

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ITM Isotope Technologies Munich SE  
Petitioner

v.

The Johns Hopkins University  
Patent Owner

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

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**EXPERT DECLARATION OF STEPHEN F. MARTIN, PH.D.**

I declare that all statements made herein of my knowledge are true, that all statements made herein on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

By: 

Date: December 24, 2024

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## **I. INTRODUCTION**

1. I have been retained by counsel for Petitioner ITM Isotope Technologies Munich SE (“Petitioner”) as an independent expert consultant in this proceeding before the U.S. Patent and Trademark Office (“USPTO”). I am being compensated for the time I spend on this matter, but no part of my compensation is dependent on the outcome of this proceeding.

2. I understand that this proceeding involves U.S. Patent No. 11,938,201 (“the ’201 patent”), issued on March 26, 2024. EX1001 at Cover. I understand that the application for the ’201 patent was filed on July 18, 2023, as U.S. Patent Application No. 18/354,282, and claims a priority date of October 23, 2017. *Id.*

3. I submit this Declaration on behalf of Petitioner as an expert in the field of organic chemistry, including bioactive natural products and molecular probes, in the above-identified proceeding. My qualifications in these areas, as well as other areas, are established below and by my *curriculum vitae* (EX1003).

### **A. Experience and Qualifications**

4. I received a B.S. degree in chemistry from the University of New Mexico in 1968 and a Ph.D. degree in chemistry from Princeton University in 1972. After postdoctoral years at the University of Munich and Massachusetts Institute of Technology, I joined the faculty at The University of Texas at Austin (UTA) in 1974

where I was a faculty member in the Department of Chemistry until my retirement in 2024; I held the M. June and J. Virgil Waggoner Regents Chair in Chemistry.

5. At the UTA, I taught courses at the undergraduate and graduate levels in the general areas of organic chemistry, including advanced courses specializing in synthetic organic, natural product, heterocyclic, and bioorganic chemistry.

6. My research interests lie broadly in organic and bioorganic chemistry and chemical biology. More specifically my research involved the synthesis of biologically active natural products, many of which were complex heterocycles, and the study of energetics and structure in protein-ligand interactions. My research also focused on the design and synthesis of nitrogen-containing heterocyclic compounds and other small molecules that may be used as molecular probes to study biological function and as potential leads to treat various diseases, including cancer, neurodegeneration, and neurological disorders by a fundamentally new approach.

7. I supervised undergraduate and graduate students, postdoctoral associates and research scientists who prepared, purified, and characterized organic compounds. I also supervised studies in chemical biology and physical biochemistry, including molecular modeling, protein isolation and crystallography, mutagenesis, mechanistic enzymology, enzyme inhibitor design, medicinal chemistry, and molecular caging. I have published approximately 360 scientific papers in primary

journals together with several patents, reviews, and book articles. Details may be found in many of my peer-reviewed publications listed in my CV. EX1003.

8. In recognition of my achievements, I have received a number of awards, including the NIH Career Development Award; the American Cyanamid Academic Award; the Alexander von Humboldt Prize; the Arthur C. Cope Scholar Award; the Japanese Society for the Promotion of Science Award; the Wyeth Research Award; the International Society of Heterocyclic Chemistry Senior Award; the Ernest Guenther Award in the Chemistry of Natural Products (ACS); and the Gund-Harrington Scholar Award.

9. I am a fellow of the American Association for the Advancement of Science and of the American Chemical Society. I have also served as the regional editor of *Tetrahedron* for the Americas and Chairman of the Executive Board of Editors of Tetrahedron Publications.

10. Since 1999, I have acted as a member of the Advisory Board of the scientific book series *Organic Synthesis*, which publishes checked procedures for the synthesis of organic compounds. From 1991-1999, I served as a member of the Board of Editors of that publication. In that capacity, I was responsible for evaluating and checking synthetic procedures that had been submitted by other chemists.

11. I have served as a consultant in medicinal and process chemistry for a number of pharmaceutical companies, including Procter and Gamble, Athena Neuroscience, Elan Pharmaceutical, ICOS Corporation, and Abbott Laboratories.

12. I am co-author of the popular undergraduate laboratory book *Experimental Organic Chemistry: A Miniscale and Microscale Approach*. This text generally describes the basic techniques of experimental organic chemistry as well as the practical aspects of performing many standard reactions in the laboratory. It is used in our first-year organic chemistry laboratory class at UTA, as well as at other institutions.

13. As the president of NuvoNuro and principal investigator on a major NIH HEAL grant, I currently supervise all activities related to early drug discovery and development, including molecular modeling, ligand design and synthesis, and interpretation of *in vitro* and *in vivo* experimental data.

14. I am being compensated for my time working on this matter at my customary rate of \$800 per hour. No part of my compensation is contingent upon my opinions, my performance, or the outcome of this matter or any issue in it.

**B. Review and Use of Documents and Other Materials**

15. In forming my opinions, I have considered the documents and materials cited herein. I additionally have based my opinions on my professional and academic experience in the broad areas of organic chemistry and chemical biology.

## **II. SUMMARY OF MY OPINIONS**

16. It is my opinion, based on my review of the prior art, that it would have been obvious to a POSA as of October 23, 2017, to combine the teachings of Jansen I, Jansen II, Zimmerman, and Pomper in order to arrive at the claimed subject matter and that the alleged unexpected results provided by Patent Owner during prosecution are not commensurate in scope with the '201 patent claims.

17. Further, based on my review of the prior art, it is my opinion that it would have also been obvious to a POSA to combine the teachings of Dvořáková and Pomper in order to arrive at the '201 patent claimed subject matter.

18. It is also my opinion that the '201 patent claims do not satisfy the written description or enablement requirements. Given the breadth of the '201 patent claims and the functional language recited therein, the disclosure of the '201 patent does not provide adequate written description for its claims, and it would require undue experimentation to make and use the full scope of the claims.

19. Finally, in my opinion, the term “low molecular weight” in the '201 patent claims is indefinite. The '201 patent and its file history does not provide numerical boundaries for the term “low molecular weight” and, based on my experience, knowledge, and review of the materials in this case, it is my opinion that the claims fail to inform those skilled in the art about the scope of the claims with reasonable certainty.

### **III. LEGAL PRINCIPLES**

20. I have no formal legal training, and I have relied on the lawyers representing Petitioner in this case for the applicable legal standards governing my analyses and opinions. I have applied those standards in providing my opinions regarding validity. The legal standards that were provided to me are set forth below.

21. I understand that patentability must be analyzed from the perspective of “a person of ordinary skill in the art” (POSA) in the same field as the challenged patent as of the “effective filing date” of the claims. I understand that a POSA is a hypothetical individual presumed to know the relevant art as of the “effective filing date” and has the same level of skill as the ordinary practitioner of the art at issue.

22. I understand that the meaning of a particular claim term is to be viewed from the perspective of one of ordinary skill in the art at the time of the invention, and my opinions below are offered from this perspective. I also understand that patent claims must be read in view of the patent’s written description, drawings, and prosecution history. My opinions are offered from this perspective.

23. I understand that a patent claim is unpatentable for obviousness if any subject matter within the scope of the claim would have been obvious to a POSA, considering (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention, and (3) the level of ordinary skill in the art, and (4) any secondary considerations of non-obviousness, including unexpected results,

commercial success of products or processes using the invention, long-felt need for the invention, failure of others to make the invention, industry acceptance of the invention, and copying of the invention by others.

24. I further understand that a claim may be obvious based on multiple references combined with one another, or pursuant to the knowledge and skill of a POSA. I also understand there must have been a reason that would have prompted a POSA to combine the features of the prior art in the way the claimed invention does.

25. I also understand that a person skilled in the art must have reasonably expected that the combination will work. That is, obviousness requires a “reasonable expectation of success” in achieving the claimed subject matter.

26. I understand that the specification must include a written description of the claimed subject matter. It is my understanding that the patent statute imposes a written description requirement that is met if the patent specification describes the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the full scope of the claimed subject matter at the time the application was filed.

27. I also understand that the written description requirement requires the specification, when considered as a whole, to convey to a person of ordinary skill in the art, either explicitly or inherently, that the inventor invented the subject matter claimed in the patent. I further understand that the description requirement of the

patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention.

28. I understand that the specification must also enable a person of ordinary skill in the art relevant to the patent to practice the claimed subject matter without undue experimentation. I also understand that the scope of support must be commensurate in scope with the claims. More specifically, I understand that the specification must “teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.”

29. I understand that the following “*Wands*” factors may be considered to determine whether “undue experimentation” by a person of ordinary skill would be required:

- 1) the breadth of the claims;
- 2) the quantity of experimentation needed to make or use the invention;
- 3) the nature of the invention;
- 4) the existence of working examples;
- 5) the amount of direction provided by the inventor;
- 6) the state of the prior art;
- 7) the level of predictability in the art;
- 8) the level of skill in the art.

30. I also understand that although they are two separate requirements, written description and enablement may rely on the same facts and have overlapping analyses.

31. I understand that patent claims must “particularly point out and distinctly claim” the subject matter the inventor regards as his invention. More specifically, I understand that patent claims are invalid as indefinite when, read in light of the specification delineating the patent, and the prosecution history, they “fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.” I have also been informed that an underlying principle is that without sufficient precision, there would be “[a] zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement claims.”

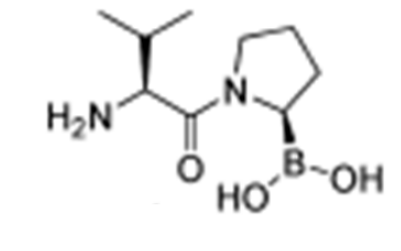
#### **IV. TECHNOLOGY BACKGROUND**

##### **A. FAP Inhibitors**

32. Fibroblast-activation protein (FAP, FAP- $\alpha$ , seprase, alpha2 antiplasmin converting enzyme) is a type II transmembrane serine protease and a member of the prolyl oligopeptidase subfamily S9b. EX1007 at 1:16-19. This family of serine proteases, which preferentially cleaves peptides after proline residues, also includes prolyl oligopeptidase (PREP) and the dipeptidyl peptidases (DPPs) DPPIV, DPPII, and DPP8/9.1. EX1010 at 491.

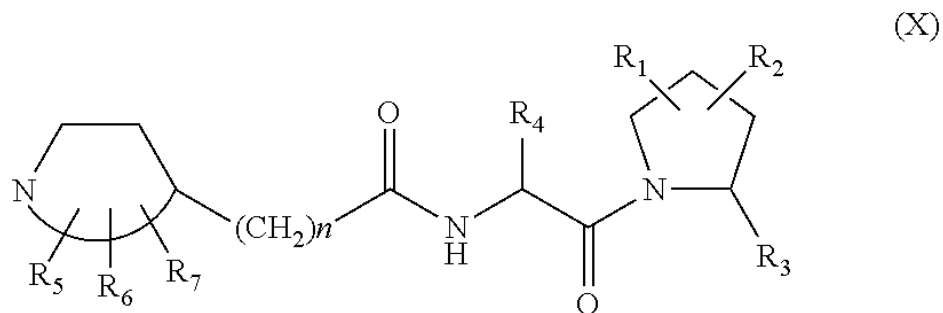
33. In over 90% of human epithelial tumors, FAP expression is associated with activated stromal fibroblasts and pericytes, and FAP is generally not expressed in healthy tissues. *Id.* Studies have shown that FAP expression promotes tumorigenesis, while FAP inhibition can mediate tumor growth. *Id.* Thus, research has focused on developing a map of the physiological substrate spectrum to develop FAP inhibitors. Improved FAP inhibitors should have combined low nanomolar FAP inhibition and high selectivity for FAP over related proteases, including DPPs and PREP. *Id.*

34. Initial development of FAP inhibitors focused on compounds including pyrrolidine-2-boronic acid derivatives, such as the structure below:

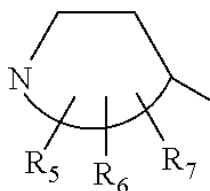


*Id.* at Figure 1. However, the pyrrolidine-2-boronic acid derivatives were shown to not be sufficiently selective, leading to safety concerns. *Id.* at 491.

35. Further research, as disclosed in Jansen I and Jansen II, focused on the development of FAP inhibitors with high selectivity. Exemplary embodiments of Jansen I include the following:

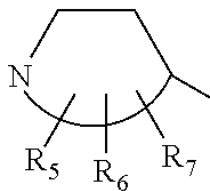


with specific focus on varying the substituent:

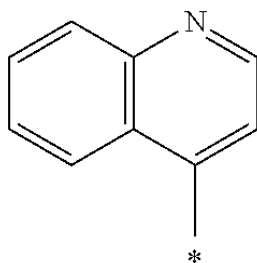


EX1007 at 98:50-59, Table 4. The selectivity of most of the compounds for FAP over PREP was reported as 50x higher than the reference compounds. *Id.* at 95:47-50.

36. However, Jansen I points to the position of the nitrogen atom in the

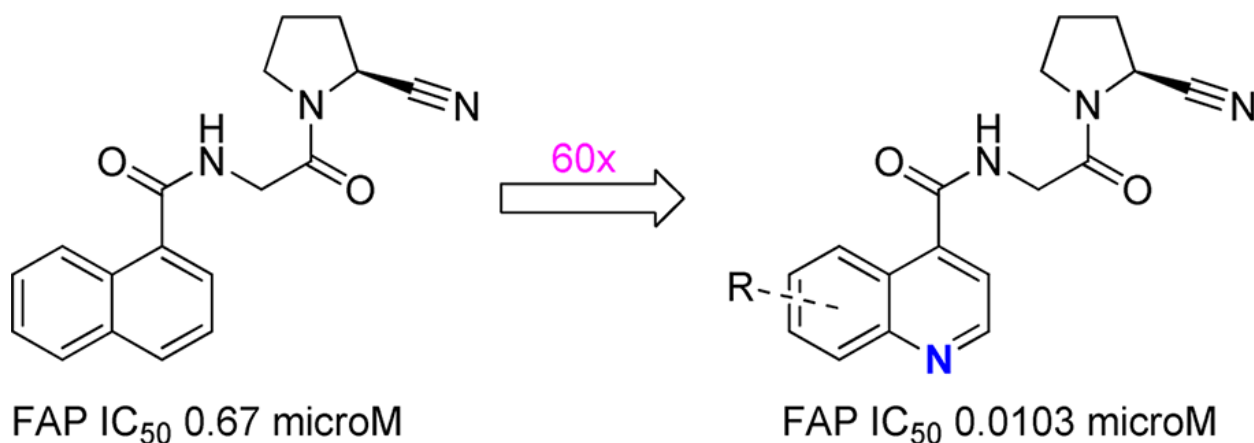


substituent as having “pivotal importance”, stating that “the 4-quinolinoyl ring clearly displays the best results.” EX1007 at 78:24-31.



4-quinolinoyl ring

37. This is further affirmed by the findings of Jansen II, which concluded that the presence of a 4-quinolinoyl ring resulted in higher selectivity as shown in the Abstract Figure of Jansen II, reproduced below.



38. Therefore, as of October 23, 2017, FAP inhibitors, including the structures taught by Jansen I and Jansen II, were known to have high selectivity and performance compared to earlier FAP inhibitors, such as pyrrolidine-2-boronic acid derivatives.

## B. Optical and Radioimaging Agents

39. The expression of distinct proteins, such as FAP, on the surface of tumor cells of many cancer types allows the possibility of diagnosing,

characterizing, and treating the disease by probing the phenotypic identity, biochemical composition, and activity of the tumor. EX1009 at ¶ 5. The association and expression of FAP on tumors makes it a desirable candidate to exploit for noninvasive imaging. *Id.* Examples of diagnostic approaches for targeting FAP include in vivo optical imaging and radioimaging.

