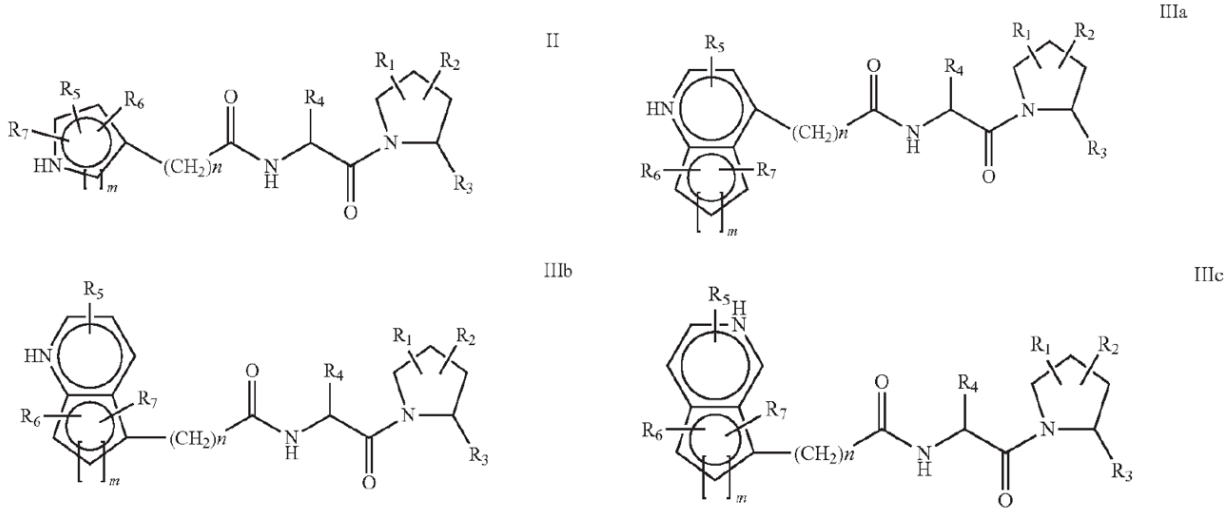
1 (n = 15, R = F)
2 (n = 5, R = F)
3 (n = 15, R = H)
4 (n = 5, R = H)

"bound to an ATTO488 dye via a HPMA copolymer (Figure 2)." *Id.*at 1178. The Office specifically pointed to



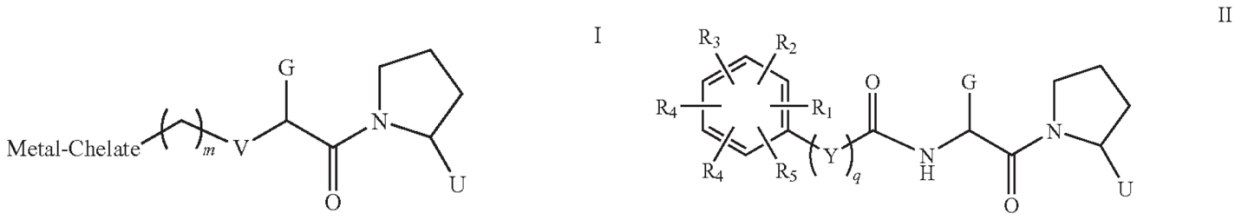
as disclosing the linker L, the ATTO488 dye as disclosing the B moiety, and Compounds 1-4 as disclosing the targeting moiety for FAP-α, A. *Id.*

With respect to the obviousness rejection under § 103, the Office stated that Jansen I discloses the following FAP inhibitors as having structures that overlap with the targeting moiety for FAP-α, A, as recited by the '201 patent claims:



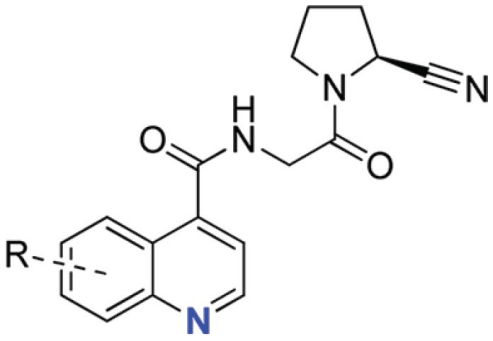
Id. at 1179.

While Jansen I "does not disclose an optical or radiolabeled functional group," the Office recognized that Zimmerman discloses "radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease comprising:



Id. at 1180-81.

In addition, Jansen II (labeled erroneously as Jensen in the Office Action) discloses FAP inhibitors having the following structure:



Id. at 1181. Jansen II also teaches that quinoline containing compounds have 60 times more FAP-affinity than the initial N-(1-naphthoyl) based FAP inhibitors. *Id.*

The Office therefore concluded that it would have been obvious to a POSA to combine the teachings of Jansen I, Zimmerman, and Jansen II to arrive at the subject matter of the claim, and that this combination would have been predictable with a reasonable expectation of success. *Id.* at 1181-82.

In response to this non-final rejection, the Applicant submitted a December 13, 2023, Office Action Response (EX1004 at 1209-25), along with a declaration from one of the inventors, Dr. Pomper ("Pomper Declaration"; EX1004 at 1195-1206), followed by a December 18, 2023 Supplemental Office Action Response (EX1004 at 1267-83). These responses included claim amendments in which the term "low molecular weight"—which is nowhere defined in the specification (EX1002 at ¶ 87)—was added to the preamble of the claim in addition to two new claims, claims 30 and 31.

New claim 30 was directed to "The compound of claim 1, wherein B is any radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy". EX1004 at 1211 (Office Action Response).

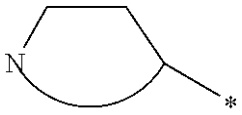
New claim 31 was directed to "A low molecular weight compound consisting essentially of components B-L-A," wherein A, B, and L had the same definitions as in pending claim 29. *Id.* at 1211-12 (Office Action Response).

Patent Owner argued that the addition of "low molecular weight" into the preamble of claim 29 and new claim 31 distinguishes "the pending claims from a large molecule imaging agents containing anti-FAP moieties" and that "[i]n contrast to the instant application, the compound disclosed in Dvořáková (compound 1) is a large molecule compound." *Id.* at 1213-14 (Office Action Response); *see also id.* 1197-98 (Pomper Declaration), 1271-72 (Office Action Response). In addition, Patent Owner argued that a POSA would recognize the term "low molecular weight" to mean approximately 50-1,500 Da and that the specification distinguishes polymers from "low molecular weight compounds," and thus alleges that the claims exclude polymers. *Id.* at 1213-15 (Office Action Response); *see also id.* at 1197-99 (Pomper Declaration), 1271-73 (Supplemental Amendment).

Regarding the obviousness rejection, Patent Owner argued that Zimmerman does not provide motivation to attach the FAP inhibitor (A) of Jansen I or Jansen II

to an optical or radiolabeled functional group (B) via a linker (L). *Id.* at 1217-19 (Office Action Response); *see also id*. at 1275-77 (Supplemental Amendment). Patent Owner also argued that "[t]here was no reasonable expectation of success in modifying any compounds in Jansen I or Jansen II to arrive at the compounds of the pending claims." *Id.* at 1219-21 (Office Action Response); *see also id.* at 1277-79 (Supplemental Amendment). Lastly, Patent Owner argued that "[t]here are unexpected results associated with the claimed compounds to rebut any showing of prima facie obviousness" and that "[s]urprisingly, the specificity of compounds falling under the scope of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors." *Id.* at 1221-24 (Office Action Response); *see also id.* at 1203-05 (Pomper Declaration), 1279-83 (Supplemental Amendment). Patent Owner concluded that "[s]uch differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected," and therefore the obviousness rejection should be removed. *Id.* at 1221-24 (Office Action Response); *see also id.* at 1203-05 (Pomper Declaration), 1279-83 (Supplemental Amendment).

The December 18, 2023 Supplemental Amendment contained substantially the same arguments as the December 13, 2023 Office Action Response. In addition to including the new claim limitation of a "low molecular weight," however, the scope of the substituents R_{5x}, R_{6x}, R_{7x}, v, and



of the FAP-α targeting moiety, A, of the compound of Formula (I) were changed in both independent claims, as shown in the following section. EX1004 at 1268-70 (Supplemental Amendment); EX1002 at ¶ 91.

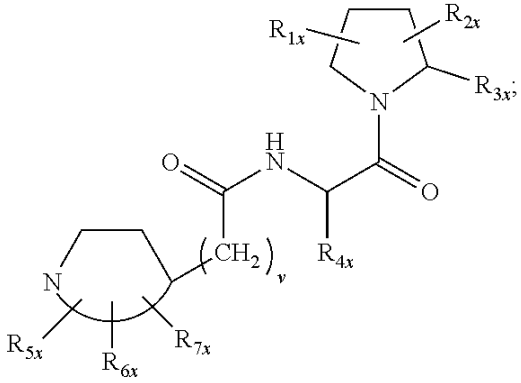
The Examiner issued a Notice of Allowance on January 10, 2024 ("Notice of Allowance"; EX1004 at 1303-09), which indicated that the claims were allowed because of the addition of the phrase "low molecular weight" and the purportedly unexpected results provided in the Office Action Response, Pomper Declaration, and Supplemental Amendment. EX1004 at 1308 (Notice of Allowance). However, the additional claim amendments provided in the Supplemental Amendment were not entered before issuance and thus a Certificate of Correction was requested by the Applicant and subsequently entered by the Examiner. EX1001, Certificate of Correction, claims 1, 3.

C. Claims

Following the entry of the Certificate of Correction, the '201 patent recites the following three claims:

Independent claim 1 recites "[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:



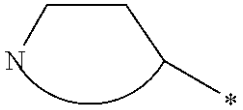
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, —O—C_{1-6} alkyl, and —S—C_{1-6} alkyl;

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

R_{4x} is H;

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

v is 0;



represents a quinolinyl ring;

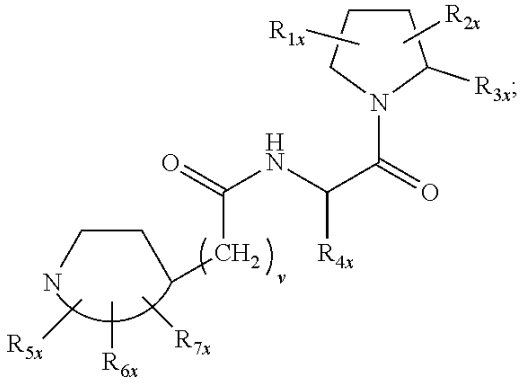
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and

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." EX1001, Certificate of Correction, claim 1.

Dependent claim 2 recites "[t]he compound of claim 1, wherein B is any radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy." *Id.* at 65:64-67.

Independent claim 3, contains substantially the same limitations as claim 1 but with the transitional phrase "consisting essentially of", reciting "[a] low molecular weight compound consisting essentially of components B-L-A; wherein:

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



wherein:

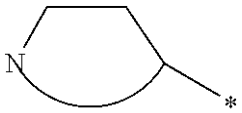
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, —O—C_{1-6} alkyl, and —S—C_{1-6} alkyl;

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

R_{4x} is H;

R_{5x}, R_{6x}, and R_{7x} are 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." *Id.* at Certificate of Correction, claim 3.

III. STATEMENT OF PRECISE RELIEF REQUESTED

Claims 1-3 are unpatentable and should be canceled in view of the following grounds:

Ground #	Basis
Ground I	Claims 1-3 would have been obvious over Jansen I and/or Jansen II taken in view of Zimmerman and Pomper under 35 U.S.C. § 103
Ground II	Claims 1-3 would have been obvious over Dvořáková in view of Pomper under 35 U.S.C. § 103
Ground III	Claims 1-3 lack enablement under 35 U.S.C. § 112
Ground IV	Claims 1-3 lack written description under 35 U.S.C. § 112
Ground V	Claims 1-3 are indefinite under 35 U.S.C. § 112

IV. LEVEL OF ORDINARY SKILL IN THE ART

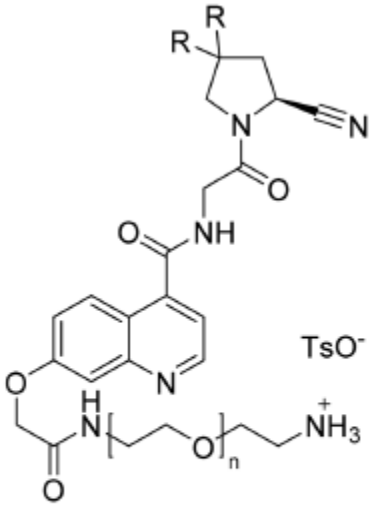
A POSA would comprise a person possessing a Bachelor's degree in organic chemistry or a related field such as medicinal chemistry and two to five years of experience employing organic chemistry as a tool for the development of molecules with targeted biological activity. EX1002 at ¶ 95. A POSA could also include individuals with a Master's degree or a Ph.D. in chemistry or a related field with comparatively less experience. *Id.* A POSA would have an understanding of processes employed for synthesis and evaluation of imaging and radiotherapeutics agents that selectively target a specific protein and would be able to evaluate published literature and patents to ascertain those features of a molecule that contribute to its affinity and selectivity for a particular drug target. *Id*.

V. SCOPE OF THE PRIOR ART

A. Dvořáková

Dvořáková is a scientific paper entitled "Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein" which was published on September 27, 2017 and is prior art under AIA 35 U.S.C. § 102(a)(1). EX1008. Its prior art accessibility is evidenced at least by its date of online publication in reputable journal "Journal of Medicinal Chemistry" on September 27, 2017, as reported by the American Chemical Society, an established publisher of scientific works. EX1008 at 8385; *see Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 19–20 (PTAB Dec. 20, 2019) (precedential) ("[T]he book is a textbook from an established publisher, O'Reilly, and a well-known book series."). Dvořáková was cited by the Examiner during prosecution and Patent Owner did not dispute its prior art status. EX1004 at 1209-25 (Office Action Response); *Id.* at 1267-83 (Supplemental Amendment).

