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CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)				
First Named Inventor:	Xing YANG	Nonprovisional Application N known):	lumber (if	
Title of Invention:	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA			
APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.				
 The processing fee set forth in 37 CFR 1.17(i)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently \$0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application. 				
 I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed. 				
3. The applicable box is checked below:				
I. <u> Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)</u>				
i. (a) The This	application is an original nonprov certification and request is being OR-	risional utility applicatic i filed with the utility ap 	n filed under 35 U.S.C. 111(a). plication via EFS-Web.	
(b) The This	application is an original nonprovice retification and request is being	/isional plant applicatio i filed with the plant ap	n filed under 35 U.S.C. 111(a). blication in paper.	
ii. An exec invento filed wit	cuted inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each r, <u>or</u> the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is h the application.			
II. Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)				
 A request for continued examination has been filed with, or prior to, this form. If the application is a utility application, this certification and request is being filed via EFS-Web. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2). 				
_{Signature} /Jeffr	ey W. Childers/		Date 2023-07-18	
Name (Print/Typed) Jeffrey W. Childers		Practitioner Registration Number 58126		
<u>Note</u>: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.*				

 \checkmark *Total of <u>1</u> forms are submitted.

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The information provided by you in this form will be subject to the following routine uses:

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- 7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
- 8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
- 9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application 16/758,182, filed April 22, 2020, which is a U.S. §371 National Entry Application of PCT/US2018/057086, filed October 23, 2018, which claims the benefit of U.S. Provisional Application No. 62/575,607, filed October 23, 2017, each of which is incorporated herein by reference in its entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under CA197470 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Fibroblast-activation protein- α (FAP- α) expression has been detected on the surface of fibroblasts in the stroma surrounding >90% of the epithelial cancers examined, including malignant breast, colorectal, skin, prostate and pancreatic cancers. (Garin-Chesa, et al., 1990; Rettig, et al., 1993; Tuxhorn, et al., 2002; Scanlan, et al., 1994). It is a characteristic marker for carcinoma-associated-fibroblast (CAF), which plays a critical role in promoting angiogenesis, proliferation, invasion, and inhibition of tumor cell death. (Allinen, et al., 2004; Franco, et al., 2010). In healthy adult tissues, FAP- α expression is only limited to areas of tissue remodeling or wound healing. (Scanlan, et al., 1994; Yu, et al., 2010; Bae, et al., 2008; Kraman, et al., 2010). In addition, FAP- α -positive cells are observed during embryogenesis in areas of chronic inflammation, arthritis, and fibrosis, as well as in soft tissue and bone sarcomas. (Scanlan, et al., 1994; Yu, et al., 2010). These characteristics make FAP- α a potential imaging and radiotherapeutic target for cancer and inflammation diseases.

Because FAP- α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and nontarget tissue clearance (normally 2–5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP- α .

SUMMARY

In some aspects, the presently disclosed subject matter provides a compound of Formula (I):

B—L—A (I)

wherein: A is a targeting moiety for FAP- α ; B is any optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

In particular aspects, A is an FAP-a targeting moiety having the structure of:



wherein each y is independently an integer selected from the group consisting of 0, 1, and 2; R_{1x} , R_{2x} , and $R_{3x'}$, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is H; R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃; R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Het₂ is a 5- or 6membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from -NR_{13x}R_{14x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl, and -S-C₁₋₆alkyl; 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; wherein $\frac{\xi}{2}$ indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

In more particular aspects, A is an FAP- α targeting moiety having the structure of:



wherein ξ indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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

Attorney Docket: JHU-36631.303



In other aspects, the presently disclosed subject matter provides a pharmaceutical composition comprising a compound of formula (I).

In some aspects, the presently disclosed subject matter provides a method for imaging a disease or disorder associated with fibroblast-activation protein- α (FAP- α), the method comprising administering a compound of formula (I), wherein the compound of formula (I) comprises an optical or radiolabeled functional group suitable for optical imaging, PET imaging, or SPECT imaging; and obtaining an image.

In other aspects, the presently disclosed subject matter provides a method for inhibiting fibroblast-activation protein- α (FAP- α), the method comprising administering to a subject in need thereof an effective amount of a compound of formula (I).

In yet other aspects, the presently disclosed subject matter provides a method for treating a fibroblast-activation protein- α (FAP- α)-related disease or disorder, the method comprising administering to a subject in need of treatment thereof an effective amount of a compound of formula (I), wherein the compound of formula (I) comprises a radiolabeled functional group suitable for radiotherapy.

In certain aspects, the (FAP- α)-related disease or disorder is selected from the group consisting of a proliferative disease, including, but not limited to, breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone and connective tissue sarcomas, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, and adenocarcinoma; diseases characterized by tissue remodeling and/or chronic inflammation; disorders involving endocrinological dysfunction; and blood clotting disorders.

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when taken in connection with the accompanying Examples and Figures as best described herein below.

BRIEF DESCRIPTION OF THE FIGURES

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

Having thus described the presently disclosed subject matter in general terms, reference will now be made to the accompanying Figures, which are not necessarily drawn to scale, and wherein:

FIG. 1A, FIG. 1B, and FIG. 1C show the synthetic pathway and structures of representative FAP-targeted agents, **XY-FAP-01** and [¹¹¹**In**]-**XY-FAP-02**. FIG. 1A shows the multi-step synthesis of the ligand precursor, tert-butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate. After each step, the reaction mixture was loaded onto a 25-g C18 cartridge and purified with a MeCN/water/TFA gradient. Identity of intermediate products was confirmed with ¹H NMR. FIG. 1B shows the full structure of optical imaging agent, **XY-FAP-01**. **XY-FAP-01** was produced with a one step reaction between the precursor and IRDye800CW-NHS. The major product was obtained at a yield of 85% after purification with HPLC. FIG. 1C shows the full structure of the SPECT imaging agent, [¹¹¹In]-XY-FAP-02. First, the precursor was functionalized with DOTA via a one step reaction between the precursor and DOTA-GA(t-Bu)₄-NHS. Unlabeled product was purified via HPLC to produce XY-FAP-02. Subsequent radiolabeling with ¹¹¹In and HPLC purification resulted in the radiolabeled product, [¹¹¹In]-XY-FAP-02;

FIG. 2 shows the inhibitory activity of **XY-FAP-01** on human recombinant FAP. The inhibitory activity of **XY-FAP-01** was determined using a fluorogenic FAP assay kit. Enzymatic activity of human recombinant FAP on a native substrate was inhibited in a concentration dependent fashion by **XY-FAP-01**. Semi-log inhibitory curves of **XY-FAP-01** activity were generated and the determined Ki value of **XY-FAP-01** was 1.26 nM;

FIG. 3A, FIG. 3B, and FIG. 3C show the assessment of the *in vitro* binding ability and specificity of **XY-FAP-01** and [¹¹¹**In**]-**XY-FAP-02**. FIG. 3A shows the concentration dependent uptake of **XY-FAP-01** in various cell lines. Cells incubated with various concentrations (range: 50 nM to 0.78 nM) of **XY-FAP-01** were imaged with the LI-COR Pearl Impulse Imager to assess uptake of agent in various FAP-positive and FAP-negative cell lines (left). Dose-response curves of **XY-FAP-01**

uptake in FAP-positive cell lines (NCIH2228, U87, and SKMEL24) and FAPnegative cell lines (PC3, NCIH226, and HCT116) were generated (right). FIG. 3B shows the inhibition of **XY-FAP-01** uptake in FAP-positive cell-lines. Cells incubated with 25-nM **XY-FAP-01** were incubated with various concentrations of either a DPPIV and FAP inhibitor, Talabostat, or a DPPIV-only inhibitor, Sitagliptin. Uptake of **XY-FAP-01** was measured and semi-log inhibitor-response curves were generated for both Talabostat and Sitagliptin. FIG. 3C shows the uptake of [¹¹¹In]-**XY-FAP-02** in FAP-positive U87 and FAP-negative PC3 cell lines. Cells were incubated with 1 μ Ci [¹¹¹In]-**XY-FAP-02** and were washed with cold PBS. Radioactivity of the cell pellets was measured and normalized to the incubated dose;

FIG. 4 is a table showing the ex vivo tissue biodistribution of [¹¹¹In]-XY-FAP-**01** in tumor bearing mice. At 5 min, 0.5 h, 2 h, 6 h, and 12 h after injection of 10 μ Ci [¹¹¹In]-XY-FAP-01, NOD/SKID mice bearing U87 and PC3 tumor xenografts were sacrificed and tissues were collected for biodistribution analysis. Additionally, mice co-injected with unlabeled XY-FAP-02 and 10 μ Ci [¹¹¹In]-XY-FAP-01 were sacrificed at 6 h post-injection to study the effect of blocking on uptake of the radiolabeled compound. Data presented as mean ± standard deviation. ^aStudent's t test comparison of mean %ID/g of PC3 tumor versus U87 tumor demonstrated significant difference between the two groups at 5 min, 0.5 h, 2 h, and 6 h post injection (p < 0.0001). No significant difference between the two groups were seen in the blocking study at 6 h. bStudent's t test comparison of mean %ID/g of PC3 tumor versus U87 tumor demonstrated significant difference between the two groups at 12 h post injection (p=0.0006). ^cStudent's t test comparing %ID/g between PC3 tumor and U87 tumors at 6 h post injection showed significant difference between %ID/g tumors in the blocking study at 6 h versus the normal biodistribution results at 6 h (p<0.0001);

FIG. 5A and FIG. 5B show the time-activity relationship of the *ex vivo* biodistribution of [¹¹¹In]-XY-FAP-02. FIG. 5A shows tissue time activity curves (TACs) of [¹¹¹In]-XY-FAP-02 activity in U87 tumor, PC3 tumor, and blood. FIG. 5B shows the ratios of %ID/g between U87 tumor and PC3 tumor, blood, and muscle (mm) versus time;

FIG. 6 shows serial NIRF-imaging of XY-FAP-01 in tumor bearing mice. NOD/SKID mice bearing FAP-positive U87 (yellow circle) and FAP-negative PC3 (red circle) tumor xenografts were injected with 10 nmol of XY-FAP-01 via the tail vein followed by serial NIRF-imaging on the LI-COR Pearl Impulse Imager. Representative images at 0.5 h, 1 h, 2.5 h, and 4 h after injection are shown;

FIG. 7 shows SPECT-CT images of [¹¹¹In]-XY-FAP-02 at 30 min, 2 h, 6 h, and 24 h after injection in NOD/SKID female mice bearing U87 and PC3 tumor xenografts in the upper flanks; and

FIG. 8 show three-dimensional SPECT-CT images of [¹¹¹In]-XY-FAP-02 at 30 min, 2 h, 6 h, and 24 h after injection in NOD/SKID female mice bearing U87 and PC3 tumor xenografts in the upper flanks.

DETAILED DESCRIPTION

The presently disclosed subject matter now will be described more fully hereinafter with reference to the accompanying Figures, in which some, but not all embodiments of the presently disclosed subject matter are shown. Like numbers refer to like elements throughout. The presently disclosed subject matter may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions and the associated Figures. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.

I. IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-α (FAP-α)

FAP- α is a type II integral membrane serine protease of the prolyl oligopeptidase family, which are distinguished by their ability to cleave the Pro-AA peptide bond (where AA represents any amino acid). It has been shown to play a role in cancer by modifying bioactive signaling peptides through this enzymatic activity (Kelly, et al., 2005; Edosada, et al., 2006). FAP- α expression has been detected on the surface of fibroblasts in the stroma surrounding greater than 90% of the epithelial cancers, including, but not limited to, malignant breast, colorectal, skin, prostate,

pancreatic cancers, and the like, and inflammation diseases, including, but not limited to, arthritis, fibrosis, and the like, with nearly no expression in healthy tissues. Accordingly, imaging and radiotherapeutic agents specifically targeting FAP- α is of clinical importance.

FAP- α exists as a homodimer to carry out its enzymatic function. Inhibitors selectively targeting FAP- α has been reported (Lo, et al., 2009; Tsai, et al., 2010; Ryabtsova, et al., 2012; Poplawski, et al., 2013; Jansen, et al., 2013; Jansen, et al., 2014). The presently disclosed subject matter provides, in part, a FAP- α selective targeting moiety that can be modified with an optical dye, a radiometal chelation complex, and other radiolabeled prosthetic groups, thus providing a platform for the imaging and radiotherapy targeting FAP- α .

Radionuclide molecular imaging, including positron emission tomography (PET), is the most mature molecular imaging technique without tissue penetration limitations. Due to its advantages of high sensitivity and quantifiability, radionuclide molecular imaging plays an important role in clinical and preclinical research (Youn, et al., 2012; Chen, et al., 2014). Many radionuclides, primarily β - and alpha emitters, have been investigated for targeted radioimmunotherapy and include both radiohalogens and radiometals (see Table 1 for representative therapeutic radionuclides).

Table 1. Representative Therapeutic Radionuclides			
β -particle emitters	⁹⁰ Y, ¹³¹ I, ¹⁷⁷ Lu, ¹⁵³ Sm, ¹⁸⁶ Re, ¹⁸⁸ Re, ⁶⁷ Cu, ²¹² Pb		
α-particle emitters	²²⁵ Ac, ²¹³ Bi, ²¹² Bi, ²¹¹ At, ²¹² Pb		
Auger electron emitters	125 I, 123 I, 67 Ga, 111 In		

The highly potent and specific binding moiety targeting FAP- α enables its use in nuclear imaging and radiotherapy. The presently disclosed subject matter provides the first synthesis of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to FAP- α .

Accordingly, in some embodiments, the presently disclosed subject matter provides potent and selective low-molecular-weight (LMW) ligands of FAP- α , i.e., an FAP- α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable *in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α. Importantly, the presently disclosed compounds can be modified, e.g., conjugated with, labeling groups without significantly losing their potency. The presently disclosed approach allows for the convenient labeling of the FAP-α ligand with optical dyes and PET or SPECT isotopes, including, but not limited to, ⁶⁸Ga, ⁶⁴Cu, ¹⁸F, ⁸⁶Y, ⁹⁰Y, ⁸⁹Zr, ¹¹¹In, ^{99m}Tc, ¹²⁵I, ¹²⁴I, for FAP-α related imaging applications. Further, the presently disclosed approach allows for the radiolabeling of the FAP-α ligand with radiotherapeutic isotopes, including but not limited to, ⁹⁰Y, ¹⁷⁷Lu, ¹²⁵I, ¹³¹I, ²¹¹At, ¹¹¹In, ¹⁵³Sm, ¹⁸⁶Re, ¹⁸⁸Re, ⁶⁷Cu, ²¹²Pb, ²²⁵Ac, ²¹³Bi, ²¹²Bi, ²¹²Pb, and ⁶⁷Ga, for FAP-α related radio-therapy.

In a particular embodiment, an optical agent conjugated with IRDye-800CW (**XY-FAP-01**) was synthesized and showed selective uptake *in vitro* on a FAP- α + U87 cell line and *in vivo* on a FAP- α + U87 tumor and clearly detected the tumor. In another particular embodiment, an ¹¹¹In labeled ligand (**XY-FAP-02-[¹¹¹In]**) was successfully obtained in high yield and purity from its precursor with a metal chelator. The *in vivo* study showed clear tumor radiotracer uptake in mice bearing FAP- α -positive U87 tumors with minimum non-specific organ uptake, which allows the specific imaging of FAP- α expressing tumors. The presently disclosed FAP- α targeting moiety can be adapted for use with optical dyes and radioisotopes known in the art for imaging and therapeutic applications targeting FAP- α .

More particularly, in some embodiments, the presently disclosed subject matter provides a compound of the general structure of Formula (I):

B—L—A (I)

wherein: A is a targeting moiety for FAP- α ; 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.

Representative targeting moieties for FAP- α are disclosed in U.S. Patent Application Publication No. US2014/0357650 for Novel FAP Inhibitors to Jansen et al., published Dec. 4, 2014; U.S. Patent No. 9,346,814 for Novel FAP Inhibitors to Jansen et al., issued May 24, 2016; and International PCT Patent Publication No. WO 2013/107820 for Novel FAP Inhibitors to Jansen et al., published July 25, 2013, each of which are incorporate by reference in their entirety. More particularly, U.S. Patent No. 9,346,814 to Jansen et al., discloses FAP- α inhibitors of formula (X), or a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof, which are suitable for use with the presently disclosed subject matter:



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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

 R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

 \checkmark_{*}

represents a 5 to 10-membered N-containing aromatic or non-aromatic monoor bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S.

In particular embodiments, $N \rightarrow *$ is selected from the group consisting

of:



wherein * indicates the point of attachment of the 5 to 10-membered Ncontaining aromatic or non-aromatic mono- or bicyclic heterocycle to –(CH₂)_v–. Accordingly, in some embodiments, A is an FAP-α targeting moiety having the structure of:



wherein each y is independently an integer selected from the group consisting of 0, 1, and 2;

 R_{1x} , R_{2x} , and $R_{3x'}$, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

 R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic monoor bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

wherein $\frac{\xi}{\xi}$ indicates a point of attachment of the FAP- α binding ligand to a linker, e.g., L, or a reporter moiety, such as an optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging or radiotherapy, wherein the point of attachment can be through any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

In particular embodiments, $N \rightarrow *$ is selected from the group consisting of:



In some embodiments, A is an FAP- α targeting moiety having the structure of:



wherein y, R_{1x} , R_{2x} and $R_{3x'}$ are defined as hereinabove; ξ indicates a point of attachment of the FAP- α binding ligand to a linker, e.g., L, or a reporter moiety, such as an optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging or radiotherapy, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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



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



and stereoisomers thereof.

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

of:



In some embodiments, the combination of L and B can be represented by:



wherein the subunits associated with elements p_1 , p_2 , p_3 and p_4 may be in any order; t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; p₁, p_3 , and p_4 are each independently 0 or 1; p_2 is an integer selected from the group consisting of 0, 1, 2, and 3, and when p_2 is 2 or 3, each R_1 is the same or different; m_1 and m_2 are each an integer independently selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6; W_1 is selected from the group consisting of a bond, $-S_{-}$, $-C(=O)-NR_{-}$, and -NR-C(=O)-; W₂ is selected from the group consisting of a bond, -S-, -CH₂-C(=O)-NR-, -C(O)-, -NRC(O)-, -NR'C(O)NR-, -NRC(S)NR'2-, -NRC(O)O-, -OC(O)NR-, -OC(O)-, -C(O)NR-, -NR-C(O)-, -C(O)O-, -(O-CH₂-CH₂)_q- and -(CH₂-CH₂-O)_a-, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-OR_4$, wherein R_4 is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove; Tz is a triazole group that can be present or absent and, if present, is selected from the group consisting of



and ; each R₁ is independently H, C₁-C₆ alkyl, C₃-C₁₂ aryl, $-(CH_2)_q$ -C₃-C₁₂ aryl, $-C_4$ -C₁₆ alkylaryl, or $-(CH_2)_q$ -C₄-C₁₆ alkylaryl; R₂ and R₃ are each independently H and $-CO_2R_5$, wherein R₅ is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₁₂ aryl, and C₄-C₁₆ alkylaryl, wherein when one of R₂ or R₃ is CO₂R₅, then the other is H; V is selected from the group consisting of – C(O)–, -C(S)-, –NRC(O)–, –NRC(S)–, and –OC(O)–; B is any optical or radiolabeled functional group suitable for optical, PET, or SPECT imaging or radiotherapy; and stereoisomers and pharmaceutically acceptable salts thereof.

In some embodiments, L has the following general structure:



wherein p_1 , p_2 , p_3 , m_1 , m_2 , q, t, Tz, W_2 , R, R_1 , R_2 , R_3 , and V are defined as hereinabove.

In some embodiments, L is selected from the group consisting of $-L_1$ -, $-L_2$ -L₃-, and $-L_1$ -L₂-L₃-, wherein:

L₁ is -NR-(CH₂)_q-[O-CH₂-CH₂-O]_q-(CH₂)_q-C(=O)-;

L₂ is -NR-(CH₂)_q-C(COOR₅)-NR-; and

$$L_3 \text{ is -(O=)C-(CH_2)_q-C(=O)-;}$$

wherein each q is independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

In particular embodiments, L is:

 $-(CR_{6}H)_{q}-(CH_{2})_{q}-C(=O)-NR-(CH_{2})_{q}-O- or -NR-(CH_{2})_{q}-O-;$

wherein each q and R is defined hereinabove; and R₆ is H or -COOR₅.

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



wherein u is an integer selected from 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

Suitable linkers are disclosed in U.S. Patent Application Publication No. US2011/0064657 A1, for "Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA), Biological Evaluation, and Use as Imaging Agents," published March 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. US2012/0009121 A1, for "PSMA-Targeting Compounds and Uses Thereof," published January 12, 2012, to Pomper et al, each of which is incorporated by reference in its entirety. In some embodiments, B is a radiolabeled prosthetic group comprising a radioisotope selected from the group consisting of ¹⁸F, ¹²⁴I, ¹²⁵I, ¹³¹I, and ²¹¹At. Representative radiolabeled prosthetic groups include, but are not limited to:



wherein each X is independently a radioisotope selected from the group consisting of ¹⁸F, ¹²⁴I, ¹²⁵I, ¹³¹I, and ²¹¹At; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20.

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



In other embodiments, B comprises a chelating agent. Representative chelating agents include, but are not limited to:



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In some embodiments, B comprises an optical dye, e.g., in particular embodiments, a fluorescent dye. In some embodiments, the fluorescent dye moiety comprises carbocyanine, indocarbocyanine, oxacarbocyanine, thiacarbocyanine and merocyanine, polymethine, coumarine, rhodamine, xanthene, fluorescein, borondipyrromethane (BODIPY), Cy5, Cy5.5, Cy7, VivoTag-680, VivoTag-S680, VivoTag-S750, AlexaFluor660, AlexaFluor680, AlexaFluor700, AlexaFluor750, AlexaFluor790, Dy677, Dy676, Dy682, Dy752, Dy780, DyLight547, Dylight647, HiLyte Fluor 647, HiLyte Fluor 680, HiLyte Fluor 750, IRDye 800CW, IRDye 800RS, IRDye 700DX, ADS780WS, ADS830WS, and ADS832WS.

Representative optical dyes include, but are not limited to:







In some embodiments, the presently disclosed subject matter provides a compound selected from the group consisting of:



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





B. Pharmaceutical Compositions and Administration

In another aspect, the present disclosure provides a pharmaceutical comprising a compound of formula (I) in admixture with a pharmaceutically acceptable carrier, diluent, excipient, or adjuvant. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts or hydrates of the compounds described above.

Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art and include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent or by ion exchange, whereby one basic counterion (base) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt.

When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange, whereby one acidic counterion (acid) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, ptoluenesulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Accordingly, pharmaceutically acceptable salts suitable for use with the presently disclosed subject matter include, by way of example but not limitation, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

In therapeutic and/or diagnostic applications, the compounds of the disclosure can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-slow release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, by inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articular, intra -sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

For injection, the agents of the disclosure may be formulated and diluted in

aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (e.g., patient) to be treated.

For nasal or inhalation delivery, the agents of the disclosure also may be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances, such as saline; preservatives, such as benzyl alcohol; absorption promoters; and fluorocarbons.

Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, the compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A non-limiting dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, the bioavailability of the compound(s), the adsorption, distribution, metabolism, and excretion (ADME) toxicity of the compound(s), and the preference and experience of the attending physician.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl- cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

C. Methods of Imaging using the Compounds of Formula (I), or Pharmaceutical Compositions Thereof

In some embodiments, presently disclosed subject matter provides a method for imaging a disease or disorder associated with fibroblast-activation protein- α (FAP- α), the method comprising administering a compound of formula (I), wherein the compound of formula (I) comprises an optical or radiolabeled functional group suitable for optical imaging, PET imaging, or SPECT imaging; and obtaining an image.

Accordingly, in some embodiments, the presently disclosed subject matter provides a method for imaging one or more cells, organs, or tissues, the method comprising exposing cells or administering to a subject an effective amount of a compound of formula (I) with an optical or radioisotopic label suitable for imaging. In some embodiments, the one or more organs or tissues include prostate tissue, kidney tissue, brain tissue, vascular tissue, or tumor tissue.

The imaging methods of the invention are suitable for imaging any physiological process or feature in which FAP- α is involved, for example, identifying areas of tissues or targets which exhibit or express high concentrations of FAP- α . Physiological processes in which FAP- α is involved include, but are not limited to: (a) proliferation diseases (including but not limited to cancer); (b) tissue remodeling and/or chronic inflammation (including but not limited to fibrotic disease, wound healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation); and (c) endocrinological disorders (including but not limited to disorders of glucose metabolism).

In certain embodiments, the radiolabeled compound is stable in vivo.

In certain embodiments, the radiolabeled compound is detected by positron emission tomography (PET) or single photon emission computed tomography (SPECT).

In certain embodiments, the optical reporting moiety is detected by fluorescence, such as fluorescence microscopy.

In certain embodiments, the presently disclosed compounds are excreted from tissues of the body quickly to prevent prolonged exposure to the radiation of the radiolabeled compound administered to the subject. Typically, the presently disclosed compounds are eliminated from the body in less than about 24 hours. More typically, the presently disclosed compounds are eliminated from the body in less than about 24 hours. More typically, the presently disclosed compounds are eliminated from the body in less than about 24 hours. More typically, the presently disclosed compounds are eliminated from the body in less than about 16 hours, 12 hours, 8 hours, 6 hours, 4 hours, 2 hours, 90 minutes, or 60 minutes. Exemplary compounds are eliminated in between about 60 minutes and about 120 minutes. In certain embodiments, the presently disclosed compounds are stable in vivo such that substantially all, e.g., more than about 50%, 60%, 70%, 80%, or 90% of the injected compound is not metabolized by the body prior to excretion.

Additionally, for in vitro applications, such as in vitro diagnostic and research applications, body fluids and cell samples of the above subjects will be suitable for use, such as mammalian, particularly primate such as human, blood, urine or tissue samples, or blood urine or tissue samples of the animals mentioned for veterinary applications.

Other embodiments provide kits comprising a compound of formula (I). In certain embodiments, the kit provides packaged pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of formula (I). In certain embodiments the packaged pharmaceutical composition will comprise the reaction precursors necessary to generate the compound of formula (I) upon combination with a radiolabeled precursor. Other packaged pharmaceutical compositions for preparing compounds of formula (I) from supplied precursors, instructions for using the composition to image cells or tissues expressing FAP- α .

In certain embodiments, a kit containing from about 1 to about 30 mCi of the radionuclide-labeled imaging agent described above, in combination with a pharmaceutically acceptable carrier, is provided. The imaging agent and carrier may be provided in solution or in lyophilized form. When the imaging agent and carrier of the kit are in lyophilized form, the kit may optionally contain a sterile and physiologically acceptable reconstitution medium such as water, saline, buffered saline, and the like. The kit may provide a compound of formula (I) in solution or in lyophilized form, and these components of the kit may optionally contain stabilizers such as NaCl, silicate, phosphate buffers, ascorbic acid, gentisic acid, and the like. Additional stabilization of kit components may be provided in this embodiment, for example, by providing the reducing agent in an oxidation-resistant form. Determination and optimization of such stabilizers and stabilization methods are well within the level of skill in the art.

In certain embodiments, a kit provides a non-radiolabeled precursor to be combined with a radiolabeled reagent on-site.

Imaging agents may be used in accordance with the presently disclosed methods by one of skill in the art. Images can be generated by virtue of differences in the spatial distribution of the imaging agents which accumulate at a site when contacted with FAP- α . The spatial distribution may be measured using any means suitable for the particular label, for example, a gamma camera, a PET apparatus, a SPECT apparatus, and the like. The extent of accumulation of the imaging agent may be quantified using known methods for quantifying radioactive emissions or fluorescence. A particularly useful imaging approach employs more than one imaging agent to perform simultaneous studies.

In general, a detectably effective amount of the imaging agent of the invention is administered to a subject. A "detectably effective amount" of the imaging agent is defined as an amount sufficient to yield an acceptable image using equipment which is available for clinical use. A detectably effective amount of the imaging agent may be administered in more than one injection. The detectably effective amount of the imaging agent of the invention can vary according to factors such as the degree of susceptibility of the individual, the age, sex, and weight of the individual, idiosyncratic responses of the individual, and the dosimetry. Detectably effective amounts of the imaging agent also can vary according to instrument and film-related factors. Optimization of such factors is well within the level of skill in the art. The amount of imaging agent used for diagnostic purposes and the duration of the imaging study will depend upon the radionuclide used to label the agent, the body mass of the patient, the nature and severity of the condition being treated, the nature of therapeutic treatments which the patient has undergone, and on the idiosyncratic responses of the patient. Ultimately, the attending physician will decide the amount of imaging agent to administer to each individual patient and the duration of the imaging study.

D. Methods of Treating a FAP-α Related Disease or Disorder using the Compounds of Formula (I), or Pharmaceutical Compositions Thereof

In other embodiments, the presently disclosed compounds of formula (I) can be used to treat a subject afflicted with one or more FAP- α related diseases or disorders including, but not limited to: (a) proliferation (including but not limited to cancer); (b) tissue remodeling and/or chronic inflammation (including but not limited to fibrotic disease, wound healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation); and (c) endocrinological disorders (including but not limited to disorders of glucose metabolism).

Accordingly, in some embodiments, the one or more FAP- α related disease or disorder is selected from the group consisting of a proliferative disease, including, but not limited to, breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone and

connective tissue sarcomas, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, and adenocarcinoma; diseases characterized by tissue remodeling and/or chronic inflammation; disorders involving endocrinological dysfunction; and blood clotting disorders.

In general, the "effective amount" of an active agent or drug delivery device refers to the amount necessary to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of an agent or device may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the makeup of the pharmaceutical composition, the target tissue, and the like.

In other embodiments, the method can be practiced *in vitro* or *ex vivo* by introducing, and preferably mixing, the compound and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube. The method can be practiced *in vivo*, in which case contacting means exposing the target in a subject to at least one compound of the presently disclosed subject matter, such as administering the compound to a subject via any suitable route. According to the presently disclosed subject matter, contacting may comprise introducing, exposing, and the like, the compound at a site distant to the cells to be contacted, and allowing the bodily functions of the subject, or natural (e.g., diffusion) or man-induced (e.g., swirling) movements of fluids to result in contact of the compound and the target.

The subject treated by the presently disclosed methods in their many embodiments is desirably a human subject, although it is to be understood that the methods described herein are effective with respect to all vertebrate species, which are intended to be included in the term "subject." Accordingly, a "subject" can include a human subject for medical purposes, such as for the treatment of an existing condition or disease or the prophylactic treatment for preventing the onset of a condition or disease, or an animal (non-human) subject for medical, veterinary purposes, or developmental purposes. Suitable animal subjects include mammals including, but not limited to, primates, e.g., humans, monkeys, apes, and the like; bovines, e.g., cattle, oxen, and the like; ovines, e.g., sheep and the like; caprines, e.g., goats and the like; porcines, e.g., pigs, hogs, and the like; equines, e.g., horses, donkeys, zebras, and the like; felines, including wild and domestic cats; canines, including dogs; lagomorphs, including rabbits, hares, and the like; and rodents, including mice, rats, and the like. An animal may be a transgenic animal. In some

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embodiments, the subject is a human including, but not limited to, fetal, neonatal, infant, juvenile, and adult subjects. Further, a "subject" can include a patient afflicted with or suspected of being afflicted with a condition or disease. Thus, the terms "subject" and "patient" are used interchangeably herein. In some embodiments, the subject is human. In other embodiments, the subject is non-human.

As used herein, the term "treating" can include reversing, alleviating, inhibiting the progression of, preventing or reducing the likelihood of the disease, or condition to which such term applies, or one or more symptoms or manifestations of such disease or condition.

"Preventing" refers to causing a disease, condition, or symptom or manifestation of such, or worsening of the severity of such, not to occur. Accordingly, the presently disclosed compounds can be administered prophylactically to prevent or reduce the incidence or recurrence of the disease, or condition.

II. DEFINITIONS

Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this presently described subject matter belongs.

While the following terms in relation to compounds of formula (I) are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter. These definitions are intended to supplement and illustrate, not preclude, the definitions that would be apparent to one of ordinary skill in the art upon review of the present disclosure.

The terms substituted, whether preceded by the term "optionally" or not, and substituent, as used herein, refer to the ability, as appreciated by one skilled in this art, to change one functional group for another functional group on a molecule, provided that the valency of all atoms is maintained. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The substituents also may be further substituted (e.g., an aryl group substituent may have another substituent off it, such as another aryl group, which is further substituted at one or more positions).

Where substituent groups or linking groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O$ - is equivalent to $-OCH_2$ -; -C(=O)O- is equivalent to -OC(=O)-; -OC(=O)NR- is equivalent to -NRC(=O)O-, and the like.

When the term "independently selected" is used, the substituents being referred to (e.g., R groups, such as groups R_1 , R_2 , and the like, or variables, such as "m" and "n"), can be identical or different. For example, both R_1 and R_2 can be substituted alkyls, or R_1 can be hydrogen and R_2 can be a substituted alkyl, and the like.

The terms "a," "an," or "a(n)," when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is Rsubstituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

A named "R" or group will generally have the structure that is recognized in the art as corresponding to a group having that name, unless specified otherwise herein. For the purposes of illustration, certain representative "R" groups as set forth above are defined below.

Descriptions of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.
Unless otherwise explicitly defined, a "substituent group," as used herein, includes a functional group selected from one or more of the following moieties, which are defined herein:

The term hydrocarbon, as used herein, refers to any chemical group comprising hydrogen and carbon. The hydrocarbon may be substituted or unsubstituted. As would be known to one skilled in this art, all valencies must be satisfied in making any substitutions. The hydrocarbon may be unsaturated, saturated, branched, unbranched, cyclic, polycyclic, or heterocyclic. Illustrative hydrocarbons are further defined herein below and include, for example, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, allyl, vinyl, *n*-butyl, *tert*-butyl, ethynyl, cyclohexyl, and the like.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent groups, having the number of carbon atoms designated (i.e., C_1 - C_{10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term "alkyl" refers to C_{1-20} inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons, linear (i.e., "straight-chain"), branched, or cyclic, saturated or at least partially and in some cases fully unsaturated (i.e., alkenyl and alkynyl) hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single hydrogen atom.

Representative saturated hydrocarbon groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *sec*-pentyl, isopentyl, neopentyl, *n*-hexyl, *sec*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*-undecyl, dodecyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and homologs and isomers thereof.

"Branched" refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain. "Lower alkyl" refers to an alkyl group having 1 to about 8 carbon atoms (i.e., a C_{1-8} alkyl), e.g., 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. "Higher alkyl" refers to an alkyl group having about 10 to about 20 carbon atoms, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. In certain embodiments, "alkyl" refers, in particular, to C_{1-8} straight-chain alkyls. In other embodiments, "alkyl" refers, in particular, to C_{1-8} branched-chain alkyls. Alkyl groups can optionally be substituted (a "substituted alkyl") with one or more alkyl group substituents, which can be the same or different. The term "alkyl group substituent" includes but is not limited to alkyl, substituted alkyl, halo, alkylamino, arylamino, acyl, hydroxyl, aryloxyl, alkoxyl, alkylthio, arylthio, aralkyloxyl, aralkylthio, carboxyl, alkoxycarbonyl, oxo, and cycloalkyl. There can be optionally inserted along the alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, lower alkyl (also referred to herein as "alkylaminoalkyl"), or aryl.

Thus, as used herein, the term "substituted alkyl" includes alkyl groups, as defined herein, in which one or more atoms or functional groups of the alkyl group are replaced with another atom or functional group, including for example, alkyl, substituted alkyl, halogen, aryl, substituted aryl, alkoxyl, hydroxyl, nitro, amino, alkylamino, dialkylamino, sulfate, and mercapto.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon group, or combinations thereof, consisting of at least one carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃.

As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)NR', -NR'R'', -OR', -SR, -S(O)R, and/or $-S(O_2)R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R or the like, it will be understood that the terms heteroalkyl and -NR'R'' are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

"Cyclic" and "cycloalkyl" refer to a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, e.g., 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The cycloalkyl group can be optionally partially unsaturated. The cycloalkyl group also can be optionally substituted with an alkyl group substituent as defined herein, oxo, and/or alkylene. There can be optionally inserted along the cyclic alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, unsubstituted alkyl, substituted alkyl, aryl, or substituted aryl, thus providing a heterocyclic group. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, and cycloheptyl. Multicyclic cycloalkyl rings include adamantyl, octahydronaphthyl, decalin, camphor, camphane, and noradamantyl, and fused ring systems, such as dihydro- and tetrahydronaphthalene, and the like.

The term "cycloalkylalkyl," as used herein, refers to a cycloalkyl group as defined hereinabove, which is attached to the parent molecular moiety through an alkyl group, also as defined above. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

The terms "cycloheteroalkyl" or "heterocycloalkyl" refer to a non-aromatic ring system, unsaturated or partially unsaturated ring system, such as a 3- to 10member substituted or unsubstituted cycloalkyl ring system, including one or more heteroatoms, which can be the same or different, and are selected from the group consisting of nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), and silicon (Si), and optionally can include one or more double bonds.

The cycloheteroalkyl ring can be optionally fused to or otherwise attached to other cycloheteroalkyl rings and/or non-aromatic hydrocarbon rings. Heterocyclic rings include those having from one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. In certain embodiments, the term heterocylic refers to a non-aromatic 5-, 6-, or 7- membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected ring has

0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds, and each 7membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative cycloheteroalkyl ring systems include, but are not limited to pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, quinuclidinyl, morpholinyl, thiomorpholinyl, thiadiazinanyl, tetrahydrofuranyl, and the like.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4- morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 -piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl."

More particularly, the term "alkenyl" as used herein refers to a monovalent group derived from a C_{1-20} inclusive straight or branched hydrocarbon moiety having at least one carbon-carbon double bond by the removal of a single hydrogen molecule. Alkenyl groups include, for example, ethenyl (i.e., vinyl), propenyl, butenyl, 1-methyl-2-buten-1-yl, pentenyl, hexenyl, octenyl, allenyl, and butadienyl.

The term "cycloalkenyl" as used herein refers to a cyclic hydrocarbon containing at least one carbon-carbon double bond. Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, 1,3-cyclohexadienyl, cycloheptenyl, cycloheptatrienyl, and cyclooctenyl. The term "alkynyl" as used herein refers to a monovalent group derived from a straight or branched C_{1-20} hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon triple bond. Examples of "alkynyl" include ethynyl, 2-propynyl (propargyl), 1-propynyl, pentynyl, hexynyl, and heptynyl groups, and the like.

The term "alkylene" by itself or a part of another substituent refers to a straight or branched bivalent aliphatic hydrocarbon group derived from an alkyl group having from 1 to about 20 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. The alkylene group can be straight, branched or cyclic. The alkylene group also can be optionally unsaturated and/or substituted with one or more "alkyl group substituents." There can be optionally inserted along the alkylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms (also referred to herein as "alkylaminoalkyl"), wherein the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups include methylene (-CH₂-); ethylene (-CH₂-CH₂-); propylene (-(CH₂)₃-); cyclohexylene (-C₆H₁₀-); -CH=CH-CH=CH-, -CH=CH-CH₂-, -CH₂CH₂CH₂CH₂CH₂-, -CH2CH=CHCH2-, -CH2CsCCH2-, -CH2CH2CH(CH2CH2CH3)CH2-, $-(CH_2)_q-N(R)-(CH_2)_r$, wherein each of q and r is independently an integer from 0 to about 20, e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, and R is hydrogen or lower alkyl; methylenedioxyl (-O-CH₂-O-); and ethylenedioxyl (-O-(CH₂)₂–O–). An alkylene group can have about 2 to about 3 carbon atoms and can further have 6-20 carbons. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being some embodiments of the present disclosure. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The term "heteroalkylene" by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (e.g., alkyleneoxo, alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)OR'- represents both -C(O)OR'- and –R'OC(O)-.

The term "aryl" means, unless otherwise stated, 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. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrazolyl, 2imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4- oxazolyl, 5oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2pyrimidyl, 4- pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1isoquinolyl, 5- isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent forms of aryl and heteroaryl, respectively.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms "arylalkyl" and "heteroarylalkyl" are meant to include those groups in which an aryl or heteroaryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, furylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(l-naphthyloxy)propyl, and the like). However, the term "haloaryl," as used herein is meant to cover only aryls substituted with one or more halogens.

Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" refers to a carbon or heteroatom.

Further, a structure represented generally by the formula:



as used herein refers to a ring structure, for example, but not limited to a 3-carbon, a 4-carbon, a 5-carbon, a 6-carbon, a 7-carbon, and the like, aliphatic and/or aromatic cyclic compound, including a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure, comprising a substituent R group, wherein the R group can be present or absent, and when present, one or more R groups can each be substituted on one or more available carbon atoms of the ring structure. The presence or absence of the R group and number of R groups is determined by the value of the variable "n," which is an integer generally having a value ranging from 0 to the number of carbon atoms on the ring available for substitution. Each R group, if more than one, is substituted on an available carbon of the ring structure rather than on another R group. For example, the structure above where n is 0 to 2 would comprise compound groups including, but not limited to:



and the like.

A dashed line representing a bond in a cyclic ring structure indicates that the bond can be either present or absent in the ring. That is, a dashed line representing a bond in a cyclic ring structure indicates that the ring structure is selected from the group consisting of a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure.

The symbol (***********) denotes the point of attachment of a moiety to the remainder of the molecule.

When a named atom of an aromatic ring or a heterocyclic aromatic ring is defined as being "absent," the named atom is replaced by a direct bond.

Each of above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl, and "heterocycloalkyl", "aryl," "heteroaryl," "phosphonate," and "sulfonate" as well as their divalent derivatives) are meant to include both substituted and unsubstituted forms of the indicated group. Optional substituents for each type of group are provided below.

Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent

and divalent derivative groups (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R", -OC(O)R', -C(O)R', -CO₂R', -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R", -NR"C(O)OR', -NR-C(NR'R")=NR", -S(O)R', -S(O)₂R', -S(O)₂NR'R", -NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such groups. R', R", R"" and R"" each may independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. As used herein, an "alkoxy" group is an alkyl attached to the remainder of the molecule through a divalent oxygen. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R" and R" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7- membered ring. For example, -NR'R" is meant to include, but not be limited to, 1- pyrrolidinyl and 4morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

Similar to the substituents described for alkyl groups above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, -OR', -NR'R", -SR', -SiR'R"R", -OC(O)R', -C(O)R', -CO₂R', -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)R", -NR"C(O)OR', -NR-C(NR'R"R")=NR"", -NR-C(NR'R")=NR" -S(O)R', -S(O)₂R', -S(O)₂NR'R", -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxo, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R", R" and R"" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted or unsubstituted or unsubstituted heteroalkyl, substituted or

unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R" and R" groups when more than one of these groups is present.

Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CRR')_s-X'- (C"R'")_d-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituents R, R', R" and R'" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the term "acyl" refers to an organic acid group wherein the -OH of the carboxyl group has been replaced with another substituent and has the general formula RC(=O)-, wherein R is an alkyl, alkenyl, alkynyl, aryl, carbocylic, heterocyclic, or aromatic heterocyclic group as defined herein). As such, the term "acyl" specifically includes arylacyl groups, such as a 2-(furan-2-yl)acetyl)- and a 2-phenylacetyl group. Specific examples of acyl groups include acetyl and benzoyl. Acyl groups also are intended to include amides, -RC(=O)NR', esters, -RC(=O)OR', ketones, -RC(=O)R', and aldehydes, -RC(=O)H.

The terms "alkoxyl" or "alkoxy" are used interchangeably herein and refer to a saturated (i.e., alkyl–O–) or unsaturated (i.e., alkenyl–O– and alkynyl–O–) group attached to the parent molecular moiety through an oxygen atom, wherein the terms "alkyl," "alkenyl," and "alkynyl" are as previously described and can include C_{1-20} inclusive, linear, branched, or cyclic, saturated or unsaturated oxo-hydrocarbon chains, including, for example, methoxyl, ethoxyl, propoxyl, isopropoxyl, *n*-butoxyl, *sec*-butoxyl, *tert*-butoxyl, and *n*-pentoxyl, neopentoxyl, *n*-hexoxyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkyl-O-alkyl ether, for example, a methoxyethyl or an ethoxymethyl group.

"Aryloxyl" refers to an aryl-O- group wherein the aryl group is as previously described, including a substituted aryl. The term "aryloxyl" as used herein can refer to phenyloxyl or hexyloxyl, and alkyl, substituted alkyl, halo, or alkoxyl substituted phenyloxyl or hexyloxyl.

"Aralkyl" refers to an aryl-alkyl-group wherein aryl and alkyl are as previously described and includes substituted aryl and substituted alkyl. Exemplary aralkyl groups include benzyl, phenylethyl, and naphthylmethyl.

"Aralkyloxyl" refers to an aralkyl-O– group wherein the aralkyl group is as previously described. An exemplary aralkyloxyl group is benzyloxyl, i.e., C₆H₅-CH₂-O-. An aralkyloxyl group can optionally be substituted.

"Alkoxycarbonyl" refers to an alkyl-O-C(=O)– group. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, butyloxycarbonyl, and *tert*-butyloxycarbonyl.

"Aryloxycarbonyl" refers to an aryl-O-C(=O)– group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxy-carbonyl.

"Aralkoxycarbonyl" refers to an aralkyl-O-C(=O)– group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

"Carbamoyl" refers to an amide group of the formula $-C(=O)NH_2$. "Alkylcarbamoyl" refers to a R'RN-C(=O)- group wherein one of R and R' is hydrogen and the other of R and R' is alkyl and/or substituted alkyl as previously described. "Dialkylcarbamoyl" refers to a R'RN-C(=O)- group wherein each of R and R' is independently alkyl and/or substituted alkyl as previously described.

The term carbonyldioxyl, as used herein, refers to a carbonate group of the formula -O-C(=O)-OR.

"Acyloxyl" refers to an acyl-O- group wherein acyl is as previously described.

The term "amino" refers to the –NH₂ group and also refers to a nitrogen containing group as is known in the art derived from ammonia by the replacement of one or more hydrogen radicals by organic radicals. For example, the terms "acylamino" and "alkylamino" refer to specific N-substituted organic radicals with acyl and alkyl substituent groups respectively.

An "aminoalkyl" as used herein refers to an amino group covalently bound to an alkylene linker. More particularly, the terms alkylamino, dialkylamino, and trialkylamino as used herein refer to one, two, or three, respectively, alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. The term alkylamino refers to a group having the structure –NHR' wherein R' is an alkyl group, as previously defined; whereas the term dialkylamino refers to a group having the structure –NR'R", wherein R' and R" are each independently selected from the group consisting of alkyl groups. The term trialkylamino refers to a group having the structure –NR'R"R", wherein R', R", and R" are each independently selected from the group consisting of alkyl groups. Additionally, R', R", and/or R"" taken together may optionally be –(CH₂)_k– where k is an integer from 2 to 6. Examples include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, isopropylamino, piperidino, trimethylamino, and propylamino.

The amino group is -NR'R", wherein R' and R" are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The terms alkylthioether and thioalkoxyl refer to a saturated (i.e., alkyl–S–) or unsaturated (i.e., alkenyl–S– and alkynyl–S–) group attached to the parent molecular moiety through a sulfur atom. Examples of thioalkoxyl moieties include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

"Acylamino" refers to an acyl-NH– group wherein acyl is as previously described. "Aroylamino" refers to an aroyl-NH– group wherein aroyl is as previously described.

The term "carbonyl" refers to the -C(=O)- group, and can include an aldehyde group represented by the general formula R-C(=O)H.

The term "carboxyl" refers to the –COOH group. Such groups also are referred to herein as a "carboxylic acid" moiety.

The terms "halo," "halide," or "halogen" as used herein refer to fluoro, chloro, bromo, and iodo groups. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1 - C_4)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "hydroxyl" refers to the -OH group.

The term "hydroxyalkyl" refers to an alkyl group substituted with an –OH group.

The term "mercapto" refers to the -SH group.

The term "oxo" as used herein means an oxygen atom that is double bonded to a carbon atom or to another element.

The term "nitro" refers to the -NO₂ group.

The term "thio" refers to a compound described previously herein wherein a carbon or oxygen atom is replaced by a sulfur atom.

The term "sulfate" refers to the -SO₄ group.

The term thiohydroxyl or thiol, as used herein, refers to a group of the formula –SH.

More particularly, the term "sulfide" refers to compound having a group of the formula –SR.

The term "sulfone" refers to compound having a sulfonyl group $-S(O_2)R$.

The term "sulfoxide" refers to a compound having a sulfinyl group -S(O)R

The term ureido refers to a urea group of the formula -NH-CO-NH₂.

Throughout the specification and claims, a given chemical formula or name shall encompass all tautomers, congeners, and optical- and stereoisomers, as well as racemic mixtures where such isomers and mixtures exist.

Certain compounds of the present disclosure may possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as D- or L- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those which are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic, scalemic, and optically pure forms. Optically active (R)- and (S)-, or D- and L-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefenic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

As used herein the term "monomer" refers to a molecule that can undergo polymerization, thereby contributing constitutional units to the essential structure of a macromolecule or polymer.

A "polymer" is a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer.

A "dendrimer" is highly branched, star-shaped macromolecules with nanometer-scale dimensions.

As used herein, an "oligomer" includes a few monomer units, for example, in contrast to a polymer that potentially can comprise an unlimited number of monomers. Dimers, trimers, and tetramers are non-limiting examples of oligomers.

The term "protecting group" refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd ed. John Wiley & Sons (1999). It may be advantageous, where different protecting groups are employed, that each (different) protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions allow differential removal of such protecting groups. For example, protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and tert-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile

groups such as tert-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while coexisting amino groups may be blocked with fluoride labile silyl carbamates.

Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or piacid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a palladium(O)- catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

Typical blocking/protecting groups include, but are not limited to the following moieties:



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Following long-standing patent law convention, the terms "a," "an," and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a subject" includes a plurality of subjects, unless the context clearly is to the contrary (e.g., a plurality of subjects), and so forth.

Throughout this specification and the claims, the terms "comprise," "comprises," and "comprising" are used in a non-exclusive sense, except where the context requires otherwise. Likewise, the term "include" and its grammatical variants are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about" even though the term "about" may not expressly appear with the value, amount or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off, measurement error and the like, and other factors known to those of skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term "about," when referring to a value can be meant to encompass variations of, in some embodiments, $\pm 100\%$ in some embodiments \pm 50%, in some embodiments \pm 20%, in some embodiments \pm 10%, in some embodiments \pm 5%, in some embodiments \pm 1%, in some embodiments \pm 0.5%, and in some embodiments $\pm 0.1\%$ from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Further, the term "about" when used in connection with one or more numbers or numerical ranges, should be understood to refer to all such numbers, including all numbers in a range and modifies that range by extending the boundaries above and below the numerical values set forth. The recitation of numerical ranges by endpoints includes all numbers, e.g., whole integers, including fractions thereof, subsumed within that range (for example, the recitation of 1 to 5 includes 1, 2, 3, 4, and 5, as well as fractions thereof, e.g., 1.5, 2.25, 3.75, 4.1, and the like) and any range within that range.

EXAMPLES

The following Examples have been included to provide guidance to one of ordinary skill in the art for practicing representative embodiments of the presently disclosed subject matter. In light of the present disclosure and the general level of skill in the art, those of skill can appreciate that the following Examples are intended to be exemplary only and that numerous changes, modifications, and alterations can be employed without departing from the scope of the presently disclosed subject matter. The synthetic descriptions and specific examples that follow are only intended for the purposes of illustration, and are not to be construed as limiting in any manner to make compounds of the disclosure by other methods.

EXAMPLE 1

Experimental Procedures

1.1 Synthesis of XY-FAP-01.



Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**): 6-Hydroxyquinoline-4carboxylic acid (**1**) 210 mg (1.1 mmol), methyl glycinate HCl salt (**2**) 143 mg (1.1 mmol), HBTU 420 mg (1.1 mmol) and HOBt 170 mg (1.1 mmol) were dissolved in 12 mL dry DMF. To the solution, 0.77 mL of DIPEA (4.4 mmol) was added. The reaction was stirred at room temperature for 6 h. After the solvent was removed under vacuum, the mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada) and the product was purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 290 mg of product **3** was obtained as a yellow powder with a yield of 76%. ¹H-NMR (400 MHz, CD₃OD): δ 8.69 (s, 1H), 7.94 (d, J = 7.92 Hz, 1H), 7.57–7.51 (m, 3H), 7.42–7.37 (m, 1H), 4.21 (s, 2H), 3.81 (s, 3H). ¹³C-NMR (100 MHz, CD₃OD): δ 172.4, 160.9, 145.1, 143.7, 129.7, 129.4, 128.3, 121.8, 119.6, 112.4, 109.1, 56.8, 44.8. MS: calculated for $[C_{13}H_{13}N_2O_4]^+$, 261.3 $[M + H]^+$; found 261.1.



Methyl (6-(3-((tert-butoxycarbonyl)amino)propoxy)quinoline-4carbonyl)glycinate (**5**): Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**) 360 mg (1.0 mmol), tert-butyl (3-bromopropyl)carbamate (**4**) 500 mg (2.1 mmol) were dissolved in 20 mL DMF. Cs₂CO₃ 1 g (3.0 mmol) was added to the solution and the reaction was stirred at room temperature overnight. After filtration, the solvent was removed under vacuum and the remaining mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada). The product was purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 270 mg of product **5** was obtained with a yield of 54%. ¹H-NMR (400 MHz, CDCl₃): δ 8.68–8.37 (m, 2H), 8.02 (d, J = 9.1 Hz, 1H), 7.80 (s, 1H), 7.72–7.64 (m, 1H), 7.40 (d, J = 9.1 Hz, 1H), 4.94 (br s, 1H), 4.41–4.31 (m, 2H), 4.27–4.18 (m, 2H), 3.85 (s, 3H), 3.44–3.30 (m, 2H), 2.13–2.00 (m, 2H), 1.43 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 170.1, 167.2, 158.4, 144.7, 142.3, 128.4, 126.1, 124.7, 119.1, 103.7, 79.5, 60.4, 52.5, 41.4, 37.7, 29.3, 28.4. MS: calculated for [C₂₁H₂₈N₃O₆]⁺, 418.5 [M + H]⁺; found 418.3.



tert-Butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-

oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate (7): Compound **5** 110 mg (0.21 mmol) and LiOH 30 mg (1.2 mmol) was stirred in 4 mL of H₂O/THF (1/1) for 6 hours. After most of the THF was removed under vacuum, the mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada) and eluded with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1) to remove the salts. The product **6** obtained was mixed with (S)-pyrrolidine-2-carbonitrile 53 mg (0.4 mmol), HOBT 68 mg (0.4 mmol), HBTU 152 mg (0.4 mmol) and DIPEA 0.56 mL (1.6 mmol) in dry 10 mL DMF. After 6 hours, the solvent was removed under vacuum and the remaining mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada). The product was

purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 99 mg of 7 was obtained with a yield of 80%. ¹H NMR (400 MHz, CDCl₃): δ 8.73 (s, 1H), 7.95 (d, J = 10.2 Hz, 1H), 7.68 (br s, 1H), 7.63–7.56 (m, 1H), 7.56–7.48 (m, 1H), 7.38–7.29 (m, 1H), 5.27 (br s, 1H), 4.84–4.72 (m, 1H), 4.46–4.35 (m, 1H), 4.33–4.20 (m, 1H), 4.17–4.09 (m, 2H), 3.78–3.64 (m, 1H), 3.59–3.46 (m, 1H), 3.36 (s, 2H), 2.38–2.17 (m, 4H), 1.42 (s, 9H), 1.35–1.27 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 167.5, 157.9, 156.2, 146.3, 130.2, 125.7, 123.7, 119.3, 118.0, 103.3, 79.0, 65.9, 46.8, 45.7, 42.2, 37.6, 29.8, 29.3, 28.4, 25.1. MS: calculated for [C₂₅H₃₂N₅O₅]⁺, 482.6 [M + H]⁺; found 482.3.



XY-FAP-01. Compound 7 (1 mg, 1.7 μ mol) was treated with a 1 mL solution of TFA/methylene chloride (1/1) for 2 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMSO. To the solution, LICOR800CW-NHS ester 0.5 mg (0.43 μ mol) and Et₃N 10 μ L were added. After 1 h at room temperature, the solvent was removed and the product was purified by HPLC. 0.5 mg product was obtained with a yield of 85%. HPLC condition: column Phenomenex, Luna 10 x 250 mm, 10 u. Gradient 10/90/0.1 MeCN/H₂O/TFA to 80/20/0.1 MeCN/H₂O/TFA within 15 min at a flow of 3 mL/min. The product was eluted at 10.1 min. MS: Calculated for[C₆₆H₇₆N₇O₁₇S₄]⁺, 1366.4[M+H]⁺; found 1366.8.

1.2 Synthesis of XY-FAP-02



 $2,2',2''-(10-(1-\text{Carboxy-4-((3-((4-((2-((S)-2-\text{cyanopyrrolidin-1-yl})-2-oxoethyl)\text{carbamoyl})\text{quinolin-6-yl})\text{oxy})\text{propyl}) amino)-4-oxobutyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid ($ **XY-FAP-02**): Compound 7 (15 mg, 31.3 µmol) was treated with a 1-mL solution of TFA/methylene chloride (1/1) for 1 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMF. To the solution, DIPEA (27 µL, 156.5 µmol) was added, followed by dropwise addition of a solution of DOTA-GA(t-Bu)₄-NHS (25 mg, 31.3 µL) in 0.5

mL of DMF. The reaction mixture was stirred for 4 h at ambient temperature and then concentrated under vacuum. The t-Bu-protected intermediate was deprotected in situ without further purification using a 1 mL mixture of TFA, H₂O and triethylsilane (TES) (95:2.5:2.5). Reaction mixture was then concentrated and purified by semipreparative HPLC, to afford the product as a white solid (8.5 mg, 33% yield). MS: calculated for $[C_{39}H_{54}N_9O_{12}]^+$, 840.9 $[M + H]^+$; found 840.5. HPLC (10 mm x 250 mm Phenomenex Luna C18 column, 10 µm, mobile phase 95/5/0.1% to 75/25/0.1% water/acetonitrile/TFA over 20 min, flow 5 mL/min) **XY-FAP-02** eluted at 11.8 min.



XY-FAP-02-[In]. ^{113/115}Indium(III) 2,2',2"-(10-(1-Carboxy-4-((3-((4-((2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl) amino)-4-oxobutyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (**XY-FAP-02-[In]**): To a solution of 2 mg (2.4 µmol) of **XY-FAP-02** in 1 mL of 0.2M AcONa, a solution of 1.4 mg (4.6 µmol) of In(NO₃)₃ in 0.5 mL water is added and warmed in a 60 °C bath for 30 min. After cooling to ambient temperature, the mixture was purified by semipreparative HPLC. The product was obtained as a white solid (1.8 mg, 79% yield). MS: calculated for $[C_{39}H_{51}N_9O_{12}In]^+$, 951.7 $[M + H]^+$; found 952.5. HPLC (10 mm x 250 mm Phenomenex Luna C18 column, 10 µm, mobile phase 95/5/0.1% to 75/25/0.1% water/acetonitrile/TFA over 20 min, flow 5 mL/min) **XY-FAP-02-[In]** eluted at 14.0 min.

1.3 Radiolabeling Methods. Briefly, 20 mg **XY-FAP-02** solution in 20 mL of 0.2 M NaOAc was added to 10 mL 4.6 mCi ¹¹¹InCl₃ solution (Nordion, Ottawa, Canada) and adjusted to a final pH of 5.5-6. The mixture was heated in a water bath at 70 °C for 30 min and, after the reaction completed, was diluted with 200 mL of water for HPLC purification. The solution was purified using a Phenomenex 5 μ m C₁₈ Luna 4.6 x 250 mm² column (Torrance, CA) with a flow rate of 0.6 mL/min with water (0.1% TFA) (A) and MeCN (0.1% TFA) (B) as the eluting solvents. An isocractic solution of 88% A and 12% B was utilized for purification, resulting in the labeled compound, ¹¹¹In-XY-FAP-02, eluting first at 18.6 min followed by the unlabeled

starting material at 23.5 min. 3.2 mCi of labeled compound was obtained as pure product with a yield of 69%. Another reaction with the identical condition was performed with 74% yield. The collected radioactivity was diluted with 20 mL of water and loaded onto activated Sep-Pak (WAT020515, Waters, Milford, MA). After the Sep-Pak was washed with 10 mL of water, ¹¹¹In-XY-FAP-02 was eluted with 1.5 mL of ethanol. The ethanol was evaporated under a gentle stream of N₂ (to a total volume of < 50 µL). The resulting solution was formulated in saline for the imaging and biodistribution studies.

1.4 FAP Inhibition Assay. The inhibitory activity of **XY-FAP-01** was determined using a fluorogenic FAP Assay Kit (BPS Bioscience, San Diego, CA). Briefly, **XY-FAP-01**, DPP substrate, and human recombinant FAP were loaded into a 96 well plate to initiate the enzyme reaction. The reaction was left for 10 minutes at room temperature before fluorescence was measured with a VICTOR3 V multilabel plate reader (PerkinElmer Inc., Waltham, MA). Data was normalized and semi-log inhibition curves were generated in order to determine the IC₅₀ value (concentration of **XY-FAP-01** where the enzyme activity is 50% inhibited) for **XY-FAP-01** and subsequent enzyme inhibition curves and IC50 values were done using GraphPad Prism (San Diego, CA).