40. In vivo optical imaging is a non-invasive imaging technique that uses visible or near-infrared light to visualize biological processes within a living organism by detecting photons emitted from optically active probes administered into the body. EX1017 at Introduction. In other words, optical probes, such as dyes, can be administered to a patient and following excitation with a light source, the light emitted by the optical probes can be monitored to provide insight related to diagnostics and/or treatment. *Id.* Most commonly, near-infrared (NIR) fluorescent probes are employed because biological tissues show very low absorption and autofluorescence in the NIR spectrum window. *Id.* The use of this approach in diagnostic and intraoperative imaging and in the monitoring of treatment response has been demonstrated for many diseases. *Id.*

41. Thus, molecular imaging probes which target FAP would enable classification of cancer patients for FAP-targeted therapy. For example, Rüger provides anti-FAP-IL, which is a fluorescence-activatable liposome (fluorescence-quenched during circulation and fluorescence activation upon cellular uptake),

bearing specific single-chain fragments directed against FAP. *Id.* at Abstract. Only FAP-expressing cells were able to take up and activate fluorescence of the anti-FAP-IL, and therefore the fluorescence of the probe could be used to monitor cancerous cells. *Id.*

42. In addition, Dvořáková developed a polymer conjugate including a FAP targeting moiety and an optical dye (ATTO488). EX1008 at 8389. By including the FAP targeting moiety, the polymer conjugate directly targeted and bound selectively to only FAP expressing cells. *Id.* at 8390. The FAP expressing cells internalized the polymer conjugate, and the presence of the optical dye was utilized for imaging purposes. *Id.* at 8390-91. Thus, the FAP expressing cells produced a fluorescence signal from the optical dye, which allowed visualization of the tumors. *Id.* at 8391.

43. Therefore, as of October 23, 2017, it was known to combine optical probes with FAP inhibitors that target FAP expressing cells to selectively visualize FAP-expressing cells.

44. Radioimaging is another non-invasive imaging technique that employs radioactive substances rather than optical dyes. Examples of radioimaging techniques include positron-emission tomography (PET) imaging and single-photon emission computed tomography (SPECT) imaging. These techniques are some of

the earliest and most mature molecular imaging techniques having high sensitivity and quantifiability. EX1018 at 1-2.

45. In PET, a radioactive substance that emits positrons is injected into the patient, and positron emission is subsequently detected. *Id.* Examples of positron emitting isotopes are  $^{11}\text{C}$ ,  $^{15}\text{O}$ ,  $^{18}\text{F}$ , and  $^{131}\text{I}$ . *Id.* SPECT imaging occurs in a similar manner; however, the radioactive substance emits gamma radiation rather than positrons. *Id.* Examples of gamma emitting isotopes include  $^{99\text{m}}\text{Tc}$ ,  $^{111}\text{In}$ ,  $^{123}\text{I}$ , and  $^{177}\text{Lu}$ . *Id.* Another approach is the use of these small molecules as carriers of radioactivity into the tumor for both radioimaging and radiotherapy. *Id.*

46. Furthermore, molecules that include radioactive or radiolabeled moieties and can selectively bind to specific tumor cell surface proteins allow for the use of noninvasive imaging techniques for detecting the presence and quantity of tumor associated proteins. EX1009 at ¶ 5. This selective binding can provide information related to the diagnosis and extent of disease as well as prognosis and therapeutic management options, while minimally affecting other areas of the patient. *Id.* Thus, radiopharmaceuticals are not only capable of imaging the disease but also of delivering a therapeutic radionucleotide to the diseased tissue for treatment. *Id.*

47. Again, as the expression of FAP is associated with tumors, research has focused on the development of radioimaging and radiotherapy agents which

specifically bind to FAP. For example, Zimmerman discloses “[s]mall molecule inhibitors of seprase [FAP] [] 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].” *Id.* at ¶ 7. The FAP inhibitors are bound to a metal chelate including a radionucleotide. The radionucleotide is defined as a “molecule that is capable of generating a detectable image that can be detected either by the naked eye or using an appropriate instrument, e.g. positron emission tomography (PET) and single photon emission computed tomography (SPECT).” *Id.* at ¶ 49.

48. Thus, as of October 23, 2017, it was known to combine radiolabeled functional groups with FAP inhibitors that target FAP expressing cells to visualize and/or treat FAP-related diseases.

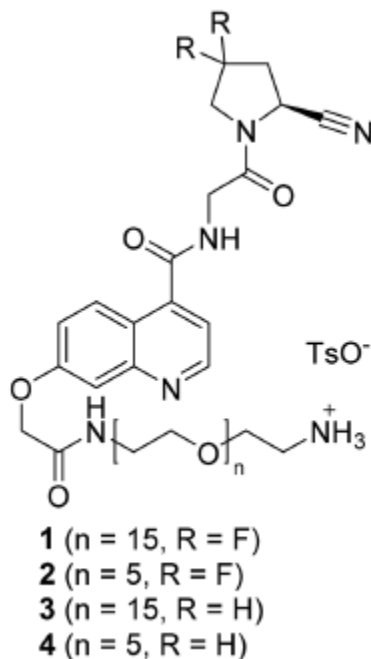
### **C. Prior Art References**

#### **1. Dvořáková**

49. Dvořáková is a scientific paper entitled “Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein” that was published in the Journal of Medicinal Chemistry on September 27, 2017. EX1008 at 8385. I understand that Dvořáková is therefore prior art to the ’201 patent.

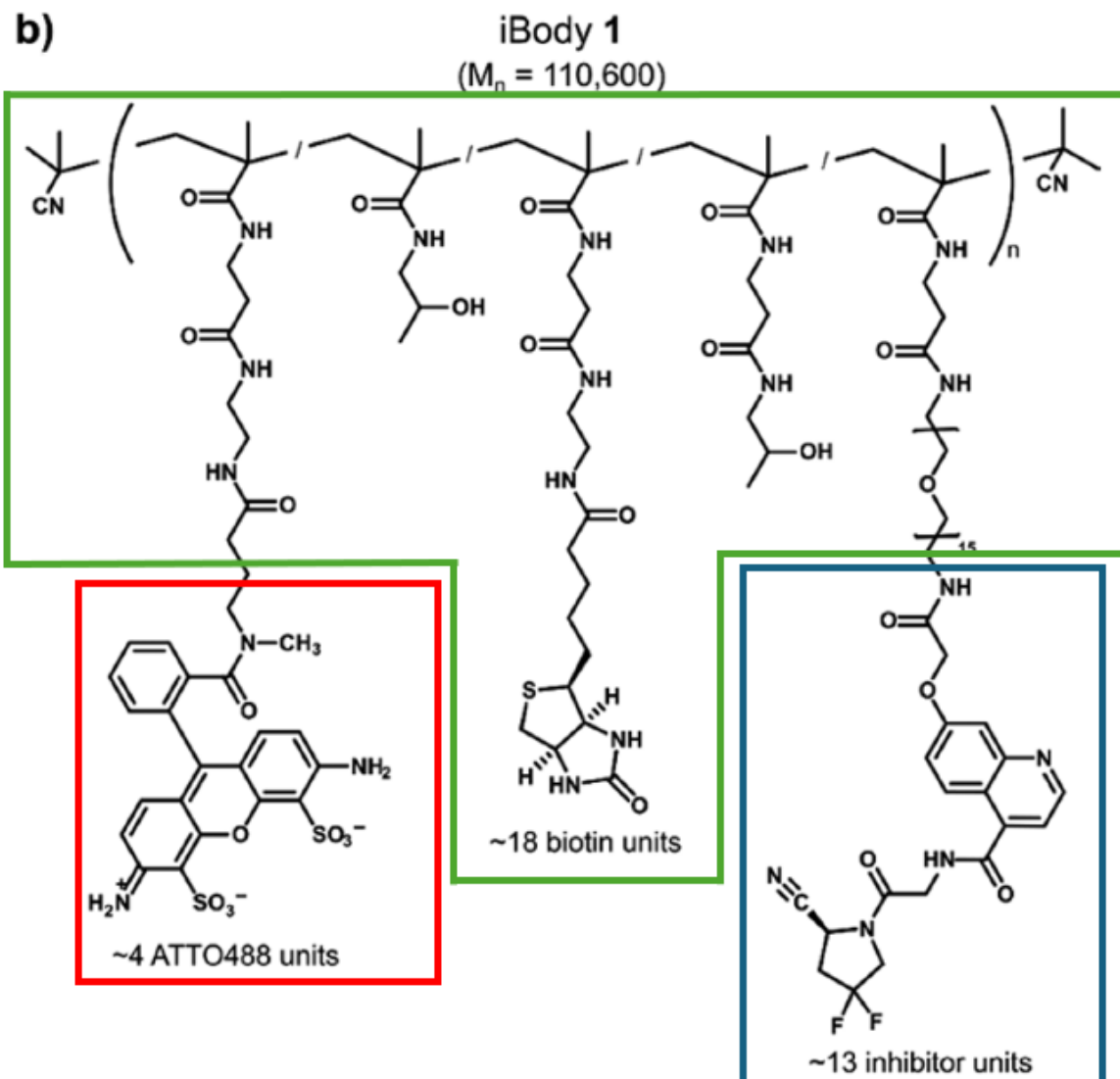
50. Dvořáková relates to developing polymer conjugates decorated with FAP inhibitors for application of imaging of FAP expressing cells. *Id.* at 8385, 8387.

To target FAP, the conjugates therefore include “[s]pecific [i]nhibitors of FAP modified with PEG linkers” (Compounds 1-4) having the following structures:



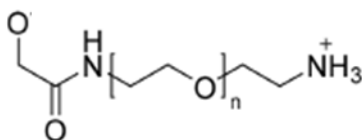
*Id.* at Scheme 1.

51. As for the application of imaging, the FAP inhibitors (Compounds 1-4) are bound to an ATTO488 dye via a HPMA copolymer:



*Id.* at Figure 2b (emphasis added to the ATTO488 dye in red, the FAP inhibitor in blue, and the linker in green). 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.

52. The distance between the FAP inhibitor and the HPMA copolymer can be varied with the incorporation of a PEG linker as shown below:



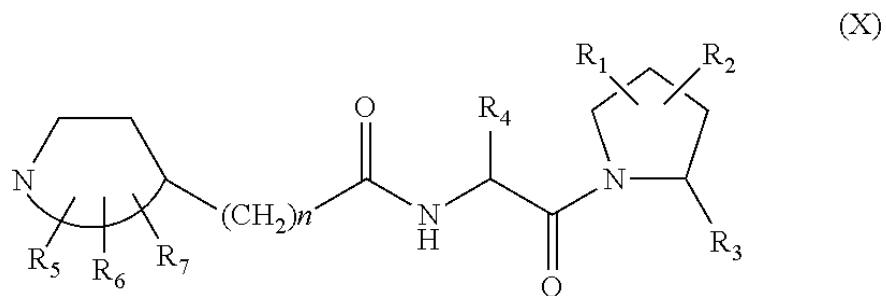
EX1008 at Figure 2a.

53. Dvořáková concludes that the inhibitor-decorated polymer conjugate can be used as a tool for the specific imaging of FAP-positive cells. *Id.* at 8387. The conjugate binds only to FAP-expressing cells and not to cells lacking FAP, and 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. *Id.* Without the incorporation of the FAP inhibitor on the polymer conjugate, it does not bind to any cells. *Id.* Thus, Dvořáková concludes, “anti-FAP iBodies may represent an attractive theranostic tool for future in vivo imaging and selective drug delivery into the tumor microenvironment.” *Id.* at 8391.

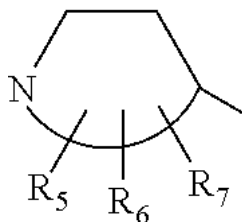
## 2. Jansen I

54. Jansen I is U.S. Patent No. 9,346,814. Jansen I was issued on May 24, 2016. EX1007 at Cover. I therefore understand that Jansen I is prior art to the '201 patent.

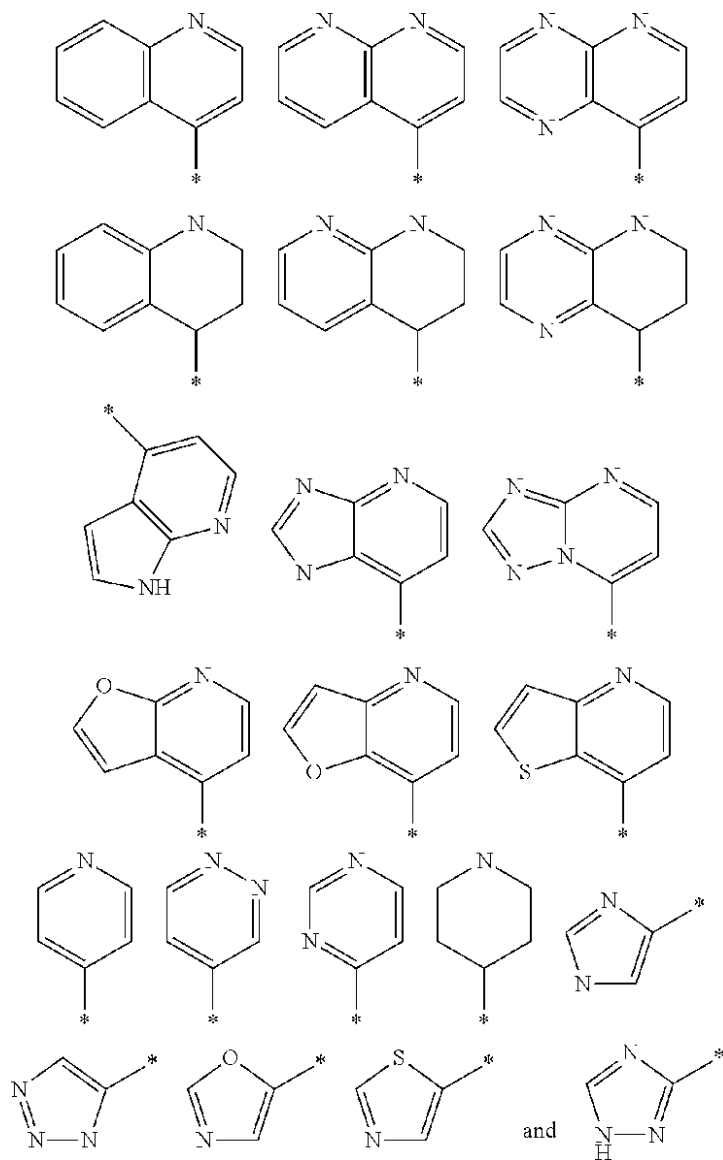
55. Jansen I relates to the development of inhibitor compounds with high selectivity and specificity for FAP. *Id.* at Abstract. Exemplary embodiments of FAP inhibitors disclosed in Jansen I include the following structure:



with a specific focus on varying the following substituent:

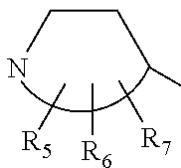


*Id.* at 98:50-59, Table 4. Jansen I further discloses that several different substituents can be featured at this position, including the following:

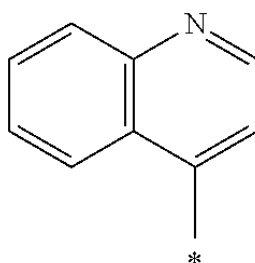


*Id.* at 100:26-60.

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



substituent as being of “pivotal importance,” stating that “the 4-quinolinoyl ring clearly displays the best results.” *Id.* at 95:47-50.



**4-quinolinoyl ring**

### **3. Zimmerman**

57. Zimmerman is a U.S. Patent Publication No. 2010/009633 that was published on April 22, 2010. EX1009 at Cover. I therefore understand that Zimmerman is prior art to the '201 patent.

58. 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 as the targeting group and a radionuclide adapted for radioimaging and/or radiotherapy. *Id.* at Abstract.