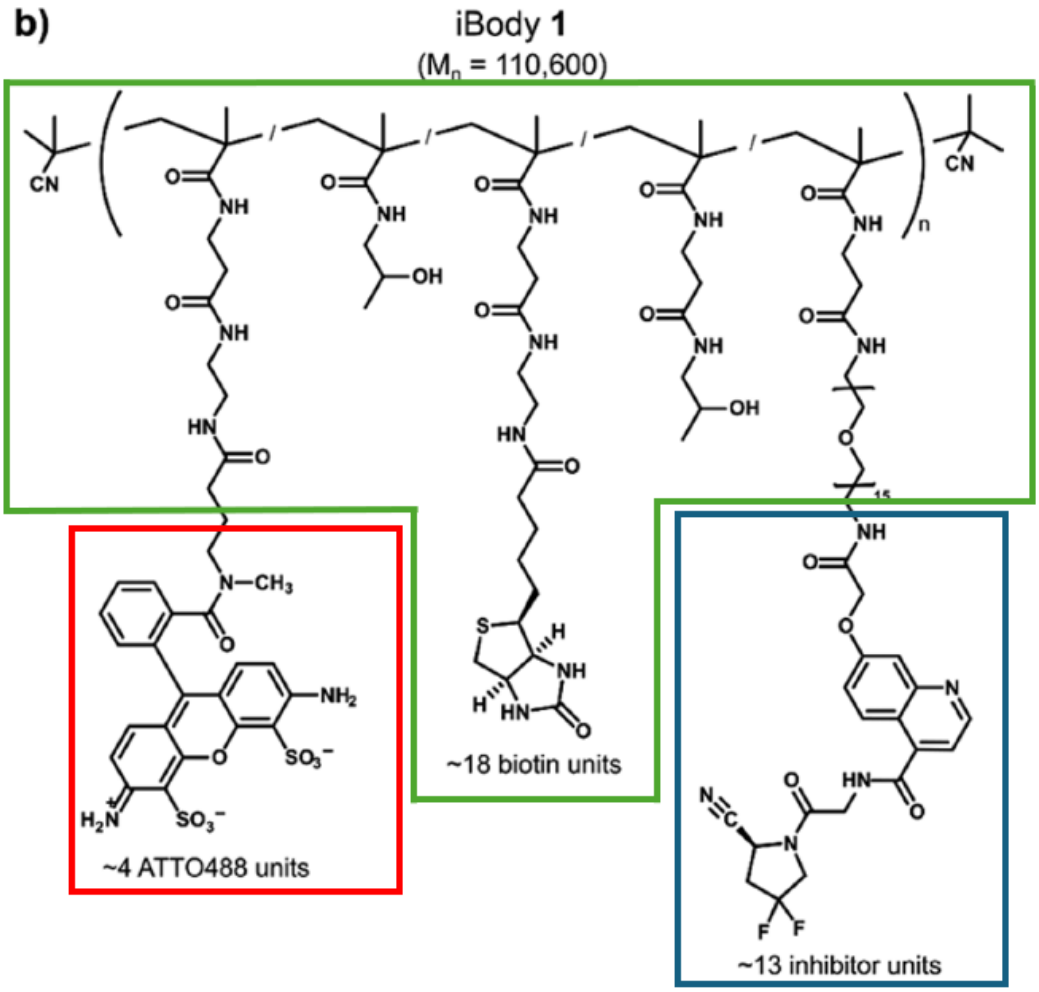
Dvořáková relates to developing polymer conjugates decorated with FAP inhibitors for application of imaging of FAP expressing cells. EX1008 at 8385, 8387; EX1002 at ¶ 50. Dvořáková discloses "[s]pecific [i]nhibitors of FAP modified with PEG linkers" (Compounds 1-4) having the following structures:



1 (n = 15, R = F)
2 (n = 5, R = F)
3 (n = 15, R = H)
4 (n = 5, R = H)

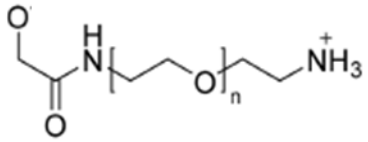
EX1008 at Scheme 1; EX1002 at ¶ 50.

Dvořáková discloses attaching its Compounds 1-4 to an ATTO488 dye via a HPMA copolymer with the following structure:



EX1008 at Figure 2b (reproduced below) (emphasis added to the ATTO488 dye in red, the FAP inhibitor in blue, and the linker in green); EX1002 at ¶ 51. ATTO488 dye is a fluorophore that contains a rhodamine-based structure and is known to be "highly suitable for single-molecule detection applications and high-resolution microscopy." EX1011; EX1002 at ¶ 51.

The distance between the FAP inhibitor and the HPMA copolymer is varied with the incorporation of the PEG linker as shown below:



EX1008 at Figure 2a; EX1002 at ¶ 52.

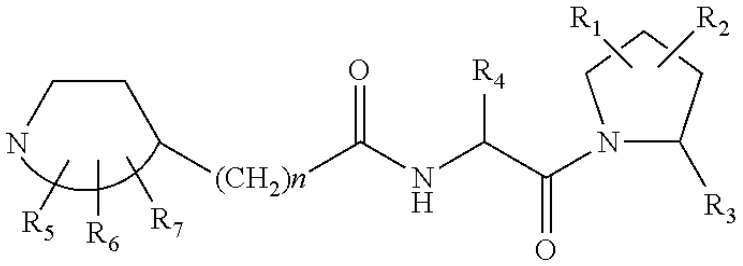
Dvořáková concludes that the developed inhibitor-decorated polymer conjugate can be used as a tool for the specific imaging of FAP-positive cells. EX1008 at 8387; EX1002 at ¶ 53. The conjugate binds only to FAP-expressing cells and not to cells lacking FAP. EX1008 at 8387; EX1002 at ¶ 53. Upon binding to FAP on the cell surface, the conjugate undergoes slow internalization, resulting in a optical signal from the ATTO488 dye inside the cell. EX1008 at 8387; EX1002 at ¶ 53. Yet without the incorporation of the FAP inhibitor on the polymer conjugate, it does not bind to any cells. EX1008 at 8387; EX1002 at ¶ 53. Thus, molecules including FAP inhibitors and optical imaging agents can be used for in vivo imaging and selective drug delivery into the tumor microenvironment. EX1008 at 8391; EX1002 at ¶ 53.

B. Jansen I

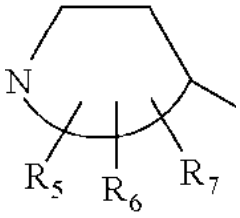
Jansen I is U.S. Patent No. 9,346,814 titled "FAP Inhibitors." Jansen I was issued on May 24, 2016 and claims priority to applications filed in 2012. EX1007 at cover. It is prior art under AIA 35 U.S.C. § 102(a)(1), (2).

Jansen I relates to the development of inhibitor compounds with high selectivity and specificity for FAP. EX1007 at Abstract; EX1002 at ¶ 55. Exemplary embodiments of FAP inhibitors disclosed in Jansen I include the following:

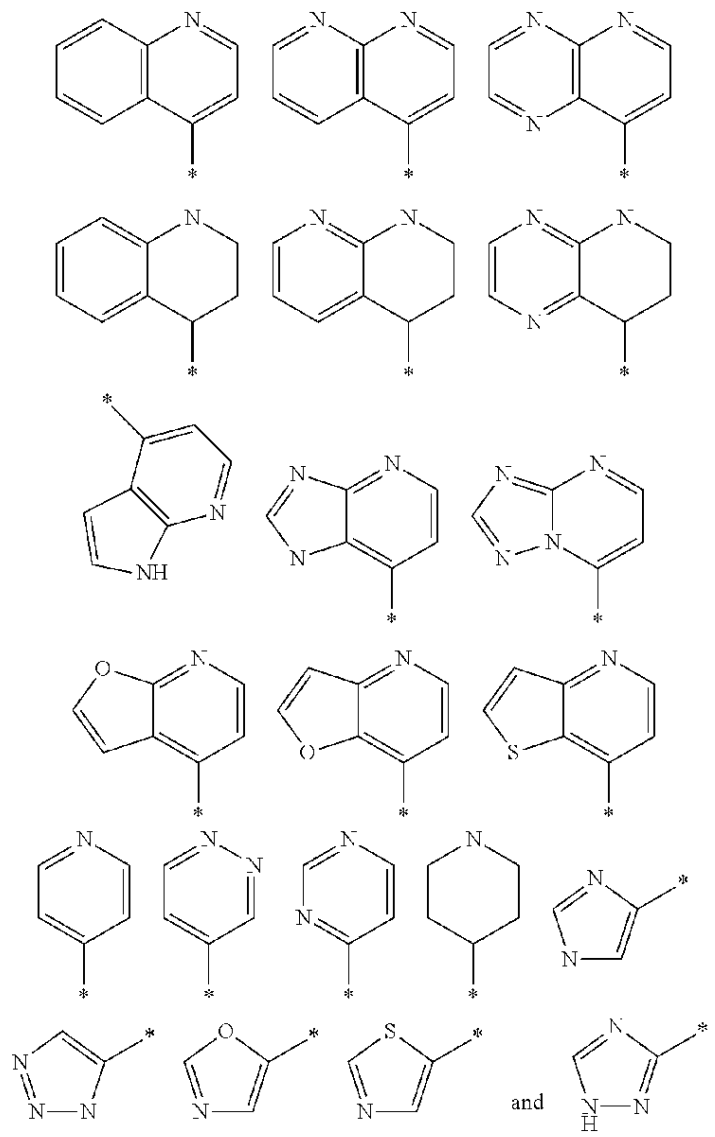
(X)



with specific focus on varying the following substituent:

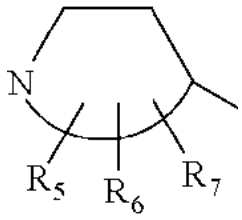


EX1007 at 98:50-59 and Table 4; EX1002 at ¶ 55. For example, Jansen I discloses that this substituent can be chosen from among the following:

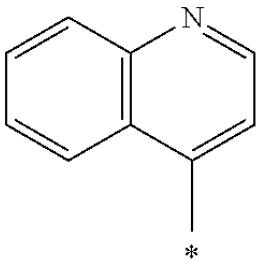


EX1007 at 100:26-60; EX1002 at ¶ 55.

While the selectivity of most of the compounds for FAP over PREP was reported as 50 times higher than reference compounds, Jansen I points to the position of the nitrogen in the



substituent as being of "pivotal importance," stating that "the 4-quinolinoyl ring clearly displays the best results." EX1007 at 78:24-31; EX1002 at ¶ 56.

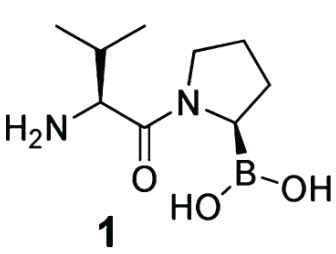


4-quinolinoyl ring

C. Jansen II

Jansen II is a scientific paper entitled "Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold." Jansen II was published on March 18, 2013 and is prior art under AIA 35 U.S.C. § 102(a)(1). EX1010 at 491. Its prior art accessibility is evidenced at least by its date of online publication in reputable journal "ACS Medicinal Chemistry Letters" on March 18, 2013, as reported by the American Chemical Society, an established publisher of scientific works. EX1010 at 491; *see Hulu*, IPR2018-01039, Paper 29 at 19–20.

Jansen II relates to the development of FAP inhibitors having combined low nanomolar FAP inhibition and high selectivity indices. EX1010 at Abstract; EX1002 at ¶ 64. Jansen II teaches that previously reported FAP inhibitors were not selective enough, which lead to safety concerns and halted further development. EX1010 at 491; EX1002 at ¶ 64. These prior FAP inhibitors include pyrrolidine-2-boronic acid derivatives (also referred to as Val-boroPro or Talabostat) (1) and linagliptin (2), as shown below:



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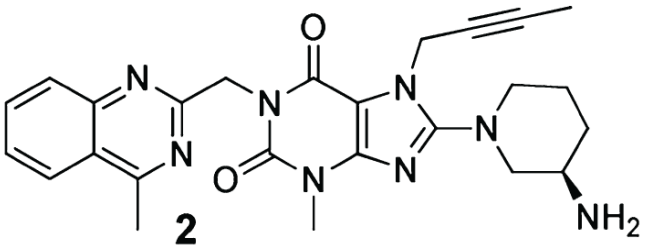
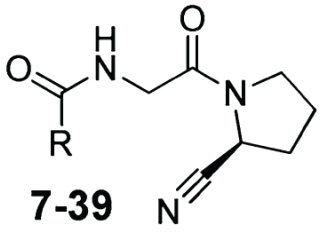


2

EX1010 at Figure 1; EX1002 at ¶ 64.

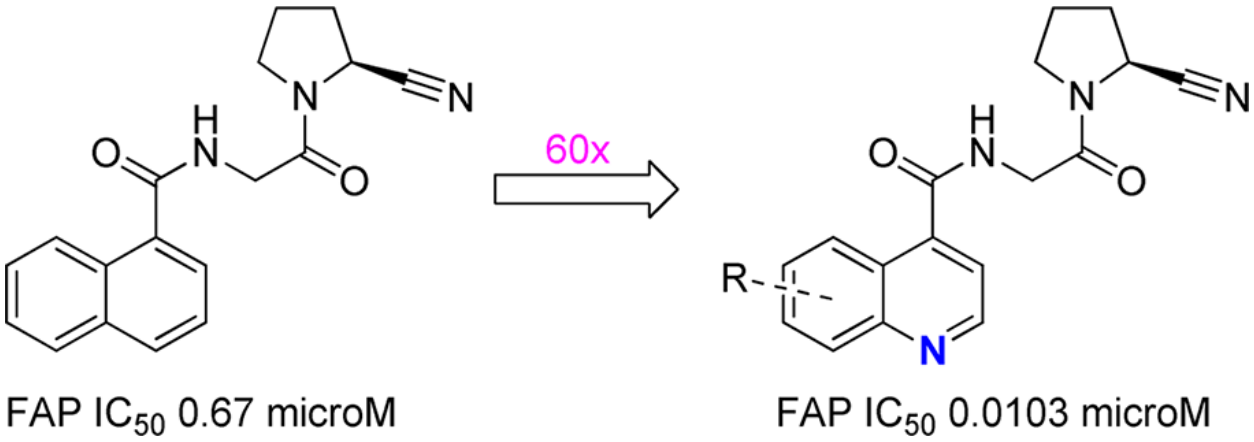
Jansen II discloses compounds 7-39 having the following general structure:



7-39

EX1010 at 493; EX1002 at ¶ 65. The R group substituents of the general structure are varied to determine optimal performance. EX1002 at ¶ 65. Jansen II teaches that quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-

naphthoyl) based FAP inhibitors, as shown in the Abstract figure of Jansen II, reproduced below:



EX1010 at Abstract figure; EX1002 at ¶ 65.

D. Zimmerman

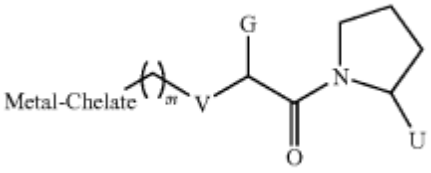
Zimmerman is U.S. Patent Publication No. 2010/009633. EX1009 at Cover. Zimmerman was published on April 22, 2010 and is prior art under AIA 35 U.S.C. § 102(a)(1), (2). *Id.*

Zimmerman is directed to radiopharmaceuticals that are useful in diagnostic imaging and therapeutic treatment of FAP related diseases, where the radiopharmaceuticals include complexes that contain a proline moiety and a radionuclide adapted for radioimaging and/or radiotherapy. EX1009 at Abstract; EX1002 at ¶ 58. Zimmerman teaches that there is a strong desire for the development of compounds which specifically target FAP and have imaging or therapy capabilities. EX1002 at ¶ 59. For example, Zimmerman teaches that:

> "Radioactive molecules that selectively bind to specific tumor cell surface proteins allow for the use of noninvasive imaging techniques, such as molecular imaging or nuclear medicine, for detecting the presence and quantity of tumor associated proteins. Such methods may provide vital information related to the diagnosis and extent of disease, prognosis and therapeutic management options. For example, therapy may be realized through the use of ***radiopharmaceuticals*** that are not only capable of ***imaging disease,*** but also are capable of delivering a therapeutic radionuclide to the diseased tissue. The expression of seprase ***[FAP-α] on tumors makes it an attractive target to exploit for noninvasive imaging as well as targeted radiotherapy.***"

EX1009 at ¶ 5 (emphasis added); EX1002 at ¶ 59.