1.5 Cell lines. Six human cancer cell lines were used to assess binding to FAP: glioblastoma (U-87-MG), melanoma (SK-MEL-24), prostate (PC-3), non-small cell lung cancer (NCI-H2228), colorectal carcinoma (HCT 116), and lung squamous cell carcinoma (NCI-H226). From the literature, U-87-MG, SK-MEL-24, and NCI-H2228 cell lines were identified as having high levels of FAP expression [FAP-positive (+)] whereas PC-3, NCI-H226, and HCT 116 cells expressed very low levels of FAP [FAP-negative(-)]. These expression profiles were further confirmed via flow cytometry with an APC-conjugated anti-FAP antibody (R&D Systems, Minneapolis, MN) and quantitative real-time PCR. All cell lines were purchased from American Type Culture Collection (ATCC, Manassas, VA).

U-87-MG cells were maintained in MEM medium (Corning Cellgro, Manassas, VA), containing 10% fetal bovine serum (FBS) (Sigma-Aldrich, St. Louis, MO) and 1% penicillin-streptomycin (Corning Cellgro, Manassas, VA), supplemented with sodium bicarbonate (Corning), sodium pyruvate (Gibco, Gaithersburg, MD), and MEM non-essential amino acids (Gibco). SK-MEL-24 cells were maintained in MEM medium, containing 15% FBS and 1% penicillinstreptomycin, supplemented with sodium bicarbonate, sodium pyruvate, and MEM non-essential amino acids. PC-3 cells were grown in Ham's F-12K medium (Corning Cellgro) supplemented with 10% FBS and 1% penicillin-streptomycin. NCI-H2228, NCI-H226, and HCT 116 cells were cultured in RPMI 1640 medium (Corning Cellgro) supplemented with 10% FBS and 1% penicillin-streptomycin. All cell cultures were maintained at 37 °C and 5% carbon dioxide (CO₂) in a humidified incubator.

1.6 Cellular Uptake Studies. All cellular uptake and specific binding studies were performed in triplicate to ensure reproducibility. Cells were detached using 0.05% trypsin (Corning), resuspended in 1 million cell aliquots in binding buffer, and incubated with various concentrations (range, 50 nM to 0.78 nM) of XY-FAP-01 for 1 hour at 37 °C and 5% CO₂. To assess the specific uptake of **XY-FAP-02**, cells were preblocked with a FAP and DPP-IV specific inhibitor (Val-boroPro, MilliporeSigma, Burlington, MA) or a DPP-IV specific inhibitor (Sitagliptin, Santa Cruz Biotechnology, Inc., Dallas, TX) at various concentrations (range, 10⁻¹⁰ M to 10⁻⁴ M) prior to incubation with 25 nM XY-FAP-02 solution in binding buffer for 1 hour at 37 °C and 5% CO₂. Cellular uptake was terminated by washing cells with ice cold PBS (1x) three times. Cells were resuspended in binding buffer and transferred to a 96-well plate for imaging. Images were acquired on the LI-COR Pearl Impulse Imager (Lincoln, NE) using an excitation wavelength of 785 nm and detection of the emission wavelength at 800 nm. Images were analyzed using the LI-COR Pearl Impulse Software (Version 2.0) and fluorescence intensity was corrected for background signal and normalized to well area.

Cellular Uptake of ¹¹¹In-XY-FAP-02 was also assessed in cells. Cell aliquots (1 million) were incubated with 1 μ Ci ¹¹¹In-XY-FAP-02 in saline for 30 minutes at 37 °C and 5% CO₂. Cells were washed three times with cold PBS (1x) and activity of the cell pellets was measured with the 1282 CompuGamma CS gamma well counter (Pharmacia/LKB Nuclear, Inc., Gaithersburg, MD). The percent uptake of the administered activity was calculated by comparison with samples of a standard dose.

1.7 Small-Animal Near Infrared Fluorescence (NIRF) Imaging. NIRF images were acquired on the LI-COR Pearl Impulse Imager using an excitation wavelength of 785 nm and a detection wavelength of 800 nm. Mice utilized for imaging studies were anesthetized with 3% isofluorane (v/v) and maintained at 1.5% isofluorane for the imaging procedure. NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts were injected with 10 nmol of **XY-FAP-01** via tail vein injection and images were acquired at 30 min, 1 h, 2 h, 2.5 h, and 4 h after injection of tracer. Data were displayed and analyzed using the LI-COR Pearl Impulse Software (Version 2.0).

1.8 Small-Animal SPECT-CT Imaging. SPECT-CT studies were performed on NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts. For imaging studies, mice were anesthetized with 3% isoflurane prior to being placed on the scanner bed and kept warm with an external light source. Isoflurane levels were decreased to 1.5% for the rest of the imaging procedure. After mice were injected with 300 µCi ¹¹¹In-XY-FAP-02 in 200 µL saline, SPECT-CT imaging was carried out using a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA) at the indicated timepoints (30 min, 2 h, 6 h, and 24 h) post radiotracer injection. A CT scan was performed at the end of each SPECT scan for anatomical co-registration. Obtained data sets were reconstructed using the provided Gamma Medica-Ideas software and final data visualization and image generation were prepared using Amira® software (FEI, Hillsboro, OR).

1.9 Ex-vivo Biodistribution. NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts were injected with 10 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline via the tail vein. At 5 min, 30 min, 2 h, 6 h, and 12 hr post injection, mice (n=4) were sacrificed by CO₂ asphyxiation and blood was immediately collected by cardiac puncture. Additionally, the heart, lungs, liver, stomach, pancreas, spleen, fat, kidney, small intestine, large intestine, bladder, muscle, femur, FAP+ U-87-MG xenograft, and FAP- PC-3 xenograft were collected for biodistribution analysis. Each tissue was weighed and radioactivity was measuring using a 2480 Wizard² automated gamma counter (PerkinElmer, Waltham, MA). Radioactivity measurements were corrected for decay and compared with samples of a standard dilution of the initial dose to calculated percent injected dose per gram (%ID/g).

For blocking studies, mice (n=5 per group) were co-injected with unlabeled **XY-FAP-02** (50 μ g per mouse) and 10 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline. Mice (n=5) injected with 10 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline served as a control. At 6 h post injection, mice were sacrificed, tissues were collected, and radioactivity was measured with the gamma well counter.

1.10 Data Analysis. Data are expressed at mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, CA) was used for analysis and statistical significance was calculated using a two-tailed Student's t test. A P-value <0.05 was considered significant.

1.11 Xenograft Tumor Model. 6-week old female NOD/SCID mice were subcutaneously injected in the upper left and right flanks with 1 million U87(FAP+) cells and PC3 cells (FAP-) in RPMI 1640 media supplemented with 1% FBS. Mice were monitored for tumor size and used for optical or SPECT/CT imaging when the size of tumor reached around 100 mm³.

EXAMPLE 2

Representative Results

2.1 FAP Inhibitory Assay. **XY-FAP-01** demonstrated high binding affinity to human recombinant FAP. The enzyme inhibitory constant (Ki) for the compound was determined to be 1.26 nM.

2.2 Cellular Uptake Studies. FAP-positive cell lines showed concentration dependent uptake of **XY-FAP-01** whereas FAP-negative cell lines showed no significant binding of **XY-FAP-01** at all concentrations (see, e.g., FIG. 3A). Saturated binding of **XY-FAP-01** was observed at concentration of 25 nM, which was subsequently used as the base concentration for all binding inhibition studies. When preblocked with a FAP and DPP-IV specific inhibitor, **XY-FAP-01** binding was significantly inhibited in FAP-positive cells (FIG. 3B). Interestingly, this phenomenon was not observed in FAP-positive cell lines preblocked with a DPP-IV specific inhibitor. These results further justify the specificity of **XY-FAP-01** for FAP over DPPIV, since blocking of DPPIV did not result in a change of binding ability of **XY-FAP-01**.

Similar specificity was observed with the radioactive analog, ¹¹¹In-XY-FAP-02. FAP positive cell line, U-87-MG, demonstrated over 30% uptake of administered radioactive dose after incubation whereas the FAP negative cell line, PC-3, had uptake of 0.01% of administered dose (FIG. 3C). Taken together, these results support the specificity of XY-FAP-01 and ¹¹¹In-XY-FAP-02 in the engagement of FAP *in vitro*.

2.3 Ex-vivo Biodistribution. Ex-vivo biodistribution of ¹¹¹In-XY-FAP-02 results correlated with the observed imaging results (FIG. 4). Initially, the blood pool activity is very high, with over 10% %ID/g at 30 minutes post injection. With clearance of the compound, we see the blood pool activity drop significantly after 2

hours of distribution and remained less than 5% %ID/g from 2 hours post injection (FIG. 5A). High activity was also observed in pancreas, small intestines, and bladder until 2 hours post injection. Positive tumor uptake peaked at 30 minutes post injection and remained between 13-11% %ID/g up to 6 hours. Washout of tumor was observed at 12 hours post injection, with %ID/g dropping to below 5%. The PC-3, FAP negative xenograft had less than 3.5% %ID/g for all timepoints.

Co-injection of cold compound with ¹¹¹In-XY-FAP-02 resulted in significant blocking of tracer uptake in U-87 xenografts, with %ID/g dropping from 11.20% without blocking versus 0.27% with blocking (p < 0.0001). Additionally, blocking with cold compound resulted in %ID/g of all tissues dropping significantly, with most values being less than 0.1%. This decrease in uptake is most likely due to the blocking of non-specific binding of tracer to non-target tissues and the blocking of specific binding of FAP in U-87 xenografts.

2.4 Small-Animal Near Infrared Fluorescence (NIRF) Imaging. NIRF imaging of **XY-FAP-01** demonstrated specific uptake of tracer in the U-87-MG xenograft as early as 30 minutes post injection (FIG. 6). After one hour of distribution, tracer clearance via the bladder was observed with retained tracer uptake in the FAP positive xenograft. Tracer uptake was retained in the positive xenograft after four hours of distribution. In contrast, no significant uptake of tracer was observed in the FAP negative tumor at all imaging time points.

REFERENCES

All publications, patent applications, patents, and other references mentioned in the specification are indicative of the level of those skilled in the art to which the presently disclosed subject matter pertains. All publications, patent applications, patents, and other references (e.g., websites, databases, etc.) mentioned in the specification are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent application, patent, and other reference was specifically and individually indicated to be incorporated by reference. It will be understood that, although a number of patent applications, patents, and other references are referred to herein, such reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art. In case of a conflict between the specification and any of the incorporated references, the specification (including any amendments thereof, which may be based on an incorporated reference), shall control. Standard art-accepted meanings of terms are used herein unless indicated otherwise. Standard abbreviations for various terms are used herein.

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- U.S. Patent No. 9,346,814 for Novel FAP Inhibitors to Jansen et al., issued May 24, 2016.
- International PCT Patent Publication No. WO 2013/107820 for Novel FAP Inhibitors to Jansen et al., published July 25, 2013.

Although the foregoing subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be understood by those skilled in the art that certain changes and modifications can be practiced within the scope of the appended claims. Attorney Docket No. JHU-36631.303

<u>REMARKS</u>

Upon entry of this amendment claims 28 is pending. Claims 1-27 are canceled without prejudice. Applicant reserves the right to pursue the canceled subject matter in one or more continuation and/or divisional applications. Claim 28 is newly added. Support for the newly added claim can be found in the specification and claims as originally filed. No new matter is added.

CONCLUSION

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney at 608-662-1277. Early passage of the subject application to issue is earnestly solicited.

Respectfully Submitted,

CASIMIR JONES, S.C.

Date: July 18, 2023

/JEFFREY W. CHILDERS/ Jeffrey W. Childers, Ph.D. Registration No. 58126 Customer No. 101943 Doc Code: PA.. Document Description: Power of Attorney

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The undersigned	whose title is supplied below	v) is authorized to act	on behalf of the applicant	e.g., where the applicar	nt is a juristic entity).
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DEC	CARE A SPECIAL CONTRACTION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-alpha (FAP-alpha)
As the belo	w named inventor, I hereby declars that.
This declar is directed	ation The attached application, or
	United States application or PCT international application number <u>16/758,182</u> field on <u>22-Apr-2020</u>
The above-	identified application was made or authorized to be made by me.
I believe the	It I am the original inventor or an original joint inventor of a claimed invention in the application.
l hereby acl by fine or in	mowledge that any willful take statement made in this declaration is punishable under 18 U.S.C. 1801 prisonment of not more than five (5) years, or both.
	WARNING:
Petitioner/aj contribute to (other than i to support a petitioners/a uspTO. Pe application (patent Fun referenced i PTO-2038 s	plicant is cautioned to avoid submitting personal information in documents filed in a patent application that may identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO petition or an application. If this type of personal information is included in documents submitted to the USPTO, popicants should consider redacting such personal information from the documents before submitting them to the information request that the record of a patent application is available to the public after publication of the unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a hermore, the record from an abandoned application may also be available to the public if the application is n a published application or an issued patent (see 37 CFR 1.14). Checks and credit card, authorization forms ubmitted for payment purposes are not retained in the application file and therefore are not, publicly available.
LEGAL N	WE OF INVENTOR
Inventor:	Xing Yang Date (Optional) : 06/24/2020
Signature:	Xing lang
Note: An appl been previous	cation data street (PTO/SB/14 or equivalent), including naming the entire inventive antity, must accompany this form or must have by filed. Use an additional PTO/ALAOI form for each additional inventor.
This collection of by the USPTO to complete, includ comments on the Patent and Trad third ANNEESS	Information is required by 35 U.S.C. 515 and 37 CPR 1.63. The information is required to obtain or relatin a barrelit by the public which is to file (and process) an application. Confidentiatly is governed by 35 U.S.C. 122 and 37 CPR 1.11 and 1.14. This collection is estimated to take 1 minute to no gathering, organizing, and submitting the conspleted pagescalar (or to file 1.91 and 1.14. This collection is estimated to take 1 minute to no gathering. Unsee submitting the consplete files (pagescalar (or to file) (pagescalar (or to file) (pagescalar (or to file))). The will have sent to the Chief Information Officer, U.S. amount of time your requires to complete files from and/or suggestions for reducing this burriers, should be sent to the Chief Information Officer, U.S. amount of the Complete and Complete files from and/or suggestions for reducing this burriers, should be sent to the Chief Information Officer, U.S. amount of the Complete and Complete files for a motor suggestions for reducing this burriers, should be sent to the Chief Information Officer, U.S. and the Complete and Complete files for a motor suggestion for reducing the DNOT SERD DEFES OF COMPLETED REDUctions for and the Complete files (or complete files (o

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Title of IM Invention FI	AGING AND RADIOTHERAPEUTICS AGENTS TARGETING 3ROBLAST-ACTIVATION PROTEIN-alpha (FAP-alpha)
As the below ha	med inventor, thereby declare that:
This declaration	The altached application, or
ye an elonen ne	United States application or PCT international application number <u>16/758,182</u>
Via atomacidan	Miad application was made or authorized to be made by me
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believe that I a	m the original inventor or an original joint inventor of a claimed invention in the application
hereby acknow y line or impria	ledge that any wiliful false statement made in this declaration is punishable under 18 U.S.C. 1001 onment of not more than five (5) years, or both.
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Petitioner/applic contribute to idea other than a che o support a petitioners/applic etitioners/applic SPTO. Petition pplication (unle retent. Furthern eferenced in a p TO-2038 subm	ant is cautioned to avoid submitting personal information in documents filed in a patent application that may hitly theft. Personal information such as social security numbers, bank account numbers, or credit card number lock or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO, tion or an application. If this type of personal information is included in documents submitted to the USPTO, pants should consider redacting such personal information from the documents before submitting them to the per/applicant is advised that the record of a patent application is available to the public after publication of the ss is non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a nore, the record from an abandoned application may also be available to the public if the application is sublished application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms itted for payment purposes are not retained in the application file and therefore are not publicity available.
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Inventor Stic	ihar Nimmagadda
Signature:	N SS W
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING Title of Invention FIBROBLAST-ACTIVATION PROTEIN-alpha (FAP-alpha)

As the below named inventor, I hereby declare that:

This declaration is directed to:

The attached application, or

United States application or PCT international application number 16/758,182 filed on 22-Apr-2020

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Steven Rowe inventor:

Signature:

Date (Optional) : 9-2.5-20.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN **APPLICATION DATA SHEET (37 CFR 1.76)**

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING Title of Invention FIBROBLAST-ACTIVATION PROTEIN-alpha (FAP-alpha)

As the below named inventor, I hereby declare that:

This declaration is directed to:

The attached application, or

United States application or PCT international application number 16/758,182 filed on 22-Apr-2020

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Stephanie Slania

Janie

Date (Optional): June 24th, 2020

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)
Title of IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING Invention FIBROBLAST-ACTIVATION PROTEIN-alpha (FAP-alpha)
As the below named inventor, I hereby declare that:
This declaration The attached application, or
United States application or PCT international application number <u>16/758,182</u> filed on <u>22-Apr-2020</u> .
The above-identified application was made or authorized to be made by me.
I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.
WARNING:
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LEGAL NAME OF INVENTOR
Inventor: Martin G. Pomper Date (Optional) June 23, 2020
Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must hav been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.
This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to tile (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450, DO NOT SEND FEES OR COMPLETED FORMS TO

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THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450. If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.
Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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- 8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
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ELECTRONIC PAYMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 07/18/2023 03:48:57 PM	ET	attorney docket # J HU-36631.303
Title of Invention	l		
IMAGING AND RAD PROTEIN-ALPHA (I	DIOTHERAPEUTICS AGENTS FAP-ALPHA)	TARGETING FIBROBL	AST-ACTIVATION
Application Infor	mation		
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Stephanie Filandrinos
PATENT CENTER #	62461174	AUTHORIZED BY	J effrey Childers
CUSTOMER #	101943	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

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PAYMENT MET CARD / 0638	THOD PAYMENT TRANSACTION E 20237HF49225607	PAYMENT TRANSACTION ID E 20237HF 49225607		RIZED BY inos
FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2830	PROCESSING FEE, EXCEPT IN PROVISIONAL APPLICATIONS	56.00	1	56.00
2817	REQUEST FOR PRIORITIZED EXAMINATION	1680.00	1	1680.00
2111	UTILITY PATENT APPL. SEARCH FEE	280.00	1	280.00
4011	BASIC FILING FEE- UTILITY	64.00	1	64.00
2311	EXAMINATION OF ORIGINAL PATENT APPLICATION	320.00	1	320.00

TOTAL AMOUNT: \$2,400.00

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New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 07/18/2023 03:48:57 PM	ET	attorney docket # J HU-36631.303
Title of Inventio	n		
IMAGING AND RA PROTEIN-ALPHA	ADIOTHERAPEUTICS AGENTS T (FAP-ALPHA)	TARGETING FIBROBL	AST-ACTIVATION
Application Info	ormation		
APPLICATION TYP	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION	# 7536	FILED BY	Stephanie Filandrinos
PATENT CENTER	# 62461174	FILING DATE	-
CUSTOMER	# 101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENC	-	AUTHORIZED BY	J effrey Childers

Documents

TOTAL DOCUMENTS: 13

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
2023-07- 18_36631.303_PA.pdf		4	-	146 KB
2023-07-18_36631.303_PA- A.PE.pdf	(1-1)	1	Preliminary Amendment	128 KB
2023-07-18_36631.303_PA- CLM.pdf	(2-3)	2	Claims	90 KB
2023-07-18_36631.303_PA- REM.pdf	(4-4)	1	Applicant Arguments/Remarks Made in an Amendment	88 KB
2023-07- 18_36631.303_Track1.pdf		2	Track One Request	109 KB

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2023-07- 18_36631.303_Application.pd f		77	-	1541 KB
2023-07- 18_36631.303_Application- SPEC.pdf	(1-61)	61	Specification	1035 KB
2023-07- 18_36631.303_Application- CLM.pdf	(62-76)	15	Claims	597 KB
2023-07- 18_36631.303_Application- ABST.pdf	(77-77)	1	Abstract	122 KB
2023-07- 18_36631.303_FIGURES.pdf		9	Drawings-only black and white line drawings	2952 KB
2023-07- 18_36631.303_ExecDecls_Al l.pdf		7	Oath or Declaration filed	3575 KB

2023-07-	2	Internet Communications	76 KB
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DOCUMENT	MESSAGE DIGEST(SHA-512)
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2023-07-	E D282DE 61F B 526452378B 17C 5A 82B E 68B C B D A 86163471834F
18_36631.303_Application-	1F F F B E E 721D B 418A D 86E 4A 64151A D 8178405A 7E C 185E 6366F
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New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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				Comp	olete if Known
				Application Number	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)			RE	Filing Date	
			NT	First Named Inventor	YANG
				Art Unit	
		Examiner Name			
Sheet	Sheet 1 of 4		Attorney Docket Number	JHU-36631.303	

	U.S. PATENTS						
Exami ner Initials*	Cite No. ¹	Document Number Number-Kind Code ² (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear		
		9346814	2016-05-24	JANSEN et al.			

U.S. PUBLISHED PATENT APPLICATIONS							
Exami	Cite	Document Number	Issue or	Name of Patentee or	Pages, Columns, Lines,		
ner Initials*	No. ³	Number-Kind Code ⁴ (if known)	Publication Date YYYY-MM-DD	Applicant of Cited Document	Where Relevant Passages or Relevant Figures Appear		
		20080280856	2008-11-13	COHEN et al.			
		20140357650	2014-12-04	JANSEN et al.			

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

	FOREIGN PATENT DOCUMENTS						
Exami ner Initials [*]	Cite No. ¹	Foreign Patent Document Country Code ⁵ Number ⁶ Kind Code ⁷ (<i>if known</i>)	Publication Date YYYY-MM- DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translati on ⁸	
		WO 2013/107820	2013-07-25	UNIVERSITEIT ANTWERPEN et al.			
		WO 2014/001538	2014-01-03	GE HEALTHCARE LTD			
		WO 2015/114166	2015-08-06	PHILOCHEM AG			
		WO 2016/149188	2016-09-22	THE JOHNS HOPKINS UNIVERSITY			

	Examiner Signature		Date Considered		
E	EXAMINER:	Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9. Draw line through	

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Comp	olete if Known
				Application Number	
INF(ORMATION D	ISCLOSU	RE	Filing Date	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	YANG
	(Use as many sheets	as necessary)		Art Unit	
				Examiner Name	
Sheet	2	of	4	Attorney Docket Number	JHU-36631.303

		NONPATENT LITERATURE DOCUMENTS	
Examin er Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translatio n ⁶
		ALLINEN et al., Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004 Jul;6(1):17-32.	
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		FRANCO et al., Cancer associated fibroblasts in cancer pathogenesis. Semin Cell Dev Biol. 2010 Feb;21(1):33-9.	
		GARIN-CHESA et al., Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. Proc Natl Acad Sci U S A. 1990 Sep;87(18):7235-9. PMCID: PMC54718.	
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		KELLY, Fibroblast activation protein-alpha and dipeptidyl peptidase IV (CD26): cell- surface proteases that activate cell signaling and are potential targets for cancer therapy. Drug Resist Updat. 2005 Feb-Apr;8(1-2):51-8.	

	Examiner Signature		Date Considered	
Ē	XAMINER:	Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9. Draw line through

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				Comp	olete if Known
				Application Number	
INF(ORMATION D	ISCLOSU	RE	Filing Date	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	YANG
	(Use as many sheets	as necessary)		Art Unit	
				Examiner Name	
Sheet	3	of	4	Attorney Docket Number	JHU-36631.303

	NONPATENT LITERATURE DOCUMENTS
	KRAMAN et al., Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. Science. 2010 Nov 5;330(6005):827-30.
	LAVERMAN et al., Immuno-PET and Immuno-SPECT of Rheumatoid Arthritis with Radiolabeled Anti-Fibroblast Activation Protein Antibody Correlates with Severity of Arthritis. J Nucl Med. 2015 May;56(5):778-83.
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	YOUN et al., In vivo noninvasive small animal molecular imaging. Osong Public Health Res Perspect. 2012; 3 :48-59.
Examiner	Date

 Examine
 Considered

 EXAMINER:
 Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Comp	olete if Known
				Application Number	
INFO	DRMATION D	ISCLOSU	RE	Filing Date	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	YANG
	(Use as many sheets	as necessary)		Art Unit	
				Examiner Name	
Sheet	4	of	4	Attorney Docket Number	JHU-36631.303

NONPATENT LITERATURE DOCUMENTS					
	YU et al., The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J. 2010 Mar;277(5):1126-44.				
	International Search Report and Written Opinion for PCT/US2018/057086, mailed May 10, 2019, 12 pages				
	Extended EP Search Report for EP 18871298.8, mailed May 20, 2021, 7 pages				

	Examiner		Date	
	Signature		Considered	
Ē	EXAMINER:	Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9. Draw line through

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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INF(ORMATION D	ISCLOSU	RE	Filing Date	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	YANG
	(Use as many sheets	as necessary)		Art Unit	
				Examiner Name	
Sheet	5	of	4	Attorney Docket Number	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

Γ

See attached certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.



A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-07-18
Printed Name	Jeffrey W. Childers	Registration Number	58126

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Doc Code: ECOMM.AUTH/ECOMM.WTDW

Doc Description: Internet Communications Authorized/Internet Communications Authorization Withdrawn

		PTO/SB/439 (11-15)				
AUTHORIZATION FOR INTERNET	Application No.					
COMMUNICATIONS IN A PATENT	Filing Date	07/18/2023				
APPLICATION OR REQUEST TO	First Named Inventor	YANG				
WITHDRAW AUTHORIZATION FOR	Art Unit					
INTERNET COMMUNICATIONS	Examiner Name					
	Practitioner Docket No.	JHU-36631.303				
To: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450						
I. To authorize permission for Internet Com	munications.					
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attorney or agent acting under a	37 CFR 1.34. Registrati	on number				
/Jeffrey W. Childers/	_20	2023-07-18				
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Jeffrev W. Childers		08-662-1277				
Typed or printed name	Typed or printed name Telephone Number					
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- 8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
- 9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



Fig. 1A



Fig. 1B



Fig. 1*C*



Fig. 2

FAP Binding









	5 min (a= 3)	0.5 h {n= 4}	2 a (n= 3)	6 hr (n= 4)	6 h - blocking {n=4}	12 h (n= 4)
boold	15.13 ± 0.62	10.64 ± 1.54	4.10 ± 0.39	2.01 ± 0.18	0.02 ± 0.091	0.42 ± 0.04
heart	6.68 ± 0.99	4.98 ± 0.71	2.61 ± 0.09	1.07 ± 0.09	9.02 ± 0.092	0.46 ± 0.04
lungs	6.99±1.37	5.60 ± 0.89	2.59 ± 0.32	1.38 ± 0.13	0.04 ± 0.005	0.39 ± 0.03
liver	6.32 ± 0.77	4.90 ± 0.59	2.58 ± 0.09	2.51 ± 0.09	0.33 ± 0.058	1.66 ± 0.22
stomach	3.28 ± 0.46	2.62 ± 0.23	1.69 ± 0.14	1.19 ± 0.15	0.06 ± 0.032	0.34 ± 0.05
pancreas	14.54 ± 1.66	12.14 ± 2.85	8.11 ± 0.34	3.28 ± 0.27	0.03 ± 0.005	1.15 ± 0.52
spieen	2.93 ± 0.25	2.48 ± 0.47	1.77 ± 0.27	1.54 ± 0.19	0.06 ± 0.008	1.10 ± 0.13
fat	0.74 ± 0.09	0.73±0.13	0.61±0.19	9.45 ± 0.16	0.02 ± 0.017	0.15 ± 0.08
kidney	4.60 ± 0.57	3.56 ± 0.18	1.95 ± 0.06	1.79 ± 0.21	1.18 ± 0.158	0.73 ± 0.05
sns. int.	8.80 ± 1.97	8.41 ± 1.35	3.64 ± 0.45	1.66 ± 0.22	0.09 ± 0.052	0.76 ± 0.14
irg. int.	4.67 ± 0.42	4.57 ± 0.57	2.98 ± 0.27	1.37 ± 0.47	0.36 ± 0.342	0.55 ± 0.04
bladder	2.96 ± 0.95	13.60 ± 8.80	8.94 ± 8.48	3.41 ± 0.84	1.04 ± 0.486	2.25 ± 0.57
muscle	3.00 ± 0.22	3.53 ± 0.16	2.80 ± 0.07	1.79 ± 0.15	9.02 ± 0.095	0.60 ± 0.03
femur	4.76 ± 0.12	5.83 ± 0.72	4.95 ± 0.83	3.91 ± 0.70	9.68 ± 0.021	1.38 ± 0.20
U87	9.71 ± 0.24^{a}	12.89 ± 1.45 ²	12.28 ± 1.95*	11.20 ± 1.03^{8}	0.27 ± 0.019°	4.57 ± 0.54 ^b
PC3	2.20 ± 0.20	3.10 ± 0.57	2.75±0.11	3.40 ± 0.34	6.11 ± 0.624°	0.95 ± 0.06
U87:PC3	4.43 ± 0.31	4.23 ± 0.72	4.46 ± 0.62	3.30 ± 0.14	2.61 ± 0.440	4.82 ± 0.28
U87:blood	0.64 ± 0.04	1.22 ± 0.07	3.00 ± 0.38	5.58 ± 0.38	18.97 ± 1.197	\$0.94 ± 0.93
U87:mm	3.25 ± 0.26	3.68 ± 0.44	4.38 ± 0.86	6.29 ± 0.82	11.81 ± 2.686	7.68 ± 0.97

Fig. 4









0.5 h

1 h

2.5 h

4 h

Fig. 6



Fig. 7



30 min

2 hr

Fig. 8

IN THE CLAIMS:

The present listing of claims replaces all previous versions of the claims.

1.-27. (Canceled)

28. (New) A compound of Formula (I):

B-L-A (I) wherein:

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

Wherein:

R1x and R2x are each independently selected from the group consisting of H, OH, halogen, C1-6alk-yl, -O-C1-6alkyl, and -S-C1-6alkyl;

R3x is selected from the group consisting of H, -CN, -B(OH)2 -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)2aryl, -CO2H, -SO3H, -SO2NH2, -PO3H2, and 5tetrazolyl;

R4x is H;

R5x, R6x and R7x are each independently selected from the group consisting of

H, -OH, oxo, halogen, -C1-6alkyl, -O-C1-6alkyl, -S-C1-6alkyl, -NR8xR9x, -

OR12x, -Het2

and -Ar2; each of C1-6alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

R8x, R9x and R12x are each independently selected from the group consisting of H, -OH, halo, -C1-6alkyl, -O-C1-6alkyl, -S-C1-6alkyl, and -Ar3;

R10x, R11x, R13x and R14x are each independently selected from the group

consisting of H, -OH, halogen, -C1-6alkyl, -O-C1-6alkyl, and -S-C1-6alkyl; Ar1,

Ar2 and

Ar3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar1, Ar2 and

Ar3 being optionally and independently substituted with from 1 to 3 substituents selected from -NR10xR11x, -C1-6alkyl, -O-C1-6alkyl, and -S-C1-6alkyl;

Het2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1

or 2 heteroatoms selected from O, N and S; Het2 being optionally substituted with from 1 to 3 substituents selected from -NR13xR14x, -C1-6alkyl, -O-C1-6alkyl, and -S-C1-6alkyl;

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, PET imaging, SPECT imaging, or radiotherapy; and

L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

- 3 -

THAT WHICH IS CLAIMED:

1. A compound of Formula (I): B—L—A (I)

wherein:

A is a targeting moiety for FAP- α ;

B is any optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging, or radiotherapy; and

L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

2. The compound of claim 1, wherein A is an FAP- α targeting moiety having the structure of:



wherein each y is independently an integer selected from the group consisting of 0, 1, and 2;

 R_{1x} , R_{2x} , and $R_{3x'}$, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

 R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic monoor bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

wherein $\frac{\xi}{\xi}$ indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle thereof;

and stereoisomers and pharmaceutically acceptable salts thereof.

3. The compound of claim 2, wherein N is selected from the group consisting of:

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wherein * indicates the point of attachment of the 5 to 10-membered Ncontaining aromatic or non-aromatic mono- or bicyclic heterocycle to $-(CH_2)_{v}$ -.

4. The compound of claim 2, wherein A is an FAP- α targeting moiety having the structure of:



wherein $\frac{\xi}{2}$ indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

5. The compound of claim 4, wherein A is selected from the group consisting of:

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6. The compound of claim 5, wherein A is selected from the group consisting of:



and stereoisomers thereof.

7. The compound of claim 5, wherein A is selected from the group consisting of:



8. The compound of any of claims 1-7, wherein L and B are selected from the group consisting of (a), (b), (c), or (d):



wherein:

p₁, p₂, p₃ and p₄ may be in any order;

t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; p₁, p₃, and p₄ are each independently 0 or 1;

 p_2 is an integer selected from the group consisting of 0, 1, 2, and 3, and when p_2 is 2 or 3, each R_1 is the same or different;

 m_1 and m_2 are each an integer independently selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

 W_1 is selected from the group consisting of a bond, -S-, -C(=O)-NR-, and -NR-C(=O)-;

W₂ is selected from the group consisting of a bond, -S-, -CH₂-C(=O)-NR-, – C(O)–, –NRC(O)–, –NR'C(O)NR–, –NRC(S)NR'₂–, –NRC(O)O–, –OC(O)NR–, – OC(O)–, –C(O)NR–, –NR–C(O)–, –C(O)O–, –(O–CH₂–CH₂)_q– and –(CH₂-CH₂-O)_q, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and –OR₄, wherein R₄ is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove;

Tz is a triazole group that can be present or absent and, if present, is selected



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

V is selected from the group consisting of -C(O)-, -C(S)-, -NRC(O)-, -NRC(O)-, -NRC(O)-, and -OC(O)-;



wherein p_1 , p_2 , p_3 , m_1 , m_2 , Tz, W_2 , R, R_1 , R_2 , R_3 , and V are defined as hereinabove;

(c) $-L_1$ -, $-L_2$ - L_3 -, or $-L_1$ - L_2 - L_3 -, wherein:

 L_1 is -NR-(CH₂)_q-[O-CH₂-CH₂-O]_q-(CH₂)_q-C(=O)-;

L₂ is -NR-(CH₂)_q-C(COOR₅)-NR-; and

 $L_3 \text{ is -(O=)C-(CH_2)q-C(=O)-;}$

(b)

wherein each q is independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove;

(d) $B-(CR_6H)_q-(CH_2)_q-C(=O)-NR-(CH_2)_q-O-$ or $B-NR-(CH_2)_q-O-$; wherein each q and R is defined hereinabove; and R_6 is H or $-COOR_5$; and

B is any optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging, or radiotherapy; and stereoisomers and pharmaceutically acceptable salts thereof.

9. The compound of any of claims 1-8, wherein L is selected from the group consisting of:



wherein u is an integer selected from 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

10. The compound of any of claims 1-9, wherein B is a radiolabeled prosthetic group comprising a radioisotope selected from the group consisting of 18 F, 124 I, 125 I, 131 I, and 211 At.

11. The compound of claim 10, wherein the radiolabeled prosthetic group is selected from the group consisting of:

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wherein each X is independently a radioisotope selected from the group consisting of ¹⁸F, ¹²⁴I, ¹²⁵I, ¹³¹I, and ²¹¹At; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20.

12. The compound of claim 11, wherein the radiolabeled prosthetic group is selected from the group consisting of:



13. The compound of any of claims 1-9, wherein B comprises a chelating agent.

14. The compound of claim 13, wherein the chelating agent is selected from the group consisting of:



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15. The compound of any of claims 1-9, wherein B comprises an optical dye.

16. The compound of claim 15, wherein the optical dye comprises a fluorescent dye.

17. The compound of claim 16, wherein the fluorescent dye is selected from the group consisting of carbocyanine, indocarbocyanine, oxacarbocyanine, thiacarbocyanine and merocyanine, polymethine, coumarine, rhodamine, xanthene, fluorescein, boron-dipyrromethane (BODIPY), Cy5, Cy5.5, Cy7, VivoTag-680, VivoTag-S680, VivoTag-S750, AlexaFluor660, AlexaFluor680, AlexaFluor700, AlexaFluor750, AlexaFluor790, Dy677, Dy676, Dy682, Dy752, Dy780, DyLight547, Dylight647, HiLyte Fluor 647, HiLyte Fluor 680, HiLyte Fluor 750, IRDye 800CW, IRDye 800RS, IRDye 700DX, ADS780WS, ADS830WS, and ADS832WS.

18. The compound of claim 15, wherein the optical dye is selected from the group consisting of:





19. The compound of claims 1-9, wherein the compound is selected from the group consisting of:

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20. The compound of claim 19, wherein the compound is selected from the group consisting of:



XY-FAP-02

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21. A pharmaceutical composition comprising the compound of any of claims 1-20.

22. The composition of claim 21, further comprising one or more of pharmaceutically acceptable carriers, diluents, excipients, or adjuvants.

23. A method for imaging a disease or disorder associated with fibroblastactivation protein- α (FAP- α), the method comprising administering a compound according to any of claims 1-20 or a pharmaceutical composition of claim 21 to a subject, wherein the compound of formula (I) comprises an optical or radiolabeled functional group suitable for optical imaging, PET imaging, or SPECT imaging; and obtaining an image.

24. A method for inhibiting fibroblast-activation protein- α (FAP- α), the method comprising administering to a subject in need thereof an effective amount of a compound according to any of claims 1-20 or a pharmaceutical composition of claim 21.

25. A method for treating a fibroblast-activation protein- α (FAP- α)-related disease or disorder, the method comprising administering to a subject in need of treatment thereof an effective amount of a compound according to any of claims 1-20 or a pharmaceutical composition of claim 21, wherein the compound of formula (I) comprises a radiolabeled functional group suitable for radiotherapy.

26. The method of claim 25, wherein $(FAP-\alpha)$ -related disease or disorder is selected from the group consisting of a proliferative disease; diseases characterized by tissue remodeling and/or chronic inflammation; disorders involving endocrinological dysfunction; and blood clotting disorders.

27. The method of claim 26, wherein the proliferative disease is selected from the group consisting of breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone and connective tissue sarcomas, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, and adenocarcinoma.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.303		
		Application Number			
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)				
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.					

This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Invent	Inventor 1 Remove									
Legal	Name									
Prefix	Give	en Name		Middle Name	e		Family Name			Suffix
	Xing						Yang			
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	Sridl	nar			Nimmagadda					
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City	Balti	more		State/Province	MD	4D Country of Residence US				
Mailing	Addr	ess of Invent	or:							
Addre	ss 1		c/o The Johns	Hopkins University						
Addre	ss 2		3400 North Cl	narles Street				_		
City		Baltimroe				State/Prov	vince	MD		
Postal	Cod	9	21218		Cour	ntry i	US			
Invent	or	3						R	emove	
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PTO/AIA/14 (02-18) Approved for use through 11/30/2020. OMB 0651-0032 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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						Attorney	Docke	t Number	JHU-366	31.303		
Appli	icatio	on Da	ta Sh	eet 37 CFR	1.76	6 Applicatio	on Nur	nber				
Title of	Title of Invention IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)							N-				
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Mailing	Addr	ess of	Invent	tor:								
Addre	ss 1			c/o The John	s Hopl	kins University						
Addre	ss 2			3400 North C	harles	s Street						
City		Baltin	nore					State/Pro	vince	MD		
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City		Baltin	nore			State/Provinc			vince	MD		
Posta	l Code	•		21218		Country		US				
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Addre	ss 1			c/o The John	s Hopl	kins University						
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Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

An Address is being provided for the correspondence Information of this application.

Application Data Sheet 37 CER 1 76			Attorney Docket Number	JHU-36	631.303	
Application Data Sheet 37 Cr K 1.70		Application Number				
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)					
Customer Number 101943						
Email Address docketing@casimirjo		nes.com		Add Email	Remove Email	

Application Information:

Title of the Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)		
Attorney Docket Number	JHU-36631.303 Small Entity Status Claimed		
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		9	Suggested Figure for Publication (if any)

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

Request Early Publication (Fee required at time of Request 37 CFR 1.219)

Request Not to Publish. I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	Customer Number	O US Patent Practitioner	Limited Recognition (37 CFR 11.9)
Customer Number	101943		

Application Da	ta Sheet 37 CER 1 76	Attorney Docket Number	JHU-36631.303	
Application Data Sheet 37 Cr R 1.70		Application Number		
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)			

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
	Continuation of	16758182	2020-04-22		
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
16758182	a 371 of international	PCT/US2018/057086	2018-10-23		
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
PCT/US2018/057086	Claims benefit of provisional	62575607	2017-10-23		
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.					

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)¹ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

		_	Remove		
Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)		
Additional Foreign Priority Data may be generated within this form by selecting the Add button.					

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.303		
		Application Number			
Title of Invention	Title of Invention IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)				
 This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013. NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013. will be examined under the first inventor to file provisions of the AIA. 					

Application Da	ta Sheet 37 CER 1 76	Attorney Docket Number	JHU-36631.303	
		Application Number		
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)			

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant <u>must opt-out</u> of the authorization by checking the corresponding box A or B or both in subsection 2 below.

<u>NOTE</u>: This section of the Application Data Sheet is **<u>ONLY</u>** reviewed and processed with the <u>**INITIAL**</u> filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. <u>Priority Document Exchange (PDX)</u> - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h) (1).

B. <u>Search Results from U.S. Application to EPO</u> - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby <u>grants the USPTO authority</u> to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

A. Applicant <u>DOES NOT</u> authorize the USPTO to permit a participating foreign IP office access to the instant
 application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

B. Applicant <u>DOES NOT</u> authorize the USPTO to transmit to the EPO any search results from the instant patent
 application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.303
		Application Number	
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.					
Applicant 1	Applicant 1				
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.					
Assignee		Legal Representative ur	nder 35 U.S.C. 117	Joint Inventor	
Person to whom the inv	ventor is oblig	gated to assign.	Person who sho	ows sufficient proprietary interest	
If applicant is the legal r	epresentati	ve, indicate the authority to	file the patent applicat	ion, the inventor is:	
Name of the Deceased or Legally Incapacitated Inventor:					
If the Applicant is an Organization check here.					
Organization Name	Organization Name The Johns Hopkins University				
Mailing Address Information For Applicant:					
Address 1 3400 North Charles Street					
Address 2			1	1	
City	Baltin	nore	State/Province	MD	
Country US			Postal Code	21218	
Phone Number			Fax Number		
Email Address					
Additional Applicant Data may be generated within this form by selecting the Add button.					

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.303
		Application Number	
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)		

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here.				
Prefix	Given Name	Middle Name	Family Name	Suffix
Mailing Address Information For Assignee including Non-Applicant Assignee:				
Address 1				
Address 2				
City		State/Pro	ovince	
Country		Postal Co	ode	
Phone Number		Fax Num	ber	
Email Address				
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.				

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application** Data Sheet is submitted with the <u>INITIAL</u> filing of the application <u>and</u> either box A or B is <u>not</u> checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, <u>all</u> joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of <u>all</u> joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Jeffrey W. Childers/		Date (YYYY-MM-DD)	2023-07-18	
First Name	Jeffrey W.	Last Name	Childers	Registration Number	58126
			·		

Additional Signature may be generated within this form by selecting the Add button.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.303
		Application Number	
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

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- 2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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- 4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
- 5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.
- 6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
- 7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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- 9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

ABSTRACT

Imaging and radiotherapeutics agents targeting fibroblast-activation protein- α (FAP- α) and their use in imaging and treating FAP- α related diseases and disorders are disclosed.

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JHU-36631.252_P14847-03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.

Confirmation No.: TBD

Serial No.: TBD

Filed: July 18, 2023

Examiner: TBD

Art Unit: TBD

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir or Madam:

Please amend the application as indicated on the following pages.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 4 of this paper.

-1-

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 18354282

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.

Serial No.: 18/354,282

Filed: July 18, 2023

Confirmation No.: 7536

Art Unit: TBD

Examiner: TBD

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir or Madam:

Please amend the application as indicated on the following pages.

Amendments to the Specification begin on page 2 of this paper. Amendments to the Drawings begin on page 3 of this paper.

Amendments to the Claims begin on page 4 of this paper.

Remarks begin on page 6 of this paper.

-1-

Attorney Docket No. JHU-36631.303

AMENDMENTS TO THE SPECIFICATION

Please replace the originally filed specification with the substitute specification filed herewith.

Attorney Docket No. JHU-36631.303

AMENDMENTS TO THE DRAWINGS:

Please replace the originally filed figures with the replacement figures filed herewith.

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application 16/758,182, filed April 22, 2020, which is a U.S. §371 National Entry Application of PCT/US2018/057086, filed October 23, 2018, which claims the benefit of U.S. Provisional Application No. 62/575,607, filed October 23, 2017, each of which is incorporated herein by reference in its entirety.

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FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under CA197470 awarded by the National Institutes of Health. The government has certain rights in the invention.

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BACKGROUND

Fibroblast-activation protein- α (FAP- α) expression has been detected on the surface of fibroblasts in the stroma surrounding >90% of the epithelial cancers examined, including malignant breast, colorectal, skin, prostate and pancreatic

- cancers. (Garin-Chesa, et al., 1990; Rettig, et al., 1993; Tuxhorn, et al., 2002;
 Scanlan, et al., 1994). It is a characteristic marker for carcinoma-associated-fibroblast (CAF), which plays a critical role in promoting angiogenesis, proliferation, invasion, and inhibition of tumor cell death. (Allinen, et al., 2004; Franco, et al., 2010). In healthy adult tissues, FAP-α expression is only limited to areas of tissue remodeling
- or wound healing. (Scanlan, et al., 1994; Yu, et al., 2010; Bae, et al., 2008; Kraman, et al., 2010). In addition, FAP-α-positive cells are observed during embryogenesis in areas of chronic inflammation, arthritis, and fibrosis, as well as in soft tissue and bone sarcomas. (Scanlan, et al., 1994; Yu, et al., 2010). These characteristics make FAP-α a potential imaging and radiotherapeutic target for cancer and inflammation diseases.
- Because FAP-α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis.

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(Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and nontarget tissue clearance (normally 2–5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a

higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP-α.

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SUMMARY

In some aspects, the presently disclosed subject matter provides a compound of Formula (I):

15 wherein: A is a targeting moiety for FAP-α; B is any optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

In particular aspects, A is an FAP- α targeting moiety having the structure of:



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wherein each y is independently an integer selected from the group consisting of 0, 1, and 2; R_{1x} , R_{2x} , and $R_{3x'}$, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is
H; R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃; R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and

- 5 Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms
- selected from O, N and S; Het₂ being optionally substituted with from 1 to 3
 substituents selected from -NR_{13x}R_{14x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; v is
 0, 1, 2, or 3; and



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or

- 15 bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S; wherein ^ξ indicates a point of attachment of the FAP-α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle thereof; and
- 20 stereoisomers and pharmaceutically acceptable salts thereof.

In more particular aspects, A is an FAP- α targeting moiety having the structure of:



wherein [§] indicates a point of attachment of the FAP-α binding ligand to the
linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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



In other aspects, the presently disclosed subject matter provides a pharmaceutical composition comprising a compound of formula (I).

In some aspects, the presently disclosed subject matter provides a method for imaging a disease or disorder associated with fibroblast-activation protein-α (FAP-α), the method comprising administering a compound of formula (I), wherein the compound of formula (I) comprises an optical or radiolabeled functional group suitable for optical imaging, PET imaging, or SPECT imaging; and obtaining an image.

In other aspects, the presently disclosed subject matter provides a method for inhibiting fibroblast-activation protein-α (FAP-α), the method comprising administering to a subject in need thereof an effective amount of a compound of formula (I).

In yet other aspects, the presently disclosed subject matter provides a method
 for treating a fibroblast-activation protein-α (FAP-α)-related disease or disorder, the
 method comprising administering to a subject in need of treatment thereof an effective
 amount of a compound of formula (I), wherein the compound of formula (I)
 comprises a radiolabeled functional group suitable for radiotherapy.

In certain aspects, the (FAP- α)-related disease or disorder is selected from the

20 group consisting of a proliferative disease, including, but not limited to, breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone and connective tissue sarcomas, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, and adenocarcinoma; diseases characterized by tissue remodeling and/or chronic inflammation; disorders

25 involving endocrinological dysfunction; and blood clotting disorders.

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when taken in connection with the accompanying Examples and Figures as best described

30 herein below.

BRIEF DESCRIPTION OF THE FIGURES

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

Having thus described the presently disclosed subject matter in general terms, reference will now be made to the accompanying Figures, which are not necessarily drawn to scale, and wherein:

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FIG. 1A, FIG. 1B, and FIG. 1C show the synthetic pathway and structures of representative FAP-targeted agents, **XY-FAP-01** and [¹¹¹In]-XY-FAP-02</sup>. FIG. 1A

- 10 shows the multi-step synthesis of the ligand precursor, tert-butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate. After each step, the reaction mixture was loaded onto a 25-g C18 cartridge and purified with a MeCN/water/TFA gradient. Identity of intermediate products was confirmed with ¹H NMR. FIG. 1B shows the full structure of optical imaging agent,
- 15 XY-FAP-01. XY-FAP-01 was produced with a one step reaction between the precursor and IRDye800CW-NHS. The major product was obtained at a yield of 85% after purification with HPLC. FIG. 1C shows the full structure of the SPECT imaging agent, [¹¹¹In]-XY-FAP-02. First, the precursor was functionalized with DOTA via a one step reaction between the precursor and DOTA-GA(t-Bu)₄-NHS. Unlabeled
- 20 product was purified via HPLC to produce XY-FAP-02. Subsequent radiolabeling with ¹¹¹In and HPLC purification resulted in the radiolabeled product, [¹¹¹In]-XY-FAP-02;

FIG. 2 shows the inhibitory activity of **XY-FAP-01** on human recombinant FAP. The inhibitory activity of **XY-FAP-01** was determined using a fluorogenic FAP

25 assay kit. Enzymatic activity of human recombinant FAP on a native substrate was inhibited in a concentration dependent fashion by XY-FAP-01. Semi-log inhibitory curves of XY-FAP-01 activity were generated and the determined Ki value of XY-FAP-01 was 1.26 nM;

FIG. 3A, FIG. 3B, and FIG. 3C show the assessment of the *in vitro* binding
ability and specificity of XY-FAP-01 and [¹¹¹In]-XY-FAP-02. FIG. 3A shows the concentration dependent uptake of XY-FAP-01 in various cell lines. Cells incubated with various concentrations (range: 50 nM to 0.78 nM) of XY-FAP-01 were imaged with the LI-COR Pearl Impulse Imager to assess uptake of agent in various FAP-positive and FAP-negative cell lines (left). Dose-response curves of XY-FAP-01

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uptake in FAP-positive cell lines (NCIH2228, U87, and SKMEL24) and FAPnegative cell lines (PC3, NCIH226, and HCT116) were generated (right). FIG. 3B shows the inhibition of **XY-FAP-01** uptake in FAP-positive cell-lines. Cells incubated with 25-nM **XY-FAP-01** were incubated with various concentrations of

- either a DPPIV and FAP inhibitor, Talabostat, or a DPPIV-only inhibitor, Sitagliptin. Uptake of XY-FAP-01 was measured and semi-log inhibitor-response curves were generated for both Talabostat and Sitagliptin. FIG. 3C shows the uptake of [¹¹¹In]-XY-FAP-02 in FAP-positive U87 and FAP-negative PC3 cell lines. Cells were incubated with 1 μCi [¹¹¹In]-XY-FAP-02 and were washed with cold PBS.
- Radioactivity of the cell pellets was measured and normalized to the incubated dose;
 FIG. 4 is a table showing the *ex vivo* tissue biodistribution of [¹¹¹In]-XY-FAP-01 in tumor bearing mice. At 5 min, 0.5 h, 2 h, 6 h, and 12 h after injection of 10 μCi
 [¹¹¹In]-XY-FAP-01, NOD/SKID mice bearing U87 and PC3 tumor xenografts were sacrificed and tissues were collected for biodistribution analysis. Additionally, mice
- 15 co-injected with unlabeled **XY-FAP-02** and 10 μ Ci [¹¹¹In]-XY-FAP-01 were sacrificed at 6 h post-injection to study the effect of blocking on uptake of the radiolabeled compound. Data presented as mean \pm standard deviation. ^aStudent's t test comparison of mean %ID/g of PC3 tumor versus U87 tumor demonstrated significant difference between the two groups at 5 min, 0.5 h, 2 h, and 6 h post injection
- 20 (p<0.0001). No significant difference between the two groups were seen in the blocking study at 6 h. ^bStudent's t test comparison of mean %ID/g of PC3 tumor versus U87 tumor demonstrated significant difference between the two groups at 12 h post injection (p=0.0006). ^cStudent's t test comparing %ID/g between PC3 tumor and U87 tumors at 6 h post injection showed significant difference between %ID/g tumors
- 25 in the blocking study at 6 h versus the normal biodistribution results at 6 h (p<0.0001);</p>

FIG. 5A and FIG. 5B show the time-activity relationship of the *ex vivo* biodistribution of [¹¹¹In]-XY-FAP-02. FIG. 5A shows tissue time activity curves (TACs) of [¹¹¹In]-XY-FAP-02 activity in U87 tumor, PC3 tumor, and blood. FIG. 5B

30 shows the ratios of %ID/g between U87 tumor and PC3 tumor, blood, and muscle (mm) versus time;

FIG. 6 shows serial NIRF-imaging of XY-FAP-01 in tumor bearing mice. NOD/SKID mice bearing FAP-positive U87 (yellow circle) and FAP-negative PC3 (red circle) tumor xenografts were injected with 10 nmol of XY-FAP-01 via the tail

vein followed by serial NIRF-imaging on the LI-COR Pearl Impulse Imager. Representative images at 0.5 h, 1 h, 2.5 h, and 4 h after injection are shown;

FIG. 7 shows SPECT-CT images of [¹¹¹In]-XY-FAP-02 at 30 min, 2 h, 6 h, and 24 h after injection in NOD/SKID female mice bearing U87 and PC3 tumor xenografts in the upper flanks; and

FIG. 8 show three-dimensional SPECT-CT images of [¹¹¹In]-XY-FAP-02 at 30 min, 2 h, 6 h, and 24 h after injection in NOD/SKID female mice bearing U87 and PC3 tumor xenografts in the upper flanks.

DETAILED DESCRIPTION

The presently disclosed subject matter now will be described more fully hereinafter with reference to the accompanying Figures, in which some, but not all embodiments of the presently disclosed subject matter are shown. Like numbers refer to like elements throughout. The presently disclosed subject matter may be embodied

- 15 in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains
- 20 having the benefit of the teachings presented in the foregoing descriptions and the associated Figures. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.
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I. IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-α (FAP-α)

FAP-α is a type II integral membrane serine protease of the prolyl oligopeptidase family, which are distinguished by their ability to cleave the Pro-AA
peptide bond (where AA represents any amino acid). It has been shown to play a role in cancer by modifying bioactive signaling peptides through this enzymatic activity (Kelly, et al., 2005; Edosada, et al., 2006). FAP-α expression has been detected on the surface of fibroblasts in the stroma surrounding greater than 90% of the epithelial cancers, including, but not limited to, malignant breast, colorectal, skin, prostate,

pancreatic cancers, and the like, and inflammation diseases, including, but not limited to, arthritis, fibrosis, and the like, with nearly no expression in healthy tissues. Accordingly, imaging and radiotherapeutic agents specifically targeting FAP- α is of clinical importance.

- FAP-α exists as a homodimer to carry out its enzymatic function. Inhibitors selectively targeting FAP-α has been reported (Lo, et al., 2009; Tsai, et al., 2010; Ryabtsova, et al., 2012; Poplawski, et al., 2013; Jansen, et al., 2013; Jansen, et al., 2014). The presently disclosed subject matter provides, in part, a FAP-α selective targeting moiety that can be modified with an optical dye, a radiometal chelation
- 10 complex, and other radiolabeled prosthetic groups, thus providing a platform for the imaging and radiotherapy targeting FAP-α.

Radionuclide molecular imaging, including positron emission tomography (PET), is the most mature molecular imaging technique without tissue penetration limitations. Due to its advantages of high sensitivity and quantifiability, radionuclide

15 molecular imaging plays an important role in clinical and preclinical research (Youn, et al., 2012; Chen, et al., 2014). Many radionuclides, primarily β - and alpha emitters, have been investigated for targeted radioimmunotherapy and include both radiohalogens and radiometals (see Table 1 for representative therapeutic radionuclides).

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Table 1. Representative Therapeutic Radionuclides		
β-particle emitters	⁹⁰ Y, ¹³¹ I, ¹⁷⁷ Lu, ¹⁵³ Sm, ¹⁸⁶ Re, ¹⁸⁸ Re, ⁶⁷ Cu, ²¹² Pb	
α-particle emitters	²²⁵ Ac, ²¹³ Bi, ²¹² Bi, ²¹¹ At, ²¹² Pb	
Auger electron emitters	¹²⁵ I, ¹²³ I, ⁶⁷ Ga, ¹¹¹ In	

The highly potent and specific binding moiety targeting FAP- α enables its use in nuclear imaging and radiotherapy. The presently disclosed subject matter provides the first synthesis of nuclear imaging and radiotherapy agents based on this deal terr stine mainten to FAP a

25 dual-targeting moiety to FAP- α .

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

and metal complexes, which enable *in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP- α . Importantly, the presently disclosed compounds can be modified, e.g., conjugated with, labeling groups without significantly losing their potency. The presently disclosed approach allows for the

5 convenient labeling of the FAP-α ligand with optical dyes and PET or SPECT isotopes, including, but not limited to, ⁶⁸Ga, ⁶⁴Cu, ¹⁸F, ⁸⁶Y, ⁹⁰Y, ⁸⁹Zr, ¹¹¹In, ^{99m}Tc, ¹²⁵I, ¹²⁴I, for FAP-α related imaging applications. Further, the presently disclosed approach allows for the radiolabeling of the FAP-α ligand with radiotherapeutic isotopes, including but not limited to, ⁹⁰Y, ¹⁷⁷Lu, ¹²⁵I, ¹³¹I, ²¹¹At, ¹¹¹In, ¹⁵³Sm, ¹⁸⁶Re,

¹⁸⁸Re, ⁶⁷Cu, ²¹²Pb, ²²⁵Ac, ²¹³Bi, ²¹²Bi, ²¹²Pb, and ⁶⁷Ga, for FAP-α related radio-therapy. In a particular embodiment, an optical agent conjugated with IRDye-800CW (XY-FAP-01) was synthesized and showed selective uptake *in vitro* on a FAP-α+ U87 cell line and *in vivo* on a FAP-α+ U87 tumor and clearly detected the tumor. In another particular embodiment, an ¹¹¹In labeled ligand (XY-FAP-02-[¹¹¹In]) was

- successfully obtained in high yield and purity from its precursor with a metal chelator.
 The *in vivo* study showed clear tumor radiotracer uptake in mice bearing FAP-α positive U87 tumors with minimum non-specific organ uptake, which allows the
 specific imaging of FAP-α expressing tumors. The presently disclosed FAP-α
 targeting moiety can be adapted for use with optical dyes and radioisotopes known in
- 20 the art for imaging and therapeutic applications targeting FAP- α .

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More particularly, in some embodiments, the presently disclosed subject matter provides a compound of the general structure of Formula (I):

B—L—A (I)

wherein: A is a targeting moiety for FAP- α ; B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET)

25 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.

Representative targeting moieties for FAP-α are disclosed in U.S. Patent
30 Application Publication No. US2014/0357650 for Novel FAP Inhibitors to Jansen et al., published Dec. 4, 2014; U.S. Patent No. 9,346,814 for Novel FAP Inhibitors to Jansen et al., issued May 24, 2016; and International PCT Patent Publication No. WO 2013/107820 for Novel FAP Inhibitors to Jansen et al., published July 25, 2013, each of which are incorporate by reference in their entirety.

More particularly, U.S. Patent No. 9,346,814 to Jansen et al., discloses FAP- α inhibitors of formula (X), or a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof, which are suitable for use with the presently disclosed subject matter:



wherein:

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 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

 R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl being optionally substituted with from 1 to 3 substituents

15 selected from -OH and halogen;

 R_{8x} , R_{9x} , and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and

20 Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1

or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from -NR_{13x}R_{14x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic monoor bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S.

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

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wherein * indicates the point of attachment of the 5 to 10-membered Ncontaining aromatic or non-aromatic mono- or bicyclic heterocycle to –(CH₂)_v–. Accordingly, in some embodiments, A is an FAP-α targeting moiety having the structure of:



wherein each y is independently an integer selected from the group consisting of 0, 1, and 2;

 R_{1x} , R_{2x} , and $R_{3x'}$, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

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 R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃

20 being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic monoor bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

- wherein indicates a point of attachment of the FAP-α binding ligand to a
 linker, e.g., L, or a reporter moiety, such as an optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging or radiotherapy, wherein the point of attachment can be through any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle thereof; and stereoisomers and pharmaceutically acceptable salts thereof.
- 10 In particular embodiments, * is selected from the group consisting of:



In some embodiments, A is an FAP- α targeting moiety having the structure of:



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wherein y, R_{1x} , R_{2x} and $R_{3x'}$ are defined as hereinabove; ξ indicates a point of attachment of the FAP- α binding ligand to a linker, e.g., L, or a reporter moiety, such as an optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging or radiotherapy, wherein the point of attachment can be

5 through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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



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



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and stereoisomers thereof.

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

of:



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In some embodiments, the combination of L and B can be represented by:


wherein the subunits associated with elements p_1 , p_2 , p_3 and p_4 may be in any order; t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; p_1 , p_3 , and p_4 are each independently 0 or 1; p_2 is an integer selected from the group consisting of 0, 1, 2, and 3, and when p_2 is 2 or 3, each R_1 is the same or different; m_1

- and m₂ are each an integer independently selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6; W₁ is selected from the group consisting of a bond, -S-, -C(=O)-NR-, and -NR-C(=O)-; W₂ is selected from the group consisting of a bond, -S-, -CH₂-C(=O)-NR-, -C(O)-, -NRC(O)-, -NR'C(O)NR-, -NRC(S)NR'₂-, -NRC(O)O-, -OC(O)NR-, -OC(O)-, -C(O)NR-, -NR-C(O)-, -C(O)O-, -(O-CH₂-CH₂)_q- and -
- 10 (CH₂-CH₂-O)_q-, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -OR₄, wherein R₄ is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted alkyl, cycloalkyl,
- 15 heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove; Tz is a triazole group that can be present or absent and, if present, is selected from the group consisting of



; each R₁ is independently H, C₁-C₆ alkyl, C₃-

 $C_{12} \text{ aryl}, \text{-}(CH_2)_q\text{-}C_3\text{-}C_{12} \text{ aryl}, \text{-}C_4\text{-}C_{16} \text{ alkylaryl}, \text{ or -}(CH_2)_q\text{-}C_4\text{-}C_{16} \text{ alkylaryl}; R_2 \text{ and } C_1 \text{-}C_1 \text{-}C_1$

- R₃ are each independently H and -CO₂R₅, wherein R₅ is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₁₂ aryl, and C₄-C₁₆ alkylaryl, wherein when one of R₂ or R₃ is CO₂R₅, then the other is H; V is selected from the group consisting of C(O)–, -C(S)-, –NRC(O)–, –NRC(S)–, and –OC(O)–; B is any optical or radiolabeled functional group suitable for optical, PET, or SPECT imaging or radiotherapy; and
- 25 stereoisomers and pharmaceutically acceptable salts thereof.

In some embodiments, L has the following general structure:



wherein p_1 , p_2 , p_3 , m_1 , m_2 , q, t, Tz, W_2 , R, R_1 , R_2 , R_3 , and V are defined as hereinabove.

In some embodiments, L is selected from the group consisting of $-L_1$ -, $-L_2$ -L₃-, and $-L_1$ -L₂-L₃-, wherein:

L2 is -NR-(CH2)q-C(COOR5)-NR-; and

$$L_3$$
 is -(O=)C-(CH₂)_q-C(=O)-;

wherein each q is independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

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-(CR₆H) $_q$ -(CH₂) $_q$ -C(=O)-NR-(CH₂) $_q$ -O- or -NR-(CH₂) $_q$ -O-;

wherein each q and R is defined hereinabove; and R₆ is H or -COOR₅.

is:

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



wherein u is an integer selected from 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

Suitable linkers are disclosed in U.S. Patent Application Publication No.
US2011/0064657 A1, for "Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA), Biological Evaluation, and Use as Imaging Agents," published March 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. US2012/0009121 A1, for "PSMA-Targeting Compounds and Uses Thereof," published January 12, 2012, to Pomper et al, each of which is incorporated by reference in its entirety.

In some embodiments, B is a radiolabeled prosthetic group comprising a radioisotope selected from the group consisting of ¹⁸F, ¹²⁴I, ¹²⁵I, ¹³¹I, and ²¹¹At. Representative radiolabeled prosthetic groups include, but are not limited to:



wherein each X is independently a radioisotope selected from the group consisting of ¹⁸F, ¹²⁴I, ¹²⁵I, ¹³¹I, and ²¹¹At; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20.

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



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In other embodiments, B comprises a chelating agent. Representative chelating agents include, but are not limited to:



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- In some embodiments, B comprises an optical dye, e.g., in particular embodiments, a fluorescent dye. In some embodiments, the fluorescent dye moiety comprises carbocyanine, indocarbocyanine, oxacarbocyanine, thiacarbocyanine and merocyanine, polymethine, coumarine, rhodamine, xanthene, fluorescein, borondipyrromethane (BODIPY), Cy5, Cy5.5, Cy7, VivoTag-680, VivoTag-S680, VivoTag-S750, AlexaFluor660, AlexaFluor680, AlexaFluor700, AlexaFluor750,
- AlexaFluor790, Dy677, Dy676, Dy682, Dy752, Dy780, DyLight547, Dylight647,
 HiLyte Fluor 647, HiLyte Fluor 680, HiLyte Fluor 750, IRDye 800CW, IRDye
 800RS, IRDye 700DX, ADS780WS, ADS830WS, and ADS832WS.

Representative optical dyes include, but are not limited to:



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In some embodiments, the presently disclosed subject matter provides a compound selected from the group consisting of:



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



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; and



B. Pharmaceutical Compositions and Administration

In another aspect, the present disclosure provides a pharmaceutical comprising a compound of formula (I) in admixture with a pharmaceutically acceptable carrier, diluent, excipient, or adjuvant. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts or hydrates of the compounds described above.

Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art and include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the

15 desired base, either neat or in a suitable inert solvent or by ion exchange, whereby one basic counterion (base) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt.

When compounds of the present disclosure contain relatively basic
functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange, whereby one acidic counterion (acid) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric,

25 hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic,

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benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, ptoluenesulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical

5 Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Accordingly, pharmaceutically acceptable salts suitable for use with the presently disclosed subject matter include, by way of example but not limitation,

- 10 acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate,
- 15 pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). In therapeutic and/or diagnostic applications, the compounds of the disclosure
- 20 can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-slow release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, by

30 inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articular, intra -sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

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For injection, the agents of the disclosure may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in

10 particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (e.g., patient) to be treated.

For nasal or inhalation delivery, the agents of the disclosure also may be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances, such as saline; preservatives, such as benzyl alcohol; absorption

20 promoters; and fluorocarbons.

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Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure

- 25 provided herein. Generally, the compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A non-limiting dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the
- 30 form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, the bioavailability of the compound(s), the adsorption, distribution, metabolism, and excretion (ADME) toxicity of the compound(s), and the preference and experience of the attending physician.

In addition to the active ingredients, these pharmaceutical compositions may

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contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

5 Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for

10 example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl- cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

15 Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-

stuffs or pigments may be added to the tablets or dragee coatings for identification or 20 to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants

25 such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

C. Methods of Imaging using the Compounds of Formula (I), or 30 Pharmaceutical Compositions Thereof

In some embodiments, presently disclosed subject matter provides a method for imaging a disease or disorder associated with fibroblast-activation protein- α (FAP- α), the method comprising administering a compound of formula (I), wherein the compound of formula (I) comprises an optical or radiolabeled functional group

suitable for optical imaging, PET imaging, or SPECT imaging; and obtaining an image.

Accordingly, in some embodiments, the presently disclosed subject matter provides a method for imaging one or more cells, organs, or tissues, the method

5 comprising exposing cells or administering to a subject an effective amount of a compound of formula (I) with an optical or radioisotopic label suitable for imaging. In some embodiments, the one or more organs or tissues include prostate tissue, kidney tissue, brain tissue, vascular tissue, or tumor tissue.

The imaging methods of the invention are suitable for imaging any

- physiological process or feature in which FAP-α is involved, for example, identifying areas of tissues or targets which exhibit or express high concentrations of FAP-α.
 Physiological processes in which FAP-α is involved include, but are not limited to:
 (a) proliferation diseases (including but not limited to cancer); (b) tissue remodeling and/or chronic inflammation (including but not limited to fibrotic disease, wound
- 15 healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation); and (c) endocrinological disorders (including but not limited to disorders of glucose metabolism).

In certain embodiments, the radiolabeled compound is stable in vivo. In certain embodiments, the radiolabeled compound is detected by positron

20 emission tomography (PET) or single photon emission computed tomography (SPECT).

In certain embodiments, the optical reporting moiety is detected by fluorescence, such as fluorescence microscopy.

In certain embodiments, the presently disclosed compounds are excreted from tissues of the body quickly to prevent prolonged exposure to the radiation of the radiolabeled compound administered to the subject. Typically, the presently disclosed compounds are eliminated from the body in less than about 24 hours. More typically, the presently disclosed compounds are eliminated from the body in less than about 16 hours, 12 hours, 8 hours, 6 hours, 4 hours, 2 hours, 90 minutes, or 60 minutes.

30 Exemplary compounds are eliminated in between about 60 minutes and about 120 minutes. In certain embodiments, the presently disclosed compounds are stable in vivo such that substantially all, e.g., more than about 50%, 60%, 70%, 80%, or 90% of the injected compound is not metabolized by the body prior to excretion.

Additionally, for in vitro applications, such as in vitro diagnostic and research applications, body fluids and cell samples of the above subjects will be suitable for use, such as mammalian, particularly primate such as human, blood, urine or tissue samples, or blood urine or tissue samples of the animals mentioned for veterinary

5 applications.

Other embodiments provide kits comprising a compound of formula (I). In certain embodiments, the kit provides packaged pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of formula (I). In certain embodiments the packaged pharmaceutical composition will comprise the

- 10 reaction precursors necessary to generate the compound of formula (I) upon combination with a radiolabeled precursor. Other packaged pharmaceutical compositions further comprise indicia comprising at least one of: instructions for preparing compounds of formula (I) from supplied precursors, instructions for using the composition to image cells or tissues expressing FAP-α.
- 15 In certain embodiments, a kit containing from about 1 to about 30 mCi of the radionuclide-labeled imaging agent described above, in combination with a pharmaceutically acceptable carrier, is provided. The imaging agent and carrier may be provided in solution or in lyophilized form. When the imaging agent and carrier of the kit are in lyophilized form, the kit may optionally contain a sterile and
- 20 physiologically acceptable reconstitution medium such as water, saline, buffered saline, and the like. The kit may provide a compound of formula (I) in solution or in lyophilized form, and these components of the kit may optionally contain stabilizers such as NaCl, silicate, phosphate buffers, ascorbic acid, gentisic acid, and the like. Additional stabilization of kit components may be provided in this embodiment, for
- example, by providing the reducing agent in an oxidation-resistant form.Determination and optimization of such stabilizers and stabilization methods are well within the level of skill in the art.

In certain embodiments, a kit provides a non-radiolabeled precursor to be combined with a radiolabeled reagent on-site.

30 Imaging agents may be used in accordance with the presently disclosed methods by one of skill in the art. Images can be generated by virtue of differences in the spatial distribution of the imaging agents which accumulate at a site when contacted with FAP-α. The spatial distribution may be measured using any means suitable for the particular label, for example, a gamma camera, a PET apparatus, a

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SPECT apparatus, and the like. The extent of accumulation of the imaging agent may be quantified using known methods for quantifying radioactive emissions or fluorescence. A particularly useful imaging approach employs more than one imaging agent to perform simultaneous studies.

5 In general, a detectably effective amount of the imaging agent of the invention is administered to a subject. A "detectably effective amount" of the imaging agent is defined as an amount sufficient to yield an acceptable image using equipment which is available for clinical use. A detectably effective amount of the imaging agent may be administered in more than one injection. The detectably effective amount of the

- 10 imaging agent of the invention can vary according to factors such as the degree of susceptibility of the individual, the age, sex, and weight of the individual, idiosyncratic responses of the individual, and the dosimetry. Detectably effective amounts of the imaging agent also can vary according to instrument and film-related factors. Optimization of such factors is well within the level of skill in the art. The
- 15 amount of imaging agent used for diagnostic purposes and the duration of the imaging study will depend upon the radionuclide used to label the agent, the body mass of the patient, the nature and severity of the condition being treated, the nature of therapeutic treatments which the patient has undergone, and on the idiosyncratic responses of the patient. Ultimately, the attending physician will decide the amount of imaging agent
- 20 to administer to each individual patient and the duration of the imaging study.

D. Methods of Treating a FAP-α Related Disease or Disorder using the Compounds of Formula (I), or Pharmaceutical Compositions Thereof

In other embodiments, the presently disclosed compounds of formula (I) can be used to treat a subject afflicted with one or more FAP-α related diseases or disorders including, but not limited to: (a) proliferation (including but not limited to cancer); (b) tissue remodeling and/or chronic inflammation (including but not limited to fibrotic disease, wound healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation); and (c) endocrinological disorders (including but not limited to disorders of glucose

30 metabolism).

Accordingly, in some embodiments, the one or more FAP- α related disease or disorder is selected from the group consisting of a proliferative disease, including, but not limited to, breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone and

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connective tissue sarcomas, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, and adenocarcinoma; diseases characterized by tissue remodeling and/or chronic inflammation; disorders involving endocrinological dysfunction; and blood clotting disorders.

In general, the "effective amount" of an active agent or drug delivery device refers to the amount necessary to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of an agent or device may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the makeup of the pharmaceutical composition, the target

10 tissue, and the like.

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In other embodiments, the method can be practiced *in vitro* or *ex vivo* by introducing, and preferably mixing, the compound and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube. The method can be practiced *in vivo*, in which case contacting means exposing the target in a subject to at least

15 one compound of the presently disclosed subject matter, such as administering the compound to a subject via any suitable route. According to the presently disclosed subject matter, contacting may comprise introducing, exposing, and the like, the compound at a site distant to the cells to be contacted, and allowing the bodily functions of the subject, or natural (e.g., diffusion) or man-induced (e.g., swirling) 20 movements of fluids to result in contact of the compound and the target.

The subject treated by the presently disclosed methods in their many embodiments is desirably a human subject, although it is to be understood that the methods described herein are effective with respect to all vertebrate species, which are intended to be included in the term "subject." Accordingly, a "subject" can

- 25 include a human subject for medical purposes, such as for the treatment of an existing condition or disease or the prophylactic treatment for preventing the onset of a condition or disease, or an animal (non-human) subject for medical, veterinary purposes, or developmental purposes. Suitable animal subjects include mammals including, but not limited to, primates, e.g., humans, monkeys, apes, and the like;
- 30 bovines, e.g., cattle, oxen, and the like; ovines, e.g., sheep and the like; caprines, e.g., goats and the like; porcines, e.g., pigs, hogs, and the like; equines, e.g., horses, donkeys, zebras, and the like; felines, including wild and domestic cats; canines, including dogs; lagomorphs, including rabbits, hares, and the like; and rodents, including mice, rats, and the like. An animal may be a transgenic animal. In some

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embodiments, the subject is a human including, but not limited to, fetal, neonatal, infant, juvenile, and adult subjects. Further, a "subject" can include a patient afflicted with or suspected of being afflicted with a condition or disease. Thus, the terms "subject" and "patient" are used interchangeably herein. In some

5 embodiments, the subject is human. In other embodiments, the subject is nonhuman.

As used herein, the term "treating" can include reversing, alleviating, inhibiting the progression of, preventing or reducing the likelihood of the disease, or condition to which such term applies, or one or more symptoms or manifestations of

10 such disease or condition.

"Preventing" refers to causing a disease, condition, or symptom or manifestation of such, or worsening of the severity of such, not to occur. Accordingly, the presently disclosed compounds can be administered prophylactically to prevent or reduce the incidence or recurrence of the disease, or condition.

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II. DEFINITIONS

Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly

20 understood by one of ordinary skill in the art to which this presently described subject matter belongs.

While the following terms in relation to compounds of formula (I) are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter. These

25 definitions are intended to supplement and illustrate, not preclude, the definitions that would be apparent to one of ordinary skill in the art upon review of the present disclosure.

The terms substituted, whether preceded by the term "optionally" or not, and substituent, as used herein, refer to the ability, as appreciated by one skilled in this art,

30 to change one functional group for another functional group on a molecule, provided that the valency of all atoms is maintained. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The substituents also may be further substituted (e.g., an aryl group substituent may

have another substituent off it, such as another aryl group, which is further substituted at one or more positions).

Where substituent groups or linking groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically

identical substituents that would result from writing the structure from right to left,
e.g., -CH₂O- is equivalent to -OCH₂-; -C(=O)O- is equivalent to -OC(=O)-;
-OC(=O)NR- is equivalent to -NRC(=O)O-, and the like.

When the term "independently selected" is used, the substituents being referred to (e.g., R groups, such as groups R_1 , R_2 , and the like, or variables, such as

10 "m" and "n"), can be identical or different. For example, both R₁ and R₂ can be substituted alkyls, or R₁ can be hydrogen and R₂ can be a substituted alkyl, and the like.

The terms "a," "an," or "a(n)," when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted

15 with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

A named "R" or group will generally have the structure that is recognized in the art as corresponding to a group having that name, unless specified otherwise herein. For the purposes of illustration, certain representative "R" groups as set forth above are defined below.

Descriptions of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and

30 several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

Unless otherwise explicitly defined, a "substituent group," as used herein, includes a functional group selected from one or more of the following moieties, which are defined herein:

The term hydrocarbon, as used herein, refers to any chemical group 5 comprising hydrogen and carbon. The hydrocarbon may be substituted or unsubstituted. As would be known to one skilled in this art, all valencies must be satisfied in making any substitutions. The hydrocarbon may be unsaturated, saturated, branched, unbranched, cyclic, polycyclic, or heterocyclic. Illustrative hydrocarbons are further defined herein below and include, for example, methyl, ethyl, *n*-propyl,

10 isopropyl, cyclopropyl, allyl, vinyl, *n*-butyl, *tert*-butyl, ethynyl, cyclohexyl, and the like.

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., C₁-C₁₀ means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term "alkyl" refers to C₁₋₂₀ inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons, linear (i.e., "straight-chain"), branched, or cyclic, saturated or at least
- 20 partially and in some cases fully unsaturated (i.e., alkenyl and alkynyl) hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single hydrogen atom.

Representative saturated hydrocarbon groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl,

25 *sec*-pentyl, isopentyl, neopentyl, *n*-hexyl, *sec*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*undecyl, dodecyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and homologs and isomers thereof.

"Branched" refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain. "Lower alkyl" refers to an alkyl group having 1 to about 8 carbon atoms (i.e., a C₁₋₈ alkyl), e.g., 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms. "Higher alkyl" refers to an alkyl group having about 10 to about 20 carbon atoms, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. In certain embodiments, "alkyl" refers, in particular, to C₁₋₈ straight-chain alkyls. In other embodiments, "alkyl" refers, in particular, to C₁₋₈ branched-chain alkyls.

Alkyl groups can optionally be substituted (a "substituted alkyl") with one or more alkyl group substituents, which can be the same or different. The term "alkyl group substituent" includes but is not limited to alkyl, substituted alkyl, halo, alkylamino, arylamino, acyl, hydroxyl, aryloxyl, alkoxyl, alkylthio, arylthio,

5 aralkyloxyl, aralkylthio, carboxyl, alkoxycarbonyl, oxo, and cycloalkyl. There can be optionally inserted along the alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, lower alkyl (also referred to herein as "alkylaminoalkyl"), or aryl.

Thus, as used herein, the term "substituted alkyl" includes alkyl groups, as defined herein, in which one or more atoms or functional groups of the alkyl group are replaced with another atom or functional group, including for example, alkyl, substituted alkyl, halogen, aryl, substituted aryl, alkoxyl, hydroxyl, nitro, amino, alkylamino, dialkylamino, sulfate, and mercapto.

The term "heteroalkyl," by itself or in combination with another term, means,

- 15 unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon group, or combinations thereof, consisting of at least one carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S
- and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-CH₂-S(CH₃), -CH₂-CH₂-S(O)₂-CH₃, -CH₂-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-CH₂-S(O)₂-CH₂-S(O)₂-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-S(O)₂-CH₂-S(O)₂-CH₃, -CH₂-S(O)₂-CH₂-S(O)₂-CH₃, -CH₂-S(O)₂-CH₂-S(O)₂-CH₂-S(O)₂-CH₂-S(O)₂-CH₂-S(O)₂-CH₂-S(O)₂-CH₂-S(O)₂-CH₂-S(O)₂-CH₂
- 25 -CH=CH-N(CH₃)- CH₃, O-CH₃, -O-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃.

As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as

30 -C(O)NR', -NR'R", -OR', -SR, -S(O)R, and/or -S(O₂)R'. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific

heteroalkyl groups, such as -NR'R" or the like.

"Cyclic" and "cycloalkyl" refer to a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, e.g., 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The cycloalkyl group can be optionally partially unsaturated. The cycloalkyl

- 5 group also can be optionally substituted with an alkyl group substituent as defined herein, oxo, and/or alkylene. There can be optionally inserted along the cyclic alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, unsubstituted alkyl, substituted alkyl, aryl, or substituted aryl, thus providing a heterocyclic group. Representative
- 10 monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, and cycloheptyl. Multicyclic cycloalkyl rings include adamantyl, octahydronaphthyl, decalin, camphor, camphane, and noradamantyl, and fused ring systems, such as dihydro- and tetrahydronaphthalene, and the like.

The term "cycloalkylalkyl," as used herein, refers to a cycloalkyl group as defined hereinabove, which is attached to the parent molecular moiety through an alkyl group, also as defined above. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

The terms "cycloheteroalkyl" or "heterocycloalkyl" refer to a non-aromatic ring system, unsaturated or partially unsaturated ring system, such as a 3- to 10-

20 member substituted or unsubstituted cycloalkyl ring system, including one or more heteroatoms, which can be the same or different, and are selected from the group consisting of nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), and silicon (Si), and optionally can include one or more double bonds.

The cycloheteroalkyl ring can be optionally fused to or otherwise attached to other cycloheteroalkyl rings and/or non-aromatic hydrocarbon rings. Heterocyclic rings include those having from one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. In certain embodiments, the term heterocylic refers to a non-aromatic 5-, 6-, or 7-

30 membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from the oxygen, sulfur, and nitrogen, wherein (i) each 5-membered ring has

0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds, and each 7membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring.

5 Representative cycloheteroalkyl ring systems include, but are not limited to pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, quinuclidinyl, morpholinyl, thiomorpholinyl, thiadiazinanyl, tetrahydrofuranyl, and the like.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like.

15 Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4- morpholinyl, 3morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 -piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of

20 cycloalkyl and heterocycloalkyl, respectively.

25

An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl."

More particularly, the term "alkenyl" as used herein refers to a monovalent group derived from a C_{1-20} inclusive straight or branched hydrocarbon moiety having at least one carbon-carbon double bond by the removal of a single hydrogen molecule. Alkenyl groups include, for example, ethenyl (i.e., vinyl), propenyl, butenyl, 1-

30 methyl-2-buten-1-yl, pentenyl, hexenyl, octenyl, allenyl, and butadienyl.

The term "cycloalkenyl" as used herein refers to a cyclic hydrocarbon containing at least one carbon-carbon double bond. Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, 1,3-cyclohexadienyl, cycloheptenyl, cycloheptatrienyl, and cyclooctenyl.

The term "alkynyl" as used herein refers to a monovalent group derived from a straight or branched C_{1-20} hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon triple bond. Examples of "alkynyl" include ethynyl, 2-propynyl (propargyl), 1-propynyl, pentynyl, hexynyl, and heptynyl groups, and the like

5 and the like.

The term "alkylene" by itself or a part of another substituent refers to a straight or branched bivalent aliphatic hydrocarbon group derived from an alkyl group having from 1 to about 20 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. The alkylene group can be straight,

- 10 branched or cyclic. The alkylene group also can be optionally unsaturated and/or substituted with one or more "alkyl group substituents." There can be optionally inserted along the alkylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms (also referred to herein as "alkylaminoalkyl"), wherein the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups
- include methylene (-CH₂-); ethylene (-CH₂-CH₂-); propylene (-(CH₂)₃-); cyclohexylene (-C₆H₁₀-); -CH=CH-CH=CH-; -CH=CH-CH₂-; -CH₂CH₂CH₂CH₂CH₂CH₂-, -CH₂CH=CHCH₂-, -CH₂CSCCH₂-, -CH₂CH₂CH₂CH₂CH₂CH₃)CH₂-, -(CH₂)_q-N(R)-(CH₂)_r-, wherein each of q and r is independently an integer from 0 to about 20, e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20,
- 20 and R is hydrogen or lower alkyl; methylenedioxyl (-O-CH₂-O-); and ethylenedioxyl (-O-(CH₂)₂-O-). An alkylene group can have about 2 to about 3 carbon atoms and can further have 6-20 carbons. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being some embodiments of the present disclosure. A "lower alkyl" or
- 25 "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The term "heteroalkylene" by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂-and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups,

30 heteroatoms also can occupy either or both of the chain termini (e.g., alkyleneoxo, alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)OR'- represents both -C(O)OR'- and -R'OC(O)-.

The term "aryl" means, unless otherwise stated, 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. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in

- 5 the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrazolyl, 2-
- imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4- oxazolyl, 5 oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5 thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2 pyrimidyl, 4- pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1 isoquinolyl, 5- isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-
- 15 quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent forms of aryl and heteroaryl, respectively.

For brevity, the term "aryl" when used in combination with other terms (e.g.,

- 20 aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms "arylalkyl" and "heteroarylalkyl" are meant to include those groups in which an aryl or heteroaryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, furylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an
- 25 oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(l-naphthyloxy)propyl, and the like). However, the term "haloaryl," as used herein is meant to cover only aryls substituted with one or more halogens.

Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" refers to a carbon

30 or heteroatom.

Further, a structure represented generally by the formula:





as used herein refers to a ring structure, for example, but not limited to a 3-carbon, a 4-carbon, a 5-carbon, a 6-carbon, a 7-carbon, and the like, aliphatic and/or aromatic cyclic compound, including a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure, comprising a substituent R group, wherein

- 5 the R group can be present or absent, and when present, one or more R groups can each be substituted on one or more available carbon atoms of the ring structure. The presence or absence of the R group and number of R groups is determined by the value of the variable "n," which is an integer generally having a value ranging from 0 to the number of carbon atoms on the ring available for substitution. Each R group, if
- 10 more than one, is substituted on an available carbon of the ring structure rather than on another R group. For example, the structure above where n is 0 to 2 would comprise compound groups including, but not limited to:



and the like.

15 A dashed line representing a bond in a cyclic ring structure indicates that the bond can be either present or absent in the ring. That is, a dashed line representing a bond in a cyclic ring structure indicates that the ring structure is selected from the group consisting of a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure.

20 The symbol (**********) denotes the point of attachment of a moiety to the remainder of the molecule.

When a named atom of an aromatic ring or a heterocyclic aromatic ring is defined as being "absent," the named atom is replaced by a direct bond.

Each of above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl, and

25 "heterocycloalkyl", "aryl," "heteroaryl," "phosphonate," and "sulfonate" as well as their divalent derivatives) are meant to include both substituted and unsubstituted forms of the indicated group. Optional substituents for each type of group are provided below.

Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent

and divalent derivative groups (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen,

- 5 -SiR'R"R", -OC(O)R', -C(O)R', -CO₂R',-C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R", -NR"C(O)OR', -NR-C(NR'R")=NR", -S(O)R', -S(O)₂R', -S(O)₂NR'R", -NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such groups. R', R", R"" and R"" each may independently refer to hydrogen, substituted or unsubstituted
- 10 heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. As used herein, an "alkoxy" group is an alkyl attached to the remainder of the molecule through a divalent oxygen. When a compound of the disclosure includes
- 15 more than one R group, for example, each of the R groups is independently selected as are each R', R", R" and R" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7- membered ring. For example, -NR'R" is meant to include, but not be limited to, 1- pyrrolidinyl and 4-
- 20 morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

Similar to the substituents described for alkyl groups above, exemplary
substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are
varied and are selected from, for example: halogen, -OR', -NR'R", -SR',
-SiR'R"R", -OC(O)R', -C(O)R', -CO₂R', -C(O)NR'R", -OC(O)NR'R", NR"C(O)R', -NR'-C(O)NR"R", -NR"C(O)OR', -NR-C(NR'R"R")=NR"",
-NR-C(NR'R")=NR" -S(O)R', -S(O)₂R', -S(O)₂NR'R", -NRSO₂R', -CN and -NO₂,

-R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxo, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R", R" and R"" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted or unsubstituted

unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R" and R" groups when more than one of these groups is present.

- 5 Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and
- 10 B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula

15 -(CRR')s-X'- (C"R")d-, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -S(O)2-, or -S(O)2NR'-. The substituents R, R', R" and R" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

- As used herein, the term "acyl" refers to an organic acid group wherein the -OH of the carboxyl group has been replaced with another substituent and has the general formula RC(=O)-, wherein R is an alkyl, alkenyl, alkynyl, aryl, carbocylic, heterocyclic, or aromatic heterocyclic group as defined herein). As such, the term "acyl" specifically includes arylacyl groups, such as a 2-(furan-2-yl)acetyl)- and a 2-
- 25 phenylacetyl group. Specific examples of acyl groups include acetyl and benzoyl. Acyl groups also are intended to include amides, -RC(=O)NR', esters, -RC(=O)OR', ketones, -RC(=O)R', and aldehydes, -RC(=O)H.

The terms "alkoxyl" or "alkoxy" are used interchangeably herein and refer to a saturated (i.e., alkyl–O–) or unsaturated (i.e., alkenyl–O– and alkynyl–O–) group

30 attached to the parent molecular moiety through an oxygen atom, wherein the terms "alkyl," "alkenyl," and "alkynyl" are as previously described and can include C₁₋₂₀ inclusive, linear, branched, or cyclic, saturated or unsaturated oxo-hydrocarbon chains, including, for example, methoxyl, ethoxyl, propoxyl, isopropoxyl, *n*-butoxyl, *sec*-butoxyl, *tert*-butoxyl, and *n*-pentoxyl, neopentoxyl, *n*-hexoxyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkyl-O-alkyl ether, for example, a methoxyethyl or an ethoxymethyl group.

"Aryloxyl" refers to an aryl-O- group wherein the aryl group is as previously described, including a substituted aryl. The term "aryloxyl" as used herein can refer

to phenyloxyl or hexyloxyl, and alkyl, substituted alkyl, halo, or alkoxyl substituted phenyloxyl or hexyloxyl.

"Aralkyl" refers to an aryl-alkyl-group wherein aryl and alkyl are as previously described and includes substituted aryl and substituted alkyl. Exemplary aralkyl groups include benzyl, phenylethyl, and naphthylmethyl.

"Aralkyloxyl" refers to an aralkyl-O- group wherein the aralkyl group is as previously described. An exemplary aralkyloxyl group is benzyloxyl, i.e.,
 C₆H₅-CH₂-O-. An aralkyloxyl group can optionally be substituted.

"Alkoxycarbonyl" refers to an alkyl-O-C(=O)– group. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, butyloxycarbonyl,

15 and *tert*-butyloxycarbonyl.

"Aryloxycarbonyl" refers to an aryl-O-C(=O)– group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxy-carbonyl.

"Aralkoxycarbonyl" refers to an aralkyl-O-C(=O)– group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

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"Carbamoyl" refers to an amide group of the formula $-C(=O)NH_2$. "Alkylcarbamoyl" refers to a R'RN-C(=O)- group wherein one of R and R' is hydrogen and the other of R and R' is alkyl and/or substituted alkyl as previously described. "Dialkylcarbamoyl" refers to a R'RN-C(=O)- group wherein each of R and R' is independently alkyl and/or substituted alkyl as previously described.

The term carbonyldioxyl, as used herein, refers to a carbonate group of the formula -O-C(=O)-OR.

"Acyloxyl" refers to an acyl-O- group wherein acyl is as previously described. The term "amino" refers to the $-NH_2$ group and also refers to a nitrogen

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one or more hydrogen radicals by organic radicals. For example, the terms "acylamino" and "alkylamino" refer to specific N-substituted organic radicals with acyl and alkyl substituent groups respectively.

containing group as is known in the art derived from ammonia by the replacement of

An "aminoalkyl" as used herein refers to an amino group covalently bound to an alkylene linker. More particularly, the terms alkylamino, dialkylamino, and

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trialkylamino as used herein refer to one, two, or three, respectively, alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. The term alkylamino refers to a group having the structure –NHR' wherein R' is an alkyl group, as previously defined; whereas the term dialkylamino refers to a group

- 5 having the structure –NR'R", wherein R' and R" are each independently selected from the group consisting of alkyl groups. The term trialkylamino refers to a group having the structure –NR'R"R", wherein R', R", and R" are each independently selected from the group consisting of alkyl groups. Additionally, R', R", and/or R" taken together may optionally be –(CH₂)_k– where k is an integer from 2 to 6.
- 10 Examples include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, isopropylamino, piperidino, trimethylamino, and propylamino.

The amino group is -NR'R", wherein R' and R" are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl,

15 substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The terms alkylthioether and thioalkoxyl refer to a saturated (i.e., alkyl–S–) or unsaturated (i.e., alkenyl–S– and alkynyl–S–) group attached to the parent molecular moiety through a sulfur atom. Examples of thioalkoxyl moieties include, but are not

20 limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

"Acylamino" refers to an acyl-NH– group wherein acyl is as previously described. "Aroylamino" refers to an aroyl-NH– group wherein aroyl is as previously described.

The term "carbonyl" refers to the -C(=O)- group, and can include an aldehyde 25 group represented by the general formula R-C(=O)H.

The term "carboxyl" refers to the –COOH group. Such groups also are referred to herein as a "carboxylic acid" moiety.

The terms "halo," "halide," or "halogen" as used herein refer to fluoro, chloro, bromo, and iodo groups. Additionally, terms such as "haloalkyl," are meant to

30 include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C₁-C₄)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "hydroxyl" refers to the -OH group.

The term "hydroxyalkyl" refers to an alkyl group substituted with an –OH group.

The term "mercapto" refers to the -SH group.

The term "oxo" as used herein means an oxygen atom that is double bonded to a carbon atom or to another element.

The term "nitro" refers to the -NO₂ group.

The term "thio" refers to a compound described previously herein wherein a carbon or oxygen atom is replaced by a sulfur atom.

The term "sulfate" refers to the -SO₄ group.

10 The term thiohydroxyl or thiol, as used herein, refers to a group of the formula –SH.

More particularly, the term "sulfide" refers to compound having a group of the formula –SR.

The term "sulfone" refers to compound having a sulfonyl group $-S(O_2)R$.

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The term "sulfoxide" refers to a compound having a sulfinyl group -S(O)RThe term ureido refers to a urea group of the formula -NH—CO— NH_2 . Throughout the specification and claims, a given chemical formula or name

shall encompass all tautomers, congeners, and optical- and stereoisomers, as well as racemic mixtures where such isomers and mixtures exist.

- 20 Certain compounds of the present disclosure may possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as D- or L- for amino acids, and individual isomers are encompassed within the scope of the present
- disclosure. The compounds of the present disclosure do not include those which are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic, scalemic, and optically pure forms.
 Optically active (R)- and (S)-, or D- and L-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the
- 30 compounds described herein contain olefenic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each

asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

As used herein the term "monomer" refers to a molecule that can undergo polymerization, thereby contributing constitutional units to the essential structure of a macromolecule or polymer.

A "polymer" is a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer.

15 A "dendrimer" is highly branched, star-shaped macromolecules with nanometer-scale dimensions.

As used herein, an "oligomer" includes a few monomer units, for example, in contrast to a polymer that potentially can comprise an unlimited number of monomers. Dimers, trimers, and tetramers are non-limiting examples of oligomers.

- 20 The term "protecting group" refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd ed. John Wiley & Sons (1999). It may be advantageous, where
- 25 different protecting groups are employed, that each (different) protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions allow differential removal of such protecting groups. For example, protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and tert-butyldimethylsilyl are acid
- 30 labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile

groups such as tert-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine

- 5 groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while coexisting amino groups may be blocked with fluoride labile silyl carbamates.
- Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or piacid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a palladium(O)- catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is
- 15 attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

Typical blocking/protecting groups include, but are not limited to the following moieties:



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Following long-standing patent law convention, the terms "a," "an," and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a subject" includes a plurality of subjects, unless the context clearly is to the contrary (e.g., a plurality of subjects), and so forth.

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Throughout this specification and the claims, the terms "comprise," "comprises," and "comprising" are used in a non-exclusive sense, except where the context requires otherwise. Likewise, the term "include" and its grammatical variants are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in

- 15 all instances by the term "about" even though the term "about" may not expressly appear with the value, amount or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off,
- 20 measurement error and the like, and other factors known to those of skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term "about," when referring to a value can be meant to encompass variations of, in some embodiments, $\pm 100\%$ in some embodiments $\pm 50\%$, in some embodiments $\pm 20\%$, in some embodiments $\pm 10\%$, in
- some embodiments \pm 5%, in some embodiments \pm 1%, in some embodiments \pm 0.5%, and in some embodiments \pm 0.1% from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Further, the term "about" when used in connection with one or more numbers or numerical ranges, should be understood to refer to all such numbers, including all

30 numbers in a range and modifies that range by extending the boundaries above and below the numerical values set forth. The recitation of numerical ranges by endpoints includes all numbers, e.g., whole integers, including fractions thereof, subsumed within that range (for example, the recitation of 1 to 5 includes 1, 2, 3, 4, and 5, as

well as fractions thereof, e.g., 1.5, 2.25, 3.75, 4.1, and the like) and any range within that range.

EXAMPLES

- 5 The following Examples have been included to provide guidance to one of ordinary skill in the art for practicing representative embodiments of the presently disclosed subject matter. In light of the present disclosure and the general level of skill in the art, those of skill can appreciate that the following Examples are intended to be exemplary only and that numerous changes, modifications, and alterations can
- 10 be employed without departing from the scope of the presently disclosed subject matter. The synthetic descriptions and specific examples that follow are only intended for the purposes of illustration, and are not to be construed as limiting in any manner to make compounds of the disclosure by other methods.

EXAMPLE 1

Experimental Procedures

1.1 Synthesis of XY-FAP-01.

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Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**): 6-Hydroxyquinoline-4carboxylic acid (**1**) 210 mg (1.1 mmol), methyl glycinate HCl salt (**2**) 143 mg (1.1 mmol), HBTU 420 mg (1.1 mmol) and HOBt 170 mg (1.1 mmol) were dissolved in 12 mL dry DMF. To the solution, 0.77 mL of DIPEA (4.4 mmol) was added. The reaction was stirred at room temperature for 6 h. After the solvent was removed under vacuum, the mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada) and the

product was purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 290 mg of product 3 was obtained as a yellow powder with a yield of 76%. ¹H-NMR (400 MHz, CD₃OD): δ 8.69 (s, 1H), 7.94 (d, J = 7.92 Hz, 1H), 7.57–7.51 (m, 3H), 7.42–7.37 (m, 1H), 4.21 (s, 2H), 3.81 (s, 3H). ¹³C-NMR (100 MHz, CD₃OD): δ

172.4, 160.9, 145.1, 143.7, 129.7, 129.4, 128.3, 121.8, 119.6, 112.4, 109.1, 56.8, 44.8. MS: calculated for $[C_{13}H_{13}N_2O_4]^+$, 261.3 $[M + H]^+$; found 261.1.



Methyl (6-(3-((tert-butoxycarbonyl)amino)propoxy)quinoline-4-

- 5 carbonyl)glycinate (5): Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (3) 360 mg (1.0 mmol), tert-butyl (3-bromopropyl)carbamate (4) 500 mg (2.1 mmol) were dissolved in 20 mL DMF. Cs₂CO₃ 1 g (3.0 mmol) was added to the solution and the reaction was stirred at room temperature overnight. After filtration, the solvent was removed under vacuum and the remaining mixture was loaded onto a 25 g C18
- cartridge (Silicycle, Canada). The product was purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 270 mg of product 5 was obtained with a yield of 54%. ¹H-NMR (400 MHz, CDCl₃): δ 8.68-8.37 (m, 2H), 8.02 (d, J = 9.1 Hz, 1H), 7.80 (s, 1H), 7.72-7.64 (m, 1H), 7.40 (d, J = 9.1 Hz, 1H), 4.94 (br s, 1H), 4.41-4.31 (m, 2H), 4.27-4.18 (m, 2H), 3.85 (s, 3H), 3.44-3.30 (m, 2H), 2.13-2.00 (m, 2H),
- 15 1.43 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 170.1, 167.2, 158.4, 144.7, 142.3, 128.4, 126.1, 124.7, 119.1, 103.7, 79.5, 60.4, 52.5, 41.4, 37.7, 29.3, 28.4. MS: calculated for [C₂₁H₂₈N₃O₆]⁺, 418.5 [M + H]⁺; found 418.3.



tert-Butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-

- 20 oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate (7): Compound 5 110 mg (0.21 mmol) and LiOH 30 mg (1.2 mmol) was stirred in 4 mL of H₂O/THF (1/1) for 6 hours. After most of the THF was removed under vacuum, the mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada) and eluded with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1) to remove the salts. The product 6 obtained was
- mixed with (S)-pyrrolidine-2-carbonitrile 53 mg (0.4 mmol), HOBT 68 mg (0.4 mmol), HBTU 152 mg (0.4 mmol) and DIPEA 0.56 mL (1.6 mmol) in dry 10 mL DMF. After 6 hours, the solvent was removed under vacuum and the remaining mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada). The product was
purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 99 mg of 7 was obtained with a yield of 80%. ¹H NMR (400 MHz, CDCl₃): δ 8.73 (s, 1H), 7.95 (d, J = 10.2 Hz, 1H), 7.68 (br s, 1H), 7.63–7.56 (m, 1H), 7.56–7.48 (m, 1H), 7.38–7.29 (m, 1H), 5.27 (br s, 1H), 4.84–4.72 (m, 1H), 4.46–4.35 (m, 1H), 4.33–4.20 (m, 1H),

4.17-4.09 (m, 2H), 3.78-3.64 (m, 1H), 3.59-3.46 (m, 1H), 3.36 (s, 2H), 2.38-2.17 (m, 4H), 1.42 (s, 9H), 1.35-1.27 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 167.5, 157.9, 156.2, 146.3, 130.2, 125.7, 123.7, 119.3, 118.0, 103.3, 79.0, 65.9, 46.8, 45.7, 42.2, 37.6, 29.8, 29.3, 28.4, 25.1. MS: calculated for [C₂₅H₃₂N₅O₅]⁺, 482.6 [M + H]⁺; found 482.3.

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XY-FAP-01. Compound 7 (1 mg, 1.7 μ mol) was treated with a 1 mL solution of TFA/methylene chloride (1/1) for 2 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMSO. To the solution, LICOR800CW-NHS ester 0.5 mg (0.43 μ mol) and Et₃N 10 μ L were added. After 1 h

- at room temperature, the solvent was removed and the product was purified by HPLC.
 0.5 mg product was obtained with a yield of 85%. HPLC condition: column
 Phenomenex, Luna 10 x 250 mm, 10 u. Gradient 10/90/0.1 MeCN/H₂O/TFA to
 80/20/0.1 MeCN/H₂O/TFA within 15 min at a flow of 3 mL/min. The product was
 eluted at 10.1 min. MS: Calculated for[C₆₆H₇₆N₇O₁₇S₄]⁺, 1366.4[M+H]⁺; found
- 20 1366.8.

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1.2 Synthesis of XY-FAP-02



2,2',2"-(10-(1-Carboxy-4-((3-((4-((2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl) amino)-4-oxobutyl)-1,4,7,10-

25 tetraazacyclododecane-1,4,7-triyl)triacetic acid (**XY-FAP-02**): Compound 7 (15 mg, 31.3 μmol) was treated with a 1-mL solution of TFA/methylene chloride (1/1) for 1 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMF. To the solution, DIPEA (27 μL, 156.5 μmol) was added, followed by dropwise addition of a solution of DOTA-GA(t-Bu)₄-NHS (25 mg, 31.3 μL) in 0.5

mL of DMF. The reaction mixture was stirred for 4 h at ambient temperature and then concentrated under vacuum. The t-Bu-protected intermediate was deprotected in situ without further purification using a 1 mL mixture of TFA, H₂O and triethylsilane (TES) (95:2.5:2.5). Reaction mixture was then concentrated and purified by

semipreparative HPLC, to afford the product as a white solid (8.5 mg, 33% yield).
MS: calculated for [C₃₉H₅₄N₉O₁₂]⁺, 840.9 [M + H]⁺; found 840.5. HPLC (10 mm x 250 mm Phenomenex Luna C18 column, 10 μm, mobile phase 95/5/0.1% to 75/25/0.1% water/acetonitrile/TFA over 20 min, flow 5 mL/min) XY-FAP-02 eluted at 11.8 min.



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XY-FAP-02-[In]. ^{113/115}Indium(III) 2,2',2"-(10-(1-Carboxy-4-((3-((4-((2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl) amino)-4oxobutyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (**XY-FAP-02-[In]**): To a solution of 2 mg (2.4 μmol) of **XY-FAP-02** in 1 mL of 0.2M AcONa, a solution

of 1.4 mg (4.6 μmol) of In(NO₃)₃ in 0.5 mL water is added and warmed in a 60 °C bath for 30 min. After cooling to ambient temperature, the mixture was purified by semipreparative HPLC. The product was obtained as a white solid (1.8 mg, 79% yield). MS: calculated for [C₃₉H₅₁N₉O₁₂In]⁺, 951.7 [M + H]⁺; found 952.5. HPLC (10 mm x 250 mm Phenomenex Luna C18 column, 10 μm, mobile phase 95/5/0.1% to

20 75/25/0.1% water/acetonitrile/TFA over 20 min, flow 5 mL/min) **XY-FAP-02-[In]** eluted at 14.0 min.

1.3 Radiolabeling Methods. Briefly, 20 mg XY-FAP-02 solution in 20 mL of
0.2 M NaOAc was added to 10 mL 4.6 mCi ¹¹¹InCl₃ solution (Nordion, Ottawa,
Canada) and adjusted to a final pH of 5.5-6. The mixture was heated in a water bath at

- 25 70 °C for 30 min and, after the reaction completed, was diluted with 200 mL of water for HPLC purification. The solution was purified using a Phenomenex 5 μm C₁₈ Luna 4.6 x 250 mm² column (Torrance, CA) with a flow rate of 0.6 mL/min with water (0.1% TFA) (A) and MeCN (0.1% TFA) (B) as the eluting solvents. An isocractic solution of 88% A and 12% B was utilized for purification, resulting in the labeled
- 30 compound, ¹¹¹In-XY-FAP-02, eluting first at 18.6 min followed by the unlabeled

starting material at 23.5 min. 3.2 mCi of labeled compound was obtained as pure product with a yield of 69%. Another reaction with the identical condition was performed with 74% yield. The collected radioactivity was diluted with 20 mL of water and loaded onto activated Sep-Pak (WAT020515, Waters, Milford, MA). After

5 the Sep-Pak was washed with 10 mL of water, ¹¹¹In-XY-FAP-02 was eluted with 1.5 mL of ethanol. The ethanol was evaporated under a gentle stream of N_2 (to a total volume of $< 50 \ \mu$ L). The resulting solution was formulated in saline for the imaging and biodistribution studies.

1.4 FAP Inhibition Assay. The inhibitory activity of XY-FAP-01 was

- 10 determined using a fluorogenic FAP Assay Kit (BPS Bioscience, San Diego, CA). Briefly, XY-FAP-01, DPP substrate, and human recombinant FAP were loaded into a 96 well plate to initiate the enzyme reaction. The reaction was left for 10 minutes at room temperature before fluorescence was measured with a VICTOR3 V multilabel plate reader (PerkinElmer Inc., Waltham, MA). Data was normalized and semi-log
- inhibition curves were generated in order to determine the IC₅₀ value (concentration of XY-FAP-01 where the enzyme activity is 50% inhibited) for XY-FAP-01 and subsequent enzyme inhibition constant (K_i) using the Cheng-Prusoff conversion. Generation of semi-log inhibition curves and IC50 values were done using GraphPad Prism (San Diego, CA).
- 20 1.5 Cell lines. Six human cancer cell lines were used to assess binding to FAP: glioblastoma (U-87-MG), melanoma (SK-MEL-24), prostate (PC-3), non-small cell lung cancer (NCI-H2228), colorectal carcinoma (HCT 116), and lung squamous cell carcinoma (NCI-H226). From the literature, U-87-MG, SK-MEL-24, and NCI-H2228 cell lines were identified as having high levels of FAP expression [FAP-
- 25 positive (+)] whereas PC-3, NCI-H226, and HCT 116 cells expressed very low levels of FAP [FAP-negative(-)]. These expression profiles were further confirmed via flow cytometry with an APC-conjugated anti-FAP antibody (R&D Systems, Minneapolis, MN) and quantitative real-time PCR. All cell lines were purchased from American Type Culture Collection (ATCC, Manassas, VA).
- U-87-MG cells were maintained in MEM medium (Corning Cellgro,
 Manassas, VA), containing 10% fetal bovine serum (FBS) (Sigma-Aldrich, St. Louis,
 MO) and 1% penicillin-streptomycin (Corning Cellgro, Manassas, VA),
 supplemented with sodium bicarbonate (Corning), sodium pyruvate (Gibco,
 Gaithersburg, MD), and MEM non-essential amino acids (Gibco). SK-MEL-24 cells

were maintained in MEM medium, containing 15% FBS and 1% penicillinstreptomycin, supplemented with sodium bicarbonate, sodium pyruvate, and MEM non-essential amino acids. PC-3 cells were grown in Ham's F-12K medium (Corning Cellgro) supplemented with 10% FBS and 1% penicillin-streptomycin. NCI-H2228,

- 5 NCI-H226, and HCT 116 cells were cultured in RPMI 1640 medium (Corning Cellgro) supplemented with 10% FBS and 1% penicillin-streptomycin. All cell cultures were maintained at 37 °C and 5% carbon dioxide (CO₂) in a humidified incubator.
- 1.6 Cellular Uptake Studies. All cellular uptake and specific binding studies
 were performed in triplicate to ensure reproducibility. Cells were detached using
 0.05% trypsin (Corning), resuspended in 1 million cell aliquots in binding buffer, and
 incubated with various concentrations (range, 50 nM to 0.78 nM) of XY-FAP-01 for
 1 hour at 37 °C and 5% CO₂. To assess the specific uptake of XY-FAP-02, cells were
 preblocked with a FAP and DPP-IV specific inhibitor (Val-boroPro, MilliporeSigma,
- Burlington, MA) or a DPP-IV specific inhibitor (Sitagliptin, Santa Cruz Biotechnology, Inc., Dallas, TX) at various concentrations (range, 10⁻¹⁰ M to 10⁻⁴ M) prior to incubation with 25 nM XY-FAP-02 solution in binding buffer for 1 hour at 37 °C and 5% CO₂. Cellular uptake was terminated by washing cells with ice cold PBS (1x) three times. Cells were resuspended in binding buffer and transferred to a
- 20 96-well plate for imaging. Images were acquired on the LI-COR Pearl Impulse Imager (Lincoln, NE) using an excitation wavelength of 785 nm and detection of the emission wavelength at 800 nm. Images were analyzed using the LI-COR Pearl Impulse Software (Version 2.0) and fluorescence intensity was corrected for background signal and normalized to well area.
- Cellular Uptake of ¹¹¹In-XY-FAP-02 was also assessed in cells. Cell aliquots (1 million) were incubated with 1 μCi ¹¹¹In-XY-FAP-02 in saline for 30 minutes at 37 °C and 5% CO₂. Cells were washed three times with cold PBS (1x) and activity of the cell pellets was measured with the 1282 CompuGamma CS gamma well counter (Pharmacia/LKB Nuclear, Inc., Gaithersburg, MD). The percent uptake of the

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administered activity was calculated by comparison with samples of a standard dose. *1.7 Small-Animal Near Infrared Fluorescence (NIRF) Imaging.* NIRF images were acquired on the LI-COR Pearl Impulse Imager using an excitation wavelength of 785 nm and a detection wavelength of 800 nm. Mice utilized for imaging studies were anesthetized with 3% isofluorane (v/v) and maintained at 1.5% isofluorane for the

imaging procedure. NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts were injected with 10 nmol of **XY-FAP-01** via tail vein injection and images were acquired at 30 min, 1 h, 2 h, 2.5 h, and 4 h after injection of tracer. Data were displayed and analyzed using the LI-COR Pearl Impulse Software (Version 2.0).

- 5 *1.8 Small-Animal SPECT-CT Imaging.* SPECT-CT studies were performed on NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts. For imaging studies, mice were anesthetized with 3% isoflurane prior to being placed on the scanner bed and kept warm with an external light source. Isoflurane levels were decreased to 1.5% for the rest of the imaging procedure. After mice were injected
- 10 with 300 µCi ¹¹¹In-XY-FAP-02 in 200 µL saline, SPECT-CT imaging was carried out using a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA) at the indicated timepoints (30 min, 2 h, 6 h, and 24 h) post radiotracer injection. A CT scan was performed at the end of each SPECT scan for anatomical co-registration. Obtained data sets were reconstructed using the provided Gamma Medica-Ideas

15 software and final data visualization and image generation were prepared using Amira® software (FEI, Hillsboro, OR).

1.9 Ex-vivo Biodistribution. NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts were injected with 10 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline via the tail vein. At 5 min, 30 min, 2 h, 6 h, and 12 hr post injection, mice (n=4)

- 20 were sacrificed by CO₂ asphyxiation and blood was immediately collected by cardiac puncture. Additionally, the heart, lungs, liver, stomach, pancreas, spleen, fat, kidney, small intestine, large intestine, bladder, muscle, femur, FAP+ U-87-MG xenograft, and FAP- PC-3 xenograft were collected for biodistribution analysis. Each tissue was weighed and radioactivity was measuring using a 2480 Wizard² automated gamma
- 25 counter (PerkinElmer, Waltham, MA). Radioactivity measurements were corrected for decay and compared with samples of a standard dilution of the initial dose to calculated percent injected dose per gram (%ID/g).

For blocking studies, mice (n=5 per group) were co-injected with unlabeled **XY-FAP-02** (50 μ g per mouse) and 10 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline. Mice

30 (n=5) injected with 10 µCi ¹¹¹In-XY-FAP-02 in 200 µL saline served as a control. At
 6 h post injection, mice were sacrificed, tissues were collected, and radioactivity was measured with the gamma well counter.

1.10 Data Analysis. Data are expressed at mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, CA) was used for analysis and statistical

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significance was calculated using a two-tailed Student's t test. A P-value <0.05 was considered significant.

1.11 Xenograft Tumor Model. 6-week old female NOD/SCID mice were subcutaneously injected in the upper left and right flanks with 1 million U87(FAP+)

5 cells and PC3 cells (FAP-) in RPMI 1640 media supplemented with 1% FBS. Mice were monitored for tumor size and used for optical or SPECT/CT imaging when the size of tumor reached around 100 mm³.

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EXAMPLE 2

Representative Results

2.1 FAP Inhibitory Assay. **XY-FAP-01** demonstrated high binding affinity to human recombinant FAP. The enzyme inhibitory constant (Ki) for the compound was determined to be 1.26 nM.

2.2 Cellular Uptake Studies. FAP-positive cell lines showed concentration
dependent uptake of XY-FAP-01 whereas FAP-negative cell lines showed no
significant binding of XY-FAP-01 at all concentrations (see, e.g., FIG. 3A). Saturated
binding of XY-FAP-01 was observed at concentration of 25 nM, which was
subsequently used as the base concentration for all binding inhibition studies. When
preblocked with a FAP and DPP-IV specific inhibitor, XY-FAP-01 binding was

20 significantly inhibited in FAP-positive cells (FIG. 3B). Interestingly, this phenomenon was not observed in FAP-positive cell lines preblocked with a DPP-IV specific inhibitor. These results further justify the specificity of XY-FAP-01 for FAP over DPPIV, since blocking of DPPIV did not result in a change of binding ability of XY-FAP-01.

Similar specificity was observed with the radioactive analog, ¹¹¹In-XY-FAP 02. FAP positive cell line, U-87-MG, demonstrated over 30% uptake of administered radioactive dose after incubation whereas the FAP negative cell line, PC-3, had uptake of 0.01% of administered dose (FIG. 3C). Taken together, these results support the specificity of XY-FAP-01 and ¹¹¹In-XY-FAP-02 in the engagement of FAP *in vitro*.

2.3 Ex-vivo Biodistribution. Ex-vivo biodistribution of ¹¹¹In-XY-FAP-02 results correlated with the observed imaging results (FIG. 4). Initially, the blood pool activity is very high, with over 10% %ID/g at 30 minutes post injection. With clearance of the compound, we see the blood pool activity drop significantly after 2

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hours of distribution and remained less than 5% %ID/g from 2 hours post injection (FIG. 5A). High activity was also observed in pancreas, small intestines, and bladder until 2 hours post injection. Positive tumor uptake peaked at 30 minutes post injection and remained between 13-11% %ID/g up to 6 hours. Washout of tumor was observed

5 at 12 hours post injection, with %ID/g dropping to below 5%. The PC-3, FAP negative xenograft had less than 3.5% %ID/g for all timepoints.

Co-injection of cold compound with ¹¹¹In-XY-FAP-02 resulted in significant blocking of tracer uptake in U-87 xenografts, with %ID/g dropping from 11.20% without blocking versus 0.27% with blocking (p < 0.0001). Additionally, blocking

10 with cold compound resulted in %ID/g of all tissues dropping significantly, with most values being less than 0.1%. This decrease in uptake is most likely due to the blocking of non-specific binding of tracer to non-target tissues and the blocking of specific binding of FAP in U-87 xenografts.

2.4 Small-Animal Near Infrared Fluorescence (NIRF) Imaging. NIRF

15 imaging of XY-FAP-01 demonstrated specific uptake of tracer in the U-87-MG xenograft as early as 30 minutes post injection (FIG. 6). After one hour of distribution, tracer clearance via the bladder was observed with retained tracer uptake in the FAP positive xenograft. Tracer uptake was retained in the positive xenograft after four hours of distribution. In contrast, no significant uptake of tracer was

20 observed in the FAP negative tumor at all imaging time points.

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All publications, patent applications, patents, and other references mentioned in the specification are indicative of the level of those skilled in the art to which the

- 25 presently disclosed subject matter pertains. All publications, patent applications, patents, and other references (e.g., websites, databases, etc.) mentioned in the specification are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent application, patent, and other reference was specifically and individually indicated to be incorporated by reference. It will be
- 30 understood that, although a number of patent applications, patents, and other references are referred to herein, such reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art. In case of a conflict between the specification and any of the incorporated references, the specification (including any amendments thereof, which may be based on an

incorporated reference), shall control. Standard art-accepted meanings of terms are used herein unless indicated otherwise. Standard abbreviations for various terms are used herein.

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- U.S. Patent Application Publication No. US2014/0357650 for Novel FAP Inhibitors to Jansen et al., published Dec. 4, 2014.
- U.S. Patent No. 9,346,814 for Novel FAP Inhibitors to Jansen et al., issued May 24, 2016.
- 10 International PCT Patent Publication No. WO 2013/107820 for Novel FAP Inhibitors to Jansen et al., published July 25, 2013.

Although the foregoing subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be

15 understood by those skilled in the art that certain changes and modifications can be practiced within the scope of the appended claims.

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application 16/758,182, filed April 22, 2020, which is a U.S. §371 National Entry Application of PCT/US2018/057086, filed October 23, 2018, which claims the benefit of U.S. Provisional Application No. 62/575,607, filed October 23, 2017, each of which is incorporated herein by reference in its entirety.

FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under CA197470 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Fibroblast-activation protein- α (FAP- α) expression has been detected on the surface of fibroblasts in the stroma surrounding >90% of the epithelial cancers examined, including malignant breast, colorectal, skin, prostate and pancreatic cancers. (Garin-Chesa, et al., 1990; Rettig, et al., 1993; Tuxhorn, et al., 2002; Scanlan, et al., 1994). It is a characteristic marker for carcinoma-associated-fibroblast (CAF), which plays a critical role in promoting angiogenesis, proliferation, invasion, and inhibition of tumor cell death. (Allinen, et al., 2004; Franco, et al., 2010). In healthy adult tissues, FAP- α expression is only limited to areas of tissue remodeling or wound healing. (Scanlan, et al., 1994; Yu, et al., 2010; Bae, et al., 2008; Kraman, et al., 2010). In addition, FAP- α -positive cells are observed during embryogenesis in areas of chronic inflammation, arthritis, and fibrosis, as well as in soft tissue and bone sarcomas. (Scanlan, et al., 1994; Yu, et al., 2010). These characteristics make FAP- α a potential imaging and radiotherapeutic target for cancer and inflammation diseases.

Because FAP- α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis.

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(Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and nontarget tissue clearance (normally 2–5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP- α .

SUMMARY

In some aspects, the presently disclosed subject matter provides a compound of Formula (I):

B—L—A (I)

wherein: A is a targeting moiety for FAP- α ; B is any optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

In particular aspects, A is an FAP-a targeting moiety having the structure of:



wherein each y is independently an integer selected from the group consisting of 0, 1, and 2; R_{1x} , R_{2x} , and $R_{3x'}$, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is H; R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃; R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Het₂ is a 5- or 6membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from -NR_{13x}R_{14x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl, and -S-C₁₋₆alkyl; 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; wherein $\frac{\xi}{2}$ indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

In more particular aspects, A is an FAP- α targeting moiety having the structure of:



wherein ξ indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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



In other aspects, the presently disclosed subject matter provides a pharmaceutical composition comprising a compound of formula (I).

In some aspects, the presently disclosed subject matter provides a method for imaging a disease or disorder associated with fibroblast-activation protein- α (FAP- α), the method comprising administering a compound of formula (I), wherein the compound of formula (I) comprises an optical or radiolabeled functional group suitable for optical imaging, PET imaging, or SPECT imaging; and obtaining an image.

In other aspects, the presently disclosed subject matter provides a method for inhibiting fibroblast-activation protein- α (FAP- α), the method comprising administering to a subject in need thereof an effective amount of a compound of formula (I).

In yet other aspects, the presently disclosed subject matter provides a method for treating a fibroblast-activation protein- α (FAP- α)-related disease or disorder, the method comprising administering to a subject in need of treatment thereof an effective amount of a compound of formula (I), wherein the compound of formula (I) comprises a radiolabeled functional group suitable for radiotherapy.

In certain aspects, the (FAP- α)-related disease or disorder is selected from the group consisting of a proliferative disease, including, but not limited to, breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone and connective tissue sarcomas, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, and adenocarcinoma; diseases characterized by tissue remodeling and/or chronic inflammation; disorders involving endocrinological dysfunction; and blood clotting disorders.

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when taken in connection with the accompanying Examples and Figures as best described herein below.

BRIEF DESCRIPTION OF THE FIGURES

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

Having thus described the presently disclosed subject matter in general terms, reference will now be made to the accompanying Figures, which are not necessarily drawn to scale, and wherein:

FIG. 1A, FIG. 1B, and FIG. 1C show the synthetic pathway and structures of representative FAP-targeted agents, **XY-FAP-01** and [¹¹¹**In**]-**XY-FAP-02**. FIG. 1A shows the multi-step synthesis of the ligand precursor, tert-butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate. After each step, the reaction mixture was loaded onto a 25-g C18 cartridge and purified with a MeCN/water/TFA gradient. Identity of intermediate products was confirmed with ¹H NMR. FIG. 1B shows the full structure of optical imaging agent, **XY-FAP-01**. **XY-FAP-01** was produced with a one step reaction between the precursor and IRDye800CW-NHS. The major product was obtained at a yield of 85% after purification with HPLC. FIG. 1C shows the full structure of the SPECT imaging agent, [¹¹¹In]-XY-FAP-02. First, the precursor was functionalized with DOTA via a one step reaction between the precursor and DOTA-GA(t-Bu)₄-NHS. Unlabeled product was purified via HPLC to produce XY-FAP-02. Subsequent radiolabeling with ¹¹¹In and HPLC purification resulted in the radiolabeled product, [¹¹¹In]-XY-FAP-02;

FIG. 2 shows the inhibitory activity of **XY-FAP-01** on human recombinant FAP. The inhibitory activity of **XY-FAP-01** was determined using a fluorogenic FAP assay kit. Enzymatic activity of human recombinant FAP on a native substrate was inhibited in a concentration dependent fashion by **XY-FAP-01**. Semi-log inhibitory curves of **XY-FAP-01** activity were generated and the determined Ki value of **XY-FAP-01** was 1.26 nM;

FIG. 3A, FIG. 3B, and FIG. 3C show the assessment of the *in vitro* binding ability and specificity of **XY-FAP-01** and [¹¹¹**In**]-**XY-FAP-02**. FIG. 3A shows the concentration dependent uptake of **XY-FAP-01** in various cell lines. Cells incubated with various concentrations (range: 50 nM to 0.78 nM) of **XY-FAP-01** were imaged with the LI-COR Pearl Impulse Imager to assess uptake of agent in various FAP-positive and FAP-negative cell lines (left). Dose-response curves of **XY-FAP-01**

uptake in FAP-positive cell lines (NCIH2228, U87, and SKMEL24) and FAPnegative cell lines (PC3, NCIH226, and HCT116) were generated (right). FIG. 3B shows the inhibition of **XY-FAP-01** uptake in FAP-positive cell-lines. Cells incubated with 25-nM **XY-FAP-01** were incubated with various concentrations of either a DPPIV and FAP inhibitor, Talabostat, or a DPPIV-only inhibitor, Sitagliptin. Uptake of **XY-FAP-01** was measured and semi-log inhibitor-response curves were generated for both Talabostat and Sitagliptin. FIG. 3C shows the uptake of [¹¹¹In]-**XY-FAP-02** in FAP-positive U87 and FAP-negative PC3 cell lines. Cells were incubated with 1 μ Ci [¹¹¹In]-**XY-FAP-02** and were washed with cold PBS. Radioactivity of the cell pellets was measured and normalized to the incubated dose;

FIG. 4 is a table showing the ex vivo tissue biodistribution of [¹¹¹In]-XY-FAP-**01** in tumor bearing mice. At 5 min, 0.5 h, 2 h, 6 h, and 12 h after injection of 10 μ Ci [¹¹¹In]-XY-FAP-01, NOD/SKID mice bearing U87 and PC3 tumor xenografts were sacrificed and tissues were collected for biodistribution analysis. Additionally, mice co-injected with unlabeled XY-FAP-02 and 10 µCi [¹¹¹In]-XY-FAP-01 were sacrificed at 6 h post-injection to study the effect of blocking on uptake of the radiolabeled compound. Data presented as mean ± standard deviation. ^aStudent's t test comparison of mean %ID/g of PC3 tumor versus U87 tumor demonstrated significant difference between the two groups at 5 min, 0.5 h, 2 h, and 6 h post injection (p < 0.0001). No significant difference between the two groups were seen in the blocking study at 6 h. bStudent's t test comparison of mean %ID/g of PC3 tumor versus U87 tumor demonstrated significant difference between the two groups at 12 h post injection (p=0.0006). ^cStudent's t test comparing %ID/g between PC3 tumor and U87 tumors at 6 h post injection showed significant difference between %ID/g tumors in the blocking study at 6 h versus the normal biodistribution results at 6 h (p<0.0001);

FIG. 5A and FIG. 5B show the time-activity relationship of the *ex vivo* biodistribution of [¹¹¹In]-XY-FAP-02. FIG. 5A shows tissue time activity curves (TACs) of [¹¹¹In]-XY-FAP-02 activity in U87 tumor, PC3 tumor, and blood. FIG. 5B shows the ratios of %ID/g between U87 tumor and PC3 tumor, blood, and muscle (mm) versus time;

FIG. 6 shows serial NIRF-imaging of XY-FAP-01 in tumor bearing mice. NOD/SKID mice bearing FAP-positive U87 (yellow circle) and FAP-negative PC3 (red circle) tumor xenografts were injected with 10 nmol of XY-FAP-01 via the tail

vein followed by serial NIRF-imaging on the LI-COR Pearl Impulse Imager. Representative images at 0.5 h, 1 h, 2.5 h, and 4 h after injection are shown;

FIG. 7 shows SPECT-CT images of [¹¹¹In]-XY-FAP-02 at 30 min, 2 h, 6 h, and 24 h after injection in NOD/SKID female mice bearing U87 and PC3 tumor xenografts in the upper flanks; and

FIG. 8 show three-dimensional SPECT-CT images of [¹¹¹In]-XY-FAP-02 at 30 min, 2 h, 6 h, and 24 h after injection in NOD/SKID female mice bearing U87 and PC3 tumor xenografts in the upper flanks.

DETAILED DESCRIPTION

The presently disclosed subject matter now will be described more fully hereinafter with reference to the accompanying Figures, in which some, but not all embodiments of the presently disclosed subject matter are shown. Like numbers refer to like elements throughout. The presently disclosed subject matter may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein; rather, these embodiments are provided so that this disclosure will satisfy applicable legal requirements. Indeed, many modifications and other embodiments of the presently disclosed subject matter set forth herein will come to mind to one skilled in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the foregoing descriptions and the associated Figures. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the appended claims.

I. IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-α (FAP-α)

FAP- α is a type II integral membrane serine protease of the prolyl oligopeptidase family, which are distinguished by their ability to cleave the Pro-AA peptide bond (where AA represents any amino acid). It has been shown to play a role in cancer by modifying bioactive signaling peptides through this enzymatic activity (Kelly, et al., 2005; Edosada, et al., 2006). FAP- α expression has been detected on the surface of fibroblasts in the stroma surrounding greater than 90% of the epithelial cancers, including, but not limited to, malignant breast, colorectal, skin, prostate,

pancreatic cancers, and the like, and inflammation diseases, including, but not limited to, arthritis, fibrosis, and the like, with nearly no expression in healthy tissues. Accordingly, imaging and radiotherapeutic agents specifically targeting FAP- α is of clinical importance.

FAP- α exists as a homodimer to carry out its enzymatic function. Inhibitors selectively targeting FAP- α has been reported (Lo, et al., 2009; Tsai, et al., 2010; Ryabtsova, et al., 2012; Poplawski, et al., 2013; Jansen, et al., 2013; Jansen, et al., 2014). The presently disclosed subject matter provides, in part, a FAP- α selective targeting moiety that can be modified with an optical dye, a radiometal chelation complex, and other radiolabeled prosthetic groups, thus providing a platform for the imaging and radiotherapy targeting FAP- α .

Radionuclide molecular imaging, including positron emission tomography (PET), is the most mature molecular imaging technique without tissue penetration limitations. Due to its advantages of high sensitivity and quantifiability, radionuclide molecular imaging plays an important role in clinical and preclinical research (Youn, et al., 2012; Chen, et al., 2014). Many radionuclides, primarily β - and alpha emitters, have been investigated for targeted radioimmunotherapy and include both radiohalogens and radiometals (see Table 1 for representative therapeutic radionuclides).

Table 1. Representative Therapeutic Radionuclides	
β-particle emitters	⁹⁰ Y, ¹³¹ I, ¹⁷⁷ Lu, ¹⁵³ Sm, ¹⁸⁶ Re, ¹⁸⁸ Re, ⁶⁷ Cu, ²¹² Pb
α-particle emitters	²²⁵ Ac, ²¹³ Bi, ²¹² Bi, ²¹¹ At, ²¹² Pb
Auger electron emitters	125 I, 123 I, 67 Ga, 111 In

The highly potent and specific binding moiety targeting FAP- α enables its use in nuclear imaging and radiotherapy. The presently disclosed subject matter provides the first synthesis of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to FAP- α .

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

and metal complexes, which enable *in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP-α. Importantly, the presently disclosed compounds can be modified, e.g., conjugated with, labeling groups without significantly losing their potency. The presently disclosed approach allows for the convenient labeling of the FAP-α ligand with optical dyes and PET or SPECT isotopes, including, but not limited to, ⁶⁸Ga, ⁶⁴Cu, ¹⁸F, ⁸⁶Y, ⁹⁰Y, ⁸⁹Zr, ¹¹¹In, ^{99m}Tc, ¹²⁵I, ¹²⁴I, for FAP-α related imaging applications. Further, the presently disclosed approach allows for the radiolabeling of the FAP-α ligand with radiotherapeutic isotopes, including but not limited to, ⁹⁰Y, ¹⁷⁷Lu, ¹²⁵I, ¹³¹I, ²¹¹At, ¹¹¹In, ¹⁵³Sm, ¹⁸⁶Re, ¹⁸⁸Re, ⁶⁷Cu, ²¹²Pb, ²²⁵Ac, ²¹³Bi, ²¹²Bi, ²¹²Pb, and ⁶⁷Ga, for FAP-α related radio-therapy.

In a particular embodiment, an optical agent conjugated with IRDye-800CW (**XY-FAP-01**) was synthesized and showed selective uptake *in vitro* on a FAP- α + U87 cell line and *in vivo* on a FAP- α + U87 tumor and clearly detected the tumor. In another particular embodiment, an ¹¹¹In labeled ligand (**XY-FAP-02-[¹¹¹In]**) was successfully obtained in high yield and purity from its precursor with a metal chelator. The *in vivo* study showed clear tumor radiotracer uptake in mice bearing FAP- α -positive U87 tumors with minimum non-specific organ uptake, which allows the specific imaging of FAP- α expressing tumors. The presently disclosed FAP- α targeting moiety can be adapted for use with optical dyes and radioisotopes known in the art for imaging and therapeutic applications targeting FAP- α .

More particularly, in some embodiments, the presently disclosed subject matter provides a compound of the general structure of Formula (I):

B—L—A (I)

wherein: A is a targeting moiety for FAP- α ; 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.

Representative targeting moieties for FAP- α are disclosed in U.S. Patent Application Publication No. US2014/0357650 for Novel FAP Inhibitors to Jansen et al., published Dec. 4, 2014; U.S. Patent No. 9,346,814 for Novel FAP Inhibitors to Jansen et al., issued May 24, 2016; and International PCT Patent Publication No. WO 2013/107820 for Novel FAP Inhibitors to Jansen et al., published July 25, 2013, each of which are incorporate by reference in their entirety.

More particularly, U.S. Patent No. 9,346,814 to Jansen et al., discloses FAP- α inhibitors of formula (X), or a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof, which are suitable for use with the presently disclosed subject matter:



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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

 R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic monoor bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S.

In particular embodiments, $N \rightarrow *$ is selected from the group consisting

of:



wherein * indicates the point of attachment of the 5 to 10-membered Ncontaining aromatic or non-aromatic mono- or bicyclic heterocycle to –(CH₂)_v–. Accordingly, in some embodiments, A is an FAP-α targeting moiety having the structure of:



wherein each y is independently an integer selected from the group consisting of 0, 1, and 2;

 R_{1x} , R_{2x} , and $R_{3x'}$, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

 R_{5x} , R_{6x} , and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic monoor bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

wherein ξ indicates a point of attachment of the FAP- α binding ligand to a linker, e.g., L, or a reporter moiety, such as an optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging or radiotherapy, wherein the point of attachment can be through any of the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

In particular embodiments, \checkmark is selected from the group consisting of:



In some embodiments, A is an FAP- α targeting moiety having the structure of:



wherein y, R_{1x} , R_{2x} and $R_{3x'}$ are defined as hereinabove; ξ indicates a point of attachment of the FAP- α binding ligand to a linker, e.g., L, or a reporter moiety, such as an optical or radiolabeled functional group suitable for optical imaging, PET imaging, SPECT imaging or radiotherapy, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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



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



and stereoisomers thereof.

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

of:



In some embodiments, the combination of L and B can be represented by:



wherein the subunits associated with elements p_1 , p_2 , p_3 and p_4 may be in any order; t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; p₁, p_3 , and p_4 are each independently 0 or 1; p_2 is an integer selected from the group consisting of 0, 1, 2, and 3, and when p_2 is 2 or 3, each R_1 is the same or different; m_1 and m_2 are each an integer independently selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6; W_1 is selected from the group consisting of a bond, $-S_{-}$, $-C(=O)-NR_{-}$, and -NR-C(=O)-; W₂ is selected from the group consisting of a bond, -S-, -CH₂-C(=O)-NR-, -C(O)-, -NRC(O)-, -NR'C(O)NR-, -NRC(S)NR'2-, -NRC(O)O-, -OC(O)NR-, -OC(O)-, -C(O)NR-, -NR-C(O)-, -C(O)O-, -(O-CH2-CH2)q- and -(CH₂-CH₂-O)_a-, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $-OR_4$, wherein R_4 is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove; Tz is a triazole group that can be present or absent and, if present, is selected from the group consisting of



and , each R_1 is independently H, C_1 - C_6 alkyl, C_3 - C_{12} aryl, $-(CH_2)_q$ - C_3 - C_{12} aryl, $-C_4$ - C_{16} alkylaryl, or $-(CH_2)_q$ - C_4 - C_{16} alkylaryl; R_2 and R_3 are each independently H and $-CO_2R_5$, wherein R_5 is selected from the group consisting of H, C_1 - C_6 alkyl, C_3 - C_{12} aryl, and C_4 - C_{16} alkylaryl, wherein when one of R_2 or R_3 is CO_2R_5 , then the other is H; V is selected from the group consisting of -C(O)-, -C(S)-, -NRC(O)-, -NRC(S)-, and -OC(O)-; B is any optical or radiolabeled functional group suitable for optical, PET, or SPECT imaging or radiotherapy; and stereoisomers and pharmaceutically acceptable salts thereof.

In some embodiments, L has the following general structure:



wherein p_1 , p_2 , p_3 , m_1 , m_2 , q, t, Tz, W_2 , R, R_1 , R_2 , R_3 , and V are defined as hereinabove.

In some embodiments, L is selected from the group consisting of $-L_1$ -, $-L_2$ -L₃-, and $-L_1$ -L₂-L₃-, wherein:

L₁ is -NR-(CH₂)_q-[O-CH₂-CH₂-O]_q-(CH₂)_q-C(=O)-;

L2 is -NR-(CH2)q-C(COOR5)-NR-; and

$$L_3 \text{ is -(O=)C-(CH_2)_q-C(=O)-;}$$

wherein each q is independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

In particular embodiments, L is:

 $-(CR_{6}H)_{q}-(CH_{2})_{q}-C(=O)-NR-(CH_{2})_{q}-O- or -NR-(CH_{2})_{q}-O-;$

wherein each q and R is defined hereinabove; and R₆ is H or -COOR₅.

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



wherein u is an integer selected from 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

Suitable linkers are disclosed in U.S. Patent Application Publication No. US2011/0064657 A1, for "Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA), Biological Evaluation, and Use as Imaging Agents," published March 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. US2012/0009121 A1, for "PSMA-Targeting Compounds and Uses Thereof," published January 12, 2012, to Pomper et al, each of which is incorporated by reference in its entirety.

In some embodiments, B is a radiolabeled prosthetic group comprising a radioisotope selected from the group consisting of ¹⁸F, ¹²⁴I, ¹²⁵I, ¹³¹I, and ²¹¹At. Representative radiolabeled prosthetic groups include, but are not limited to:



wherein each X is independently a radioisotope selected from the group consisting of ¹⁸F, ¹²⁴I, ¹²⁵I, ¹³¹I, and ²¹¹At; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20.

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



In other embodiments, B comprises a chelating agent. Representative chelating agents include, but are not limited to:



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In some embodiments, B comprises an optical dye, e.g., in particular embodiments, a fluorescent dye. In some embodiments, the fluorescent dye moiety comprises carbocyanine, indocarbocyanine, oxacarbocyanine, thiacarbocyanine and merocyanine, polymethine, coumarine, rhodamine, xanthene, fluorescein, borondipyrromethane (BODIPY), Cy5, Cy5.5, Cy7, VivoTag-680, VivoTag-S680, VivoTag-S750, AlexaFluor660, AlexaFluor680, AlexaFluor700, AlexaFluor750, AlexaFluor790, Dy677, Dy676, Dy682, Dy752, Dy780, DyLight547, Dylight647, HiLyte Fluor 647, HiLyte Fluor 680, HiLyte Fluor 750, IRDye 800CW, IRDye 800RS, IRDye 700DX, ADS780WS, ADS830WS, and ADS832WS.

Representative optical dyes include, but are not limited to:















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In some embodiments, the presently disclosed subject matter provides a compound selected from the group consisting of:



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





B. Pharmaceutical Compositions and Administration

In another aspect, the present disclosure provides a pharmaceutical comprising a compound of formula (I) in admixture with a pharmaceutically acceptable carrier, diluent, excipient, or adjuvant. One of skill in the art will recognize that the pharmaceutical compositions include the pharmaceutically acceptable salts or hydrates of the compounds described above.

Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art and include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent or by ion exchange, whereby one basic counterion (base) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt.

When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange, whereby one acidic counterion (acid) in an

ionic complex is substituted for another. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, ptoluenesulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al, "Pharmaceutical Salts", Journal of Pharmaceutical Science, 1977, 66, 1-19). Certain specific compounds of the present disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

Accordingly, pharmaceutically acceptable salts suitable for use with the presently disclosed subject matter include, by way of example but not limitation, acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, carnsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

In therapeutic and/or diagnostic applications, the compounds of the disclosure can be formulated for a variety of modes of administration, including systemic and topical or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000).

Depending on the specific conditions being treated, such agents may be formulated into liquid or solid dosage forms and administered systemically or locally. The agents may be delivered, for example, in a timed- or sustained-slow release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.)

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Lippincott, Williams & Wilkins (2000). Suitable routes may include oral, buccal, by inhalation spray, sublingual, rectal, transdermal, vaginal, transmucosal, nasal or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intra-articular, intra -sternal, intra-synovial, intra-hepatic, intralesional, intracranial, intraperitoneal, intranasal, or intraocular injections or other modes of delivery.

For injection, the agents of the disclosure may be formulated and diluted in aqueous solutions, such as in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For such transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

Use of pharmaceutically acceptable inert carriers to formulate the compounds herein disclosed for the practice of the disclosure into dosages suitable for systemic administration is within the scope of the disclosure. With proper choice of carrier and suitable manufacturing practice, the compositions of the present disclosure, in particular, those formulated as solutions, may be administered parenterally, such as by intravenous injection. The compounds can be formulated readily using pharmaceutically acceptable carriers well known in the art into dosages suitable for oral administration. Such carriers enable the compounds of the disclosure to be formulated as tablets, pills, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a subject (e.g., patient) to be treated.

For nasal or inhalation delivery, the agents of the disclosure also may be formulated by methods known to those of skill in the art, and may include, for example, but not limited to, examples of solubilizing, diluting, or dispersing substances, such as saline; preservatives, such as benzyl alcohol; absorption promoters; and fluorocarbons.

Pharmaceutical compositions suitable for use in the present disclosure include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. Determination of the effective amounts is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. Generally, the compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. A non-limiting dosage is 10 to

30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, the bioavailability of the compound(s), the adsorption, distribution, metabolism, and excretion (ADME) toxicity of the compound(s), and the preference and experience of the attending physician.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. The preparations formulated for oral administration may be in the form of tablets, dragees, capsules, or solutions.

Pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl- cellulose, sodium carboxymethyl-cellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired, disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers may be added.

C. Methods of Imaging using the Compounds of Formula (I), or Pharmaceutical Compositions Thereof

In some embodiments, presently disclosed subject matter provides a method for imaging a disease or disorder associated with fibroblast-activation protein- α (FAP- α), the method comprising administering a compound of formula (I), wherein the compound of formula (I) comprises an optical or radiolabeled functional group suitable for optical imaging, PET imaging, or SPECT imaging; and obtaining an image.

Accordingly, in some embodiments, the presently disclosed subject matter provides a method for imaging one or more cells, organs, or tissues, the method comprising exposing cells or administering to a subject an effective amount of a compound of formula (I) with an optical or radioisotopic label suitable for imaging. In some embodiments, the one or more organs or tissues include prostate tissue, kidney tissue, brain tissue, vascular tissue, or tumor tissue.

The imaging methods of the invention are suitable for imaging any physiological process or feature in which FAP- α is involved, for example, identifying areas of tissues or targets which exhibit or express high concentrations of FAP- α . Physiological processes in which FAP- α is involved include, but are not limited to: (a) proliferation diseases (including but not limited to cancer); (b) tissue remodeling and/or chronic inflammation (including but not limited to fibrotic disease, wound healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation); and (c) endocrinological disorders (including but not limited to disorders of glucose metabolism).

In certain embodiments, the radiolabeled compound is stable in vivo.

In certain embodiments, the radiolabeled compound is detected by positron emission tomography (PET) or single photon emission computed tomography (SPECT).

In certain embodiments, the optical reporting moiety is detected by fluorescence, such as fluorescence microscopy.

In certain embodiments, the presently disclosed compounds are excreted from tissues of the body quickly to prevent prolonged exposure to the radiation of the radiolabeled compound administered to the subject. Typically, the presently disclosed compounds are eliminated from the body in less than about 24 hours. More typically, the presently disclosed compounds are eliminated from the body in less than about 16

hours, 12 hours, 8 hours, 6 hours, 4 hours, 2 hours, 90 minutes, or 60 minutes. Exemplary compounds are eliminated in between about 60 minutes and about 120 minutes. In certain embodiments, the presently disclosed compounds are stable in vivo such that substantially all, e.g., more than about 50%, 60%, 70%, 80%, or 90% of the injected compound is not metabolized by the body prior to excretion.

Additionally, for in vitro applications, such as in vitro diagnostic and research applications, body fluids and cell samples of the above subjects will be suitable for use, such as mammalian, particularly primate such as human, blood, urine or tissue samples, or blood urine or tissue samples of the animals mentioned for veterinary applications.

Other embodiments provide kits comprising a compound of formula (I). In certain embodiments, the kit provides packaged pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of formula (I). In certain embodiments the packaged pharmaceutical composition will comprise the reaction precursors necessary to generate the compound of formula (I) upon combination with a radiolabeled precursor. Other packaged pharmaceutical compositions for preparing compounds of formula (I) from supplied precursors, instructions for using the composition to image cells or tissues expressing FAP- α .

In certain embodiments, a kit containing from about 1 to about 30 mCi of the radionuclide-labeled imaging agent described above, in combination with a pharmaceutically acceptable carrier, is provided. The imaging agent and carrier may be provided in solution or in lyophilized form. When the imaging agent and carrier of the kit are in lyophilized form, the kit may optionally contain a sterile and physiologically acceptable reconstitution medium such as water, saline, buffered saline, and the like. The kit may provide a compound of formula (I) in solution or in lyophilized form, and these components of the kit may optionally contain stabilizers such as NaCl, silicate, phosphate buffers, ascorbic acid, gentisic acid, and the like. Additional stabilization of kit components may be provided in this embodiment, for example, by providing the reducing agent in an oxidation-resistant form. Determination and optimization of such stabilizers and stabilization methods are well within the level of skill in the art.

In certain embodiments, a kit provides a non-radiolabeled precursor to be combined with a radiolabeled reagent on-site.

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Imaging agents may be used in accordance with the presently disclosed methods by one of skill in the art. Images can be generated by virtue of differences in the spatial distribution of the imaging agents which accumulate at a site when contacted with FAP- α . The spatial distribution may be measured using any means suitable for the particular label, for example, a gamma camera, a PET apparatus, a SPECT apparatus, and the like. The extent of accumulation of the imaging agent may be quantified using known methods for quantifying radioactive emissions or fluorescence. A particularly useful imaging approach employs more than one imaging agent to perform simultaneous studies.

In general, a detectably effective amount of the imaging agent of the invention is administered to a subject. A "detectably effective amount" of the imaging agent is defined as an amount sufficient to yield an acceptable image using equipment which is available for clinical use. A detectably effective amount of the imaging agent may be administered in more than one injection. The detectably effective amount of the imaging agent of the invention can vary according to factors such as the degree of susceptibility of the individual, the age, sex, and weight of the individual, idiosyncratic responses of the individual, and the dosimetry. Detectably effective amounts of the imaging agent also can vary according to instrument and film-related factors. Optimization of such factors is well within the level of skill in the art. The amount of imaging agent used for diagnostic purposes and the duration of the imaging study will depend upon the radionuclide used to label the agent, the body mass of the patient, the nature and severity of the condition being treated, the nature of therapeutic treatments which the patient has undergone, and on the idiosyncratic responses of the patient. Ultimately, the attending physician will decide the amount of imaging agent to administer to each individual patient and the duration of the imaging study.

D. Methods of Treating a FAP-α Related Disease or Disorder using the Compounds of Formula (I), or Pharmaceutical Compositions Thereof

In other embodiments, the presently disclosed compounds of formula (I) can be used to treat a subject afflicted with one or more FAP- α related diseases or disorders including, but not limited to: (a) proliferation (including but not limited to cancer); (b) tissue remodeling and/or chronic inflammation (including but not limited to fibrotic disease, wound healing, keloid formation, osteoarthritis, rheumatoid arthritis and related disorders involving cartilage degradation); and (c) endocrinological disorders (including but not limited to disorders of glucose

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metabolism).

Accordingly, in some embodiments, the one or more FAP- α related disease or disorder is selected from the group consisting of a proliferative disease, including, but not limited to, breast cancer, colorectal cancer, ovarian cancer, prostate cancer, pancreatic cancer, kidney cancer, lung cancer, melanoma, fibrosarcoma, bone and connective tissue sarcomas, renal cell carcinoma, giant cell carcinoma, squamous cell carcinoma, and adenocarcinoma; diseases characterized by tissue remodeling and/or chronic inflammation; disorders involving endocrinological dysfunction; and blood clotting disorders.

In general, the "effective amount" of an active agent or drug delivery device refers to the amount necessary to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of an agent or device may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the makeup of the pharmaceutical composition, the target tissue, and the like.

In other embodiments, the method can be practiced *in vitro* or *ex vivo* by introducing, and preferably mixing, the compound and cell(s) or tumor(s) in a controlled environment, such as a culture dish or tube. The method can be practiced *in vivo*, in which case contacting means exposing the target in a subject to at least one compound of the presently disclosed subject matter, such as administering the compound to a subject via any suitable route. According to the presently disclosed subject matter, contacting may comprise introducing, exposing, and the like, the compound at a site distant to the cells to be contacted, and allowing the bodily functions of the subject, or natural (e.g., diffusion) or man-induced (e.g., swirling) movements of fluids to result in contact of the compound and the target.

The subject treated by the presently disclosed methods in their many embodiments is desirably a human subject, although it is to be understood that the methods described herein are effective with respect to all vertebrate species, which are intended to be included in the term "subject." Accordingly, a "subject" can include a human subject for medical purposes, such as for the treatment of an existing condition or disease or the prophylactic treatment for preventing the onset of a condition or disease, or an animal (non-human) subject for medical, veterinary purposes, or developmental purposes. Suitable animal subjects include mammals including, but not limited to, primates, e.g., humans, monkeys, apes, and the like;

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bovines, e.g., cattle, oxen, and the like; ovines, e.g., sheep and the like; caprines, e.g., goats and the like; porcines, e.g., pigs, hogs, and the like; equines, e.g., horses, donkeys, zebras, and the like; felines, including wild and domestic cats; canines, including dogs; lagomorphs, including rabbits, hares, and the like; and rodents, including mice, rats, and the like. An animal may be a transgenic animal. In some embodiments, the subject is a human including, but not limited to, fetal, neonatal, infant, juvenile, and adult subjects. Further, a "subject" can include a patient afflicted with or suspected of being afflicted with a condition or disease. Thus, the terms "subject" and "patient" are used interchangeably herein. In some embodiments, the subject is human. In other embodiments, the subject is non-human.

As used herein, the term "treating" can include reversing, alleviating, inhibiting the progression of, preventing or reducing the likelihood of the disease, or condition to which such term applies, or one or more symptoms or manifestations of such disease or condition.

"Preventing" refers to causing a disease, condition, or symptom or manifestation of such, or worsening of the severity of such, not to occur. Accordingly, the presently disclosed compounds can be administered prophylactically to prevent or reduce the incidence or recurrence of the disease, or condition.

II. DEFINITIONS

Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this presently described subject matter belongs.

While the following terms in relation to compounds of formula (I) are believed to be well understood by one of ordinary skill in the art, the following definitions are set forth to facilitate explanation of the presently disclosed subject matter. These definitions are intended to supplement and illustrate, not preclude, the definitions that would be apparent to one of ordinary skill in the art upon review of the present disclosure.

The terms substituted, whether preceded by the term "optionally" or not, and substituent, as used herein, refer to the ability, as appreciated by one skilled in this art,

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to change one functional group for another functional group on a molecule, provided that the valency of all atoms is maintained. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The substituents also may be further substituted (e.g., an aryl group substituent may have another substituent off it, such as another aryl group, which is further substituted at one or more positions).

Where substituent groups or linking groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., -CH₂O- is equivalent to -OCH₂-; -C(=O)O- is equivalent to -OC(=O)-; -OC(=O)NR- is equivalent to -NRC(=O)O-, and the like.

When the term "independently selected" is used, the substituents being referred to (e.g., R groups, such as groups R_1 , R_2 , and the like, or variables, such as "m" and "n"), can be identical or different. For example, both R_1 and R_2 can be substituted alkyls, or R_1 can be hydrogen and R_2 can be a substituted alkyl, and the like.

The terms "a," "an," or "a(n)," when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is Rsubstituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

A named "R" or group will generally have the structure that is recognized in the art as corresponding to a group having that name, unless specified otherwise herein. For the purposes of illustration, certain representative "R" groups as set forth above are defined below.

Descriptions of compounds of the present disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and

several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

Unless otherwise explicitly defined, a "substituent group," as used herein, includes a functional group selected from one or more of the following moieties, which are defined herein:

The term hydrocarbon, as used herein, refers to any chemical group comprising hydrogen and carbon. The hydrocarbon may be substituted or unsubstituted. As would be known to one skilled in this art, all valencies must be satisfied in making any substitutions. The hydrocarbon may be unsaturated, saturated, branched, unbranched, cyclic, polycyclic, or heterocyclic. Illustrative hydrocarbons are further defined herein below and include, for example, methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, allyl, vinyl, *n*-butyl, *tert*-butyl, ethynyl, cyclohexyl, and the like.

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e., unbranched) or branched chain, acyclic or cyclic hydrocarbon group, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent groups, having the number of carbon atoms designated (i.e., C_1 - C_{10} means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term "alkyl" refers to C_{1-20} inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons, linear (i.e., "straight-chain"), branched, or cyclic, saturated or at least partially and in some cases fully unsaturated (i.e., alkenyl and alkynyl) hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single hydrogen atom.

Representative saturated hydrocarbon groups include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *sec*-pentyl, isopentyl, neopentyl, *n*-hexyl, *sec*-hexyl, *n*-heptyl, *n*-octyl, *n*-decyl, *n*-undecyl, dodecyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and homologs and isomers thereof.

"Branched" refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain. "Lower alkyl" refers to an alkyl group having 1 to about 8 carbon atoms (i.e., a C₁₋₈ alkyl), e.g., 1, 2, 3, 4, 5, 6, 7,

or 8 carbon atoms. "Higher alkyl" refers to an alkyl group having about 10 to about 20 carbon atoms, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. In certain embodiments, "alkyl" refers, in particular, to C_{1-8} straight-chain alkyls. In other embodiments, "alkyl" refers, in particular, to C_{1-8} branched-chain alkyls.

Alkyl groups can optionally be substituted (a "substituted alkyl") with one or more alkyl group substituents, which can be the same or different. The term "alkyl group substituent" includes but is not limited to alkyl, substituted alkyl, halo, alkylamino, arylamino, acyl, hydroxyl, aryloxyl, alkoxyl, alkylthio, arylthio, aralkyloxyl, aralkylthio, carboxyl, alkoxycarbonyl, oxo, and cycloalkyl. There can be optionally inserted along the alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, lower alkyl (also referred to herein as "alkylaminoalkyl"), or aryl.

Thus, as used herein, the term "substituted alkyl" includes alkyl groups, as defined herein, in which one or more atoms or functional groups of the alkyl group are replaced with another atom or functional group, including for example, alkyl, substituted alkyl, halogen, aryl, substituted aryl, alkoxyl, hydroxyl, nitro, amino, alkylamino, dialkylamino, sulfate, and mercapto.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon group, or combinations thereof, consisting of at least one carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH₂-S-CH₂-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, -CH₂-CH₂-S(O)₂-CH₃, O-CH₃, -O-CH₂-CH₃, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃.

As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)NR', -NR'R'', -OR', -SR, -S(O)R, and/or $-S(O_2)R'$. Where "heteroalkyl" is

recited, followed by recitations of specific heteroalkyl groups, such as -NR'R or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

"Cyclic" and "cycloalkyl" refer to a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms, e.g., 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms. The cycloalkyl group can be optionally partially unsaturated. The cycloalkyl group also can be optionally substituted with an alkyl group substituent as defined herein, oxo, and/or alkylene. There can be optionally inserted along the cyclic alkyl chain one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms, wherein the nitrogen substituent is hydrogen, unsubstituted alkyl, substituted alkyl, aryl, or substituted aryl, thus providing a heterocyclic group. Representative monocyclic cycloalkyl rings include cyclopentyl, cyclohexyl, and cycloheptyl. Multicyclic cycloalkyl rings include adamantyl, octahydronaphthyl, decalin, camphor, camphane, and noradamantyl, and fused ring systems, such as dihydro- and tetrahydronaphthalene, and the like.

The term "cycloalkylalkyl," as used herein, refers to a cycloalkyl group as defined hereinabove, which is attached to the parent molecular moiety through an alkyl group, also as defined above. Examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclopentylethyl.

The terms "cycloheteroalkyl" or "heterocycloalkyl" refer to a non-aromatic ring system, unsaturated or partially unsaturated ring system, such as a 3- to 10member substituted or unsubstituted cycloalkyl ring system, including one or more heteroatoms, which can be the same or different, and are selected from the group consisting of nitrogen (N), oxygen (O), sulfur (S), phosphorus (P), and silicon (Si), and optionally can include one or more double bonds.

The cycloheteroalkyl ring can be optionally fused to or otherwise attached to other cycloheteroalkyl rings and/or non-aromatic hydrocarbon rings. Heterocyclic rings include those having from one to three heteroatoms independently selected from oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. In certain embodiments, the term heterocylic refers to a non-aromatic 5-, 6-, or 7membered ring or a polycyclic group wherein at least one ring atom is a heteroatom

selected from O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from the oxygen, sulfur, and nitrogen, wherein (i) each 5-membered ring has 0 to 2 double bonds, each 6-membered ring has 0 to 2 double bonds, and each 7membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring. Representative cycloheteroalkyl ring systems include, but are not limited to pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, quinuclidinyl, morpholinyl, thiomorpholinyl, thiadiazinanyl, tetrahydrofuranyl, and the like.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4- morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 -piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl."

More particularly, the term "alkenyl" as used herein refers to a monovalent group derived from a C_{1-20} inclusive straight or branched hydrocarbon moiety having at least one carbon-carbon double bond by the removal of a single hydrogen molecule. Alkenyl groups include, for example, ethenyl (i.e., vinyl), propenyl, butenyl, 1-methyl-2-buten-1-yl, pentenyl, hexenyl, octenyl, allenyl, and butadienyl.

The term "cycloalkenyl" as used herein refers to a cyclic hydrocarbon containing at least one carbon-carbon double bond. Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, 1,3-cyclohexadienyl, cycloheptenyl, cycloheptatrienyl, and cyclooctenyl.

The term "alkynyl" as used herein refers to a monovalent group derived from a straight or branched C₁₋₂₀ hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon triple bond. Examples of "alkynyl" include ethynyl, 2-propynyl (propargyl), 1-propynyl, pentynyl, hexynyl, and heptynyl groups, and the like.

The term "alkylene" by itself or a part of another substituent refers to a straight or branched bivalent aliphatic hydrocarbon group derived from an alkyl group having from 1 to about 20 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. The alkylene group can be straight, branched or cyclic. The alkylene group also can be optionally unsaturated and/or substituted with one or more "alkyl group substituents." There can be optionally inserted along the alkylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms (also referred to herein as "alkylaminoalkyl"), wherein the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups include methylene (-CH₂-); ethylene (-CH₂-CH₂-); propylene (-(CH₂)₃-); cyclohexylene (-C₆H₁₀-); -CH=CH-CH=CH-; -CH=CH-CH₂-; -CH₂CH₂CH₂CH₂-, -CH2CH=CHCH2-, -CH2CsCCH2-, -CH2CH2CH(CH2CH2CH3)CH2-, $-(CH_2)_q-N(R)-(CH_2)_r$, wherein each of q and r is independently an integer from 0 to about 20, e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, and R is hydrogen or lower alkyl; methylenedioxyl (-O-CH₂-O-); and ethylenedioxyl (-O-(CH₂)₂-O-). An alkylene group can have about 2 to about 3 carbon atoms and can further have 6-20 carbons. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being some embodiments of the present disclosure. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The term "heteroalkylene" by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, -CH₂-CH₂-S-CH₂-CH₂-and -CH₂-S-CH₂-CH₂-and -CH₂-S-CH₂-CH₂-. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (e.g., alkyleneoxo,

alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)OR'- represents both -C(O)OR'- and -R'OC(O)-.

The term "aryl" means, unless otherwise stated, 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. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrazolyl, 2imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4- oxazolyl, 5oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2pyrimidyl, 4- pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1isoquinolyl, 5- isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent forms of aryl and heteroaryl, respectively.

For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms "arylalkyl" and "heteroarylalkyl" are meant to include those groups in which an aryl or heteroaryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl, furylmethyl, and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxymethyl, 2-pyridyloxymethyl, 3-(l-naphthyloxy)propyl, and the like). However, the term "haloaryl," as used herein is meant to cover only aryls substituted with one or more halogens.

Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" refers to a carbon or heteroatom.

Further, a structure represented generally by the formula:



as used herein refers to a ring structure, for example, but not limited to a 3-carbon, a 4-carbon, a 5-carbon, a 6-carbon, a 7-carbon, and the like, aliphatic and/or aromatic cyclic compound, including a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure, comprising a substituent R group, wherein the R group can be present or absent, and when present, one or more R groups can each be substituted on one or more available carbon atoms of the ring structure. The presence or absence of the R group and number of R groups is determined by the value of the variable "n," which is an integer generally having a value ranging from 0 to the number of carbon atoms on the ring available for substitution. Each R group, if more than one, is substituted on an available carbon of the ring structure rather than on another R group. For example, the structure above where n is 0 to 2 would comprise compound groups including, but not limited to:



and the like.

A dashed line representing a bond in a cyclic ring structure indicates that the bond can be either present or absent in the ring. That is, a dashed line representing a bond in a cyclic ring structure indicates that the ring structure is selected from the group consisting of a saturated ring structure, a partially saturated ring structure, and an unsaturated ring structure.

The symbol (***********) denotes the point of attachment of a moiety to the remainder of the molecule.

When a named atom of an aromatic ring or a heterocyclic aromatic ring is defined as being "absent," the named atom is replaced by a direct bond.

Each of above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl, and "heterocycloalkyl", "aryl," "heteroaryl," "phosphonate," and "sulfonate" as well as

their divalent derivatives) are meant to include both substituted and unsubstituted forms of the indicated group. Optional substituents for each type of group are provided below.

Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent and divalent derivative groups (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R", -OC(O)R', -C(O)R', -CO₂R',-C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R", -NR"C(O)OR', -NR-C(NR'R")=NR", -S(O)R', -S(O)₂R', -S(O)₂NR'R", -NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+l), where m' is the total number of carbon atoms in such groups. R', R", R" and R"" each may independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. As used herein, an "alkoxy" group is an alkyl attached to the remainder of the molecule through a divalent oxygen. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R" and R" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7- membered ring. For example, -NR'R" is meant to include, but not be limited to, 1- pyrrolidinyl and 4morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (e.g., -CF₃ and -CH₂CF₃) and acyl (e.g., -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

Similar to the substituents described for alkyl groups above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, -OR', -NR'R", -SR', -SiR'R"R", -OC(O)R', -C(O)R', -CO₂R', -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R", -NR"C(O)OR', -NR-C(NR'R"R")=NR"", -NR-C(NR'R")=NR'" -S(O)R', -S(O)₂R', -S(O)₂NR'R", -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxo, and fluoro(C₁-C₄)alkyl, in a number ranging

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from zero to the total number of open valences on aromatic ring system; and where R', R", R" and R"" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the disclosure includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R" and R"" groups when more than one of these groups is present.

Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C"R'")_d$, where s and d are independently integers of from 0 to 3, and X' is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituents R, R', R" and R'" may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the term "acyl" refers to an organic acid group wherein the -OH of the carboxyl group has been replaced with another substituent and has the general formula RC(=O)-, wherein R is an alkyl, alkenyl, alkynyl, aryl, carbocylic, heterocyclic, or aromatic heterocyclic group as defined herein). As such, the term "acyl" specifically includes arylacyl groups, such as a 2-(furan-2-yl)acetyl)- and a 2-phenylacetyl group. Specific examples of acyl groups include acetyl and benzoyl. Acyl groups also are intended to include amides, -RC(=O)NR', esters, -RC(=O)OR', ketones, -RC(=O)R', and aldehydes, -RC(=O)H.

The terms "alkoxyl" or "alkoxy" are used interchangeably herein and refer to a saturated (i.e., alkyl–O–) or unsaturated (i.e., alkenyl–O– and alkynyl–O–) group attached to the parent molecular moiety through an oxygen atom, wherein the terms

"alkyl," "alkenyl," and "alkynyl" are as previously described and can include C₁₋₂₀ inclusive, linear, branched, or cyclic, saturated or unsaturated oxo-hydrocarbon chains, including, for example, methoxyl, ethoxyl, propoxyl, isopropoxyl, *n*-butoxyl, *sec*-butoxyl, *tert*-butoxyl, and *n*-pentoxyl, neopentoxyl, *n*-hexoxyl, and the like.

The term "alkoxyalkyl" as used herein refers to an alkyl-O-alkyl ether, for example, a methoxyethyl or an ethoxymethyl group.

"Aryloxyl" refers to an aryl-O- group wherein the aryl group is as previously described, including a substituted aryl. The term "aryloxyl" as used herein can refer to phenyloxyl or hexyloxyl, and alkyl, substituted alkyl, halo, or alkoxyl substituted phenyloxyl or hexyloxyl.

"Aralkyl" refers to an aryl-alkyl-group wherein aryl and alkyl are as previously described and includes substituted aryl and substituted alkyl. Exemplary aralkyl groups include benzyl, phenylethyl, and naphthylmethyl.

"Aralkyloxyl" refers to an aralkyl-O– group wherein the aralkyl group is as previously described. An exemplary aralkyloxyl group is benzyloxyl, i.e., $C_{6}H_{5}$ -CH₂-O-. An aralkyloxyl group can optionally be substituted.

"Alkoxycarbonyl" refers to an alkyl-O-C(=O)– group. Exemplary alkoxycarbonyl groups include methoxycarbonyl, ethoxycarbonyl, butyloxycarbonyl, and *tert*-butyloxycarbonyl.

"Aryloxycarbonyl" refers to an aryl-O-C(=O)– group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxy-carbonyl.

"Aralkoxycarbonyl" refers to an aralkyl-O-C(=O)– group. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

"Carbamoyl" refers to an amide group of the formula $-C(=O)NH_2$. "Alkylcarbamoyl" refers to a R'RN-C(=O)- group wherein one of R and R' is hydrogen and the other of R and R' is alkyl and/or substituted alkyl as previously described. "Dialkylcarbamoyl" refers to a R'RN-C(=O)- group wherein each of R and R' is independently alkyl and/or substituted alkyl as previously described.

The term carbonyldioxyl, as used herein, refers to a carbonate group of the formula -O-C(=O)-OR.

"Acyloxyl" refers to an acyl-O- group wherein acyl is as previously described.

The term "amino" refers to the $-NH_2$ group and also refers to a nitrogen containing group as is known in the art derived from ammonia by the replacement of one or more hydrogen radicals by organic radicals. For example, the terms

"acylamino" and "alkylamino" refer to specific N-substituted organic radicals with acyl and alkyl substituent groups respectively.

An "aminoalkyl" as used herein refers to an amino group covalently bound to an alkylene linker. More particularly, the terms alkylamino, dialkylamino, and trialkylamino as used herein refer to one, two, or three, respectively, alkyl groups, as previously defined, attached to the parent molecular moiety through a nitrogen atom. The term alkylamino refers to a group having the structure –NHR' wherein R' is an alkyl group, as previously defined; whereas the term dialkylamino refers to a group having the structure –NR'R", wherein R' and R" are each independently selected from the group consisting of alkyl groups. The term trialkylamino refers to a group having the structure –NR'R"R", wherein R', R", and R"" are each independently selected from the group consisting of alkyl groups. Additionally, R', R", and/or R'" taken together may optionally be –(CH₂)_k– where k is an integer from 2 to 6. Examples include, but are not limited to, methylamino, dimethylamino, ethylamino, diethylamino, diethylaminocarbonyl, methylethylamino, isopropylamino, piperidino, trimethylamino, and propylamino.

The amino group is -NR'R", wherein R' and R" are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The terms alkylthioether and thioalkoxyl refer to a saturated (i.e., alkyl–S–) or unsaturated (i.e., alkenyl–S– and alkynyl–S–) group attached to the parent molecular moiety through a sulfur atom. Examples of thioalkoxyl moieties include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, *n*-butylthio, and the like.

"Acylamino" refers to an acyl-NH– group wherein acyl is as previously described. "Aroylamino" refers to an aroyl-NH– group wherein aroyl is as previously described.

The term "carbonyl" refers to the -C(=O)- group, and can include an aldehyde group represented by the general formula R-C(=O)H.

The term "carboxyl" refers to the –COOH group. Such groups also are referred to herein as a "carboxylic acid" moiety.

The terms "halo," "halide," or "halogen" as used herein refer to fluoro, chloro, bromo, and iodo groups. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo (C_1-C_4) alkyl"

is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4chlorobutyl, 3-bromopropyl, and the like.

The term "hydroxyl" refers to the -OH group.

The term "hydroxyalkyl" refers to an alkyl group substituted with an –OH group.

The term "mercapto" refers to the -SH group.

The term "oxo" as used herein means an oxygen atom that is double bonded to a carbon atom or to another element.

The term "nitro" refers to the -NO2 group.

The term "thio" refers to a compound described previously herein wherein a carbon or oxygen atom is replaced by a sulfur atom.

The term "sulfate" refers to the -SO₄ group.

The term thiohydroxyl or thiol, as used herein, refers to a group of the formula –SH.

More particularly, the term "sulfide" refers to compound having a group of the formula –SR.

The term "sulfone" refers to compound having a sulfonyl group $-S(O_2)R$. The term "sulfoxide" refers to a compound having a sulfinyl group -S(O)RThe term ureido refers to a urea group of the formula -NH—CO—NH₂.

Throughout the specification and claims, a given chemical formula or name shall encompass all tautomers, congeners, and optical- and stereoisomers, as well as racemic mixtures where such isomers and mixtures exist.

Certain compounds of the present disclosure may possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as D- or L- for amino acids, and individual isomers are encompassed within the scope of the present disclosure. The compounds of the present disclosure do not include those which are known in art to be too unstable to synthesize and/or isolate. The present disclosure is meant to include compounds in racemic, scalemic, and optically pure forms. Optically active (R)- and (S)-, or D- and L-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefenic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include

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both E and Z geometric isomers.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the disclosure.

It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure. The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

As used herein the term "monomer" refers to a molecule that can undergo polymerization, thereby contributing constitutional units to the essential structure of a macromolecule or polymer.

A "polymer" is a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer.

A "dendrimer" is highly branched, star-shaped macromolecules with nanometer-scale dimensions.

As used herein, an "oligomer" includes a few monomer units, for example, in contrast to a polymer that potentially can comprise an unlimited number of monomers. Dimers, trimers, and tetramers are non-limiting examples of oligomers.

The term "protecting group" refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, 3rd ed. John Wiley & Sons (1999). It may be advantageous, where different protecting groups are employed, that each (different) protective group be removable by a different means. Protective groups that are cleaved under totally disparate reaction conditions allow differential removal of such protecting groups. For example, protective groups can be removed by acid, base, and hydrogenolysis. Groups such as trityl, dimethoxytrityl, acetal and tert-butyldimethylsilyl are acid labile and may be used to protect carboxy and hydroxy reactive moieties in the presence of amino groups protected with Cbz groups, which are removable by

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hydrogenolysis, and Fmoc groups, which are base labile. Carboxylic acid and hydroxy reactive moieties may be blocked with base labile groups such as, without limitation, methyl, ethyl, and acetyl in the presence of amines blocked with acid labile groups such as tert-butyl carbamate or with carbamates that are both acid and base stable but hydrolytically removable.

Carboxylic acid and hydroxy reactive moieties may also be blocked with hydrolytically removable protective groups such as the benzyl group, while amine groups capable of hydrogen bonding with acids may be blocked with base labile groups such as Fmoc. Carboxylic acid reactive moieties may be blocked with oxidatively-removable protective groups such as 2,4-dimethoxybenzyl, while coexisting amino groups may be blocked with fluoride labile silyl carbamates.

Allyl blocking groups are useful in the presence of acid- and base- protecting groups since the former are stable and can be subsequently removed by metal or pi-acid catalysts. For example, an allyl-blocked carboxylic acid can be deprotected with a palladium(O)- catalyzed reaction in the presence of acid labile t-butyl carbamate or base-labile acetate amine protecting groups. Yet another form of protecting group is a resin to which a compound or intermediate may be attached. As long as the residue is attached to the resin, that functional group is blocked and cannot react. Once released from the resin, the functional group is available to react.

Typical blocking/protecting groups include, but are not limited to the following moieties:

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Following long-standing patent law convention, the terms "a," "an," and "the" refer to "one or more" when used in this application, including the claims. Thus, for example, reference to "a subject" includes a plurality of subjects, unless the context clearly is to the contrary (e.g., a plurality of subjects), and so forth.

Throughout this specification and the claims, the terms "comprise," "comprises," and "comprising" are used in a non-exclusive sense, except where the context requires otherwise. Likewise, the term "include" and its grammatical variants are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

For the purposes of this specification and appended claims, unless otherwise indicated, all numbers expressing amounts, sizes, dimensions, proportions, shapes, formulations, parameters, percentages, quantities, characteristics, and other numerical values used in the specification and claims, are to be understood as being modified in all instances by the term "about" even though the term "about" may not expressly appear with the value, amount or range. Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are not and need not be exact, but may be approximate and/or larger or smaller as desired, reflecting tolerances, conversion factors, rounding off,

measurement error and the like, and other factors known to those of skill in the art depending on the desired properties sought to be obtained by the presently disclosed subject matter. For example, the term "about," when referring to a value can be meant to encompass variations of, in some embodiments, $\pm 100\%$ in some embodiments $\pm 50\%$, in some embodiments $\pm 20\%$, in some embodiments $\pm 10\%$, in some embodiments $\pm 5\%$, in some embodiments $\pm 1\%$, in some embodiments $\pm 0.5\%$, and in some embodiments $\pm 0.1\%$ from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Further, the term "about" when used in connection with one or more numbers or numerical ranges, should be understood to refer to all such numbers, including all numbers in a range and modifies that range by extending the boundaries above and below the numerical values set forth. The recitation of numerical ranges by endpoints includes all numbers, e.g., whole integers, including fractions thereof, subsumed within that range (for example, the recitation of 1 to 5 includes 1, 2, 3, 4, and 5, as well as fractions thereof, e.g., 1.5, 2.25, 3.75, 4.1, and the like) and any range within that range.

EXAMPLES

The following Examples have been included to provide guidance to one of ordinary skill in the art for practicing representative embodiments of the presently disclosed subject matter. In light of the present disclosure and the general level of skill in the art, those of skill can appreciate that the following Examples are intended to be exemplary only and that numerous changes, modifications, and alterations can be employed without departing from the scope of the presently disclosed subject matter. The synthetic descriptions and specific examples that follow are only intended for the purposes of illustration, and are not to be construed as limiting in any manner to make compounds of the disclosure by other methods.

EXAMPLE 1

Experimental Procedures

1.1 Synthesis of XY-FAP-01.



Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**): 6-Hydroxyquinoline-4carboxylic acid (**1**) 210 mg (1.1 mmol), methyl glycinate HCl salt (**2**) 143 mg (1.1 mmol), HBTU 420 mg (1.1 mmol) and HOBt 170 mg (1.1 mmol) were dissolved in 12 mL dry DMF. To the solution, 0.77 mL of DIPEA (4.4 mmol) was added. The reaction was stirred at room temperature for 6 h. After the solvent was removed under vacuum, the mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada) and the product was purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 290 mg of product **3** was obtained as a yellow powder with a yield of 76%. ¹H-NMR (400 MHz, CD₃OD): δ 8.69 (s, 1H), 7.94 (d, J = 7.92 Hz, 1H), 7.57–7.51 (m, 3H), 7.42–7.37 (m, 1H), 4.21 (s, 2H), 3.81 (s, 3H). ¹³C-NMR (100 MHz, CD₃OD): δ 172.4, 160.9, 145.1, 143.7, 129.7, 129.4, 128.3, 121.8, 119.6, 112.4, 109.1, 56.8, 44.8. MS: calculated for [C₁₃H₁₃N₂O₄]⁺, 261.3 [M + H]⁺; found 261.1.



Methyl (6-(3-((tert-butoxycarbonyl)amino)propoxy)quinoline-4carbonyl)glycinate (**5**): Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**) 360 mg (1.0 mmol), tert-butyl (3-bromopropyl)carbamate (**4**) 500 mg (2.1 mmol) were dissolved in 20 mL DMF. Cs₂CO₃ 1 g (3.0 mmol) was added to the solution and the reaction was stirred at room temperature overnight. After filtration, the solvent was removed under vacuum and the remaining mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada). The product was purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 270 mg of product **5** was obtained with a yield of 54%. ¹H-NMR (400 MHz, CDCl₃): δ 8.68–8.37 (m, 2H), 8.02 (d, J = 9.1 Hz, 1H), 7.80 (s, 1H), 7.72–7.64 (m, 1H), 7.40 (d, J = 9.1 Hz, 1H), 4.94 (br s, 1H), 4.41–4.31 (m, 2H), 4.27–4.18 (m, 2H), 3.85 (s, 3H), 3.44–3.30 (m, 2H), 2.13–2.00 (m, 2H), 1.43 (s, 9H). ¹³C NMR (100 MHz, CDCl₃): δ 170.1, 167.2, 158.4, 144.7, 142.3,

128.4, 126.1, 124.7, 119.1, 103.7, 79.5, 60.4, 52.5, 41.4, 37.7, 29.3, 28.4. MS: calculated for $[C_{21}H_{28}N_3O_6]^+$, 418.5 $[M + H]^+$; found 418.3.



tert-Butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-

oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate (7): Compound 5 110 mg (0.21 mmol) and LiOH 30 mg (1.2 mmol) was stirred in 4 mL of H₂O/THF (1/1) for 6 hours. After most of the THF was removed under vacuum, the mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada) and eluded with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1) to remove the salts. The product 6 obtained was mixed with (S)-pyrrolidine-2-carbonitrile 53 mg (0.4 mmol), HOBT 68 mg (0.4 mmol), HBTU 152 mg (0.4 mmol) and DIPEA 0.56 mL (1.6 mmol) in dry 10 mL DMF. After 6 hours, the solvent was removed under vacuum and the remaining mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada). The product was purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 99 mg of 7 was obtained with a yield of 80%. ¹H NMR (400 MHz, CDCl₃): δ 8.73 (s, 1H), 7.95 (d, J = 10.2 Hz, 1H), 7.68 (br s, 1H), 7.63–7.56 (m, 1H), 7.56–7.48 (m, 1H), 7.38–7.29 (m, 1H), 5.27 (br s, 1H), 4.84–4.72 (m, 1H), 4.46–4.35 (m, 1H), 4.33–4.20 (m, 1H), 4.17-4.09 (m, 2H), 3.78-3.64 (m, 1H), 3.59-3.46 (m, 1H), 3.36 (s, 2H), 2.38-2.17 (m, 4H), 1.42 (s, 9H), 1.35–1.27 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 167.5, 157.9, 156.2, 146.3, 130.2, 125.7, 123.7, 119.3, 118.0, 103.3, 79.0, 65.9, 46.8, 45.7, 42.2, 37.6, 29.8, 29.3, 28.4, 25.1. MS: calculated for [C₂₅H₃₂N₅O₅]⁺, 482.6 [M + H]⁺; found 482.3.



XY-FAP-01. Compound 7 (1 mg, 1.7 μ mol) was treated with a 1 mL solution of TFA/methylene chloride (1/1) for 2 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMSO. To the solution, LICOR800CW-NHS ester 0.5 mg (0.43 μ mol) and Et₃N 10 μ L were added. After 1 h at room temperature, the solvent was removed and the product was purified by HPLC. 0.5 mg product was obtained with a yield of 85%. HPLC condition: column

Phenomenex, Luna 10 x 250 mm, 10 u. Gradient 10/90/0.1 MeCN/H₂O/TFA to 80/20/0.1 MeCN/H₂O/TFA within 15 min at a flow of 3 mL/min. The product was eluted at 10.1 min. MS: Calculated for[C₆₆H₇₆N₇O₁₇S₄]⁺, 1366.4[M+H]⁺; found 1366.8.

1.2 Synthesis of XY-FAP-02



2,2',2"-(10-(1-Carboxy-4-((3-((4-((2-((S)-2-cyanopyrrolidin-1-yl)-2oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl) amino)-4-oxobutyl)-1,4,7,10tetraazacyclododecane-1,4,7-triyl)triacetic acid (XY-FAP-02): Compound 7 (15 mg, 31.3 μ mol) was treated with a 1-mL solution of TFA/methylene chloride (1/1) for 1 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMF. To the solution, DIPEA (27 µL, 156.5 µmol) was added, followed by dropwise addition of a solution of DOTA-GA(t-Bu)₄-NHS (25 mg, 31.3 µL) in 0.5 mL of DMF. The reaction mixture was stirred for 4 h at ambient temperature and then concentrated under vacuum. The t-Bu-protected intermediate was deprotected in situ without further purification using a 1 mL mixture of TFA, H₂O and triethylsilane (TES) (95:2.5:2.5). Reaction mixture was then concentrated and purified by semipreparative HPLC, to afford the product as a white solid (8.5 mg, 33% yield). MS: calculated for $[C_{39}H_{54}N_9O_{12}]^+$, 840.9 $[M + H]^+$; found 840.5. HPLC (10 mm x 250 mm Phenomenex Luna C18 column, 10 µm, mobile phase 95/5/0.1% to 75/25/0.1% water/acetonitrile/TFA over 20 min, flow 5 mL/min) XY-FAP-02 eluted at 11.8 min.



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XY-FAP-02-[In]. ^{113/115}Indium(III) 2,2',2"-(10-(1-Carboxy-4-((3-((4-((2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl) amino)-4-oxobutyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (**XY-FAP-02-[In]**): To a solution of 2 mg (2.4 µmol) of **XY-FAP-02** in 1 mL of 0.2M AcONa, a solution of 1.4 mg (4.6 µmol) of In(NO₃)₃ in 0.5 mL water is added and warmed in a 60 °C bath for 30 min. After cooling to ambient temperature, the mixture was purified by semipreparative HPLC. The product was obtained as a white solid (1.8 mg, 79% yield). MS: calculated for $[C_{39}H_{51}N_9O_{12}In]^+$, 951.7 $[M + H]^+$; found 952.5. HPLC (10 mm x 250 mm Phenomenex Luna C18 column, 10 µm, mobile phase 95/5/0.1% to 75/25/0.1% water/acetonitrile/TFA over 20 min, flow 5 mL/min) **XY-FAP-02-[In]** eluted at 14.0 min.

1.3 Radiolabeling Methods. Briefly, 20 mg XY-FAP-02 solution in 20 mL of 0.2 M NaOAc was added to 10 mL 4.6 mCi ¹¹¹InCl₃ solution (Nordion, Ottawa, Canada) and adjusted to a final pH of 5.5-6. The mixture was heated in a water bath at 70 °C for 30 min and, after the reaction completed, was diluted with 200 mL of water for HPLC purification. The solution was purified using a Phenomenex 5 μ m C₁₈ Luna $4.6 \times 250 \text{ mm}^2$ column (Torrance, CA) with a flow rate of 0.6 mL/min with water (0.1% TFA) (A) and MeCN (0.1% TFA) (B) as the eluting solvents. An isocractic solution of 88% A and 12% B was utilized for purification, resulting in the labeled compound, ¹¹¹In-XY-FAP-02, eluting first at 18.6 min followed by the unlabeled starting material at 23.5 min. 3.2 mCi of labeled compound was obtained as pure product with a yield of 69%. Another reaction with the identical condition was performed with 74% yield. The collected radioactivity was diluted with 20 mL of water and loaded onto activated Sep-Pak (WAT020515, Waters, Milford, MA). After the Sep-Pak was washed with 10 mL of water, ¹¹¹In-XY-FAP-02 was eluted with 1.5 mL of ethanol. The ethanol was evaporated under a gentle stream of N₂ (to a total volume of $< 50 \,\mu$ L). The resulting solution was formulated in saline for the imaging and biodistribution studies.

1.4 FAP Inhibition Assay. The inhibitory activity of **XY-FAP-01** was determined using a fluorogenic FAP Assay Kit (BPS Bioscience, San Diego, CA). Briefly, **XY-FAP-01**, DPP substrate, and human recombinant FAP were loaded into a 96 well plate to initiate the enzyme reaction. The reaction was left for 10 minutes at room temperature before fluorescence was measured with a VICTOR3 V multilabel plate reader (PerkinElmer Inc., Waltham, MA). Data was normalized and semi-log inhibition curves were generated in order to determine the IC₅₀ value (concentration of **XY-FAP-01** where the enzyme activity is 50% inhibited) for **XY-FAP-01** and subsequent enzyme inhibition curves and IC50 values were done using GraphPad Prism (San Diego, CA).

1.5 Cell lines. Six human cancer cell lines were used to assess binding to FAP: glioblastoma (U-87-MG), melanoma (SK-MEL-24), prostate (PC-3), non-small cell lung cancer (NCI-H2228), colorectal carcinoma (HCT 116), and lung squamous cell carcinoma (NCI-H226). From the literature, U-87-MG, SK-MEL-24, and NCI-H2228 cell lines were identified as having high levels of FAP expression [FAP-positive (+)] whereas PC-3, NCI-H226, and HCT 116 cells expressed very low levels of FAP [FAP-negative(-)]. These expression profiles were further confirmed via flow cytometry with an APC-conjugated anti-FAP antibody (R&D Systems, Minneapolis, MN) and quantitative real-time PCR. All cell lines were purchased from American Type Culture Collection (ATCC, Manassas, VA).

U-87-MG cells were maintained in MEM medium (Corning Cellgro, Manassas, VA), containing 10% fetal bovine serum (FBS) (Sigma-Aldrich, St. Louis, MO) and 1% penicillin-streptomycin (Corning Cellgro, Manassas, VA), supplemented with sodium bicarbonate (Corning), sodium pyruvate (Gibco, Gaithersburg, MD), and MEM non-essential amino acids (Gibco). SK-MEL-24 cells were maintained in MEM medium, containing 15% FBS and 1% penicillinstreptomycin, supplemented with sodium bicarbonate, sodium pyruvate, and MEM non-essential amino acids. PC-3 cells were grown in Ham's F-12K medium (Corning Cellgro) supplemented with 10% FBS and 1% penicillin-streptomycin. NCI-H2228, NCI-H226, and HCT 116 cells were cultured in RPMI 1640 medium (Corning Cellgro) supplemented with 10% FBS and 1% penicillin-streptomycin. All cell cultures were maintained at 37 °C and 5% carbon dioxide (CO₂) in a humidified incubator.

1.6 Cellular Uptake Studies. All cellular uptake and specific binding studies were performed in triplicate to ensure reproducibility. Cells were detached using 0.05% trypsin (Corning), resuspended in 1 million cell aliquots in binding buffer, and incubated with various concentrations (range, 50 nM to 0.78 nM) of XY-FAP-01 for 1 hour at 37 °C and 5% CO₂. To assess the specific uptake of XY-FAP-02, cells were preblocked with a FAP and DPP-IV specific inhibitor (Val-boroPro, MilliporeSigma, Burlington, MA) or a DPP-IV specific inhibitor (Sitagliptin, Santa Cruz Biotechnology, Inc., Dallas, TX) at various concentrations (range, 10⁻¹⁰ M to 10⁻⁴ M) prior to incubation with 25 nM XY-FAP-02 solution in binding buffer for 1 hour at 37 °C and 5% CO₂. Cellular uptake was terminated by washing cells with ice cold PBS (1x) three times. Cells were resuspended in binding buffer and transferred to a 96-well plate for imaging. Images were acquired on the LI-COR Pearl Impulse Imager (Lincoln, NE) using an excitation wavelength of 785 nm and detection of the emission wavelength at 800 nm. Images were analyzed using the LI-COR Pearl Impulse Software (Version 2.0) and fluorescence intensity was corrected for background signal and normalized to well area.

Cellular Uptake of ¹¹¹In-XY-FAP-02 was also assessed in cells. Cell aliquots (1 million) were incubated with 1 μ Ci ¹¹¹In-XY-FAP-02 in saline for 30 minutes at 37 °C and 5% CO₂. Cells were washed three times with cold PBS (1x) and activity of the cell pellets was measured with the 1282 CompuGamma CS gamma well counter (Pharmacia/LKB Nuclear, Inc., Gaithersburg, MD). The percent uptake of the administered activity was calculated by comparison with samples of a standard dose.

1.7 Small-Animal Near Infrared Fluorescence (NIRF) Imaging. NIRF images were acquired on the LI-COR Pearl Impulse Imager using an excitation wavelength of 785 nm and a detection wavelength of 800 nm. Mice utilized for imaging studies were anesthetized with 3% isofluorane (v/v) and maintained at 1.5% isofluorane for the imaging procedure. NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts were injected with 10 nmol of **XY-FAP-01** via tail vein injection and images were acquired at 30 min, 1 h, 2 h, 2.5 h, and 4 h after injection of tracer. Data were displayed and analyzed using the LI-COR Pearl Impulse Software (Version 2.0).

1.8 Small-Animal SPECT-CT Imaging. SPECT-CT studies were performed on NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts. For imaging studies, mice were anesthetized with 3% isoflurane prior to being placed on the scanner bed and kept warm with an external light source. Isoflurane levels were

decreased to 1.5% for the rest of the imaging procedure. After mice were injected with 300 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline, SPECT-CT imaging was carried out using a CT-equipped Gamma Medica-Ideas SPECT scanner (Northridge, CA) at the indicated timepoints (30 min, 2 h, 6 h, and 24 h) post radiotracer injection. A CT scan was performed at the end of each SPECT scan for anatomical co-registration. Obtained data sets were reconstructed using the provided Gamma Medica-Ideas software and final data visualization and image generation were prepared using Amira® software (FEI, Hillsboro, OR).

1.9 Ex-vivo Biodistribution. NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts were injected with 10 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline via the tail vein. At 5 min, 30 min, 2 h, 6 h, and 12 hr post injection, mice (n=4) were sacrificed by CO₂ asphyxiation and blood was immediately collected by cardiac puncture. Additionally, the heart, lungs, liver, stomach, pancreas, spleen, fat, kidney, small intestine, large intestine, bladder, muscle, femur, FAP+ U-87-MG xenograft, and FAP- PC-3 xenograft were collected for biodistribution analysis. Each tissue was weighed and radioactivity was measuring using a 2480 Wizard² automated gamma counter (PerkinElmer, Waltham, MA). Radioactivity measurements were corrected for decay and compared with samples of a standard dilution of the initial dose to calculated percent injected dose per gram (%ID/g).

For blocking studies, mice (n=5 per group) were co-injected with unlabeled **XY-FAP-02** (50 μ g per mouse) and 10 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline. Mice (n=5) injected with 10 μ Ci ¹¹¹In-XY-FAP-02 in 200 μ L saline served as a control. At 6 h post injection, mice were sacrificed, tissues were collected, and radioactivity was measured with the gamma well counter.

1.10 Data Analysis. Data are expressed at mean ± standard deviation (SD). Prism software (GraphPAD, San Diego, CA) was used for analysis and statistical significance was calculated using a two-tailed Student's t test. A P-value <0.05 was considered significant.

1.11 Xenograft Tumor Model. 6-week old female NOD/SCID mice were subcutaneously injected in the upper left and right flanks with 1 million U87(FAP+) cells and PC3 cells (FAP-) in RPMI 1640 media supplemented with 1% FBS. Mice were monitored for tumor size and used for optical or SPECT/CT imaging when the size of tumor reached around 100 mm³.

EXAMPLE 2

Representative Results

2.1 FAP Inhibitory Assay. **XY-FAP-01** demonstrated high binding affinity to human recombinant FAP. The enzyme inhibitory constant (Ki) for the compound was determined to be 1.26 nM.

2.2 Cellular Uptake Studies. FAP-positive cell lines showed concentration dependent uptake of **XY-FAP-01** whereas FAP-negative cell lines showed no significant binding of **XY-FAP-01** at all concentrations (see, e.g., FIG. 3A). Saturated binding of **XY-FAP-01** was observed at concentration of 25 nM, which was subsequently used as the base concentration for all binding inhibition studies. When preblocked with a FAP and DPP-IV specific inhibitor, **XY-FAP-01** binding was significantly inhibited in FAP-positive cells (FIG. 3B). Interestingly, this phenomenon was not observed in FAP-positive cell lines preblocked with a DPP-IV specific inhibitor. These results further justify the specificity of **XY-FAP-01** for FAP over DPPIV, since blocking of DPPIV did not result in a change of binding ability of **XY-FAP-01**.

Similar specificity was observed with the radioactive analog, ¹¹¹In-XY-FAP-02. FAP positive cell line, U-87-MG, demonstrated over 30% uptake of administered radioactive dose after incubation whereas the FAP negative cell line, PC-3, had uptake of 0.01% of administered dose (FIG. 3C). Taken together, these results support the specificity of XY-FAP-01 and ¹¹¹In-XY-FAP-02 in the engagement of FAP *in vitro*.

2.3 Ex-vivo Biodistribution. Ex-vivo biodistribution of ¹¹¹In-XY-FAP-02 results correlated with the observed imaging results (FIG. 4). Initially, the blood pool activity is very high, with over 10% %ID/g at 30 minutes post injection. With clearance of the compound, we see the blood pool activity drop significantly after 2 hours of distribution and remained less than 5% %ID/g from 2 hours post injection (FIG. 5A). High activity was also observed in pancreas, small intestines, and bladder until 2 hours post injection. Positive tumor uptake peaked at 30 minutes post injection and remained between 13-11% %ID/g up to 6 hours. Washout of tumor was observed at 12 hours post injection, with %ID/g dropping to below 5%. The PC-3, FAP negative xenograft had less than 3.5% %ID/g for all timepoints.

Co-injection of cold compound with ¹¹¹In-XY-FAP-02 resulted in significant blocking of tracer uptake in U-87 xenografts, with %ID/g dropping from 11.20%

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without blocking versus 0.27% with blocking (p < 0.0001). Additionally, blocking with cold compound resulted in %ID/g of all tissues dropping significantly, with most values being less than 0.1%. This decrease in uptake is most likely due to the blocking of non-specific binding of tracer to non-target tissues and the blocking of specific binding of FAP in U-87 xenografts.

2.4 Small-Animal Near Infrared Fluorescence (NIRF) Imaging. NIRF imaging of **XY-FAP-01** demonstrated specific uptake of tracer in the U-87-MG xenograft as early as 30 minutes post injection (FIG. 6). After one hour of distribution, tracer clearance via the bladder was observed with retained tracer uptake in the FAP positive xenograft. Tracer uptake was retained in the positive xenograft after four hours of distribution. In contrast, no significant uptake of tracer was observed in the FAP negative tumor at all imaging time points.

REFERENCES

All publications, patent applications, patents, and other references mentioned in the specification are indicative of the level of those skilled in the art to which the presently disclosed subject matter pertains. All publications, patent applications, patents, and other references (e.g., websites, databases, etc.) mentioned in the specification are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent application, patent, and other reference was specifically and individually indicated to be incorporated by reference. It will be understood that, although a number of patent applications, patents, and other references are referred to herein, such reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art. In case of a conflict between the specification and any of the incorporated references, the specification (including any amendments thereof, which may be based on an incorporated reference), shall control. Standard art-accepted meanings of terms are used herein unless indicated otherwise. Standard abbreviations for various terms are used herein.

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U.S. Patent No. 9,346,814 for Novel FAP Inhibitors to Jansen et al., issued May 24, 2016.

International PCT Patent Publication No. WO 2013/107820 for Novel FAP Inhibitors to Jansen et al., published July 25, 2013.

Although the foregoing subject matter has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be understood by those skilled in the art that certain changes and modifications can be practiced within the scope of the appended claims. Attorney Docket No. JHU-36631.303

<u>REMARKS</u>

Upon entry of this amendment claim 29 is pending. Claims 1-27 remain canceled without prejudice. Claim 28 has been canceled. Applicant reserves the right to pursue the canceled subject matter in one or more continuation and/or divisional applications. Claim 29 is newly added. Support for new claim 29 can be found in provisional patent application serial no. 62/575,607, filed October 23, 2017, on page 6, line 13, through page 8, line 3, as originally filed. No new matter is added.

Applicants have amended the specification and drawings. The specification and drawings have been amended to correct an obvious error in the chemical structure of the compound XY-FAP-02. Support for amendments to the specification and FIG. 1C can be found on page 50, lines 23-29, of the application as originally filed, which discloses that the compound XY-FAP-02 has the chemical name of 2,2',2"-(10-(1-Carboxy-4-((3-((4-((2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl) amino)-4-oxobutyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid and is formed by reaction of compound **8** with DOTA-GA(t-Bu)₄-NHS. No new matter is added.

CONCLUSION

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney at 608-662-1277. Early passage of the subject application to issue is earnestly solicited.

Respectfully Submitted,

CASIMIR JONES, S.C.

Date: July 24, 2023

/JEFFREY W. CHILDERS/ Jeffrey W. Childers, Ph.D. Registration No. 58126 Customer No. 101943

- 6 -



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 07/24/2023 02:23:01 PM	ET S	attorney docket # JHU-36631.303
Title of Invention IMAGING AND RAD PROTEIN-ALPHA (F	DIOTHERAPEUTICS AGENTS ⁻ FAP-ALPHA)	TARGETING FIBROBL	AST-ACTIVATION
Application Infor	mation		
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Stephanie Filandrinos
PATENT CENTER #	62491443	FILING DATE	-
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 8

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
2023-07- 24_36631.303_PA2.pdf		6	-	194 KB
2023-07- 24_36631.303_PA2- SApdf	(1-1)	1	Supplemental Response or Supplemental Amendment	131 KB
2023-07- 24_36631.303_PA2- SPEC.pdf	(2-2)	1	Specification	88 KB
2023-07- 24_36631.303_PA2- DRW.pdf	(3-3)	1	Drawings-only black and white line drawings	88 KB

				Page 2 of 3
2023-07- 24_36631.303_PA2- CLM.pdf	(4-5)	2	Claims	132 KB
2023-07- 24_36631.303_PA2- REM.pdf	(6-6)	1	Applicant Arguments/Remarks Made in an Amendment	132 KB
2023-07- 24_36631.303_SubSpec- marked.pdf		62	Specification	1123 KB
2023-07- 24_36631.303_SubSpec- clean.pdf		61	Specification	1083 KB
2023-07- 24_36631.303_ReplcementF gures.pdf	1	9	Drawings-only black and white line drawings	3020 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-07- 24_36631.303_PA2.pdf	F39DF42D8DB3AF2782DDD73663E9CDDE163E90E4BA63D144 9A73D8EFE5F89BD76735A8C100D5EA658794A10193B010E108 EFEFB0091C3B4044D62010CDA6A24B
2023-07-24_36631.303_PA2- SApdf	10FB294B23D744BC60F9831AC47A001EAEADFB8B4963B5FFC FF379E47E6C44F42AA1159EF3B28664E32E519C4D051C79A48 71DC6368DCFEC3525E8E1AF1E1062
2023-07-24_36631.303_PA2- SPEC.pdf	DCF1D119222C82BE271A6609AABE7B9F7B66F5D58F840B13E D5DB584B4205C001EED36D96C79D4A27405B064D45C0685BD EA3688FC094C361541D4746A61675B
2023-07-24_36631.303_PA2- DRW.pdf	47BAABA42FC99C3AF8EB12C7FB0A3A7C5A86B8C6B1D79961 795029404F99C30C49135BDC6608A06EF4E434DA766FB6A34

C4AC33A	A9A26	E8950A	CF36E880	A7C5D
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2023-07-24_36631.303_PA2- CLM.pdf	B357F341D488E935AFDF5D6A4521DB655EF39F414FA50A4AA F822D083DB98530192BAD8279248C4A95B97A0EA5B1BF55DA E8902BDB16799E27206F82AFF127A6
2023-07-24_36631.303_PA2- REM.pdf	FAFD657DF82965DE22682CA1402DB963566CF22409FD8DF8C 53A87790108A1B10A540E923F77F09387AE7F0D41AE99E32BA E136AFA9EB20FAF0D0A531E2BD7EA
2023-07-	60FB1A3ABF7C34BD3E82821118D3A2EC89538474EA6697CAF
24_36631.303_SubSpec-	9D34917EA372F17B6ED1BBC49CE0E536B4F94C3AA7E87644A
marked.pdf	C68AA47068A9D26AC9FB858A87BDBB
2023-07-	A25B955AE4838D0E364AF869FC429612CD956EE38B2B0BC20
24_36631.303_SubSpec-	BE4E42F211994B136CCDF47AAF07CFD7C206D88CD60A1D15
clean.pdf	7FEECCCA40B88D9698D1844903DA416
2023-07-	ED37576B13EBCB8D0AE3BE72252E5E23645B4C696C299D04E
24_36631.303_ReplcementFigu	8556FA0EA84847CB5616806B97D5FC8A8A2DA930E625A631A
res.pdf	F7FDDEFE6DBE9BBA755F4C9BCB4759

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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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Fig. 1A



Fig. 1B

...



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FAP Binding

Fig. 2

REPLACEMENT SHEEET











Petitioner GE Healthcare – Ex. 1002, p. 261

REPLACEMENT SHEEET

	5 min	0.5 h	2 ង	6 br	6 h - blocking	12 h
	{n= 3}	(n= 4)	{n= 3}	(n= 4)	(n=4)	(n= 4)
blood	15.13 ± 0.62	10.64 ± 1.54	4.10 ± 0.39	2.01 ± 0.18	0.62 ± 0.091	0.42 ± 0.04
heart	6.68 ± 0.99	4.98 ± 0.71	2.61 ± 0.09	1.07 ± 0.09	0.02 ± 0.092	0.46 ± 0.04
lungs	6.99±1.37	5.60 ± 0.89	2.59 ± 0.32	1.38 ± 0.13	0.04 ± 0.005	0.39 ± 0.03
liver	6.32 ± 0.77	4.90 ± 0.59	2.58 ± 0.09	2.51 ± 0.09	0.33 ± 0.058	1.66 ± 0.22
stomach	3.28 ± 0.46	2.62 ± 0.23	1.69 ± 0.14	1.19 ± 0.15	0.06 ± 0.032	0.34 ± 0.05
pancreas	14.54 ± 1.66	12.14 ± 2.85	8.11±0.34	3.28 ± 0.27	0.03 ± 0.005	1.15 ± 0.52
spleen	2.93 ± 0.25	2.48 ± 0.47	1.77 ± 0.27	1.54 ± 0.19	0.06 ± 0.008	1.10 ± 0.13
fat	0.74 ± 0.09	0.73±0.13	0.61±0.19	9.45 ± 0.16	0.02 ± 0.017	0.15 ± 0.08
kidney	4.60 ± 0.57	3.56 ± 0.18	1.95 ± 0.06	1.79 ± 0.21	1.18 ± 0.158	0.73 ± 0.05
sm. int.	8.80 ± 1.97	8.41 ± 1.35	3.64 ± 0.45	1.66 ± 0.22	0.09 ± 0.052	0.76 ± 0.14
irg. int.	4.67 ± 0.42	4.57 ± 0.57	2.98 ± 0.27	1.97 ± 0.47	0.36 ± 0.342	0.55 ± 0.04
bladder	2.98 ± 0.95	13.60 ± 8.80	8.94 ± 6.48	3.41 ± 0.84	1.04 ± 0.466	2.25 ± 0.57
muscle	3.00 ± 0.22	3.53 ± 0.16	2.80 ± 0.07	1.79 ± 0.15	9.02 ± 0.095	0.60 ± 0.03
femur	4.76 ± 0.12	5.83 ± 0.72	4.95 ± 0.63	3.91 ± 0.70	9.08 ± 0.021	1.38 ± 0.20
U87	9.71 ± 0.24^{a}	12.89 ± 1.45²	12.28 ± 1.95⁼	11.20 ± 1.03^{8}	$0.27 \pm 0.019^{\circ}$	4.87 ± 0.54°
PC3	2.20 ± 0.20	3.10 ± 0.57	2.75 ± 0.11	3.40 ± 0.34	$6.11 \pm 0.024^{\circ}$	0.95 ± 0.06
U87:PC3	4.43 ± 0.31	4.23 ± 0.72	4.46 ± 0.62	3.30 ± 0.14	2.61 ± 0.440	4.82 ± 0.28
U87:blood	0.64 ± 0.04	1.22 ± 0.07	3.00 ± 0.38	5.58 ± 0.38	18.07 ± 1.197	10.94 ± 0.93
U87:mm	3.25 ± 0.26	3.68 ± 0.44	4.38 ± 0.86	6.29 ± 0.82	11.81 ± 2.686	7.68 ± 0.97

Fig. 4



Fig. 5A





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0.5 h

1 h

2.5 h

4 h

Fig. 6



Fig. 7

Petitioner GE Healthcare – Ex. 1002, p. 265



30 min

2 hr

Fig. 8

Attorney Docket No. JHU-36631.303

AMENDMENTS TO THE CLAIMS:

The present listing of claims replaces all previous versions of the claims.

1.-27. (Canceled)

- 28. (Canceled)
- 29. (New) A compound of Formula (I):

B-L-A(I)

wherein:

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



wherein:

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

R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from $-NR_{10x}R_{11x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

B is any optical or radiolabeled functional group suitable for optical imaging, positronemission 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.

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	Jnited State	<u>s Patent</u>	and Tradema	ARK OFFICE UNITED STATES DEPA United States Patent an Address: COMMISSIONER F PO. Box 1450 Alexandria, Virginia 223 www.uspi.gov	RTMENT OF CO ad Trademark (OR PATENTS 13-1450)MMERCE)ffice
APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/354,282	07/18/2023		664	JHU-36631.303	1	1
101943 The Johns Ho c/o Casimir Jo 2275 Deming ' Suite 310 Middleton, WI	pkins University nes Way 53562	1				NO. 7536

Date Mailed: 08/08/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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Inventor(s)

Xing Yang, Baltimore, MD; Sridhar Nimmagadda, Balimore, MD; Steven Rowe, Parkville, MA; Stephanie Slania, Baltimore, MD; Martin G. Pomper, Baltimore, MD;

Applicant(s)

The Johns Hopkins University, Baltimore, MD;

Power of Attorney: The patent practitioners associated with Customer Number 101943

Domestic Priority data as claimed by applicant

This application is a CON of 16/758,182 04/22/2020 which is a 371 of PCT/US18/57086 10/23/2018 which claims benefit of 62/575,607 10/23/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <u>http://www.uspto.gov</u> for more information.) - None. *Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.*

Permission to Access Application via Priority Document Exchange: Yes

page 1 of 4

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If Required, Foreign Filing License Granted: 08/04/2023 The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is US 18/354,282 Projected Publication Date: 11/16/2023 Non-Publication Request: No Early Publication Request: No ** SMALL ENTITY ** Title

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Electronic Acknowledgement Receipt		
EFS ID:	48408930	
Application Number:	18354282	
International Application Number:		
Confirmation Number:	7536	
Title of Invention:	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST- ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)	
First Named Inventor/Applicant Name:	Xing Yang	
Customer Number:	101943	
Filer:	Jeffrey Childers./Aaron Bottjen	
Filer Authorized By:	Jeffrey Childers.	
Attorney Docket Number:	JHU-36631.303	
Receipt Date:	08-AUG-2023	
Filing Date:	18-JUL-2023	
Time Stamp:	15:30:15	
Application Type:	Utility under 35 USC 111(a)	

Payment information:

Submitted wi	th Payment		no						
File Listing:									
Document Number	Document Description		File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)			
1	Information Disclosure Statement (IDS)		2023-08-08_36631-303-	46022	no	4			
	Form (SB08)		IDS_SB08.pdf	247bb7f5587f230539953ed88b79c5bcca8 9799d					
Warnings:									

Information:					
This is not an U	SPTO supplied IDS fillable form				
			17148949		
2	Foreign Reference	EP18199641.pdf	f3a2a5725fd108ce02d07d18f88e834bd410 0292	no	149
Warnings:					
Information:					•
			23045549		
3	Foreign Reference	JP2021512949A.pdf	f5c29b108e53b17139acba43921c6ac626a 69396	no	171
Warnings:					•
Information:					
			3823640		
4	Foreign Reference	WO2010014933A2.pdf	1ec298234312be44fa6893719216d196d72 8435d	no	64
Warnings:					•
Information:					
			8515844		
5	Foreign Reference	WO2010108125A2.pdf	506ba62b29e0bfb5e34964a46e1bfb51b26 eddb2	no	159
Warnings:					
Information:					
			5159352		
6	Foreign Reference	WO2016065142A2.pdf	3b4a125bb48b122831526d523b31ae79aa c5be79	no	128
Warnings:					
Information:					
			18470573		
7	Foreign Reference	WO2019154886A1_Original_d ocument.pdf	440e432818dd839dc9f75574695f4559cae5 5b8f	no	195
Warnings:					
Information:			1		
			384520		
8	Other reference-Patent/Application/ Search Documents	ThirdPartyPreissuance-16-758- 182.pdf	a06781ffdfe7e7ea44486db2b2dc7aae390c cfbf	no	6
Warnings:					
Information:					

9	Other reference-Patent/Application/ Search Documents	ThirdPartyObservation_JP2020- 523010.pdf	281640 82e6ab8429dc3a5a5be498e97e6ef3ac1b4 d40cf	no	7		
Warnings:							
Information:					-		
	Other reference Datast/Analisation (334885				
10	Search Documents	0871298.pdf	f338935e84831506137afdea18cbccde0cf4 7493	no	7		
Warnings:							
Information:							
			8749380				
11	Non Patent Literature	BERNHARD_2012.pdf	03284bc7c67fcc802ef3b247219049176ad0 23bf	no	8		
Warnings:							
Information:					-		
			23794390				
12	Non Patent Literature	JAMOUS_2013.pdf	965b6f4ed231bfbd3c07a80c833b475d0db ae8c9	no	31		
Warnings:							
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		Total Files Size (in bytes)	109	754744			
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. New Applications Under 35 U.S.C. 111 If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. National Stage of an International Application under 35 U.S.C. 371 If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. New International Application Filed with the USPTO as a Receiving Office If a new international application is being filed and the international application includes the necessary components for an international Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.							

				Comp	olete if Known
				Application Number	18/354,282
INFO	DRMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023
STA	STATEMENT BY APPLICANT			First Named Inventor	Yang
	(Use as many sheets	as necessary)		Art Unit	
				Examiner Name	
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303

	U.S. PATENTS								
Examiner Initials⁺	Cite No.1	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear				

U.S. PUBLISHED PATENT APPLICATIONS								
Examiner Initials*	Cite No. ³	Document Number	Issue or Publication Date	Name of Patentee or Applicant of Cited	Pages, Columns, Lines, Where			
		Number-Kind Code⁴ <i>(if known)</i>	YYYY-MM-DD	Document	Relevant Passages or Relevant Figures Appear			
	1.	2021/0038749	2021-02-11	HABERKORN et al.				

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

		FOR	EIGN PATENT	DOCUMENTS		
Examiner Initials*	Cite No.1	Foreign Patent Document Country Code ⁵ Number ⁶ Kind Code ⁷ (<i>if known</i>)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation ⁸
	1.	EP 18199641.4	2018-10-10	UNIV HEIDELBERG		
	2.	JP2021-512949A	2021-05-20	UNIV HEIDELBERG		Х
	3.	WO 2010/014933	2010-02-04	THE JOHNS HOPKINS UNIVERSITY		
	4.	WO 2010/108125	2010-09-23	THE JOHNS HOPKINS UNIVERSITY		
	5.	WO 2016/065142	2016-04-28	THE JOHNS HOPKINS UNIVERSITY		
	6.	WO 2019/154886	2019-08-15	UNIV HEIDELBERG		

	Examiner Signature		Date Considered	
É		Initial if reference considered, whether or not citation is in conformance	e with MPEP 600	Draw line through

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Comp	olete if Known
				Application Number	18/354,282
INF	ORMATION D	ISCLOSU	IRE	Filing Date	18-Jul-2023
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang
	(Use as many sheets	as necessary)		Art Unit	
				Examiner Name	
Sheet 2 of 3			3	Attorney Docket Number	JHU-36631.303

FOREIGN PATENT DOCUMENTS

		NONPATENT LITERATURE DOCUMENTS	
Examiner Initials*	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation 6
	1.	Third Party Preissuance Submission filed in USSN 16/758, 182, filed February 23, 2022, 6 pages.	
	2.	Third Party Observations Japanese Patent Application no. 2020- 523010. Dated 24 Oct 2022. 7 pages.	
	3.	Third Party Observations for application number EP20180871298. Dated 04/03/2022. 7 pages.	
	4.	BERNHARD et al., DOTAGA-anhydride: a valuable building block for the preparation of DOTA-like chelating agents. Chemistry. 2012 Jun 18;18(25):7834-41.	
	5.	JAMOUS et al., Synthesis of peptide radiopharmaceuticals for the therapy and diagnosis of tumor diseases. Molecules. 2013 Mar 14;18(3):3379-409.	

	Examiner		Date	
	Signature		Considered	
Ē	EXAMINER:	Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9. Draw line through

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Complete if Known		
				Application Number	18/354,282	
INFO	ORMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang	
	(Use as many sheets	as necessary)		Art Unit		
				Examiner Name		
Sheet	3	of	3	Attorney Docket Number	JHU-36631.303	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

L

See attached certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

Х

A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on ______. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-08-08
Name/Print	Jeffrey W. Childers	Registration Number	58,126

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¹ Applicant's unique citation designation number (optional).

² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

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⁵ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

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⁷ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

⁸ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536
101943 The Johns Hop	7590 08/30/202 kins University	3	EXAM	IINER
c/o Casimir Jon	les	CENTRAL, DOCKET		
2275 Deming V Suite 310	Vay		ART UNIT	PAPER NUMBER
Middleton, WI	53562		OPAP	
			NOTIFICATION DATE	DELIVERY MODE
			08/30/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com jwchilders@casimirjones.com

	Decisio	n Granting Request for	Application No. 18/354,282	Applicant(s) Yang et al.				
	Prioritiz	ed Examination (Track I)	Examiner CHERYL P GIBSON BAYLOR	Art Unit OPET	AIA (FITF) Status Yes			
1.	1. THE REQUEST FILED <u>18 July 2023</u> IS GRANTED .							
	The abov A. B.	ve-identified application has met the requirements for prioritized examination						
2.	 The above-identified application will undergo prioritized examination. The application will be accorded special status throughout its entire course of prosecution until one of the following occurs: 							
	Α.	filing a petition for extension	of time to extend the time period for filing a reply;					
	В.	B. filing an amendment to amend the application to contain more than four independent claims, more than thirty total claims , or a multiple dependent claim;						
	C.	C. filing a request for continued examination ;						
	D.	filing a notice of appeal;						
	E.	filing a request for suspension of action;						
	F.	mailing of a notice of allowance;						
	G.	. mailing of a final Office action;						
	Н.	. completion of examination as defined in 37 CFR 41.102; or						
	I.	abandonment of the application	۱.					
	Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at							
(371)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.								
	Paralega	I GIBSON BAYLOR/ Il Specialist, OPET						

U.S. Patent and Trademark Office PTO-2298 (Rev. 02-2012)

PE2E SEARCH - Search History (Prior Art)

Ref#	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L2	74816	FAP OR (fibroblast near2 activation)	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 08:42 PM
L3	27353058	radionuclide OR radioisotop\$6 OR radiolabel\$3 OR dye OR optical OR cyanine OR IRdye800 OR DOTA OR chelat\$3 OR BODIPY OR vivotag OR alexaflour OR Hilyte OR ADS780 OR ADS830 OR ADS832 OR Dy677 OR Dy676 OR Dy682 OR Dy752 OR Dy780 OR Dylight OR Cy5 OR cy7 OR cv5.5	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:00 PM
L4	49880	L2 AND L3	(US-PGPUB; USPAT; USOCR; FIT (AU, AP, AT, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, OA, RU, SU, WO, MC, MD, MY, NL, NO, NZ, PH, PL, PT, RO, RS, SE, SG, SI, SK, TH, TN, TR, TW, UA, VN); FPRS; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:00 PM
L5	644	cyano near2 proline	(US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS,	OR	ON	ON	2023/09/19 09:01 PM

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L6	58	L4 AND L5	IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO; JPO; DERWENT) (US-PGPUB; USPAT; USOCR; FIT (AP, AT, AU, BE, BG, BR, BY, CA, CH, CN, CS, CU, CZ, DD, DE, DK, EA, EE, EP, ES, FI, FR, GB, HR, HU, ID, IE, IL, IS, IT, JP, KR, LT, LU, LV, MA, MC, MD, MY, NL, NO, NZ, OA, PH, PL, PT, RO, RS, RU, SE, SG, SI, SK, SU, TH, TN, TR, TW, UA, VN, WO); FPRS; EPO;	OR	ON	ON	2023/09/19 09:01 PM
L7	504	((("YANG") near3 ("Xing")) OR (("NIMMAGADDA") near3 ("Sridhar")) OR (("ROWE") near3 ("Steven")) OR (("SLANIA") near3 ("Stephanie")) OR (("POMPER") near3 ("Martin"))).INV.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:08 PM
L8	7	L2 AND L7	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:08 PM
L9	2	L8 AND L3	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:11 PM
L10	5921	(A61K51/0485 OR A61K47/545 OR A61K51/0478 OR A61K51/0482).cpc.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:12 PM
L11	201	L2 AND L10	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:12 PM
L12	165	L3 AND L11	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:12 PM
L13	41	L12 AND ((@py<="2017"))	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2023/09/19 09:12 PM

PE2E SEARCH - Search History (Interference)

There are no Interference searches to show.

Web Search History

date, time	web site	search string
9/19/2023 3:19:02 PM	Google Scholar	FAP-alpha radionuclide [after:2000] [before:2018]
9/19/2023 3:19:04 PM	Google Scholar	FAP-alpha radionuclide
9/19/2023 3:19:11 PM	Google Scholar	FAP-alpha DOTA
9/19/2023 3:38:51 PM	Google	fap ibody
9/19/2023 6:24:06 PM	Google	cyanoproline fap
9/19/2023 6:31:35 PM	Google Scholar	cyanoproline fap
9/19/2023 6:40:13 PM	Google Scholar	cyanoproline fibroblast activation protein
9/19/2023 6:41:11 PM	Google Scholar	radiolabeled fibroblast activation protein
9/19/2023 6:51:54 PM	Google Scholar	anit-fap ibody radiolabeled
9/19/2023 8:43:06 PM	Google Scholar	FAP dye
9/19/2023 8:54:56 PM	Google	cyanoproline fap dye
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9/19/2023 8:55:44 PM	Google Scholar	cyanoproline fap cyanine dye
9/19/2023 8:55:50 PM	Google Scholar	fap cyanine dye
9/19/2023 8:58:06 PM	Google Scholar	fap targeting cyanine dye

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NEWS	4	APR	4	The enhanced Derwent World Patents Index(R) is now	
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NEWS	6	JUN	22	Claims for Four Additional Patent Authorities Added to	
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NEWS	12	OCT	24	Links to National Patent Registers Now Available in Patent Databases on CAS STNext	
NEWS	13	NOV	7	PCTFULL Reload Provides Additional Coverage, Independent	
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NEWS	17	DEC	05	New Implementation of Derwent Drug File (DRUGU/DDFU) Makes Searching More Convenient	
NEWS	18	DEC	23	New Interactive Claim Viewer in EPFULL and PCTFULL	
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NEWS	19	DEC	30	2023 MeSH now available in MeDLine on STNext	
NEWS	20	FEB	23	Derwent world Patents Index - Manual Code revision 2023	
NEWS	21	MAR	10	MEDLINE(R) Reloaded and MeSH Thesaurus Updated for	
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NEWS	27	SEP	08	Ultimate Owner Information Included in CA/CAplus Aids	
				in Determining Current IP Rights Owners	
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L3	7288	FILE	CAPLUS
L4	58	FILE	CHEMCATS
L5	9	FILE	CHEMLIST
L6	11564	FILE	EMBASE
L7	2202	FILE	ESBIOBASE
L8	7288	FILE	HCAPLUS
L9	9	FILE	HCHEMLIST
L10	6	FILE	KOSMET
L11	4	FILE	LEMBASE
L12	7190	FILE	MEDLINE
L13	355	FILE	REGISTRY
L14	8627	FILE	SCISEARCH
L15	7288	FILE	ZCAPLUS
L16	355	FILE	ZREGISTRY

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=> s radionuclide OR "Radioactive substances" OR "Radioisotopes" OR "Isotopic radioelements" OR "Radioelement" OR "Radioelement isotopes" OR "Radioactive elements" OR "Radioactive nuclides" OR "Radioactive isotopes" OR "Radioelement complexes" OR "Radioelement conjugates"

L18	44015	FILE	BIOSIS
L19	1432	FILE	BIOTECHNO
L20	141489	FILE	CAPLUS
L21	22	FILE	CHEMCATS
L22	116	FILE	CHEMLIST
L23	72885	FILE	EMBASE
L24	18475	FILE	ESBIOBASE
L25	141489	FILE	HCAPLUS
L26	116	FILE	HCHEMLIST
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L36	2	FILE	BIOTECHNO
L37	156	FILE	CAPLUS
L38	0	FILE	CHEMCATS
L39	0	FILE	CHEMLIST
L40	130	FILE	EMBASE
L41	2	FILE	ESBIOBASE
L42	156	FILE	HCAPLUS
L43	0	FILE	HCHEMLIST
L44	0	FILE	KOSMET
L45	0	FILE	LEMBASE
L46	278	FILE	MEDLINE
L47	0	FILE	REGISTRY
L48	81	FILE	SCISEARCH
L49	156	FILE	ZCAPLUS
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L55	0	FILE	CHEMCATS
L56	0	FILE	CHEMLIST
L57	23	FILE	EMBASE
L58	4	FILE	ESBIOBASE
L59	15	FILE	HCAPLUS
L60	0	FILE	HCHEMLIST
L61	0	FILE	KOSMET
L62	0	FILE	LEMBASE
L63	6	FILE	MEDLINE
L64	0	FILE	REGISTRY
L65	14	FILE	SCISEARCH
L66	15	FILE	ZCAPLUS
L67	0	FILE	ZREGISTRY

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L78 L79	0 FILE KOSMET 0 FILE LEMBASE
L80	O FILE MEDLINE
L81	0 FILE REGISTRY
L82 L83	O FILE SCISEARCH O FILE ZCAPLUS
L84	0 FILE ZREGISTRY
TOTAL FOR A	ALL FILES
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L87 тоо	0 FILE BIOTECHNO
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L90	0 FILE CHEMLIST
L91	3 FILE EMBASE
L92	0 FILE ESBIOBASE
L93 T 04	3 FILE HCAPLUS
L94 L95	0 FILE KOSMET
L96	O FILE LEMBASE
L97	2 FILE MEDLINE
L98	16 FILE REGISTRY
L99 L100	0 FILE SCISEARCH 3 FILE ZCADLUS
L101	16 FILE ZREGISTRY
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L103	0 FILE BIOSIS
L104	0 FILE BIOTECHNO
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L107	0 FILE CHEMLIST
L108	O FILE EMBASE
L109	0 FILE ESBIOBASE
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ыттт Т.112	O FILE KOSMET
L113	O FILE LEMBASE
L114	O FILE MEDLINE
L115	O FILE REGISTRY
L116	0 FILE SCISEARCH
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TOTAL FOR ALL FILES L119 0 L51 AND L102

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L120	1583858	FILE	BIOSIS
L121	22740	FILE	BIOTECHNO
L122	1616544	FILE	CAPLUS
L123	2148	FILE	CHEMCATS
L124	2311	FILE	CHEMLIST
L125	2616449	FILE	EMBASE
L126	282971	FILE	ESBIOBASE
L127	1616544	FILE	HCAPLUS
L128	2311	FILE	HCHEMLIST
L129	3229	FILE	KOSMET
L130	650	FILE	LEMBASE
L131	2636196	FILE	MEDLINE
L132	28650	FILE	REGISTRY
L133	1545961	FILE	SCISEARCH
L134	1616544	FILE	ZCAPLUS
L135	28650	FILE	ZREGISTRY

TOTAL FOR ALL FILES L136 13605756 DYE OR "FLUORESCENT DYES" OR "IR-ABSORBING DYES" OR CYANINE OR DYLIGHT OR IMAGING OR "RADIOIMMUNOIMAGING" OR "INFRARED IMAGING" OR "SPECTRAL IMAGING" OR "LUMINESCENT IMAGING"

=> s l17 and l136

L137	530	FILE	BIOSIS
L138	2	FILE	BIOTECHNO
L139	626	FILE	CAPLUS
L140	0	FILE	CHEMCATS
L141	0	FILE	CHEMLIST
L142	1431	FILE	EMBASE
L143	76	FILE	ESBIOBASE
L144	626	FILE	HCAPLUS
L145	0	FILE	HCHEMLIST
L146	0	FILE	KOSMET
L147	0	FILE	LEMBASE
L148	903	FILE	MEDLINE
L149	1	FILE	REGISTRY
L150	660	FILE	SCISEARCH
L151	626	FILE	ZCAPLUS
L152	1	FILE	ZREGISTRY

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L153	5482	L17	AND	L136	

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0	FILE	CHEMCATS
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0	FILE	ESBIOBASE
0	FILE	HCAPLUS
0	FILE	HCHEMLIST
0	FILE	KOSMET
0	FILE	LEMBASE
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T-170 2 L153 AND L102 => d bib 1179 1-2 L179 NOT FOUND The L-number entered has not been defined in this session, or it has been deleted. To see the L-numbers currently defined in this session, enter DISPLAY HISTORY at an arrow prompt (=>). => d bib 1170 1-2 L170 ANSWER 1 OF 2 EMBASE COPYRIGHT (c) 2023 Elsevier B.V. All rights reserved on STN 20230385996 EMBASE Full-text AN 2024158278 PMID: 37117123 DN Advanced Fibroblast Activation Protein-Ligand Developments: FAP ΤI Imaging Agents: A Review of the Structural Requirements. DiMagno, Stephen G.; Babich, John W., PhD (correspondence) Ratio Therapeutics, Inc., One Design Center Place, Suite# 19-601, Boston, AU CS MA, 02210, United States. jbabich@ratiotx.com PET Clinics, (July 2023) Vol. 18, No. 3, pp. 287-294. SO Refs: 55 ISSN: 1556-8598; E-ISSN: 1879-9809 10.1016/j.cpet.2023.03.002 DOI PB W.B. Saunders. PUI S 1556-8598(23)00028-7 CY United States Journal; General Review; (Review) DTIntellectual Indexing FS 016 Cancer 023 Nuclear Medicine 037 Drug Literature Index FS ClinicalTrials.gov NCT NCT04939610 LA English EDEntered Embase: 2 May 2023 Last Updated on Embase: 14 Jun 2023 Indexing Added: 14 Jun 2023 First Entered Embase or Embase Alert: 2 May 2023 L170 ANSWER 2 OF 2 MEDLINE ® on STN AN 2027165793 MEDLINE Full-text PubMed ID: 37117123 DN Advanced Fibroblast Activation Protein-Ligand Developments: FAP ΤI Imaging Agents: A Review of the Structural Requirements. AU DiMagno Stephen G CS Ratio Therapeutics, Inc., One Design Center Place, Suite# 19-601, Boston, MA 02210, USA. AU Babich John W Ratio Therapeutics, Inc., One Design Center Place, Suite# 19-601, Boston, CS MA 02210, USA. jbabich@ratiotx.com PET clinics, (2023 Jul) Vol. 18, No. 3, pp. 287-294. Electronic SO Publication Date: 26 Apr 2023 Journal code: 101260152. E-ISSN: 1879-9809. L-ISSN: 1556-8598. DOI http://dx.doi.org/10.1016/j.cpet.2023.03.002 United States CY DTJournal; Article; (JOURNAL ARTICLE) General Review; (REVIEW) LA English MEDLINE; Priority Journals FS FS Print; Electronic 202306 EMEntered STN: 30 Apr 2023 Last Updated on STN: 2 Jun 2023 EDIndexing Added: 2 Jun 2023 Entered Medline: 2 Jun 2023

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Pavel; Sedo, Aleksi; Konvalinka, Jan Institute of Organic Chemistry and Biochemistry of The Czech Academy of CS Sciences, Prague 6, 16610, Czech Rep. Journal of Medicinal Chemistry (2017), 60(20), 8385-8393 so CODEN: JMCMAR; ISSN: 0022-2623 DOI 10.1021/acs.jmedchem.7b00767 ΡB American Chemical Society DTJournal; (online computer file) LΑ English os CASREACT 169:205864 OSC.G 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS) THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD RE.CNT 52 ALL CITATIONS AVAILABLE IN THE RE FORMAT L187 ANSWER 4 OF 4 ZCAPLUS COPYRIGHT 2023 ACS on STN 2017:1570779 ZCAPLUS Full-text AN DN 169:205864 ΤI Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein Dvorakova, Petra; Busek, Petr; Knedlik, Tomas; Schimer, Jiri; Etrych, AIJ Tomas; Kostka, Libor; Stollinova Sromova, Lucie; Subr, Vladimir; Sacha, Pavel; Sedo, Aleksi; Konvalinka, Jan CS Institute of Organic Chemistry and Biochemistry of The Czech Academy of Sciences, Prague 6, 16610, Czech Rep. Journal of Medicinal Chemistry (2017), 60(20), 8385-8393 SO CODEN: JMCMAR; ISSN: 0022-2623 DOI 10.1021/acs.jmedchem.7b00767 PB American Chemical Society Journal; (online computer file) DTEnglish LA os CASREACT 169:205864 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS) OSC.G 16 RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

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	Application/Control No.	Applicant(s)/Patent Under Reexamination
Search Notes	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC - Searched*						
Symbol	Date	Examiner				

CPC Combination Sets - Searched*					
Symbol	Date	Examiner			

US Classification - Searched*						
Class Subclass Date Examiner						

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes						
Search Notes	Date	Examiner				
google scholar	09/19/2023	MP				
inventor search	09/19/2023	MP				
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STNext	09/20/2023	MP				

Interference Search							
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Index of Claims	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

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U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	А	US-20100098633-A1	04-2010	ZIMMERMAN; Craig	C07D401/14	424/1.85
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Tahtis et al. (Mol. Cancer Therap. 2003, 2, 729-737)
	V	Terry et al. (J. Nucl. Med. 2016, 57, 467-472)
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STA	TEMENT BY	APPLICA	NT	First Named Inventor	YANG	
	(Use as many sheets	as necessary)		Art Unit		
				Examiner Name		
Sheet 1 of 4		Attorney Docket Number	JHU-36631.303			

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Exami ner Initials*	Cite No. ¹	Document Number Number-Kind Code ² (if known)	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear				
		9346814	2016-05-24	JANSEN et al.					

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Exami	Cite	Document Number	Issue or Publication Date YYYY-MM-DD	Name of Patentee or	Pages, Columns, Lines,				
ner Initials*	NO.3	Number-Kind Code ⁴ (if known)		Applicant of Cited Document	Where Relevant Passages or Relevant Figures Appear				
		20080280856	2008-11-13	COHEN et al.					
		20140357650	2014-12-04	JANSEN et al.					

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Exami ner Initials* Cite No.1 Foreign Patent Document Country Code ⁵ Number ⁶ Kind Code ⁷ (if known) Country Code ⁵ Number ⁶ Kind Code ⁷		Publication Date YYYY-MM- DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translati on ⁸				
		WO 2013/107820	2013-07-25	UNIVERSITEIT ANTWERPEN et al.					
		WO 2014/001538	2014-01-03	GE HEALTHCARE LTD					
		WO 2015/114166	2015-08-06	PHILOCHEM AG					
		WO 2016/149188	2016-09-22	THE JOHNS HOPKINS UNIVERSITY					

	Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023
F		Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9 Draw line through

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

				Complete if Known		
				Application Number		
INFO	ORMATION D	ISCLOSU	RE	Filing Date		
STA	TEMENT BY	APPLICA	NT	First Named Inventor	YANG	
	(Use as many sheets	as necessary)		Art Unit		
				Examiner Name		
Sheet 2 of 4		Attorney Docket Number	JHU-36631.303			

		NONPATENT LITERATURE DOCUMENTS	
Examin er Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translatio n ⁶
		ALLINEN et al., Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004 Jul;6(1):17-32.	
		BAE et al., Fibroblast activation protein alpha identifies mesenchymal stromal cells from human bone marrow. Br J Haematol. 2008 Sep;142(5):827-30.	
		CHEN et al., Advance of molecular imaging technology and targeted imaging agent in imaging and therapy. Biomed Res Int. 2014; 2014 : 819324. PMCID: PMC3943245.	
		COENEN et al., Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727–740.	
		CHO et al., Biodistribution, tumor detection, and radiation dosimetry of 18F-DCFBC, a low-molecular-weight inhibitor of prostate-specific membrane antigen, in patients with metastatic prostate cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2012; 53:1883–1891.	
		DVORAKOVA et al., Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein. J Med Chem. 2017;60:8385-8393.	
		EDOSADA et al., Peptide substrate profiling defines fibroblast activation protein as an endopeptidase of strict Gly(2)-Pro(1)-cleaving specificity. FEBS Lett. 2006 Mar 6;580(6):1581-6.	
		FISCHER et al., Radioimmunotherapy of fibroblast activation protein positive tumors by rapidly internalizing antibodies. Clin Cancer Res. 2012;18:6208–6218.	
		FRANCO et al., Cancer associated fibroblasts in cancer pathogenesis. Semin Cell Dev Biol. 2010 Feb;21(1):33-9.	
		GARIN-CHESA et al., Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers. Proc Natl Acad Sci U S A. 1990 Sep;87(18):7235-9. PMCID: PMC54718.	
		JANSEN et al., Selective Inhibitors of Fibroblast Activation Protein (FAP) with a (4- Quinolinoyl)-glycyl-2-cyanopyrrolidine Scaffold. ACS Med Chem Lett. 2013 Mar 18;4(5):491-6.	
		JANSEN et al., Extended structure-activity relationship and pharmacokinetic investigation of (4-quinolinoyl)glycyl-2-cyanopyrrolidine inhibitors of fibroblast activation protein (FAP). J Med Chem. 2014 Apr 10;57(7):3053-74.	
		KELLY, Fibroblast activation protein-alpha and dipeptidyl peptidase IV (CD26): cell- surface proteases that activate cell signaling and are potential targets for cancer therapy. Drug Resist Updat. 2005 Feb-Apr;8(1-2):51-8.	

	Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023				
Ē	EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through							
C	citation if not in conformance and not considered. Include copy of this form with next communication to applicant.							

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	(Use as many sheets	as necessary)		Art Unit		
				Examiner Name		
Sheet 3 of 4		Attorney Docket Number	JHU-36631.303			

	NONPATENT LITERATURE DOCUMENTS						
	KRAMAN et al., Suppression of antitumor immunity by s	tromal cells e	pressing				
	fibroblast activation protein-alpha. Science. 2010 Nov 5;	330(6005):82	7-30.				
	LAVERMAN et al., Immuno-PET and Immuno-SPECT of R	heumatoid Art	thritis with				
	Radiolabeled Anti-Fibroblast Activation Protein Antibody	/ Correlates w	ith Severity of				
	Arthritis. J Nucl Med. 2015 May;56(5):778-83.						
	LI et al., Activatable Near-Infrared Fluorescent Probe for	In Vivo Imagii	ng of Fibroblast				
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	POPLAWSKI et al., Identification of selective and potent inhibitors of fibroblast						
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	REILLY et al., Advancing Novel Molecular Imaging Agents from Preclinical Studies to						
	First-in-Humans Phase I Clinical Trials in Academia-A Roadmap for Overcoming						
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	protein in normal and transformed cells of mesenchymal and neuroectodermal origin						
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	KYABISOVA et al., Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast						
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	SCANI AN et al. Molecular cloping of fibreblact activation protein clobe, a member of						
	the serine protects family selectively expressed in strong	n protein aipn al fibroblasts	of enithelial				
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	TSAL et al., Substituted 4-carboxymethylpyroglutamic ac	id diamides as	potent and				
	selective inhibitors of fibroblast activation protein. J Me	d Chem. 2010	Sep				
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	TUXHORN et al., Reactive stroma in human prostate can	cer: induction	of				
	myofibroblast phenotype and extracellular matrix remo	deling. Clin Ca	ncer Res. 2002				
	Sep;8(9):2912-23.						
	WELT et al., Antibody targeting in metastatic colon cancer: a phase I study of						
	monoclonal antibody F19 against a cell-surface protein of reactive tumor stromal						
	fibroblasts. J Clin Oncol. 1994 Jun;12(6):1193-203.						
	YOUN et al., In vivo noninvasive small animal molecular imaging. Osong Public Health						
	Res Perspect. 2012; 3 :48-59.						
Examiner		Date	09/20/202	3			
Signature	/MELISSA J PERREIRA/	Considered	001201202	~			

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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				Application Number		
INFO	ORMATION D	ISCLOSU	RE	Filing Date		
STA	TEMENT BY	APPLICA	NT	First Named Inventor	YANG	
	(Use as many sheets	as necessary)		Art Unit		
				Examiner Name		
Sheet 4 of 4		Attorney Docket Number	JHU-36631.303			

NONPATENT LITERATURE DOCUMENTS				
	YU et al., The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J. 2010 Mar;277(5):1126-44.			
	International Search Report and Written Opinion for PCT/US2018/057086, mailed May 10, 2019, 12 pages			
	Extended EP Search Report for EP 18871298.8, mailed May 20, 2021, 7 pages			

	Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023	
Ē		Initial if reference considered, whether or not citation is in conformance	o with MDED 60	0 Draw line through	_

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				Application Number		
INF(ORMATION D	ISCLOSU	RE	Filing Date		
STA	TEMENT BY	APPLICA	NT	First Named Inventor	YANG	
	(Use as many sheets	as necessary)		Art Unit		
				Examiner Name		
Sheet 5 of 4		Attorney Docket Number	JHU-36631.303			

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

_

See attached certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.



A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-07-18
Printed Name	Jeffrey W. Childers	Registration Number	58126

PTO Notes regarding this form:

¹ Applicant's unique citation designation number (optional).

² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

³ Applicant's unique citation designation number (optional).

⁴ See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

⁵ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

⁶ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

⁷ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

⁸ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

				Complete if Known		
				Application Number	18/354,282	
INFO	ORMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang	
	(Use as many sheets	as necessary)		Art Unit		
				Examiner Name		
Sheet 1 of 3			3	Attorney Docket Number	JHU-36631.303	

	U.S. PATENTS								
Examiner Initials⁺	Cite No.1	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear				

U.S. PUBLISHED PATENT APPLICATIONS							
Examiner Initials*	iner Cite Documen Is* No. ³ Number		Issue or Publication Date	Name of Patentee or Applicant of Cited	Pages, Columns, Lines, Where		
		Number-Kind Code⁴ <i>(if known)</i>	YYYY-MM-DD	Document	Relevant Passages or Relevant Figures Appear		
	1.	2021/0038749	2021-02-11	HABERKORN et al.			

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

	FOREIGN PATENT DOCUMENTS						
Examiner Initials [*]	Cite No.1	Foreign Patent Document Country Code ⁵ Number ⁶ Kind Code ⁷ (<i>if known</i>)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	Translation ⁸	
	1.	EP 18199641.4	2018-10-10	UNIV HEIDELBERG			
	2.	JP2021-512949A	2021-05-20	UNIV HEIDELBERG		Х	
	3.	WO 2010/014933	2010-02-04	THE JOHNS HOPKINS UNIVERSITY			
	4.	WO 2010/108125	2010-09-23	THE JOHNS HOPKINS UNIVERSITY			
	5.	WO 2016/065142	2016-04-28	THE JOHNS HOPKINS UNIVERSITY			
	6.	WO 2019/154886	2019-08-15	UNIV HEIDELBERG			

	Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023
Ē		Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9 Draw line through

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

				Complete if Known		
INFORMATION DISCLOSURE				Application Number	18/354,282	
				Filing Date	18-Jul-2023	
STATEMENT BY APPLICANT			NT	First Named Inventor	Yang	
	(Use as many sheets	as necessary)		Art Unit		
				Examiner Name		
Sheet 2 of 3				Attorney Docket Number	JHU-36631.303	

FOREIGN PATENT DOCUMENTS						

NONPATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation 6	
	1.	Third Party Preissuance Submission filed in USSN 16/758, 182, filed February 23, 2022, 6 pages.		
	2.	Third Party Observations Japanese Patent Application no. 2020- 523010. Dated 24 Oct 2022. 7 pages.		
	3.	Third Party Observations for application number EP20180871298. Dated 04/03/2022. 7 pages.		
	4.	BERNHARD et al., DOTAGA-anhydride: a valuable building block for the preparation of DOTA-like chelating agents. Chemistry. 2012 Jun 18;18(25):7834-41.		
	5.	JAMOUS et al., Synthesis of peptide radiopharmaceuticals for the therapy and diagnosis of tumor diseases. Molecules. 2013 Mar 14;18(3):3379-409.		

	Examiner Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023
Ē	EXAMINER:	Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9. Draw line through

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				Com	olete if Known
				Application Number	18/354,282
INF	ORMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang
	(Use as many sheets	as necessary)		Art Unit	
				Examiner Name	
Sheet	3	of	3	Attorney Docket Number	JHU-36631.303

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

		ļ

See attached certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.



A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on ______. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-08-08
Name/Print	Jeffrey W. Childers	Registration Number	58,126

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¹ Applicant's unique citation designation number (optional).

² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

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⁵ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

⁶ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

⁷ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

⁸ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536
101943 7590 09/26/2023 The Johns Hopkins University		EXAMINER		
c/o Casimir Jones			PERREIRA, M	ELISSA JEAN
Suite 310	vay		ART UNIT	PAPER NUMBER
Middleton, WI	53562		1618	
			NOTIFICATION DATE	DELIVERY MODE
			09/26/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com jwchilders@casimirjones.com

	Application No. 18/354.282	Applicant(s	3)		
Office Action Summary	Examiner	Art Unit	AIA (FITF) Status		
	MELISSA J PERREIRA	1618	Yes		
The MAILING DATE of this communication app Period for Beply	ears on the cover sheet with the d	corresponder	nce address		
A SHORTENED STATUTORY PERIOD FOR REPL'	Y IS SET TO EXPIRE <u>3</u> MONT⊦	IS FROM TH	IE MAILING		
 DATE OF THIS CONVINUNICATION. Extensions of time may be available under the provisions of 37 CFR 1.1 date of this communication. If NO period for reply is specified above, the maximum statutory period v Failure to reply within the set or extended period for reply will, by statute Any reply received by the Office later than three months after the mailing 	36(a). In no event, however, may a reply be tir vill apply and will expire SIX (6) MONTHS from , cause the application to become ABANDON date of this communication. even if timely file	nely filed after SIX n the mailing date ED (35 U.S.C. § 1: d. may reduce an	 (6) MONTHS from the mailing of this communication. 33). v earned patent term 		
adjustment. See 37 CFR 1.704(b).			, , , , , , , , , , , , , , , , , , ,		
1) Responsive to communication(s) filed on 7/2	4/23.				
A declaration(s)/affidavit(s) under 37 CFR	I.130(b) was/were filed on				
2a) This action is FINAL . 2b)	This action is non-final.				
3) An election was made by the applicant in res	ponse to a restriction requirem	ent set forth	during the interview		
on; the restriction requirement and ele	ction have been incorporated in	nto this actic	on.		
4) Since this application is in condition for allow closed in accordance with the practice under	rance except for formal matters <i>Ex parte Quayle</i> , 1935 C.D. 1	, prosecutio 1, 453 O.G.	n as to the merits is 213.		
Disposition of Claims*					
5) 🗹 Claim(s) 29 is/are pending in the applic	ation.				
5a) Of the above claim(s) is/are withdr	awn from consideration.				
6) 🔲 Claim(s) is/are allowed.					
7) 🗹 Claim(s) <u>29</u> is/are rejected.					
8) 🔲 Claim(s) is/are objected to.					
9) Claim(s) are subject to restriction a	nd/or election requirement				
* If any claims have been determined <u>allowable</u> , you may be el	igible to benefit from the Patent Pro	secution Hig	hway program at a		
participating intellectual property office for the corresponding at	oplication. For more information, ple	ase see			
nttp://www.uspto.gov/patents/init_events/ppn/index.jsp or send	an inquiry to <u>PPHTeedback@usptc</u>	<u>o.gov.</u>			
Application Papers					
10) The specification is objected to by the Exami	ner.	–			
11) I he drawing(s) filed on $\frac{7/18/23}{10}$ is/are: a)	accepted or b) v objected to	by the Exan	niner.		
Applicant may not request that any objection to the d	rawing(s) be held in abeyance. See a name of the second seco	37 CFR 1.85(a	l). 17 CER 1 121(d)		
heplacement drawing sheet(s) including the correction			or of fr 1.121(d).		
12) Acknowledgment is made of a claim for forei	gn priority under 35 U.S.C. § 1	19(a)-(d) or	(f).		
a) All b) Some** c) None of t	'he'				
1. Certified copies of the priority docur	nents have been received.				
2. Certified copies of the priority docur	nents have been received in A	polication No	0		
3. Copies of the certified copies of the priority documents have been received in this National Stage					
application from the International Bureau (PCT Rule 17.2(a)).					
²² See the attached detailed Office action for a list of the certified copies not received.					
Attachment(s)					
1) 🖌 Notice of References Cited (PTO-892)	3) 🗌 Interview Summar	y (PTO-413)			
 Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/S Paper No(s)/Mail Date 	B/08b) Paper No(s)/Mail I 4) Other:	Date			
U.S. Patent and Trademark Office PTOL-326 (Rev. 11-13) Office A	ction Summary	Part of Paper No./N	Mail Date 20230920		

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Claims Status

Claim 29 is pending in the application.

Drawings

Color photographs and color drawings are not accepted in utility applications unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), one set of color drawings or color photographs, as appropriate, if submitted via EFS-Web or three sets of color drawings or color photographs, as appropriate, if not submitted via EFS-Web, and, unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Claim Rejections - 35 USC § 102

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory

basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of

rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same

under either status.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis

for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

Claim(s) 29 is/are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Dvořáková et al. (J.

Med. Chem. 2017, 60, 8385-8393).

Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) teaches of the anti-FAP iBody FAP



inhibitors comprising

(Scheme 1) bound to an ATTO488

dye via a HMPA copolymer (Figure 2).

The compounds 1-4 anticipate the targeting moiety for FAP- α , A, of the instant claims.

moiety bound to HMPA anticipates the linker, L, of the instant claims.

The ATTO488 dye anticipates the optical functional group, B, of the instant claims.

The anti-FAP iBody is for imaging of FAP-expressing cells (p8387, left column, first full paragraph;

p8387, Use of Anti-FAP iBody 1 for detection and visualization of FAP; p8387, Application of Anti-FAP

iBody 1 for imaging of FAP-expressing cells).

Claim Rejections - 35 USC § 103

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102

and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory

basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of

rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same

under either status.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections

set forth in this Office action:

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim(s) 29 is/are rejected under 35 U.S.C. 103 as being unpatentable over Jansen et al.

(US2014/0357650A1) in view of Zimmerman et al. (US2010/0098633A1) and Jensen et al. (ACS Med.

Chem. Lett. 2013, 14, 491-496).

Jansen et al. (US2014/0357650A1) discloses the FAP inhibitors



wherein R1 and R2

are H, -OH, halogen, etc. and encompass the corresponding R_{1x} and R_{2x} are H, -OH, halogen, etc. of the instant claims.

Page 4

The R_3 is H, -CN, -B(OH)₂, etc. of the disclosure encompasses the corresponding R_{3x} is H, -CN, -

B(OH)₂, etc. of the instant claims.

The R_4 is H of the disclosure encompasses the corresponding R_{4x} is H of the instant claims.



heterocycle of the instant claims.

The R₅-R₇ are H, -OH, oxo, -halo, C₁₋₆alkyl, -O-C₁₋₆alkyl optionally substituted with 1-3 substituents selected from -halo, etc. of the disclosure encompasses the corresponding R_{5x}-R_{7x} are H, -OH, oxo, halogen, C₁₋₆alkyl, -O-C₁₋₆alkyl, etc. of the instant claims. (p4-6, [0050-0089]; p10, [0113-0122]; p13-16, [0176-0215])

The inhibitors may comprise stereoisomers, tautomers, racemates, salts, hydrates or solvates thereof (p3, [0024]; p10, [0113]) which encompasses the stereoisomers, tautomers, racemates, salts, hydrates or solvates thereof of the instant claims.

Jansen et al. (US2014/0357650A1) does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

Zimmerman et al. (US2010/0098633A1) discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease comprising

Metal-Chelate

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wherein U is $-B(OH)_2$, -CN, etc.; G is H, alkyl, etc.; V is a bond, etc.; the metal is a metallic moiety include a radionuclide for PET, SPECT; chelate is a chelating moiety that coordinates with the radionuclide; Y is $-CH_2$ -, etc.; and R₁-R₅ may comprise radiohalogen, etc. (p1-2, [0008-0028]; p3, [0048-0049]; p6, [0087-0099]; p9, [0111-0117]; p13,).

Jensen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) discloses FAP inhibitors of the structure



Table 3).

The quinoline containing compounds have 60 times more FAP-affinity than the initial N-(1-



naphthoyl) based FAP inhibitors

(p492, right column, second full paragraph).

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the FAP inhibitors of Jansen et al. (US2014/0357650A1) with a radiohalogen via a linker, such as a C_{1-6} alkyl, -O- C_{1-6} alkyl as Jansen et al. (US2014/0357650A1) teaches that the C_{1-6} alkyl, -O- C_{1-6} alkyl may be halogenated and Zimmerman et al. teaches of radiohalogenation of FAP inhibitors for the advantage of diagnostic imaging and therapeutic treatment of diseases.

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of Jansen et al. (US2014/0357650A1) with a radiohalogen via a linker, such as a C₁₋₆alkyl, -O-C₁₋₆alkyl as Jensen et al. (*ACS Med. Chem. Lett.* **2013**, *14*, 491-496) teaches that the quinoline containing FAP inhibitors have 60

times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

Therefore, it would have been predictable to one of ordinary skill in the art to utilize a radiohalogenated heteroaromatic FAP inhibitor for imaging FAP with an expectation of success as the quinoline derivative provides 60 times more FAP-affinity than the naphthoyl derivative.

Double Patenting

Claim 29 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1,2,13,15,16 and 21-25 of copending Application No. 16/762,873 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because the compound of Formula (I) B-L-A of copending Application No. 16/762,873 encompasses the compound of Formula (I) B-L-A of the instant claims. The targeting moiety for FAP- α , A, of copending Application No. 16/762,873 is analogous to the targeting moiety for FAP- α , A, of the instant claims. The linker, L, of copending Application No. 16/762,873 is analogous to the linker, L, of the instant claims. The optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy, B, of copending Application No. 16/762,873 is analogous to the optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy, B, of the instant claims.

The compound of Formula (I) of copending Application No. 16/762,873 and the compound of Formula (I) of the instant claims, have the same properties and are capable of the same functions, such as being used for the method of inhibiting fibroblast-activation protein- α and the method for treating a fibroblast-activation protein- α disease or disorder.

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim

patentable and does not render the old composition patentably new to the discoverer. In re Best, 562

F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Relevant Prior Art

Tahtis et al. (Mol. Cancer Therap. 2003, 2, 729-737) discloses iodine-131-labeled humanized anti-FAP monoclonal antibody (BIBH-7).

Terry et al. (J. Nucl. Med. 2016, 57, 467-472) discloses ¹¹¹In-28H1 (anti-FAP).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA JEAN PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached M9-3, T9-3, W9-3, Th9-2, F9-2.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit

https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and

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assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or

571-272-1000.

/MELISSA J PERREIRA/ Examiner, Art Unit 1618



ELECTRONIC PAYMENT RECEIPT

	APPLICATION # 18/354,282	RECEIPT DATE / TIME 10/30/2023 10:53:51 AM ET		attorney docket # J HU-36631.303			
	Title of Invention IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)						
Application Information							
	APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-			
	CONFIRMATION #	7536	FILED BY	Van Nguyen			
	PATENT CENTER #	63107112	AUTHORIZED BY	J effrey Childers			
	CUSTOMER #	101943	FILING DATE	07/18/2023			
	CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang			
	Payment Information						
	PAYMENT METHOD CARD / 0638	PAYMENT TRANSACTION ID E20230TA54136455	PAYMEN Van Ngu	T AUTHORIZED BY yen			

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
			TOTAL AMOUNT:	\$104.00

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 10/30/2023 10:53:51 AM	ЕТ	attorney docket # J HU-36631.303		
Title of Invention					
IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)					
Application Infor	mation				
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-		
CONFIRMATION #	7536	FILED BY	Van Nguyen		
PATENT CENTER #	63107112	FILING DATE	07/18/2023		
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang		
CORRESPONDENCE ADDRESS		AUTHORIZED BY	J effrey Childers		

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-10-30 - Supp IDS.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	33 KB

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Azhdarinia et.pdf 8 Non Patent Literature 770 K	Azhdarinia et.pdf	8	Non Patent Literature	770 KB
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Digest

DOCUMENT

MESSAGE DIGEST(SHA-512)

2023-10-30 - Supp IDS.pdf	B954EE41A724E80D01515F926EB742F932937B05159CCC85A2 B3F397DC116FB6E53DB13026C69212CCCAEDC7FBD8CAD05 3AAC6C631B88AA045426ACDDA862DCD
Azhdarinia et.pdf	8B7C1ADD1C50CB3D987C4734551ABC0BA7E98B1323C365DE 3EE3666F6597E2545B89A712F029C6D0B76FC38D320911D3AF

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New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

				Complete if Known		
INFORMATION DISCLOSURE				Application Number	18/354,282	
				Filing Date	18-Jul-2023	
STATEMENT BY APPLICANT (Use as many sheets as necessary)			NT	First Named Inventor	Yang	
				Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet 1 of 3		Attorney Docket Number	JHU-36631.303			

U.S. PATENTS							
Examiner Initials⁺	Cite No.1	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear		

U.S. PUBLISHED PATENT APPLICATIONS								
Examiner Initials*	Cite No. ³	Document Number Number-Kind Code ⁴ <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD		Name of Patentee or Applicant of Cited Document		Pages, Columr Where Relevant Pass Relevar Figures Ap	ns, Lines, e sages or nt opear

	NONPATENT LITERATURE DOCUMENTS						
Examiner Initials [*]	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation 6				
	1.	AZHDARINIA et al., "Characterization of chemical, radiochemical and optical properties of a dual-labeled MMP-9 targeting peptide". Bioorganic & Medicinal Chemistry, Vol. 19, Issue 12, May 6, 2011, 3769-3776.					

	Examiner Signature		Date Considered	
Ē	EXAMINER:	Initial if reference considered, whether or not citation is in conformanc	e with MPEP 60	9. Draw line through

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Complete if Known		
				Application Number	18/354,282	
INFORMATION DISCLOSURE				Filing Date	18-Jul-2023	
STA	STATEMENT BY APPLICANT			First Named Inventor	Yang	
(Use as many sheets as necessary)				Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet 2 of 3		Attorney Docket Number	JHU-36631.303			

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.



Х

A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on ______. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-10-30
Name/Print	Jeffrey W. Childers	Registration Number	58,126
PTO Notes regarding this form:

¹ Applicant's unique citation designation number (optional).
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/354,282	07/18/2023	Xing Yang	JHU-36631.303
			CONFIRMATION NO. 7536
101943		PUBLICA	TION NOTICE
The Johns Hopkins Unive c/o Casimir Jones 2275 Deming Way Suite 310 Middleton, WI 53562	rsity		OC000000064632153*

Date Mailed: 11/16/2023

Title:IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Publication No.US-2023-0364274-A1 Publication Date:11/16/2023

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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page 1 of 1

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

<u>Status</u>

Claim 29 is pending in the Application and stands rejected. New claims 30 and 31 have been added. No new matter has been added. Upon entry of this Amendment, claims 29-31 will be pending in the Application.

Applicant-Initiated Interview Summary

Applicant appreciates the consideration of the Examiner during the telephonic interview of December 11, 2023. Participating in the interview were Examiner Perreira, Jeffrey W. Childers, Dr. Martin Pomper, Sangeeta Ray, Andrew G. Horti, Qi (Chee) Zhuo, and Don Ho. The rejection of claim 29 under 35 U.S.C. § 102(a)(1) and 35 U.S.C. § 103 was discussed. No agreement was reached.

<u>Drawings</u>

The Office Action notes that color photographs and color drawings are not accepted in utility applications unless a petition filed under 37 CFR 1.84(a)(2) is granted. Applicant submits herewith a Petition under 37 CFR 1.84(a)(2) and accompanying fee. Applicant respectfully requests that the color drawings be accepted at this time.

Claim Rejections - 35 USC § 102

Claim 29 is rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter "Dvořáková").

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

and may offer a shorter path to regulatory approval. Support for "low molecular weight" can be found at least on page 1, lines 28-34, page 2, lines 1-7, and page 8, lines 26-29, page 9, lines 1-2 of the instant specification:

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

page 8, lines 26-29, page 9, lines 1-2.

Because FAP- α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP- α .

page 1, lines 28-34, page 2, lines 1-7.

Further, the instant specification on page 45, lines 12-14, defines a "polymer" as a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer, which distinguishes "low molecular weight compounds" from "polymers."

In 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 **HMPA copolymer**. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol. *See* Dvořáková, page 8387, left column, first full paragraph. The high molecular weight of compound 1 of Dvořáková compares in sharp contrast with the low molecular weight of the compounds of the instant application. In particular, the molecular weight of representative compounds of the instant application, i.e., XY-FAP-02, is about 840 g/mole and XY-FAP-01 is about 1367 g/mole; further LMW compounds of the current claims with molecular weights are presented in the table on pages 14-15 herein below. Thus, one of ordinary skill in the art upon reading and understanding of the instant specification in view of Dvořáková would appreciate that the presently claimed compounds are "low molecular weight" compounds.

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).")

New claim 30 further defines B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy. Support for this amendment can be found in claim 29 as originally filed. Applicant notes that Dvořáková only discloses optical imaging agents.

New claim 31 includes the transitional phrase "consisting essentially of." As provided in MPEP § 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Applicant notes that in the present claims, the compound of formula (I) is limited then to components B-L-A, and would not include the HMPA copolymer carrier disclosed and which forms the basis of the iBodies disclosed in Dvořáková.

Because every pending claim (claims 29-31) of the instant application requires the claimed compound to be "low molecular weight", Dvořáková cannot anticipate the pending claims because Dvořáková does not disclose a compound having low molecular weight.

Claim Rejections - 35 USC § 103

Claim 29 is rejected under 35 U.S.C. § 103 as being unpatentable over Jansen et al. (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al. (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) (hereinafter "Jansen II").

The Office Action asserts that Jansen I discloses FAP inhibitors that encompass aspects of the instant claims. The Office Action acknowledges, however, that Jansen I does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

The Office Action asserts that Zimmerman discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease, which, in some embodiments, include a metal chelating moiety that includes a radionuclide or, in other embodiments, a radiohalogen.

The Office Action asserts that Jensen II discloses quinoline-containing FAP inhibitors that are 60 times more FAP-affinity than the naphthoyl derivative of Jansen I.

The Office Action then concludes that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6} alkyl, -O- C_{1-6} alkyl as Jansen I teaches that the C_{1-6} alkyl, -O- C_{1-6} alkyl may be halogenated and Zimmerman teaches radiohalogenation of FAP inhibitors for the advantage of diagnostic imaging and therapeutic treatment of diseases.

The Office Action further concludes that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6} alkyl, - O- C_{1-6} alkyl as Jensen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

The Office Action finally concludes that it would have been predictable to one of ordinary skill in the art to utilize a radiohalogenated heteroaromatic FAP inhibitor for imaging FAP with an expectation of success as the quinoline derivative provides 60 times more FAPaffinity than the naphthoyl derivative.

Applicant respectfully disagrees for the reasons set forth below.

i. <u>There was no motivation for one of ordinary skill in the art to select and</u> <u>modify any compounds of Jansen I and Jansen II to arrive at the claimed</u> <u>compounds</u>

As provided in MPEP § 2143(I)(E), in cases involving new chemical compounds, it is necessary to identify some reason that would have led a chemist to select a lead compound and subsequently modify the lead compound in a particular manner to establish prima facie obviousness of new claimed compounds. Takeda v. Alphapharm., 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Office Action argues that the compounds of Jansen I may be modified with a radiohalogen via a linker. The Office Action appears to take the position that the C_{1-6} alkyl or -O- C_{1-6} alkyl that may be attached to the heterocyclic group of the FAP moiety in Jansen I may serve as a "linker" within the meaning of the pending claims. In particular, the Office Action points out that the C₁₋₆alkyl, -O-C₁₋₆alkyl may be halogenated. An implicit but necessary position of the Office Action is that the C_{1-6} alkyl or the -O- C_{1-6} alkyl group may be interpreted as a "linker" only when it is selected as a substituent group in preference to the numerous other equally viable alternatives, and further, only when it is halogenated, and then further only when the halogen is a radiohalogen. Applicant respectfully points out that C₁₋₆alkyl and the -O-C₁₋₆alkyl are among a wide variety of alternative functional groups that may optionally be attached to the heterocyclic group of a generic structure of the FAP inhibitor compounds disclosed in Jansen I. See Pomper Affidavit, Para. 23. Furthermore, among 43 representative compounds disclosed in Jansen I and 39 representative compounds in Jansen II, only a single compound with a halogenated C_{1-6} alkyl or -O-C₁₋₆alkyl is disclosed. See Pomper Affidavit, Para. 24; Jansen I, Example 11, Table 4; Jansen II, Compound No. 28, Table 3. Thus, the prior art provides no motivation or indication to select C_{1-6} alkyl or the -O- C_{1-6} alkyl from a large group of functional groups as a substituent group on the FAP inhibitors disclosed in Jansen I or Jansen II; even if C₁₋₆alkyl or the -O-C₁₋₆alkyl is selected as a substituent group, Jansen I or Jansen II provides no motivation to further substitute the C₁₋₆alkyl or the -O-C₁₋₆alkyl group with a halogen. In fact, in most of the halogenated compounds disclosed in Jansen I and Jansen II, the halogen is directly attached to the heterocyclic group, instead of via a C₁₋₆alkyl or the -O-C₁₋₆alkyl group.

Further, one of ordinary skill in the art also would not select the single FAP inhibitor substituted with the halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl disclosed in Jansen I and Jansen II as a starting point or a lead compound to modify, because this compound has mediocre bioactivities compared with the other compounds disclosed in the prior art. In particular, many other FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II, which is substituted with a trifluoromethoxy group. *See* Pomper Affidavit, Para. 26. For example, compound Example 11 of Jansen I with the trifluoromethoxy substitution has a IC₅₀ of 0.012 µm and a selectivity index of 59, which do not compare favorably to a number of compounds including compound Example 15, which has a IC₅₀ of 0.0062 µm and a selectivity index of 193. *Id.*

Even assuming for arguments sake a skilled person made the non-obvious steps of selecting a compound with a halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl group of Jansen I or Jansen II for modification, there is still no explicit or implicit motivation in the cited prior art to substitute the alkyl group with a radiohalogenated group to render the C_{1-6} alkyl or -O- C_{1-6} alkyl as a "linker" within the meaning of the pending claims. In fact, the vast majority of the representative compounds disclosed in Jansen I and Jansen II do not have a halogenated C_{1-6} alkyl or the -O- C_{1-6} alkyl. To successfully argue that a new compound is obvious, the prior art must show "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda*, 492 F.3d at 1356. The cited prior art clearly does not suggest anything that may motivate one of ordinary skill in the art to make the specific modification of substituting the C_{1-6} alkyl or -O- C_{1-6} alkyl with a radiohalogen.

The Office Action appears to correlate the substitution of a C_{1-6} alkyl or -O- C_{1-6} alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6} alkyl, -O- C_{1-6} alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

Office Action dated September 26, 2023, pages 6-7. Applicant respectfully points out that Jansen II merely discloses that quinoline-containing FAP inhibitors have a 60 times higher FAP-

affinity than the N-(1-naphthoyl) FAP inhibitors. Pomper Affidavit, Para. 27. Jansen II does not suggest that substitution of the quinoline ring of the quinoline-containing FAP inhibitors would, let alone could, improve the FAP affinity or selectivity of the FAP inhibitors. *Id.* On the contrary, Jansen II observed that substitution of the quinoline ring has little or even negative effects on the potency of the quinoline-containing FAP inhibitors:

Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19–24, having a clearly negative effect on this parameter.

Janssen II, page 493, left column. Pomper Affidavit, Para. 28. In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e. Example 11 of Jansen I or Compound 28 of Jansen II, has both an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without the trifluoromethoxy substitution. ¹ *Id.* Therefore, there is no motivation to substitute the quinoline moiety of the FAP inhibitor, not to mention to halogenate the quinoline moiety via a trifluoromethoxy substitution. Applicant would like to emphasize again that without a radiohalogenated trifluoromethoxy substitution on the FAP inhibitor of Jansen I or Jansen II, any FAP inhibitors modified based Jansen I or Jansen II cannot be interpreted as containing a "linker" within the meaning of the pending claims.

Accordingly, in view of the totality of the disclosure in Jansen I and Jansen II, there is no explicit or implicit teachings, suggestion, or motivation for one of ordinary skill in the art to select and modify any compounds in Jansen I and Jansen II to arrive at the claimed compounds. There is no prima facie obviousness because there is no reason that would have led a chemist to select and modify a known compound in a particular manner to establish prima facie obviousness of the compounds of the pending claims. *See* Takeda, 492 F.3d at 1357.

ii. <u>There was no reasonable expectation of success in modifying any compounds</u> <u>in Jansen I or Jansen II to arrive at the compounds of the pending claims</u>

The Office Action also fails to demonstrate a reasonable expectation of success in modifying and making the structural changes to the compounds of Jansen I and Jansen II to

¹ See Jansen I, Table 4. IC₅₀ for FAP (an indicator of the FAP affinity) is 0.012 μ M for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μ M for the unsubstituted FAP inhibitor; selectivity index is 59 versus 83.

arrive at the compounds of the pending claims. The examiner is required to show a reasonable expectation of success when trying to establish prima facie obviousness by modifying or combing the prior art to achieve the claimed invention. MPEP § 2143.02; see also Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007) ("[T]he challenger of the patent [must] show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so."). For a medical imaging agent used to diagnose disease, it is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with the medical condition. See the Pomper Affidavit, Para. 31. The high specificity allows the imaging agent to selectively bind to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical conditions from interfering with the binding between the imaging agent with the target protein. Id. The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. Id. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

The Office Action takes the position that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen as Zimmerman teaches radiohalogenation of FAP inhibitors for diagnostic imaging and therapeutic treatment of diseases. However, at the time the instant application was filed, one of ordinary skill in the art recognized the unpredictability associated with the development of medical imaging agents, including the optimization of the specificity. Accordingly, there was no reasonable expectation of success for one of ordinary skill in the art to modify the compounds to arrive at the compounds of pending claims, even if the compound substituted with halogenated C_{1-6} alkyl or $-O-C_{1-6}$ alkyl were selected as the lead compound, which one of ordinary skill in the art had no motivation to do in the first place as discussed.

In fact, one of ordinary skill in the art knew that the FAP imaging agents of Zimmerman most likely would not function well because of the poor specificity associated with the compounds of Zimmerman. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for

atherosclerotic plaque, and was determined as not suitable for the application. See Meletta etc., Molecules. 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta"); Pomper Affidavit, Paras. 33-35. As provided on page 2089 of Meletta, although pronounced binding of [¹²⁵I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Pomper Affidavit, Para. 34. Based on these data, Maletta could not conclude on the selectivity of [¹²⁵I]MIP-1232 for FAP. Accordingly, because of the low specificity MIP-1232 displayed in the investigation, Meletta concluded that MIP-1232 was not suitable for the medical imaging for the medical condition. See Procter & Gamble v. Teva, 566 F.3d 989, 997 (Fed. Cir. 2009) (Upholding decision of the District Court that there was no reasonable expectation of success in modifying the prior art compound to produce a "improved, safe, and effective" drug because researchers had no basis to expect it to be as good as or better than the prior art compound). The lack of reasonable expectation of success is especially telling in view of the failure by others in the art to use the compounds of Zimmerman cited by the Office Action. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir.2003) ("While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure."); In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("Failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.")

Applicant respectfully submits, based on the unpredictability in the art and failure and uncertainty observed by Maletta associated with the prior art compound, that one of ordinary skill in the art would not have a reasonable expectation of success in arriving at a selective FAP imaging agent by merely modifying the FAP inhibitors of Jansen I and/or Jansen II with the radiohalogen of Zimmerman.

iii. <u>There are unexpected results associated with the claimed compounds to</u> rebut any showing of prima facie obviousness

The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Pomper Affidavit, Paras. 38-42. As provided in the Pomper Affidavit, specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to

selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [¹²⁵I]MIP-1232 for FAP (above section ii), the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents is shown in the current application US 2020/0330624 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C). Pomper Affidavit, Para. 40.

Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 41. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4. Representative compounds of the pending claims are provided in the table below with PREP/FAP values for comparison. Surprisingly, the specificity of compounds <u>falling under the scope</u> of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. Pomper Affidavit, Para. 42. In particular, as shown in the Table below, MIP-1232, which is a representative compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims. *Id.*, Para. 42. It is also notable that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. *Id.* Such differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected.

Reference Compound	PREP/FAP	Molecular structure of Representative Compounds	PREP/FAP
Molecular Structure	Ratio	of Formula (I)	Ratio
¹²⁵ HO-B OH	32 *	F molecular weight: 370.38 g/mol	4,111





* Data from R. Meletta et al., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference.

Accordingly, Applicant respectfully submits that claim 29 is not obvious over Jansen I in view of Zimmerman and Jansen II. Applicant respectfully requests that the rejection of claim 29 under 35 U.S.C. § 103 as being unpatentable over Jansen I in view of Zimmerman and Jansen II be withdrawn at this time.

Double Patenting

Claim 29 is provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 2, 13, 15, 16 and 21-25 of copending Application No. 16/762,873.

Applicant notes that it appears that the Office Action intended to cite Application No. 16/758,182.

Without acquiescing to the assertions made in the Office Action, Applicant has submitted herewith a Terminal Disclaimer over Application No. 16/758,182.

Applicant respectfully requests that the rejection of claim 29 under nonstatutory double patenting over Application No. 16/758,182 be withdrawn at this time.

CONCLUSION

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney at 919-724-8699 or 608-662-1277. Early passage of the subject application to issue is earnestly solicited.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment associated with this filing to Deposit Account Number 50-4302. If an extension of time for this paper is required, petition for extension is herewith made.

Respectfully Submitted, CASIMIR JONES, S.C.

Date: December 13, 2023

/JEFFREY W. CHILDERS/

Jeffrey W. Childers, Ph.D. Registration No. 58126 Customer No. 101943

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.

Serial No.: 18/354,282

Filed: July 18, 2023

Confirmation No.: 7536

Art Unit: 1618

Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

PETITION TO ACCEPT COLOR DRAWINGS UNDER 37 C.F.R. § 1.84(a)(2)

This Petition is submitted to request acceptance of the color drawings previously filed in the above-referenced Application. Applicants submit that color drawings are the only practical medium by which to disclose the subject matter sought to be patented. The present application is directed to imaging and radiotherapeutics agents targeting fibroblast-activation protein- α . Specifically, Figures 6-8, show color images of tumor bearing mice using the exemplary imaging and radiotherapeutic agents. The figures illustrate the uptake of agents after set amounts of time. Thus, Applicant believes that color drawings are necessary as the only practicable medium by which to disclose the subject matter sought to be patented.

As the color drawings were filed electronically via EFS-Web, only one set of color drawings were submitted and were categorized as "Drawings-other than black and white line drawings." Please note that the specification incorporates the language regarding color drawings as required by 37 C.F.R. § 1.84(a)(2)(iii). The small entity fee required under 37 C.F.R. § 1.17(h) in the amount of \$56 is submitted herewith. No further fees are believed to be due. Please charge any additional fees or credit any overpayment of fees in connection with this Petition to Deposit Account No. 50-4302.

Respectfully,

Dated: December 13, 2023

/Jeffrey W. Childers/

Jeffrey W. Childers Registration No. 58126 Casimir Jones, S.C. 2275 Deming Way Suite 310 Middleton, WI 53562 608 662 1277



ELECTRONIC PAYMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 12/13/2023 03:39:21 PM 2	ATTORNEY DOCKET # JHU-36631.303						
Title of Invention								
IMAGING AND RAU PROTEIN-ALPHA (I	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)							
Application Infor	rmation							
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	~					
CONFIRMATION #	7536	FILED BY	Van Nguyen					
PATENT CENTER #	63593228	AUTHORIZED BY	Jeffrey Childers					
CUSTOMER #	101943	FILING DATE	07/18/2023					
CORRESPONDENCE ADDRESS		FIRST NAMED INVENTOR	Xing Yang					

Payment Information

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PAYMENT METHODPAYMENT TRANSACTIONCARD / 0636E2023BCF40079520		NID	RIZED BY	
FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
2464	PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III)	56.00	1	56.00
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	Ŷ	170.00
			TOTAL AMOUNT:	\$330.00

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 12/13/2023 03:39:21 PM 2	ZET	ATTORNEY DOCKET # JHU-36631.303						
Title of Invention									
IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)									
Application Infor	mation								
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-						
CONFIRMATION #	7536	FILED BY	Van Nguyen						
PATENT CENTER #	63593228	FILING DATE	07/18/2023						
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang						
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers						

Documents

TOTAL DOCUMENTS: 12

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2023-12-13- 36631.303 Supp IDS.pdf	4	Information Disclosure Statement (IDS) Form (SB08)	34 KB
Warning: This is not a USPTO supplie automatically loaded to other USPTO	d IDS fillable forn systems.	n. Data in the form cannot be	

Small molecules Metabolomics.pdf	5	Non Patent Literature	209 KB
Meletta artic.pdf	20	Non Patent Literature	1061 KB
Beebe 2014.pdf	8	Non Patent Literature	1071 KB

Page 2 of 4

Ferreira2014.pdf		10	Non Patent Literature	2597 KB
Llewellyn 201.pdf		7	Non Patent Literature	3383 KB
2023-12-13 - JHU-36631.303 TD.pdf		2	Terminal Disclaimer Filed	213 KB
2023-12-13 - 36631_303 RNFOApdt.pdf		17	~	442 KB
2023-12-13 - 36631_303 RNFOApdf-Apdf	(1-1)	Ţ	Amendment/Request for Reconsideration-After Non- Final Rejection	35 KB
2023-12-13 - 36631_303 RNFOApdf-CLM.pdf	(2-4)	3	Claims	55 KB
2023-12-13 - 36631_303 RNFOApdf-REM.pdf	(5-17)	13	Applicant Arguments/Remarks Made in an Amendment	396 KB
2023-12-13 - 36631_303 Declaration 1.132.pdf		12	Affidavit-traversing rejections or objections rule 132	615 KB
2023-12-13 -36631.303 Petition 1.84.pdf		2	A petition from Applicant to accept Color Drawings or Color Photographs	28 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-12-13- 36631.303 Supp IDS.pdf	7B4C838340F91E9A5BA30832A04FD5B424BD816CECACCCCA E4373F87A1EFD2EB69F056DCB1FD162CA8F732B814CE95C0 E826739563DE32C9738849C371CF1E16
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2023-12-13 - 36631_303 RNFOApdf-REM.pdf	34D3B3FBE8C6834DB88450784B545EBCA964B9290FF65C8A9 69B4BC658D620A64C54B2EBC9F8D23C102381300A286AE779 0867BC1AEAB86B2FD19BBFA9F9D9C3
2023-12-13 - 36631_303 Declaration 1.132.pdf	F3993FEF9318D0397B2409722BCDC279406FA612A0A350E24C 715DADAAE459ADC65978ABEAA7A54F502AFB9B1109522113E C3189F5D4D388A94A0430CDD37D80

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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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				Complete if Known		
INFORMATION DISCLOSURE				Application Number	18/354,282	
				Filing Date	18-Jul-2023	
STATEMENT BY APPLICANT			NT	First Named Inventor	Yang	
(Use as many sheets as necessary)				Art Unit	1618	
		Examiner Name	MELISSA JEAN PERREIRA			
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303	

U.S. PATENTS							
Examine r Initials [*]	Cite No.	Document Number Number-Kind Code ² <i>(if known)</i>	lssue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear		

	U.S. PUBLISHED PATENT APPLICATIONS								
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		NONPATENT LITERATURE DOCUMENTS	
Examine r Initials [*]	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translatio n ⁶
		BEEBE et al., "Understanding the Apothecaries Within: The Necessity of a Systematic Approach for Defining the Chemical Output of the Human Microbiome". Clin Transl Sci. 2014 Feb; 7(1): 74–81.	
		FERREIRA et al., "Monitoring Alcoholic Fermentation: An Untargeted Approach". Journal of Agricultural and Food Chemistry, 2014, 62, 6784–6793.	
		LLEWELLYN et al., "Using community metabolomics as a new approach to discriminate marine microbial particulate organic matter in the western English Channel". Progress in Oceanography, Volume 137, Part B, September 2015, p. 421-433.	
		MELETTA et al., "Evaluation of the radiolabeled boronic acid-based FAP inhibitor MIP-1232 for atherosclerotic plaque imaging". Molecules, 2015 Jan 27;20(2):2081-99.	
		METABOLOMICS – EMBL-EBI, https://www.ebi.ac.uk/training/online/courses/metabolomics- introduction/what-is/small-molecules/, retrieved on 2023-12-12. 5 pages.	

	Examiner Signature		Date Considered	
E	EXAMINER:	Initial if reference considered, whether or not citation is in conformanc	e with MPEP 60	9. Draw line through

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Complete if Known		
				Application Number	18/354,282	
INF(ORMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang	
	(Use as many sheets	as necessary)		Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet	2	of	3	Attorney Docket Number	JHU-36631.303	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):



That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

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See attached certification statement.



The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

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A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

				Comp	olete if Known
				Application Number	18/354,282
INFC	RMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023
STATEMENT BY APPLICANT				First Named Inventor	Yang
	(Use as many sheets	as necessary)		Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet	3	of	3	Attorney Docket Number	JHU-36631.303

Signature	/Jeffrey W. Childers/	Date (YYYY-MM- DD)	2023-12-13
Name/Print	Jeffrey W. Childers	Registration Number	58,126

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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION Docket Number (Optional) JHU-36631.303 In re Application of YANG, et al. Application of YANG, et al. Application No:: 18/354.282 File: 	TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION In re Application of: YANG, et al. Application No.: 18/354,282 Filed: July 18, 2023 For: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA) The applicant, The Johns Hopkins University, owner of100 percent interest in the disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instat beyond the expiration date of the full statutory term of any patent granted on pending reference Application N filed, April 22, 2020, as the term of any patent granted on said reference application may be shorted filed prior to the grant of any patent on the pending reference application. The applicant hereby agrees that an application shall be enforceable only for and during such period that it and any patent granted on the reference owned. This agreement runs with any patent granted on the instant application and is binding upon the granted in making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the is said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or and patient or the owner that the terminal part of any patent or any patent or as be shortened by any terminal disclaimer filed prior to the grant of any patent or and by the run we have the terminal part of any patent or any patent or and is binding upon the grant of any patent or and is binding upon the grant or any patent or and is binding upon the grant or any patent or and is binding upon the grant or any patent or andisclaimer filed prior to the grant of any patent or a	Docket Number (Optional) JHU-36631.303 The instant application hereby ant application which would exten lumber 16/758,182 need by any terminal disclaimer y patent so granted on the instant application are commonly b, its successors or assigns.
In re Application of: YANG, et al. Application No: 18/354.282 File:: July 18, 2023 For	In re Application of: YANG, et al. Application No.: 18/354,282 Filed: July 18, 2023 For: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING For: FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA) The applicant, The Johns Hopkins University, owner of100percent interest in the disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instation date of the full statutory term of any patent granted on pending reference Application N filed, April 22, 2020, as the term of any patent granted on said reference application may be shorted filed prior to the grant of any patent on the pending reference application. The applicant hereby agrees that an application shall be enforceable only for and during such period that it and any patent granted on the reference owned. This agreement runs with any patent granted on the instant application and is binding upon the granted In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the is said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or any patent or any patent granted on said reference application, "as is said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or	e instant application hereby ant application which would exter lumber 16/758,182 ned by any terminal disclaimer y patent so granted on the instan a application are commonly b, its successors or assigns.
Application No.: 18/354,282 First Fills, 2013 For: MAXING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST.ACTIVATION PROTEIN-ALPHA (FAP-ALPHA) The applicant, The Johns Hopkins University	Application No.: 18/354,282 Filed: July 18, 2023 For: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA) The applicant, The Johns Hopkins University, owner of00 percent interest in the disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instat- beyond the expiration date of the full statutory term of any patent granted on pending reference Application N filed, April 22, 2020, as the term of any patent granted on said reference application may be shorter filed prior to the grant of any patent on the pending reference application. The applicant hereby agrees that an application shall be enforceable only for and during such period that it and any patent granted on the reference owned. This agreement runs with any patent granted on the instant application and is binding upon the granted In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the is said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or patient or in the ownert that the provide the provide reference application, "as it said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or patient or in the ownert that pay end the provide reference application filed prior to the grant of any patent or patient or in the ownert that the pay end patent granted on the instant application filed prior to the grant of any patent or patient or the pay of the pay end patent provide and the particle	e instant application hereby ant application which would exter lumber 16/758,182 ned by any terminal disclaimer y patent so granted on the instan a application are commonly b, its successors or assigns.
File:: July 18, 2023 For: MAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST.ACTIVATION PROTEIN-ALPHA (RAP-ALPHA) The applicant, The Johns Hopkins University	Filed: July 18, 2023 For: FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA) The applicant, The Johns Hopkins University, owner of 100 percent interest in the disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instation the expiration date of the full statutory term of any patent granted on pending reference Application N filed, April 22, 2020, as the term of any patent granted on said reference application may be shorted filed prior to the grant of any patent on the pending reference application. The applicant hereby agrees that an application shall be enforceable only for and during such period that it and any patent granted on the reference owned. This agreement runs with any patent granted on the instant application and is binding upon the granted In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the is said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or any patent or any patent granted on said reference application, "as is said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or any patent or said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or any patent or patient or the grant of any patent or any patent granted on said reference application, "as is applied to the owner their part of up by patent granted on the nordine comic for for the grant of any patent or any	e instant application hereby ant application which would exten lumber <u>16/758,182</u> ned by any terminal disclaimer y patent so granted on the instant a application are commonly , its successors or assigns.
Proc. MACING AND PADIOTHERAPEUTICS AGENTS TARGETING FIERDBLASTACTIVATION PROTEIN-ALPHA (FAP-ALPHA) The applicant, The Johns Hopkins University	For: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA) The applicant, The Johns Hopkins University , owner of 100 percent interest in the disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instat beyond the expiration date of the full statutory term of any patent granted on pending reference Application N filed, <u>April 22, 2020</u> , as the term of any patent granted on said reference application may be shorted filed prior to the grant of any patent on the pending reference application. The applicant hereby agrees that an application shall be enforceable only for and during such period that it and any patent granted on the reference owned. This agreement runs with any patent granted on the instant application and is binding upon the granted In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the is said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or application is to use this to use with any patent granted by any terminal disclaimer filed prior to the grant of any patent or application is to use the to the grant of any patent or any patent or any patent or application is to use the prior to the grant of any patent or any patent or application is to the out the travelow patent granted by any terminal disclaimer filed prior to the grant of any patent or application is to prior to the grant of any patent or any patent or any patent or any patent or application is to prior to the patent or any patent by any terminal disclaimer filed prior to the grant of any patent or application is to prior to the grant of any patent or any patent	e instant application hereby ant application which would exten lumber 16/758,182 aned by any terminal disclaimer y patent so granted on the instant a application are commonly b, its successors or assigns.
The applicant, The Johns Hopkins University, owner of	The applicant, The Johns Hopkins University , owner of 100 percent interest in the disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instate beyond the expiration date of the full statutory term of any patent granted on pending reference Application N filed, April 22, 2020 , as the term of any patent granted on said reference application may be shorted filed prior to the grant of any patent on the pending reference application. The applicant hereby agrees that an application shall be enforceable only for and during such period that it and any patent granted on the reference owned. This agreement runs with any patent granted on the instant application and is binding upon the granted on the i extend to the expiration date of the full statutory term of any patent granted on said reference application, "as is asid reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or any patent granted on the instant application and is binding upon the granted on the i extend to the expiration date of the full statutory term of any patent granted on said reference application, "as is asid reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or any patent or any patent or the granted on the instant application and is binding upon the granted on the issue reference application."	e instant application hereby ant application which would exten lumber 16/758,182 aned by any terminal disclaimer y patent so granted on the instant e application are commonly e, its successors or assigns.
In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted or application," in the event that any such patent granted on the pending reference application expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdicton, is statutority disclaimer file prior to the grant of any patent granted on application expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdicton, is statutority disclaimer file prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant. Check either box 1 or 2 below, if appropriate. The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee. I hereby acknowledge that any willful faise statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both. The undersigned is an attorney or agent of record. Reg. No. <u>58126</u> <u>Juffrey W. Childers/</u> <u>December 13, 2023</u> <u>Juffrey W. Childers/</u> <u>December 13, 2023</u> <u>Signature</u> <u>Coll to fail to a should not be included on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2033.</u> 	In making the above disclaimer, the applicant does not disclaim the terminal part of any patent granted on the i extend to the expiration date of the full statutory term of any patent granted on said reference application, "as i said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent or application of any patent granted on the nonding reference application for any patent granted on the said reference application for any patent or application of the terminal disclaimer filed prior to the grant of any patent or application of the terminal disclaimer filed prior to the grant of any patent or application.	
Check either box 1 or 2 below, if appropriate. 1. The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee. 1. I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both. 2. Image: The undersigned is an attorney or agent of record. Reg. No. 58126	held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or ter CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated j statutory term as shortened by any terminal disclaimer filed prior to its grant.	nstant application that would the term of any patent granted on t the pending reference to pay a maintenance fee, is minally disclaimed under 37 orior to the expiration of its full
1. □ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee. 1. lereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both. 2. ✓ The undersigned is an attorney or agent of record. Reg. No. 58126 December 13, 2023	Check either box 1 or 2 below, if appropriate.	
I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both. 2. The undersigned is an attorney or agent of record. Reg. No. <u>58126</u> <u>/Jeffrey W. Childers/</u> <u>December 13, 2023</u> Signature <u>Date</u> <u>Jeffrey W. Childers</u> <u>Typed or printed name</u> <u>Attorney of Record</u> <u>608.662.1277</u> <u>Title</u> <u>Telephone Number</u> Telephone Number Telephone Number Telephone Number Attorney factor on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.	1. The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to ac	t on behalf of the assignee.
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A Federal agency may not conduct or sponsor, and a person is not required to respond to. nor shall a person be subject to a penalty for failure to comply with an	WARNING: Information on this form may become public. Credit card information e be included on this form. Provide credit card information and authorization on P	should not YTO-2038.
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IN THE CLAIMS:

29. (Presently Amended) A <u>low molecular weight</u> compound of Formula (I): B-L-A (I)

wherein:

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



wherein:

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

 R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

 R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

B is any optical or radiolabeled functional group suitable for optical imaging, positronemission 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.

30. (New) The compound of claim 29, wherein B is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.

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

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



wherein:

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

R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

N \rightarrow

B is any optical or radiolabeled functional group suitable for optical imaging, positronemission 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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.

Confirmation No.: 7536

Serial No.: 18/354,282

Filed: July 18, 2023

Art Unit: 1618

Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Examiner Perreira:

1. I, Martin Pomper, am the Principal Investigator and co-inventor of the subject matter described and claimed in the above-referenced patent application (the "Application"). The research leading to the subject matter of the Application was conducted in my laboratory.

2. I am currently Chair of the Department of Radiology at University of Texas Southwestern Medical Center. Previously, I was Professor of Radiology and Radiological Science, Professor of Oncology and Radiation Oncology and Molecular Radiation Services, Research Chief of Nuclear Medicine, Director of the Division of Nuclear Medicine and Molecular Imaging, Associate Dean of Entrepreneurship and Technology Development, and Director of the Johns Hopkins Center for Translational Molecular Imaging at the Johns Hopkins School of Medicine.

3. I received my B.Sc. degree, Ph.D. degree, and MD degrees all from the University of Illinois at Urbana-Champaign.

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4. I completed my postgraduate medical training at Johns Hopkins that included a medical internship, residencies in diagnostic radiology and nuclear medicine, and a fellowship in neuroradiology, before I joined the Johns Hopkins faculty in 1996.

5. I have authored hundreds scientific articles and am inventor of numerous issued patents or patent applications in the field of medical diagnostic imaging.

6. I have read the non-final Office Action dated September 26, 2023, in the subject Application and the references cited therein.

7. I understand the Office Action rejected claim 29 on numerous grounds, including anticipation under 35 U.S.C. § 102(a) and obviousness under 35 U.S.C. § 103.

8. I understand that the pending claims are directed to a low molecular weight compound of Formula (I):

B-L-A

wherein A is a targeting moiety for FAP- α defined by a specific structure, B is an optical or radiolabeled functional group, and L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

9. The office action asserts that prior claim 29 is anticipated under 35 U.S.C. §
 102(a)(1) by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter "Dvořáková").

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

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

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12. Support for "low molecular weight" can be found at least on page 1, lines 28-34,

page 2, lines 1-7, and page 8, lines 26-29, page 9, lines 1-2 of the instant specification:

[T]he presently disclosed subject matter provides potent and selective low-molecularweight (LMW) ligands of FAP- α , i.e., an FAP- α selective inhibitor, conjugated with a targeting moiety feasible for modification with optical dyes and radiolabeling groups, including metal chelators and metal complexes, which enable *in vivo* optical imaging, nuclear imaging (optical, PET and SPECT), and radiotherapy targeting FAP- α [Page 8, lines 26-29, page 9, lines 1-2].

Because FAP- α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP- α [Page 1, lines 28-34, page 2, lines 1-7].

13. Further, the instant specification on page 45, lines 12-14, defines a "polymer" as a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer, which distinguishes "low molecular weight compounds" from "polymers."

14. In 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 <u>HMPA copolymer</u>. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol. *See* Dvořáková, page 8387, left column, first full paragraph. The high molecular weight of compound 1 of Dvořáková compares in sharp contrast with the low molecular weight of the compounds of the instant application. In particular, the molecular weight of representative compounds of the instant application, i.e., XY-FAP-02, is about 840 g/mole and XY-FAP-01 is about 1367 g/mole.

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15. Further, I have provided additional low molecular weight compounds of the current claims with molecular weights in the below table in paragraph 42.

16. I, upon reading and understanding of the instant specification in view of Dvořáková, would appreciate that the presently claimed compounds are "low molecular weight" compounds.

17. I observe that the term of "low molecular weight" is well accepted in the chemical arts. In particular, when used in the scientific references in the chemical arts, I 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).")

The Office Action asserts that claim 29 is obvious over Jansen et al.
 (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al.
 (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett.
 2013, 14, 491-496) (hereinafter "Jansen II").

19. I understand that the Office Action took the position that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Janssen I with a radiohalogen (taught in Zimmerman) via a linker, such as C_{1-6} alkyl or -O- C_{1-6} alkyl as Jansen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.
Page 5 of 12

20. Based on my review of the Office Action and prior art references cited in the Office Action, I disagree with the obviousness rejections for the following reasons:

21. First, I found that there are no teachings or suggestions in the cited reference to make a compound with a linker having a bi-functionalization which binds to the FAP inhibitor moiety A and the optical or radiolabeled moiety B.

22. The Office Action took the position that the C_{1-6} alkyl or -O- C_{1-6} alkyl group disclosed in Jansen I may serve as the linker when the compounds containing the C_{1-6} alkyl or -O- C_{1-6} alkyl of Jansen I are modified with a radiohalogen.

I observed that C₁₋₆alkyl and the -O-C₁₋₆alkyl are among a variety of functional groups that may be attached to the heterocyclic group of the FAP inhibitor compounds disclosed in Jansen I, including —H, —OH, —oxo, —halo, —C₁₋₆alkyl, —O—C₁₋₆alkyl, —S—C₁₋₆alkyl, —NR₈R₉, —OR₁₂, —Het₂ and —Ar₂, wherein the C₁₋₆alkyl may be optionally substituted with —OH and —halo.

24. Further, I observed that the vast majority of the representative compounds disclosed in either Jansen I or Jansen II do not contain a halogenated C_{1-6} alkyl substitution. Out of 43 representative FAP inhibitors in Jansen I, only one of them is substituted with a halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl. *See* Jansen I, Table 4, Example 11. The same compound is also the only FAP inhibitor substituted with a halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl out of 39 representative FAP inhibitors in Jansen II. *See* Jansen II, Table 3, Compound 28.

25. FAP inhibitors substituted with a halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl clearly do not stand out of the many FAP inhibitors including those unsubstituted or substituted with other functional groups or elements disclosed in Jansen I or Jansen II. There is no suggestion in the cited references as to why a FAP inhibitor substituted with a halogenated C_{1-6} alkyl should be selected for modification with a radiohalogen.

26. I notice that the single FAP inhibitor substituted with the halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl disclosed in Jansen I and Jansen II has worse bioactivities compared with the other compounds disclosed in the prior art. In particular, many FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II which is substituted with a trifluoromethoxy group. See Example 11, Table 4, Jansen I; Compound No. 28, Table 3, Jansen II. For example, compound Example 11 of

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Jansen I with the trifluoromethoxy substitution has a IC_{50} of 0.012 µm and a selectivity index of 59, which do not compare favorably to a number of compounds. For example, compound Example 15 of Jansen I has a IC_{50} of 0.0062 µm and a selectivity index of 193. Accordingly, one of ordinary skill in the art would not select the FAP inhibitor substituted with a trifluoromethoxy group for modification.

27. The Office Action appeared to correlate the substitution of a C_{1-6} alkyl or -O- C_{1-6} alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6} alkyl, -O- C_{1-6} alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy. [Office Action dated September 26, 2023, pages 6-7].

I would point out that Jansen II merely discloses that quinoline containing FAP inhibitors have 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Jansen II does not suggest that substitution of the quinoline ring of the quinoline containing FAP inhibitors will improve the FAP-affinity or selectivity of the FAP inhibitors.

28. On the contrary, Jansen II observed that substitution of the quinoline ring has little or negative effects on the FAP-affinity of the quinoline containing FAP inhibitors:

Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19–24, having a clearly negative effect on this parameter. [Janssen II, page 493, left column].

In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e., Example 11 of Jansen I or Compound 28 of Jansen II, has an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without any substitution. Specifically, IC₅₀ for FAP (an indicator of the FAP affinity; a higher value means a lower FAP affinity) is 0.012 μ M for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μ M for the unsubstituted FAP inhibitor. Selectivity index (a higher selectivity index means a higher selectivity) is 59 for the former versus 83 for the latter. *See* Jansen I, Table 4.

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29. Accordingly, the cited references not only fail to suggest selecting and modifying FAP inhibitors, but also may discourage one of ordinary skill in the art to substitute the FAP inhibitors with any functional groups, including the C_{1-6} alkyl or -O- C_{1-6} alkyl.

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

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

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

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

[¹²⁵I]MIP-1232

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

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

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

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

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

38. Further, I am of the opinion that there are unexpectedly superior FAP specificities associated with the compounds of the pending claims based on the testing results from my lab.

39. Specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a medical condition, therefore enabling the imaging agent to diagnose the medical condition more accurately.

40. While Meletta could not conclude on the selectivity of the compound of Zimmerman [¹²⁵I]MIP-1232 for FAP (above), we found the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents as shown in the current application US 2020/0330624 A1 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C).

41. Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase

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(PREP) versus FAP. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4.

42. In the process of developing FAP imaging agents, my lab tested the specificity of a number of FAP imaging agents, some of which have molecular structures covered by the pending claims of this application, and some of which have molecular structures not covered by the pending claims and which are used as reference compounds. The results are summarized in the Table below, together with the specificity data for MIP-1232 extracted from Melleta. MIP-1232 and the compounds not covered by the pending claims tested in my lab are labeled as "Reference Compound" in the table below.



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Reference Compound	PREP/FAP	Molecular structure of Representative Compounds	PREP/FAP
Molecular Structure	Ratio	of Formula (I)	Ratio
		molecular weight: 876.94 g/mol	
	15.7	$F = \begin{bmatrix} CO_2H & O_1 & O_2H \\ H & H & H & O_1 & O_2H \\ F & H & CO_2H & O_2H & O_1 & O_2H \\ F & H & CO_2H & O_1 & O_2H & O_2H \\ T & T & T & T & T & T & T \\ T & T & T$	5,807
	241	HOOC HOOC HOOC HOOC HOOC HOOC HOOC HOOC	779
	17	F H H H H H H H H H H H H H	1,693
	3	The second secon	407
		HO = V = V = V = V = V = V = V = V = V =	10,694

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Reference Compound	PREP/FAP	Molecular structure of Representative Compounds	PREP/FAP
Molecular Structure	Ratio	of Formula (I)	Ratio
			11,893
		molecular weight: 761.39 g/mol	
		$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \\ \\ \\ \\ \\ \end{array} \\$	1,313
		molecular weight: 1282.43 g/mol	

* Data from R. Meletta etc., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference

43. Surprisingly, the specificity of the compounds covered by the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds. In particular, as shown in the Table below, MIP-1232, which is a compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for the representative compounds of the pending claims. I also observe that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. Such differences in specificity between the reference compounds and the compounds of the pending claims are surprising and unexpected. The higher specificity of the compounds of the pending claims certainly is beneficial for successfully developing a medical imaging agent.

44. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further 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, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Respectfully Submitted,

12/12/2023

Martin Pomper Date

Attorney Docket No. JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al. Serial No.: 18/354,282 Filed: July 18, 2023 Confirmation No.: 7536 Art Unit: 1618 Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

Dear Examiner Perreira:

This communication is responsive to the non-final Office Action mailed September 26, 2023.

1

Amendments to the Claims begin on page 2 of this paper.Remarks begin on page 5 of this paper.

Application No. 18/354,282 JHU-36631.303 IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.

Confirmation No.: 7536

Serial No.: 18/354,282

Art Unit: 1618

Filed: July 18, 2023

Examiner: Perreira, Melissa Jean

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Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

Mail Stop Amendment Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Examiner Perreira:

1. I, Martin Pomper, am the Principal Investigator and co-inventor of the subject matter described and claimed in the above-referenced patent application (the "Application"). The research leading to the subject matter of the Application was conducted in my laboratory.

2. I am currently Chair of the Department of Radiology at University of Texas Southwestern Medical Center. Previously, I was Professor of Radiology and Radiological Science, Professor of Oncology and Radiation Oncology and Molecular Radiation Services, Research Chief of Nuclear Medicine, Director of the Division of Nuclear Medicine and Molecular Imaging, Associate Dean of Entrepreneurship and Technology Development, and Director of the Johns Hopkins Center for Translational Molecular Imaging at the Johns Hopkins School of Medicine. Page 2 of 9

3. I received my B.Sc. degree, Ph.D. degree, and MD degrees all from the University of Illinois at Urbana-Champaign.

4. I completed my postgraduate medical training at Johns Hopkins that included a medical internship, residencies in diagnostic radiology and nuclear medicine, and a fellowship in neuroradiology, before I joined the Johns Hopkins faculty in 1996.

5. I have authored hundreds scientific articles and am inventor of numerous issued patents or patent applications in the field of medical diagnostic imaging.

6. I have read the non-final Office Action dated September 26, 2023, in the subject Application and the references cited therein.

7. I understand the Office Action rejected the claim 29 on numerous grounds, including anticipation under 35 U.S.C. § 102(a) and obviousness under 35 U.S.C. § 103. I will focus on the obviousness rejection under 35 U.S.C. § 103 in this Affidavit based on my technical expertise and knowledge in the art of medical diagnostic imaging.

8. I understand that the pending claims are directed to a low molecular weight compound of Formula (I):

B-L-A

wherein A is a targeting moiety for FAP- α defined by a specific structure, B is an optical or radiolabeled functional group, and L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

9. The Office Action asserts that claim 29 is obvious over Jansen et al.
(US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al.
(US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett.
2013, 14, 491-496) (hereinafter "Jansen II").

10. I understand that the Office Action took the position that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Janssen I with a radiohalogen (taught in Zimmerman) via a linker, such as C_{1-6} alkyl or -O- C_{1-6} alkyl as Jansen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

11. Based on my review of the Office Action and prior art references cited in the Office Action, I disagree with the obviousness rejections for the following reasons:

Page 3 of 9

12. First, I found that there are no teachings or suggestions in the cited reference to make a compound with a linker having a bi-functionalization which binds to the FAP inhibitor moiety A and the optical or radiolabeled moiety B.

13. The Office Action took the position that the C_{1-6} alkyl or -O- C_{1-6} alkyl group disclosed in Jansen I may serve as the linker when the compounds containing the C_{1-6} alkyl or -O- C_{1-6} alkyl of Jansen I are modified with a radiohalogen.

I observed that C₁₋₆alkyl and the -O-C₁₋₆alkyl are among a variety of functional groups that may be attached to the heterocyclic group of the FAP inhibitor compounds disclosed in Jansen I, including —H, —OH, —oxo, —halo, —C₁₋₆alkyl, —O—C₁₋₆alkyl, —S—C₁₋₆alkyl, —NR₈R₉, —OR₁₂, —Het₂ and —Ar₂, wherein the C₁₋₆alkyl may be optionally substituted with —OH and —halo.

15. Further, I observed that the vast majority of the representative compounds disclosed in either Jansen I or Jansen II do not contain a halogenated C_{1-6} alkyl substitution. Out of 43 representative FAP inhibitors in Jansen I, only one of them is substituted with a halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl. *See* Jansen I, Table 4, Example 11. The same compound is also the only FAP inhibitor substituted with a halogenated C_{1-6} alkyl out of 39 representative FAP inhibitors in Jansen II. *See* Jansen II, Table 3, Compound 28.

16. FAP inhibitors substituted with a halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl clearly do not stand out of the many FAP inhibitors including those unsubstituted or substituted with other functional groups or elements disclosed in Jansen I or Jansen II. There is no suggestion in the cited references as to why a FAP inhibitor substituted with a halogenated C_{1-6} alkyl should be selected for modification with a radiohalogen.

17. I notice that the single FAP inhibitor substituted with the halogenated C_{1-6} alkyl or -O-C₁₋₆alkyl disclosed in Jansen I and Jansen II has worse bioactivities compared with the other compounds disclosed in the prior art. In particular, many FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II which is substituted with a trifluoromethoxy group. See Example 11, Table 4, Jansen I; Compound No. 28, Table 3, Jansen II. For example, compound Example 11 of Jansen I with the trifluoromethoxy substitution has a IC₅₀ of 0.012 µm and a selectivity index of 59, which do not compare favorably to a number of compounds. For example, compound Application No. 18/354,282

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Example 15 of Jansen I has a IC_{50} of 0.0062 μ m and a selectivity index of 193. Accordingly, one of ordinary skill in the art would not select the FAP inhibitor substituted with a trifluoromethoxy group for modification.

18. The Office Action appeared to correlate the substitution of a C_{1-6} alkyl or -O- C_{1-6} alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C₁₋₆alkyl, -O-C₁₋₆alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy. [Office Action dated September 26, 2023, pages 6-7].

I would point out that Jansen II merely discloses that quinoline containing FAP inhibitors have 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Jansen II does not suggest that substitution of the quinoline ring of the quinoline containing FAP inhibitors will improve the FAP-affinity or selectivity of the FAP inhibitors.

19. On the contrary, Jansen II observed that substitution of the quinoline ring has little or negative effects on the FAP-affinity of the quinoline containing FAP inhibitors:

Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19–24, having a clearly negative effect on this parameter. [Janssen II, page 493, left column].

In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e. Example 11 of Jansen I or Compound 28 of Jansen II, has an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without any substitution. Specifically, IC₅₀ for FAP (an indicator of the FAP affinity; a higher value means a lower FAP affinity) is 0.012 μ M for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μ M for the unsubstituted FAP inhibitor. Selectivity index (a higher selectivity index means a higher selectivity) is 83 for the former versus 59 for the latter. *See* Jansen I, Table 4.

20. Accordingly, the cited references not only fail to suggest selecting and modifying FAP inhibitors, but also may discourage one of ordinary skill in the art to substitute the FAP inhibitors with any functional groups, including the C_{1-6} alkyl or -O- C_{1-6} alkyl.

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

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

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

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



[¹²⁵f]MIP-1232

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

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

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

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

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

29. Further, I am of the opinion that there are unexpectedly superior FAP specificity associated with the compounds of the pending claims based on the testing results from my lab.

30. Specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a medical condition, therefore enabling the imaging agent to diagnose the medical condition more accurately.

31. While Meletta could not conclude on the selectivity of the compound of Zimmerman [¹²⁵I]MIP-1232 for FAP (above), we found the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents as shown in the current application US 2020/0330624 A1 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C).

32. Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4.

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33. In the process of developing FAP imaging agents, my lab tested the specificity of a number of FAP imaging agents, some of which have molecular structures covered by the pending claims of this application, and some of which have molecular structures not covered by the pending claims and which are used as reference compounds. The results are summarized in the Table below, together with the specificity data for MIP-1232 extracted from Melleta. MIP-1232 and the compounds not covered by the pending claims tested in my lab are labeled as "Reference Compound" in the table below.



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* Data from R. Meletta etc., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference

34. Surprisingly, the specificity of the compounds covered by the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors used as reference compounds. In particular, as shown in the Table below, MIP-1232, which is a compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for the representative compounds of the pending claims. I also observe that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. Such differences in specificity between the reference compounds and the compounds of the pending claims are surprising and unexpected. The higher specificity of the compounds of the pending claims certainly is beneficial for successfully developing a medical imaging agent.

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31. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further 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, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully Submitted,

DRAFT-DRAFT-DRAFT

Martin Pomper Date

INTERVIEW AGENDA

In re Application of: YANG, et al. Serial No.: 18/354,282 Filed: July 18, 2023 Attorney Docket No.: JHU-36631.303 Confirmation No.: 7536 Art Unit: 1618 Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Date: December 11, 2023 Time: 11:00 am (EST) Call-in Number: 1-877-304-9269

Pass code: 7695903

Attendees:

Examiner Melissa Jean Perreira, USPTO

Jeffrey W. Childers, Ph.D, Attorney of Record (Reg. No. 58,126)

Dr. Martin Pomper, Inventor, Chair of the Department of Radiology at University of

Texas Southwestern Medical Center

Sangeeta Ray, Ph.D., M.S., Associate Professor of Radiology and Radiological Science, Johns Hopkins University School of Medicine

Andrew G. Horti, Ph.D., M.S., Professor of Radiology and Radiological Science, Johns Hopkins University School of Medicine

Qi (Chee) Zhuo, Sr. Intellectual Property Manager, Johns Hopkins Technology Ventures Don Ho, Ph.D., Licensee Representative, Director of Intellectual Property, Neuraly, Inc.

Agenda Outline

A. Summary of Claimed Invention

B. Claim Rejections and Distinction Over the Art

i. Rejection under 35 U.S.C. § 102(a)(1) as allegedly being anticipated by Dvořáková et al., J. Med. Chem. 2017, 60, 8385-8393.

ii. Rejection under 35 U.S.C. § 103 as allegedly being unpatentable over Jansen et al.

(US2014/0357650A1) in view of Zimmerman et al. (US2010/0098633A1) and Jansen et al.,

ACS Med. Chem. Lett. 2013, 14, 491-496.

C. Proposed claim amendments

D. Proposed new claims

Proposed Claim Amendments

29. (Presently Amended) A low molecular weight compound of Formula (I):

$$B-L-A(I)$$

wherein:

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



wherein:

 R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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



represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

B is any optical or radiolabeled functional group suitable for optical imaging, positronemission 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.

30. (New) The compound of claim 29, wherein B is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.

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

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



wherein:

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

R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

B is any optical or radiolabeled functional group suitable for optical imaging, positronemission 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.

Proposed Arguments

Claim Rejections - 35 USC § 102

Claim 29 is rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter "Dvořáková").

Claim 29 is amended and further defines the compound of formula (I) as being "low molecular weight" ("LMW"). The instant patent application distinguishes the LMW compound of the pending claims from large molecule imaging agents containing anti-FAP moieties. In particular, the instant application characterizes the large molecule imaging agents as having numerous disadvantages, including pharmacokinetic limitations, including slow blood and non-target tissue clearance and non-specific organ uptake. Page 1, lines 28-34; page 2, lines 1-7. In contrast, the LMW imaging agents of the instant application possess numerous advantages compared with the large molecule imaging agents. *Id.* Specifically, LMW imaging agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. *Id.* They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. Support for "low molecular weight" can be found at least on page 1, lines 28-34, page 2, lines 1-7, and page 8, lines 26-29, page 9, lines 1-2 of the instant specification:

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

page 8, lines 26-29, page 9, lines 1-2.

Because FAP-α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010;

Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP- α .

page 1, lines 28-34, page 2, lines 1-7.

Further, the instant specification on page 45, lines 12-14, defines a "polymer" as a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer, which distinguishes "low molecular weight compounds" from "polymers."

In 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 **HMPA copolymer**. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol. *See* Dvořáková, page 8387, left column, first full paragraph. The high molecular weight of compound 1 of Dvořáková compares in sharp contrast with the low molecular weight of the compounds of the instant application. In particular, the molecular weight of representative compounds of the instant application, i.e., XY-FAP-02, is about 840 g/mole and XY-FAP-01 is about 1367 g/mole. Thus, one of ordinary skill in the art upon reading and understanding of the instant specification in view of Dvořáková would appreciate that the presently claimed compounds are "low molecular weight" compounds.

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/small-

<u>molecules/</u> ("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).")

New claim 30 further defines B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy. Support for this amendment can be found in claim 29 as originally filed. Applicant notes that Dvořáková only discloses optical imaging agents.

New claim 31 includes the transitional phrase "consisting essentially of." As provided in MPEP § 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Applicant notes that in the present claims, the compound of formula (I) is limited then to components B-L-A, and would not include the HMPA copolymer carrier disclosed and which forms the basis of the iBodies disclosed in Dvořáková.

Because every pending claim (claims 29-31) of the instant application requires the claimed compound to be "low molecular weight", Dvořáková cannot anticipate the pending claims because Dvořáková does not disclose a compound having low molecular weight.

Claim Rejections - 35 USC § 103

Claim 29 is rejected under 35 U.S.C. § 103 as being unpatentable over Jansen et al. (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al. (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) (hereinafter "Jansen II").

The Office Action asserts that Jansen I discloses FAP inhibitors that encompass aspects of the instant claims. The Office Action acknowledges, however, that Jansen I does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

The Office Action asserts that Zimmerman discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease, which, in some embodiments, include a metal chelating moiety that includes a radionuclide or, in other embodiments, a radiohalogen.

The Office Action asserts that Jensen II discloses quinoline-containing FAP inhibitors that are 60 times more FAP-affinity than the naphthoyl derivative of Jansen I.

The Office Action then concludes that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C₁₋₆alkyl, -O-C₁₋₆alkyl as Jansen I teaches that the C₁₋₆alkyl, -O-C₁₋₆alkyl may be halogenated and Zimmerman teaches radiohalogenation of FAP inhibitors for the advantage of diagnostic imaging and therapeutic treatment of diseases.

The Office Action further concludes that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6} alkyl, - O- C_{1-6} alkyl as Jensen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

The Office Action finally concludes that it would have been predictable to one of ordinary skill in the art to utilize a radiohalogenated heteroaromatic FAP inhibitor for imaging FAP with an expectation of success as the quinoline derivative provides 60 times more FAPaffinity than the naphthoyl derivative.

Applicant respectfully disagrees for the reasons set forth below.

i. <u>There was no motivation for one of ordinary skill in the art to select and</u> <u>modify any compounds of Jansen I and Jansen II to arrive at the claimed</u> <u>compounds</u>

As provided in MPEP § 2143(I)(E), in cases involving new chemical compounds, it is necessary to identify some reason that would have led a chemist to select a lead compound and subsequently modify the lead compound in a particular manner to establish prima facie obviousness of new claimed compounds. Takeda v. Alphapharm., 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Office Action argues that the compounds of Jansen I may be modified with a radiohalogen via a linker. The Office Action appears to take the position that the C_{1-6} alkyl or -O- C_{1-6} alkyl that may be attached to the heterocyclic group of the FAP moiety in Jansen I may serve as a "linker" within the meaning of the pending claims. In particular, the Office Action points out that the C_{1-6} alkyl, -O- C_{1-6} alkyl may be halogenated. An implicit but necessary position of the Office Action is that the C_{1-6} alkyl or the -O- C_{1-6} alkyl group may be interpreted as a "linker" only when it is selected as a substituent group in preference to the numerous other equally viable alternatives, and further, only when it is halogenated, and then further only when the halogen is a radiohalogen. Applicant respectfully points out that C_{1-6} alkyl and the -O- C_{1-6} alkyl are among a

wide variety of alternative functional groups that may optionally be attached to the heterocyclic group of a generic structure of the FAP inhibitor compounds disclosed in Jansen I. See Pomper Affidavit, Para. 14. Furthermore, among 43 representative compounds disclosed in Jansen I and 39 representative compounds in Jansen II, only a single compound with a halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl is disclosed. *See* Pomper Affidavit, Para. 15; Jansen I, Example 11, Table 4; Jansen II, Compound No. 28, Table 3. Thus, the prior art provides no motivation or indication to select C_{1-6} alkyl or the -O- C_{1-6} alkyl from a large group of functional groups as a substituent group on the FAP inhibitors disclosed in Jansen I or Jansen II; even if C_{1-6} alkyl or the -O- C_{1-6} alkyl is selected as a substituent group, Jansen I or Jansen II provides no motivation to further substitute the C_{1-6} alkyl or the -O- C_{1-6} alkyl group with a halogen. In fact, in most of the halogenated compounds disclosed in Jansen I and Jansen II, the halogen is directly attached to the heterocyclic group, instead of via a C_{1-6} alkyl or the -O- C_{1-6} alkyl group.

Further, one of ordinary skill in the art also would not select the single FAP inhibitor substituted with the halogenated C_{1-6} alkyl or $-O-C_{1-6}$ alkyl disclosed in Jansen I and Jansen II as a starting point or a lead compound to modify, because this compound has mediocre bioactivities compared with the other compounds disclosed in the prior art. In particular, many other FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II, which is substituted with a trifluoromethoxy group. *See* Pomper Affidavit, Para. 17. For example, compound Example 11 of Jansen I with the trifluoromethoxy substitution has a IC₅₀ of 0.012 μ m and a selectivity index of 59, which do not compare favorably to a number of compounds including compound Example 15, which has a IC₅₀ of 0.0062 μ m and a selectivity index of 193. *Id*.

Even assuming for arguments sake a skilled person made the non-obvious steps of selecting a compound with a halogenated C_{1-6} alkyl or $-O-C_{1-6}$ alkyl group of Jansen I or Jansen II for modification, there is still no explicit or implicit motivation in the cited prior art to substitute the alkyl group with a radiohalogenated group to render the C_{1-6} alkyl or $-O-C_{1-6}$ alkyl as a "linker" within the meaning of the pending claims. In fact, the vast majority of the representative compounds disclosed in Jansen I and Jansen II do not have a halogenated C_{1-6} alkyl or the $-O-C_{1-6}$ alkyl or the $-O-C_{1-6}$ alkyl. To successfully argue that a new compound is obvious, the prior art must show "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda*, 492 F.3d at 1356. The cited prior art clearly does not suggest

anything that may motivate one of ordinary skill in the art to make the specific modification of substituting the C_{1-6} alkyl or -O- C_{1-6} alkyl with a radiohalogen.

The Office Action appears to correlate the substitution of a C_{1-6} alkyl or -O- C_{1-6} alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C₁₋₆alkyl, -O-C₁₋₆alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

Office Action dated September 26, 2023, pages 6-7. Applicant respectfully points out that Jansen II merely discloses that quinoline-containing FAP inhibitors have a 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Pomper Affidavit, Para. 18. Jansen II does not suggest that substitution of the quinoline ring of the quinoline-containing FAP inhibitors would, let alone could, improve the FAP affinity or selectivity of the FAP inhibitors. *Id.* On the contrary, Jansen II observed that substitution of the quinoline ring has little or even negative effects on the potency of the quinoline-containing FAP inhibitors:

Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19–24, having a clearly negative effect on this parameter.

Janssen II, page 493, left column. *Id.*, Para. 19. In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e. Example 11 of Jansen I or Compound 28 of Jansen II, has both an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without the trifluoromethoxy substitution. ¹ *Id.* Therefore, there is no motivation to substitute the quinoline moiety of the FAP inhibitor, not to mention to halogenate the quinoline moiety via a trifluoromethoxy substitution. Applicant would like to emphasize again that without a radiohalogenated trifluoromethoxy substitution on the FAP inhibitor of Jansen II, any

¹ See Jansen I, Table 4. IC₅₀ for FAP (an indicator of the FAP affinity) is 0.012 μ M for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μ M for the unsubstituted FAP inhibitor; selectivity index is 83 versus 59.

FAP inhibitors modified based Jansen I or Jansen II cannot be interpreted as containing a "linker" within the meaning of the pending claims.

Accordingly, in view of the totality of the disclosure in Jansen I and Jansen II, there is no explicit or implicit teachings, suggestion, or motivation for one of ordinary skill in the art to select and modify any compounds in Jansen I and Jansen II to arrive at the claimed compounds. There is no prima facie obviousness because there is no reason that would have led a chemist to select and modify a known compound in a particular manner to establish prima facie obviousness of the compounds of the pending claims. *See* Takeda, 492 F.3d at 1357.

ii. <u>There was no reasonable expectation of success in modifying any compounds</u> <u>in Jansen I or Jansen II to arrive at the compounds of the pending claims</u>

The Office Action also fails to demonstrate a reasonable expectation of success in modifying and making the structural changes to the compounds of Jansen I and Jansen II to arrive at the compounds of the pending claims. The examiner is required to show a reasonable expectation of success when trying to establish prima facie obviousness by modifying or combing the prior art to achieve the claimed invention. MPEP § 2143.02; see also Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007) ("[T]he challenger of the patent [must] show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.") For a medical imaging agent used to diagnose disease, it is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with the medical condition. See the Pomper Affidavit, Para. 22. The high specificity allows the imaging agent to selectively bind to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical conditions from interfering with the binding between the imaging agent with the target protein. Id. The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. Id. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

The Office Action takes the position that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen as Zimmerman teaches radiohalogenation of FAP inhibitors for diagnostic imaging and therapeutic treatment of diseases. However, at the time the instant application was filed, one of ordinary skill in the art recognized the unpredictability associated with the development of medical imaging agents, including the optimization of the specificity. Accordingly, there was no reasonable expectation of success for one of ordinary skill in the art to modify the compounds to arrive at the compounds of pending claims, even if the compound substituted with halogenated C_{1-6} alkyl or $-O-C_{1-6}$ alkyl were selected as the lead compound, which one of ordinary skill in the art had no motivation to do in the first place as discussed.

In fact, one of ordinary skill in the art knew that the FAP imaging agents of Zimmerman most likely would not function well because of the poor specificity associated with the compounds of Zimmerman. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for atherosclerotic plaque, and was determined as not suitable for the application. See Meletta etc., Molecules. 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta"); Pomper Affidavit, Para. 24 As provided on page 2089 of Meletta, although pronounced binding of [125I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Pomper Affidavit, Para. 25. Based on these data, Maletta could not conclude on the selectivity of ¹²⁵I]MIP-1232 for FAP. Accordingly, because of the low specificity MIP-1232 displayed in the investigation, Meletta concluded that MIP-1232 was not suitable for the medical imaging for the medical condition. See Procter & Gamble v. Teva, 566 F.3d 989, 997 (Fed. Cir. 2009) (Upholding decision of the District Court that there was no reasonable expectation of success in modifying the prior art compound to produce a "improved, safe, and effective" drug because researchers had no basis to expect it to be as good as or better than the prior art compound). The lack of reasonable expectation of success is especially telling in view of the failure by others in the art to use the compounds of Zimmerman cited by the Office Action. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir.2003) ("While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure."); In re

Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("Failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.")

Applicant respectfully submits, based on the unpredictability in the art and failure and uncertainty observed by Maletta associated with the prior art compound, that one of ordinary skill in the art would not have a reasonable expectation of success in arriving at a selective FAP imaging agent by merely modifying the FAP inhibitors of Jansen I and/or Jansen II with the radiohalogen of Zimmerman.

iii. <u>There are unexpected results associated with the claimed compounds to</u> rebut any showing of prima facie obviousness

The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Dr. Pomper's Rule 132 Declaration (hereinafter "the Pomper Declaration"), Paragraphs 28-30. As provided in the Pomper Affidavit, specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [¹²⁵I]MIP-1232 for FAP (above section ii), the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents is shown in the current application US 2020/0330624 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C). Id., Para. 31.

Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 32. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4. Representative compounds of the pending claims are provided in the table below with PREP/FAP values for comparison. Surprisingly, the specificity of compounds <u>falling under the</u> <u>scope</u> of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. Id., Para. 33. In particular, as shown in the Table below, MIP-1232, which is a representative compound of Zimmerman, has a PREP/FAP ratio of 32,

compared with the lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims. *Id.*, Para. 34. It is also notable that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. *Id.* Such differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected.





* Data from R. Meletta etc., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference

Accordingly, Applicant respectfully submits that claim 29 is not obvious over Jansen I in view of Zimmerman and Jansen II. Applicant respectfully requests that the rejection of claim 29 under 35 U.S.C. § 103 as being unpatentable over Jansen I in view of Zimmerman and Jansen II be withdrawn at this time.

UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.	
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536	
101943 7590 12/15/2023 The Johns Honkins University		3	EXAMINER		
c/o Casimir Jones			PERREIRA, MELISSA JEAN		
Suite 310	vay		ART UNIT	PAPER NUMBER	
Middleton, WI	53562		1618		
			NOTIFICATION DATE	DELIVERY MODE	
			12/15/2023	ELECTRONIC	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com jwchilders@casimirjones.com

	Application No. 18/354,282	Applicant(s) Yang et al.		
Applicant-Initiated Interview Summary	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (First Inventor to File) Status Yes	Page 1 of 2

All Participants (applicant, applicants representative, PTO personnel)	Title	Туре
MELISSA J PERREIRA	Examiner	Telephonic
Jeffrey Childers	Attorney of Record	
Dr. Martin Pomper	Inventor	
Sangeeta Ray	Associate Professor	
Andrew Horti	Professor of Radiol	
Qi (Chee) Zhuo	Sr. Intellectual prop	
Don Ho	Licensee Representative	

Date of Interview: 11 December 2023

Issues Discussed:

Proposed Amendment(s)

The applicant asserts that the compounds of the instant claims are low molecular weight compounds wherein low molecular weight is defined as compounds under ~1500Da.

The proposed amendments and declaration were discussed as to include a number of representative examples of the low molecular weight compounds exhibiting the unexpected and advantageous results to be commensurate in scope with the instant claims.

The examples provided in the declaration have an identical quinoline but does not provide any compounds with other N-containing aromatic or non-aromatic mono- or bicyclic heterocycles. The applicant stated that they have optimized the linkers.

Other

The examiner indicated that she used an incorrect application number in the NSDP rejection. The applicant stated that they corrected the application number in their response.

Attachment

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618
Applicant is reminded that a complete written statement as to the application file. It is the applicants responsibility to provi by the Examiner and the Examiner has indicated that a writte Please further see: MPEP 713.04 Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph 37 CFR § 1.2 Business to be transacted in writing	b the substance of the interview must be made of record in de the written statement, unless the interview was initiated n summary will be provided. See MPEP 713.04

Interview Summary

Paper No. 20231211
	Application No. 18/354,282	Applicant(s) Yang et al.			
Applicant-Initiated Interview Summary	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (First Inventor to File) Status YeS	Page 2 of 2	

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

PTO/SB/06 (09-11) Approved for use through 1/31/2014. OMB 0651-0032 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, the form and/ 1 200 Alexandria, VA 22313-1450.

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Attorney Docket No. JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al. Serial No.: 18/354,282 Filed: July 18, 2023 Confirmation No.: 7536 Art Unit: 1618 Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT TO NON-FINAL OFFICE ACTION

Dear Examiner Perreira:

This communication is responsive to the non-final Office Action mailed September 26, 2023, and the Applicant-Initiated Interview Summary mailed December 15, 2023.

1

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

<u>Status</u>

Claim 29 is pending in the Application and stands rejected. New claims 30 and 31 have been added. Claim 29 and new claim 31 have been amended. No new matter has been added. Upon entry of this Amendment, claims 29-31 will be pending in the Application.

Applicant-Initiated Interview Summary

Applicant acknowledges the Applicant-Initiated Interview Summary mailed December 15, 2023.

Drawings

The Office Action notes that color photographs and color drawings are not accepted in utility applications unless a petition filed under 37 CFR 1.84(a)(2) is granted. Applicant submits herewith a Petition under 37 CFR 1.84(a)(2) and accompanying fee. Applicant respectfully requests that the color drawings be accepted at this time.

Claim Amendments

Original claim 29 and new claim 31 have been amended to further define the 5- to 10membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle to be a quinolinyl ring. Support for this amendment can be found on page 8, line 5, of U.S. provisional patent application no. 62/575,607, filed October 23, 2017. Original claim 29 and new claim 31 also have been amended to define the variable "v" as being zero. No new matter has been added.

Claim Rejections - 35 USC § 102

Claim 29 is rejected under 35 U.S.C. § 102(a)(1) as being anticipated by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter "Dvořáková").

Claim 29 is amended and further defines the compound of formula (I) as being "low molecular weight" ("LMW"). The instant patent application distinguishes the LMW compound of the pending claims from large molecule imaging agents containing anti-FAP moieties. In particular, the instant application characterizes the large molecule imaging agents as having numerous disadvantages, including pharmacokinetic limitations, including slow blood and non-target tissue clearance and non-specific organ uptake. Page 1, lines 28-34; page 2, lines 1-7. In

contrast, the LMW imaging agents of the instant application possess numerous advantages compared with the large molecule imaging agents. *Id.* Specifically, LMW imaging agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. *Id.* They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. Support for "low molecular weight" can be found at least on page 1, lines 28-34, page 2, lines 1-7, and page 8, lines 26-29, page 9, lines 1-2 of the instant specification:

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

page 8, lines 26-29, page 9, lines 1-2.

Because FAP- α is expressed in tumor stroma, anti-FAP antibodies have been investigated for radioimmunotargeting of malignancies, including murine F19, sibrotuzumab (a humanized version of the F19 antibody), ESC11, ESC14, and others. (Welt, et al., 1994; Scott, et al., 2003; Fischer, et al., 2012). Antibodies also demonstrated the feasibility of imaging inflammation, such as rheumatoid arthritis. (Laverman, et al., 2015). The use of antibodies as molecular imaging agents, however, suffers from pharmacokinetic limitations, including slow blood and non-target tissue clearance (normally 2-5 days or longer) and non-specific organ uptake. Low molecular weight (LMW) agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval. (Coenen, et al., 2010; Coenen, et al., 2012; Reilly, et al., 2015). To date, however, no LMW ligand has been reported with ideal properties for nuclear imaging of FAP- α .

page 1, lines 28-34, page 2, lines 1-7.

Further, the instant specification on page 45, lines 12-14, defines a "polymer" as a molecule of high relative molecule mass, the structure of which essentially comprises the multiple repetition of unit derived from molecules of low relative molecular mass, i.e., a monomer, which distinguishes "low molecular weight compounds" from "polymers."

In 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 <u>HMPA copolymer</u>. The molecular weight of compound 1, an iBody, disclosed by Dvořáková is 149,900 g/mol. *See* Dvořáková, page 8387, left column, first full paragraph. The high molecular weight of compound 1 of Dvořáková compares in sharp contrast with the low molecular weight of the compounds of the instant application. In particular, the molecular weight of representative compounds of the instant application, i.e., XY-FAP-02, is about 840 g/mole and XY-FAP-01 is about 1367 g/mole; further LMW compounds of the current claims with molecular weights are presented in the table on pages 14-15 herein below. Thus, one of ordinary skill in the art upon reading and understanding of the instant specification in view of Dvořáková would appreciate that the presently claimed compounds are "low molecular weight" compounds.

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).")

New claim 30 further defines B to any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy. Support for this amendment can be found in claim 29 as originally filed. Applicant notes that Dvořáková only discloses optical imaging agents.

New claim 31 includes the transitional phrase "consisting essentially of." As provided in MPEP § 2111.03, the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel

characteristic(s)" of the claimed invention. Applicant notes that in the present claims, the compound of formula (I) is limited then to components B-L-A, and would not include the HMPA copolymer carrier disclosed and which forms the basis of the iBodies disclosed in Dvořáková.

Because every pending claim (claims 29-31) of the instant application requires the claimed compound to be "low molecular weight", Dvořáková cannot anticipate the pending claims because Dvořáková does not disclose a compound having low molecular weight.

Claim Rejections - 35 USC § 103

Claim 29 is rejected under 35 U.S.C. § 103 as being unpatentable over Jansen et al. (US2014/0357650A1) (hereinafter "Jansen I") in view of Zimmerman et al. (US2010/0098633A1) (hereinafter "Zimmerman") and Jansen et al. (ACS Med. Chem. Lett. 2013, 14, 491-496) (hereinafter "Jansen II").

The Office Action asserts that Jansen I discloses FAP inhibitors that encompass aspects of the instant claims. The Office Action acknowledges, however, that Jansen I does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

The Office Action asserts that Zimmerman discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease, which, in some embodiments, include a metal chelating moiety that includes a radionuclide or, in other embodiments, a radiohalogen.

The Office Action asserts that Jensen II discloses quinoline-containing FAP inhibitors that are 60 times more FAP-affinity than the naphthoyl derivative of Jansen I.

The Office Action then concludes that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6} alkyl, -O- C_{1-6} alkyl as Jansen I teaches that the C_{1-6} alkyl, -O- C_{1-6} alkyl may be halogenated and Zimmerman teaches radiohalogenation of FAP inhibitors for the advantage of diagnostic imaging and therapeutic treatment of diseases.

The Office Action further concludes that it would have been obvious to substitute the heteroaromatic FAP inhibitors of Jansen I with a radiohalogen via a linker, such as a C_{1-6} alkyl, - O- C_{1-6} alkyl as Jensen II teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

The Office Action finally concludes that it would have been predictable to one of ordinary skill in the art to utilize a radiohalogenated heteroaromatic FAP inhibitor for imaging FAP with an expectation of success as the quinoline derivative provides 60 times more FAP-affinity than the naphthoyl derivative.

Applicant respectfully disagrees for the reasons set forth below.

i. <u>There was no motivation for one of ordinary skill in the art to select and</u> <u>modify any compounds of Jansen I and Jansen II to arrive at the claimed</u> <u>compounds</u>

As provided in MPEP § 2143(I)(E), in cases involving new chemical compounds, it is necessary to identify some reason that would have led a chemist to select a lead compound and subsequently modify the lead compound in a particular manner to establish prima facie obviousness of new claimed compounds. Takeda v. Alphapharm., 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Office Action argues that the compounds of Jansen I may be modified with a radiohalogen via a linker. The Office Action appears to take the position that the C₁₋₆alkyl or -O- C_{1-6} alkyl that may be attached to the heterocyclic group of the FAP moiety in Jansen I may serve as a "linker" within the meaning of the pending claims. In particular, the Office Action points out that the C_{1-6} alkyl, -O- C_{1-6} alkyl may be halogenated. An implicit but necessary position of the Office Action is that the C_{1-6} alkyl or the -O- C_{1-6} alkyl group may be interpreted as a "linker" only when it is selected as a substituent group in preference to the numerous other equally viable alternatives, and further, only when it is halogenated, and then further only when the halogen is a radiohalogen. Applicant respectfully points out that C₁₋₆alkyl and the -O-C₁₋₆alkyl are among a wide variety of alternative functional groups that may optionally be attached to the heterocyclic group of a generic structure of the FAP inhibitor compounds disclosed in Jansen I. See Pomper Affidavit, Para. 23. Furthermore, among 43 representative compounds disclosed in Jansen I and 39 representative compounds in Jansen II, only a single compound with a halogenated C_{1-6} alkyl or -O-C₁₋₆alkyl is disclosed. See Pomper Affidavit, Para. 24; Jansen I, Example 11, Table 4; Jansen II, Compound No. 28, Table 3. Thus, the prior art provides no motivation or indication to select C_{1-6} alkyl or the -O- C_{1-6} alkyl from a large group of functional groups as a substituent group on the FAP inhibitors disclosed in Jansen I or Jansen II; even if C₁₋₆alkyl or the -O-C₁₋₆alkyl is selected as a substituent group, Jansen I or Jansen II provides no motivation to further substitute the C_{1-6} alkyl or the -O-C₁₋₆ alkyl group with a halogen. In fact, in most of the halogenated

compounds disclosed in Jansen I and Jansen II, the halogen is directly attached to the heterocyclic group, instead of via a C_{1-6} alkyl or the -O- C_{1-6} alkyl group.

Further, one of ordinary skill in the art also would not select the single FAP inhibitor substituted with the halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl disclosed in Jansen I and Jansen II as a starting point or a lead compound to modify, because this compound has mediocre bioactivities compared with the other compounds disclosed in the prior art. In particular, many other FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II, which is substituted with a trifluoromethoxy group. *See* Pomper Affidavit, Para. 26. For example, compound Example 11 of Jansen I with the trifluoromethoxy substitution has a IC₅₀ of 0.012 µm and a selectivity index of 59, which do not compare favorably to a number of compounds including compound Example 15, which has a IC₅₀ of 0.0062 µm and a selectivity index of 193. *Id.*

Even assuming for arguments sake a skilled person made the non-obvious steps of selecting a compound with a halogenated C_{1-6} alkyl or -O- C_{1-6} alkyl group of Jansen I or Jansen II for modification, there is still no explicit or implicit motivation in the cited prior art to substitute the alkyl group with a radiohalogenated group to render the C_{1-6} alkyl or -O- C_{1-6} alkyl as a "linker" within the meaning of the pending claims. In fact, the vast majority of the representative compounds disclosed in Jansen I and Jansen II do not have a halogenated C_{1-6} alkyl or the -O- C_{1-6} alkyl. To successfully argue that a new compound is obvious, the prior art must show "that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." *Takeda*, 492 F.3d at 1356. The cited prior art clearly does not suggest anything that may motivate one of ordinary skill in the art to make the specific modification of substituting the C_{1-6} alkyl or -O- C_{1-6} alkyl with a radiohalogen.

The Office Action appears to correlate the substitution of a C_{1-6} alkyl or -O- C_{1-6} alkyl on the quinoline ring of the FAP inhibitors as a "linker" to the fact the quinoline-containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6} alkyl, -O- C_{1-6} alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy.

Office Action dated September 26, 2023, pages 6-7. Applicant respectfully points out that Jansen II merely discloses that quinoline-containing FAP inhibitors have a 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Pomper Affidavit, Para. 27. Jansen II does not suggest that substitution of the quinoline ring of the quinoline-containing FAP inhibitors would, let alone could, improve the FAP affinity or selectivity of the FAP inhibitors. *Id.* On the contrary, Jansen II observed that substitution of the quinoline ring has little or even negative effects on the potency of the quinoline-containing FAP inhibitors:

Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19–24, having a clearly negative effect on this parameter.

Janssen II, page 493, left column. Pomper Affidavit, Para. 28. In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e. Example 11 of Jansen I or Compound 28 of Jansen II, has both an inferior FAP-infinity and an inferior selectivity compared with the FAP-inhibitor without the trifluoromethoxy substitution. ¹ *Id.* Therefore, there is no motivation to substitute the quinoline moiety of the FAP inhibitor, not to mention to halogenate the quinoline moiety via a trifluoromethoxy substitution. Applicant would like to emphasize again that without a radiohalogenated trifluoromethoxy substitution on the FAP inhibitor of Jansen I or Jansen II, any FAP inhibitors modified based Jansen I or Jansen II cannot be interpreted as containing a "linker" within the meaning of the pending claims.

Accordingly, in view of the totality of the disclosure in Jansen I and Jansen II, there is no explicit or implicit teachings, suggestion, or motivation for one of ordinary skill in the art to select and modify any compounds in Jansen I and Jansen II to arrive at the claimed compounds. There is no prima facie obviousness because there is no reason that would have led a chemist to select and modify a known compound in a particular manner to establish prima facie obviousness of the compounds of the pending claims. *See* Takeda, 492 F.3d at 1357.

ii. <u>There was no reasonable expectation of success in modifying any compounds</u> <u>in Jansen I or Jansen II to arrive at the compounds of the pending claims</u>

¹ See Jansen I, Table 4. IC₅₀ for FAP (an indicator of the FAP affinity) is 0.012 μ M for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μ M for the unsubstituted FAP inhibitor; selectivity index is 59 versus 83.

The Office Action also fails to demonstrate a reasonable expectation of success in modifying and making the structural changes to the compounds of Jansen I and Jansen II to arrive at the compounds of the pending claims. The examiner is required to show a reasonable expectation of success when trying to establish prima facie obviousness by modifying or combing the prior art to achieve the claimed invention. MPEP § 2143.02; see also Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1361 (Fed. Cir. 2007) ("[T]he challenger of the patent [must] show by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so."). For a medical imaging agent used to diagnose disease, it is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with the medical condition. See the Pomper Affidavit, Para. 31. The high specificity allows the imaging agent to selectively bind to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical conditions from interfering with the binding between the imaging agent with the target protein. Id. The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. Id. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

The Office Action takes the position that it would have been obvious to substitute the FAP inhibitors of Jansen I with a radiohalogen as Zimmerman teaches radiohalogenation of FAP inhibitors for diagnostic imaging and therapeutic treatment of diseases. However, at the time the instant application was filed, one of ordinary skill in the art recognized the unpredictability associated with the development of medical imaging agents, including the optimization of the specificity. Accordingly, there was no reasonable expectation of success for one of ordinary skill in the art to modify the compounds to arrive at the compounds of pending claims, even if the compound substituted with halogenated C_{1-6} alkyl or $-O-C_{1-6}$ alkyl were selected as the lead compound, which one of ordinary skill in the art had no motivation to do in the first place as discussed.

In fact, one of ordinary skill in the art knew that the FAP imaging agents of Zimmerman most likely would not function well because of the poor specificity associated with the

compounds of Zimmerman. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for atherosclerotic plaque, and was determined as not suitable for the application. See Meletta etc., Molecules. 2015 Jan 27;20(2):2081-99 (hereinafter "Meletta"); Pomper Affidavit, Paras. 33-35. As provided on page 2089 of Meletta, although pronounced binding of [¹²⁵I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Pomper Affidavit, Para. 34. Based on these data, Maletta could not conclude on the selectivity of [¹²⁵I]MIP-1232 for FAP. Accordingly, because of the low specificity MIP-1232 displayed in the investigation, Meletta concluded that MIP-1232 was not suitable for the medical imaging for the medical condition. See Procter & Gamble v. Teva, 566 F.3d 989, 997 (Fed. Cir. 2009) (Upholding decision of the District Court that there was no reasonable expectation of success in modifying the prior art compound to produce a "improved, safe, and effective" drug because researchers had no basis to expect it to be as good as or better than the prior art compound). The lack of reasonable expectation of success is especially telling in view of the failure by others in the art to use the compounds of Zimmerman cited by the Office Action. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F.3d 1339, 1354 (Fed. Cir.2003) ("While absolute certainty is not necessary to establish a reasonable expectation of success, there can be little better evidence negating an expectation of success than actual reports of failure."); In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) ("Failures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling.")

Applicant respectfully submits, based on the unpredictability in the art and failure and uncertainty observed by Maletta associated with the prior art compound, that one of ordinary skill in the art would not have a reasonable expectation of success in arriving at a selective FAP imaging agent by merely modifying the FAP inhibitors of Jansen I and/or Jansen II with the radiohalogen of Zimmerman.

iii. <u>There are unexpected results associated with the claimed compounds to</u> rebut any showing of prima facie obviousness

The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Pomper Affidavit, Paras. 38-42.

As provided in the Pomper Affidavit, specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [¹²⁵I]MIP-1232 for FAP (above section ii), the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents is shown in the current application US 2020/0330624 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C). Pomper Affidavit, Para. 40.

Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 41. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds disclosed in Jansen I. *See* Jansen I, pages 42-51, Tables 3 and 4. Representative compounds of the pending claims are provided in the table below with PREP/FAP values for comparison. Surprisingly, the specificity of compounds <u>falling under the scope</u> of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. Pomper Affidavit, Para. 42. In particular, as shown in the Table below, MIP-1232, which is a representative compound of Zimmerman, has a PREP/FAP ratio of 32, compared with the lowest value of 779 and highest value of 1,418,440 for representative compounds of the pending claims. *Id.*, Para. 42. It is also notable that the other reference compounds which share the same FAP moieties but do not have a linker also have a significantly lower PREP/FAP ratio in the range from 3 to 403. *Id.* Such differences in specificity between the reference compounds of the prior art and the compounds of the pending claims are surprising and unexpected.

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Reference Compound	PREP/FAP	Molecular structure of Representative Compounds	PREP/FAP
Molecular Structure	Ratio	of Formula (I)	Ratio
	17	^μ ^μ ^μ ^μ ^μ ^μ ^μ ^μ	1,693
	3	molecular weight: 1266.39 g/mol	407
			10,694
		molecular weight: 889.39 g/mol	
		molecular weight: 761.39 g/mol	11,893
		$ \begin{array}{c} \begin{pmatrix} & & \\ & $	1,313

* Data from R. Meletta et al., Molecules, 2015 Jan 27;20(2):2081-99. Molecular structure of this reference compound corresponds to MIP-1232 of the Meletta reference.

Accordingly, Applicant respectfully submits that claim 29 is not obvious over Jansen I in view of Zimmerman and Jansen II. Applicant respectfully requests that the rejection of claim 29

under 35 U.S.C. § 103 as being unpatentable over Jansen I in view of Zimmerman and Jansen II be withdrawn at this time.

Double Patenting

Claim 29 is provisionally rejected on the ground of nonstatutory double patenting as allegedly being unpatentable over claims 1, 2, 13, 15, 16 and 21-25 of copending Application No. 16/762,873.

Applicant notes that it appears that the Office Action intended to cite Application No. 16/758,182.

Without acquiescing to the assertions made in the Office Action, Applicant has submitted herewith a Terminal Disclaimer over Application No. 16/758,182.

Applicant respectfully requests that the rejection of claim 29 under nonstatutory double patenting over Application No. 16/758,182 be withdrawn at this time.

CONCLUSION

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney at 919-724-8699 or 608-662-1277. Early passage of the subject application to issue is earnestly solicited.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment associated with this filing to Deposit Account Number 50-4302. If an extension of time for this paper is required, petition for extension is herewith made.

Respectfully Submitted, CASIMIR JONES, S.C.

Date: December 18, 2023

/JEFFREY W. CHILDERS/

Jeffrey W. Childers, Ph.D. Registration No. 58126 Customer No. 101943



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 12/18/2023 01:35:41 PM 2	ZET	ATTORNEY DOCKET # JHU-36631.303			
Title of Invention						
IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)						
Application Infor	mation					
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-			
CONFIRMATION #	7536	FILED BY	Van Nguyen			
PATENT CENTER #	63647076	FILING DATE	07/18/2023			
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang			
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers			

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
2023-12-18 - 36631.303 Supp Amendment NFOA.pdf		17	•	439 KB
2023-12-18 - 36631.303 Supp Amendment NFOA- SApdf	(1-1)	4	Supplemental Response or Supplemental Amendment	35 KB
2023-12-18 - 36631.303 Supp Amendment NFOA- CLM.pdf	(2-4)	3	Claims	57 KB
2023-12-18 - 36631.303 Supp Amendment NFOA- Apdf	(5-17)	13	Amendment/Request for Reconsideration-After Non- Final Rejection	392 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-12-18 - 36631.303 Supp Amendment NFOA.pdf	A243C9BC115DAA8E31970D3E00A50693D766640C629D4D6F4 6257C622266E34EF3AA5EAE3250A1AE87C73E3217F86827B73 589316A7F33472A0B7D598EA42578
2023-12-18 - 36631.303 Supp Amendment NFOA-SApdf	17956623C7889FECDEEF5084893367B770BA4459EEC754E3C 95A9F2C5A2318B6829CF9C26419249DA5C0E8F027BA36FA04 0BD264F69F7F5E3ED4D763DE203500
2023-12-18 - 36631.303 Supp Amendment NFOA-CLM.pdf	B60C1AE0EBF4246B30CEEB95A807336E01ABF9E0322E79B74 3B5E860596DBE7A584DD90617C7754EFB83065234FED26592 DD937821DCC48F655022B8CB525253
2023-12-18 - 36631.303 Supp Amendment NFOA-Apdf	C7A6DD5081F86ABAB3900C09D15F01C3AC1A6DBABCACD75 108CBAD2A64F668838A623DE25DCF3F9E0C5BDBCD3454B3E 4A288DDF195BDA84B9F65417797E7C126

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE CLAIMS:

29. (Presently Amended) A <u>low molecular weight</u> compound of Formula (I):

B-L-A(I)

wherein:

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



wherein:

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

 R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

 R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

 R_{8x} , R_{9x} - and R_{12x} - are each independently selected from the group consisting of H, OH, halo, C_{1-6} alkyl, O C_{1-6} alkyl, S C_{1-6} alkyl, and Ar₃;

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

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂-being optionally substituted with from 1 to 3 substituents selected from $NR_{13*}R_{14*}$, $C_{1-6}alkyl$, O $C_{1-6}alkyl$, and S $C_{1-6}alkyl$; v is 0;; 1, 2, or 3; and



represents a <u>quinolinyl ring</u>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, positronemission 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.

30. (New) The compound of claim 29, wherein B is any radiolabeled functional group suitable for positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy.

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

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



wherein:

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

R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl being optionally substituted with from 1 to 3 substituents selected from OH and halogen; $R_{8*}, R_{9*} \text{ and } R_{12*} \text{ are each independently selected from the group consisting of H, -OH,}$ halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

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

Het₂ is a 5 or 6 membered non aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂-being optionally substituted with from 1 to 3 substituents selected from -NR_{13x}R_{14x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

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

represents a <u>quinolinyl ring</u> 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;

N,

B is any optical or radiolabeled functional group suitable for optical imaging, positronemission 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.

Application Number * 18/354 282 *	Application/Control No.		Applicant(s)/Patent under Reexamination		
10/00-7,202	18/354,282		Yang et al.		
	Examiner		Art Unit		
	PERREIRA, MELI	SSA JEAN	1618		
Document Code - DISQ	Internal	Document - D	O NOT MAIL		

TERMINAL DISCLAIMER	☑ APPROVED	DISAPPROVED
Date Filed: <u>13 December 2023</u>	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
/KIMBERLY R WHITE/
Technology Center: OPLC
Telephone: <u>(571)272-6179</u>

U.S. Patent and Trademark Office TSS-IFW

Terminal Disclaimer

Part of Paper No. 20231219

PE2E SEARCH - Search History (Prior Art)

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref#	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	21238	FAP OR (fibroblast near2 activation)	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:23 PM
N2	1519	(cyano OR boron OR sulfona\$3 OR phospho\$5 OR carboxyl\$4) near2 proline	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:26 PM
N3	122	N1 AND N2	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:26 PM
N4	87	N3 AND ((@py<="2017"))	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:26 PM
N5	7715089	optical OR fluoresce\$4 OR chelate OR radionuclide OR radioisotop\$6 OR radioactive OR imag\$4 OR PET OR SPECT	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:27 PM
N6	18611	N1 AND N5	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:27 PM
N7	65	N4 AND N5	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:27 PM
N8	247117	quinolin\$4	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:34 PM
N9	3079	N6 AND N8	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:34 PM
N10	19	N7 AND N8	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:34 PM
N11	448	((("YANG") near3 ("Xing")) OR (("NIMMAGADDA") near3 ("Sridhar")) OR (("ROWE") near3 ("Steven")) OR (("SLANIA") near3 ("Stephanie")) OR (("POMPER") near3 ("Martin"))).INV.	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:39 PM
N12	7	N1 AND N11	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:39 PM
N14	363857	(A61K51/0485 OR A61K47/545 OR A61K51/0478 OR A61K51/0482 OR A61K49/0032 OR	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:41 PM

		A61K49/0052 OR A61K51/0455 OR A61K51/0497 OR C07D403/14 OR A61P5/00 OR A61P7/04 OR A61P29/00 OR A61P29/00 OR A61P35/00 OR A61P43/00 OR C07D401/14 OR C07B2200/07 OR A61K51/0474 OR A61K2121/00 OR A61K2123/00).cpc.					
N15	9891	N1 AND N14	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:41 PM
N16	2339	N8 AND N15	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:41 PM
N17	1162	N16 AND ((@py<="2017"))	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:42 PM
N18	1067	N5 AND N17	(US-PGPUB; USPAT)	OR	ON	ON	2023/12/24 03:42 PM

Web Search History

date, time	web site	search string
12/19/2023 10:09:56 AM	Google Scholar	proline quinoline FAP
12/19/2023 10:10:36 AM	Google Scholar	proline quinoline FAP [after:2000] [before:2017]
12/19/2023 10:17:42 AM	Google Scholar	[after:2000] [before:2017] proline quinoline FAP imaging
12/19/2023 10:20:10 AM	Google Scholar	[after:2000] [before:2017] proline quinoline FAP 18F
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12/19/2023 10:28:12 AM	Google Scholar	[after:2000] [before:2017] radiolabeled proline FAP
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12/19/2023 11:00:22 AM	Google Scholar	[after:2000] [before:2017] proline FAP cyanine dye
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12/19/2023 11:50:09 AM	Google Scholar	[after:2000] [before:2017] cyanoproline FAP imaging

	Application/Control No.	Applicant(s)/Patent Under Reexamination
Search Notes	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC - Searched*				
Symbol Date Examiner				

CPC Combination Sets - Searched*				
Symbol Date Examiner				

US Classification - Searched*					
Class	ss Subclass Date Examiner				

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes				
Search Notes	Date	Examiner		
google scholar	09/19/2023	MP		
inventor search	09/19/2023	MP		
PE2E search	09/19/2023	MP		
STNext	09/20/2023	MP		
PE2E search	12/24/2023	MP		
google scholar	12/19/2023	MP		
allowability conference (SPE Mike Hartley)	01/04/2024	MP		

/MELISSA J PERREIRA/
Examiner, Art Unit 1618

	Application/Control No.	Applicant(s)/Patent Under Reexamination
Search Notes	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

Interference Search				
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner	
A61K	51/0485	12/24/2023	MP	
A61K	47/545	12/24/2023	MP	
A61K	51/0478	12/24/2023	MP	
A61K	51/0482	12/24/2023	MP	
A61K	49/0032	12/24/2023	MP	
A61K	49/0052	12/24/2023	MP	
A61K	51/0455	12/24/2023	MP	
A61K	51/0497	12/24/2023	MP	
A61K	51/0474	12/24/2023	MP	
A61K	2121/00	12/24/2023	MP	
A61K	2123/00	12/24/2023	MP	
A61P	5/00	12/24/2023	MP	
A61P	7/04	12/24/2023	MP	
A61P	29/00	12/24/2023	MP	
A61P	35/00	12/24/2023	MP	
A61P	43/00	12/24/2023	MP	
C07D	403/14	12/24/2023	MP	
C07D	401/14	12/24/2023	MP	
C07B	2200/07	12/24/2023	MP	

/MELISSA J PERREIRA/ Examiner, Art Unit 1618

ok to enter

/M.J.P/

Attorney Docket No. JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al. Serial No.: 18/354,282 Filed: July 18, 2023 Confirmation No.: 7536 Art Unit: 1618 Examiner: Perreira, Melissa Jean

FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

SUPPLEMENTAL AMENDMENT TO NON-FINAL OFFICE ACTION

Dear Examiner Perreira:

This communication is responsive to the non-final Office Action mailed September 26, 2023, and the Applicant-Initiated Interview Summary mailed December 15, 2023.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

	Application/Control No.	Applicant(s)/Patent Under Reexamination
Issue Classification	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

CPC					
Symbol			Туре	Version	
A61K	/ 51		0485	F	2013-01-01
A61K	47	7	545	1	2017-08-01
A61K	/ 51		0478	I	2013-01-01
A61K	51		0482	I	2013-01-01

CPC Combination Sets					
Symbol	Туре	Set	Ranking	Version	

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	05 January 2024	Total Claims Allowed:		
(Assistant Examiner)	(Date)	3		
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	05 January 2024	O.G. Print Claim(s)	O.G. Print Figure	
(Primary Examiner)	(Date)	1	none	
U.S. Patent and Trademark Office		Pa	rt of Paper No.: 20240105	

	Application/Control No.	Applicant(s)/Patent Under Reexamination
Issue Classification	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

INTERNATIONAL CLASSIFICATION								
CLAIMED								
A61K	/ 51	00						
A61M	/ 36	/ 14						
NON-CLAIMED								

US ORIGINAL CLASSIFICATION							
	CLASS	SUBCLASS					
424		1.89					
CROSS REFERENCE	S(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)						

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	05 January 2024	Total Claims Allowed:		
(Assistant Examiner)	(Date)	3		
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	05 January 2024	O.G. Print Claim(s)	O.G. Print Figure	
(Primary Examiner)	(Date)	1	none	
U.S. Patent and Trademark Office		- Pa	rt of Paper No.: 20240105	

	Application/Control No.	Applicant(s)/Patent Under Reexamination
Issue Classification	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

	☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47														
CLAIN	CLAIMS														
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19		28								
	2		11		20	1	29								
	3		12		21	2	30								
	4		13		22	3	31								
	5		14		23										
	6		15		24										
	7		16		25										
	8		17		26										
	9		18		27										

/MELISSA J PERREIRA/ Examiner, Art Unit 1618	05 January 2024	Total Claims Allowed:			
(Assistant Examiner)	(Date)	3			
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	05 January 2024	O.G. Print Claim(s)	O.G. Print Figure		
(Primary Examiner)	(Date)	1	none		
U.S. Patent and Trademark Office Part of Paper No.: 2024					

Bibliographic Data

Application No: $18/354,2$	82			
Foreign Priority claimed:	O Yes	O No		
35 USC 119 (a-d) conditions met:	Yes	No		Met After Allowance
Verified and Acknowledged:	/MELISSA	A J PERREIRA/		
	Examiner's	Signature		Initials
Title:	IMAGING FIBROBL	AND RADIOTHI AST-ACTIVATIO	ERAPI N PRO	EUTICS AGENTS TARGETING OTEIN-ALPHA (FAP-ALPHA)

APPLICANTS

The Johns Hopkins University, Baltimore, MD, UNITED STATES

INVENTORS

Xing Yang,

Sridhar Nimmagadda, Balimore, MD, UNITED STATES

Steven Rowe, Parkville, MA, UNITED STATES

Stephanie Slania, Baltimore, MD, UNITED STATES

Martin G. Pomper, Baltimore, MD, UNITED STATES

CONTINUING DATA

This application is a CON of 16758182 04/22/2020

16758182 is a 371 of PCT/US18/57086 10/23/2018

PCT/US18/57086 has PRO of 62575607 10/23/2017

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

08/04/2023

** SMALL ENTITY **

STATE OR COUNTRY

ADDRESS

The Johns Hopkins University c/o Casimir Jones 2275 Deming Way Suite 310 Middleton, WI 53562 UNITED STATES

FILING FEE RECEIVED

\$2,400

				Complete if Known			
				Application Number	18/354,282		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				Filing Date	18-Jul-2023		
				First Named Inventor	Yang		
	(Use as many sheets	as necessary)		Art Unit	1618		
				Examiner Name	MELISSA JEAN PERREIRA		
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303		

	U.S. PATENTS									
Examine r Initials [*]	Cite No.	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear					

	U.S. PUBLISHED PATENT APPLICATIONS										
Examine r Initials [*]	Cite No. ³	Document Number Number-Kind Code ⁴ <i>(if known)</i>	le Publie YYY	ssue or cation Date 'Y-MM-DD		Jame of Patentee o Applicant of Cited Document	or	Pages, Columi Where Relevant Pass Releva Figures Ap	ns, Lines, e sages or nt opear		

	NONPATENT LITERATURE DOCUMENTS						
Examine r Initials [*]	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translatio n ⁶				
		BEEBE et al., "Understanding the Apothecaries Within: The Necessity of a Systematic Approach for Defining the Chemical Output of the Human Microbiome". Clin Transl Sci. 2014 Feb; 7(1): 74–81.					
		FERREIRA et al., "Monitoring Alcoholic Fermentation: An Untargeted Approach". Journal of Agricultural and Food Chemistry, 2014, 62, 6784–6793.					
		LLEWELLYN et al., "Using community metabolomics as a new approach to discriminate marine microbial particulate organic matter in the western English Channel". Progress in Oceanography, Volume 137, Part B, September 2015, p. 421-433.					
		MELETTA et al., "Evaluation of the radiolabeled boronic acid-based FAP inhibitor MIP-1232 for atherosclerotic plaque imaging". Molecules, 2015 Jan 27;20(2):2081-99.					
		METABOLOMICS – EMBL-EBI, https://www.ebi.ac.uk/training/online/courses/metabolomics- introduction/what-is/small-molecules/, retrieved on 2023-12-12. 5 pages.					

	Examiner Signature	/MELISSA J PERREIRA/	Date Considered	12/19/2023		
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through						
citation if not in conformance and not considered. Include copy of this form with next communication to applicant.						

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

				Complete if Known		
				Application Number	18/354,282	
INF(ORMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang	
	(Use as many sheets	as necessary)		Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet	2	of	3	Attorney Docket Number	JHU-36631.303	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):



That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

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		I
		L

See attached certification statement.



The fee set forth in 37 CFR 1.17(p) has been submitted herewith.

Х

A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

				Complete if Known		
				Application Number	18/354,282	
INFO	ORMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023	
STATEMENT BY APPLICANT				First Named Inventor	Yang	
	(Use as many sheets	as necessary)		Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet	Sheet 3 of 3		Attorney Docket Number	JHU-36631.303		

Signature	/Jeffrey W. Childers/	Date (YYYY-MM- DD)	2023-12-13
Name/Print	Jeffrey W. Childers	Registration Number	58,126
PTO Notes regarding this form:

¹ Applicant's unique citation designation number (optional).
 ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

³ Applicant's unique citation designation number (optional).
 ⁴ See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

				Complete if Known			
				Application Number	18/354,282		
INFO	DRMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023		
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang		
	(Use as many sheets	as necessary)		Art Unit	1618		
				Examiner Name	MELISSA JEAN PERREIRA		
Sheet	1	of	3	Attorney Docket Number	JHU-36631.303		

	U.S. PATENTS									
Examiner Initials*	Cite No.1	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear					

U.S. PUBLISHED PATENT APPLICATIONS									
Examiner Initials*	Cite No. ³	Document Number Number-Kind Code ⁴ <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD		Name of Patentee or Applicant of Cited Document		Pages, Columr Where Relevant Pass Relevar Figures Ap	ns, Lines, sages or nt pear	

	NONPATENT LITERATURE DOCUMENTS							
Examiner Initials [*]	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation 6					
	1.	AZHDARINIA et al., "Characterization of chemical, radiochemical and optical properties of a dual-labeled MMP-9 targeting peptide". Bioorganic & Medicinal Chemistry, Vol. 19, Issue 12, May 6, 2011, 3769-3776.						

	Examiner Signature	/MELISSA J PERREIRA/	Date Considered	12/19/2023
Ē	-XAMINER	Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9 Draw line through

EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

				Complete if Known		
				Application Number	18/354,282	
INF(ORMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang	
	(Use as many sheets	as necessary)		Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet	2	of	3	Attorney Docket Number	JHU-36631.303	

CERTIFICATION STATEMENT

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OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

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See attached certification statement.

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Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on ______. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2023-10-30
Name/Print	Jeffrey W. Childers	Registration Number	58,126

PTO Notes regarding this form:

¹ Applicant's unique citation designation number (optional).
 ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

³ Applicant's unique citation designation number (optional).
 ⁴ See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

101943 75	90 01/10/2024	EXAMINER			
The Johns Hopkin	ns University	PERREIRA, MELISSA JEAN			
2275 Deming Way			ART UNIT	PAPER NUMBER	
Suite 310			1618		
Middleton, WI 535	62	DATE MAILED: 01/10/202	4		
APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.	
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536	

TITLE OF INVENTION: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0.00	\$0.00	\$480	04/10/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. <u>PROSECUTION ON THE MERITS IS CLOSED</u>. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN <u>THREE MONTHS</u> FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. <u>THIS STATUTORY PERIOD</u> <u>CANNOT BE EXTENDED</u>. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to:	y mail, send to: Mail Stop ISSUE FEE Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450				By fax, send to: (571)-273-288				
INSTRUCTIONS: This All further corresponde correspondence address fee payment, any desir	form should be used for t nce will be mailed to the ; and/or (b) indicating a se ed continuing application	transmitting the ISSUE F current correspondence eparate "FEE ADDRESS on should preferably be	EE and PUBLICATION address as indicated un " for maintenance fee no filed prior to payment	VFEE (if required). B less corrected below o otifications. Because o of this issue fee in o	locks 1 thro or directed electronic p rder not to	ugh 5 should be comp otherwise in Block 1, atent issuance may o jeopardize copende	bleted where appropriate. by (a) specifying a new becur shortly after issue ncy.		
CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)				Note: A certificate of Fee(s) Transmittal. The papers. Each additionation additionationation additionationationationationationationation	mailing ca is certificat al paper, su	in only be used for d e cannot be used for ch as an assignment	lomestic mailings of the any other accompanying or formal drawing, must		
101943	7590 01/10	0/2024	ł	ave its own certificat Ce	e of mailing rtificate of	g or transmission. Mailing or Transmi	ssion		
The Johns Hop	okins University]	hereby certify that the states Postal Service	iis Fee(s) T	ransmittal is being de	eposited with the United		
c/o Casimir Jon	es Zana		ź	ddressed to the Mail S	Stop ISSUE	FEE address above, o	r being transmitted to the (571)		
Suite 310	ay			273-2885, on the date	below.	eeuonie ming system	or by facsinine to (571)		
Middleton, WI	53562						(Typed or printed name)		
							(Jighature) (Date)		
				200	ATTODA	EV DOCKET NO			
APPLICATION NO.	FILING DATE		FIRST NAMED INVENT	.OK	ATTORN	ET DOCKET NO.	CONFIRMATION NO.		
[I	I	1						
APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE D	UE PREV. PAID ISSU	JE FEE 1	TOTAL FEE(S) DUE	DATE DUE		
nonprovisional	SMALL	\$480	\$0.00	\$0.00		\$480	04/10/2024		
EXAN	MINER	ART UNIT	CLASS-SUBCLASS						
PERREIRA, M	IELISSA JEAN	1618	424-001890						
CFR 1.363). Change of corresp Address form PTO/A "Fee Address" ind AIA/47 or PTO/SB/4 Customer Number i 3. ASSIGNEE NAME A PLEASE NOTE: Unl recorded, or filed for	condence address (or Cha IA/122 or PTO/SB/122) lication (or "Fee Address 7; Rev 03-02 or more rec s required. ND RESIDENCE DATA ess an assignee is identifi recordation, as set forth i	inge of Correspondence attached. "Indication form PTO/ cent) attached. Use of a A TO BE PRINTED ON ded below, no assignee da in 37 CFR 3.11 and 37 Cl	 (1) The names of u or agents OR, altern (2) The name of a s registered attorney 2 registered patent i listed, no name will THE PATENT (print on ta will appear on the pat FR 3.81(a). Completion 	p to 3 registered pate: natively, ingle firm (having as or agent) and the nan attorneys or agents. If be printed.	a member a les of up to no name is dentified be a substitute	1 2 3 elow, the document m for filing an assignme	ust have been previously		
(A) NAME OF ASSI	GNEE		(B) RESIDENCE: (C	TY and STATE OR (COUNTRY)			
Please check the approp	riate assignee category or	categories (will not be p	rinted on the patent) :	Individual 🖵 Corpo	oration or o	ther private group ent	ity 🖵 Government		
4a. Fees submitted:	Issue Fee Pub	lication Fee (if required)	T A						
46. Method of Payment:	(Please first reapply any	previously paid fee show	vn above)		. ,	1 12 1747			
The Director is he	nt via the USPIO patent	electronic filing system	deficiency or credit an	Non-electron	osit Accou	by credit card (Attaci	n form PTO-2038)		
	reby automzed to charge	e the required rec(s), any	denerency, or create an	, overpayment to Dep	osh recou				
 5. Change in Entity Sta Applicant certifyi Applicant assertir 	itus (from status indicate ng micro entity status. Se ng small entity status. See	ed above) ee 37 CFR 1.29 : 37 CFR 1.27	<u>NOTE:</u> Absent a valic fee payment in the mi <u>NOTE:</u> If the applicat to be a notification of	l certification of Micr cro entity amount wil ion was previously un loss of entitlement to	o Entity Sta l not be acc der micro e micro entit	tus (see forms PTO/S epted at the risk of ap entity status, checking y status.	B/15A and 15B), issue plication abandonment. this box will be taken		
Applicant changing	ng to regular undiscounte	d fee status.	<u>NOTE:</u> Checking this entity status, as applic	box will be taken to b able.	e a notifica	tion of loss of entitle	ment to small or micro		
NOTE: This form must	be signed in accordance v	with 37 CFR 1.31 and 1.3	3. See 37 CFR 1.4 for s	ignature requirements	and certific	cations.			
Authorized Signature				Date					
Typed or printed nan	ne			Registration I	No				
PTOL-85 Part B (11/23)	Approved for use throug	gh 03/31/2026	Page 2 of 3 OMB 0651-0033	U.S. Patent and Tr	ademark O	fice; U.S. DEPARTM	IENT OF COMMERCE		

SPITENT AND TRUCK UNIT	ED STATES PATEN	IT AND TRADEMARK OFFICE		
		ATES DEPARTMENT OF COM es Patent and Trademark Of MMISSIONER FOR PATENTS Box 1450 notria, Virginia 22313-1450 uspto.gov	MERCE fice	
APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536
101943 75	90 01/10/2024		EXAN	IINER
The Johns Hopkin	ns University		PERREIRA, M	ELISSA JEAN
c/o Casimir Jones			ART UNIT	PAPER NUMBER
Suite 310		1618		
Middleton, WI 535	62	DATE MAILED: 01/10/2024		

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).

https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

- 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
- 2) a federal, state, local, or international agency, in response to its request;
- 3) a contractor of the USPTO having need for the information in order to perform a contract;
- 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
- 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
- a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
- 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
- 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
- 9) the Office of Personnel Management (OPM) for personnel research purposes; and

10)the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

	Application No.	Applicant(s	5)
Notice of Allowability	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (FITF) Status Yes
The MAILING DATE of this communication approximately approximately and the second structure of the second structure of the second structure of the office of upon petition by the applicant. See 37 CFR 1.313 1. This communication is responsive to 12/18/23. A declaration(s)/affidavit(s) under 37 CFR 1.130(b) was constructed by the applicant in response to a responsive to the second structure of the second stru	ears on the cover sheet with the (OR REMAINS) CLOSED in this a or other appropriate communicati IGHTS. This application is subject and MPEP 1308. s/were filed on striction requirement set forth durin d into this action.	a corresponden application. If no on will be mailed to withdrawal fre og the interview o	<i>ce address</i> t included d in due course. THIS om issue at the initiative
3. The allowed claim(s) is/are <u>29-31</u> . As a result of the allowed Highway program at a participating intellectual property off http://www.uspto.gov/patents/init_events/pph/index.jsp	ed claim(s), you may be eligible to fice for the corresponding application or send an inquiry to PPHfeedba	benefit from the on. For more inf ick@uspto.gov	Patent Prosecution formation, please see
4. Acknowledgment is made of a claim for foreign priority und	er 35 U.S.C. § 119(a)-(d) or (f).		
a) All b) Some* c) None of the:			
1. Certified copies of the priority documents hav 2. Certified copies of the priority documents hav	re been received. re been received in Application No		
3. Copies of the certified copies of the priority de	ocuments have been received in the	nis national stag	e application from the
International Bureau (PCT Rule 17.2(a)).			
Certified copies not received:			
Applicant has THREE MONTHS FROM THE "MAILING DATE noted below. Failure to timely comply will result in ABANDON THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.	" of this communication to file a re /IENT of this application.	ply complying w	ith the requirements
5. CORRECTED DRAWINGS (as "replacement sheets") mus	t be submitted.		
 including changes required by the attached Examiner' Paper No./Mail Date 	s Amendment / Comment or in the	Office action of	
Identifying indicia such as the application number (see 37 CFR sheet. Replacement sheet(s) should be labeled as such in the h	1.84(c)) should be written on the dra eader according to 37 CFR 1.121(d).	wings in the fron	t (not the back) of each
6. DEPOSIT OF and/or INFORMATION about the deposit of l attached Examiner's comment regarding REQUIREMENT	BIOLOGICAL MATERIAL must be FOR THE DEPOSIT OF BIOLOGI	submitted. Note CAL MATERIAL	e the
Attachment(s)	_		
1. Notice of References Cited (PTO-892)	5. 🗌 Examiner's Ame	endment/Comme	ent
Paper No./Mail Date	6. 🕑 Examiner's Stat	ement of Reaso	ns for Allowance
 Examiner's Comment Regarding Requirement for Deposit of Biological Material 	7. 🔟 Other		
4. Interview Summary (PTO-413), Paper No./Mail Date.			
/Michael G. Hartley/	/MELISSA J PERR	EIRA/	
Supervisory Faterit Examiner, Art Onit 1010		1010	
U.S. Patent and Trademark Office			
PTOL-37 (Rev. 08-13) Notice	of Allowability	Part of Paper No./	'Mail Date 20240105

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Reasons for Allowance

The following is an examiner's statement of reasons for allowance: the low molecular weight quinolinyl-containing compounds of the instant claims surprisingly have a specificity (PREP/FAP ratio) for FAP that is several orders of magnitude higher than other small molecule FAP inhibitors found in the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA JEAN PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached M9-3, T9-3, W9-3, Th9-2, F9-2.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To Application/Control Number: 18/354,282 Art Unit: 1618

file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit

https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and

https://www.uspto.gov/patents/docx for information about filing in DOCX format. For additional

questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like

assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or

571-272-1000.

/MELISSA J PERREIRA/ Examiner, Art Unit 1618

/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618



ELECTRONIC PAYMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 01/16/2024 05:15:59 PM Z E	ž.	ATTORNEY DOCKET # JHU-36631.303			
Title of Invention IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA) Application Information						
	mation					
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	•			
CONFIRMATION #	7536	FILED BY	Van Nguyen			
PATENT CENTER #	63968554	AUTHORIZED BY	Jeffrey Childers			
CUSTOMER #	101943	FILING DATE	07/18/2023			
CORRESPONDENCE ADDRESS	•	FIRST NAMED INVENTOR	Xing Yang			
Payment Informa	Payment Information					
PAYMENT METHOD CARD / 0638	PAYMENT TRANSACTION ID E20241FH16479846	PAYMEN Van Ngu	T AUTHORIZED BY yen			

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
			TOTAL AMOUNT:	\$104.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 01/16/2024 05:15:59 PM 2	ZET	ATTORNEY DOCKET # JHU-36631.303
Title of Invention			
IMAGING AND RAD PROTEIN-ALPHA (F	DIOTHERAPEUTICS AGENTS ⁻ FAP-ALPHA)	TARGETING FIBROBL	AST-ACTIVATION
Application Infor	mation		
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63968554	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
WO2016196628A1.pdf	135	Foreign Reference	5262 KB
2024-01-16 - JHu-36631.303 - Supp IDS.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	39 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Third Party Observations.pdf	553	Non Patent Literature	9605 KB
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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
WO2016196628A1.pdf	515E343648E2878B7A59FC35ECD8E7564DDC2D9AF7A6E4943 ED650ABB977B3C0CCF2B3E57D934968296ED6542E71229439 04B0013C234888C773A934472A23C9
2024-01-16 - JHu-36631.303 - Supp IDS.pdf	91A5DF33719D461247F422010D6C4620CC167D3FB4C8B575C B5C14834F5D1FF57A921C469D75C560C30C4BFEFC83896F9A 3A16ADE638DE1A916D89C64AA059B6
Third Party Observations.pdf	9D1A24255E793F435B294816D357B4D479584A3CF45672812C 46E3D0990121E8D082B3C39584A6CE8DEF76F42207F9DAC07 46F58D55F3C30EBB28133A63F0084

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

				Comp	olete if Known
				Application Number	18/354,282
INFORMATION DISCLOSURE				Filing Date	18-Jul-2023
STATEMENT BY APPLICANT			NT	First Named Inventor	Yang
(Use as many sheets as necessary)				Art Unit	1618
		Examiner Name	MELISSA JEAN PERREIRA		
Sheet 1 of 3			3	Attorney Docket Number	JHU-36631.303

	U.S. PATENTS							
Examiner Initials⁺	Cite No.1	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear			

	U.S. PUBLISHED PATENT APPLICATIONS					
Examiner Initials*	Cite No. ³	Document Number Number-Kind Code ⁴ <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

	FOREIGN PATENT DOCUMENTS							
Examiner Initials*	Cite No.1	Foreign Patent Document	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited	Pages, Columns, Lines, Where Relevant Passages	Translation ⁸		
		Country Code ⁵ Number ⁶ Kind Code ⁷ (<i>if known</i>)		Document	or Relevant Figures Appear			
	1.	WO 2016/196628 A1	2016-12-08	THE JOHNS HOPKINS UNIVERSITY				

NONPATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation 6	
	1.	Third Party Observations for application number EP18871298.8 Dated January 10, 2024. 553 pages.		

	Examiner		Date Considered		
F		Initial if reference considered, whether or not citation is in conformanc	e with MPEP 60	9 Draw line through	

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Complete if Known		
INFORMATION DISCLOSURE				Application Number	18/354,282	
				Filing Date	18-Jul-2023	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang	
(Use as many sheets as necessary)				Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet	2 of 3		3	Attorney Docket Number	JHU-36631.303	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):



That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

_

See attached certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.



Х

A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on ______. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-01-16
Name/Print	Jeffrey W. Childers	Registration Number	58,126

PTO Notes regarding this form:

¹ Applicant's unique citation designation number (optional).

² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

³ Applicant's unique citation designation number (optional).

⁴ See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

⁵ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

⁶ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

⁷ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

⁸ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.



ELECTRONIC PAYMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 01/16/2024 05:1	8:26 PM Z ET	ATTORNEY DOCKET # JHU-36631.303
Title of Invention IMAGING AND RAI PROTEIN-ALPHA () DIOTHERAPEUTICS FAP-ALPHA)	AGENTS TARGETING FIBROBL	AST-ACTIVATION
Application Info	rmation		
APPLICATION TYPE	Utility - Nonprovisional under 35 USC 111(a)	Application PATENT #	~
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63968988	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS		FIRST NAMED INVENTOR	Xing Yang
Payment Information	ation		
PAYMENT METHOD CARD / 0638	PAYM E2024	IENT TRANSACTION ID PAYI N1FH19045329 Van	MENT AUTHORIZED BY Nguyen
PRE-AUTHORIZED AC	COUNT PRE-	AUTHORIZED CATEGORY	
504302	37 CF CFR 1 (Doct (Miso	R 1.16 (National application filing, searc 1.17 (Patent application and reexaminati iment supply fees); 37 CFR 1.20 (Post Is ellaneous fees and charges)	ch, and examination fees); 37 on processing fees); 37 CFR 1.19 suance fees); 37 CFR 1.21
FEE CODE DESC	RIPTION	ITEM PRICE(\$) QUANTITY	Y ITEM TOTAL(\$)

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2501	UTILITY ISSUE FEE	480.00	1	480.00
		TC)TAL AMOUNT:	\$480.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d)

and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 01/16/2024 05:18:26 PM 2	ZET	ATTORNEY DOCKET # JHU-36631.303
Title of Invention	I		
IMAGING AND RAD PROTEIN-ALPHA (F	DIOTHERAPEUTICS AGENTS ⁻ FAP-ALPHA)	TARGETING FIBROBL	AST-ACTIVATION
Application Infor	mation		
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	63968988	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-01-16 - JHU-36631.303 - Issue Fee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	143 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-01-16 - JHU-36631.303 -	4C775A38FA3EE63915A9CD7D2ED24BB19220A3B56F1B33AF2
Issue Fee Transmittal.pdf	38528BD37BC6B673A254D61E31B936A6E9D913402589A623F4
	AF522073AF44203CE6D7D341A7A5F

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to:	Mail Stop ISSUE Commissioner for P.O. Box 1450				By fax, send to	b: (571)-273-2885	
	Alexandria, Virgir	nia 22313-1450					<u> </u>
INSTRUCTIONS: This All further corresponde correspondence address fee payment, any desir	form should be used for (nce will be mailed to the ; and/or (b) indicating a se red continuing application	ransmitting the ISSUE Fl current correspondence a parate "FEE ADDRESS" n should preferably be	EE and PUBLICATION F address as indicated unles ' for maintenance fee notif filed prior to payment o	EE (if required). B s corrected below ications. Because of f this issue fee in o	or directed of electronic pat order not to je	gh 5 should be con herwise in Block tent issuance may eopardize copend	npleted where appropriate. 1, by (a) specifying a new v occur shortly after issue lency.
CURRENT CORRESPO	ONDENCE ADDRESS (Note	: Use Block 1 for any chang	no e of address) Fea pay hay	te: A certificate of e(s) Transmittal. The pers. Each addition we its own certificat	f mailing can nis certificate al paper, such te of mailing o	only be used for cannot be used for as an assignmen or transmission.	domestic mailings of the r any other accompanying t or formal drawing, must
The Johns Hop c/o Casimir Jon 2275 Deming W Suite 310	⁷⁵⁹⁰ 0 ^{01/10} okins University es Vay	/2024	I h Sta add US 27:	Ce ereby certify that the tes Postal Service bressed to the Mail S PTO via the USPT 3-2885, on the date	ertificate of M his Fee(s) Tra with sufficien Stop ISSUE Fl O patent elect below.	failing or Transn insmittal is being it postage for first EE address above, tronic filing system	nission deposited with the United class mail in an envelope or being transmitted to the m or by facsimile to (571)
Middleton, WI	53562						(Typed or printed name)
			_				(Signature) (Date)
APPLICATION NO.	FILING DATE		FIRST NAMED INVENTO	R	ATTORNEY	OOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023		Xing Yang		JHU-3	6631.303	7536
APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSU	UE FEE TO	TAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0.00	\$0.00		\$480	04/10/2024
EXAN	MINER	ART UNIT	CLASS-SUBCLASS	7			
PERREIRA, M	IELISSA JEAN	1618	424-001890	4			
I. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached. "Fee Address" indication (or "Fee Address" Indication form PTO/ AIA/17 or PTO/SB/17. Boy 03 02 or more recent) attached. Use of a			 For printing on the The names of up to or agents OR, alternative The name of a single registered attorney or 2 registered patent attorney in listed, no name will be 	patent front page, 1 o 3 registered pate ively, gle firm (having as agent) and the nan orneys or agents. If e printed.	ist ent attorneys a member a nes of up to f no name is	1 Casimir Jo 2 Jeffrey W	ones, SC . Childers
3. ASSIGNEE NAME A	is required. AND RESIDENCE DATA	A TO BE PRINTED ON	L THE PATENT (print or ty	pe)			
PLEASE NOTE: Unl recorded, or filed for	less an assignee is identifi recordation, as set forth i	ed below, no assignee dat n 37 CFR 3.11 and 37 CF	a will appear on the paten R 3.81(a). Completion o	t. If an assignee is i f this form is NOT	identified belc a substitute fo	ow, the document i or filing an assignr	must have been previously nent.
(A) NAME OF ASSI	GNEE		(B) RESIDENCE: (CIT	Y and STATE OR	COUNTRY)		
The Johns Hop	kins University		Baltimore, M	D			_
Please check the approp	riate assignee category or	categories (will not be pr	rinted on the patent) : 🖵 I	individual 🖾 Corp	oration or oth	er private group er	ntity 🖵 Government
4a. Fees submitted: 4b. Method of Payment:	Sissue Fee Pub	lication Fee (if required)	m aboua)				
Flectronic Payment.	I lease just reapply any	electronic filing system	Enclosed check	Non-electror	nic payment b	v credit card (Atta	ch form PTO-2038)
The Director is he	are by authorized to charge	the required fee(s) any	deficiency or credit any o	verpayment to Der	posit Account	No 504302	en form i 10-2050)
	ereby authorized to charge	e die required ree(s), any	deficiency, of credit any c	werpayment to Dep	Josh Account	110504502	
5. Change in Entity Sta	atus (from status indicate	d above)	NOTE: Absort a valid a	artification of Micr	o Entity Statu	s (see forms PTO)	(SP/15A and 15P) iccura
Applicant certifyi	ng micro entity status. Se	e 37 CFR 1.29	fee payment in the micro	entity amount wil	l not be accep	ted at the risk of a	pplication abandonment.
Applicant assertir	ng small entity status. See	37 CFR 1.27	<u>NOTE:</u> If the application to be a notification of lo	n was previously ur ss of entitlement to	nder micro ent micro entity s	tity status, checkin status.	ng this box will be taken
Applicant changing	ng to regular undiscounte	fee status.	NOTE: Checking this be entity status, as applicable	ox will be taken to le.	be a notification	on of loss of entitl	ement to small or micro
NOTE: This form must	be signed in accordance v	vith 37 CFR 1.31 and 1.3.	3. See 37 CFR 1.4 for sign	nature requirements	s and certificat	tions.	
Authorized Signature	/Jeffrey W. Chil	ders/		Date Ja	nuary 16, 2	024	
Typed or printed nan	ne Jeffrey W. (Childers		Registration 2	No 581	26	
			Dage 2 of 2				

PTOL-85 Part B (11/23) Approved for use through 03/31/2026

Page 2 of 3 OMB 0651-0033

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 01/22/2024 01:37:02 PM 2	ZET	ATTORNEY DOCKET # JHU-36631.303			
Title of Invention	l					
IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)						
Application Infor	mation					
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-			
CONFIRMATION #	7536	FILED BY	Aaron Bottjen			
PATENT CENTER #	64032495	FILING DATE	07/18/2023			
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang			
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers			

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-01-22_36631- 303_SUPPL_IDS_SB08.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	37 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-01-22_36631-	52AC7B410E60580F35A2549C9975CA6DE0CDEBE91092F6D89
303_SUPPL_IDS_SB08.pdf	CCF86F79E045BE686845BE62033CFC445D59F1A75D624E8CC

537D9928DBF1740DE72B838D154640

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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New International Application Filed with the USPTO as a Receiving Office

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				Complete if Known		
				Application Number	18/354,282	
INFORMATION DISCLOSURE			RE	Filing Date	18 Jul 2023	
STA	STATEMENT BY APPLICANT			First Named Inventor	Yang	
(Use as many sheets as necessary)				Art Unit	1618	
				Examiner Name	Melissa Jean Perreira	
Sheet	eet 1 of 2		Attorney Docket Number	JHU-36631.303		

U.S. PATENTS							
Examiner Initials*	Cite No.1	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear		

U.S. PUBLISHED PATENT APPLICATIONS						
Examiner	Cite	Document Number	Issue or	Name of Patentee or	Pages, Columns, Lines,	
Initials*	No. ³	Number-Kind Code ⁴ <i>(if known)</i>	Publication Date YYYY-MM-DD	Applicant of Cited Document	Where Relevant Passages or Relevant Figures Appear	
	1.	2020/0237936	2020-07-30	LOW et al.		

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No.1	Foreign Patent Document	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures	Translation ⁸		
		Kind Code ⁷ (<i>if known</i>)			Appear			

NONPATENT LITERATURE DOCUMENTS				
Examiner Initials [*]	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation 6	

Examiner Signature		Date Considered		
EXAMINEF	: Initial if reference considered, whether or not citation is in conformar	nce with MPEP	609. Draw line through	

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Complete if Known		
				Application Number	18/354,282	
INFO	ORMATION D	ISCLOSU	RE	Filing Date	18 Jul 2023	
STA	STATEMENT BY APPLICANT			First Named Inventor	Yang	
	(Use as many sheets as necessary)			Art Unit	1618	
				Examiner Name	Melissa Jean Perreira	
Sheet	2	of	2	Attorney Docket Number	JHU-36631.303	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

ned certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.



A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number filed on _____. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-01-22
Name/Print	Jeffrey W. Childers	Registration Number	58,126

PTO Notes regarding this form:

¹ Applicant's unique citation designation number (optional).

² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

³ Applicant's unique citation designation number (optional).

⁴ See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

⁵ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

⁶ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

⁷ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

⁸ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536
101943 The Johns Hon	7590 01/23/202 kins University	EXAM	IINER	
c/o Casimir Jon	ies Nov	PERREIRA, M	ELISSA JEAN	
Suite 310	vay		ART UNIT	PAPER NUMBER
Middleton, WI	53562	1618		
			NOTIFICATION DATE	DELIVERY MODE
			01/23/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com jwchilders@casimirjones.com



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents United States Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450 www.uspto.gov

The Johns Hopkins University c/o Casimir Jones 2275 Deming Way Suite 310 Middleton, WI 53562

In re Application of Yang et al.	: : DECISION ON PETITION
Application No. 18/354,282	: UNDER 37 CFR 1.84(a)(2)
Filed: 07/18/2023	:
Attorney Docket No. JHU-36631.303	:

This is a decision on the Petition to Accept Color Drawings under 37 CFR 1.84(a)(2), received in the United States Patent and Trademark Office (USPTO) on December 13, 2023.

37 CFR 1.84(a)(2) in relevant part states:

On rare occasions, color drawings may be necessary as the only practical medium by which to disclose the subject matter sought to be patented in a utility patent application. ... The Office will accept color drawings in utility patent applications only after granting a petition filed under this paragraph explaining why the color drawings are necessary. Any such petition must include the following:

- (i) Payment of the fee set forth under 37 CFR 1.17(h),
- (ii) Submission of three (3) sets of color drawings, or one (1) set of color drawings if filed by EFS-Web, and
- (iii) An amendment to the specification to insert (unless the specification contains or has been previously amended to contain) the following language as the first paragraph of the brief description of the drawings:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the office upon request and payment of the necessary fee.

MPEP § 608.02(VIII) COLOR DRAWINGS OR COLOR PHOTOGRAPHS states in relevant part:

It is anticipated that such a petition will be granted only when the U.S. Patent and Trademark Office has determined that a color drawing or color photograph is the only practical medium by which to disclose in a printed utility patent the subject matter to be patented.

A review of U.S. Patent and Trademark records indicates that all the criteria set forth in 37 CFR 1.84(a)(2) and MPEP § 608.02(VIII) have been satisfied. Accordingly, the petition under 37 CFR 1.84(a)(2) is **GRANTED**.

Petitioner is advised that this decision grants the petition to accept color drawing(s) or photograph(s) because the requirements of 37 CFR 1.84(a)(2) or (b)(2) have been met. The initial review undertaken for purposes of the petition did not identify new matter in the color drawing(s) or photograph(s). However, the grant of this

petition should not be construed as a determination that should the color drawing(s) be entered the application would be free of statutory and/or formal defects. See MPEP § 608.02(VIII) and 608.02(b). The examiner is charged with determining whether applicant's nonprovisional application as amended to include the replacement drawings complies with all statutory requirements (e.g., enablement under 35 U.S.C. 112) and other applicable requirements (e.g., other formal requirements under 37 CFR 1.84). Further, the determination of whether a petition establishes a sufficient basis to accept color drawings or photographs is separate from the examiner's ultimate determination as to whether an amendment to the drawings should be entered (e.g., based on the prohibition under 35 U.S.C. 132 against introducing new matter). See MPEP § 608.04(a), 608.02 (h), and 2163.06(l).

Should there be any questions about this decision, please contact BENNETT M CELSA, by letter addressed to Director, TC 1600, at the address listed above, or by telephone at (571)272-0807, or by facsimile sent to the general Office facsimile number, 571-273-8300.

/Zachariah Lucas/ Supervisory Patent Examiner, Technology Center 1600 /BENNETT M CELSA/ Quality Assurance Specialist , Technology Center 1600

	ITED STATES PAT	TENT AND TRADEMARK OFFICE	UNITED STATES DEPART United States Patent and Address: COMMISSIONER P.O. Box 1450 Alexandria, Virginia 22 www.uspto.gov	FMENT OF COMMERCE I Trademark Office FOR PATENTS 2313-1450
APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536
The Johns Hopl	7590 01/30/20: kins University	EXAMINER PERREIRA, MELISSA JEAN		
c/o Casimir Jones 2275 Deming Way Suite 310			ART UNIT	PAPER NUMBER
Middleton, WI 5	3562		NOTIFICATION DATE	DELIVERY MODE

NOTICE OF NON-COMPLIANT INFORMATION DISCLOSURE STATEMENT

An Information Disclosure Statement (IDS) filed 1.16.2024 in the above-identified application fails to meet the requirements of 37 CFR 1.97(d) for the reason(s) specified below. Accordingly, the IDS will be placed in the file, but the information referred to therein has not been considered.

The IDS is not compliant with 37 CFR 1.97(d) because:

The IDS lacks a statement as specified in 37 CFR 1.97(e).

- □ The IDS lacks the fee set forth in 37 CFR 1.17(p).
- The IDS was filed after the issue fee was paid. Applicant may wish to consider filing a petition to withdraw the application from issue under 37 CFR 1.313(c) to have the IDS considered. See MPEP 1308.

N. Horns, for 571-272-4200 or 1-888-786-0101

571-272-4200 or 1-888-786-0101 Application Assistance Unit Office of Data Management

Page 1 of 1

	ITED STATES PAT	ENT AND TRADEMARK OFFICE	UNITED STATES DEPART United States Patent and Address: COMMISSIONER P.O. Box 1450 Alexandria, Virginia 2: www.uspto.gov	FMENT OF COMMERCE I Trademark Office FOR PATENTS 2313-1450
APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536
The Johns Hopl	7590 01/30/20: kins University	EXAMINER PERREIRA, MELISSA JEAN		
2275 Deming W	ay	ART UNIT	PAPER NUMBER	
Suite 310			1618	
Middleton, WI 5	3562		NOTIFICATION DATE	DELIVERY MODE
			01/30/2024	ELECTRONIC

NOTICE OF NON-COMPLIANT INFORMATION DISCLOSURE STATEMENT

An Information Disclosure Statement (IDS) filed $\frac{1.22.2024}{1.22.2024}$ in the above-identified application fails to meet the requirements of 37 CFR 1.97(d) for the reason(s) specified below. Accordingly, the IDS will be placed in the file, but the information referred to therein has not been considered.

The IDS is not compliant with 37 CFR 1.97(d) because:

- □ The IDS lacks a statement as specified in 37 CFR 1.97(e).
- □ The IDS lacks the fee set forth in 37 CFR 1.17(p).
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N. Horne, for 571-272-4200 or 1-888-786-0101

Application Assistance Unit Office of Data Management

Page 1 of 1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.: 7536

Examiner: Perreira, Melissa Jean

Art Unit: 1618

In re Application of: YANG, et al. Serial No.: 18/354,282 Filed: July 18, 2023 FOR: IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

INFORMATION DISCLOSURE STATEMENT CERTIFICATION STATEMENT

Commissioner for Patents PO Box 1450 Alexandria, VA 22313-1450

Examiner Perreira:

I hereby certify that that the following items of information contained in the information disclosure statement were cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. 37 C.F.R. §1.97(e)(1).

WO 2016/196628 for The Johns Hopkins University (ref. no. 2) Third Pary Observations for application number EP 18871298.8 (ref. no. 3)

I hereby certify that the following item of information contained in the information disclosure statement was not cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

US Publication 2020/0237936 for LOW et al. (ref. no. 1)

Respectfully submitted,

Date: February 2, 2024 /Jeffrey W. Childers/

Jeffrey W. Childers Casimir Jones S.C. Registration No. 58126 2275 Deming Way, Suite 310 Middleton, WI 53562 Office: 919-724-8699 Fax: 608-662-1276

PTO/SB/09 (09-18)

CERTIFICATION AND REQUEST FOR CONSIDERATION OF AN INFORMATION DISCLOSURE STATEMENT FILED AFTER PAYMENT OF THE ISSUE FEE UNDER THE QPIDS PROGRAM					
Non-Provisional Application Number: 18/354,282	Filing Date: July 18, 2023				
First Named Inventor. Xing Yang	Title of Invention: Imaging and radiotherapeutics agents targeting fibroblast-activation proteing				
THE UNDERSIGNED HEREBY CERTIFIES AND REQUESTS THE FOLLOWING FOR THE ABOVE- IDENTIFIED APPLICATION.					
 Consideration is requested of the information disclosure statement (IDS) submitted herewith, which is being filed after payment of the issue fee. 					
 Check the box next to the appropriate selection: Each item of information contained in the IDS was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(1). 					
OR No item of information contained in the IDS was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the IDS was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the IDS. See 37 CFR 1.97(e)(2).					
OR See attached certification statement in compliance with 37 CFR 1.97(e).					
4. A Petition to Withdraw from Issue After Payment of the Issue Fee (37 CFR 1.313(c)(2)), including the petition fee set forth in 37 CFR 1.17(h), is submitted herewith as a <u>Web-based e Petition</u> . <u>WARNING</u> : Do not submit the petition as a follow-on paper via EFS-Web. Submit the petition as a Web-based ePetition by signing on to EFS-Web as a registered user, selecting the radio button next to "Existing application/patent," and then selecting the radio button next to "ePetition (for automatic processing and immediate grant, if all petitions requirements are met)." Failure to use the Web-based ePetition interface will result in automatic entry of the RCE					
5. A request for continued examination (RCE) under are submitted herewith.	A request for continued examination (RCE) under 37 CFR 1.114 and the RCE fee under 37 CFR 1.17(e) are submitted herewith.				
 The RCE will be treated as a "conditional" RCE. In the event the examiner determines that any item of information contained in the IDS necessitates the reopening of prosecution in the application, the undersigned understands that (i) the RCE will be processed and treated as an RCE under 37 CFR 1.114 and therefore (ii) the IDS fee under 37 CFR 1.17(p) will be returned in accordance with 37 CFR 1.97(b)(4). In the event that no item of information in the IDS necessitates reopening prosecution, the undersigned understands that the RCE will not be processed and the RCE fee under 37 CFR 1.17(e) will be returned. This certification and request is being filed as a <u>Web-based ePetition</u> and is not accompanied by an amendment to the application. Inclusion of an amendment will result in automatic entry of the RCE 					
Name Name Visite Visit Jeffrev W. Childers	Practitioner Registration Number 58126				
<u>Note</u> : Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below.*					
✓ *Total of 1 forms are submitted.					

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary, and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office maynot be able to process and/or examine your submission of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

- 1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
- A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
- 3. A record in this system of records maybe disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
- 4. A record in this system of records maybe disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
- A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
- A record in this system of records maybe disclosed, as a routine use, to another federal agencyfor purposes of National Securityreview (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
- 7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
- 8. A record from this system of records maybe disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
- 9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.


P.O. Box 1450 Alexandria, VA 22313 - 1450 www.uspto.gov

GRANT LETTER

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

In re Application of Xing Yang

This is an electronic decision on the petition under , filed February 02, 2024 to withdraw the above-identified application from issue after payment of the issue fee.

The request is **GRANTED.**

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

The application is being referred to Technology Center AU for

Telephone inquired concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

Office of Petitions



UNITED STATES PATENT AND TRADEMARK OFFICE P.O. Box 1450 Alexandria, VA 22313 - 1450 www.uspto.gov

PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)(2)

APPLICATION #	ATTORNEY DOCKET #	FILING DATE
18354282	JHU-36631.303	07/18/2023

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

CONFIRMATION #	7536	FILING DATE	07/18/2023
ART UNIT	1618	FIRST NAMED INVENTOR	Xing Yang
EXAMINER	MELISSA PERREIRA		

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:

(1) Petition fee; and

(2) One of the following reasons: A grantable petition requires the following items: (a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;

(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or

(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Reason for withdrawal

Consideration of a request for continued examination (Quick Path Information Disclosure Statement) - RCE request, submission, and fee are attached

Applicant claims the following entity status

Small

Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am: An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

Signature	Name	Registration #
/Jeffrey W. Childers/	Jeffrey Childers	58126



P.O. Box 1450 Alexandria, VA 22313 - 1450 www.uspto.gov

Page 1 of 2

ELECTRONIC PAYMENT RECEIPT

APPLICATION 18/354,28	# 2	RECEIPT DATE / TIME 02/02/2024 05:07:17 PM Z ET				ATTORNEY DOCKET # JHU-36631.303		
Title of In	vention	l						
IMAGING A	AND RAE ALPHA (I	DIOTHERAPE FAP-ALPHA)	UTICS AGENT	S TARGETING F	IBROBLA	ST-ACTIVA	TION	
Applicatio	on Infor	mation						
APPLICAT	ION TYPE	Utility - Nonpro under 35 USC	visional Applicatior 111(a)	1	PATENT #	-		
CONFIR	MATION #	7536			FILED BY	Jeffrey Child	lers	
PATENT (CENTER #	64194803		AUTH	ORIZED BY	-		
CUS	STOMER #	101943		FI	LING DATE	07/18/2023		
CORRESPO	ONDENCE ADDRESS	-		FIR	ST NAMED	Xing Yang		
Payment	Informa	ition						
PAYMENT METHOD PAYMEN CARD / 0638 E202422				SACTION ID 108	CTION ID PAYMENT AUTHORIZED BY 8 Jeffrey Childers			
PRE-AUTHO		COUNT	PRE-AUTHORIZ	ED CATEGORY				
504302			37 CFR 1.16 (Na CFR 1.17 (Paten 1.19 (Document (Miscellaneous	tional application fi t application and re supply fees); 37 CF fees and charges)	ling, search examinatior R 1.20 (Pos	, and examin 1 processing t Issuance fe	ation fees); 37 fees); 37 CFR es); 37 CFR 1.21	
FEE CODE	DESCRI	PTION		ITEM PRICE(\$)	QUANTI	TY ITE	EM TOTAL(\$)	
2464	PETITIC PETITIC CFR 1.1	DNS REQUIRING DN FEE SET FOF 7(H) (GROUP III)	THE RTH IN 37	56.00		1	56.00	
2801	REQUE Examin Reque	ST FOR CONTIN IATION (RCE) - 1 ST (SEE 37 CFR	UED ST 1.114)	544.00		1	544.00	
					TOT AMOUN	AL IT:	\$600.00	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



Page 1 of 3 P.O. Box 1450 Alexandria, VA 22313 - 1450 www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 02/02/2024 05:07:17 PM 2	ATTORNEY DOCKET # JHU-36631.303						
Title of Invention	1							
IMAGING AND RAE PROTEIN-ALPHA (I	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)							
Application Infor	mation							
APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-					
CONFIRMATION #	7536	FILED BY	Jeffrey Childers					
PATENT CENTER #	64194803	FILING DATE	07/18/2023					
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang					
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	-					

Documents

TOTAL DOCUMENTS: 7

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	2	ePetition Request Form	29 KB
2024-02-02 - JHU-36631.303 - Supp IDSpdf.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	39 KB
Warning: This is not a USPTO supplied IDS automatically loaded to other USPTO system	fillable form. ns.	. Data in the form cannot be	
2024-02-02 - JHU-36631.303 - RCE.pdf	3	Request for Continued Examination (RCE)	131 KB
Warning: This is not a USPTO supplied RCE automatically loaded to other USPTO system	E fillable forn ns.	n. Data in the form cannot be	
2024-02-01 - JHU-36631.303 - QPIDS.pdf	2	Quick Path Information Disclosure Statement	151 KB

			Page 2 of 3
WO2016196628A1.pdf	135	Foreign Reference	5262 KB
Third Party Observations.pdf	553	Other reference- Patent/Application/Search Documents	9605 KB
2024-02-02 - JHU-36631.303 - IDS Certification Statement.pdf	1	Letter specifying the conditions for filing under 37 CFR 1.97	20 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	24A562B12BC7CF67E5C6722EA0826261D028C88AC39617E8E B3A682E5A1A0DA48402AE7E0947487559C69E462816E3EFDD 74DF1E035F7D3FD596FC159EB63ED0
2024-02-02 - JHU-36631.303 - Supp IDSpdf.pdf	8DD1BB24F49C8A9DADA5B5A745DF6FD51DBD47EE1DD6AC 77F320ADA0C471DB22799B873A9DE73C38311DEC1657DDDE 772C7A82E22C924D6856B7EC460C755CDB
2024-02-02 - JHU-36631.303 - RCE.pdf	3FC1787EC432E484337EA03713EF5FF6BA594D11702F21CBA 7DC15E89F54560B433A2564F6752CE61FCAB1000AAFDA21A6 70EB00EFA2D2D6EF30F77784DDEF57
2024-02-01 - JHU-36631.303 - QPIDS.pdf	F01234071E6EE3FB329DAE476CC39D1A7CB244D0B99A0768 B1BD9574470652397488FBCF72113E283C8184CEEACA897A0 E2F89C07A83C048E88A892E65BAB370
WO2016196628A1.pdf	515E343648E2878B7A59FC35ECD8E7564DDC2D9AF7A6E494 3ED650ABB977B3C0CCF2B3E57D934968296ED6542E7122943 904B0013C234888C773A934472A23C9
Third Party Observations.pdf	9D1A24255E793F435B294816D357B4D479584A3CF45672812C 46E3D0990121E8D082B3C39584A6CE8DEF76F42207F9DAC07 46F58D55F3C30EBB28133A63F0084
2024-02-02 - JHU-36631.303 - IDS Certification Statement.pdf	4CB170D87AAB22FCA3F32AC3032D81F30C1172BA26BE1A0C 1C963BB4FCACBB84FDBDD80FA8769827F7FD50D32BA1E345 FE1CCF03FC5AA795E2CD9EB334BDA982

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

				Comp	lete if Known
				Application Number	18/354,282
INFORMATION DISCLOSURE				Filing Date	18-Jul-2023
STATEMENT BY APPLICANT			NT	First Named Inventor	Yang
(Use as many sheets as necessary)				Art Unit	1618
				Examiner Name	MELISSA JEAN PERREIRA
Sheet 1 of 3		Attorney Docket Number	JHU-36631.303		

U.S. PATENTS									
Examiner Initials*	Cite No.1	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear				

U.S. PUBLISHED PATENT APPLICATIONS								
Examiner Initials*	Cite No. ³	Document Number Number-Kind Code ⁴ <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear			
	1.	2020/0237936	2020-07-30	LOW et al.				

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS									
Examiner Initials*	Cite No.1	Foreign Patent Document	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited	Pages, Columns, Lines, Where Relevant Passages	Translation ⁸			
		Country Code ⁵ Number ⁶ Kind Code ⁷ (<i>if known</i>)		Document	or Relevant Figures Appear				
	2.	WO 2016/196628 A1	2016-12-08	THE JOHNS HOPKINS UNIVERSITY					

NONPATENT LITERATURE DOCUMENTS					
Examiner Initials*	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation 6		
	3.	Third Party Observations for application number EP18871298.8 Dated January 10, 2024. 553 pages.			

	Examiner Signature		Date Considered		
ł	EXAMINER:	Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9. Draw line through	

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

				Complete if Known		
				Application Number	18/354,282	
INFO	ORMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023	
STA	TEMENT BY	APPLICA	NT	First Named Inventor	Yang	
	(Use as many sheets	as necessary)		Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet 2 of 3		Attorney Docket Number	JHU-36631.303			

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

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Г	

See attached certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.



Х

A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on ______. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-02-02
Name/Print	Jeffrey W. Childers	Registration Number	58,126

PTO Notes regarding this form:

¹ Applicant's unique citation designation number (optional).

² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

³ Applicant's unique citation designation number (optional).

⁴ See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

⁵ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

⁶ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

⁷ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

⁸ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Juliet McMillan

Sale Accounting Date:02/06/2024

Sale Item Reference Number	Effective Date	
18354282	02/02/2024	

Document Number I202425J43169200 Fee C 2806

 Fee Code
 Fee Code Description

 2806
 SUBMISSION- INFORMATION DISCLOSURE STMT
 Amount Paid \$104.00 Payment Method Deposit Account

UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	FILING DATE FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	07/18/2023 Xing Yang		7536
101943 The Johns Hop	7590 02/14/202 kins University	4	EXAM	IINER
c/o Casimir Jon	ies		PERREIRA, M	ELISSA JEAN
Suite 310	vay		ART UNIT	PAPER NUMBER
Middleton, WI	53562		1618	
			NOTIFICATION DATE	DELIVERY MODE
			02/14/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com jwchilders@casimirjones.com

	Application No.	Applicant(s	5)		
Notice of Allowability	Examiner MELISSA J PERREIRA	Art Unit 1618	AIA (FITF) Status Yes		
The MAILING DATE of this communication appears on the cover sheet with the correspondence address All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS. This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308. 1. This communication is responsive to 2/02/24. A declaration(s)/affidavit(s) under 37 CFR 1.130(b) was/were filed on 2. An election was made by the applicant in response to a restriction requirement set forth during the interview on; the restriction requirement and election have been incorporated into this action. 3. The allowed claim(s) is/are 29-31. As a result of the allowed claim(s), you may be eligible to benefit from the Patent Prosecution Highway program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/poph/index.isp or send an inquiry to PPHfeedback@uspto.gov.					
 4. Acknowledgment is made of a claim for foreign priority und Certified copies: a) All b) Some* c) None of the: Certified copies of the priority documents hav Certified copies of the priority documents hav 	er 35 U.S.C. § 119(a)-(d) or (f). ve been received. ve been received in Application No)			
 Copies of the certified copies of the priority de International Bureau (PCT Rule 17.2(a)). * Certified copies not received: 	ocuments have been received in t	his national stag	e application from the		
Applicant has THREE MONTHS FROM THE "MAILING DATE noted below. Failure to timely comply will result in ABANDONN THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.	" of this communication to file a re MENT of this application.	eply complying w	ith the requirements		
5. CORRECTED DRAWINGS (as "replacement sheets") mus including changes required by the attached Examiner's Paper No./Mail Date	t be submitted. s Amendment / Comment or in the	e Office action of			
Identifying indicia such as the application number (see 37 CFR sheet. Replacement sheet(s) should be labeled as such in the he	1.84(c)) should be written on the dra eader according to 37 CFR 1.121(d)	awings in the fror	it (not the back) of each		
6. DEPOSIT OF and/or INFORMATION about the deposit of f attached Examiner's comment regarding REQUIREMENT	BIOLOGICAL MATERIAL must be FOR THE DEPOSIT OF BIOLOG	e submitted. Note ICAL MATERIAL	e the		
Attachment(s) 1. □ Notice of References Cited (PTO-892) 2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 2/2/24. 3. □ Examiner's Comment Regarding Requirement for Deposit of Biological Material 4. □ Interview Summary (PTO-413), Paper No./Mail Date /Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	5. Examiner's Am 6. Examiner's Sta 7. Other /MELISSA J PERR Examiner, Art Unit	endment/Comme tement of Reaso EIRA/ 1618	ent ns for Allowance		
L U.S. Patent and Trademark Office PTOL-37 (Rev. 08-13) Notice	l of Allowability	Part of Paper No.	/Mail Date 20240206		

				Complete if Known		
				Application Number	18/354,282	
INFO	DRMATION D	ISCLOSU	RE	Filing Date	18-Jul-2023	
STATEMENT BY APPLICANT				First Named Inventor	Yang	
(Use as many sheets as necessary)				Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet 1 of 3		Attorney Docket Number	JHU-36631.303			

U.S. PATENTS							
Examiner Initials*	Cite No.1	Document Number Number-Kind Code ² <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear		

U.S. PUBLISHED PATENT APPLICATIONS								
Examiner Initials*	Cite No. ³	Document Number Number-Kind Code ⁴ <i>(if known)</i>	Issue or Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear			
	1.	2020/0237936	2020-07-30	LOW et al.				

Note: Submission of copies of U.S. Patents and published U.S. Patent Applications is not required.

FOREIGN PATENT DOCUMENTS							
Examiner	Cite		Publication	Name of Patentee	Pages, Columns,	Translation	
Initials*	No.1	Foreign Patent Document	Date	or	Lines, Where	8	
			YYYY-MM-DD	Applicant of Cited	Relevant Passages		
		Country Code ⁵ Number ⁶		Document	or Relevant Figures		
		Kind Code ⁷ (<i>if known</i>)			Appear		
	2.	WO 2016/196628 A1	2016-12-08	THE JOHNS			
				HOPKINS			
				UNIVERSITY			

NONPATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.	Translation 6	
	3.	Third Party Observations for application number EP18871298.8 Dated January 10, 2024. 553 pages.		

	Examiner Signature	/MELISSA J PERREIRA/	Date Considered	02/06/2024
E	EXAMINER:	Initial if reference considered, whether or not citation is in conformance	e with MPEP 60	9. Draw line through

citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE				Complete if Known		
				Application Number	18/354,282	
				Filing Date	18-Jul-2023	
STA	STATEMENT BY APPLICANT			First Named Inventor	Yang	
(Use as many sheets as necessary)				Art Unit	1618	
				Examiner Name	MELISSA JEAN PERREIRA	
Sheet	2	of	3	Attorney Docket Number	JHU-36631.303	

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

		7	

See attached certification statement.

The fee set forth in 37 CFR 1.17(p) has been submitted herewith.



A certification statement is not submitted herewith.

Documents not provided herewith have been previously cited in parent U.S. patent application number ______ filed on ______. In compliance with 37 C.F.R. § 1.98(d), Applicants have not included copies of these documents.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-02-02
Name/Print	Jeffrey W. Childers	Registration Number	58,126

PTO Notes regarding this form:

¹ Applicant's unique citation designation number (optional).

² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

³ Applicant's unique citation designation number (optional).

⁴ See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04.

⁵ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

⁶ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

⁷ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

⁸ Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.



United States Patent and Trademark Office

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Document Code:WFEE

User :Sengpheth Sandara

Refund Accounting Date:02/22/2024

Effective Date	Sale	e Item Reference Number	Refund Total		
02/22/2024	183	354282	\$544.00		
Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I20242LE59085803	2801	RCE- 1ST REQUEST	\$544.00	Visa	*******************0638



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Document Code:WFEE

User :Sengpheth Sandara

Sale Adjustment Accounting Date:02/22/2024

Effective Date	Sale Accou	inting Date	Sale Item I	Reference Number	
02/22/2024	02/22/20	24	1835428	2	
Document Number	Fee Code	Fee Code Des	cription	Amount Paid	Payment Method
I20242LE59085803	2801	RCE- 1ST RE	QUEST	\$544.00	Visa

UNITED STATES PATENT AND TRADEMARK OFFICE

		UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov					
APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.			
18/354,282	03/26/2024	11938201	JHU-36631.303	7536			
101943 759	0 03/06/2024						
The Johns Hopkins	University						
c/o Casimir Jones							
2275 Deming Way							
Suite 310	Suite 310						
Middleton, WI 5356	Middleton, WI 53562						

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Xing Yang, Baltimore, MD; Sridhar Nimmagadda, Balimore, MD; Steven Rowe, Parkville, MA; Stephanie Slania, Baltimore, MD; Martin G. Pomper, Baltimore, MD;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

The Johns Hopkins University, Baltimore, MD;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit <u>SelectUSA.gov</u>.

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SCORE Placeholder Sheet for IFW Content

Application Number: 18354282

Document Date: 03/26/2024

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

• Patent Grant with Color/Grayscale Drawings

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UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023 Xing Yang		JHU-36631.303	7536
101943 The Johns Hon	7590 03/26/202 kins University	4	EXAM	IINER
c/o Casimir Jon	ies Nov		PERREIRA, M	ELISSA JEAN
Suite 310	vay		ART UNIT	PAPER NUMBER
Middleton, WI	53562		1618	
			NOTIFICATION DATE	DELIVERY MODE
			03/26/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com jwchilders@casimirjones.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/354.282	26-Mar-2024	11938201

The Johns Hopkins University c/o Casimir Jones 2275 Deming Way Middleton, WI 53562

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https:// patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants

page 1 of 1



P.O. Box 1450 Alexandria, VA 22313 - 1450 www.uspto.gov

Page 1 of 2

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # 18/354,282	RECEIPT DATE / TIME 08/22/2024 05:18:06 PM Z ET	ATTORNEY DOCKET # JHU-36631.303
Title of Invention		
IMAGING AND RADI PROTEIN-ALPHA (F.	OTHERAPEUTICS AGENTS TARGETI AP-ALPHA)	NG FIBROBLAST-ACTIVATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	11938201
CONFIRMATION #	7536	FILED BY	Jeremiah Gile
PATENT CENTER #	66893434	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-08- 22_36631.303_Request for Certificate of Correction.pdf	7	Request for Certificate of Correction	68 KB
2024-08- 22_36631.303_CoC.pdf	4	Request for Certificate of Correction	65 KB

Digest

DOCUMENT

MESSAGE DIGEST(SHA-512)

2024-08-22_36631.303_Request for Certificate of Correction.pdf 53EE3AE1AE5E327A58F848D02BBF60B33259B1A4974B218F3 60F7EBDAF72A7B7F5B61204BFCD83910B0B90047E18CF20FA 9CC0BFC094D0A13043C223AC837C44 2024-08-22_36631.303_CoC.pdf

F43EFA29A4425069313B778D9162E39E218B14D94D5BA1FAC 5AF200E49C0CE90D07D8ACDAC1E976FDE5947CBF8AF5B4D 34F1393C3B81B30F95126567C4499A67

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT Attorney Docket No.: JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	YANG, Xing	Confirmation No.	:7536
Patent No.:	11,938,201		
Issue Date:	26-Mar-2024		
Serial No.:	18/354,282	Group No.:	1618
Filing Date:	18-Jul-2023	Examiner:	PERREIRA
Entitled:	IMAGING AND RADIOTHE	RAPEUTICS AGE	ENTS TARGETING
	FIBROBLAST-ACTIVATION	PROTEIN-ALPI	HA (FAP-ALPHA)

REQUEST FOR CERTIFICATE OF CORRECTION

VIA EFS WEB

Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450

Sir or Madam,

Pursuant to 35 U.S.C. §254 and 37 C.F.R. §1.322, applicants respectfully request that the Office issue a Certificate of Correction in the above-referenced patent. Applicant submits herewith Form PTO/SB/ requests a Certificate of Correction for the above-referenced patent and hereby submits form PTO/SB/44 showing the correction that is requested.

In the Letters Patent, Claim 1, Column 64, lines 47-67, Column 65, lines 1-62:

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

B-L-A (I)

wherein:

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

;



wherein:

 R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃;

 R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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

represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

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

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

Whereas it should read:

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

B-L-A(I)

wherein:

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



wherein:

 R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, OH, oxo, halogen, - C_{1-6} alkyl, -O- C_{1-6} alkyl, -S- C_{1-6} alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C_{1-6} alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

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

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

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂-being optionally substituted with from 1 to 3 substituents selected from $NR_{13*}R_{14*}$, $C_{1-6}alkyl$, O $C_{1-6}alkyl$, and S $C_{1-6}alkyl$;

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



represents a <u>quinolinyl ring</u>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, positronemission 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.

In the Letters Patent, Claim 3, Column 66, lines 1-67, and Column 67, lines 1-4:

3. A low molecular weight compound consisting essentially of components B-L-A; wherein:

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



wherein:

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

 R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl; R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl 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, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃; R_{10x} , R_{11x} , R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from -NR_{13x}R_{14x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; 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.-

Whereas it should read:

3. A low molecular weight compound consisting essentially of components B-L-A; wherein:

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



wherein:

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

R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

 R_{4x} is H;

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

 R_{8x} , R_{9x} and R_{12x} are each independently selected from the group consisting of H, -OH, halo, C_{1-6} alkyl, -O- C_{1-6} alkyl, -S- C_{1-6} alkyl, and -Ar₃;

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

Het₂ is a 5 or 6 membered non aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from -NR_{13*}R_{14*}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

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



represents a <u>quinolinyl ring</u> 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, positronemission 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.

Applicant submits herewith a request for certificate of correction. Applicant notes that the Supplemental Amendment to Non-Final Office Action filed December 18, 2023 was entered by the Examiner. However, the amendments were not included in the granted claims.

Because the error in the patent is a result of the Office's mistake, applicant believes that no fee is due. However, in the event a fee is due, the Commissioner is hereby authorized to charge the fee, or credit any overpayment, to Deposit Account 50-4302, referencing Attorney Docket No. **JHU-36631.303.**

Respectfully submitted,

Dated: _____ August 22, 2024

/Jeffrey W. Childers/ Jeffrey W. Childers Registration No. 58126 CASIMIR JONES, S.C. 2275 Deming Way, Suite 310 Middleton, WI 53562 Phone: (608) 662-1277 PTO/SB/44 (09-07) Approved for use through 01/31/2020. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number. (Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page <u>1</u> of <u>3</u>

 PATENT NO.
 : 11,938,201

 APPLICATION NO.:
 18/354,282

 ISSUE DATE
 : 26-Mar-2024

 INVENTOR(S)
 : YANG, Xing, et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Letters Patent, Claim 1, Column 64, lines 47-67, Column 65, lines 1-62:

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

B-L-A (I)

wherein:

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



wherein:

 R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, 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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

 R_{4x} is H;

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

v is 0;

represents a quinolinyl ring;

MAILING ADDRESS OF SENDER (Please do not use Customer Number below): Casimir Jones, S.C. 2275 Deming Way, Suite 310 Middleton, WI 53562

This collection of information is required by 37 GFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 GFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, 1450, 1450.

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UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 2 of 3

 PATENT NO.
 : 11,938,201

 APPLICATION NO.:
 18/354,282

 ISSUE DATE
 : 26-Mar-2024

 INVENTOR(S)
 : YANG, Xing, et al.

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

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

in the Letters Patent, Claim 3, Column 66, lines 1-67, Column 67, lines 1-4:

3. A low molecular weight compound consisting essentially of components B-L-A; wherein:

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



wherein:

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

MAILING ADDRESS OF SENDER (Please do not use Customer Number below): Casimir Jones, S.C. 2275 Deming Way, Suite 310 Middleton, WI 53562

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/44 (09-07)
Approved for use through 01/31/2020. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page <u>3</u> of <u>3</u>

 PATENT NO.
 : 11,938,201

 APPLICATION NO.:
 18/354,282

 ISSUE DATE
 : 26-Mar-2024

 INVENTOR(S)
 : YANG, Xing, et al

 R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

 R_{4x} is H; R_{5x} , R_{6x} and R_{7x} are each H; v is 0;



represents a quinolinyl ring;

B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) maging, 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

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.
Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

- 1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
- 2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
- 3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
- 4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
- 5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
- 6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
- 7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
- 8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
- 9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536
101943 The Johns Hon	7590 09/24/202 kins University	4	EXAM	IINER
c/o Casimir Jon	ies Nov		PERREIRA, M	ELISSA JEAN
Suite 310	vay		ART UNIT	PAPER NUMBER
Middleton, WI	53562		1618	
			NOTIFICATION DATE	DELIVERY MODE
			09/24/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com jwchilders@casimirjones.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/354,282	24-Sep-2024	11938201

The Johns Hopkins University c/o Casimir Jones 2275 Deming Way Middleton, WI 53562

ELECTRONIC CERTIFICATE OF CORRECTION NOTIFICATION

Your electronic certificate of correction is now available, and can be accessed via Patent Center at https:// patentcenter.uspto.gov.

The electronic certificate of correction is the official certificate of correction under 35 U.S.C. 254 or 255. For more information, please visit https://www.uspto.gov/electronicgrants.

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

PATENT NO.	: 11,938,201 B2
APPLICATION NO.	: 18/354282
DATED	: March 26, 2024
INVENTOR(S)	: Xing Yang et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Claim 1, Column 64, Lines 47-67, Column 65, Lines 1-62 should read: 1. A low molecular weight compound of Formula (I):

wherein:

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



B-L-A(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, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

 R_{4x} is H;

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

v is 0;



represents a quinolinyl ring;

B is any optical or radiolabeled functional group suitable for optical imaging, positronemission 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.

Signed and Sealed this Twenty-fourth Day of September, 2024 Kathevine Kelly-Vidal

Katherine Kelly Vidal Director of the United States Patent and Trademark Office

Page 1 of 2

CERTIFICATE OF CORRECTION (continued) U.S. Pat. No. 11,938,201 B2

Claim 3, Column 66, Lines 1-67, Column 67, Lines 1-4 should read:

3. A low molecular weight compound consisting essentially of components B-L-A; wherein:

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



wherein:

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

 R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

 R_{4x} is H;

 R_{5x} , R_{6x} and R_{7x} are each H; v is 0;



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



ACKNOWLEDGEMENT OF LOSS OF ENTITLEMENT TO ENTITY STATUS DISCOUNT

APPLICATION #	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET #	REQUEST ID
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	305750

The entity status change request below filed through Patent Center on 11/19/2024 has been accepted.

Certifications

APPLICANT CHANGING TO REGULAR UNDISCOUNTED FEE STATUS

Signature

I certify, in accordance with 37 CFR 1.4(d)(4), that I am one of the signatories making the entity status change.

Signature	Name	Registration #
/ Jeffrey Childers /	Jeffrey Childers	58126

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Application No.:	18/354,282
Filed:	18-July-2023
Applicant:	Xing Yang, et al.
Art Unit:	1618
Examiner:	MELISSA JEAN PERREIRA
Confirmation No.:	7536
Docket No.:	JHU-36631.303
Title:	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN- ALPHA (FAP-ALPHA)

APPLICANT'S STATEMENT REGARDING OUTSTANDING FEES DUE TO ASSERTION OF LARGE ENTITY STATUS UNDER 37 CFR 1.28(c)

Pursuant to the requirements of MPEP § 509, Applicant hereby submits this Statement Regarding Outstanding Fees in connection with the above-captioned patent application. Based on the USPTO's current fee schedule corresponding to Large Entity fees, Applicant submits the following:

U.S. Patent Application No. 18/354,282 Attorney Docket No. JHU-36631.303

	Large Entity Fee Code	Large Entity Fee	Small Entity Fee Code	Small Entity Fee Paid	Date of Small Entity Fee Payment	Difference (Amount Now Owed)
Information Disclosure Statement	1806	\$260.00	2806	\$104.00	02/05/2024	\$156.00
Petition 37CFR 1.17 (H)	1464	\$ 140.00	2464	\$ 56.00	02/02/2024	\$84.00
Information Disclosure Statement	1806	\$260.00	2806	\$104.00	01/17/2024	\$156.00
Utility Issue Fee	1501	\$1,200.00	2501	\$480.00	01/17/2024	\$720.00
Petition 37CFR 1.17 (H)	1464	\$ 140.00	2464	\$ 56.00	12/13/2023	\$84.00
Information Disclosure Statement	1806	\$260.00	2806	\$104.00	12/13/2023	\$156.00
Terminal Disclaimer	1814	\$170.00	2814	\$170.00	12/13/2023	\$0.00
Information Disclosure Statement	1806	\$260.00	2806	\$104.00	10/30/2023	\$156.00
Processing Fee, Except Prov. Appls	1830	\$140.00	2830	\$56.00	07/18/2023	\$84.00
Request for Prioritized Exam	1817	\$4,200	2817	\$1,680	07/18/2023	\$2,520
Utility Filing Fee	1011	\$ 320.00	4011	\$ 64.00	07/18/2023	\$256.00
Utility Exam Fee	1311	\$ 800.00	2311	\$ 320.00	07/18/2023	\$480.00
Utility Search Fee	1111	\$ 700.00	2111	\$ 280.00	07/18/2023	\$420.00
TOTALS:		\$ 8,850.00		\$3,578.00		\$5,272.00

Applicant also hereby authorizes the Director to charge all outstanding fees as reflected in the table above, as well as any additional fees associated with the change in Applicant's entity U.S. Patent Application No. 18/354,282 Attorney Docket No. JHU-36631.303

status, to Deposit Account Number 50-4302, referencing the Attorney Docket No. above.

Respectfully submitted,

CASIMIR JONES S.C.

Date: November 19, 2024

/Jeffrey W. Childers /

Jeffrey W. Childers, Ph.D. Registration No. 58126

CASIMIR JONES, S.C. 2275 Deming Way, Suite 310 Middleton, WI 53562 Phone: 608.662.1277 Fax: 608.662.1276



P.O. Box 1450 Alexandria, VA 22313 - 1450 www.uspto.gov

Page 1 of 2

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION # RECEIPT DATE / TIME ATTORNEY DOCK 18/354 282 11/19/2024 01:47:17 PM 7 FT .IHU-36631 3		
	303	
	(FT #	

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	11938201
CONFIRMATION #	7536	FILED BY	Van Nguyen
PATENT CENTER #	68018045	FILING DATE	07/18/2023
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)	
2024-11-19 - JHU- 36631.303_Petition-Pay-LE- Fee.pdf	3	Petition for review by the Office of Petitions	29 KB	

Digest

DOCUMENT

MESSAGE DIGEST(SHA-512)

2024-11-19 - JHU-36631.303_Petition-Pay-LE-Fee.pdf D15DC3B7F868E39643787860C1734DD430D761B8F449728936 18A5A0E70DF2D8418F5F5381509BB13C10B62DE1EF65EE57B 330DD8B8B309CD0A16EED6037DAD0

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as

described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Suad Mohammed

Sale Accounting Date:12/12/2024

Sale Item Reference N	lumber Effective Date
18354282	11/19/2024

Document NumberFee CI2024BBB280793031461

Fee CodeFee Code DescriptionAmount Paid14611.28(C) SUBMISSIONS - APPLIC\$5,272.00FILE FEE

Payment Method Deposit Account

UNITED STATES PATENT AND TRADEMARK OFFICE



UNITED STATES DEPARTMENT OF COMMERCE United States Patent and Trademark Office Address: COMMISSIONER FOR PATENTS P.O. Box 1450 Alexandria, Virginia 22313-1450 www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/354,282	07/18/2023	Xing Yang	JHU-36631.303	7536
101943 The Johns Hop	7590 12/23/202 kins University	4	EXAM	IINER
c/o Casimir Jon	ies		PERREIRA, M	ELISSA JEAN
Suite 310	vay		ART UNIT	PAPER NUMBER
Middleton, WI	53562		1618	
			NOTIFICATION DATE	DELIVERY MODE
			12/23/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com jwchilders@casimirjones.com



Commissioner for Patents United States Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450 www.uspto.gov

In re Patent No. 11,938,201	:	
Issue Date: March 26, 2024	:	
Application No. 18/354,282	:	
Filed: July 18, 2023	:	NOTICE
For: IMAGING AND	:	
RADIOTHERAPEUTICS AGENTS	:	
TARGETING FIBROBLAST-	:	
ACTIVATION PROTEIN-ALPHA (FAP-	:	
ALPHA)	:	

This is a Notice regarding the request for acceptance of a fee deficiency submission under 37 CFR 1.28(c) filed November 19, 2024.

The Office no longer investigates or rejects original or reissue applications under 37 CFR 1.56. 1098 Off. Gaz. Pat. Office 502 (January 3, 1989). Therefore, nothing in this Notice is intended to imply that an investigation was done.

The fee deficiency submission under 37 CFR 1.28(c) is <u>ACCEPTED</u>. Accordingly, status as a small entity has been removed and any future fees submitted must be paid at the undiscounted rate.

Inquiries related to this communication should be directed to Ann Marie Ziegler at (571) 272-7151.

/ANN MARIE ZIEGLER/ Ann Marie Ziegler Paralegal Specialist, Office of Petitions