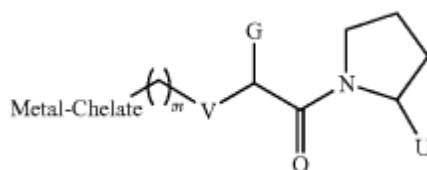
59. Zimmerman teaches that there is a strong desire for the development of compounds specifically targeting FAP and having imaging or therapy capabilities.

For example, Zimmerman states the following:

“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.*”

*Id.* at ¶ 5 (emphasis added).

60. The compounds of Zimmerman have the following general structure:

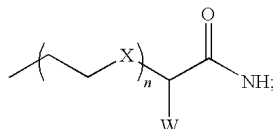


wherein:

U is selected from the group consisting of —B(OH)<sub>2</sub>, —CN, —CO<sub>2</sub>H and P(O)(OPh)<sub>2</sub>;

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,  $(\text{CH}_2\text{---CH}_2\text{---X})_n$  or a group having the following structure:



X is O, S, CH<sub>2</sub>, or NR;

R is H, Me or CH<sub>2</sub>CO<sub>2</sub>H;

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;

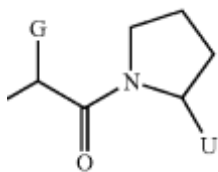
m is an integer ranging from 0 to 6;

Metal represents a metallic moiety comprising a radionuclide; and

Chelate represents a chelating moiety that chelates to said Metal.

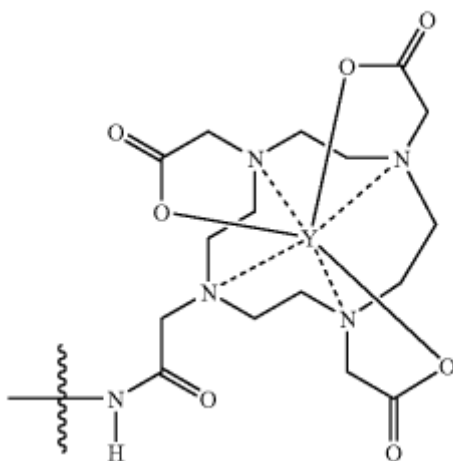
*Id.* at claim 1.

61. In the general structure, the proline moiety shown below



is attached via a tether  to a Metal-Chelate. *Id.* The proline moiety is capable of selectively inhibiting FAP, and the metal-chelate or radionuclide is adapted for radioimaging and/or radiotherapy. *Id.* at ¶ 7. 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<sub>2</sub>CH<sub>2</sub>O)<sub>n</sub>, a polyethylene amine ((CH<sub>2</sub>CH<sub>2</sub>NH)<sub>n</sub>), or the like.” *Id.* at ¶ 130.

62. Examples of the Metal-Chelate moieties of Zimmerman include the following:

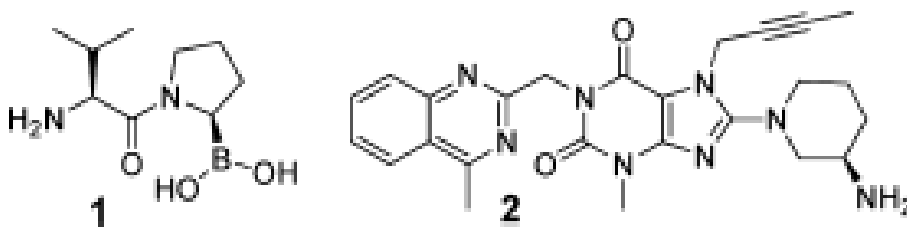


where the metal, Y, may be technetium-99m, technetium-94, rhenium-186, rhenium-188, lutetium-177, lutetium-170, yttrium-90, indium-111, gallium-67, gallium-68, copper-62, copper-64, copper-67, bismuth-212, astatine-211, strontium-89, holmium-166, samarium-153, palladium-100, palladium-109, lead-212, rhodium-105 and ruthenium-95. *Id.* at ¶¶ 49, 99.

#### 4. Jansen II

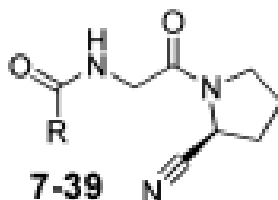
63. Jansen II is a scientific paper entitled “Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4-Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold” that was published on March 18, 2013. EX1010 at 491. It is therefore my understanding that Jansen II is prior art to the '201 patent.

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

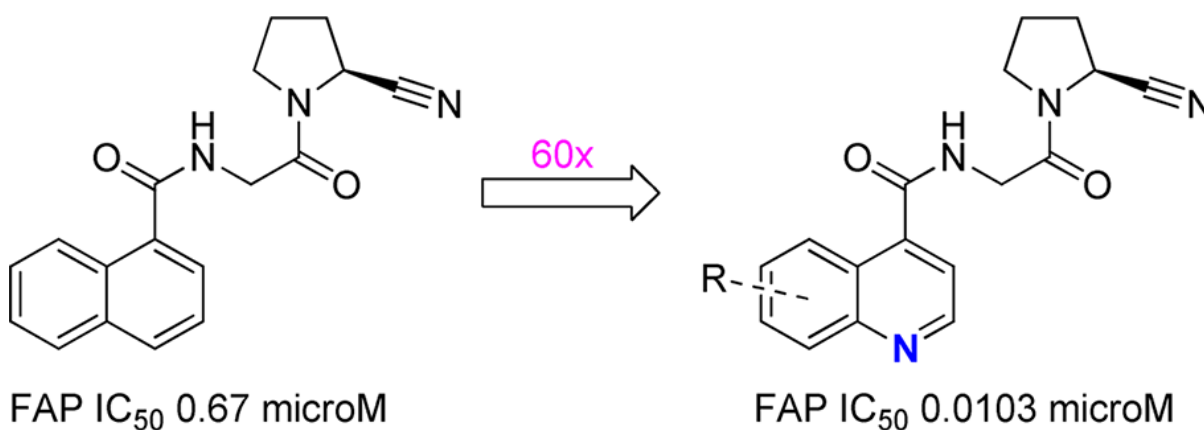


*Id.* at Figure 1.

65. Jansen II provides compounds 7-39 having the following general structure:



*Id.* at 493. The R group substituents of the general structure are varied to determine optimal performance. Jansen II teaches that quinoline-containing FAP inhibitors have 60 times greater FAP-affinity than N-(1-naphthoyl) based FAP inhibitors, as shown in the Abstract figure of Jansen II, reproduced below:



*Id.* at Abstract.

## 5. Pomper

66. Pomper is U.S. Patent Publication No. 2012/0009121. EX1006 at Cover. Pomper was published on January 12, 2012. *Id.* It is therefore my

understanding that Pomper is prior art to the '201 patent. It is further my understanding that one of the co-inventors of Pomper is also a co-inventor on the '201 patent and who submitted a declaration to the Patent Office during prosecution of the '201 patent.

67. Pomper describes new imaging and therapeutic compounds for targeting prostate cancer and cancer angiogenesis. *Id.* at Abstract, ¶ 12. These compounds include prostate-specific membrane antigen (PSMA) inhibitors used to treat cancer that are linked to a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. *Id.* at ¶¶ 31-34, 279. These imaging agents “offer better contrast between target tissues and non-target tissues,” “greater cellular retention,” and “low molecular weight.” *Id.* at ¶ 12. Pomper also discloses suitable linkers that can be used to link the PSMA inhibiting moiety and the optical or radiolabeled moiety. *Id.* at ¶¶ 102, 129.

68. 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.” *Id.* at ¶ 8. Pomper also discusses how low molecular weight inhibitors have “shown promise in preclinical imaging studies.” *Id.* at ¶ 242 (citing EX1015 and EX1016).

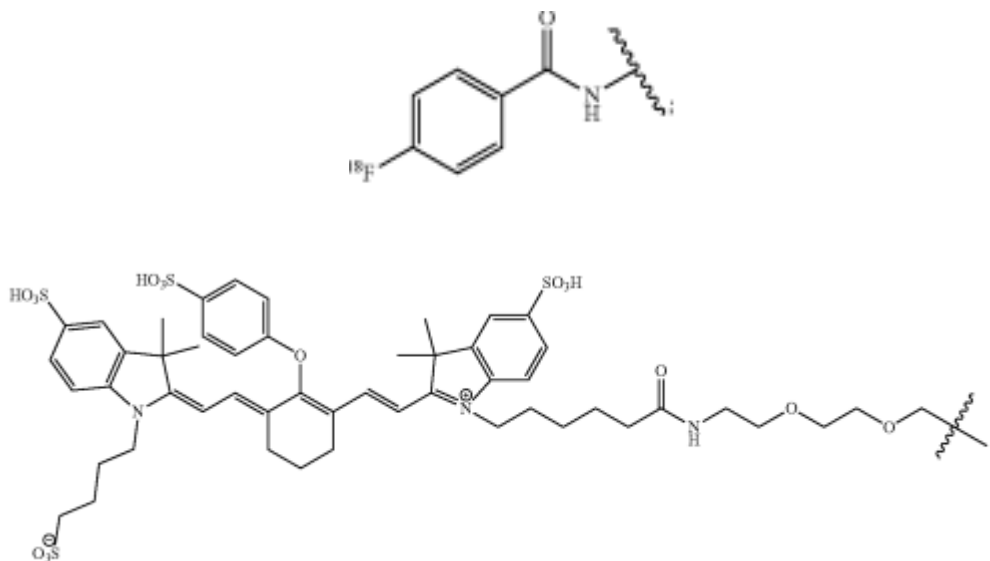
## **V. U.S. PATENT NO. 11,938,201**

### **A. Specification**

69. The '201 patent generally relates to imaging and radiotherapeutics agents targeting FAP and their use in imaging and treating FAP-related diseases and disorders. EX1001 at Abstract. These imaging and radiotherapeutic agents, referred to herein as the compounds of the '201 patent, have a general Formula (I) of B-L-A. 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. *Id.* at 2:3-12, 8:13-25, 64:46-65, 65:1-63, 66:1-67, 67:1-4.

70. 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. *Id.* at 2:4-10, 8:19-23, 15:40-44, 65:54-58, 66:64-67. 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. 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. 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:

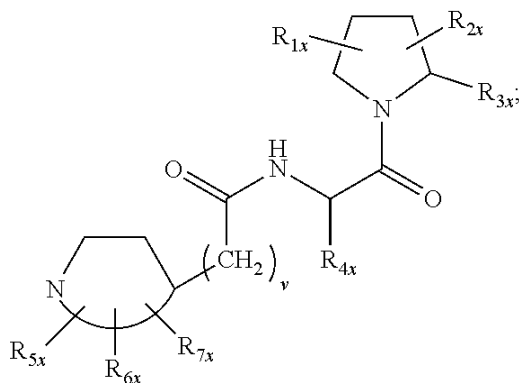


*Id.* at 18:60-66, 27:1-10.

71. The linker, L, is also broadly defined as requiring “bi-functionalization adapted to form a chemical bond with B and A.” *Id.* at 2:10-12, 8:24-25, 15:40-44, 65:58-60, 66:67, 67:1-2. The specification does not provide any additional guidance describing what specific structural features would result in compounds having “bi-functionalization”, instead relying on earlier patent applications that are incorporated into the instant specification by reference. *Id.* 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)). These references do not explain what is meant by “bi-functionalization” and do little to limit the universe of linkers. 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. 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.

72. Regarding the FAP- $\alpha$  targeting moiety, A, the '201 patent explains that the claimed genus of compounds is not new. Indeed, the '201 patent states that FAP- $\alpha$  inhibitors having the following Formula are disclosed in Jansen I:



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,  $-CN$ ,  $-B(OH)_2$ ,  $-C(O)alkyl$ ,  $-C(O)aryl$ -,  $-C=C-C(O)aryl$ ,  $-C=C-S(O)_2aryl$ ,  $-CO_2H$ ,  $-SO_3H$ ,  $-SO_2NH_2$ ,  $-PO_3H_2$ , and 5-tetrazolyl;

R<sub>4x</sub> is H;

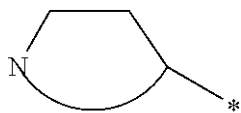
R<sub>5x</sub>, R<sub>6x</sub>, and R<sub>7x</sub> are each independently selected from the group consisting of H, -OH, oxo, halogen, —C<sub>1-6</sub> alkyl, —O—C<sub>1-6</sub> alkyl, —S—C<sub>1-6</sub> alkyl, —NR<sub>8x</sub>R<sub>9x</sub>, —OR<sub>12x</sub>, —Het<sub>2</sub> and —Ar<sub>2</sub> each of C<sub>1-6</sub> alkyl being optionally substituted with from 1 to 3 substituents selected from —OH and halogen;

R<sub>8x</sub>, R<sub>9x</sub>, and R<sub>12x</sub> are each independently selected from the group consisting of H, —OH, halo, —C<sub>1-6</sub>alkyl, —O—C<sub>1-6</sub>alkyl, —S—C<sub>1-6</sub>alkyl, and —Ar<sub>3</sub>;

R<sub>10x</sub>, R<sub>11x</sub>, R<sub>13x</sub> and R<sub>14x</sub> are each independently selected from the group consisting of H, —OH, halogen, —C<sub>1-6</sub>alkyl, —O—C<sub>1-6</sub>alkyl, and —S—C<sub>1-6</sub>alkyl; Ar<sub>1</sub>, Ar<sub>2</sub> and Ar<sub>3</sub> 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<sub>1</sub>, Ar<sub>2</sub> and Ar<sub>3</sub> being optionally and independently substituted with from 1 to 3 substituents selected from —NR<sub>10x</sub>R<sub>11x</sub>, —C<sub>1-6</sub>alkyl, —O—C<sub>1-6</sub>alkyl, and —S—C<sub>1-6</sub>alkyl;

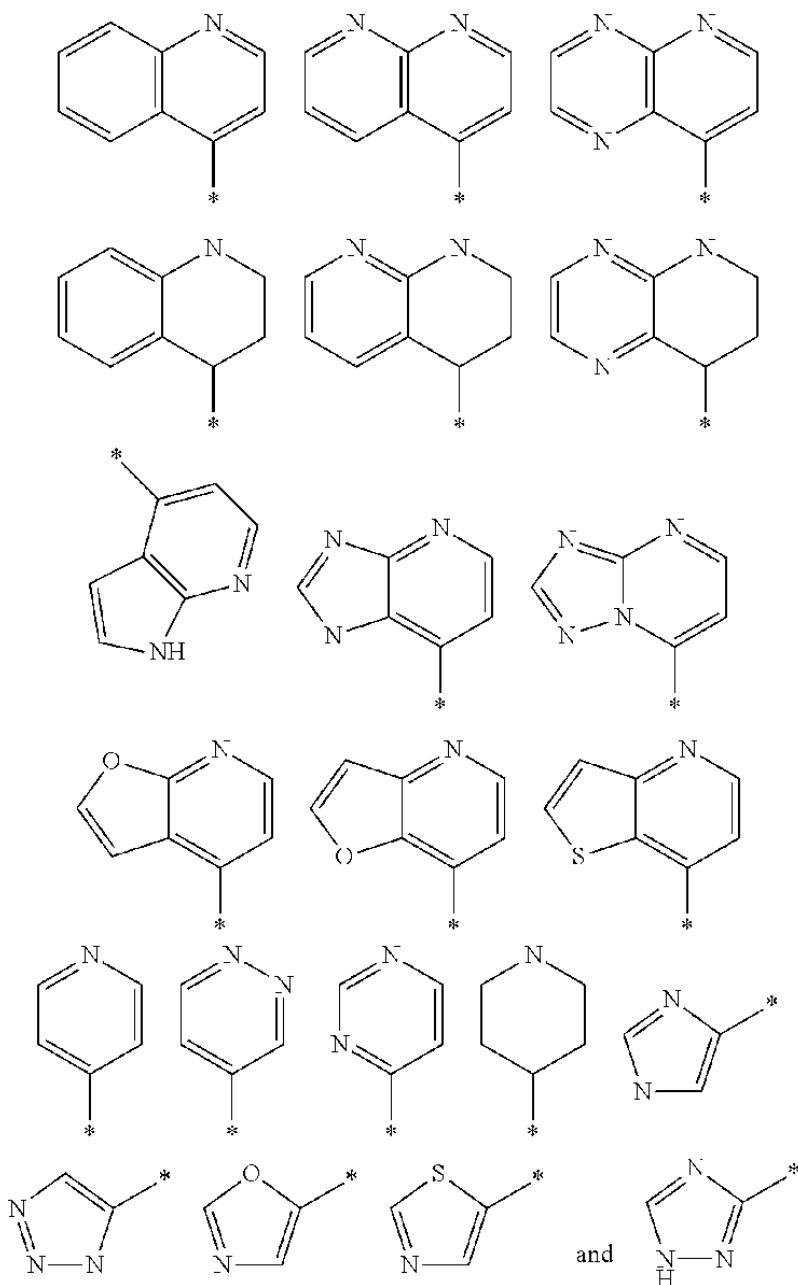
Het<sub>2</sub> is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from N and S; Het<sub>2</sub> being optionally substituted with from 1 to 3 substituents selected from —NR<sub>13x</sub>R<sub>14x</sub>, —C<sub>1-6</sub>alkyl, —O—C<sub>1-6</sub>alkyl, and —S—C<sub>1-6</sub>alkyl;

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



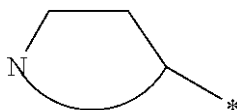
represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S. EX1001 at 8:33-9:28 (citing EX1007).