The compounds described in Zimmerman have the following general structure:

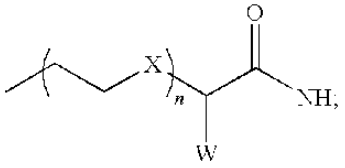


wherein:

U is selected from the group consisting of —$B(OH)_2$, —CN, —CO_2H and $P(O)(OPh)_2$;

G is selected from the group consisting of H, alkyl, substituted alkyl, carboxyalkyl, heteroalkyl, aryl, heteroaryl, heterocycle and arylalkyl;

V is a bond, O, S, NH, $(CH_2—CH_2\text{-}X)_n$ or a group of



X is O, S, CH_2, or NR;

R is H, Me or CH_2CO_2H;

W is H or NHR′;

R′ is hydrogen, acetyl, t-butyloxycarbonyl (Boc), 9H-fluoren-9-ylmethoxycarbonyl (Fmoc), trifluoroacetyl, benzoyl, benzyloxycarbonyl (Cbz) or substituted benzoyl;

n is an integer ranging from 0 to 6;

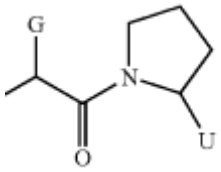
m is an integer ranging from 0 to 6;

Metal represents a metallic moiety comprising a radionuclide; and

Chelate represents a chelating moiety that chelates to said Metal.

EX1009 at claim 1.

In the general structure the proline moiety



is attached via a tether

to a Metal-Chelate. EX1009 at claim 1; EX1002 at ¶ 61. The proline moiety is capable of selectively inhibiting FAP, and the metal-chelate or radionuclide is adapted for radioimaging and/or radiotherapy. EX1009 at ¶ 7; EX1002 at ¶ 61. The tether can be varied to "explore the effect of more significant variations of the distance of the metal chelator from the proline moiety by incorporating a tether into these structures. The tether may comprise a simple alkyl chain as shown, a PEG $(CH_2CH_2O)_n$, a polyethylene amine $((CH_2CH_2NH)_n)$, or the like." EX1009 at ¶ 130; EX1002 at ¶ 61.

Zimmerman provides examples of Metal-Chelate moieties, including the following:

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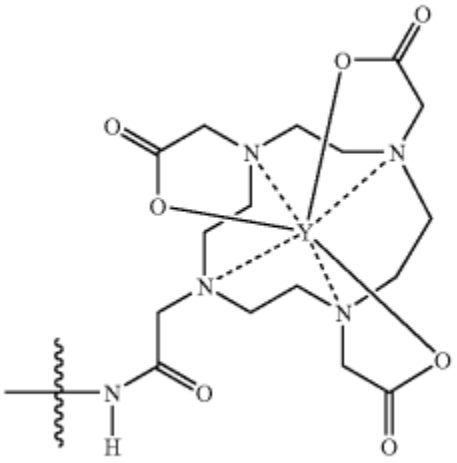


where the metal, Y, may be technetium-99m, technetium-94, rhenium-186, rhenium-188, lutetium-177, lutetium-170, yttrium-90, indium-111, gallium-67, gallium-68, copper-62, copper-64, copper-67, bismuth-212, astatine-211, strontium-89,

holmium-166, samarium-153, palladium-100, palladium-109, lead-212, rhodium-105 and ruthenium-95. EX1009 at ¶¶ 49, 99; EX1002 at ¶ 62.

E. Pomper

Pomper is U.S. Patent Publication No. 2012/0009121. EX1006 at Cover. Pomper was published on January 12, 2012 and is prior art under AIA 35 U.S.C. § 102(a)(1), (2). *Id*.

Pomper describes new imaging and therapeutic compounds for targeting cancer and cancer angiogenesis. EX1006 at Abstract, ¶ 12; EX1002 at ¶ 67. These compounds include prostate-specific membrane antigen (PSMA) inhibitors used to treat cancer linked to a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. EX1006 at ¶¶ 31-34, 279; EX1002 at ¶ 67. These imaging agents "offer better contrast between target tissues and non-target tissues," "greater cellular retention," and "low molecular weight." EX1006 at ¶ 12; EX1002 at ¶ 67. Pomper also discloses suitable linkers that can be used to link the PSMA inhibiting moiety and the optical or radiolabeled moiety. EX1006 at ¶¶ 0102, 0129; EX1002 at ¶ 67.

Pomper also teaches the benefits of low molecular weight compounds. Pomper discusses how "antibodies may have less access to tumor[s] than low molecular weight agents, which can be manipulated pharmacologically." EX1006 at ¶ 8; EX1002 at ¶ 68. Pomper also discusses how low molecular weight inhibitors

have "shown promise in preclinical imaging studies." EX1006 at ¶ 242 (citing EX1015 and EX1016); EX1002 at ¶ 68.

VI. CLAIM CONSTRUCTION

In a PGR proceeding, claim terms are to be construed using the standard under *Phillips v. AWH Corp*., 415 F.3d 1303 (Fed. Cir. 2005). In light of the intrinsic record and the state of the art as of the effective filing date of the '201 patent, a POSA would have understood the following claim terms to be construed as proposed below by Petitioner. Regardless of how the claims are construed, however, all of the challenged claims should be canceled as invalid for the reasons set forth herein.

A. "Low Molecular Weight" (Claims 1-3)

As discussed in greater detail in Section VI.E. below, the phrase "low molecular weight" appearing in independent claims 1 and 3—and, by dependency, in claim 2—is indefinite. In addition to falling squarely within the purview of *Teva Pharms. USA, Inc. v. Sandoz, Inc.,* 789 F.3d 1335 (Fed. Cir. 2015), "low molecular weight" is a relative term that is not defined in the specification and has no objective boundaries to a POSA. *See Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014).

Patent Owner may attempt to argue that "low molecular weight" was defined as "about 50 Daltons to about 1,500 Daltons" during prosecution. But such an argument should be unsuccessful, as this general, non-limiting statement about what

is typical in the unrelated field of metabolites is insufficient to define "low molecular weight" in this way. EX1002 at ¶ 102.

Although the '201 patent contains a lengthy "Definitions" section (EX1001 at 38:29-50:50), it does not define the phrase "low molecular weight." EX1002 at ¶ 100. Indeed, "low molecular weight" appears only three times in the specification of the '201 patent, and its use is not tied to any particular defined range. EX1001 at 1:60-67, 7:44-54; EX1002 at ¶ 99-100. It was not until prosecution, when Patent Owner added the phrase "low molecular weight" to the claims in an attempt to overcome the prior art, that Patent Owner argued for the first time that a POSA "would recognize that low molecular weight compounds would have a molecular weight of typically from ***about 50 Daltons to about 1,500 Daltons***" and cited literature related to metabolites. EX1004 at 1215 (Office Action Response); EX1004 at 1198 (Pomper Declaration); EX1004 at 1273 (Supplemental Amendment); EX1002 at ¶ 101. But the subject matter of the '201 patent is unrelated to metabolites and this general, non-limiting statement about what is "typical" would not have defined or otherwise informed a POSA as to the scope of the term "low molecular weight" as used in the claims. EX1002 at ¶ 102; *see Abbott Labs. v. Syntron Bioresearch, Inc*., 334 F.3d 1343, 1355 (Fed. Cir. 2003) (rejecting argument that Patent Owner assigned its own definition to term "analyte" based on a statement in the specification where other statements in the specification referred to the term

more broadly because, taken in context, it did not provide reasonable clarity, deliberateness, and precision sufficient to narrow the definition of the claim term in the manner urged).

Additionally, construing the phrase "low molecular weight" as "about 50 Daltons to about 1,500 Daltons" would improperly exclude several disclosed embodiments of the '201 patent. EX1002 at ¶ 103. As discussed in more detail in Section VII.E.1 below, the '201 patent describes several embodiments having a molecular weight greater than 1,500 Da. Courts have routinely rejected narrow claim constructions that improperly read disclosed embodiments out of the claim. *See, e.g.*, *Eko Brands, LLC v. Adrian Rivera Maynez Enterprises, Inc.*, 946 F.3d 1367, 1372-73 (Fed Cir. 2020) (affirming rejection of construction of "brewing chamber" that required a fully enclosed sealed space where specification disclosed embodiments that were not fully enclosed).

B. "C(O)Alkyl" / "Aryl"

Claims 1 and 3 include the term "C(O)alkyl" as one of several options at the R_{3x} position in the claimed structure of the A moiety. This term, also known as an "acyl" group, is commonly used in organic chemistry and the skilled artisan would understand it to refer to a functional group consisting of an alkyl group directly attached to a carbonyl (C=O) group. EX1002 at ¶ 107.

The '201 patent defines the term "alkyl" in the specification:

> The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent groups, ***having the number of carbon atoms designated (i.e., C_1-C_{10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons)***.

EX1001 at 39:43-50 (emphasis added). In other words, Patent Owner defined a particular nomenclature for situations where it wished to specify that an alkyl group was limited to a particular length or ranges of lengths. EX1002 at ¶ 108. An example of this nomenclature can be found in both claims 1 and 3, wherein Patent Owner specified that the R_{1x} and R_{2x} substituents can be chosen from a group that includes, for example, an alkyl chain containing between 1 and 6 carbon atoms, i.e., "C_{1-6}alkyl." EX1001, Certificate of Correction, claims 1, 3; EX1002 at ¶ 109. Patent Owner unquestionably knew how to claim alkyl chains of a particular length or range of lengths when it wanted to.

In contrast, the claim term "C(O)alkyl" does not provide any limit to the number of carbon atoms present in the alkyl chain. EX1002 at ¶ 110; *see Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1372 (Fed. Cir. 2005) ("A claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so."); *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1119 (Fed. Cir. 2004) ("[W]hen an applicant uses different terms in

a claim it is permissible to infer that he intended his choice of different terms to reflect a differentiation in meaning of those terms."). Accordingly, this term should be construed as an "acyl group comprising an alkyl group of any length." EX1002 at ¶ 110.

Similarly, the definitions provided in the '201 patent explain that the term "aryl," identified among the several options at the R_{3x} position in the claimed structure of the A moiety, is "an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently." EX1001 at 42:64-67; EX1002 at ¶ 111. Thus, without a number of carbon atoms or rings designated, the —C(O)aryl-, —C═C—C(O)aryl, and —C═C—$S(O)_2$aryl groups likewise should not be limited to any particular length, size or substitution. EX1002 at ¶ 111.

VII. DETAILED EXPLANATION AND EVIDENCE

A. Ground I: Claims 1-3 Would Have Been Obvious Over Jansen I and/or Jansen II Taken In View of Zimmerman and Pomper

Claims 1-3 are unpatentable under 35 U.S.C. § 103 over Jansen I and/or Jansen II taken in view of Zimmerman and Pomper.

A patent is invalid as obvious "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person

having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. Obviousness is based on underlying findings of fact, including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of non-obviousness. *Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966). The Federal Circuit has held that "an obviousness determination requires not only the existence of a motivation to combine elements from different prior art references, but also that a skilled artisan would have perceived a reasonable expectation of success in making the invention via that combination." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

The claims of the '201 patent are directed to "low molecular weight" compounds having the formula B-L-A, wherein 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; A is a targeting moiety for FAP-α having a structure falling within the genus described in the claims, and L is "a linker having bi-functionalization adapted to form a chemical bond with B and A. EX1001, Certificate of Correction, claims 1, 3.

This claimed subject matter in this particular case is nothing more than the obvious combination of known elements. EX1002 at ¶ 112. As Patent Owner readily

concedes in the specification of the ’201 patent, the genus of targeting moieties for FAP-α, A, was already disclosed in references like Jansen I and Jansen II, while components meeting the broad functional language specified for B and L were also disclosed in references like Zimmerman. EX1002 at ¶ 113 (citing EX1001 at 8:25-10:10, 17:45-53, 25:18-25, 26:18-24). Other references, including Pomper, which was of record but not applied by the Examiner during prosecution of the ’201 patent, taught that low molecular weight inhibitors may have better access to tumors than larger antibodies and that low molecular weight agents had shown promise in pre-clinical imaging studies. EX1002 at ¶ 113 (citing EX1006 at ¶¶ 8, 242). The art would have taught and motivated a POSA to design and prepare a low molecular weight compound with high affinity and selectivity for FAP that would serve as an imaging or therapeutic agent, and the art would have further motivated a POSA to combine these known features into the compounds recited in the claims of the ’201 patent with a reasonable expectation that such compounds would work for their desired purpose. EX1002 at ¶ 114.

The Examiner recognized these teachings and motivations in the prior art and rejected the claims as obvious. EX1004 at 1179 (Office Action). In response, the Patent Owner submitted a declaration from one of the ’201 patent’s co-inventors, Dr. Pomper (“Pomper Declaration”). EX1004 at 1195-1206. Dr. Pomper’s declaration asserted that the claimed compounds demonstrate an unexpectedly

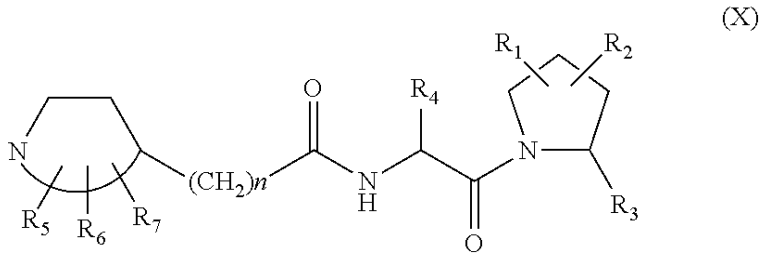
promising PREP/FAP ratio, which Dr. Pomper describes as the ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP, compared to other small molecule FAP inhibitors. EX1004 at 1203-05 (Pomper Declaration); EX1002 at ¶ 132.

But Dr. Pomper's assertion of unexpected results is based on only 11 examples, and is certainly insufficient to represent the thousands, if not millions or more, of possible FAP inhibitors, linkers, optical dyes, radiolabeling groups, and combinations thereof encompassed by the broad language used in the claims. EX1002 at ¶ 133. These alleged unexpected results were the sole basis given by the Examiner for allowing the *prima facie* obvious claimed invention over the applied prior art. EX1004 at 1308 (Notice of Allowance). That was legally improper, for Dr. Pomper's presented evidence of alleged unexpected results was not even remotely commensurate with the extremely broad scope of the claims, and the claimed invention remains obvious in light of that applied art. *See* EX1002 at ¶ 134; *see also In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003) (concluding that data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 714 F. Supp. 3d 652, 786 (N.D.W. Va. 2024) (rejecting evidence of secondary considerations that focused on narrow set of

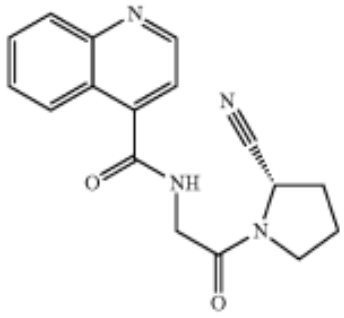
particular disorders because it was "insufficient to represent the full scope of the claimed genus").