73. The '201 patent specification also describes many of the same 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.

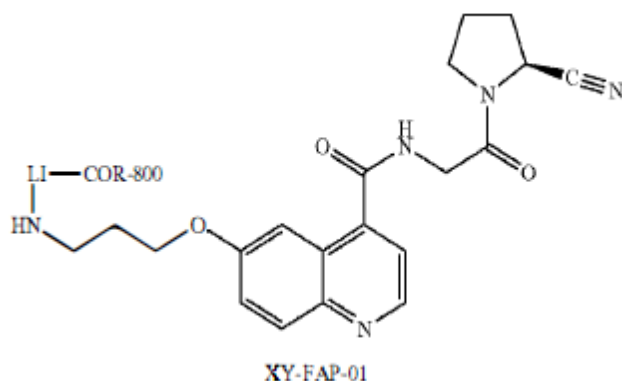
74. Notably, the A moiety recited in the claims of the '201 patent is this same genus disclosed in Jansen I, wherein  $R_{5x}$ ,  $R_{6x}$ , and  $R_{7x}$  are each H;  $v$  is 0; and

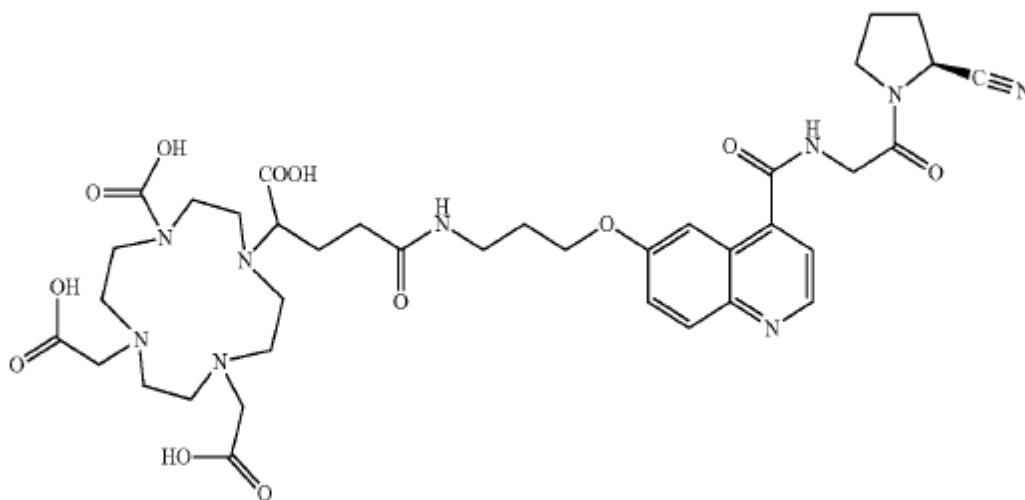


is a quinolinyl ring. EX1001, Certificate of Correction, claims 1, 3.

75. 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), (*id.* at 32:1-50:54), before eventually reaching the Examples section.

76. Of the thousands, if not millions or more, of possible combinations of FAP inhibitors, linkers, and optical or radiolabeled functional groups, XY-FAP-01 and XY-FAP-02 are the only two compounds prepared in the Examples section. *Id.* at Examples 1.1-1.2. XY-FAP-01 and XY-FAP-02 are generally prepared by 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:

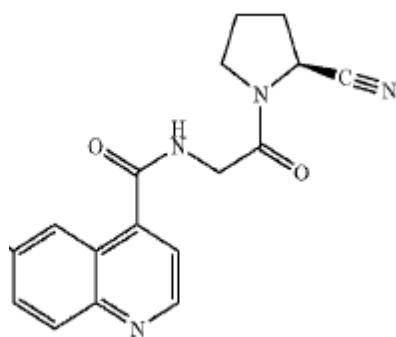


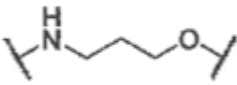


XY-FAP-02

EX1001 at 54-55.

77. Therefore, the specification only supports two compounds covered under the broad formula (B-L-A), as follows: both compounds have the same A,



both compounds have the same linker, , which is *only* ever disclosed as being 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.  
*Id.*

78. The '201 patent also 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- $\alpha$ .” *Id.* at 1:60-67. Despite identifying “low molecular weight” ligands or agents as allegedly having improved properties over anti-FAP antibodies (*id.* at 1:60-65), the '201 patent never defines the term “low molecular weight.” The '201 patent also fails to provide any guidance as to its boundaries. For example, the only other mention of “low molecular weight” in the specification states that “in some embodiments, the presently disclosed subject matter provides potent and selective low-molecular-weight (LMW) ligands of FAP- $\alpha$ , i.e., an FAP- $\alpha$  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- $\alpha$ .” *Id.* at 7:44-54.

## **B. Prosecution History**

79. 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.

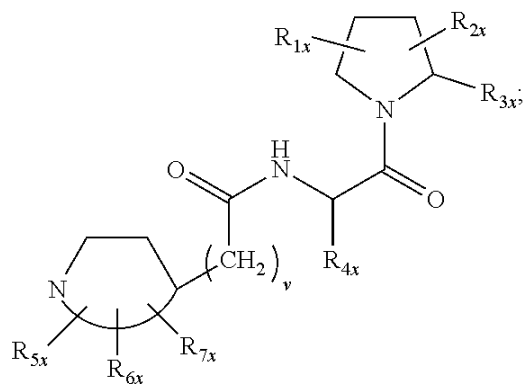
80. Following a preliminary amendment (“Preliminary Amendment”; EX1004 at 128-36) submitted soon after filing on July 24, 2023, the only pending claim (29) was as follows:

29. “A compound of Formula (I):

B-L-A (I)

wherein:

A is a targeting moiety for FAP- $\alpha$ , 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<sub>3x</sub> is selected from the group consisting of H, -CN, -B(OH)<sub>2</sub>, -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)<sub>2</sub>aryl, -CO<sub>2</sub>H, -SO<sub>3</sub>H, -SO<sub>2</sub>NH<sub>2</sub>, -PO<sub>3</sub>H<sub>2</sub>, and 5-tetrazolyl;

R<sub>4x</sub> is H;

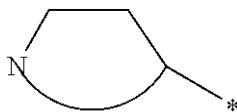
R<sub>5x</sub>, R<sub>6x</sub> and R<sub>7x</sub> are each independently selected from the group consisting of H, -OH, oxo, halogen, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, -S-C<sub>1-6</sub> alkyl, -NR<sub>8x</sub>R<sub>9x</sub>, -OR<sub>12x</sub>, -Het<sub>2</sub> and -Ar<sub>2</sub>; each of C<sub>1-6</sub> alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

R<sub>8x</sub>, R<sub>9x</sub> and R<sub>12x</sub> are each independently selected from the group consisting of H, -OH, halo, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, -S-C<sub>1-6</sub> alkyl, and -Ar<sub>3</sub>;

R<sub>10x</sub>, R<sub>11x</sub>, R<sub>13x</sub> and R<sub>14x</sub> are each independently selected from the group consisting of H, -OH, halogen, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, and -S-C<sub>1-6</sub> alkyl; Ar<sub>1</sub>, Ar<sub>2</sub> and Ar<sub>3</sub> 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<sub>1</sub>, Ar<sub>2</sub> and Ar<sub>3</sub> being optionally and independently substituted with from 1 to 3 substituents selected from -NR<sub>10x</sub>R<sub>11x</sub>, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, and -S-C<sub>1-6</sub> alkyl;

Het<sub>2</sub> is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het<sub>2</sub> being optionally substituted with from 1 to 3 substituents selected from -NR<sub>13x</sub>R<sub>14x</sub>, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, and -S-C<sub>1-6</sub> alkyl;

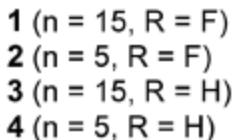
v is 0, 1, 2, or 3; and



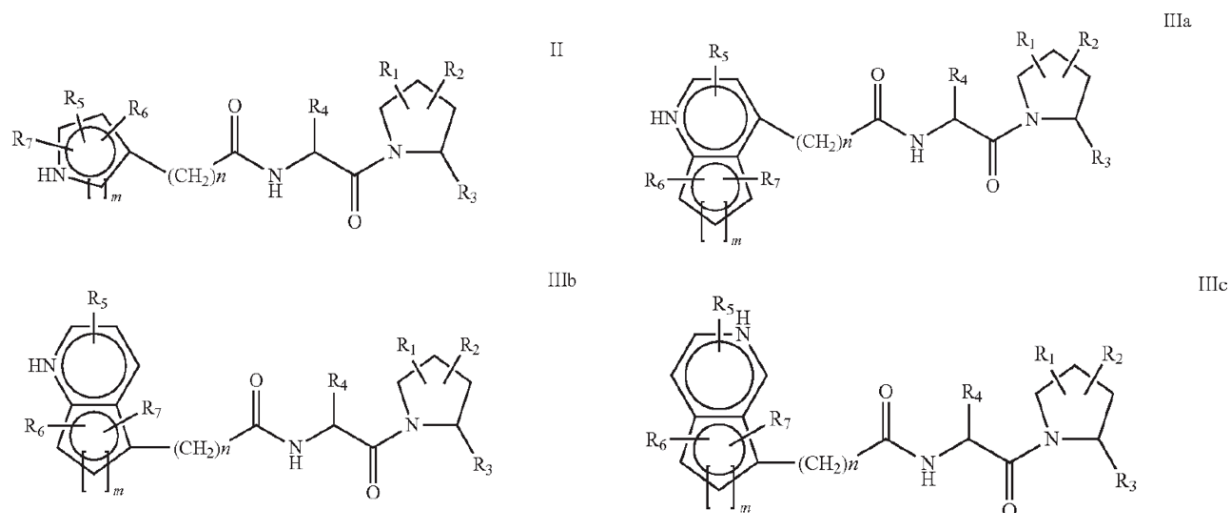
represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S; B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (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 (July 24, 2023 Preliminary Amendment).

81. 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 Dvořáková and under 35 U.S.C. § 103 as obvious over Jansen I in view of Zimmerman and Jansen II. EX1004 at 1177-82 (Sept. 26, 2023 Office Action).

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

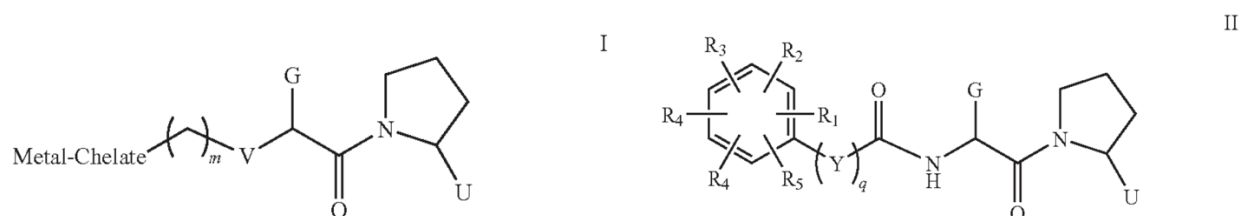

$$\text{O}^- \text{---} \text{CH}_2 \text{---} \text{C}(=\text{O}) \text{---} \text{NH} \text{---} [\text{CH}_2 \text{CH}_2 \text{O}]_n \text{---} \text{CH}_2 \text{CH}_2 \text{NH}_3^+$$

83. 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- $\alpha$ , A, as recited by the '201 patent claims:



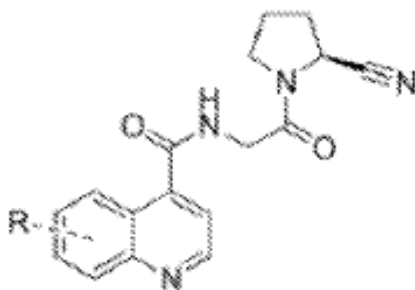
*Id.* at 1179.

84. 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.

85. 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.*

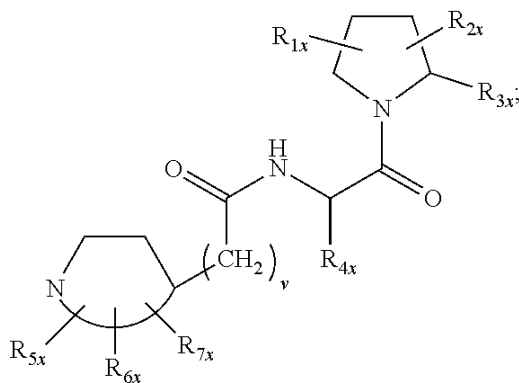
86. The Office therefore concluded that it would have been obvious to a POSA to combine the teachings of Jansen I, Zimmerman, and Jansen II to arrive at the subject matter of the claim, and that this combination would have been predictable and had a reasonable expectation of success. *Id.* at 1181-82.

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

30. (New) “The compound of claim 29, 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 (December 13, 2023 Office Action Response).

31. (New) “A low molecular weight compound consisting essentially of components B-L-A; wherein:

A is a targeting moiety for FAP- $\alpha$ , wherein A has the structure of:



wherein:

R<sub>1x</sub> and R<sub>2x</sub> are each independently selected from the group consisting of H, OH, halogen, C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, and -S-C<sub>1-6</sub> alkyl;

R<sub>3x</sub> is selected from the group consisting of H, -CN, -B(OH)<sub>2</sub>, -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)<sub>2</sub>aryl, -CO<sub>2</sub>H, -SO<sub>3</sub>H, -SO<sub>2</sub>NH<sub>2</sub>, -PO<sub>3</sub>H<sub>2</sub>, and 5-tetrazolyl;

R<sub>4x</sub> is H;

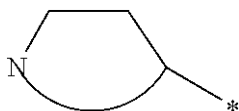
$R_{5x}$ ,  $R_{6x}$  and  $R_{7x}$  are each independently selected from the group consisting of H, -OH, oxo, halogen, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, -S-C<sub>1-6</sub> alkyl, -NR<sub>8x</sub>R<sub>9x</sub>, -OR<sub>12x</sub>, -Het<sub>2</sub> and -Ar<sub>2</sub>; each of C<sub>1-6</sub> 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<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, -S-C<sub>1-6</sub> alkyl, and -Ar<sub>3</sub>;

$R_{10x}$ ,  $R_{11x}$ ,  $R_{13x}$  and  $R_{14x}$  are each independently selected from the group consisting of H, -OH, halogen, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, and -S-C<sub>1-6</sub> alkyl; Ar<sub>1</sub>, Ar<sub>2</sub> and Ar<sub>3</sub> 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<sub>1</sub>, Ar<sub>2</sub> and Ar<sub>3</sub> being optionally and independently substituted with from 1 to 3 substituents selected from -NR<sub>10x</sub>R<sub>11x</sub>, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, and -S-C<sub>1-6</sub> alkyl;

Het<sub>2</sub> is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het<sub>2</sub> being optionally substituted with from 1 to 3 substituents selected from -NR<sub>13x</sub>R<sub>14x</sub>, -C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub> alkyl, and -S-C<sub>1-6</sub> 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.” *Id.* at 1211-12 (December 13, 2023 Office Action Response).

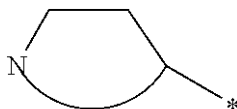
88. Patent Owner argued that the addition of low molecular weight into the preamble of claim 29 distinguishes “the pending claims from a large molecule imaging agents containing anti-FAP moieties” and that “[i]n contrast to the instant application, the compound disclosed in Dvořáková (compound 1) is a large molecule compound - as the Examiner correctly pointed out, comprising an anti-FAP moiety bound to an ATTO488 dye via a HPMA copolymer. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol.” *Id.* at 1213-14 (December 13, 2023 Office Action Response); *see also id.* at 1197-98 (Pomper Declaration), 1271-72 (December 18, 2023 Supplemental Amendment). 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 (December 13, 2023 Office Action Response); *see also id.* at 1197-99 (Pomper Declaration), 1271-73 (December 18, 2023 Supplemental Amendment).

89. 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 (December 13, 2023 Office Action Response); *see also id.* at 1275-77 (December 18, 2023 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 (December 13, 2023 Office Action Response); *see also id.* at 1277-79 (December 18, 2023 Supplemental Amendment). Lastly, the 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 (December 13, 2023 Office Action Response); *see also id.* at 1203-05 (Pomper Declaration), 1279-83 (December 18, 2023 Supplemental Amendment).

90. Patent Owner concludes 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,” therefore the obviousness rejection should be removed. *Id.* at 1221-24 (December 13, 2023 Office Action Response); *see also id.* at 1203-05 (Pomper Declaration), 1279-83 (December 18, 2023 Supplemental Amendment).

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



of the FAP- $\alpha$  targeting moiety, A, of the compound of Formula (I) were changed in both independent claims, as shown in the following section. *Id.* at 1268-70 (December 18, 2023 Supplemental Amendment).

92. 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 in light 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

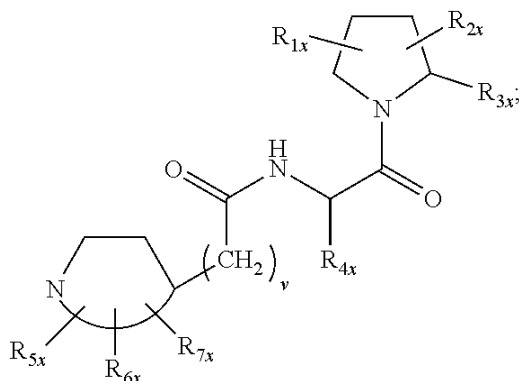
Allowance). However, the additional claim amendments provided in the Supplemental Amendment were not entered before issuance and thus a Certificate of Correction was requested by the Applicant and subsequently entered by the Examiner. EX1001, Certificate of Correction, claims 1, 3.

### C. Claims of the '201 Patent

93. The claims of the '201 Patent read as follows:

**Claim 1.** A low molecular weight compound of Formula (I): B-L-A (I) wherein:

A is a targeting moiety for FAP- $\alpha$ , wherein A has the structure of:



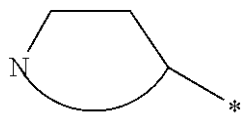
R<sub>1x</sub> and R<sub>2x</sub> are each independently selected from the group consisting of H, OH, halogen, C<sub>1-6</sub> alkyl, —O—C<sub>1-6</sub> alkyl, and —S—C<sub>1-6</sub> alkyl;

R<sub>3x</sub> is selected from the group consisting of H, —CN, —B(OH)<sub>2</sub>, —C(O)alkyl, —C(O)aryl-, —C=C—C(O)aryl, —C=C—S(O)<sub>2</sub>aryl, —CO<sub>2</sub>H, —SO<sub>3</sub>H, —SO<sub>2</sub>NH<sub>2</sub>, —PO<sub>3</sub>H<sub>2</sub>, and 5-tetrazolyl;

R<sub>4x</sub> is H;

R<sub>5x</sub>, R<sub>6x</sub>, and R<sub>7x</sub> 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.

**Claim 2.** 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.  
*Id.* at 65:64-67.

**Claim 3.** A low molecular weight compound consisting essentially of components B-L-A. . . .where B, L, and A have the same limitations as claim 1. *Id.* at Certificate of Correction, claim 3.

## **VI. PERSON OF ORDINARY SKILL IN THE ART**

94. I understand that a person of ordinary skill in the art (“POSA”) is a hypothetical person who is presumed to have a certain level of knowledge and expertise. I have also been informed that the following factors may be considered in determining the level of ordinary skill in the art: (1) type of problems encountered in the art, (2) prior art solutions to those problems, (3) rapidity with which innovations are made, (4) sophistication of the technology, and (5) educational level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate.

95. In my opinion, as of October 23, 2017 (the earliest priority date of the ’201 patent), 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. 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. A POSA would have an understanding of processes employed for synthesis and evaluation of imaging and radiotherapeutic 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.

96. By the earliest effective filing date of the '201 patent, I would have been a POSA.

## **VII. CLAIM CONSTRUCTION**

97. I understand from counsel that the first step in any validity analysis is to interpret the meaning of the claims. I understand that patent claims define the boundaries of what the patent holder has the right to exclude. I have been informed that the goal of the claim construction process is to determine what a POSA would have understood the meaning of the claims to be at the time the patent application was filed. I understand that, in the claim construction process, absent a specialized definition provided by the inventors, the plain and ordinary meaning of the words in the claim applies in claim construction. I understand that the use of the words in the claims themselves and in the context of the patent specification is the best guide to determine the meaning of the claim language in a way that would be understood by one of ordinary skill in the art. I understand that the prosecution history and other evidence may also be considered.

98. I have been asked to provide my opinion regarding the meaning of certain claim terms and phrases in the '201 patent as they would have been understood by a POSA.

**A. “Low molecular weight”**

99. The preamble of claims 1 and 3 of the '201 patent includes the phrase “low molecular weight.” EX1001, Certificate of Correction, claims 1, 3. “Low molecular weight” or “LMW” is mentioned only three times in the '201 patent specification, as follows:

*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. To date, however, no *LMW* ligand has been reported with ideal properties for nuclear imaging of FAP- $\alpha$ .

*Id.* at 1:60-67 (citations omitted) (emphasis added).

Accordingly, in some embodiments, the presently disclosed subject matter provides potent and selective *low-molecular-weight (LMW)* ligands of FAP- $\alpha$ , i.e., an FAP- $\alpha$  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- $\alpha$ .

*Id.* at 7:46-54 (emphasis added).

100. Notably, none of these passages appear in the lengthy “Definitions” section of the '201 patent. *See id.* at 38:29-50:50. Moreover, none of these passages defines “low molecular weight” or provides sufficient guidance about the Patent Owner’s intended meaning of the phrase. Because the first two mentions of the term

provide a comparison to antibodies, one would, at best, interpret a “low molecular weight” to be lower than the molecular weight of an antibody. However, the two major classes of antibody molecules have molecular weights of 150,000 and 900,000 Daltons, respectively. EX1019 at 1307. Therefore, tying the meaning of the phrase LMW to the molecular weight of an antibody introduces yet another ambiguity.

101. During prosecution of the '201 patent, after Patent Owner added the phrase “low molecular weight” to the claims in an attempt to overcome the prior art, Patent Owner provided another statement:

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/what-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 (December 13, 2023 Office Action Response); *see also id.* at 1198 (Pomper Declaration), 1273 (December 18, 2023 Supplemental Amendment).

102. A POSA would not understand this statement to constitute a definition of “low molecular weight,” but instead would understand it as a non-limiting “typical[]” general range of about 50 Da to about 1500 Da. Notably, each of the references provided in Patent Owner’s explanation is related to the field of metabolomics or the scientific study of metabolites. Yet, there is no mention of metabolomics anywhere in the ’201 patent specification. Furthermore, the ’201 patent specification specifically states that “the injected compound is ***not metabolized*** by the body prior to excretion.” EX1001 at 35:66-67 (emphasis added). Therefore, these references are unrelated to the ’201 patent, which discusses imaging and radiotherapeutics agents, further undercutting the weight a POSA would give this statement when attempting to determine the meaning of “low molecular weight.”

103. To the extent Patent Owner argues that its reference to a general range of about 50 Da to about 1500 Da constitutes a definition of the term “low molecular weight,” this argument should be rejected. The ’201 patent specification itself provides several examples of compounds that would have a molecular weight greater than 1,500 Da but would otherwise fall within the scope of the claims. For example, moiety B is 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. If any of these fluorescent dyes are included 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 considering the addition of the FAP- $\alpha$  targeting moiety, A, and the linker, L, and the additional weight those components would impart. These contradictory disclosures further demonstrates the ambiguity of the ’201 patent’s usage of the term “low molecular weight.”

104. The phrase “low molecular weight” was further discussed during prosecution. *See* EX1004 at 1214 (December 13, 2023 Office Action Response); *see also id.* at 1197 (Pomper Declaration), 1272 (December 18, 2023 Supplemental Amendment). Patent Owner pointed to its definition of “polymer” in the ’201 patent specification as “a molecule of high relative molecule mass,” and asserted that this distinguishes “low molecular weight compounds” from “polymers.” *See* EX1004 at 1214 (December 13, 2023 Office Action Response); *see also id.* at 1197 (Pomper Declaration), 1272 (December 18, 2023 Supplemental Amendment). However, like antibodies, polymers are a class of compounds having a wide range of molecular weights. *See, e.g.,* EX1020 (discussing common polymers with molecular weights ranging from 8,000 Da to 400,000).

105. A POSA would understand that the phrase “low molecular weight” could vary based on the specific field of study and types of molecules whether they be antibodies, polymers, carbohydrates, or secondary metabolites, etc. For these reasons, in my opinion, the claims lack reasonable certainty and are therefore indefinite.

**B. “C(O)Alkyl” / “Aryl”**

106. Claims 1 and 3 of the '201 patent include the following limitation for substituent R<sub>3x</sub> of the FAP- $\alpha$  targeting moiety, A:

R<sub>3x</sub> is selected from the group consisting of H, —CN, —B(OH)<sub>2</sub>, —C(O)alkyl, —C(O)aryl-, —C=C—C(O)aryl, —C=C—S(O)<sub>2</sub>aryl, —CO<sub>2</sub>H, —SO<sub>3</sub>H, —SO<sub>2</sub>NH<sub>2</sub>, —PO<sub>3</sub>H<sub>2</sub>, and 5-tetrazolyl.

EX1001, Certificate of Correction, claims 1, 3.

107. The term —C(O)alkyl, also known as an acyl group, is commonly used in organic chemistry, and a POSA would understand it to refer to a functional group consisting of an alkyl group directly attached to a carbonyl (C=O) group.

108. The term alkyl is defined as follows in the “Definitions” section of the '201 patent:

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<sub>1</sub>-C<sub>10</sub> means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons).***

*Id.* 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.

109. Based on this definition, a POSA would understand the alkyl group of the —C(O)alkyl to be limited to the number of carbons designated in the term itself. For example, in both claims 1 and 3, R<sub>1x</sub> and R<sub>2x</sub> substituents can be chosen from a group that includes an alkyl chain containing between 1 and 6 carbon atoms, i.e., “C<sub>1-6</sub>alkyl.” *Id.*, Certificate of Correction, claims 1, 3.

110. For the —C(O)alkyl substituent of R<sub>3x</sub> no range of the number of carbon atoms is provided. Thus, a POSA would understand this term to mean an acyl group comprising an alkyl group of any length.

111. Similarly, the definitions provided in the '201 patent explain that the term “aryl,” identified among the several options at the R<sub>3x</sub> 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.” *Id.* at 42:64-67. Thus, without a number of carbon atoms or rings designated, the —C(O)aryl-, —C=C—C(O)aryl, and —C=C—S(O)<sub>2</sub>aryl groups

likewise would have been understood by a POSA as not limited to any particular length, size or substitution.

## **VIII. INVALIDITY**

### **A. Ground I: Claims 1-3 Would Have Been Obvious to a POSA In View of Jansen I and/or Jansen II, Taken in View of Zimmerman and Pomper**

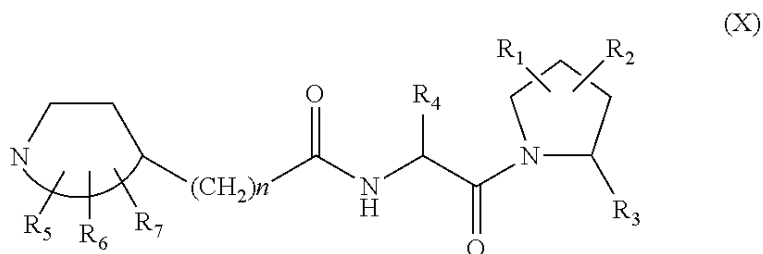
112. It is my opinion that claims 1-3 of the '201 patent are unpatentable under 35 U.S.C. § 103 because they would have been obvious to a POSA in view of Jansen I and/or Jansen II, taken in view of Zimmerman and Pomper. In my opinion, the subject matter of the claims does not go beyond the combination of familiar elements known in the art according to their known uses, specifically known FAP inhibitors attached via known linkers to known optical or radiolabeled functional groups.

113. The specification of the '201 patent explains that the genus of targeting moieties for FAP- $\alpha$ , A, was already disclosed in references like Jansen I and Jansen II (EX1001 at 8:25-10:10), while components meeting the broad functional language specified for B and L were also disclosed in references like Zimmerman (EX1001 at 17:45-53, 25:18-25, 26:18-24). Other references, including the 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. EX1006 at ¶¶ 8, 242.

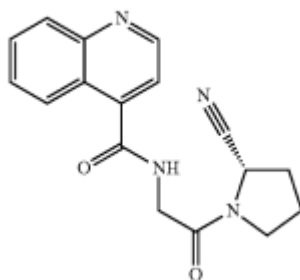
114. I have been informed that an express motivation to combine the prior art is not required where the combination represents a known alternative to one of ordinary skill in the art. In my opinion, the art, as exemplified by references like Jansen I, Jansen II, Zimmerman, and Pomper would have taught and motivated a POSA to design and prepare a potent and selective FAP inhibitor to serve as an imaging or therapeutic agent. The art would have further motivated a POSA to combine these known features into the compounds recited in the claims of the '201 patent. The art also would have provided a POSA with a reasonable expectation that such compounds would work for their desired purpose, particularly in view of the teachings of the prior art that the use of radiolabeled compounds presented advantages in diagnostic imaging and therapeutic treatment of diseases, and the teachings of the prior art that quinoline-modified FAP inhibitors have improved performance.

#### **1. Claim 1**

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

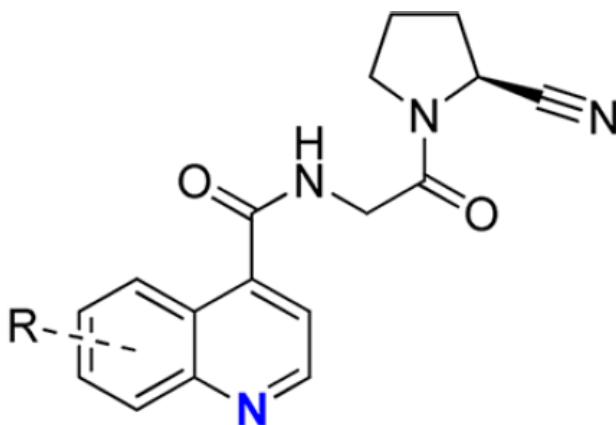


with overlapping definitions with the substituents in the '201 patent. EX1007 at 98:50-59. Specifically, Jansen I discloses FAP inhibitors having the following structure:

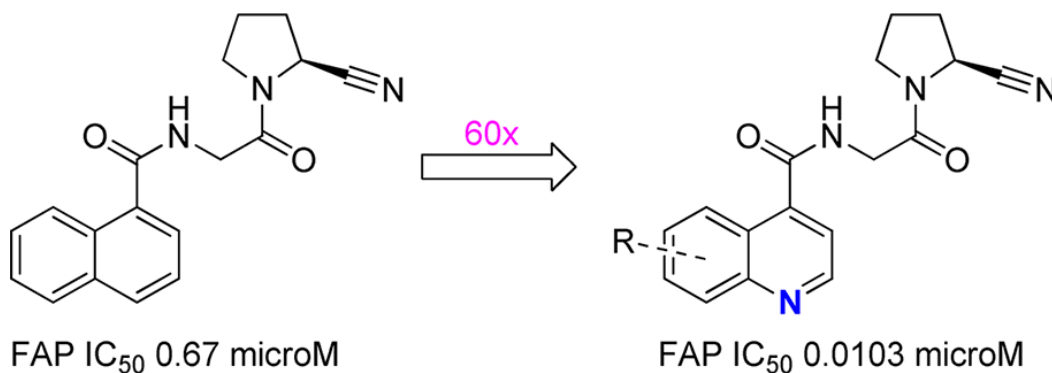


*Id.* at 47:5-18. This structure is the FAP inhibitor included in the only two embodiments in the '201 patent specification, XY-FAP-01 and XY-FAP-02-[In], and all 11 examples provided in Dr. Pomper's declaration. EX1001 at Examples 1.1-1.2; EX1004 at 1203-1205 (Pomper Declaration). It also falls within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

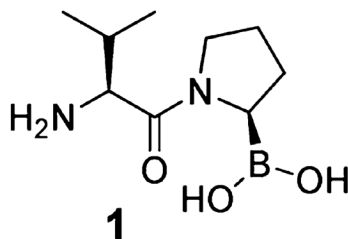
116. In addition, Jansen II discloses FAP inhibitors having the following structure:



EX1010 at Abstract. Again, this is the same structure disclosed in Jansen I, the structure featured in the two embodiments in the '201 patent specification, XY-FAP-01 and XY-FAP-02-[In], and the structure of the FAP inhibitor in each of the 11 examples of the Pomper Declaration. EX1001 at Examples 1.1-1.2; EX1004 at 1203-1205 (Pomper Declaration). 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. 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:



*Id.* at Figure 1. Jansen II teaches that Compound 1 has inferior performance to Jansen II's quinolinoyl-containing compound. *Id.* at Table 1, Table 4. Thus, these teachings of Jansen II would motivate a POSA to employ the quinoline modified FAP inhibitors over the proline-based FAP exemplified by Compound 1.

117. 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 protein targeting moieties with radiolabeled agents or optical agents for imaging and therapy purposes. *See, e.g.*, EX1018 at Section 3 (disclosing radiolabeled agents); EX1021 at 2-12 (disclosing optical agents); EX1022 at Abstract (disclosing radioimaging and optical imaging agents for prostate cancer); EX1023 at Abstract.

118. Furthermore, it was known to specifically use FAP inhibitors with radiolabeled functional groups and to provide a linker between the two moieties. For example, Zimmerman is directed to “[s]mall molecule inhibitors of seprase [FAP- $\alpha$ ] [] for use as therapeutic medicines or as radiopharmaceuticals useful in diagnostic

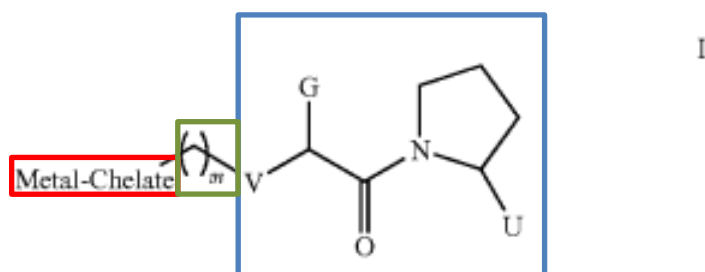
imaging and in the therapeutic treatment of diseases characterized by overexpression of seprase [FAP- $\alpha$ ]. EX1009 at ¶ 7. Zimmerman also teaches that:

“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- $\alpha$ ] on tumors makes it an attractive target to exploit for noninvasive imaging as well as targeted radiotherapy.*”

*Id.* at ¶ 5 (emphasis added). The radiopharmaceuticals disclosed in Zimmerman include “complexes or compounds that contain *a functionalized proline moiety which is capable of selectively inhibiting seprase [FAP- $\alpha$ ], and a radionuclide adapted for radioimaging and/or radiotherapy.*” *Id.* at ¶ 7 (emphasis added). 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 of the ’201 patent. Moreover, Zimmerman’s praise of these radiopharmaceuticals and their potential as imaging and therapeutic agents would have motivated a POSA to combine these functional groups with a potent and selective FAP inhibitor, like those described in Jansen I and Jansen II.

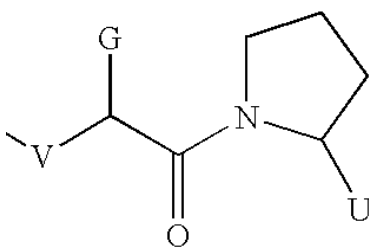
119. Zimmerman also discloses “a linker having bi-functionalization adapted to form a chemical bond with B and A.” The claims of Zimmerman have a similar structure as the claims of the '201 patent, as evident from Zimmerman's claim 1, as shown in part below:

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



*Id.* at claim 1 (annotations added to signify portion of compound corresponding to the A moiety of claim 1 of the '201 patent in blue, the portion corresponding to the B moiety of claim 1 of the '201 patent in red, and the portion corresponding to the L moiety of claim of the '201 patent in green).

120. In claim 1 there is a FAP- $\alpha$  inhibitor including a proline moiety having the following structure:



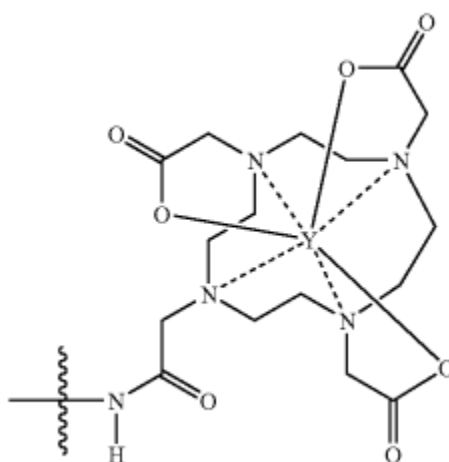
attached via a linker , to a Metal-Chelate. *Id.* at claim 1. The proline moiety is capable of selectively inhibiting FAP, and the metal-chelate or radionuclide is adapted for radioimaging and/or radiotherapy. *Id.* at ¶ 7. Claim 1 specifies that *m* is an integer of 0 to 6. *Id.* at claim 1.

121. The linker, *L*, in the '201 patent claims is not limited to any particular structure, length or atoms and is only required to have “bi-functionalization adapted to form a chemical bond with *B* and *A*.” A POSA would interpret the linker to include any combination of carbon atoms and heteroatoms. Thus, the linker, , described in Zimmerman meets the parameters of the claimed linker, *L*.

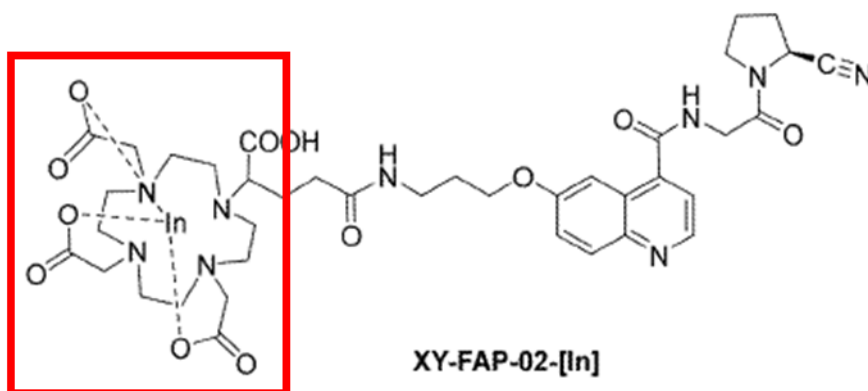
122. Although Patent Owner argued during prosecution that Zimmerman did not disclose the claimed linker, *L* (EX1004 at 1217-21 (December 13, 2023 Office Action Response); *id.* at 1275-77 (December 18, 2023 Supplemental Amendment)), this argument was, in my opinion, factually erroneous. Zimmerman merely uses the terms “linker” and “tether” interchangeably. *See, e.g.*, EX1009 at ¶¶ 130-133. 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 by incorporating a tether into these structures. The tether may comprise a simple alkyl chain as shown, a PEG (CH<sub>2</sub>CH<sub>2</sub>O)<sub>*n*</sub>, a polyethylene amine ((CH<sub>2</sub>CH<sub>2</sub>NH)<sub>*n*</sub>), or the like.” *Id.* 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.

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

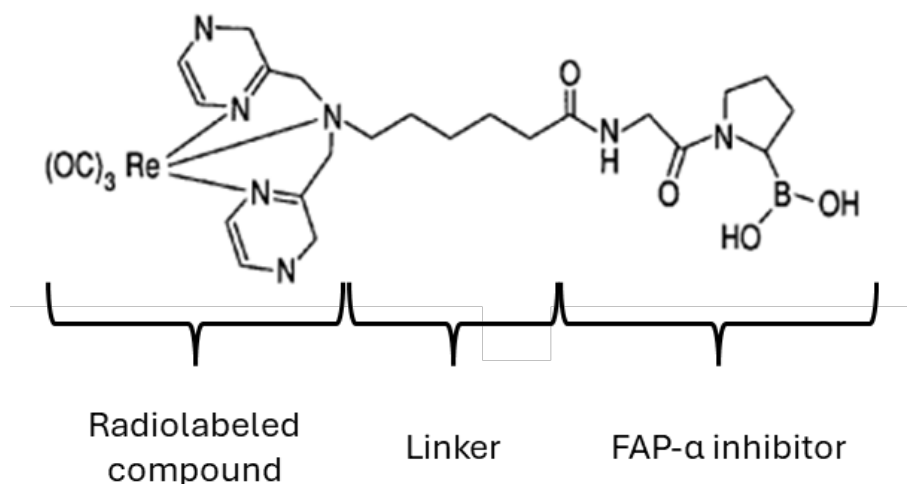


where Y may be indium (In). *Id.* at Table 4 at page 43; ¶ 99. The structure of this group is similar to that of XY-FAP-02-[In], as disclosed in the '201 patent and shown below with emphasis on the radiolabeled functional group (B):



EX1001 at Fig. 1C.

124. Zimmerman also provides the following exemplary embodiment:



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

125. In addition, Pomper describes new imaging and therapeutic compounds for targeting cancer and cancer angiogenesis. EX1006 at Abstract, ¶ 12. These compounds include a PSMA inhibitor used to treat cancer that is linked with a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. *Id.* at ¶¶ 31-34, 279. These imaging agents “offer better contrast between target tissues and non-target tissues,” “greater cellular retention,” and “low molecular weight.” *Id.* at ¶ 12. Pomper also discloses suitable linkers that can be used to link the PSMA inhibiting moiety and the optical or radiolabeled moiety. *Id.*

at ¶¶ 102, 129. Indeed, the '201 patent explains that the linkers in Pomper are suitable for use in the claimed compounds. EX1001 at 17:45-54.

126. 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. Pomper also discusses how low molecular weight inhibitors have “shown promise in preclinical imaging studies.” *Id.* at ¶ 242 (citing EX1015 and EX1016). A POSA would have been motivated by Pomper to develop a compound with a low molecular weight.

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

128. A POSA would expect to succeed because Jansen II clearly teaches that the quinoline-modified FAP inhibitors have improved performance over the proline-based FAP inhibitors. EX1010 at Table 1, Table 4. Thus, a POSA would be

motivated to swap the proline-based FAP inhibitor of Zimmerman with the higher performing quinoline-modified FAP inhibitors or Jansen I and/or Jansen II, to form a compound including a quinoline-modified FAP inhibitor attached via a linker to a radiolabeled compound.

## **2. Claim 2**

129. 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. 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, for the same reasons as claim 1.

## **3. Claim 3**

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

#### **4. No Secondary Indicia**

131. I understand that objective evidence of non-obviousness requires proof of a “nexus” with the claims and must be commensurate in scope with the claims. The patentee has the burden of production to show the required nexus between the objective indicia and the claimed invention.

132. Patent Owner argued in the Office Action Response, Pomper Declaration, and Supplemental Amendment, that the compounds of the '201 patent claims provide unexpected results, and that the additional 11 examples provided in the Pomper Declaration provide representative compounds in the claims. EX1004 at 1221-42 (December 13, 2023 Office Action Response); *see also id.* at 1203-05 (Pomper Declaration); *id.* at 1279-83 (December 18, 2023 Supplemental Amendment). Patent Owner stated that the additional examples provide evidence of a “surprising” level of specificity, measured by the FAP/PREP ratio, over reference compounds like those in Zimmerman. *Id.* at 1222 (December 13, 2023 Office Action Response); *see also id.* at 1205 (Pomper Declaration), 1280 (December 18, 2023 Supplemental Amendment).

133. In my opinion, given the broad scope of the claims, which cover a countless number of compounds, even if these results were surprising, 11 examples are not sufficient to represent the full scope of the very broad claims. 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. Meanwhile, as discussed in Section VII.B, the limitations of R<sub>3x</sub> of the FAP inhibitor (A) themselves have a vast number of possibilities. Neither the additional examples nor the specification, provide any indication as to effect of varying any one of the substituents on the FAP inhibitor (A) structure.

134. Furthermore, while the structures of the linkers (L) and optical dyes or radiolabeling groups (B) vary in the 11 provided examples, it is certainly insufficient to represent the thousands, if not millions or more, possible linkers, optical dyes, radiolabeling groups, and combinations thereof encompassed by the broad functional language used in the claims. EX1004 at 1221-42 (December 13, 2023 Office Action Response); *see also id.* at 1203-05 (Pomper Declaration); *id.* at 1279-83 (December 18, 2023 Supplemental Amendment).

135. Thus, the Pomper 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. Therefore, in my opinion, the evidence of unexpected results presented during prosecution should be given little

or no weight, and is certainly insufficient to overcome the strength of the prior art's teachings.

136. I am not aware of any other evidence of secondary indicia. However, I reserve the right to address any evidence of secondary indicia that may be raised in any responsive report submitted on Patent Owner's behalf.

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

137. It is my opinion that claims 1-3 of '201 patent are invalid as obvious over Dvořáková and Pomper under 35 U.S.C. § 103.