1. Claim 1

As discussed above in Section II.A., the specification of the '201 patent readily concedes that the claimed genus of FAP-α targeting moieties, A, is not new. EX1002 at ¶ 115. Indeed, the '201 patent explains that Jansen I discloses FAP inhibitors having the following general structure:

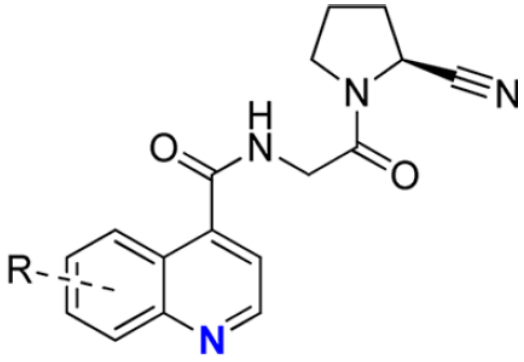


with overlapping definitions with the substituents recited in the '201 patent claims. EX1007 at 98:50-59; EX1002 at ¶ 115. Specifically, Jansen I discloses FAP inhibitors having the following structure:

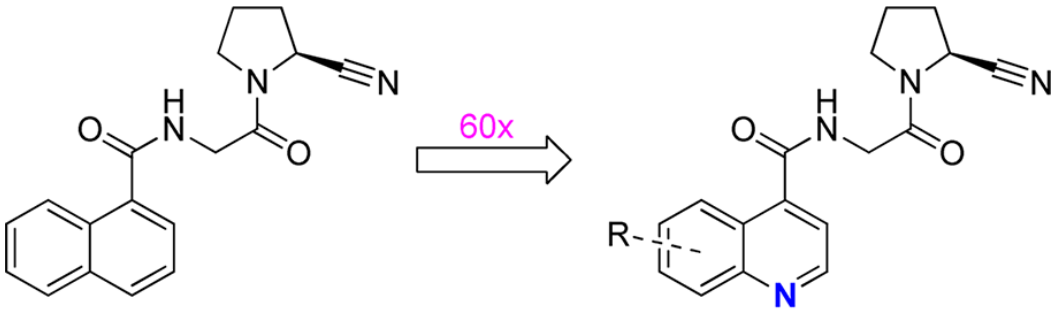


EX1007 at 47:5-18; EX1002 at ¶ 115. This structure is the FAP inhibitor included in the only two embodiments in the '201 patent specification, XY-FAP-01 and XY-FAP-02-[In], and all 11 examples provided in Dr. Pomper's declaration. EX1001 at Examples 1.1-1.2; EX1004 at 1203-1205 (Pomper Declaration); EX1002 at ¶ 115. It also falls within the scope of the claimed genus, A, when R_{1x} and R_{2x} are H and when R_{3x} is -CN. EX1002 at ¶ 115.

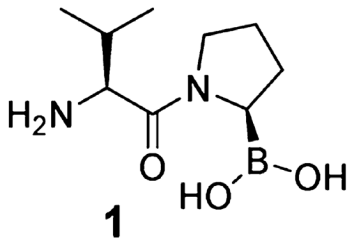
In addition, Jansen II discloses FAP inhibitors having the following structure:



EX1010 at Abstract; EX1002 at ¶ 116. Jansen II teaches that quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) based FAP inhibitors, as shown in the Abstract figure of Jansen II, reproduced below:



EX1010 at Abstract, 6; EX1002 at ¶ 116. Not only does Jansen II teach that the quinolinoyl ring improves performance, but Jansen II also directly compares the quinolinoyl-containing compound with the following labeled as Compound 1:



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EX1010 at Figure 1; EX1002 at ¶ 116. Jansen II teaches that this Compound 1 has inferior performance to Jansen II's quinolinoyl-containing compound. EX1010 at Table 1, Table 4; EX1002 at ¶ 116.

While neither Jansen I nor Jansen II discloses that the FAP inhibitor may be attached via a linker to "any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy," it was well known in the art as of the earliest effective filing date to functionalize FAP inhibitors with radiolabeled groups for optical imaging purposes and to use a linker between the two moieties. EX1002 at ¶ 117.

For example, Zimmerman is directed to "[s]mall molecule inhibitors of seprase [FAP-α] [] for use as therapeutic medicines or as radiopharmaceuticals useful in diagnostic imaging and in the therapeutic treatment of diseases

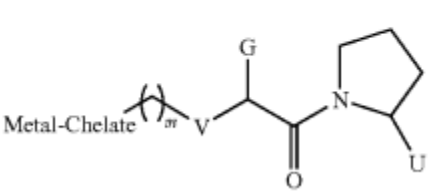
characterized by overexpression of seprase [FAP-α]. EX1009 at ¶ 7; EX1002 at ¶ 118. Zimmerman also teaches that:

> "Radioactive molecules that selectively bind to specific tumor cell surface proteins allow for the use of noninvasive imaging techniques, such as molecular imaging or nuclear medicine, for detecting the presence and quantity of tumor associated proteins. Such methods may provide vital information related to the diagnosis and extent of disease, prognosis and therapeutic management options. For example, therapy may be realized through the use of ***radiopharmaceuticals*** that are not only capable of ***imaging disease,*** but also are capable of delivering a therapeutic radionuclide to the diseased tissue. The expression of seprase ***[FAP-α] on tumors makes it an attractive target to exploit for noninvasive imaging as well as targeted radiotherapy.***"

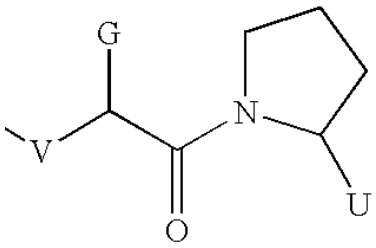
EX1009 at ¶ 5 (emphasis added); EX1002 at ¶ 118. The radiopharmaceuticals disclosed in Zimmerman include "complexes or compounds that contain ***a functionalized proline moiety which is capable of selectively inhibiting seprase [FAP-α], and a radionuclide adapted for radioimaging and/or radiotherapy***." EX1009 at ¶ 7 (emphasis added); EX1002 at ¶ 118. Thus, Zimmerman discloses the use of "any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy" with a FAP inhibitor, as recited in claim 1. EX1002 at ¶ 118.

Zimmerman also discloses "a linker having bi-functionalization adapted to form a chemical bond with B and A." EX1002 at ¶ 119. The claims of Zimmerman have a similar structure as the claims of the '201 patent (claim 1 of Zimmerman is reproduced in part below).

1. A complex of Formula I, its stereoisomer or pharmaceutically acceptable salt:



EX1002 at ¶ 119. In claim 1 there is a FAP-α inhibitor including a proline moiety having the following structure:



attached via a linker  , to a Metal-Chelate. EX1009 at claim 1; EX1002 at ¶ 120.

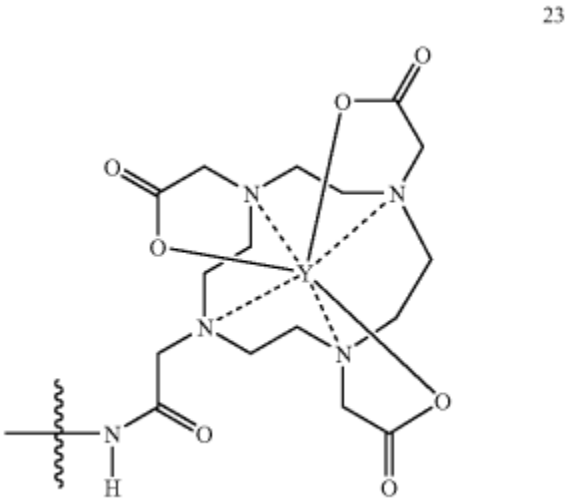
The proline moiety is capable of selectively inhibiting FAP, and the metal-chelate or radionuclide is adapted for radioimaging and/or radiotherapy. EX1009 at

¶ 7; EX1002 at ¶ 120. Claim 1 specifies that the m of the linker is an integer of 0 to 6. EX1009 at claim 1; EX1002 at ¶ 120.

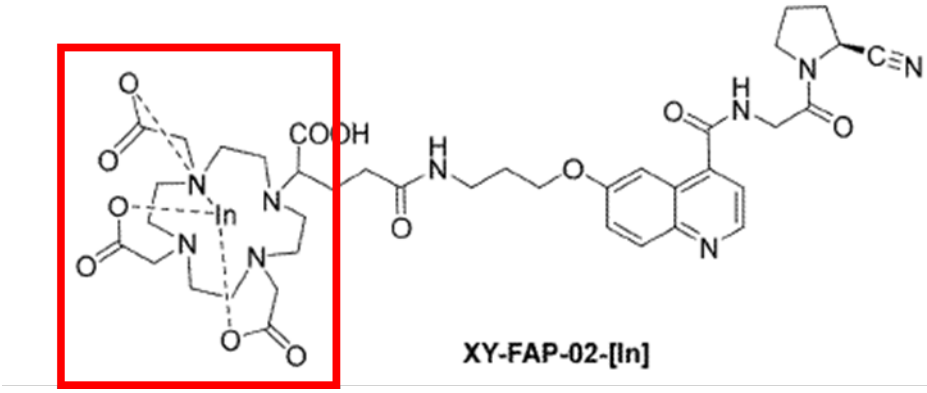
The linker, L, in the '201 patent claims is not limited to any particular structure or atoms and is only required to have "bi-functionalization adapted to form a chemical bond with B and A." EX1002 at ¶ 121 Thus, the linker,  , described in Zimmerman meets the parameters of the claimed linker, L. EX1002 at ¶ 121.

Although Patent Owner argued during prosecution that Zimmerman did not disclose the claimed linker, L (EX1004 at 1217-21 (Office Action Response); EX1004 at 1275-77 (Supplemental Amendment)), this argument was factually erroneous. EX1002 at ¶ 122. Zimmerman merely uses different terminology than the '201 patent, referring to the "linker" as a "tether." EX1009 at ¶¶ 130-133; EX1002 at ¶ 122. Zimmerman teaches that the tether can be varied to "explore the effect of more significant variations of the distance of the metal chelator from the proline moiety. . . . The tether may comprise a simple alkyl chain as shown, a PEG $(CH_2CH_2O)_n$, a polyethylene amine ($(CH_2CH_2NH)_n$), or the like." EX1009 at ¶ 130. This would be understood by a POSA as "bi-functionalization adapted to form a chemical bond with B and A." Zimmerman sufficiently teaches the use of a linker to attach a Metal-Chelate moiety and a FAP inhibitor. EX1002 at ¶ 122.

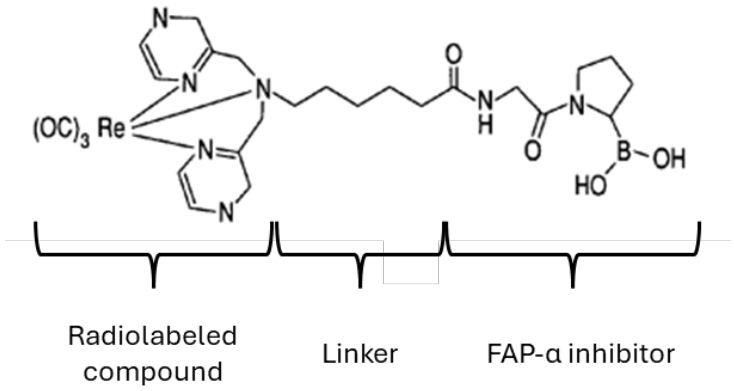
Indeed, the metal-chelate moieties of Zimmerman include the following:



where Y may be indium (In). EX1009 at Table 4, ¶ 99; EX1002 at ¶ 123. The structure of this group is similar to that of XY-FAP-02-[In], as disclosed in the '201 patent and shown below with emphasis on the radiolabeled functional group (B):



EX1002 at ¶ 123. Zimmerman also provides the following exemplary embodiment:



EX1009 at Fig. 7 (annotations added). Thus, Zimmerman discloses the components of B and L. EX1002 at ¶ 124.

Pomper describes new imaging and therapeutic compounds for targeting cancer and cancer angiogenesis. EX1006 at Abstract, ¶ 12; EX1002 at ¶ 125. These compounds include an inhibiting compound used to treat cancer coupled with a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. EX1006 at ¶¶ 31-34, 279; EX1002 at ¶ 125. These imaging agents "offer better contrast between target tissues and non-target tissues," "greater cellular retention," and "low molecular weight." EX1006 at ¶ 12; EX1002 at ¶ 125. Pomper also discloses suitable linkers that can be used to couple the inhibiting moiety and the optical or radiolabeled moiety. EX1002 at ¶ 125. Indeed, there can be no dispute that the linkers contemplated by the claims of the '201 patent are the same as those disclosed in Pomper because the '201 patent expressly states that "[s]uitable linkers

are disclosed in" Pomper and incorporates Pomper in its entirety. EX1001 at 17:45-54; EX1002 at ¶ 125.

Pomper also teaches the benefits of low molecular weight compounds. Pomper discusses how "antibodies may have less access to tumor[s] than low molecular weight agents, which can be manipulated pharmacologically." EX1006 at ¶ 8; EX1002 at ¶ 126. Pomper also discusses how low molecular weight inhibitors have "shown promise in preclinical imaging studies." EX1006 at ¶ 242 (citing EX1015 and EX1016); EX1002 at ¶ 126. A POSA would have been motivated by Pomper to develop a compound with a low molecular weight. EX1002 at ¶ 126.

In summary, a POSA at the time of filing the '201 patent application would have been motivated to prepare the FAP-α inhibitor described in Jansen I and/or Jansen II. EX1002 at ¶ 127. A POSA also would have been motivated to attach the FAP-α inhibitor of Jansen I and/or Jansen II to a radiolabeled compound via a linker for diagnostic imaging based on Zimmerman and Pomper, which teach the advantages of low molecular weight compounds, diagnostic imaging, and therapeutic treatment of diseases, to form the compound of claim 1 of the '201 patent, with a reasonable expectation of success. EX1002 at ¶¶ 127-28.

2. Claim 2

Claim 2 further specifies that B "is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission

computed tomography (SPECT) imaging, or radiotherapy." EX1001 at Claim 2. As discussed above with respect to claim 1, Zimmerman and Pomper disclose radiolabeled functional groups suitable for PET imaging, SPECT imaging, or radiotherapy. EX1002 at ¶ 129. Therefore, claim 2 would have been obvious to a POSA in view of Jansen I and/or Jansen II taken further in view of Zimmerman and Pomper. EX1002 at ¶ 129.

3. Claim 3

Claim 3 of the '201 patent is identical to claim 1 except that it includes the additional language "consisting essentially of" components B-L-A in the preamble. The semi-closed term "consisting essentially of" indicates that a claim is limited to the components specified therein "and those that do not *materially* affect the *basic* and *novel* characteristic(s)" of the claimed invention. *Application of Herz*, 537 F.2d 549, 551-52 (C.C.P.A. 1976) (quoting *Application of Janakirama-Rao*, 317 F.2d 951, 954 (C.C.P.A 1963)) (emphasis in original).