138. During prosecution, the Examiner rejected the sole pending claim as anticipated by Dvořáková. EX1004 at 1177-78 (Sept. 26, 2023 Office Action). In response, Patent Owner amended the claim to add the phrase "low molecular weight." *Id.* at 1210 (December 13, 2023 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 (December 13, 2023 Office Action Response), 1197-98 (Pomper Declaration), 1271-72 (December 13, 2023 Office Action Response).

139. Dvořáková discloses every limitation of claim 1 except "low molecular weight." Pomper, however, 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. Pomper also discusses how low molecular weight inhibitors have “shown promise in preclinical imaging studies.” *Id.* at ¶ 242 (citing EX1015 and EX1016).

140. 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. A POSA would have also readily understood how the molecular weight of Dvořáková’s compounds could be lowered. For example, a POSA would have recognized that a low molecular weight version of iBody 1 could be synthesized by, for example, reducing the number of FAP-targeting and ATTO488 groups, using a linker with a lower molecular weight, and eliminating the biotin groups. Pomper discloses several linkers with a lower molecular weight as suitable, including, “[f]or instance linking groups having alkyl, aryl, combination of alkyl and aryl, or alkyl and aryl groups having heteroatoms.” EX1006 at ¶¶ 102, 129. 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.

141. 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.

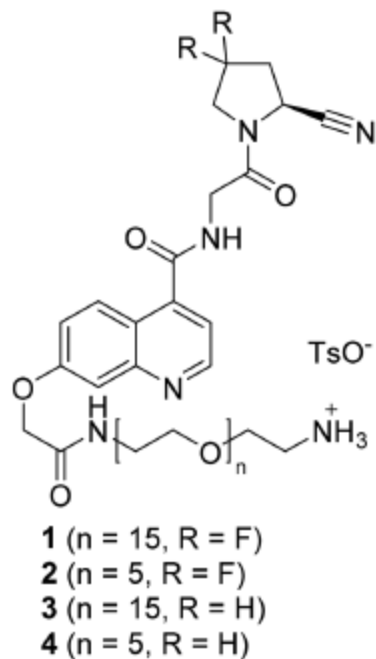
**1. Claim 1**

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

142. As discussed above, Pomper discloses inhibitor imaging agents having a low molecular weight. Dvořáková discloses compounds having the formula B-L-A, as each of B, L, and A are defined in claim 1. Each moiety is discussed in more detail below.

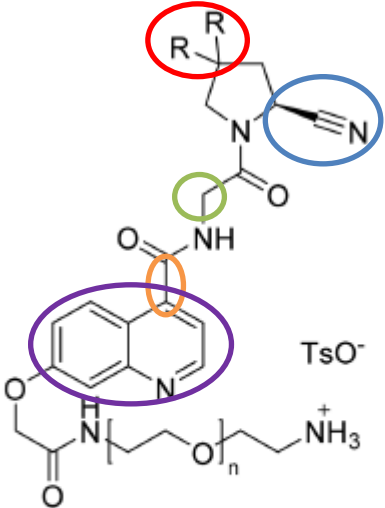
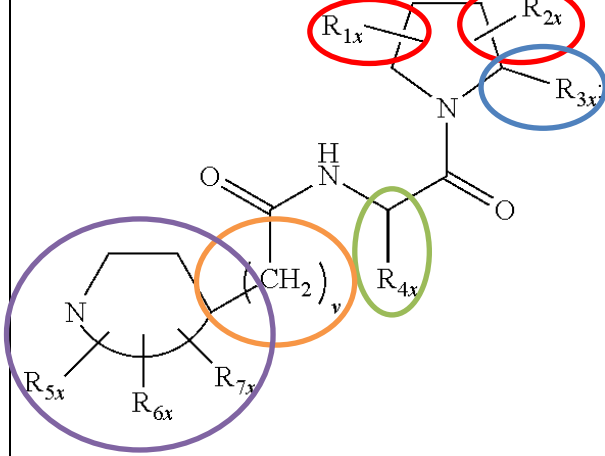
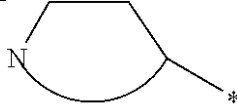
**b. [1b] “A is a targeting moiety for FAP- $\alpha$ , wherein A has the structure of . . .”**

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

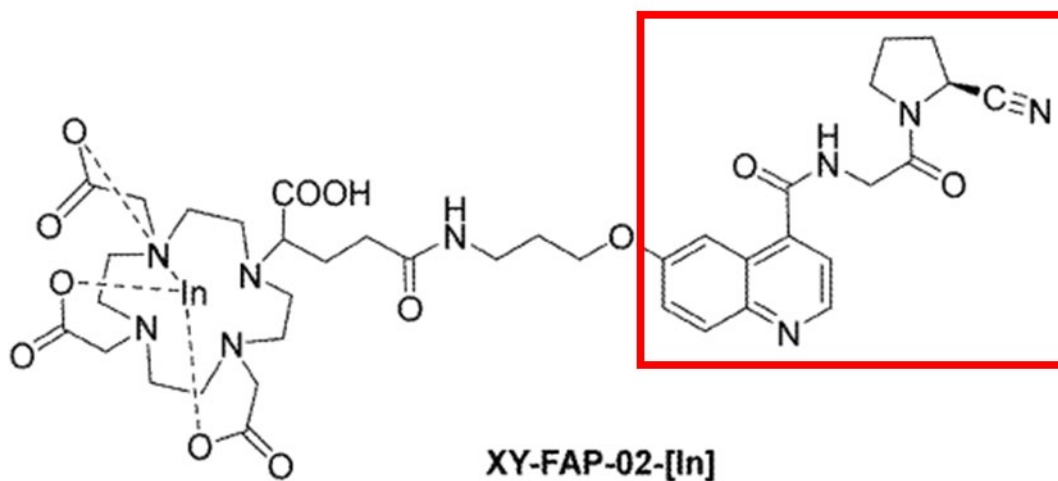
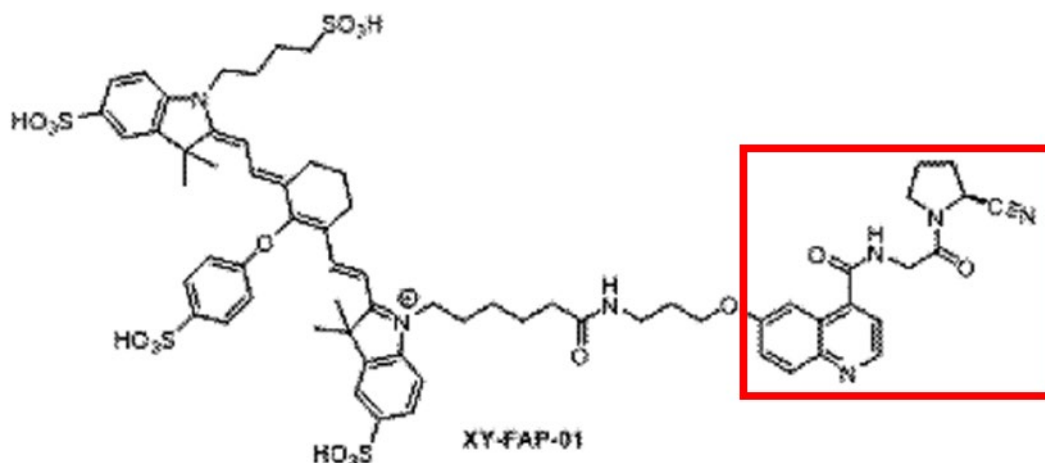


EX1008 at 8388.

144. 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                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
|  <p> <b>1</b> (<math>n = 15</math>, <math>R = F</math>)<br/> <b>2</b> (<math>n = 5</math>, <math>R = F</math>)<br/> <b>3</b> (<math>n = 15</math>, <math>R = H</math>)<br/> <b>4</b> (<math>n = 5</math>, <math>R = H</math>)         </p> |                                    |
| OVERLAPPING DEFINITIONS                                                                                                                                                                                                                                                                                                     |                                                                                                                      |
| <b>1</b> $R = F$<br><b>2</b> $R = F$<br><b>3</b> $R = H$<br><b>4</b> $R = H$                                                                                                                                                                                                                                                | $R_{1x}$ 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;                                                                                                            |
| Quinoliny ring                                                                                                                                                                                                                                                                                                              | <br>represents a quinoliny ring; |

145. Further supporting these overlapping disclosures are the only two examples in the '201 patent: XY-FAP-01 and XY-FAP-02-[In] (shown below with emphasis on the targeting moiety for FAP- $\alpha$ , A).



EX1001 at Fig. 1B, Fig. 1C. Patent Owner has asserted that both examples are covered by claim 1. EX1004 at 1214 (December 13, 2023 Office Action Response). XY-FAP-01 and XY-FAP-02-[In] both share the targeting moiety for FAP- $\alpha$ , A,

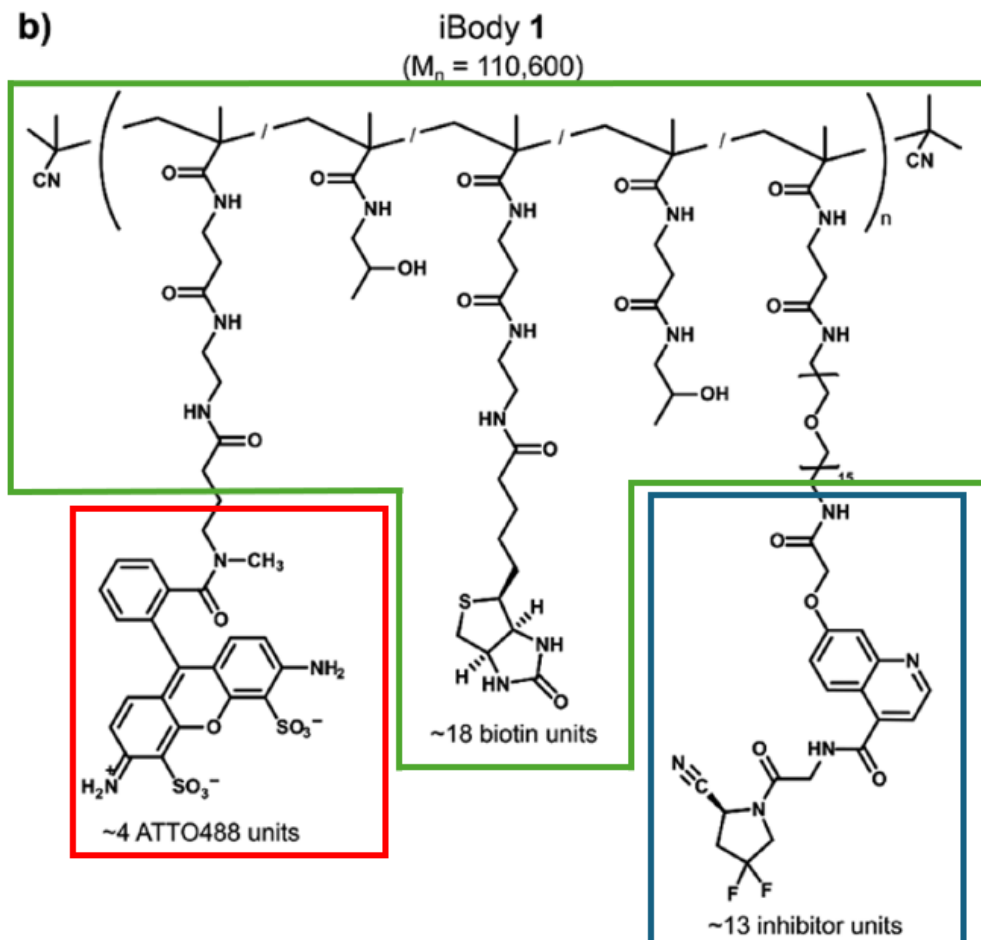
with Compounds 1-4 described in Dvořáková, specifically Compounds 3 and 4 where R = H.

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

- 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”**

147. 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, Certificate of Correction, claim 1.

148. Dvořáková discloses attaching its Compounds 1-4 to ATTO488, an optical imaging 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).

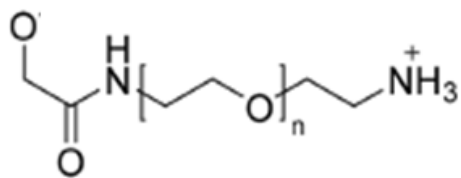
149. ATTO488 is a fluorophore that contains a rhodamine-based structure and is known to be “highly suitable for single-molecule detection applications and high-resolution microscopy.” EX1011. A POSA would interpret the optical functional group as any molecule that absorbs and emits light, and thus would have recognized ATTO488 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,” as recited in

claim 1. *See* EX1001 at 25:19-20 (“In some embodiments, B comprises an optical dye, e.g., in particular embodiments, a fluorescent dye.”). Accordingly, Dvořáková discloses the B moiety as recited in claim 1.

150. Pomper also discloses PSMA inhibitors used to treat cancer that are linked with a fluorescent dye moiety, metal isotope, or radioisotope to facilitate imaging and tumor mapping. EX1006 at ¶¶ 31-34, 279. Thus, Pomper also discloses the B moiety as recited in claim 1.

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

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



EX1008 at 8388.

152. As illustrated above, Dvořáková discloses using a linker to form a chemical bond between a targeting moiety for FAP- $\alpha$  and the optical functional group in molecules like iBody 1. *Id.* at Figure 2b. Therefore, this linker falls within the broad scope of L as recited in claim 1. In fact, Dvořáková describes its linker as

“a PEG linker for attachment to the HPMA copolymer,” which, as detailed in Section VIII.E below, is also 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.”). Thus, Dvořáková discloses L, as L is recited in claim 1.

153. Pomper also discloses suitable linkers that can be used to couple the inhibiting moiety and the optical or radiolabeled moiety. 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. Thus, Pomper also discloses L, as L is recited in claim 1.

**e. [1e] “or a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof”**

154. I have been informed and understand that when considering whether a prior art reference or combination of references renders obvious a claim, optional elements of the claim, like the optional claim element 1e, do not need to be considered. It is my opinion that claim 1 would have been obvious to a POSA at the time of invention over the combination of Dvořáková and Pomper.

**2. Claim 2**

155. 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. Therefore, claim 2 would have been obvious to a POSA in view of the combination of Dvořáková and Pomper.

### **3. Claim 3**

156. 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. I have been informed and understand that the 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 characteristics of the claimed invention.

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

### **C. Ground III: Claims 1-3 Lack of Enablement**

158. It is my opinion that the claims of the '201 patent are invalid as not enabled. In my opinion, it would require undue experimentation for a POSA to make and use the full scope of the invention as claimed. In the section below, I will go through an analysis of the so-called “*Wands*” factors identified above in Section III and listed below:

- 1) the quantity of experimentation needed to make or use the invention;
- 2) how routine any necessary experimentation is in the relevant field;
- 3) the existence of specific working examples in the patent;
- 4) the amount of guidance provided in the patent;
- 5) the nature and predictability of the field;
- 6) the level of skill in the art; and
- 7) the scope of the claimed invention.

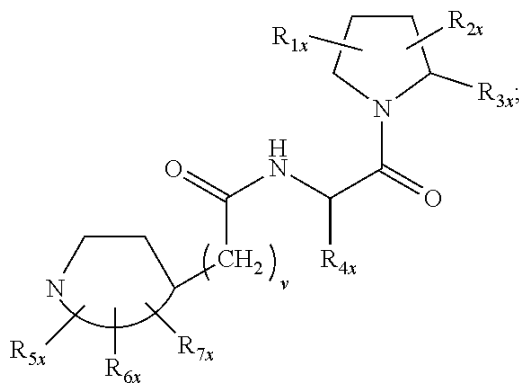
159. In my opinion, the *Wands* factors show that a POSA would have engaged in undue experimentation to practice the claimed invention.

#### **1. Scope of the Claimed Invention**

160. The scope of the claimed invention is very large. 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. This broad functional language permits a virtually unlimited number of potential candidate compounds that would need to be made and tested to determine whether the compound falls within the scope of the claims.

161. In addition to the claimed B moiety and L linker, the A moiety is defined in claims 1-3 as having the following structure:



wherein:

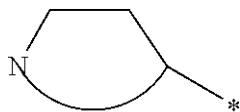
$R_{1x}$  and  $R_{2x}$  are each independently selected from the group consisting of H, OH, halogen,  $C_{1-6}$  alkyl,  $-O-C_{1-6}$  alkyl, and  $-S-C_{1-6}$  alkyl;

$R_{3x}$  is selected from the group consisting of H,  $-CN$ ,  $-B(OH)_2$ ,  $-C(O)alkyl$ ,  $-C(O)aryl$ -,  $-C=C-C(O)aryl$ ,  $-C=C-S(O)_2aryl$ ,  $-CO_2H$ ,  $-SO_3H$ ,  $-SO_2NH_2$ ,  $-PO_3H_2$ , 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.

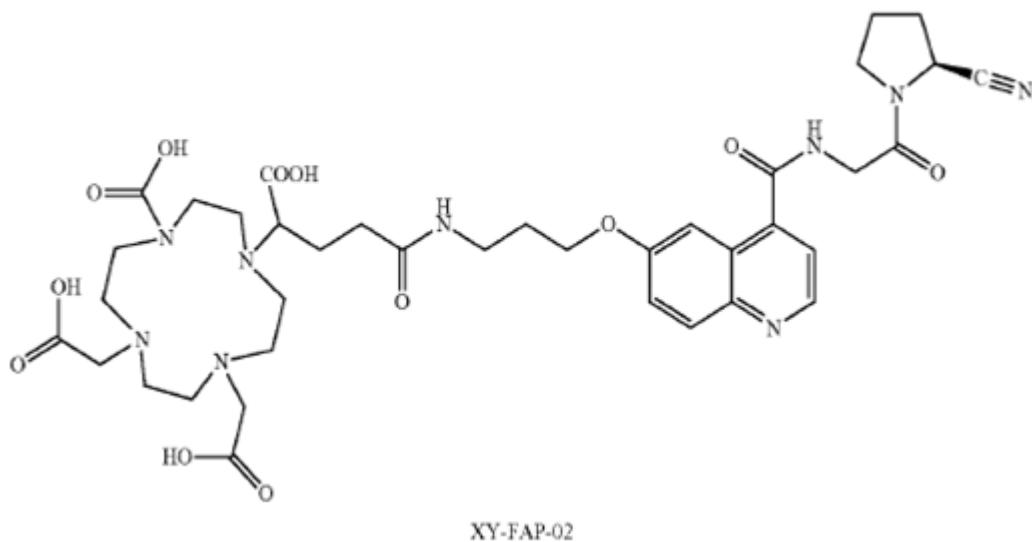
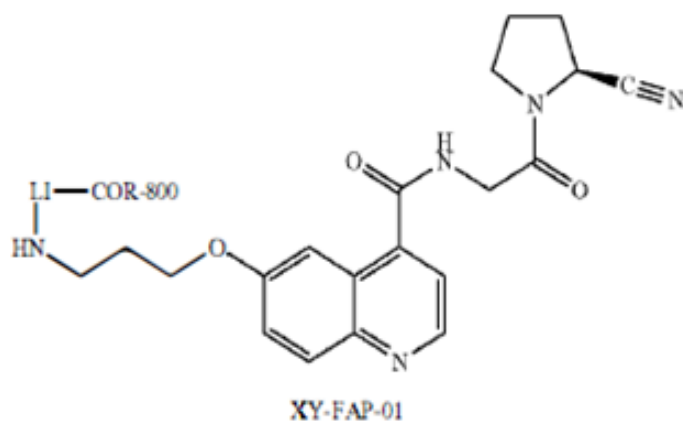
162. As discussed above in Section VII.B,  $R_{3x}$  may be, among other options “—C(O)alkyl.” The ’201 patent explains that when an “alkyl” group is intended to be limited to a chain of a certain length, it is designated as such using certain nomenclature. For example, the ’201 patent would represent an alkyl chain having between one and ten carbons as a “C<sub>1</sub>-C<sub>10</sub> alkyl.” *Id.* at 39:43-50. In contrast, a POSA would understand that the use of “alkyl” 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. Because there is no inherent limit to the number of carbons in an alkyl groups, the scope of an “alkyl” group with an unspecified number of carbons is virtually unlimited. 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.” *Id.* at 42:64-67. Thus, without a number of carbon atoms or rings designated, the —C(O)aryl-, —C=C—C(O)aryl, and —C=C—S(O)<sub>2</sub>aryl groups also have a countless number of possibilities.

163. Broadening the scope of this term even further, the '201 patent's specification explains that terms like "alkyl" and "aryl" are intended to encompass both substituted and unsubstituted forms. *Id.* 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, alkoxy, hydroxyl, nitro, amino, alkylamino, dialkylamino, sulfate, and mercapto." *Id.* at 40:20-26. A POSA would understand from this permissive, non-limiting language that each substituted form can itself be further substituted, without limit.

164. Given the vast scope of the claimed invention, it is my opinion that this factor favors a finding that a POSA would have engaged in undue experimentation to practice the claimed invention.

## **2. Existence of Specific Working Examples**

165. Although the scope of the claims is virtually unlimited, 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. Both examples feature the same A moiety. Although the two examples have different B moieties and linkers, two examples are insufficient to properly represent the vast options at these two positions given the numerous possibilities available. Moreover, the specification also fails to provide a method for determining which B moieties are “suitable” and which linkers have “bifunctionalization adapted to form a chemical bond with B and A.” A POSA would

have had to engage in an iterative, trial-and-error process to discover what will satisfy the functional language used to define the B and L moieties and what will not.

166. Given the small number of working examples and the lack of diversity in the structures of the working examples that are provided, it is my opinion that this factor favors a finding that a POSA would have engaged in undue experimentation to practice the claimed invention.

### **3. Guidance in the Specification**

167. As discussed with respect to the factor above, although the scope of the claims is very large, if not virtually unlimited, the specification provides only two examples falling within the scope of the claims: XY-FAP-01 and XY-FAP-02. *See id.* at 31:30-65. Moreover, the '201 patent contains no disclosures or explanations that would allow a POSA to determine which structural features will perform the claimed functions of the claimed B moiety or L linker. The '201 patent does not disclose any common structural (or other) aspect 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.” 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.

168. Given the lack of guidance provided in the specification, it is my opinion that this factor favors a finding that a POSA would have engaged in undue experimentation to practice the claimed invention.

#### **4. Level of Ordinary Skill in the Art**

169. In my opinion, this factor is neutral. 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. 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. 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.

170. At this level of skill, the functional limitations recited in the challenged claims would require a POSA to perform countless lengthy, sometimes challenging or difficult or unpredictable experiments to determine whether the claims are satisfied. As discussed above, 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 groups meet the functional language recited in the claims.

## **5. Nature and Predictability of the Art**

171. Patent Owner conceded during prosecution of the '201 patent that “the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.” EX1004 at 1201 (Pomper Declaration). Working in this field involves optimizing numerous parameters. Specifically, the claims of the '201 patent require a compound including (1) an A moiety that targets FAP- $\alpha$  and having a function falling within the genus recited in the claims; (2) a B moiety that is defined using functional language requiring an “optical or radiolabeled functional group suitable for” optical imaging, PET imaging, SPECT imaging, or radiotherapy; and (3) a linker moiety that is defined using functional language requiring “bi-functionalization adapted to form a chemical bond with B and A” and would vary based upon the A and B moieties used. Further, the '201 patent does not describe which features—structural or otherwise—would be needed for the compound to perform the claimed functions for the B moiety, i.e., be “suitable for” optical imaging, PET imaging, SPECT imaging, or radiotherapy, or for the linker moiety, i.e., “bi-functionalization adapted to form a chemical bond with B and A.” Instead, the '201 patent calls for a make-

and-screen approach, which merely creates an invitation for further iterative and extensive research.

## **6. Quantity of Experimentation Needed**

172. Given the breadth of the claims, a POSA would be required to conduct a vast number of experiments to determine which compounds fall within the scope of the claims, which require a compound including (1) an A moiety that targets FAP- $\alpha$  and having a function falling within the genus recited in the claims; (2) a B moiety that is defined using functional language requiring an “optical or radiolabeled functional group suitable for” optical imaging, PET imaging, SPECT imaging, or radiotherapy; and (3) a linker moiety that is defined using functional language requiring “bi-functionalization adapted to form a chemical bond with B and A.” In particular, the functional language used to define the B and L moieties would require a POSA to perform complex, difficult, and potentially unpredictable experiments to determine whether the claims are satisfied. The '201 patent does little if anything to address this complexity. It provides only two working examples falling within the scope of the claims, and does not provide any additional information 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.”

173. It is my opinion that this factor favors a finding that a POSA would have needed to engage in undue experimentation to practice the claimed invention.

**7. How Routine Any Necessary Experimentation Is in the Relevant Field**

174. In view of the broad functional limitations recited in the challenged claims, a POSA would be required to perform countless lengthy, sometimes challenging or difficult, and often unpredictable experiments to determine whether the claims are satisfied. Thus, it is my opinion that this factor favors a finding that a POSA would have engaged in undue experimentation to practice the claimed invention.

**8. Weighing the *Wands* Factors**

175. Weighing the *Wands* factors supports finding a lack of enablement for the full scope of the challenged claims. The breadth of the challenged claims include an A moiety that includes a virtually unlimited number of possible alkyl and aryl substituents, which can themselves be further substituted by a similarly unlimited number of possible alkyl and aryl substituents and so on. The claims also include a B moiety and a linker that are defined using broad functional language that results in nothing more than an unfathomably large exercise in making and testing compounds. Thus, the claims encompass a vast genus containing a virtually unlimited number of species.

176. Given the vast genus, a POSA would have looked to the '201 patent for guidance, but 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. The amount of testing and experimentation required to enable a skilled artisan to practice the full scope of the very large claimed genus would have been far more than routine—it would have been undue.

**D. Ground IV: Claims 1-3 Lack Written Description**

177. In my opinion, the claims of the '201 patent lack written description. The specification and disclosure of the of the '201 patent is insufficiently specific to indicate to a POSA that the inventors were in possession of the subject matter of the claims. In particular, the '201 patent does not provide written description support for the broad functional language recited in the claims.

178. The '201 patent claims a structurally and functionally large, if not unlimited, genus of compounds, but, in my opinion, the '201 patent does not contain a proportionally broad written description. The '201 patent specifies merely 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.” Despite using this broad functional

language, the '201 patent provides only two working examples falling within the scope of the claims and does not even describe why or how these two compounds perform the claimed functions, or why other compounds do not. The '201 patent also fails to provide any additional guidance permitting a POSA to determine what characteristics are most likely to meet these functional limitations.

179. Thus, in my opinion, the '201 patent fails to provide an adequate written description for claims 1-3.

**E. Ground V: Claims 1-3 are Indefinite**

180. The claims of the '201 patent require “[a] low molecular weight compound of Formula (I): B-L-A (I).” EX1001, Certificate of Correction, claims 1, 3. However, the meaning of the term “low molecular weight” or “LMW” can vary in the art based on the field of study and the context. The Patent Owner has not clearly defined this phrase in the '201 patent or its file history, and the Patent Owner’s statements during prosecution only introduced more uncertainty. Thus, it is my opinion that the meaning of the “low molecular weight” limitation lacks “reasonable certainty” and is indefinite.

181. The phrase “low molecular weight” or “LMW” is mentioned only three times in the '201 patent specification, as follows:

*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. To date, however, no **LMW** ligand has been reported with ideal properties for nuclear imaging of FAP- $\alpha$ .

*Id.* at 1:60-67 (citations omitted) (emphasis added).

Accordingly, in some embodiments, the presently disclosed subject matter provides potent and selective **low-molecular-weight (LMW)** ligands of FAP- $\alpha$ , i.e., an FAP- $\alpha$  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- $\alpha$ .

*Id.* at 7:46-54 (emphasis added).

182. None of these passages define “low molecular weight” or provide sufficient guidance about the Patent Owner’s intended meaning of the phrase. Because the first two mentions provide a comparison to antibodies, one would, at best, interpret a “low molecular weight” to be lower than the molecular weight of an antibody. However, the two major classes of antibody molecules have molecular weights of 150,000 and 900,000 Daltons, respectively. EX1019. Therefore, tying the meaning of the phrase LMW to the molecular weight of an antibody introduces yet another ambiguity.

183. During prosecution of the ’201 patent, after Patent Owner added the phrase “low molecular weight” to the claims in an attempt to overcome the prior art, Patent Owner provided another statement:

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/what-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 (December 13, 2023 Office Action Response); *see also id.* at 1198 (Pomper Declaration), 1273 (December 18, 2023 Supplemental Amendment).

184. I disagree with Patent Owner’s assertion that the term “low molecular weight” has a clear meaning. As I stated above, the term “low molecular weight” would be interpreted differently by scientists in various fields. The Patent Owner’s reference to a range of “about 50 Daltons to about 1500 Daltons” would not be understood by a POSA to constitute a definition of “low molecular weight,” but

instead as a non-limiting “typical[]” general range of about 50 Da to about 1500 Da. Notably, each of the references provided in Patent Owner’s explanation is related to the field of metabolomics or the scientific study of metabolites. Yet, there is no mention of metabolomics anywhere in the ’201 patent specification. Furthermore, the ’201 patent specification specifically states that “the injected compound is *not metabolized* by the body prior to excretion.” EX1001 at 35:66-67 (emphasis added). Therefore, these references are unrelated to the ’201 patent, which discusses imaging and radiotherapeutics agents, further undercutting the weight a POSA would give this statement when attempting to determine the meaning of “low molecular weight” in the ’201 patent.

185. To the extent Patent Owner argues that its reference to a general range of about 50 Da to about 1500 Da constitutes a definition of the term “low molecular weight,” I disagree. The patent specification itself provides several examples of compounds that would have a molecular weight greater than 1,500 Da but would otherwise fall within the scope of the claims. For example, moiety B is 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. If any of these fluorescent dyes are included 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 considering the addition of the FAP- $\alpha$  targeting moiety, A, and the linker, L, and the additional weight those components would impart. These contradictory disclosures further demonstrates the ambiguity of the ’201 patent’s usage of the term “low molecular weight.”

186. The phrase “low molecular weight” was further discussed during prosecution. *See* EX1004 at 1214 (December 13, 2023 Office Action Response); *see also id.* at 1197 (Pomper Declaration), 1272 (December 18, 2023 Supplemental Amendment). Patent Owner pointed to its definition of “polymer” in the ’201 patent specification as “a molecule of high relative molecule mass,” and asserted that this distinguishes “low molecular weight compounds” from “polymers.” *See id.* at 1214 (December 13, 2023 Office Action Response); *see also id.* at 1197 (Pomper Declaration), 1272 (December 18, 2023 Supplemental Amendment). However, like antibodies, polymers are a class of compounds having a wide range of molecular weights. *See, e.g.,* EX1020 (discussing common polymers with molecular weights ranging from 8,000 Da to 400,000). And, contradictorily, the ’201 patent specification discloses that polymers can be included in the claimed compounds. “Suitable” embodiments of the linker, L, are described as disclosed in Pomper. 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. EX1024 at Abstract. Accordingly, the prosecution history and the '201 patent specification contain contradictory teachings that fail to provide clarity relating to this claim term.

187. In light of the ambiguity and contradictory teachings of the '201 patent specification and prosecution history, there is no clear definition of the phrase “low molecular weight” in the claims of the '201 patent. Thus, a POSA would not be reasonably certain as to the scope of the invention and, in my opinion, the claims are indefinite.

## **IX. CONCLUSION**

188. Based on the above, it is my opinion that each of claims of the '201 patent is invalid.