As discussed above with respect to claim 1, a POSA would have been motivated with a reasonable expectation of success to combine the teachings of Jansen I and/or Jansen II with Zimmerman and Pomper to arrive at the subject matter of claim 1. Nothing in these references would require the inclusion of a component that would materially affect the basic characteristics of this combination. EX1002 at

¶ 130. Thus, claim 3 would also have been obvious over the combination of Jansen I and/or Jansen II with Zimmerman and Pomper. EX1002 at ¶ 130.

4. No Secondary Indicia

The question of obviousness requires consideration of objective indicia of nonobviousness. *See KSR*, 550 U.S. at 406 (quoting *Graham,* 383 U.S. at 17-18). Objective evidence of non-obviousness requires proof of a "nexus" with the claims and must be commensurate in scope with the claims. *Wyers v. Master Lock*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Asyst Techs. Inc.* v. *Emtrak Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008). The patentee has the burden of production to show the required nexus between the objective indicia and the claimed invention. *Prometheus*, 805 F.3d at 1101-02; *see also In re GPAC Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995) ("For objective evidence to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." (internal citations omitted)).

Patent Owner argued during prosecution that the 11 examples provided in the Pomper Declaration are evidence of unexpected results. EX1004 at 1221-42 (Office Action Response); *see also id.* at 1203-05 (Pomper Declaration); *id.* at 1279-83 (Supplemental Amendment). Yet each of the 11 new examples, along with the two examples XY-FAP-01 and XY-FAP-02-[In] in the '201 patent specification, includes the same FAP inhibitor (A) structure. EX1002 at ¶ 133. Thus, the

declaration does not provide evidence of unexpected results commensurate with the scope of the vary large, if not limitless, scope of the FAP inhibitor (A) genus described in the claims. EX1002 at ¶ 133; *see also Peterson*, 315 F.3d at 1331 (concluding that data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *Regeneron*, 714 F. Supp. 3d at 786 (rejecting evidence of secondary considerations that focused on narrow set of particular disorders because it was "insufficient to represent the full scope of the claimed genus"). Moreover, while the structures of the linkers (L) and optical dyes or radiolabeling groups (B) vary in the 11 examples provided, it is certainly insufficient to represent the thousands, if not millions or more, of possible FAP inhibitors, linkers, optical dyes, radiolabeling groups, and combinations thereof encompassed by the broad functional language used in the claims. EX1002 at ¶¶ 134-35. Thus, the Examiner's reliance on this insufficient evidence on unexpected results was improper.

No other secondary indicia of nonobviousness were relied upon during prosecution of the '201 patent. Petitioner reserves the right to rebut any alleged secondary indicia presented by Patent Owner in response to this Petition.

B. Ground II: Claims 1-3 Would Have Been Obvious In View of Dvořáková and Pomper

Claims 1-3 are unpatentable under 35 U.S.C. § 103 over the combination of Dvořáková and Pomper.

During prosecution, the Examiner rejected the sole pending claim as anticipated by Dvořáková. EX1004 at 1177-78 (Office Action). In response, Patent Owner amended the claim to add the phrase "low molecular weight." *Id.* at 1210 (Office Action Response). Patent Owner argued that the addition of "low molecular weight" into the preamble distinguished "the pending claims from a large molecule imaging agents containing anti-FAP moieties" and that "[i]n contrast to the instant application, the compound disclosed in Dvořáková (compound 1) is a large molecule compound." *Id.* at 1213-14 (Office Action Response), 1197-98 (Pomper Declaration), 1271-72 (Office Action Response).

As discussed above and below in Sections VI.A and VII.E, the phrase "low molecular weight" is indefinite and claims 1-3 should be invalidated on that basis. But, to the extent the Board concludes the phrase "low molecular weight" would be understood by a POSA with reasonable certainty, claims 1-3 should still be invalidated because they would have been obvious to a POSA over the combination of Dvořáková and Pomper.

As discussed below, Dvořáková discloses every limitation of claim 1 except "low molecular weight." EX1002 at ¶ 138. Pomper, however, teaches the benefits of low molecular weight compounds. EX1002 at ¶ 139. Pomper discusses how "antibodies may have less access to tumor[s] than low molecular weight agents, which can be manipulated pharmacologically." EX1006 at ¶ 8. Pomper also discusses how low molecular weight inhibitors have "shown promise in preclinical imaging studies." EX1006 at ¶ 242 (citing EX1015 and EX1016).

A POSA reading Dvořáková in view of Pomper would have been motivated to modify Dvořáková's disclosed compounds to have a lower molecular weight based on Pomper's teachings about how such compounds have improved pharmacokinetic properties and have shown promise in preclinical studies. EX1002 at ¶ 140. And a POSA would have readily understood how the molecular weight of Dvořáková's compounds could be lowered. *Id*. For example, a POSA would have recognized that a low molecular weight version of iBody 1 could be synthesized by using fewer inhibitor and ATTO488 units and using a linker with a lower molecular weight. EX1002 at ¶ 140. Pomper discloses several such linkers as suitable, including, "[f]or instance linking groups having alkyl, aryl, combination of alkyl and aryl, or alkyl and aryl groups having heteroatoms," are suitable. EX1006 at ¶¶ 102, 129; EX1002 at ¶ 140. And, based on Pomper's teachings about the benefits of a low molecular weight compound, a POSA would have reasonably expected a low

molecular weight version of iBody 1 to work for the desired purpose. EX1002 at ¶ 140.

Thus, the art would have taught and motivated a POSA to design and prepare a low molecular weight compound with high affinity and selectivity for FAP that would serve as an imaging or therapeutic agent, and a POSA would have had a reasonable expectation that such compounds would work for their desired purpose. EX1002 at ¶ 141.

1. Claim 1

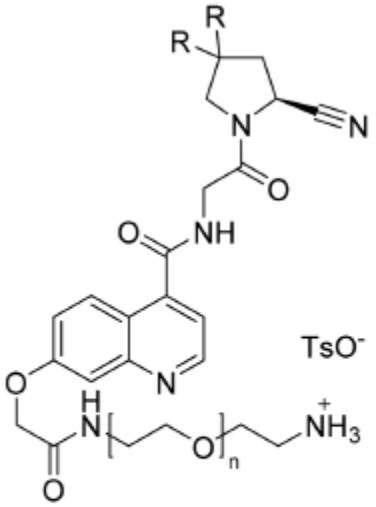
a. [1a] "A low molecular weight compound of Formula (I): B-L-A (I) wherein:"

As discussed above, Pomper discloses inhibitor imaging agents having a low molecular weight. EX1002 at ¶ 142.

Dvořáková discloses compounds having the formula B-L-A, as each of B, L, and A are defined in claim 1. EX1002 at ¶ 142. Each moiety is discussed in more detail below.

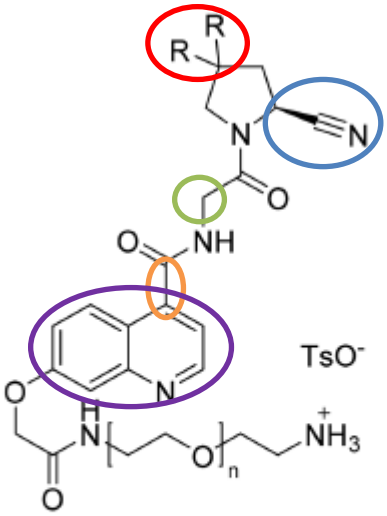
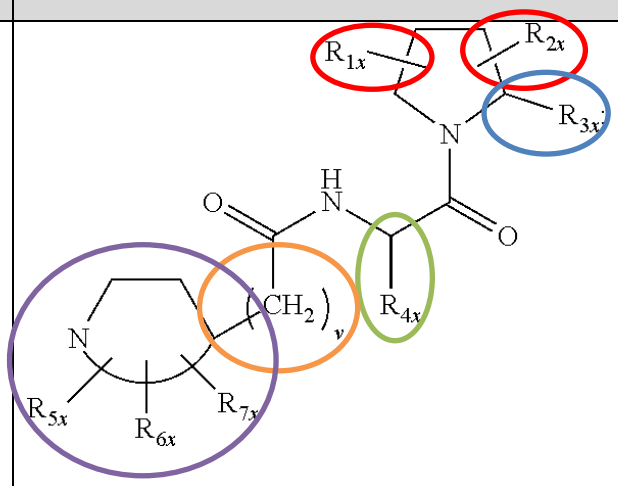
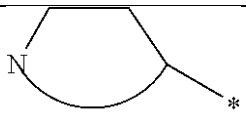
b. [1b] "A is a targeting moiety for FAP-α, wherein A has the structure of . . ."

Dvořáková discloses "[s]pecific [i]nhibitors of FAP modified with PEG linkers" (Compounds 1-4) having the following structures:



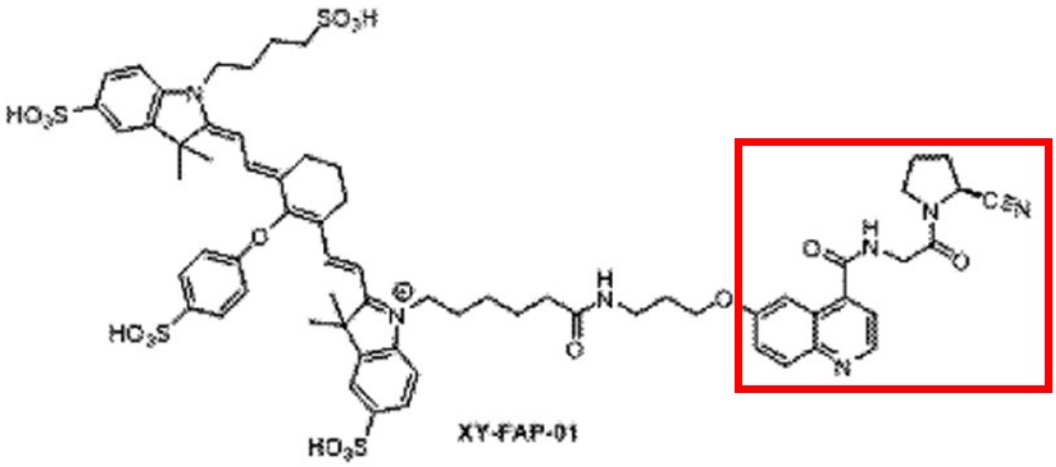
1 (n = 15, R = F)
2 (n = 5, R = F)
3 (n = 15, R = H)
4 (n = 5, R = H)

EX1008 at 8388; EX1002 at ¶ 143. This disclosure of compounds in Dvořáková overlaps with the compounds claimed in claim 1 of the ’201 patent, as shown in the table below:

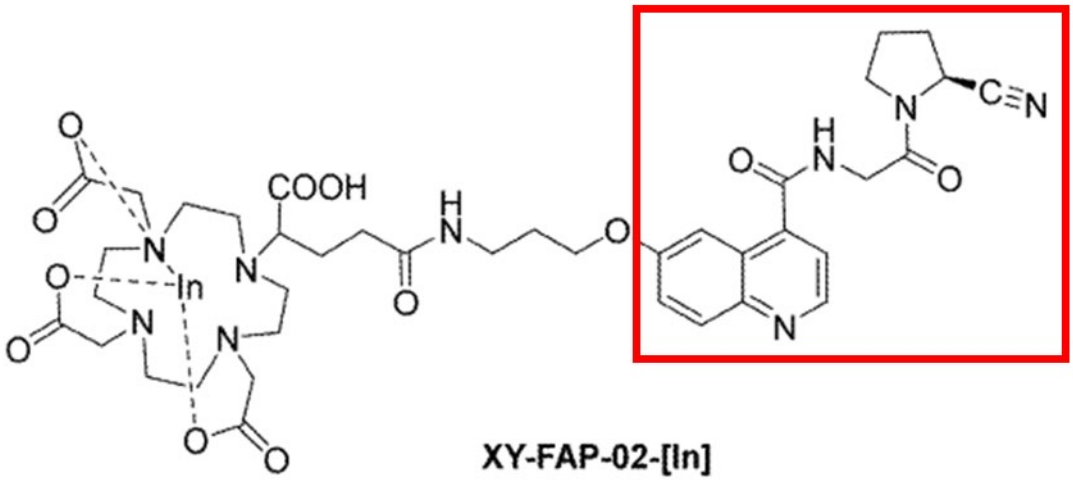
Dvořáková	U.S. Patent No. 11,938,201
 **1** (n = 15, R = F) **2** (n = 5, R = F) **3** (n = 15, R = H) **4** (n = 5, R = H)	
OVERLAPPING DEFINITIONS	
1 R = F **2** R = F **3** R = H **4** R = H	R_{1x} and R_{2x} are each independently selected from the group consisting of H and halogen [F]
—CN	R_{3x} is —CN
H	R_{4x} is H;
H	R_{5x}, R_{6x}, and R_{7x} are each H;
0	v is 0;
Quinolinyl ring	 represents a quinolinyl ring;

EX1002 at ¶ 144.

Furthermore, the only two examples in the '201 patent are XY-FAP-01 and XY-FAP-02-[In] (shown below with emphasis on the targeting moiety for FAP-α, A), which Patent Owner admits are covered by claim 1. EX1001 at Fig. 1B, Fig. 1C; EX1004 at 1214 (Office Action Response); EX1002 at ¶ 145.



XY-FAP-01



XY-FAP-02-[In]

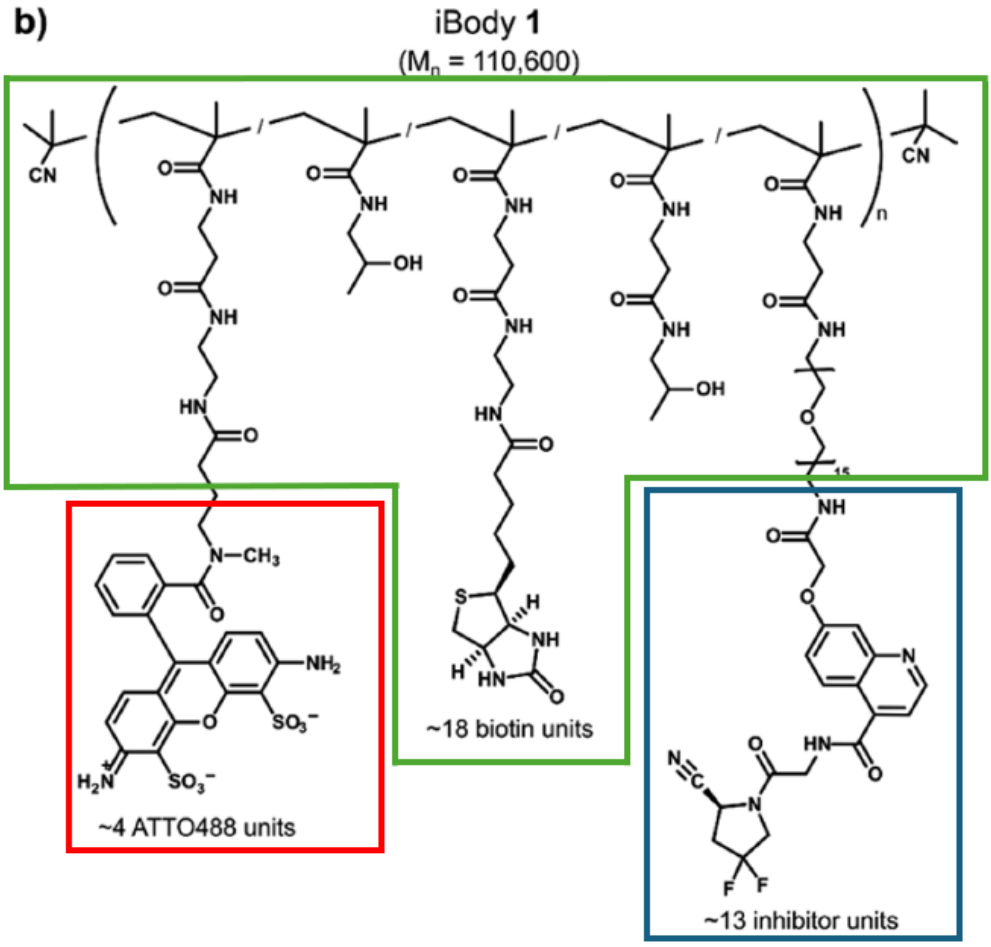
XY-FAP-01 and XY-FAP-02-[In] both have the same targeting moiety for FAP-α, A, as Dvořáková's Compounds 3 and 4 (R = H). EX1002 at ¶ 145.

Accordingly, Dvořáková discloses the A moiety as recited in claim 1. EX1002 at ¶ 146.

c. [1c] "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"

The claimed B moiety is limited to "any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy." EX1001 at Certificate of Correction, claim 1.

Dvořáková discloses attaching its Compounds 1-4 to an ATTO488 dye via a HPMA copolymer with the following structure:



EX1008 at Figure 2b (emphasis added to the ATTO488 dye in red, the FAP inhibitor in blue, and the linker in green); EX1002 at ¶ 148.

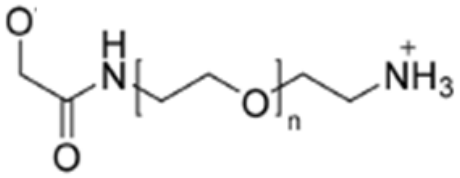
ATTO488 dye is a fluorophore that contains a rhodamine-based structure and is known to be "highly suitable for single-molecule detection applications and high-resolution microscopy." EX1011; EX1002 at ¶ 149. A POSA would have recognized ATTO488 dye as an "optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy." *See* EX1001 at 25:19-

20 ("In some embodiments, B comprises an optical dye, e.g., in particular embodiments, a fluorescent dye."); EX1002 at ¶ 149. Accordingly, Dvořáková discloses the B moiety as recited in claim 1. EX1002 at ¶ 149.

Pomper also discloses inhibiting compounds used to treat cancer coupled with a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. EX1006 at ¶¶ 31-34, 279; EX1002 at ¶ 150. Thus, Pomper also discloses the B moiety as recited in claim 1. EX1002 at ¶ 150.

d. [1d] "L is a linker having bi-functionalization adapted to form a chemical bond with B and A"

Claim 1 only limits L to "a linker having bi-functionalization adapted to form a chemical bond with B and A". EX1001 at Certificate of Correction, claim 1. Thus, there is no explicit limitation to the structure or atoms of the linker. EX1002 at ¶ 151. The structure of Compounds 1-4 of Dvořáková, shown above, includes:



EX1008 at 8388; EX1002 at ¶ 151.

Dvořáková discloses using this linker to form a chemical bond between a targeting moiety for FAP-α and the optical functional group. EX1002 at ¶ 152. Therefore, this linker falls within the scope of L as recited in claim 1. EX1002 at ¶ 152. In fact, Dvořáková describes its linker as a PEG linker, which, as detailed in

Section VII.E.2 below, is described as a suitable linker in the '201 patent specification. EX1001 at 17:50-54 (citing EX1006 at ¶ 129 ("In some embodiments, the fluorescent dye moiety includes a poly(ethyleneglycol) linker.")); EX1002 at ¶ 152. Thus, Dvořáková discloses L, as L is recited in claim 1. EX1002 at ¶ 152.

Pomper also discloses suitable linkers that can be used to couple the inhibiting moiety and the optical or radiolabeled moiety. EX1002 at ¶ 153. Pomper explains, "[f]or instance linking groups having alkyl, aryl, combination of alkyl and aryl, or alkyl and aryl groups having heteroatoms" are suitable for joining an inhibitor moiety to an optical or radiolabeled functional group. EX1006 at ¶¶ 0102, 0129; EX1002 at ¶ 153.

e. [1e] "or a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof"

In considering whether a prior art reference renders a claim obvious, courts do not consider whether that reference includes optional elements of the claim, like the optional claim element 1e. *In re Johnston*, 435 F.3d 1381, 1384 (Fed Cir. 2006) ("[O]ptional elements do not narrow the claim because they can always be omitted.").

Claim 1 would have been obvious to a POSA at the time of invention over the combination of Dvořáková and Pomper. EX1002 at ¶ 154.

2. Claim 2

Claim 2 further specifies that B "is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy." EX1001 at Claim 2. As discussed above with respect to claim 1, Dvořáková discloses compounds featuring optical functional groups while Pomper discloses optical functional groups and radiolabeled functional groups suitable for PET imaging, SPECT imaging, or radiotherapy. EX1002 at ¶ 155. Therefore, claim 2 would have been obvious to a POSA in view of the combination of Dvořáková and Pomper. EX1002 at ¶ 155.

3. Claim 3

Claim 3 of the '201 patent is identical to claim 1 except that it includes the additional language "consisting essentially of" components B-L-A in the preamble. The semi-closed term "consisting essentially of" indicates that a claim is limited to the components specified therein "and those that do not *materially* affect the *basic* and *novel* characteristic(s)" of the claimed invention. *Application of Herz*, 537 F.2d 549, 551-52 (C.C.P.A. 1976) (quoting *Application of Janakirama-Rao*, 317 F.2d 951, 954 (C.C.P.A 1963)) (emphasis in original).

As discussed above with respect to claim 1, a POSA would have been motivated with a reasonable expectation of success to combine the teachings of Dvořáková and Pomper to arrive at the subject matter of claim 1. EX1002 at ¶ 157.

Nothing in these references would require the inclusion of a component that would materially affect the basic characteristics of this combination. EX1002 at ¶ 157. Thus, claim 3 would also have been obvious over the combination of Dvořáková and Pomper. EX1002 at ¶ 157.

C. Ground III: The Claims Lack Enablement Under § 112

The enablement requirement asks whether "the specification teach[es] those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). "The specification must contain sufficient disclosure to enable an ordinarily skilled artisan to make and use the entire scope of the claimed invention." *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1345 (Fed. Cir. 2019) (quoting *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012)).

"If a patent claims an entire class of . . . compositions of matter, the patent's specification must enable a person skilled in the art to make and use the ***entire*** class," i.e., "the ***full scope*** of the invention." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610 (2023) (emphases added). So, the "more one claims, the more one must enable." *Amgen*, 598 U.S. at 610. "It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1159 (Fed. Cir. 2019). As the Supreme Court recently affirmed in *Amgen v. Sanofi*, "the

specification must enable the full scope of the invention as defined by its claims," allowing for "a reasonable amount of experimentation." *Amgen*, 598 U.S. at 610-12. In other words, "the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *MagSil*, 687 F.3d at 1380 (internal quotation marks and citation omitted).

Although not required, enablement may be assessed using the *Wands* factors articulated by the Federal Circuit, which consider: "(1) the quantity of experimentation necessary; (2) how routine any necessary experimentation is in the relevant field; (3) whether the patent discloses specific working examples of the claimed invention; (4) the amount of guidance presented in the patent; (5) the nature and predictability of the field; (6) the level of ordinary skill; and (7) the scope of the claimed invention." *Idenix*, 941 F.3d at 1156 (citing *Wands*, 858 F.2d at 737). Where the scope of the claims is large, there are few working examples disclosed in the patent, and the only guidance to practice "the full scope of the invention [is] to use trial and error to narrow down the potential candidates to those satisfying the claims' functional limitations—the asserted claims are not enabled." *Baxalta Inc. v. Genentech, Inc*., 579 F. Supp. 3d 595, 615-16 (D. Del. 2022) (Dyk, T., sitting by designation) *aff'd* 81 F.4th 1362 (Fed. Cir. 2023).

The claims of the '201 patent are a textbook example of claims that lack enablement under the controlling precedent articulated by the Supreme Court in *Amgen*. An analysis of the common disclosure under the Federal Circuit's framework for assessing undue experimentation using the *Wands* factors also warrants the same conclusion. *See* EX1002 at ¶¶ 158-76.

1. Supreme Court Precedent Confirms That the '201 Patent Does Not Enable the Full Scope of the Asserted Claims

In *Amgen*, the patents claimed all antibodies that (1) bind to specific amino acid residues on a protein known as PCSK9; and (2) block PCSK9 from binding to LDL receptors. *Amgen*, 598 U.S. at 602. The full scope of the claims covered potentially millions of antibodies, but the specification only disclosed the amino acid sequences of twenty-six antibodies that performed the two claimed functions. *Id*. at 612-13. To make and use the undisclosed claimed antibodies, POSAs could either follow the "roadmap" disclosed in the patent or employ a technique known as "conservative substitution." *Id*. at 603. The roadmap directed POSAs to:

> (1) generate a range of antibodies in the lab; (2) test those antibodies to determine whether any bind to PCSK9; (3) test those antibodies that bind to PCSK9 to determine whether any bind to the sweet spot as described in the claims; and (4) test those antibodies that bind to the sweet spot as described in the claims to determine whether any block PCSK9 from binding to LDL receptors.

Id. The conservative substitution technique directed POSAs to: "(1) start with an antibody known to perform the described functions; (2) replace select amino acids in the antibody with other amino acids known to have similar properties; and (3) test the resulting antibody to see if it also performs the described functions." *Id*.

The Supreme Court held these methods "amount to little more than two research assignments" and fail to enable the full scope of the claims. *Id.* at 612-15. The Court reasoned that Amgen's roadmap "merely describes step-by-step Amgen's own trial-and-error method for finding functional antibodies—calling on scientists to create a wide range of candidate antibodies and then screen each to see" which practice the claims. *Id*. at 614. Similarly, the conservative substitution technique simply "requires scientists to make substitutions to the amino acid sequences of antibodies known to work and then test the resulting antibodies to see if they do too—an uncertain prospect given the state of the art." *Id*. Such approaches leave POSAs to "engage in 'painstaking experimentation' to see what works," which "is not enablement." *Id.* (quoting *Consol. Elec. Light Co. v. McKeesport Light Co.*, 159 U.S. 465, 475 (1895)).

The facts of this case are analogous to those in *Amgen.* Like *Amgen*, the claims of the '201 patent contain two functional limitations: (1) B is "any optical or radiolabeled ***functional group suitable for*** optical imaging, positron-emission tomography (PET) imaging, single-photon emission computer tomography

(SPECT) imaging or radiotherapy; and (2) L is "a linker having ***bifunctionalization adapted to form*** a chemical bond with B and A." EX1001, Certificate of Correction, claims 1, 3 (emphasis added).

These limitations encompass a virtually infinite number of potential candidate structures, EX1002 at ¶¶ 160-63, but the specification provides only two examples falling within the scope of the claims: XY-FAP-01 and XY-FAP-02. *See* EX1001 at 31:30-65. Even less detailed than the road map provided in *Amgen*, the '201 patent specification fails to direct a POSA to a method for determining which B moieties are "suitable" and which linkers have "bifunctionalization adapted to form a chemical bond with B and A." EX1002 at ¶ 167. In fact, the '201 patent merely provides a non-exhaustive and structurally diverse list of examples, *see* EX1001 at 16:10-17:40, 17:60-32:65, that requires a POSA to engage in an iterative, trial-and-error process to discover what will work and what will not. EX1002 at ¶ 171. This plainly constitutes lack of enablement under *Amgen*. *Amgen*, 598 U.S. at 613-14.

Moreover, it cannot be disputed that the '201 patent contains no disclosures—such as "a quality common to every functional embodiment"—that would allow a POSA to predict which structural features will perform the claimed functions. *See id*. at 614. The '201 patent does not disclose any common structural (or other) aspects delineating which features will result in an optical or radiolabeled functional group "suitable for optical imaging, positron-emission tomography (PET) imaging,

single-photon emission computer tomography (SPECT) imaging or radiotherapy" or which linkers will have "bifunctionalization adapted to form a chemical bond with B and A." EX1002 at ¶ 167. The '201 patent does not even describe why or how the two disclosed examples—XY-FAP-01 and XY-FAP-02—perform the claimed functions, or why other compounds do not. *Id. Amgen* makes clear that this lack of detail and instruction fails to enable the broad functional genus claims at issue here. *Id*. at 614 ("[T]he . . . problem we see [is that] Amgen offers persons skilled in the art little more than advice to engage in 'trial and error.'"); *Baxalta Inc. v. Genentech, Inc.*, 81 4th 1362, 1367 (Fed Cir. 2023) ("Under *Amgen*, such random trial-and-error discovery, without more, constitutes unreasonable experimentation that falls outside the bounds required by § 112(a).").

Amgen accordingly dictates cancellation of claims 1-3 of the '201 patent.

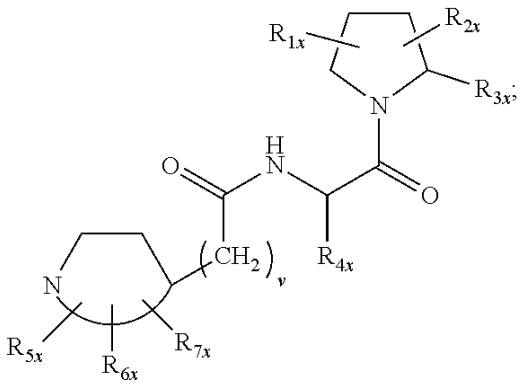
2. The Claims Also Lack Enablement Under the Wands Factors

Application of the *Wands* factors is optional in an enablement analysis, particularly when the facts are so analogous to those of *Amgen*, which did not itself apply the *Wands* factors in its analysis. *Baxalta*, 81 4th at 1367; *see also id.* at 1367 n.4 ("We see no meaningful difference between Wands' 'undue experimentation' and *Amgen*'s 'unreasonable experimentation' standards."). Nevertheless, application of the *Wands* factors to the evidence as supported by Dr. Martin's Declaration further

demonstrates by a preponderance of the evidence that claims 1-3 of the '201 patent are unpatentable as lacking enablement and should be canceled. EX1002 at ¶¶ 113-29.

a. The "Scope of the Claimed Invention" (Factor 7)

Claims 1-3 encompass a vast genus of compounds. EX1001, Certificate of Correction, claims 1-3. The claimed B moiety and L linker are defined using broad functional language that permits a virtually infinite number of potential candidate compounds that must be made and tested to determine whether they fall within the scope of the claims. EX1002 at ¶ 160. Additionally, the A moiety is defined in claims 1-3 as having the following structure:



wherein:

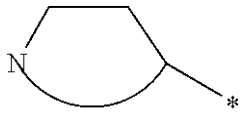
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, —O—C_{1-6} alkyl, and —S—C_{1-6} alkyl;

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

R_{4x} is H;

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

v is 0; and



represents a quinolinyl ring. EX1001, Certificate of Correction, claim 1; EX1002 at ¶ 161.

As discussed above in Section VI.B, R_{3x} may be, among other options "—C(O)alkyl." The '201 patent explains that when an "alkyl" group is intended to be limited to a chain of a certain length, it is so designated using certain nomenclature. EX1002 at ¶ 162. For example, a C_1-C_{10} alkyl represents an alkyl chain having between one and ten carbons. EX1001 at 39:43-50; EX1002 at ¶ 162. A POSA would therefore understand that the use of "alkyl" in the claims without specifying the minimum and maximum number of carbons in this manner is intended to refer to an alkyl group that can be of any length whatsoever. EX1002 at ¶ 162. Similarly, the definitions provided in the '201 patent explain that the term "aryl" is "an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such

as from 1 to 3 rings), which are fused together or linked covalently." EX1001 at 42:64-67; EX1002 at ¶ 162. Thus, without a number of carbon atoms or rings designated, the —C(O)aryl-, —C═C—C(O)aryl, and —C═C—$S(O)_2$aryl groups also have a virtually infinite number of possible carbon atoms. EX1002 at ¶ 162.

Further broadening the scope of this term, the '201 patent's specification explains that terms like "alkyl" and "aryl" are intended to encompass both substituted and unsubstituted forms. EX1001 at 44:25-29. As the '201 patent explains with respect to the term "alkyl," this means that one or more atoms or functional groups of the alkyl group may be replaced with another atom or functional group, "including for example alkyl, substituted alkyl, halogen, aryl, substituted aryl, alkoxyl, hydroxyl, nitro, amino, alkylamino, dialkylamino, sulfate, and mercapto." *Id.* at 40:20-26. A POSA would further understand from this permissive, non-limiting language that each substituted form can itself be further substituted, potentially infinitely. EX1002 at ¶ 163.

Further broadening the scope of the genus, the claims additionally include each "stereoisomer, tautomer, racemate, salt, hydrate, or solvate, thereof." EX1001 at Certificate of Correction, claims 1, 3.

As Dr. Martin explains, the specification does not specifically describe or otherwise teach a POSA how to make or use the vast number of compounds falling within the scope of this genus. EX1002 at ¶ 158.

b. The "Nature and Predictability of the Invention" (Factor 5)

Applicant readily conceded during prosecution that this is a "highly unpredictable" art, "as it involves optimizing numerous parameters." EX1004 at 1201 (Pomper Declaration). ("Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound."); EX1002 at ¶ 171. Moreover, the '201 patent does not describe which features—structural or otherwise—would cause a compound to perform the two claimed functions. EX1002 at ¶ 171. Instead, the '201 patent calls for a make-and-screen approach, which merely creates an invitation for further iterative research. *Id*. Make-and-screen strategies fall so far from the requisite teaching that they have been repeatedly held to require undue experimentation. *Idenix*, 941 F.3d at 1153, 1162-63; *Enzo Life Scis.*, 928 F.3d at 1349; *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385-86 (Fed Cir. 2013).

c. The "Level of Ordinary Skill in the Art" (Factor 6) the "Quantity of Experimentation Needed" (Factor 1), and "How Routine Any Necessary Experimentation Is in the Relevant Field" (Factor 2)

Because the '201 patent's claims relate to a genus of chemical compounds, a POSA would have a Bachelor's degree in organic chemistry or a related field such as medicinal chemistry and two to five years of experience employing organic chemistry as a tool for the development of molecules with targeted biological

activity. EX1002 at ¶ 169. A POSA could also include individuals with a Master's degree or a Ph.D. in chemistry or a related field with comparatively less experience. *Id*. A POSA would have an understanding of processes employed for synthesis and evaluation of imaging and radiotherapeutics agents that selectively target a specific protein and would be able to evaluate published literature and patents to ascertain those features of a molecule that contribute to its affinity and selectivity for a particular drug target. *Id*.

As discussed above in Section VII.C.1 and as explained by Dr. Martin, the functional limitations recited in the challenged claims would require a POSA to perform undue experimentation to determine whether the claims are satisfied. *Id.* at ¶¶ 170-74. The '201 patent provides only two working examples falling within the scope of the claims, and does not provide any additional information to the art about how to determine which optical or radiolabeled functional groups are "suitable for" optical imaging, positron-emission tomography (PET) imaging, single-photon emission computer tomography (SPECT) imaging or radiotherapy, or which linkers have "bifunctionalization adapted to form a chemical bond with B and A." *Id.* at ¶¶ 171-73.

d. The "Specific Working Examples" (Factor 3) and "Amount of Guidance" Disclosed (Factor 4)

The '201 patent discloses only two examples[1] within the vast genus of compounds encompassed by the challenged claims, and the '201 patent does not even describe how to determine if a B moiety or linker is "suitable" for the claimed function. *Id.* at ¶¶ 165-68. As confirmed by Dr. Martin, the '201 patent does not provide sufficient direction or working examples to enable a POSA to make the full scope of the claimed genus. *Id.*

e. Weighing the *Wands* factors shows no enablement of claims 1-3 of the '201 patent

The amount of testing and experimentation required to enable a skilled artisan to practice the full scope of the claimed genus would have been far more than routine—it would have been undue. EX1002 at ¶¶ 175-76. *Wands*, 858 F.2d at 737.

Weighing the *Wands* factors supports finding a lack of enablement for the full scope of the challenged claims. The breadth of the challenged claims includes an A

[1] Although Patent Owner provided during prosecution additional examples of compounds falling within the scope of the claims and described parameters allegedly important for developing a FAP imaging agent (EX1004 at 1203-05 (Pomper Declaration), this post-filing information cannot be relied on by Patent Owner to show the state of the art or to fill in disclosure gaps under § 112. *In re Wright*, 999 F.2d 1557, 1562-63 (Fed. Cir. 1992) (refusing to consider evidence of inventor's post-filing work to support enablement because "all of these developments occurred after the effective filing date of [applicant]'s application and are of no significance regarding what one skilled in the art believed as of that date); *Application of Glass*, 492 F.2d 1228, 1232 (C.C.P.A. 1974) ("[W]e now rule that application sufficiency under § 112, first paragraph, must be judged as of its filing date.").

moiety that encompasses a virtually unlimited number of possible alkyl and aryl substituents, which can themselves be further substituted by a similarly countless number of possible alkyl and aryl substituents and so on. EX1002 at ¶¶ 175-76. The claims also include a B moiety and a linker that are defined using broad functional language that is impermissible under *Amgen* and results in nothing more than an unfathomably large exercise in making and testing. Thus, the claims encompass a virtually infinite genus. *Id*.

To determine if the full scope of this vast genus is enabled, a POSA would look to the direction provided by the inventors in the patent's specification. *Storer v. Clark*, 860 F.3d 1340, 1350 (Fed. Cir. 2017) ("[F]or new chemical compounds the specification must provide sufficient guidance that undue experimentation is not required to obtain the new compounds."); *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 1000 (Fed. Cir. 2008) ("An enablement analysis begins with the disclosure in the specification."). Here, the '201 patent specification provides very little, if any, guidance. There are only two working examples and the '201 patent does not describe which features—structural or otherwise—would cause a compound to perform the two claimed functions. EX1001 at Examples 1.1-1.2; *Daiichi Sankyo Co., Ltd. v. Alethia Biotherapeutics, Inc*., IPR2015-00291, Paper 75, at *10 (P.T.A.B. June 14, 2014) ("The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art

as well as the predictability in the art."); *Wyeth*, 720 F.3d at 1386 (practicing full scope of claims requires undue experimentation where, inter alia, "[s]ynthesizing candidate compounds derived from sirolimus could, itself, require a complicated and lengthy series of experiments in synthetic organic chemistry").

As explained by Dr. Martin, given the breadth of the claims, the lack of teachings in the specification and the prior art, and the inventors' concession during prosecution discussed above, the quantity of experimentation needed to make the full scope of the claimed genus would have been undue. EX1002 at ¶¶ 158-76; *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 939-41 (Fed. Cir. 2010); *see also Atlas Powder Co. v. E.I. Du Pont de Nemours*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984) ("[I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid."). As such, each of the *Wands* factors weighs toward a finding of lack of enablement for the challenged claims of the '201 patent. EX1002 at ¶¶ 158-76.

Analysis of each of the *Wands* factors compels a finding of no enablement for challenged claims 1-3. So does the Supreme Court's opinion in *Amgen* and the Federal Circuit's opinion *Baxalta*. To be sure, other Federal Circuit precedent like that of *ALZA* warrants a similar finding of non-enablement.

In *ALZA*, the claims recited methods for treating Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD) with a dosage form comprising methylphenidate and having an ascending release rate. *ALZA*, 603 F.3d at 936-37. After agreeing that the scope of the claims encompassed both osmotic and non-osmotic dosage forms, the parties disputed enablement of the encompassed non-osmotic dosage forms (they agreed that osmotic dosage forms were enabled). *Id.* at 938-39. The Court agreed that evidence with respect to three *Wands* factors in particular—guidance provided by the specification, presence or absence of working examples, and breadth of the claims—supported finding the asserted claims non-enabled. *Id.* at 939-40.

The patent specification at issue in *ALZA* contained only a generic disclosure of approaches for achieving sustained release dosage forms. *Id.* at 941. The Federal Circuit found that it failed to disclose "any specific starting material or of any of the condition[s] under which a process can be carried out." *Id*. Instead, the Court found that the asserted patent provided "only a starting point, a direction for further research." *Id*. Based on the absence of direction or working examples, the Court found that it would have required undue experimentation to practice the full scope of the asserted claims. *Id.* at 942-43.

Similar to the patent in *ALZA*, the '201 patent disclosure fails to provide sufficient guidance or working examples to permit a POSA to delineate the

boundaries of the broadly claimed genus or compounds or how to practice the full scope of the claims. EX1002 at ¶ 176; *ALZA*, 603 F.3d at 941 ("ALZA was required to provide an adequate enabling disclosure in the specification; it cannot simply rely on the knowledge of a person of ordinary skill to serve as a substitute for the missing information in the specification.").

Thus, the '201 patent does not contain "such full, clear, concise, and exact terms as to enable any person skilled in the art" to make the full scope of the claims. 35 U.S.C. §112(a). As such, the '201 patent specification fails to enable the full scope of claims 1-3.

D. Ground IV: The Claims Lack Written Description

The written description analysis focuses on the four corners of the patent disclosure. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). Under 35 U.S.C. § 112, the test for adequate written description is whether the disclosure in a specification reasonably conveys to those skilled in the art that the inventor had "possession" of the claimed subject matter as of the asserted filing date. *Id.* at 1349. If the claims define a genus, the written description must "show that one has truly invented a genus . . . ," "[o]therwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

Where the claims recite a broad genus defined by functional language, *Ariad* requires a patentee to disclose "a representative number of species falling within the scope of the genus or structural features common to the members of the genus such that one of skill in the art can 'visualize or recognize' the members of the genus." *Ariad*, 598 F.3d at 1349 (citation omitted). Generic language, including statements in the specification discussing general concepts of functional languages, does not satisfy the written description requirement. This applies even when such language appears *ipsis verbis* in a specification. *Ariad*, 598 F.3d at 1349; *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

"[A] genus can be sufficiently disclosed by either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus." *Idenix*, 941 F.3d at 1164. "One factor in considering [written description] is how large a genus is involved and what species of the genus are described in the patent . . . [I]f the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession, of the genus." *AbbVie*, 759 F.3d at 1299-1300.

A disclosure that fails to "provide sufficient blaze marks to direct a POSA to the specific subset" of a genus with the claimed function or characteristic does not satisfy § 112(a). *Idenix*, 941 F.3d at 1164. And "merely drawing a fence around the

outer limits of a purported genus" is insufficient. *Ariad*, 598 F.3d at 1350-54. Instead, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus." *Id.* at 1349.

1. The '201 Patent Fails to Provide Adequate Blaze Marks to the Claimed Genus

Comparing the challenged patent claims to the '201 patent disclosure, it becomes readily apparent that Patent Owner did not have possession of the claimed invention by the filing date. EX1002 at ¶ 177. A patent application's undifferentiated description cannot provide adequate written description support if it lacks "blaze marks" to guide a reader "through the forest of the specification." *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1349 (Fed. Cir. 2013) (quoting *In re Ruschig*, 379 F.2d 990, 994-95 (C.C.P.A. 1967)). Instead, to satisfy the written description requirement, the application must describe the claimed subject matter "as an integrated whole rather than as a collection of independent limitations." *Novozymes*, 723 F.3d at 1349. The '201 patent falls far short of meeting this requirement and therefore fails to adequately describe what is claimed.

The '201 patent provides at best "only generalized guidance listing several variables that might, in some combination, lead to a useful result." *Novozymes*, 723

F.3d at 1346. As discussed above in Section VII.C.1 and as explained by Dr. Martin, the '201 patent specifies that the B moiety should be "suitable for" optical imaging, positron-emission tomography (PET) imaging, single-photon emission computer tomography (SPECT) imaging or radiotherapy, and that L should be a linker which has "bifunctionalization adapted to form a chemical bond with B and A," but the '201 patent provides only two working examples falling within the scope of the claims, and does not provide any additional guidance permitting a skilled artisan to determine what characteristics are most likely to meet these functional limitations. EX1002 at ¶ 178. Even if the '201 patent on its face appears to provide "formal textual support," i.e., the actual words for the claim limitations, under *Novozymes* formal textual support is not enough. *Novozymes*, 723 F.3d at 1349; *see also Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011); *Enzo Biochem., Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 968 (Fed. Cir. 2002). *Novozymes* dismissed "formal textual support" as lacking where the disclosure fails to lead a POSA "toward such species among a slew of competing possibilities." 723 F.3d at 1349. The Board should do the same here.

2. The '201 Patent Fails to Disclose Sufficient Species Within the Broadly Claimed Genus

For genus claims such as those challenged here, "an adequate written description . . . requires more than a generic statement of an invention's boundaries."

Ariad, 598 F.3d at 1349. Instead, the written description requires a representative number of species that fall within the scope of the genus. *Id*. at 1350.

As discussed above in Sections II and VII.C, the ’201 patent claims a structurally and functionally huge, if not unlimited, genus of compounds. But the ’201 patent does not contain a proportionally broad written description. EX1002 at ¶ 178. The ’201 patent contains only two working examples falling within the scope of the claims. EX1001 at Examples 1.1-1.2. The ’201 patent contains no disclosures that would allow a POSA to determine which structural (or other) features will result in an optical or radiolabeled functional group “suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computer tomography (SPECT) imaging or radiotherapy” or which linkers will have “bifunctionalization adapted to form a chemical bond with B and A.” EX1002 at ¶ 178. The ’201 patent contains only two working examples—XY-FAP-01 and XY-FAP-02—and does not even describe why or how these two compounds perform the claimed functions, or why other compounds do not. *Id.*

For at least these reasons, claims 1-3 of the ’201 patent lack adequate written description and accordingly should be canceled.

E. Ground V: The Phrase “Low Molecular Weight” Is Indefinite

Under § 112, a patent specification “shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the

inventor or a joint inventor regards as the invention." 35 U.S.C. § 112(b). To meet these requirements, "a patent's claims, viewed in light of the specification and prosecution history, [must] inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc*., 572 U.S. 898, 910 (2014). A claim is indefinite when it contains words or phrases whose meaning is "unclear in describing and defining the claimed invention." *In re Packard*, 751 F.3d 1307, 1311 (Fed. Cir. 2014). Moreover, "the claims, when read in light of the specification and the prosecution history, must provide objective boundaries for those of skill in the art." *Interval Licensing*, 766 F.3d at 1371. Indefiniteness may arise, for example, "if the claim language might mean several different things and no informed and confident choice is available among the contending definitions." *Id.* (citing *Nautilus*, 572 U.S. at 911 & n.8) (quotation marks omitted). The Board applies the *Nautilus* standard in AIA post-grant proceedings, which requires that a patent claim, read in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty.[2]

[2] *See* 2 Horwitz on Patent Litigation § 10.11[f], *PTO Memorandum: Adoption of Nautilus Approach To Indefiniteness Under 35 U.S.C. § 112 In AIA Post-grant Proceedings* ("The office now clarifies that the Board shall follow Nautilus in AIA post-grant proceedings.").

In addition, "[w]hen a claim term 'depends solely on the unrestrained, subjective opinion of a particular individual practicing the invention,' without sufficient guidance in the specification to provide objective direction to one of skill in the art, the term is indefinite." *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1260 (Fed. Cir. 2014) (quoting *Datamize, LLC v, Plumtree Software, Inc,* 417 F.3d 1342, 1350 (Fed. Cir. 2005). "A claim may, for example, prove indefinite if its language 'might mean several different things' and the patent itself identifies 'no informed and confident choice . . . among the contending definitions.'" *Otsuka Pharm. Co. v. Zydus Pharms. USA,* 151 F. Supp. 3d 525, 545 (D.N.J. 2015) (quoting *Nautilus*, 572 U.S. at 911 n.8).

1. The Claim Phrase "Low Molecular Weight" Fails to Provide Reasonable Certainty

The phrase "low molecular weight" recited in the preamble of independent claims 1 and 3 of the '201 patent is not clearly defined in the patent specification and Patent Owner's attempt to define the phrase "low molecular weight" in the prosecution history creates even more uncertainty. EX1002 at ¶ 180. This phrase is therefore closely analogous to the phrase "molecular weight" that was examined and found indefinite in *Teva Pharms. USA, Inc. v. Sandoz, Inc.,* 789 F.3d 1335, 1341-45 (Fed. Cir. 2015). The same result of indefiniteness is warranted here.

The ’201 patent uses the phrase “low molecular weight” only three times throughout the specification. EX1002 at ¶ 181. The first and second instances are in the “Background” section, stating that

> ***Low molecular weight (LMW)*** agents demonstrate faster pharmacokinetics and a higher specific signal [than anti-FAP antibodies] 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, however, no ***LMW*** ligand has been reported with ideal properties for nuclear imaging of FAP-α.

EX1001 at 1:60-67 (emphasis added). The final mention of the phrase “low molecular weight” states that

> Accordingly, in some embodiments, the presently disclosed subject matter provides potent and selective ***low-molecular-weight (LMW)*** ligands of FAP-α, i.e., an FAP-α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable in vivo optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α.

Id. at 7:44-54 (emphasis added). This provides no additional insight as to a range or definition of “low molecular weight” in the context of the ’201 patent. EX1002 at ¶ 182.

The phrase “low molecular weight” was further discussed during prosecution. EX1002 at ¶ 186; EX1004 at 1214 (Office Action Response), 1197 (Pomper

Declaration), 1272 (Supplemental Amendment). Patent Owner pointed to the discussion of "polymer" in the '201 patent specification at 48:18-19 as "a molecule of high relative molecule mass," stating that this "distinguishes" "low molecular weight compounds" from "polymers" and thus polymers would not be included in the claimed compounds. EX1002 at ¶ 186; EX1004 at 1214 (Office Action Response), 1197 (Pomper Declaration), 1272 (Supplemental Amendment).

In response to a 35 U.S.C. § 102(a)(1) rejection over Dvořáková, Patent Owner attempted to distinguish that reference by asserting that Dvořáková allegedly discloses a compound having a polymer and a high molecular weight of 149,900 g/mol compared to the purportedly "low molecular weight" of the '201 patent's two examples: XY-FAP-02 (840 g/mol) and XY-FAP-01 (1,367 g/mol). EX1004 at 1214 (Office Action Response), 1197 (Pomper Declaration), 1272 (Supplemental Amendment).

Patent Owner continued:

> The term of "low molecular weight" is well accepted in the chemical arts, and its meaning is clear to one of ordinary skill in the art. In particular, when used in the scientific references in the chemical arts, one of ordinary skill in the art would recognize that low molecular weight compounds would have a molecular weight of typically from ***about 50 Daltons to about 1,500 Daltons***. *See e.g.,* K Beebe et al., Clin Transl Sci. 2014 Feb; 7(1): 74-81 ("Metabolomics is often described as a systematic study of the low molecular weight (***approximately 50-1,500 Da***) metabolites (chemicals) within a given sample"); A.

> Ferreira et al., J. Agric. Food Chem. 2014, 62, 6784-6793 ("Metabolites are a group of low molecular weight substances (***50-1500 Da***) that includes amino acids, fatty acids . . ."); C. Llewellyn et al., Progress in Oceanography, Volume 137, p. 421-433 (Metabolomics involves the non-targeted unbiased analysis of large suites of low molecular weight organic molecules or metabolites (***typically 50-1500 Da***). . .); *see also* https ://www .ebi.ac. uk/training/ online/ courses/metabolomics-introduction/w hat-is/smallmolecules/ ("A small molecule (or metabolite) is a low molecular weight organic compound, typically involved in a biological process as a substrate or product. Metabolomics usually studies small molecules within a mass range of ***50 - 1500 daltons (Da).***")

EX1004 at 1215 (Office Action Response); *see also id.* at 1198 (Pomper Declaration), 1273 (Supplemental Amendment).

Thus, Patent Owner provides a non-limiting "typical[]" general range of about 50 to about 1500 Da for the term "low molecular weight." However, as Dr. Martin explains, the term "low molecular weight" would be relative to the field of study and the type of experiments to be performed. EX1002 at ¶ 184. Each of the references provided in Patent Owner's explanation are related to the field of metabolomics or the scientific study of metabolites. *Id*. Yet, there is no mention of metabolomics anywhere in the '201 patent specification. *Id*. Furthermore, the '201 patent specification specifically states that "the injected compound is ***not metabolized*** by the body prior to excretion." *Id.*; EX1001 at 35:66-67 (emphasis added). Therefore, these references are unrelated to the '201 patent, which discusses imaging and

radiotherapeutics agents, and a POSA would not define "low molecular weight" in the context of the '201 patent relative to the field of metabolomics. EX1002 at ¶ 184. Moreover, to the extent Patent Owner's assertion of a "typical[]" general range of "about 50 Daltons to about 1500 Daltons" is found to constitute a definition of "low molecular weight," it must also be considered a concession that the claims lack enablement and written description support because there is no support in the specification for this range.

In fact, the '201 patent specification itself discloses several examples of moiety B that have a molecular weight greater than 1,500 Da by themselves. *Id.* at ¶ 185. For example, embodiments of moiety B are described as including fluorescent dyes such as VivoTag-680 (now named IVISense 680) (molecular weight 1,856 g/mol), AlexaFluor790 (molecular weight about 1,750 g/mol), and IRDye 700DX (molecular weight about 1,954 g/mol). EX1001 at 25:19-25, 26:19-24; EX1012; EX1013; EX1014. EX1002 at ¶ 185. If any of these fluorescent dyes are including as moiety B in the claimed compounds, the molecular weight of the compound would well exceed the "typical" range of about 50 to about 1,500 Da, especially when combined with the FAP-α targeting moiety, A, and the linker, L, which would each contribute additional weight to the combined molecule. EX1002 at ¶ 185. These contradictory disclosures further demonstrate the ambiguity and indefiniteness of the term "low molecular weight." *Id*.

2. The Phrase "Molecular Weight" Was Found Indefinite in *Teva v. Sandoz*

Patent Owner concedes—indeed touts—that the purported "low molecular weight" is the key to its claimed invention. *Id.* at ¶ 186; EX1004 at 1214 (Office Action Response), 1197 (Pomper Declaration), 1272 (Supplemental Amendment). The '201 patent prosecution history attempts to exclude "high relative molecule mass" polymers from the claimed compounds. EX1002 at ¶ 186; EX1001 at 48:18-21; EX1004 at 1214 (Office Action Response), 1197 (Pomper Declaration), 1272 (Supplemental Amendment). Yet the "high relative molecule mass" of a polymer is not directly described as "relative" to the allegedly "low molecular weight" compound as claimed. EX1002 at ¶ 186.

In fact, contradictorily, the '201 patent specification discloses that polymers can be included in the claimed compounds. *Id*. "Suitable" embodiments of the linker, L, are described as disclosed in Pomper. *Id.*; EX1001 at 17:50-54. Pomper states that "[i]n some embodiments, the fluorescent dye moiety includes a poly(ethyleneglycol) linker." EX1006 at ¶ 129. Polyethyleneglycol is a polymer which can have a molecular weight varying from 62 Da (monomer) to over 35,000 Da, and accordingly the prosecution history and the '201 patent specification contain contradictory teachings. EX1002 at ¶ 186; EX1024 at Abstract. Thus, the '201 patent

contemplates the use of polymers in at least the linker of the claimed compounds. EX1002 at ¶ 186.

The claim term "molecular weight" has already been considered—and found indefinite—by the Federal Circuit. *See Teva Pharms. USA, Inc. v. Sandoz, Inc.,* 789 F.3d 1335, 1341-45 (Fed. Cir. 2015). In *Teva*, the Federal Circuit affirmed an indefiniteness finding where the prosecution history and specification contained contradictory statements and an alleged infringer would not know whether it fell within or outside the scope of the claims. *Id.* The '201 patent claims provide no greater certainty than those in *Teva* because the claims introduce the additional, relative modifier "low" without sufficiently explaining what molecular weights the claimed compounds are lower than.

As such, the claim phrase "low molecular weight" lacks the necessary clarity and claims 1-3 should be cancelled as indefinite.

VIII. DISCRETIONARY DENIAL IS NOT APPROPRIATE UNDER § 325(d)

The Board should not exercise its discretion under § 325(d) to deny institution. The Board has outlined factors it considers in determining whether to exercise discretion to deny institution under § 325(d). *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, 17-18 (Dec. 15, 2017) (precedential as to § III.C.5, first paragraph); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 8-11 (Feb. 13, 2020)

(precedential). *Advanced Bionics* explains how the *Becton, Dickinson* factors fit into a two-part framework that examines:

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
> (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics at 8. In evaluating this first factor, the Board looks to *Becton, Dickinson* factors (a), (b), and (d). *Id*. at 9-10. Factor (a) under the *Becton, Dickinson* construct assesses "the similarities and material differences between the asserted art and the prior art involved during examination." *Id*. at 9 n.10. Factor (b) considers "the cumulative nature of the asserted art and the prior art evaluated during examination." *Id*. Factor (d) weighs "the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art." *Id*.

"If, after review of factors (a), (b), and (d), it is determined that the same or substantially the same art or arguments previously were presented to the Office, then factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office." *Id*. at 10. Factor (c) assesses "the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection." *Id*. at 9 n.10. Factor (e) analyzes "whether petitioner has pointed out

sufficiently how the examiner erred in its evaluation of the asserted prior art." *Id*. Factor (f) considers "the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments." *Id*.

Advanced Bionics counsels against the Board exercising discretionary denial here. To begin with, the prosecution history does not reflect that the Examiner ever appreciated or considered the § 112 issues discussed above in Grounds III-V. *See* Sections VII.C-E, *supra*. While prior art references Dvořáková, Jansen I, Jansen II, and Zimmerman were considered during prosecution, the rejections based on these references were erroneously withdrawn based on a flawed showing of unexpected results, which were clearly not commensurate in scope with the extremely broad '201 patent claims, and only after Patent Owner added the indefinite phrase "low molecular weight" to the claims. *See* Sections VII.A.4, *supra*. Moreover, the Pomper reference discussed herein, which touts the benefits of compounds having a "low molecular weight" was not applied during prosecution. Thus, the examiner erred in its evaluation of the prior art and the claims and the additional evidence and facts presented in this Petition warrants reconsideration of the patentability of the claims. *See Advanced Bionics* at 9 n.10.

IX. MANDATORY NOTICES

A. Real Party-in-Interest Under 37 C.F.R. § 42.8(b)(1)

The real party-in-interest is ITM Isotope Technologies Munich SE. No unnamed entity is funding, controlling, or otherwise has an opportunity to control or direct this Petition or Petitioner's participation in any resulting PGR.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

Petitioner is not aware of any related matters that would affect or be affected by this proceeding.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Petitioner designates lead and back-up counsel as noted below. Powers of attorney pursuant to 37 C.F.R. § 42.10(b) accompany this Petition.

Lead Counsel	Back-Up Counsel
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D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Please address all correspondence to the lead and back-up counsel at the addresses shown above. Petitioner consents to service by email at the addresses of lead and back-up counsel shown above, as well as 16800.9000-ITM-Isotopes-Tech-All@finnegan.com.

X. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.204(a), Petitioner certifies that the '201 patent is available for PGR and that (1) neither Petitioner nor any of its privies own the '201 patent; and (2) neither Petitioner nor any of its privies have filed a U.S. civil action challenging the validity of any claim of the '201 patent. This Petition was filed within nine months of the '201 patent issuing. The '201 patent is subject to the Leahy-Smith America Invents Act ("AIA") and thus eligible for PGR because at least one claim in a patent to which the '201 patent claims priority has an effective filing date after the effective date of the AIA.

XI. CONCLUSION

The challenged claims should be canceled for the reasons discussed above.

Respectfully submitted,

Dated: December 24, 2024

By: /David M. Kohn/
David M. Kohn (Reg. No. 53,150)
LEWIS KOHN & WALKER LLP

Counsel for Petitioner ITM Isotope Technologies Munich SE

CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

Pursuant to 37 C.F.R. § 42.24(a)(1)(ii), the undersigned hereby certifies that the foregoing PETITION FOR POST-GRANT REVIEW contains 18,525 words, excluding the parts of this petition that are exempted under 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

/David M. Kohn/
David M. Kohn (Reg. No. 53,150)
LEWIS KOHN & WALKER LLP

Counsel for Petitioner ITM Isotope Technologies Munich SE

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.205(a), the undersigned certifies that on December 24, 2024, a copy of the foregoing **Petition for Post-Grant Review, the associated power of attorney**, and **Exhibits 1001-1024** were served by FedEx Priority Overnight on the correspondence address of record indicated in the Patent Office's Patent Center website for U.S. Patent No. 11,938,201:

Jeffrey W. Childers
The Johns Hopkins University
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2275 Deming Way, Suite 310
Middleton, WI 53562

Dated: December 24, 2024

By: /Geneva Eaddy/
Geneva Eaddy
Case Manager
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP