DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 18354282 Document Date: 07/18/2023

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.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via DAV or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: March 1, 2019

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Xing YANG	Nonprovisional Application Number (if known):	
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.

1. 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.

2. 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. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. 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.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Jeffrey W. Childers/	Date 2023-07-18
Name (Print/Typed) Jeffrey W. Childers	Practitioner Registration Number 58126

Note: *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.**

☑ *Total of 1 forms are submitted.

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.

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 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.

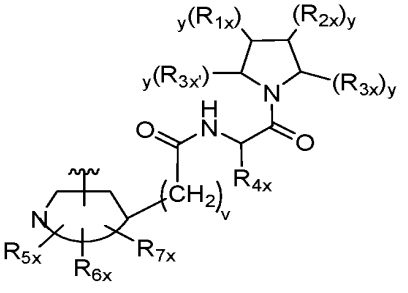
SUMMARY

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

(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.

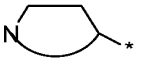
In particular aspects, A is an FAP-α targeting moiety having the structure of:



(X');

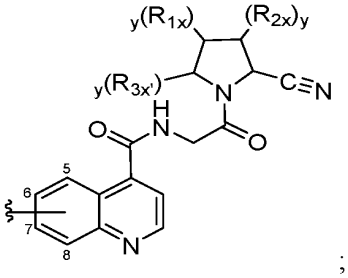
wherein each y is independently an integer selected from the group consisting of 0, 1, and 2; R_{1x}, R_{2x}, and $R_{3x'}$, are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl; R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$, -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl; R_{4x} is H; R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of $C_{1\text{-}6}$alkyl being optionally substituted with from 1 to 3 substituents

selected from -OH and halogen; R_{8x}, R_{9x}, and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and -Ar_3; R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; v is 0, 1, 2, or 3; and



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

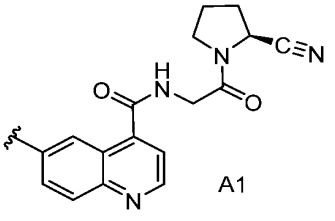
In more particular aspects, A is an FAP-α targeting moiety having the structure of:

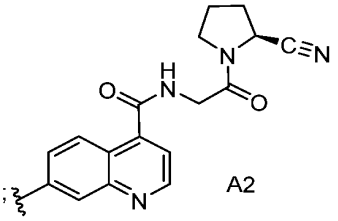


;

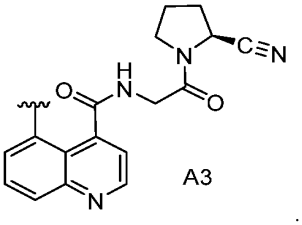
wherein ⟆ indicates a point of attachment of the FAP-α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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


A1


A2

; and


A3

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 ^{1}H 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, **[^{111}In]-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 ^{111}In and HPLC purification resulted in the radiolabeled product, **[^{111}In]-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 FAP-negative 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 **[^{111}In]-XY-FAP-02** in FAP-positive U87 and FAP-negative PC3 cell lines. Cells were incubated with 1 μCi **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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. [a]Student'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. [b]Student'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 ($p=0.0006$). [c]Student'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 **[^{111}In]-XY-FAP-02**. FIG. 5A shows tissue time activity curves (TACs) of **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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

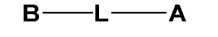
The highly potent and specific binding moiety targeting FAP-α enables its use in nuclear imaging and radiotherapy. The presently disclosed subject matter provides the first synthesis of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to FAP-α.

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, ^{68}Ga, ^{64}Cu, ^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{125}I, ^{124}I, 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, ^{90}Y, ^{177}Lu, ^{125}I, ^{131}I, ^{211}At, ^{111}In, ^{153}Sm, ^{186}Re, ^{188}Re, ^{67}Cu, ^{212}Pb, ^{225}Ac, ^{213}Bi, ^{212}Bi, ^{212}Pb, and ^{67}Ga, 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 ^{111}In labeled ligand (**XY-FAP-02-[^{111}In]**) 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):

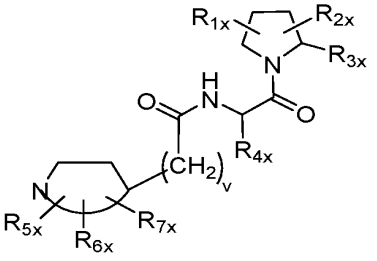


(I)

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:



(X);

wherein:

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

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

R_{4x} is H;

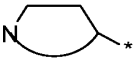
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, $-NR_{8x}R_{9x}$, $-OR_{12x}$, $-Het_2$ and $-Ar_2$; each of $C_{1\text{-}6}$alkyl being optionally substituted with 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, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, and $-Ar_3$;

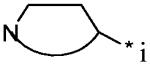
R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 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 $-NR_{10x}R_{11x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

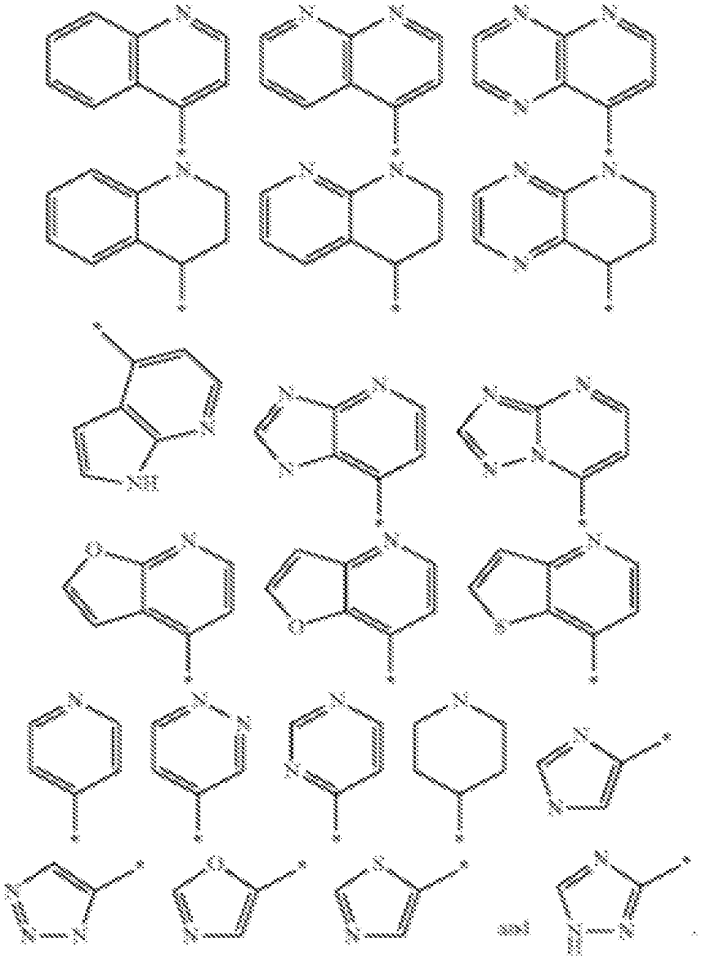
Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

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.

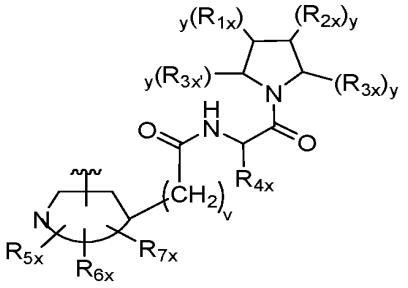
In particular embodiments,  is selected from the group consisting of:



;

wherein * indicates the point of attachment of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle to $-(CH_2)_v-$.

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



(X');

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

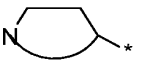
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH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

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

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

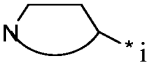
Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

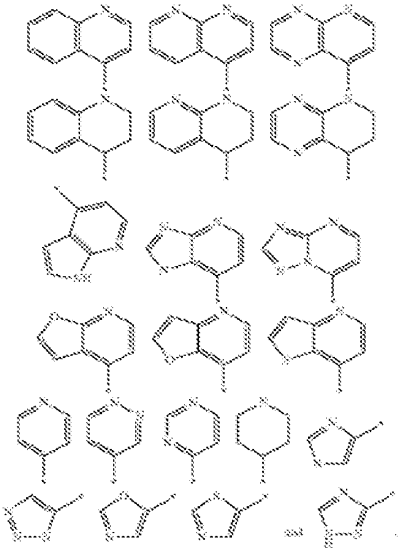
v is 0, 1, 2, or 3; and



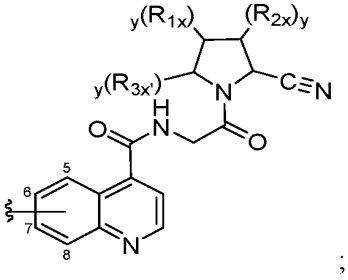
represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

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.

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



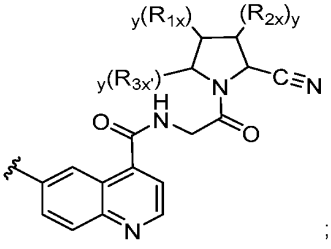
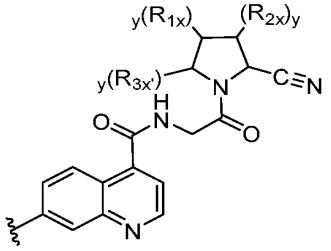
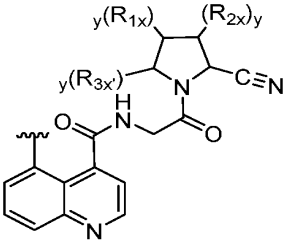
In some embodiments, A is an FAP-α targeting moiety having the structure of:



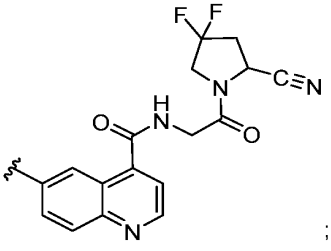
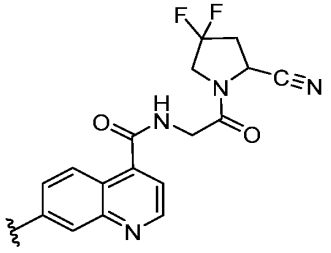
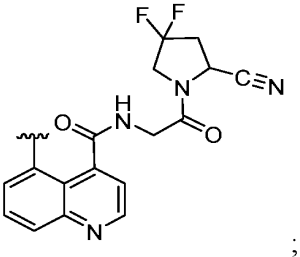
;

wherein y, R_{1x}, R_{2x} and $R_{3x'}$ are defined as hereinabove; ⟆ 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:

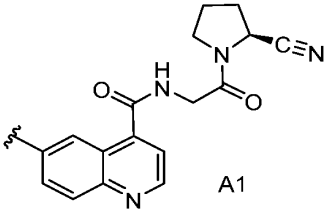
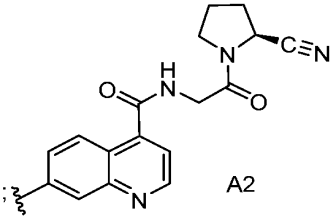
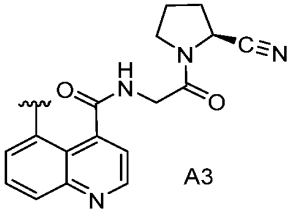

; 
; and 
.

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

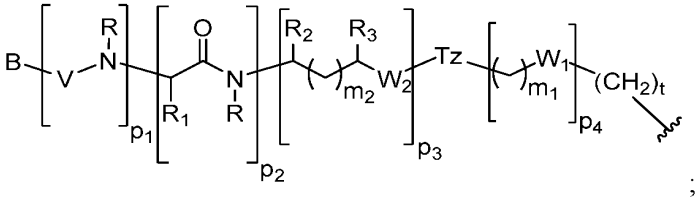

; 
; and 
;

and stereoisomers thereof.

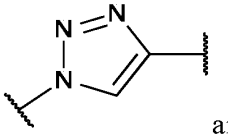
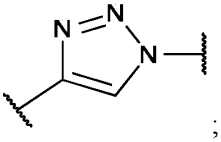
In yet more particular embodiments, A is selected from the group consisting of:


A1 ; 
A2 ; and 
A3 .

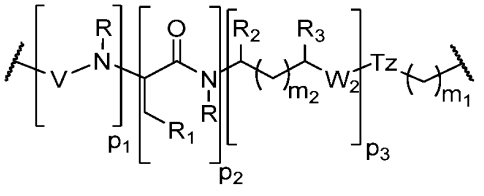
In some embodiments, the combination of L and B can be represented by:


;

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 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)–; W_2 is selected from the group consisting of a bond, -S-, -CH_2-C(=O)-NR-, –C(O)–, –NRC(O)–, –NR'C(O)NR–, –NRC(S)NR'$_2$–, –NRC(O)O–, –OC(O)NR–, –OC(O)–, –C(O)NR–, –NR–C(O)–, –C(O)O–, –(O–CH_2–CH_2)$_q$– and –(CH_2-CH_2-O)$_q$–, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and –OR_4, wherein R_4 is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove; Tz is a triazole group that can be present or absent and, if present, is selected from the group consisting of


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 $-L_1-$, $-L_2-L_3-$, and $-L_1-L_2-L_3-$, wherein:

L_1 is $-NR-(CH_2)_q-[O-CH_2-CH_2-O]_q-(CH_2)_q-C(=O)-$;

L_2 is $-NR-(CH_2)_q-C(COOR_5)-NR-$; and

L_3 is $-(O=)C-(CH_2)_q-C(=O)-$;

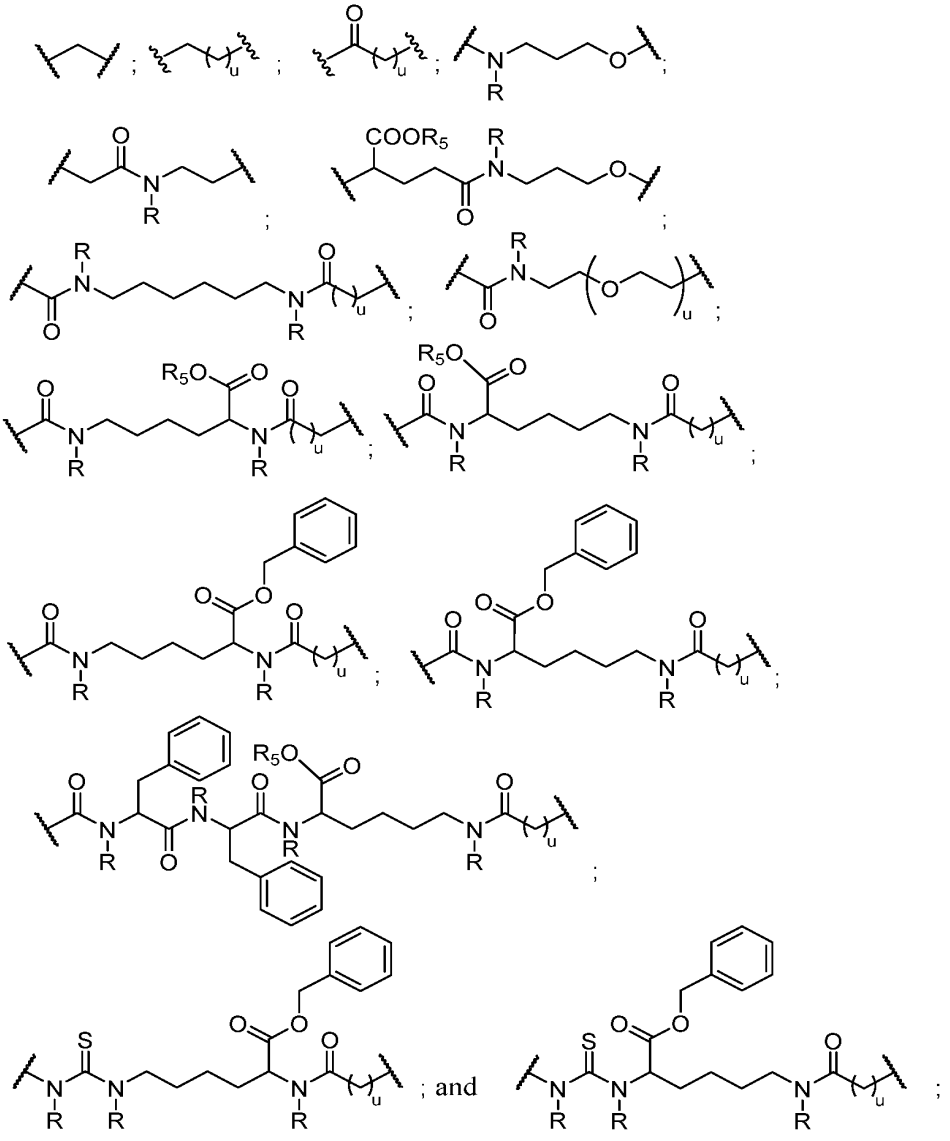
wherein each q is independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

In particular embodiments, L is:

$-(CR_6H)_q-(CH_2)_q-C(=O)-NR-(CH_2)_q-O-$ or $-NR-(CH_2)_q-O-$;

wherein each q and R is defined hereinabove; and R_6 is H or $–COOR_5$.

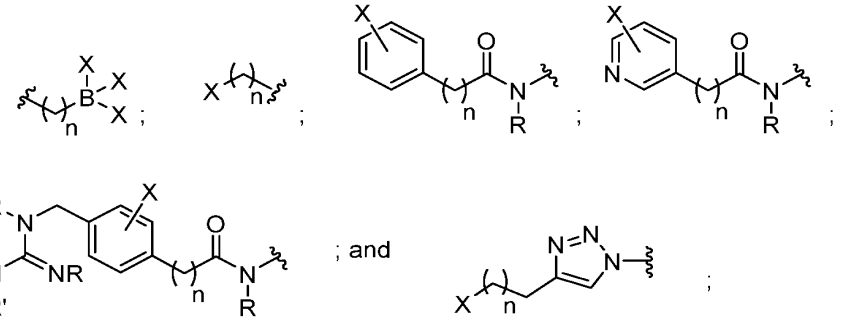
In yet more particular embodiments, L is selected from the group consisting of:



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.

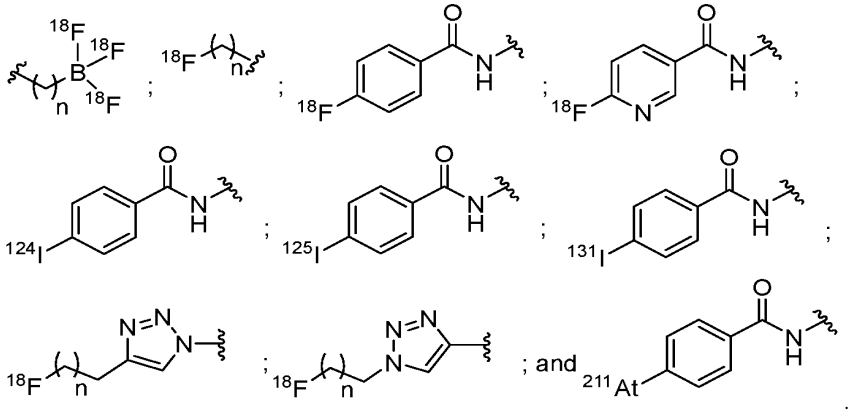
Suitable linkers are disclosed in U.S. Patent Application Publication No. US2011/0064657 A1, for "Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA), Biological Evaluation, and Use as Imaging Agents," published March 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. 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 ^{18}F, ^{124}I, ^{125}I, ^{131}I, and ^{211}At. Representative radiolabeled prosthetic groups include, but are not limited to:

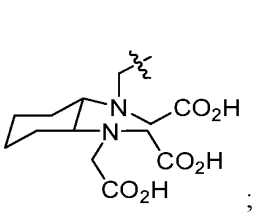
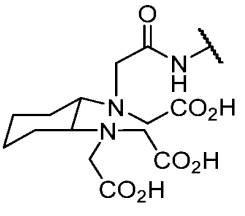
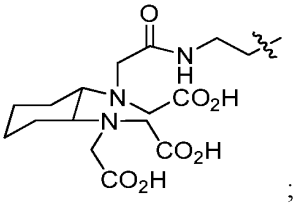
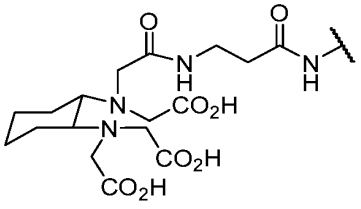
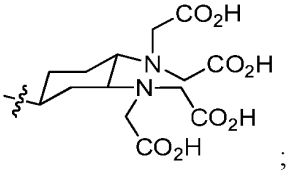
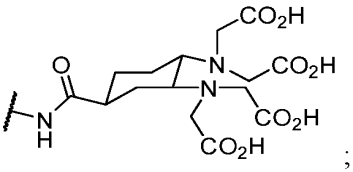
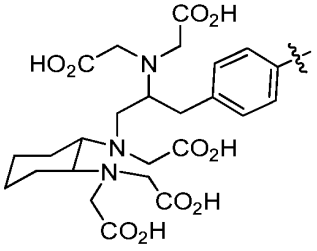
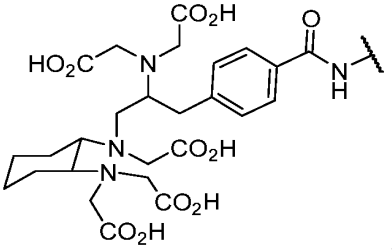
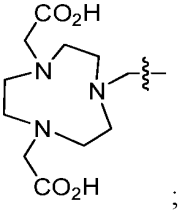
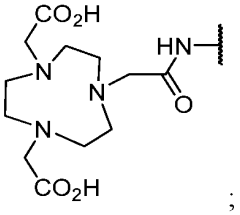
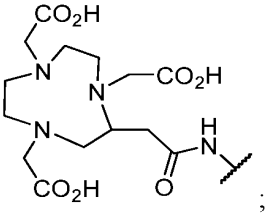
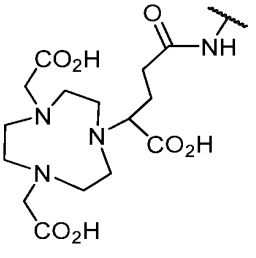
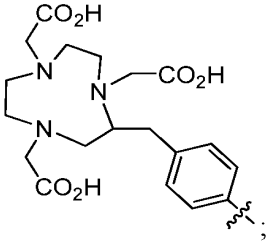
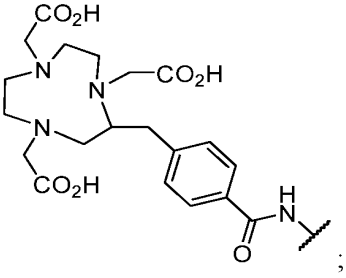
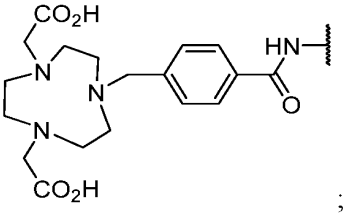
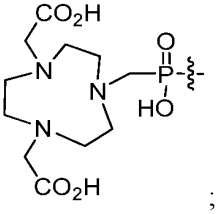
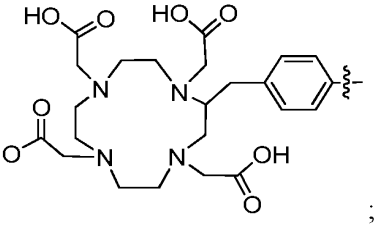
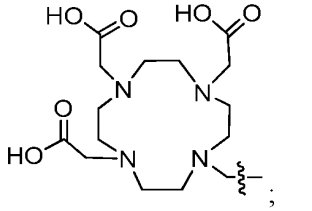


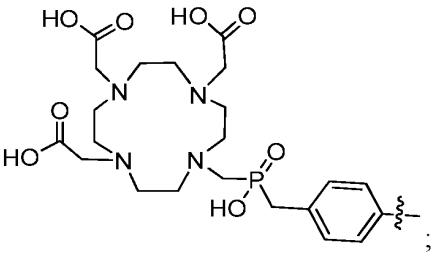
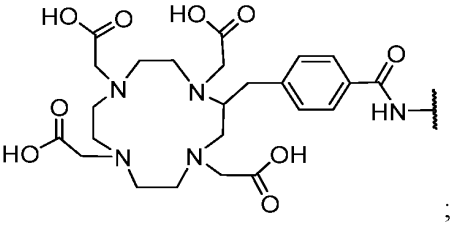
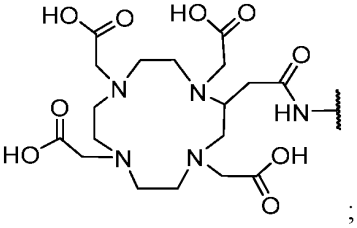
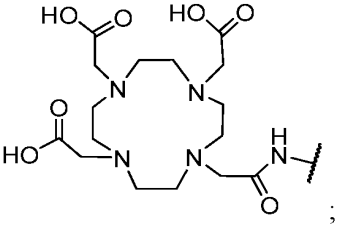
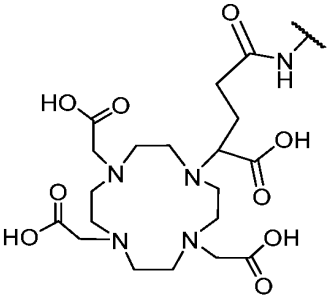
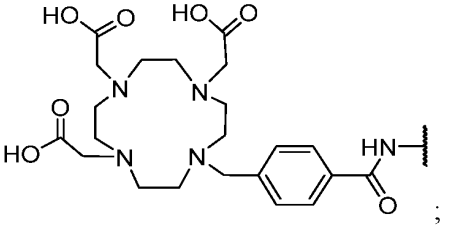
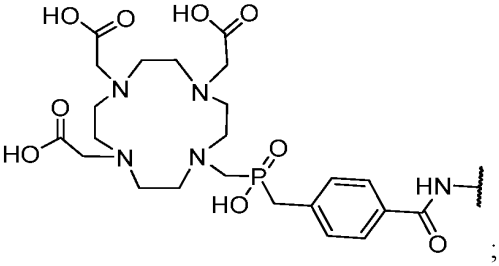
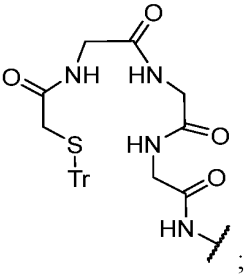
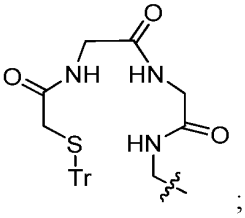
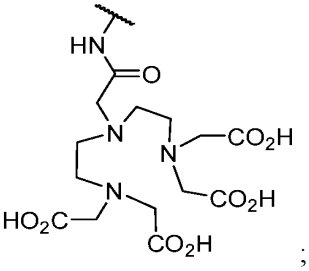
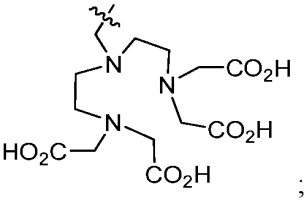
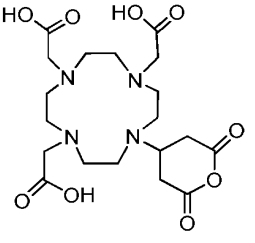
wherein each X is independently a radioisotope selected from the group consisting of ^{18}F, ^{124}I, ^{125}I, ^{131}I, and ^{211}At; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,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

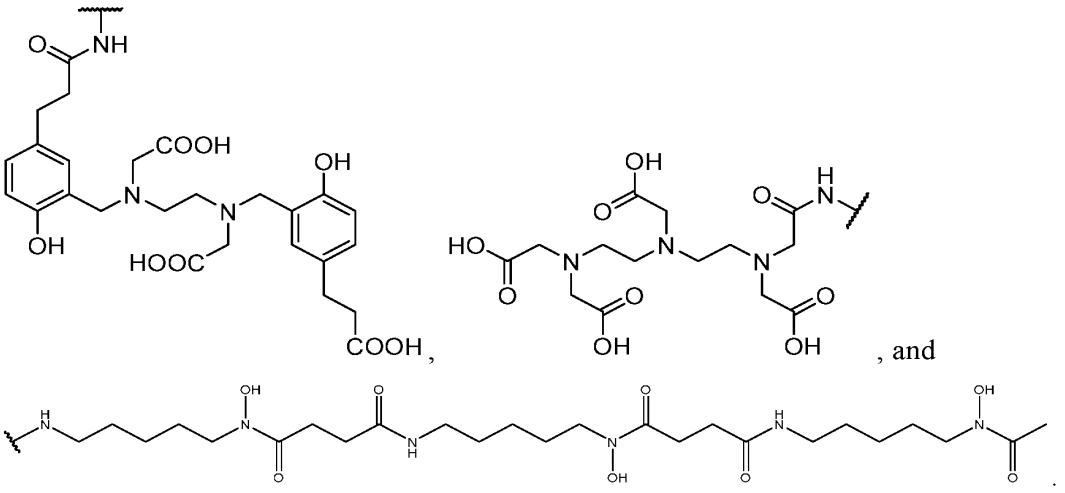
In more particular embodiments, the radiolabeled prosthetic group is selected from the group consisting of:



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

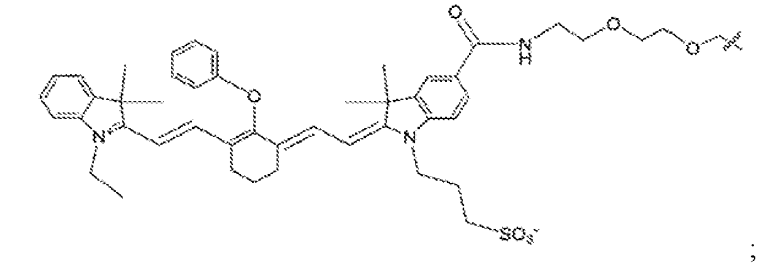

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;


;

;

;

;

;

;

;

;

;

;

;

;

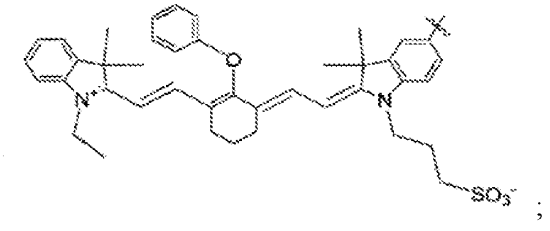


In some embodiments, B comprises an optical dye, e.g., in particular embodiments, a fluorescent dye. In some embodiments, the fluorescent dye moiety comprises carbocyanine, indocarbocyanine, oxacarbocyanine, thiacarbocyanine and merocyanine, polymethine, coumarine, rhodamine, xanthene, fluorescein, boron-dipyrromethane (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.

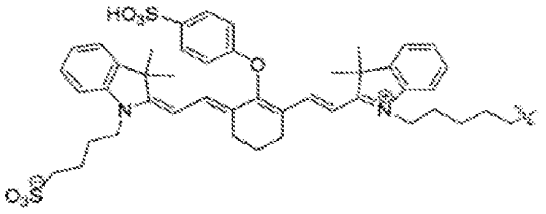
Representative optical dyes include, but are not limited to:



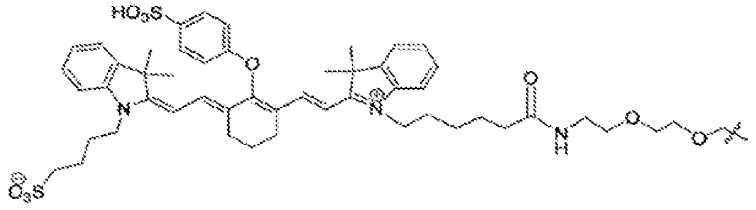
;



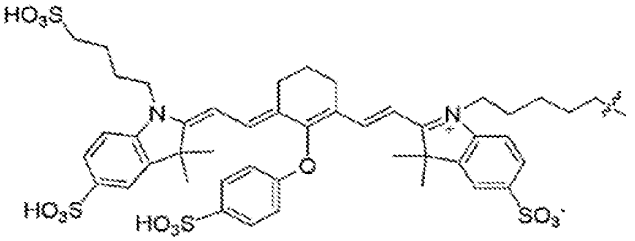
;

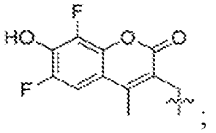


;

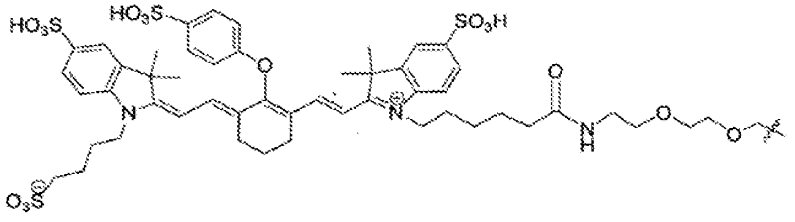


;

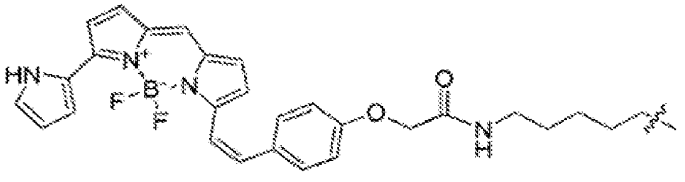


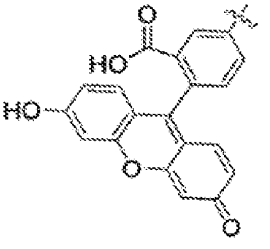


; ;

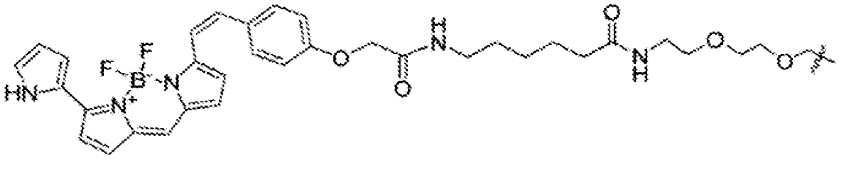


;

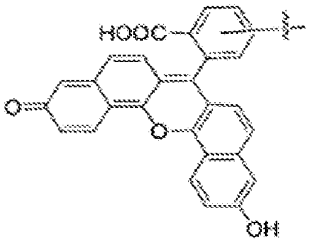




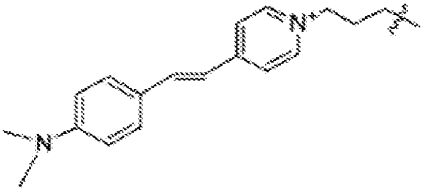
; ;



;

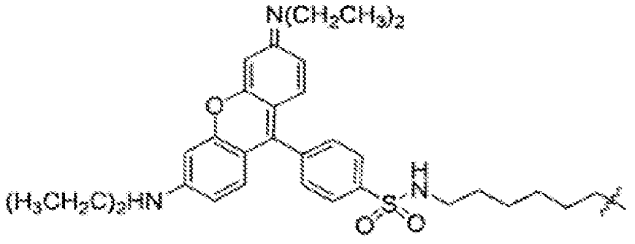


;



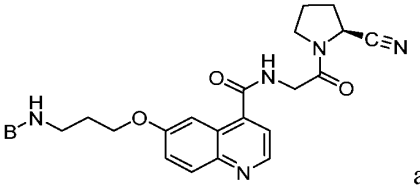
;

and

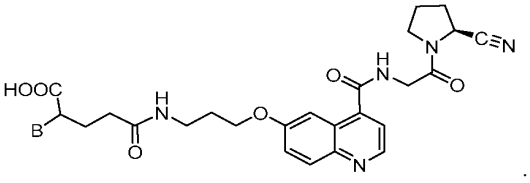


.

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

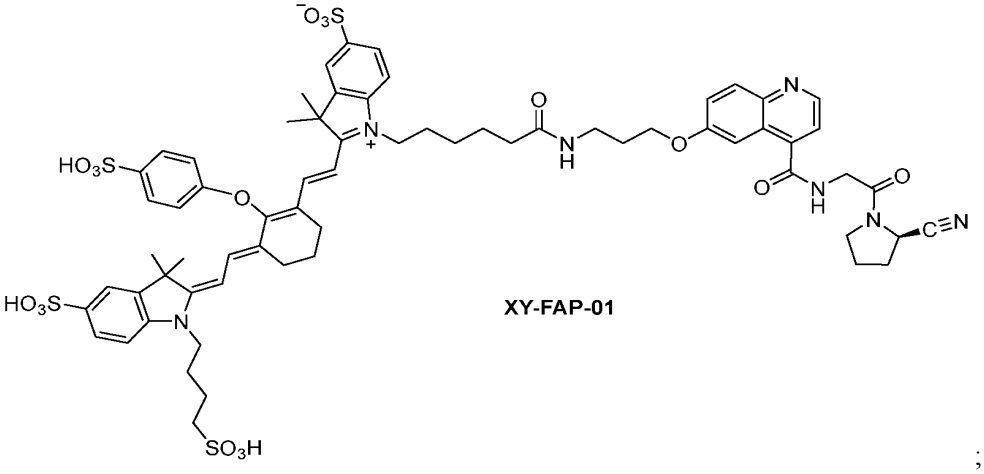


and



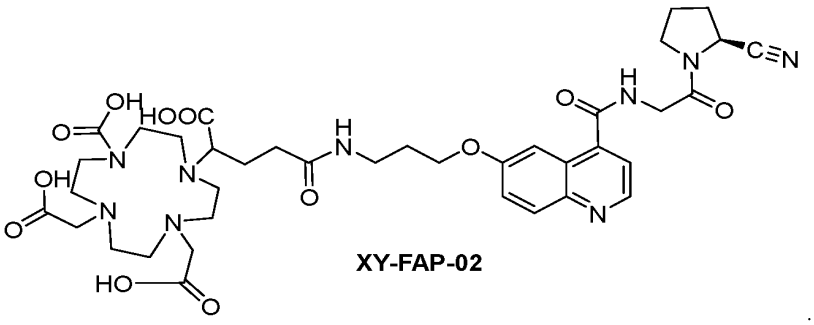
.

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



XY-FAP-01

; and



XY-FAP-02

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, p-

toluenesulfonic, 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. Dye-stuffs 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 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.

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

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 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 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, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_{25}-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

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 10-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-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 7-membered 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, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(l,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 (–CH_2–); ethylene (–CH_2–CH_2–); propylene (–$(CH_2)_3$–); cyclohexylene (–C_6H_{10}–); –CH=CH–CH=CH–; –CH=CH–CH_2–; -$CH_2CH_2CH_2CH_2$-, -CH_2CH=$CHCH_2$-, -CH_2CsCCH_2-, -$CH_2CH_2CH(CH_2CH_2CH_3)CH_2$-, -$(CH_2)_q$-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–CH_2–O–); and ethylenedioxyl (-O-$(CH_2)_2$–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.

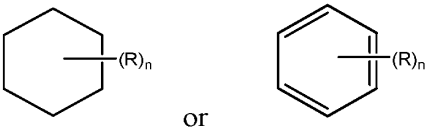
The term "heteroalkylene" by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, -CH_2-CH_2-S-CH_2-CH_2- and -CH_2-S-CH_2-CH_2-NH-CH_2-. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (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, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-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-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., 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.

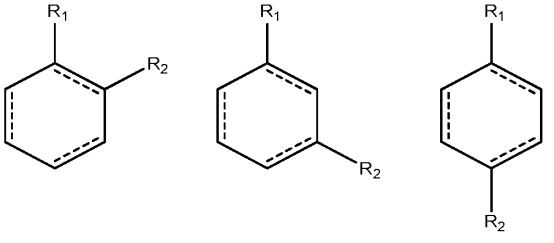
Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" refers to a carbon or heteroatom.

Further, a structure represented generally by the formula:



or

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', -CO_2R',-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', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2 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 4-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., -CF_3 and -CH_2CF_3) and acyl (e.g., -C(O)CH_3, -C(O)CF_3, -C(O)CH_2OCH_3, 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', -CO_2R', -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', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxo, and fluoro(C_1-C_4)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 cycloalkyl, substituted 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-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- 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 -$S(O)_2$NR'-. 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., C_6H_5-CH_2-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 $-(CH_2)_k-$ 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 $–NO_2$ 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 $–SO_4$ 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 $–NH—CO—NH_2$.

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.

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.

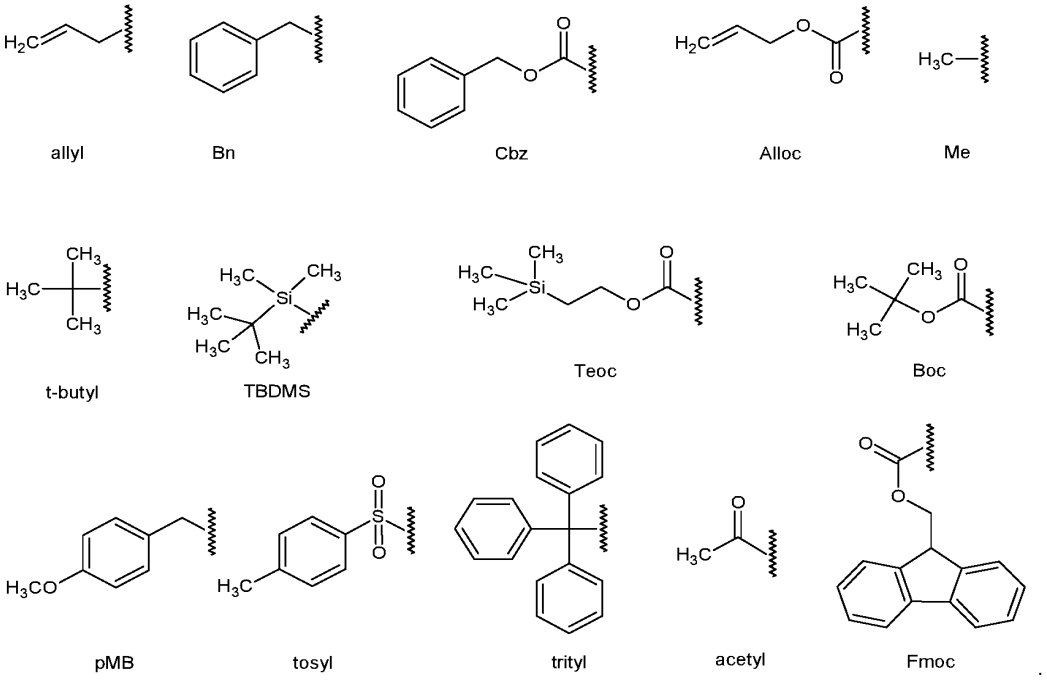
The term "protecting group" refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, Protective 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 co-existing 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:



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, ± 100% in some embodiments ± 50%, in some embodiments ± 20%, in some embodiments ± 10%, in some embodiments ± 5%, in some embodiments ±1%, in some embodiments ± 0.5%, and in some embodiments ± 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.

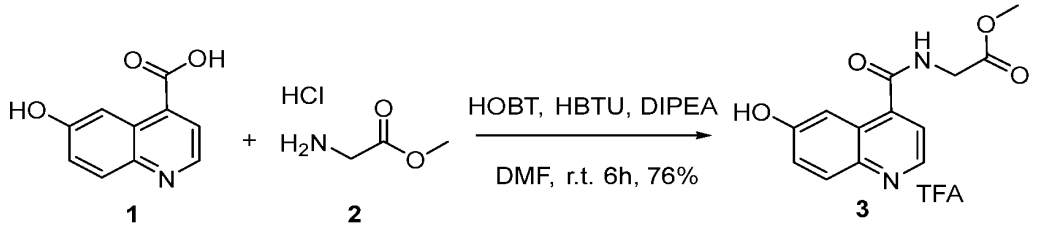
EXAMPLES

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

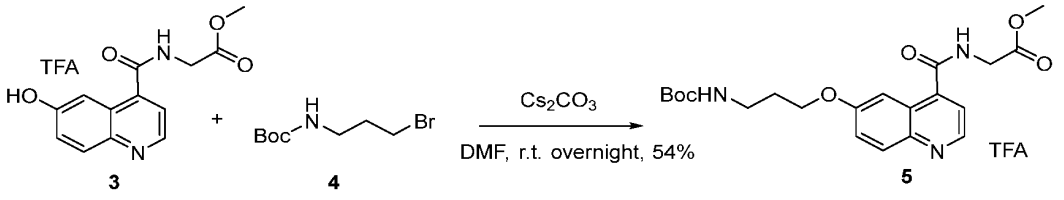
Experimental Procedures

*1.1 Synthesis of **XY-FAP-01**.*

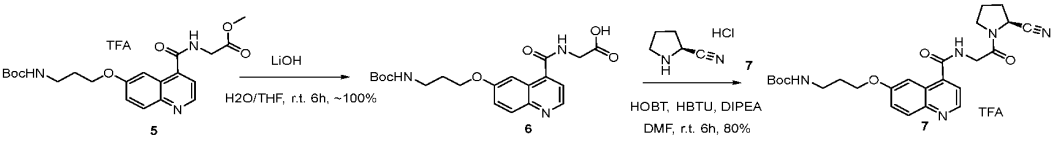


Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**): 6-Hydroxyquinoline-4-carboxylic acid (**1**) 210 mg (1.1 mmol), methyl glycinate HCl salt (**2**) 143 mg (1.1 mmol), HBTU 420 mg (1.1 mmol) and HOBt 170 mg (1.1 mmol) were dissolved in 12 mL dry DMF. To the solution, 0.77 mL of DIPEA (4.4 mmol) 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%. ^{1}H-NMR (400 MHz, CD_3OD): 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). ^{13}C-NMR (100 MHz, CD_3OD): 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.

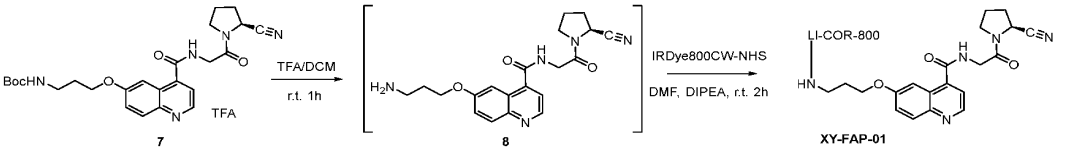


Methyl (6-(3-((tert-butoxycarbonyl)amino)propoxy)quinoline-4-carbonyl)glycinate (**5**): Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**) 360 mg (1.0 mmol), tert-butyl (3-bromopropyl)carbamate (**4**) 500 mg (2.1 mmol) were dissolved in 20 mL DMF. Cs_2CO_3 1 g (3.0 mmol) was added to the solution 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%. ^{1}H-NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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.



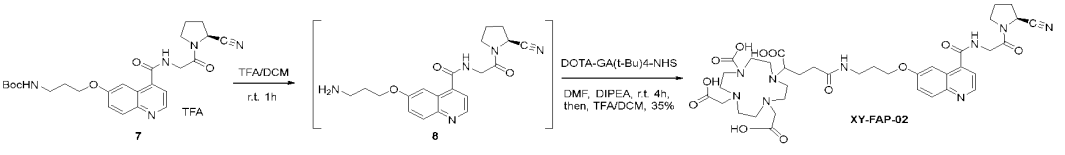
tert-Butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate (7): Compound **5** 110 mg (0.21 mmol) and LiOH 30 mg (1.2 mmol) was stirred in 4 mL of H_2O/THF (1/1) for 6 hours. After most of the THF was removed under vacuum, the mixture was loaded onto a 25 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%. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $[C_{25}H_{32}N_5O_5]^+$, 482.6 $[M + H]^+$; found 482.3.



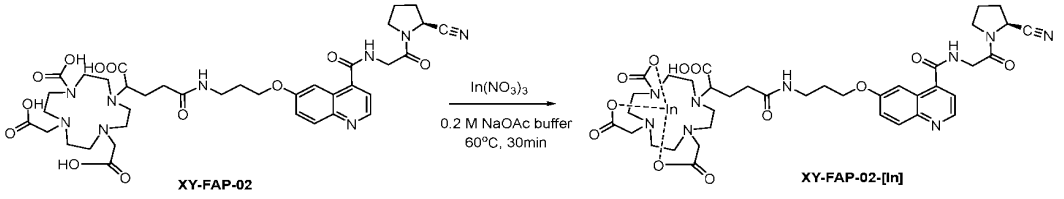
XY-FAP-01. Compound 7 (1 mg, 1.7 μmol) was treated with a 1 mL solution of TFA/methylene chloride (1/1) for 2 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMSO. To the solution, LICOR800CW-NHS ester 0.5 mg (0.43 μmol) and Et_3N 10 μL were added. After 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/H_2O/TFA to 80/20/0.1 MeCN/H_2O/TFA within 15 min at a flow of 3 mL/min. The product was eluted at 10.1 min. MS: Calculated for$[C_{66}H_{76}N_7O_{17}S_4]^+$, 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)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)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, H_2O 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 $In(NO_3)_3$ 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 $^{111}InCl_3$ 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 µm C_{18} Luna 4.6 x 250 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, **^{111}In-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, **^{111}In-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 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 IC_{50} 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).

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% penicillin-streptomycin, 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 (CO_2) 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% CO_2. 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% CO_2. 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 **^{111}In-XY-FAP-02** was also assessed in cells. Cell aliquots (1 million) were incubated with 1 μCi **^{111}In-XY-FAP-02** in saline for 30 minutes at 37 °C and 5% CO_2. 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 **^{111}In-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 μCi **^{111}In-XY-FAP-02** in 200 μL 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 CO_2 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 Wizard^2 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 μg per mouse) and 10 μCi **^{111}In-XY-FAP-02** in 200 μL saline. Mice (n=5) injected with 10 μCi **^{111}In-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

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 mm^3.

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, **^{111}In-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 **^{111}In-XY-FAP-02** in the engagement of FAP *in vitro*.

2.3 Ex-vivo Biodistribution. *Ex-vivo* biodistribution of **^{111}In-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 **^{111}In-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.

Allinen M, Beroukhim R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, Schnitt S, Sellers WR, Polyak K. Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004 Jul;6(1):17-32.

Bae S, Park CW, Son HK, Ju HK, Paik D, Jeon CJ, Koh GY, Kim J, Kim H. Fibroblast activation protein alpha identifies mesenchymal stromal cells from human bone marrow. Br J Haematol. 2008 Sep;142(5):827-30.

Chen ZY, Wang YX, Lin Y, Zhang JS, Yang F, Zhou QL, Liao YY. Advance of molecular imaging technology and targeted imaging agent in imaging and therapy. Biomed Res Int. 2014; 2014 : 819324. PMCID: PMC3943245.

Coenen HH, Elsinga PH, Iwata R, Kilbourn MR, Pillai MR, Rajan MG, Wagner HN Jr. Zaknun JJ. Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727–740.

Coenen HH, Elsinga PH, Iwata R, Kilbourn MR, Pillai MR, Rajan MG, Wagner HN Jr. Zaknun JJ. Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727–740. 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.

Edosada CY, Quan C, Tran T, Pham V, Wiesmann C, Fairbrother W, Wolf BB. 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 E, Chaitanya K, Wuest T, et al. Radioimmunotherapy of fibroblast activation protein positive tumors by rapidly internalizing antibodies. Clin Cancer Res. 2012;18:6208–6218.

Franco OE, Shaw AK, Strand DW, Hayward SW. Cancer associated fibroblasts in cancer pathogenesis. Semin Cell Dev Biol. 2010 Feb;21(1):33-9.

Garin-Chesa P, Old LJ, Rettig WJ. 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 K, Heirbaut L, Cheng JD, Joossens J, Ryabtsova O, Cos P, Maes L, Lambeir AM, De Meester I, Augustyns K, Van der Veken P. 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 K, Heirbaut L, Verkerk R, Cheng JD, Joossens J, Cos P, Maes L, Lambeir AM, De Meester I, Augustyns K, Van der Veken P. 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 T. 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.

Kraman M, Bambrough PJ, Arnold JN, Roberts EW, Magiera L, Jones JO, Gopinathan A, Tuveson DA, Fearon DT. Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. Science. 2010 Nov 5;330(6005):827-30.

Laverman P, van der Geest T, Terry SY, Gerrits D, Walgreen B, Helsen MM, Nayak TK, Freimoser-Grundschober A, Waldhauer I, Hosse RJ, Moessner E, Umana P, Klein C, Oyen WJ, Koenders MI, Boerman OC. 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.

Lo PC, Chen J, Stefflova K, Warren MS, Navab R, Bandarchi B, Mullins S, Tsao M, Cheng JD, Zheng G. Photodynamic molecular beacon triggered by fibroblast activation protein on cancer-associated fibroblasts for diagnosis and treatment of epithelial cancers. J Med Chem. 2009 Jan 22;52(2):358-68.

Poplawski SE, Lai JH, Li Y, Jin Z, Liu Y, Wu W, Wu Y, Zhou Y, Sudmeier JL, Sanford DG, Bachovchin WW. Identification of selective and potent inhibitors of fibroblast activation protein and prolyl oligopeptidase. J Med Chem. 2013 May 9;56(9):3467-77.

Reilly RM, Lam K, Chan C, Levine M. Advancing Novel Molecular Imaging Agents

from Preclinical Studies to First-in-Humans Phase I Clinical Trials in Academia-A Roadmap for Overcoming Perceived Barriers. Bioconjugate chemistry. 2015; 26:625–632.

Rettig WJ, Garin-Chesa P, Healey JH, Su SL, Ozer HL, Schwab M, Albino AP, Old LJ. Regulation and heteromeric structure of the fibroblast activation protein in normal and transformed cells of mesenchymal and neuroectodermal origin Cancer Res. 1993 Jul 15;53(14):3327-35.

Ryabtsova O, Jansen K, Van Goethem S, Joossens J, Cheng JD, Lambeir AM, De Meester I, Augustyns K, Van der Veken P. Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity. Bioorg Med Chem Lett. 2012 May 15;22(10):3412-7.

Scanlan MJ, Raj BK, Calvo B, Garin-Chesa P, Sanz-Moncasi MP, Healey JH, Old LJ, Rettig WJ. Molecular cloning of fibroblast activation protein alpha, a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. Proc Natl Acad Sci U S A. 1994 Jun 7;91(12):5657-61.

Scott AM, Wiseman G, Welt S, Adjei A, Lee FT, Hopkins W, Divgi CR, Hanson LH, Mitchell P, Gansen DN, Larson SM, Ingle JN, Hoffman EW, Tanswell P, Ritter G, Cohen LS, Bette P, Arvay L, Amelsberg A, Vlock D, Rettig WJ, Old LJ. A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res. 2003 May;9(5):1639-47.

Tsai TY, Yeh TK, Chen X, Hsu T, Jao YC, Huang CH, Song JS, Huang YC, Chien CH, Chiu JH, Yen SC, Tang HK, Chao YS, Jiaang WT. Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein. J Med Chem. 2010 Sep 23;53(18):6572-83.

Tuxhorn JA, Ayala GE, Smith MJ, Smith VC, Dang TD, Rowley DR. Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling. Clin Cancer Res. 2002 Sep;8(9):2912-23.

Welt S, Divgi CR, Scott AM, Garin-Chesa P, Finn RD, Graham M, Carswell EA, Cohen A, Larson SM, Old LJ, 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 H., Hong K. In vivo noninvasive small animal molecular imaging. Osong Public Health Res Perspect. 2012; 3 :48-59. PMCID: PMC3738683.

Yu DM, Yao TW, Chowdhury S, Nadvi NA, Osborne B, Church WB, McCaughan GW, Gorrell MD. The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J. 2010 Mar;277(5):1126-44.

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.

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.

REMARKS

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

PTO/AIA/82B (07-13)
Approved for use through 03/31/2021. OMB 0651-0035
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

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
16/758,182	22-Apr-2020

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☑ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above: 101943

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☑ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

THE JOHNS HOPKINS UNIVERSITY

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	Steve Kousouris	Date (Optional)	5/8/2020
Name	Steven Kousouris		
Title	Executive Director, Johns Hopkins Technology Ventures, The Johns Hopkins University		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☑ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. 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 1.11 and 1.14. This collection is estimated to take 3 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, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
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.

DECLARATION (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 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.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Xing Yang Date (Optional): 06/24/2020

Signature: Xing Yang

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.

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 file (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 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.

PTO/AIA/01 (05-12)
Approved for use through 11/30/2020. OMB 0651-0032
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.

DECLARATION (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 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.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Sridhar Nimmagadda Date (Optional): _____

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.

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 file (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 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.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
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.

DECLARATION (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 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.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Steven Rowe Date (Optional): 9-25-2020

Signature: Steven P. Rowe

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.

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 file (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 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.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
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.

DECLARATION (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 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.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Stephanie Slania Date (Optional): June 24th, 2020

Signature: Stephanie Slania

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.

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 file (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 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.

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.

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
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.

DECLARATION (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 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.

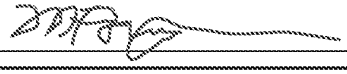
I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Martin G. Pomper Date (Optional): June 23, 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.

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 file (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 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.

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

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**07/18/2023 03:48:57 PM ET**	**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	Stephanie Filandrinos
PATENT CENTER #	62461174	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	**E20237HF49225607**	**Stephanie Filandrinos**

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**

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

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**07/18/2023 03:48:57 PM ET**	**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	Stephanie Filandrinos
PATENT CENTER #	62461174	FILING DATE	-
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey 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

2023-07-18_36631.303_IDS.pdf		6	Information Disclosure Statement (IDS) Form (SB08)	338 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems. The attached file contains comments or annotations. Comments are not recommended and may cause processing problems with the document.

2023-07-18_36631.303_ADS.pdf		10	Application Data Sheet	260 KB

Warning: This is not a USPTO supplied ADS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

2023-07-18_36631.303_EXEC_POA.pdf		1	Power of Attorney	842 KB
2023-07-18_36631.303_Application.pdf		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_All.pdf		7	Oath or Declaration filed	3575 KB

2023-07-18_36631.303_439.pdf	2	Internet Communications Authorization	76 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-07-18_36631.303_PA.pdf	589F98142A13035D0BDA4E51DD1BA0806109335269F43EC87789DC11158B9DF42B932FB5BC70C6AE0C4D1DB4A8C569CEC2EEA4BF0C76673D6918662DA2A1B2D6
2023-07-18_36631.303_PA-A.PE.pdf	C87350B484F36946BC1F00E2BA0D3DEEC72E5E563868A5B43A31C28530D4B1A79B7E6115D0CC79BFB8797AA362F13056A0FA6E0763142E736AB4F1B7FB3B6046
2023-07-18_36631.303_PA-CLM.pdf	E37326019EEF8242C9E73CB3D93D417A9C67B30215B711FE790692478FE039862CF4DE499306AB4D7E8F3C5E5F65692991090A8776511D9ACADE587B26301BE6
2023-07-18_36631.303_PA-REM.pdf	9790B3D28A854D4CC329BA5D5F1232FE263C55C0F257904549CB9CA5C20E2016500D99A27179001B34A14258DD5F99D5937F58392EE75AC1C8DECD3667D473A8
2023-07-18_36631.303_Track1.pdf	1CFA770E503CD3319E0BDF93021043D8A608F7511383802DB246BF27CA3BA83B342E64A192375CEE7F17733F27E13EB134E3A0D7F93BD673ABCAB9D2B8124C40
2023-07-18_36631.303_IDS.pdf	B9E3D9C15AA1556E42B8AF24BDEFCCEBE3DF0B46CB0703C649B3FB0BF76018C61C1F068281308CA27B6EF326B8A7740D278D20CE7B90D4E40A5BD527BBC409E7
2023-07-18_36631.303_ADS.pdf	8CA01476B26682A1346894C56533F8D114F0FD42E5FE626D0098243154CA28E4A6695CC17E9B4878D3DB35A004ABDA4BA5DF171FC782A1CD1157B33BDFB1B6D5
2023-07-18_36631.303_EXEC_POA.pdf	64099E8B5B3623CDBC0D19368EFF9BB05C127C22F1473147C0CE0990CFD37787BA6DBEACE2EE4C94B44F97EE9C26F48AAA3071A3A956F26924039FFBA17C730E

2023-07-18_36631.303_Application.pdf	7D41E713DCCE64390A7F8BBB95901E6F7D3B03827BD843D255C9FDAAF59EBC9BDBC21C3AF573C65E923B80997FA2B1C57BE3497EECAD2A732828A32A3EED221F
2023-07-18_36631.303_Application-SPEC.pdf	ED282DE61FB526452378B17C5A82BE68BCBDA86163471834F1FFFBEE721DB418AD86E4A64151AD8178405A7EC185E6366FCE2EDF4D8AA37409C3202CF07E3A94
2023-07-18_36631.303_Application-CLM.pdf	9E358B6DCD250D432C58DB1D5E3B0CF669DFC61A905756FAD1C0F46A33258BF4D4FC0B6EF6AEA6F57C69CF00C64F48E0F6F65C21AD5E5FE7181DF1B915519C62
2023-07-18_36631.303_Application-ABST.pdf	EF17C9C6F7FD9FE9684C08807F1239436EAE98F670B19C97B59BB6C45C1B519054FB3ACF56801D7D6F83AC0E8D0A8396F7CBBDD9D9C2EF745A8F903BDCCDBAD1
2023-07-18_36631.303_FIGURES.pdf	4673E55683B95B65D0CAFD7A640CC90E4C63CCDD3CB4175B6F8FBF27EFF865EB31968B6A493D0E23A3635FA28D2356BD72773CDA84A705093997187DB0E24EDC
2023-07-18_36631.303_ExecDecls_All.pdf	71F5B35CDBE683B4AAF18EE60711C44AB1FFEE464AE7D04A153526EF437860995F7B8629133EF2EBF0DFFDD3E69FE18034EA1CCE79E6F8D92C2FFE263DB9401E
2023-07-18_36631.303_439.pdf	CA8B15D710940A714443BE075B4F028BF64C37A3BA85CCEDC24FFDED11CA3C434FE125E46FBE5529DB4DF76860744F7487D4A93F5369B4936F0704FF55CD1E22

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.

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

U.S. PATENTS					
Examiner 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					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(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
		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						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[5] Number[6] Kind Code[7] *(if known)*	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]
		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	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				Art Unit	
				Examiner Name	
Sheet	2	of	4	Attorney Docket Number	JHU-36631.303

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]
		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		Date 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				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.	
		LI et al., Activatable Near-Infrared Fluorescent Probe for In Vivo Imaging of Fibroblast Activation Protein-alpha. Bioconjugate Chem. 2012 Jul. 19;23:1704-11	
		LO et al., Photodynamic molecular beacon triggered by fibroblast activation protein on cancer-associated fibroblasts for diagnosis and treatment of epithelial cancers. J Med Chem. 2009 Jan 22;52(2):358-68.	
		POPLAWSKI et al., Identification of selective and potent inhibitors of fibroblast activation protein and prolyl oligopeptidase. J Med Chem. 2013 May 9;56(9):3467-77.	
		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 Perceived Barriers. Bioconjugate chemistry. 2015; 26:625–632.	
		RETTIG et al., Regulation and heteromeric structure of the fibroblast activation protein in normal and transformed cells of mesenchymal and neuroectodermal origin Cancer Res. 1993 Jul 15;53(14):3327-35.	
		RYABTSOVA et al., Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity. Bioorg Med Chem Lett. 2012 May 15;22(10):3412-7.	
		SCANLAN et al., Molecular cloning of fibroblast activation protein alpha, a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. Proc Natl Acad Sci U S A. 1994 Jun 7;91(12):5657-61.	
		SCOTT et al., A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res. 2003 May;9(5):1639-47.	
		TSAI et al., Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein. J Med Chem. 2010 Sep 23;53(18):6572-83.	
		TUXHORN et al., Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling. Clin Cancer 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 Signature		Date 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				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		Date 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				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.

☐ 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)	2023-07-18
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**.

Doc Code: ECOMM.AUTH/ECOMM.WTDW
Doc Description: Internet Communications Authorized/Internet Communications Authorization Withdrawn

PTO/SB/439 (11-15)

AUTHORIZATION FOR INTERNET COMMUNICATIONS IN A PATENT APPLICATION OR REQUEST TO WITHDRAW AUTHORIZATION FOR INTERNET COMMUNICATIONS		
	Application No.	
	Filing Date	07/18/2023
	First Named Inventor	YANG
	Art Unit	
	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 Communications.

☑ Recognizing that Internet communications are not secure, I hereby authorize the USPTO to communicate with the undersigned and practitioners in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via video conferencing, instant messaging, or electronic mail. I understand that a copy of these communications will be made of record in the application file. (MPEP 502.03)

II. To withdraw authorization for Internet Communications.

☐ The authorization given on _____, to the USPTO to communicate with the undersigned and any practitioner in accordance with 37 CFR 1.33 and 37 CFR 1.34 concerning any subject matter of this application via Internet communications such as video conferencing, instant messaging, or electronic mail is hereby withdrawn. I understand that the withdrawal is effective when approved rather than when received.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 58126.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Jeffrey W. Childers/ — Signature

2023-07-18 — Date

Jeffrey W. Childers — Typed or printed name

608-662-1277 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Juristic entities must be represented by a patent practitioner (see 37 CFR 1.31, which is applicable to any paper filed on or after September 16, 2012, that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

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.

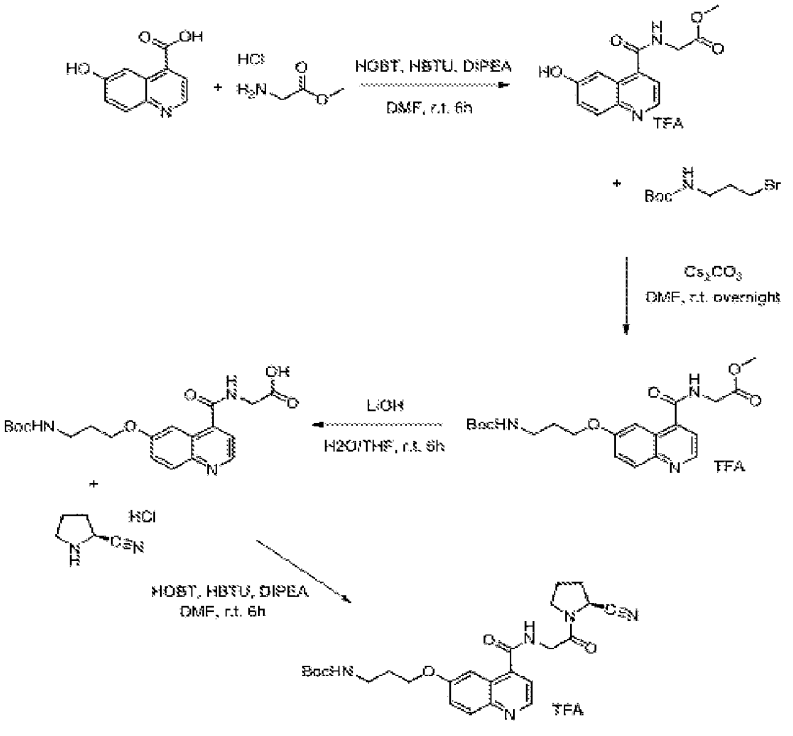

HCl
HOBT, HBTU, DIPEA
DMF, r.t. 6h
TFA
Cs2CO3
DMF, r.t. overnight
LiOH
H2O/THF, r.t. 6h
HOBT, HBTU, DIPEA
DMF, r.t. 6h

Fig. 1A

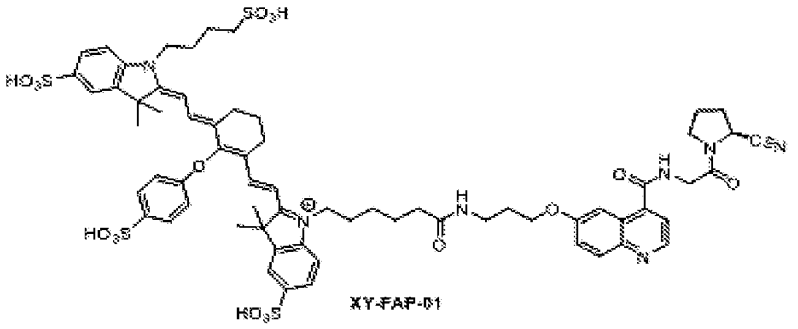


Fig. 1B

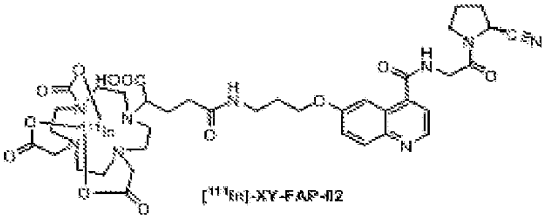


Fig. 1C

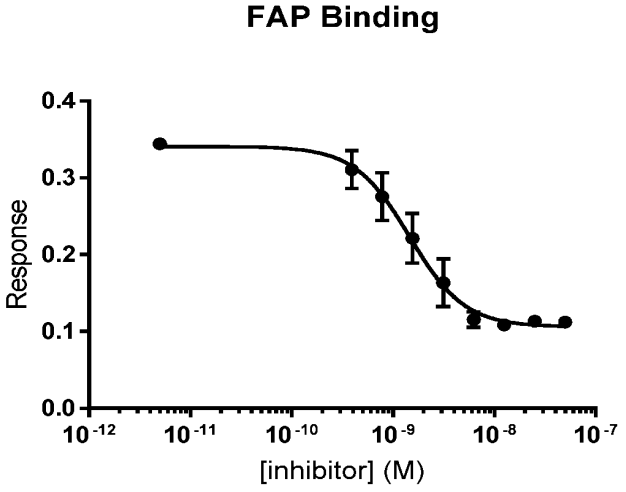

FAP Binding
Response
0.4
0.3
0.2
0.1
0.0
10-12
10-11
10-10
10-9
10-8
10-7
[inhibitor] (M)

Fig. 2

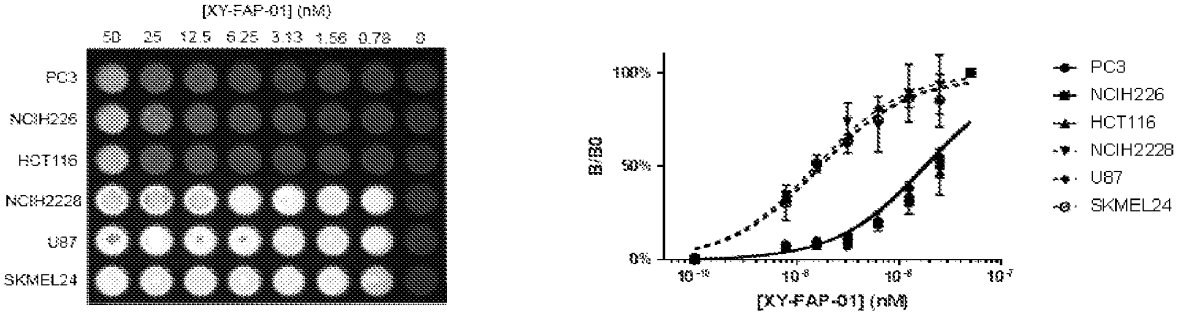


Fig. 3A

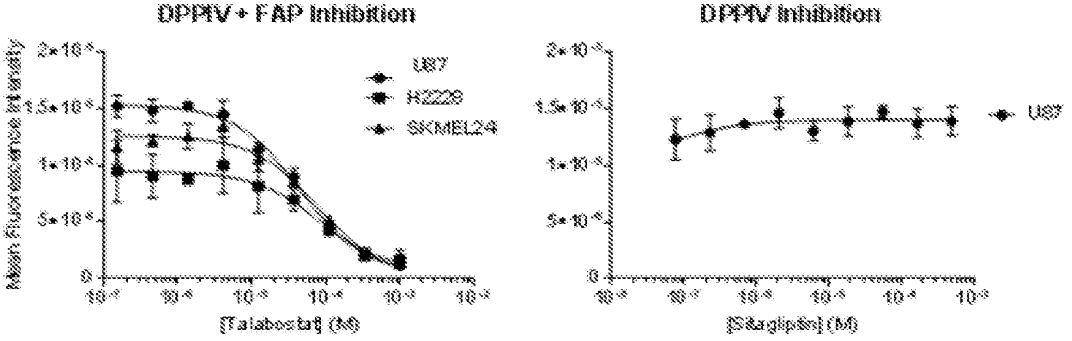


Fig. 3B

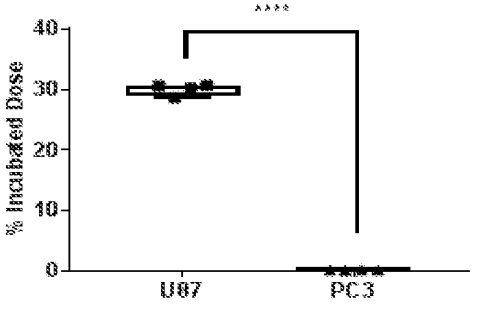


Fig. 3C

	5 min (n= 3)	0.5 h (n= 4)	2 h (n= 3)	6 hr (n= 4)	6 h - blocking (n=4)	12 h (n= 4)
blood	15.13 ± 0.62	10.64 ± 1.54	4.10 ± 0.39	2.01 ± 0.18	0.02 ± 0.001	0.42 ± 0.04
heart	6.68 ± 0.99	4.98 ± 0.71	2.61 ± 0.09	1.07 ± 0.09	0.02 ± 0.002	0.46 ± 0.04
lungs	6.99 ± 1.37	5.60 ± 0.89	2.59 ± 0.32	1.36 ± 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 ± 0.20	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	0.45 ± 0.16	0.02 ± 0.017	0.15 ± 0.08
kidney	4.80 ± 0.57	3.56 ± 0.18	1.95 ± 0.06	1.79 ± 0.21	1.16 ± 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
lrg. 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	2.96 ± 0.95	13.60 ± 8.60	8.94 ± 6.48	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	0.02 ± 0.005	0.60 ± 0.03
femur	4.76 ± 0.12	5.83 ± 0.72	4.95 ± 0.60	3.91 ± 0.70	0.08 ± 0.021	1.38 ± 0.20
U87	9.71 ± 0.24[a]	12.89 ± 1.45[a]	12.28 ± 1.95[a]	11.20 ± 1.03[a]	0.27 ± 0.019[a]	4.57 ± 0.54[a]
PC3	2.20 ± 0.29	3.10 ± 0.57	2.75 ± 0.11	3.40 ± 0.34	0.11 ± 0.024[a]	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 ± 0.36	18.07 ± 1.197	10.94 ± 0.93
U87:mm	3.25 ± 0.26	3.68 ± 0.44	4.38 ± 0.66	6.29 ± 0.82	11.81 ± 2.086	7.68 ± 0.97

Fig. 4

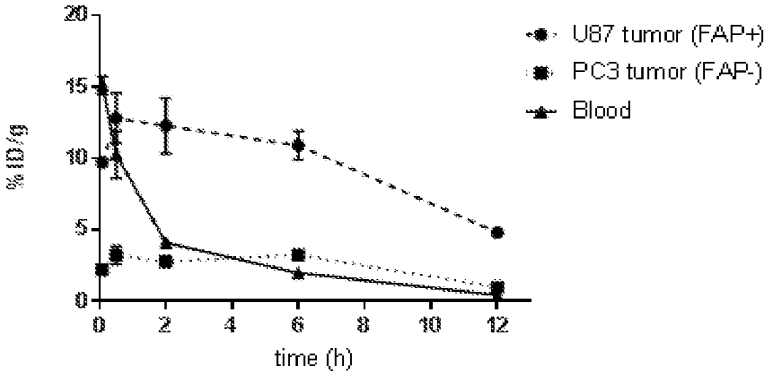

U87 tumor (FAP+)
PC3 tumor (FAP-)
Blood
%ID/g
time (h)
0
5
10
15
20
0
2
4
6
8
10
12

Fig. 5A

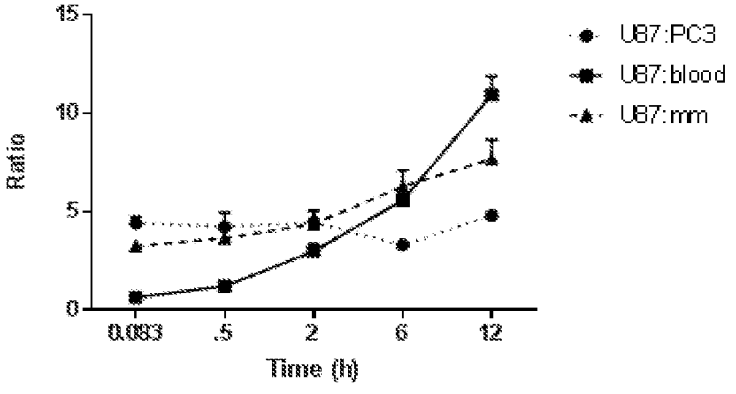

U87:PC3
U87:blood
U87:mm
Ratio
Time (h)
0
5
10
15
0.083
.5
2
6
12

Fig. 5B

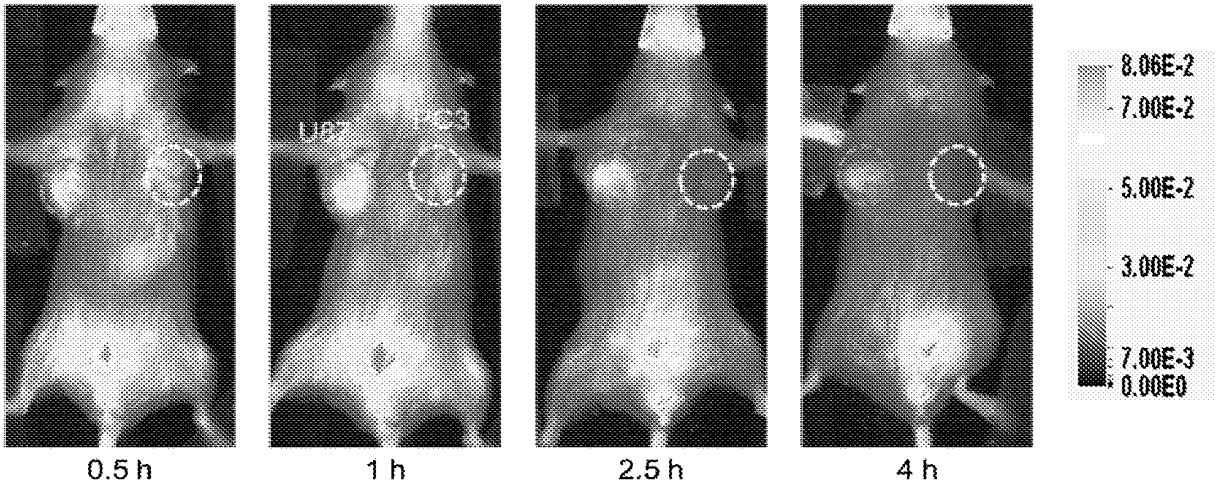


Fig. 6

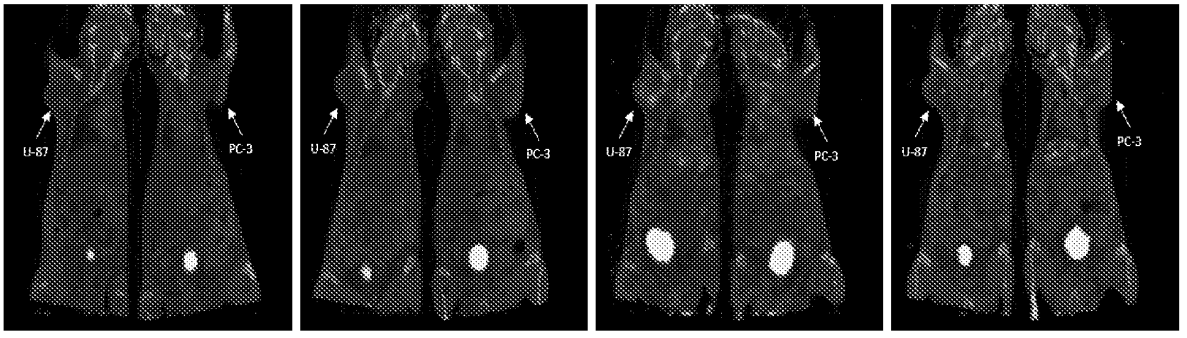


Fig. 7

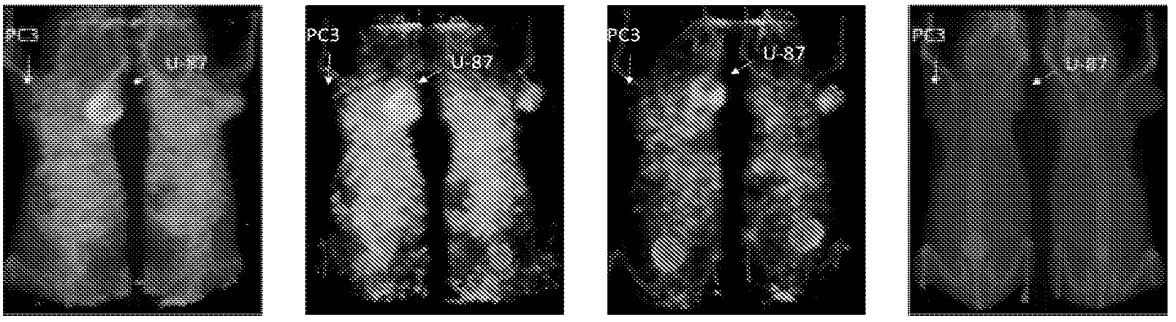


Fig. 8

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 5-tetrazolyl;

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.

THAT WHICH IS CLAIMED:

1. A compound of Formula (I):

B——L——A (I)

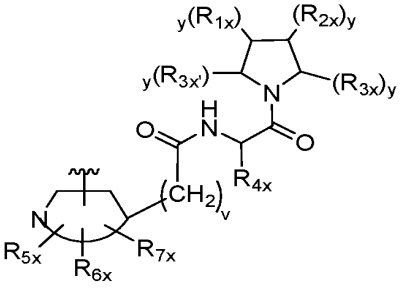
wherein:

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:



(X');

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-$S(O)_2$aryl, $-CO_2H$, $-SO_3H$, $-SO_2NH_2$, $-PO_3H_2$, and 5-tetrazolyl;

R_{4x} is H;

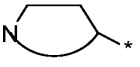
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, $-NR_{8x}R_{9x}$, $-OR_{12x}$, $-Het_2$ and $-Ar_2$; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected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

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

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

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

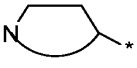
v is 0, 1, 2, or 3; and

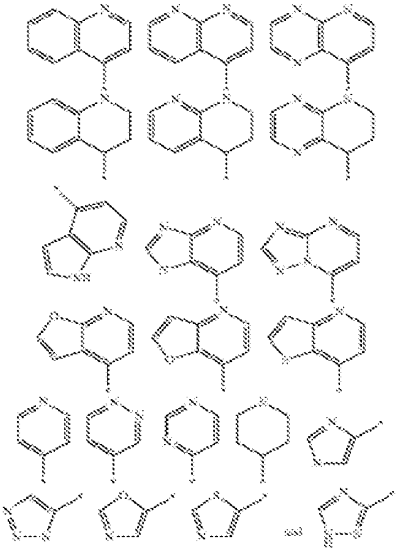


represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

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 the carbon atoms of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle thereof;

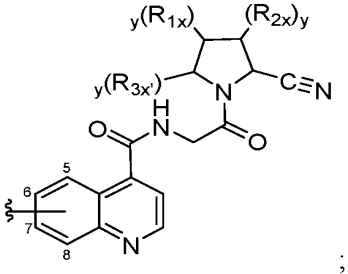
and stereoisomers and pharmaceutically acceptable salts thereof.

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


;

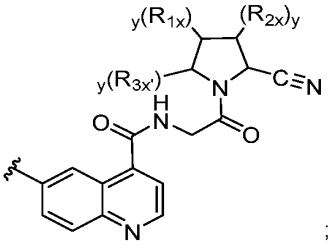
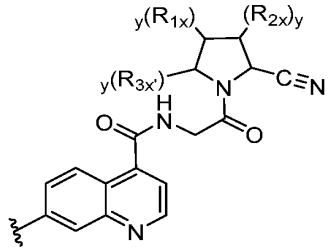
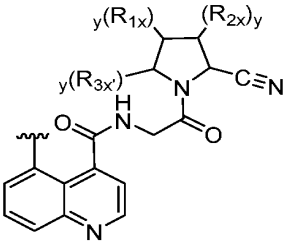
wherein * indicates the point of attachment of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle to $-(CH_2)_v-$.

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

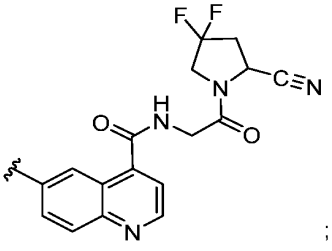
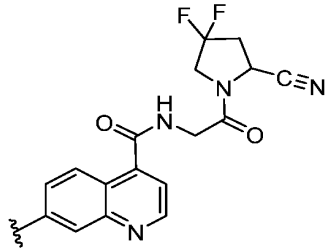
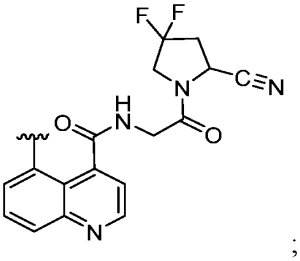

;

wherein ⟆ 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:

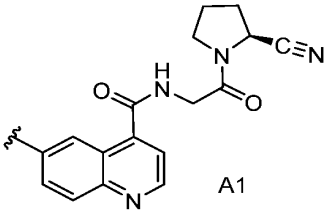
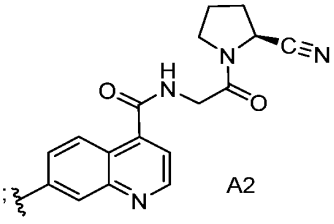
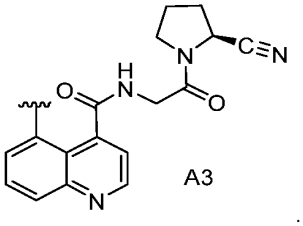

; 
; and 
.

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

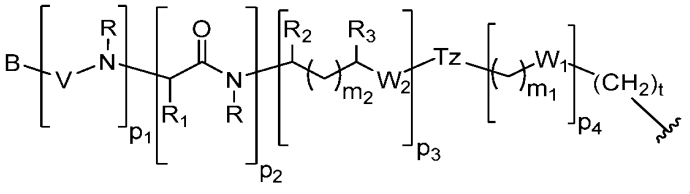

; 
; and 
;

and stereoisomers thereof.

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


A1 ; 
A2 ; and 
A3 .

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):


(a) ;

wherein:

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;

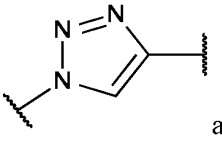
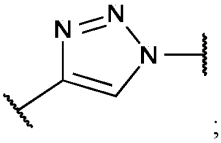
p_2 is an integer selected from the group consisting of 0, 1, 2, and 3, and when p_2 is 2 or 3, each R_1 is the same or different;

m_1 and 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)–;

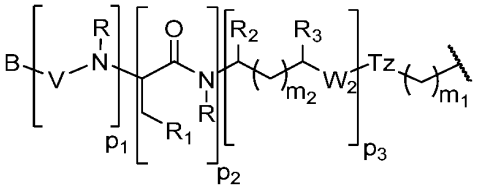
W_2 is selected from the group consisting of a bond, -S-, $-CH_2-C(=O)-NR-$, –C(O)–, –NRC(O)–, –NR'C(O)NR–, –NRC(S)NR'$_2$–, –NRC(O)O–, –OC(O)NR–, –OC(O)–, –C(O)NR–, –NR–C(O)–, –C(O)O–, $–(O–CH_2–CH_2)_q–$ and $–(CH_2-CH_2-O)_q$, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and $–OR_4$, wherein R_4 is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove;

Tz is a triazole group that can be present or absent and, if present, is selected from the group consisting of  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)

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 $-NR-(CH_2)_q-[O-CH_2-CH_2-O]_q-(CH_2)_q-C(=O)-$;

L_2 is $-NR-(CH_2)_q-C(COOR_5)-NR-$; and

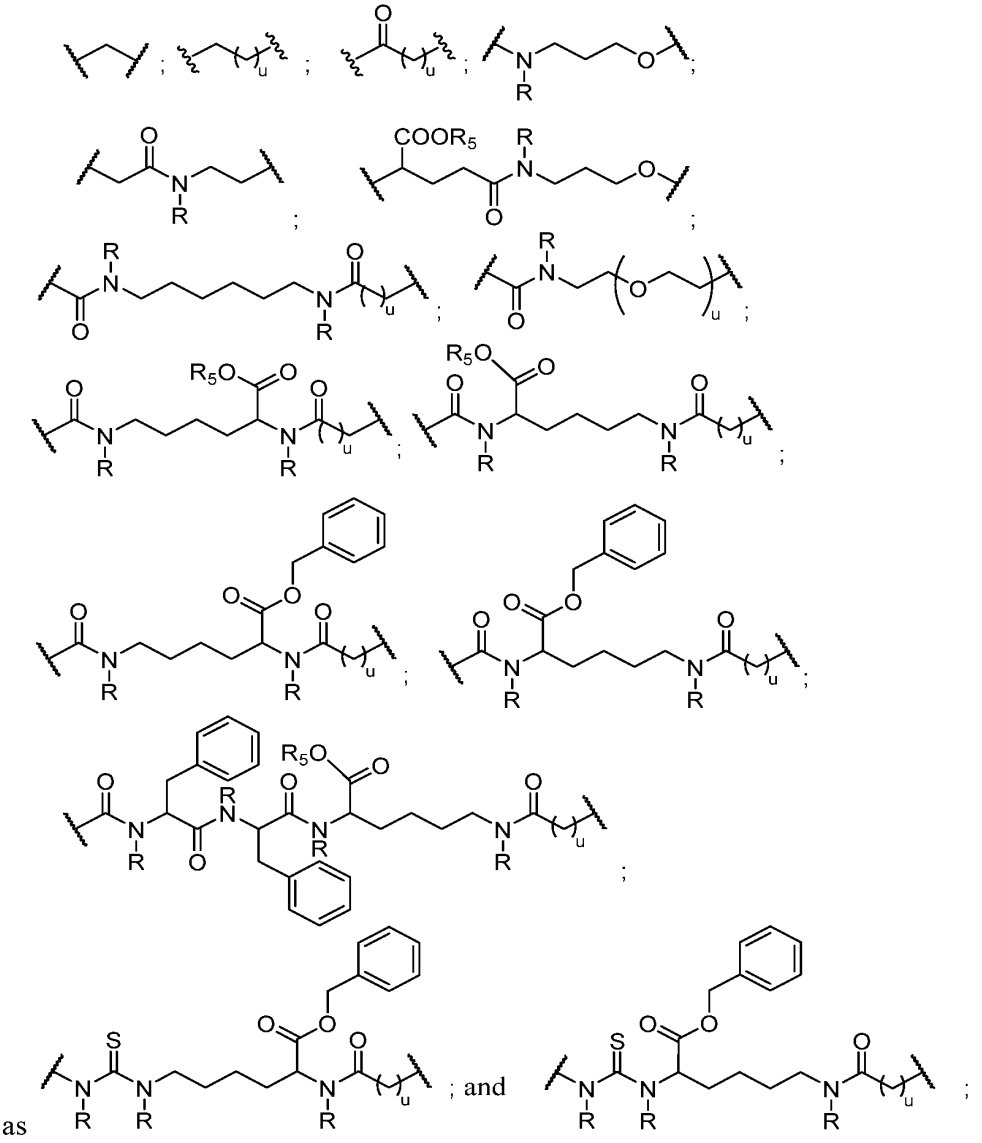
L_3 is $-(O=)C-(CH_2)_q-C(=O)-$;

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;

(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:

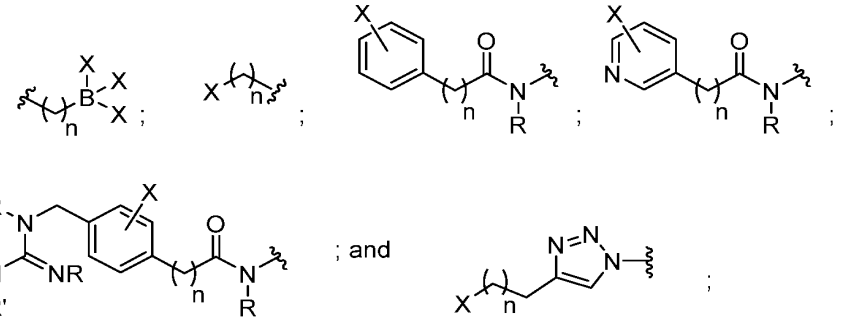


as ; and ;

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.

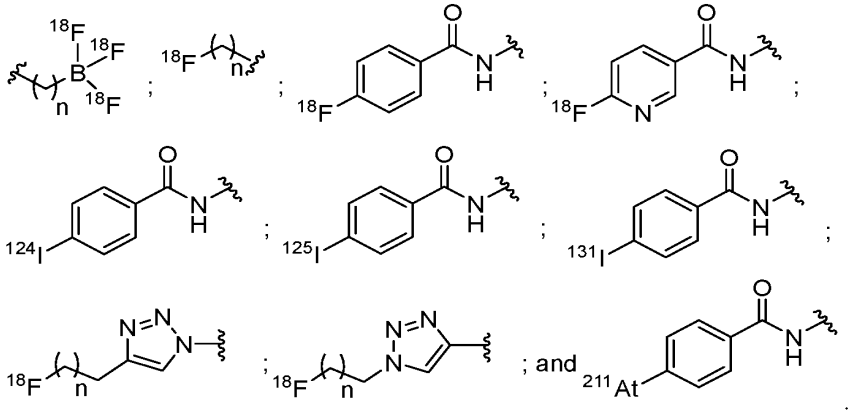
10. The compound of any of claims 1-9, wherein B is a radiolabeled prosthetic group comprising a radioisotope selected from the group consisting of ^{18}F, ^{124}I, ^{125}I, ^{131}I, and ^{211}At.

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



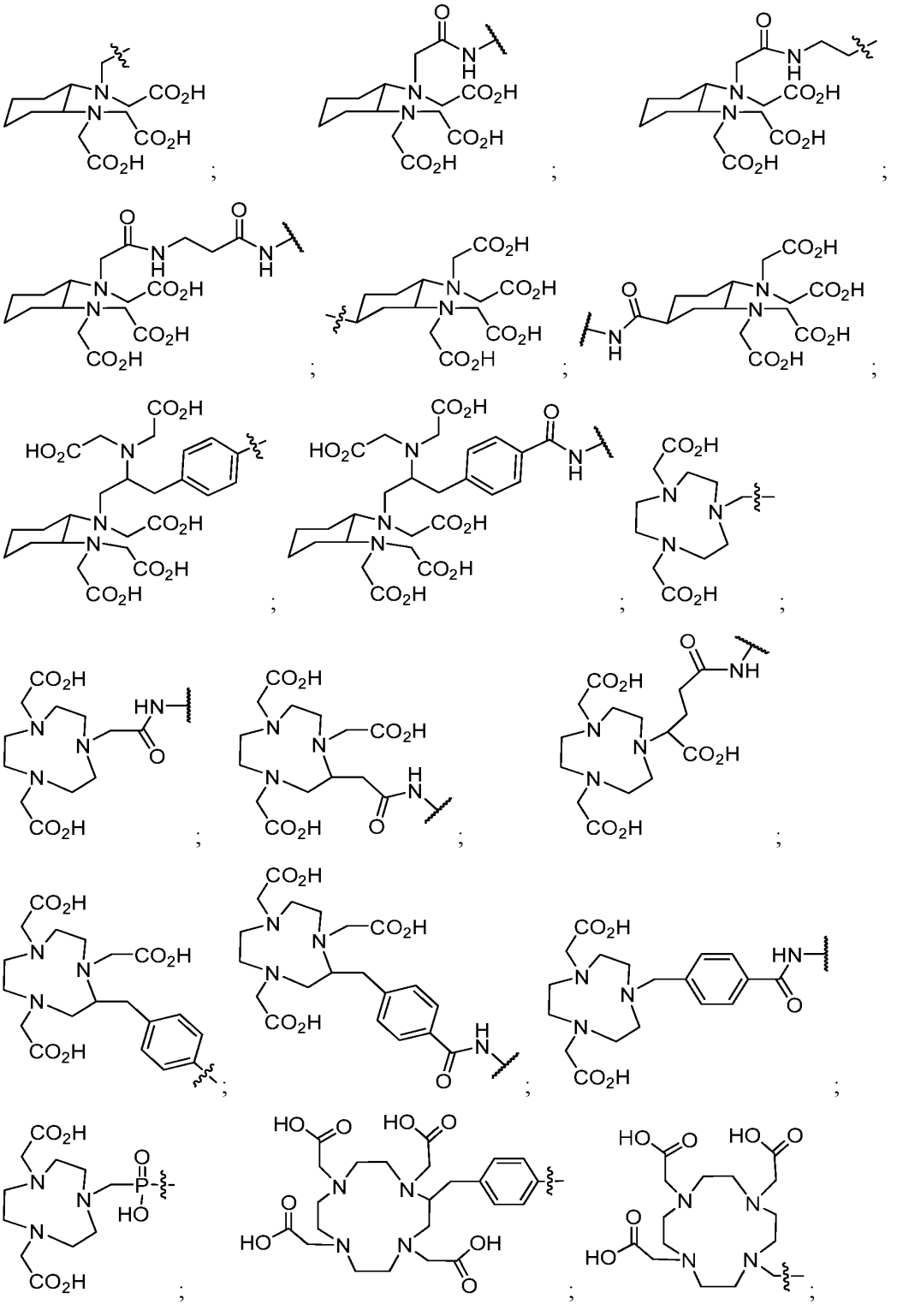
wherein each X is independently a radioisotope selected from the group consisting of ^{18}F, ^{124}I, ^{125}I, ^{131}I, and ^{211}At; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,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

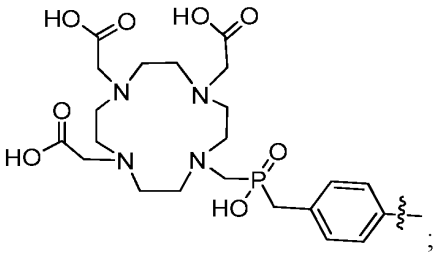
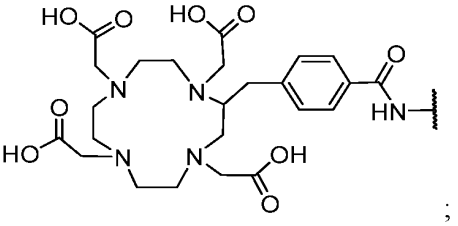
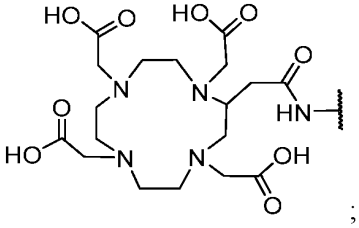
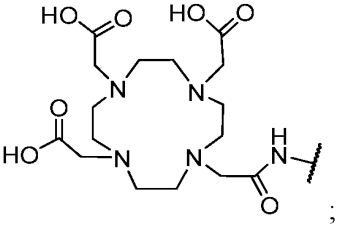
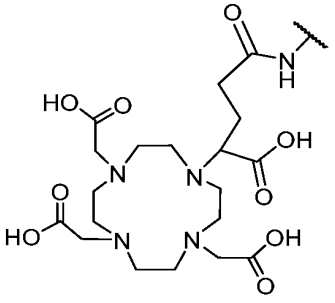
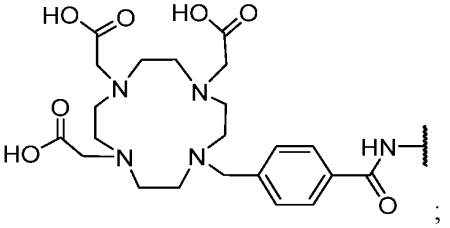
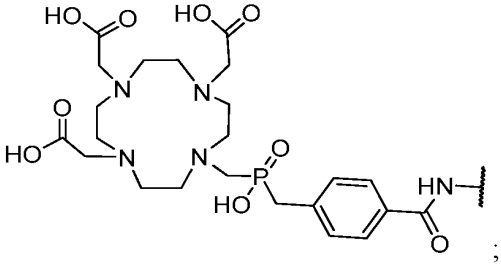
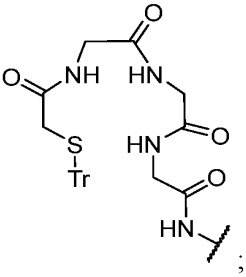
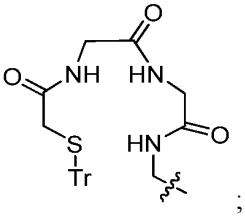
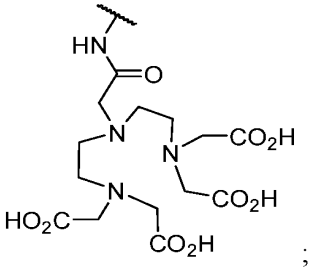
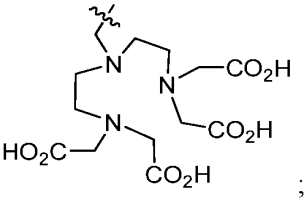
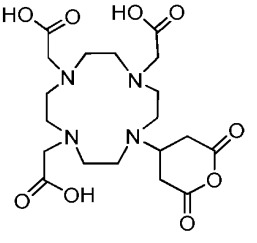
12. The compound of claim 11, wherein the radiolabeled prosthetic group is selected from the group consisting of:

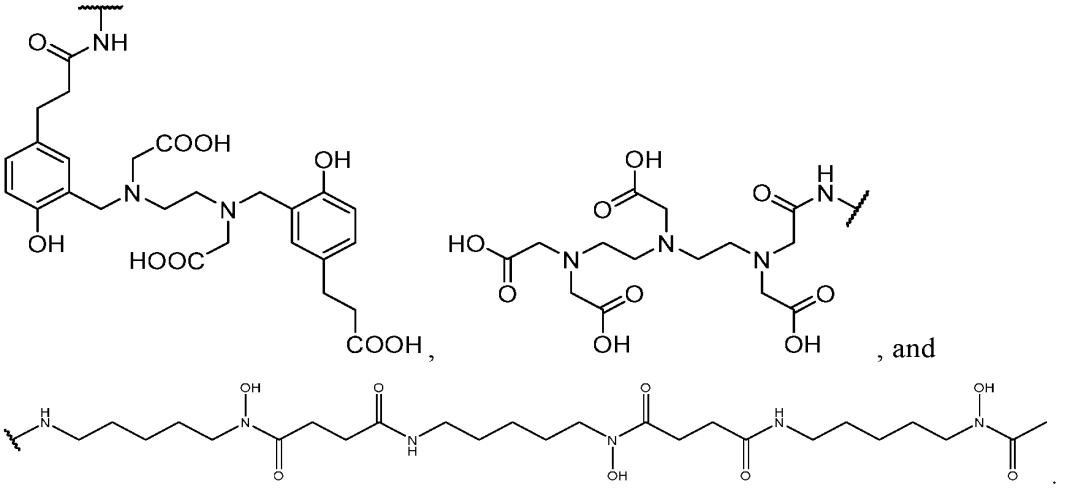


13. The compound of any of claims 1-9, wherein B comprises a chelating agent.

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




;

;

;

;

;

;

;

;

;

;

;

;

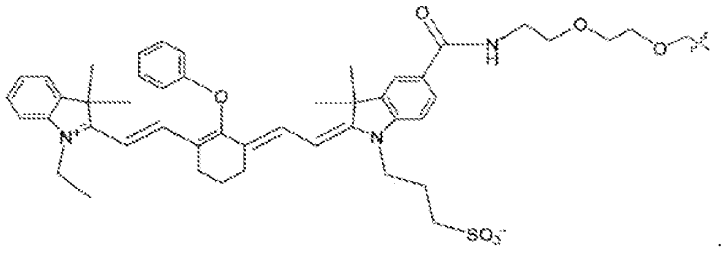


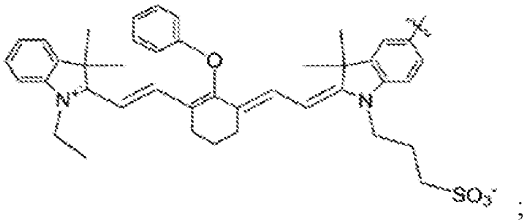
15. The compound of any of claims 1-9, wherein B comprises an optical dye.

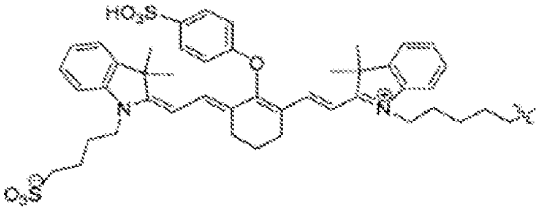
16. The compound of claim 15, wherein the optical dye comprises a fluorescent dye.

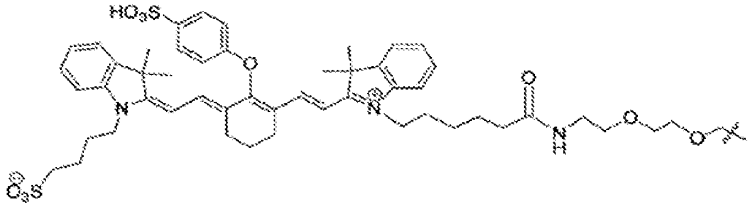
17. The compound of claim 16, wherein the fluorescent dye is selected from the group consisting of carbocyanine, indocarbocyanine, oxacarbocyanine, thiacarbocyanine and merocyanine, polymethine, coumarine, rhodamine, xanthene, fluorescein, boron-dipyrromethane (BODIPY), Cy5, Cy5.5, Cy7, VivoTag-680, 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.

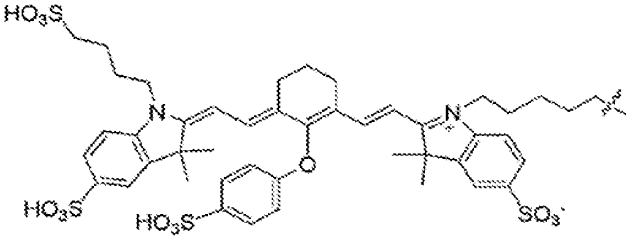
18. The compound of claim 15, wherein the optical dye is selected from the group consisting of:

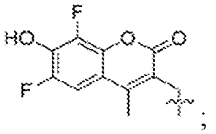

;

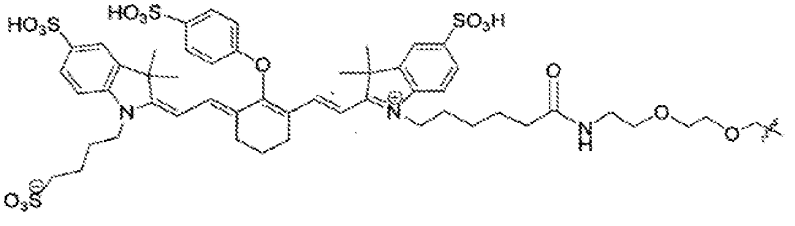

;

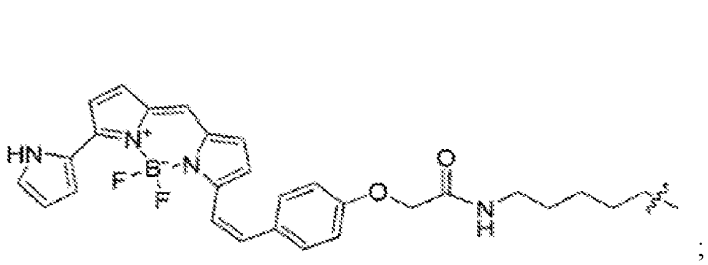
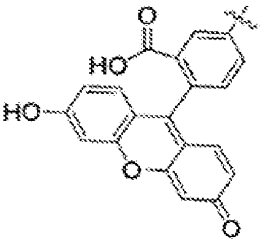
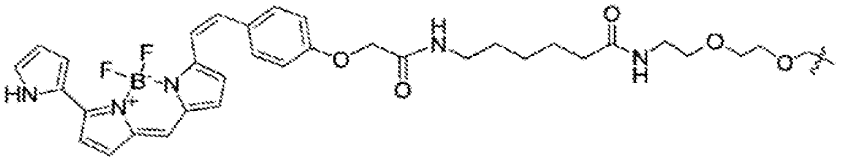
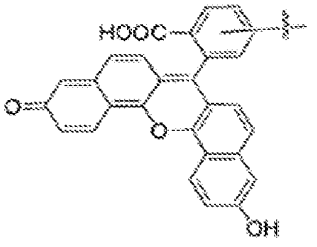
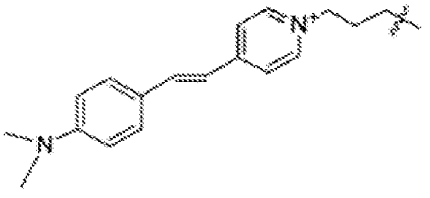
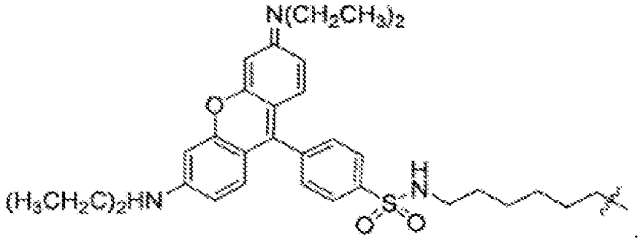

;


;

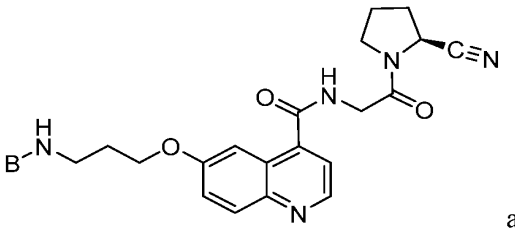

;


;

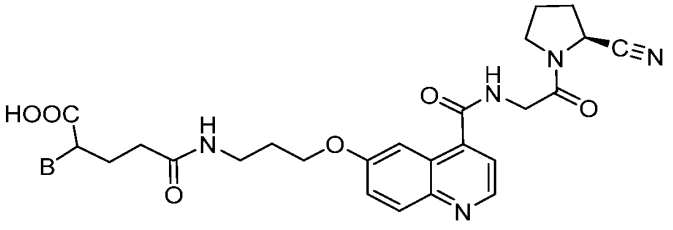

;


;

;

;

;

;
and

.

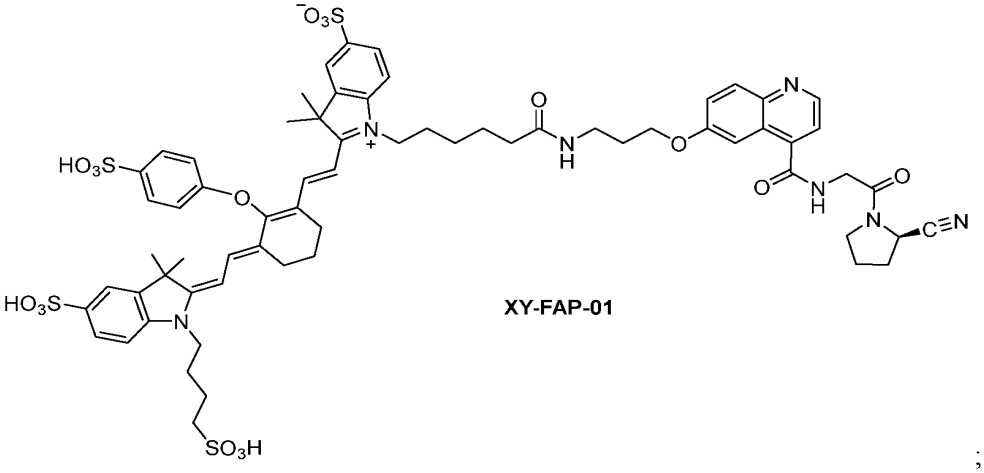
19. The compound of claims 1-9, wherein the compound is selected from the group consisting of:



and

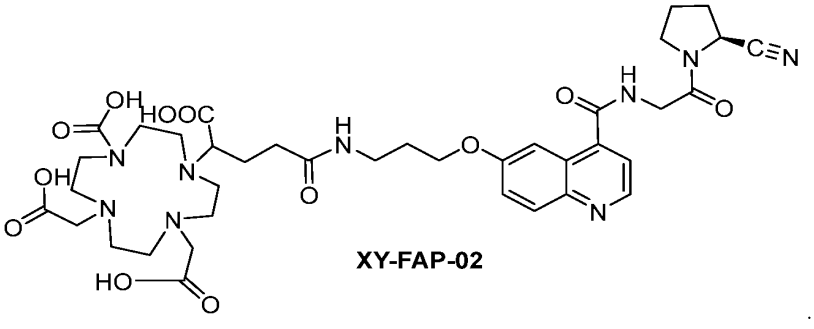


20. The compound of claim 19, wherein the compound is selected from the group consisting of:



XY-FAP-01

; and



XY-FAP-02

.

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 fibroblast-activation 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-α)-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.

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Xing		Yang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Baltimore	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o The Johns Hopkins University
Address 2	3400 North Charles Street

City	Baltimore	State/Province	MD
Postal Code	21218	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sridhar		Nimmagadda	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Baltimore	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o The Johns Hopkins University
Address 2	3400 North Charles Street

City	Baltimroe	State/Province	MD
Postal Code	21218	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Steven		Rowe	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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)	

City	Parkville	State/Province	MA	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o The Johns Hopkins University		
Address 2	3400 North Charles Street		
City	Baltimore	State/Province	MD
Postal Code	21218	Country	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Stephanie		Slania	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Baltimore	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o The Johns Hopkins University		
Address 2	3400 North Charles Street		
City	Baltimore	State/Province	MD
Postal Code	21218	Country	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Martin	G.	Pomper	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Baltimore	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	c/o The Johns Hopkins University		
Address 2	3400 North Charles Street		
City	Baltimore	State/Province	MD
Postal Code	21218	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

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.**

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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)	

Customer Number	101943		
Email Address	docketing@casimirjones.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	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	101943		

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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)	

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)[i] 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

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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 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.

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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)	

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 **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** 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. Priority Document Exchange (PDX) - 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. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** 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 **DOES NOT** 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 **DOES NOT** 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.

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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

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.

Clear

(•) Assignee	( ) Legal Representative under 35 U.S.C. 117	( ) Joint Inventor
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. [x]

Organization Name	The Johns Hopkins University

Mailing Address Information For Applicant:

Address 1	3400 North Charles Street		
Address 2			
City	Baltimore	**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.

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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/Province**	
Country		Postal Code	
Phone Number		Fax Number	
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 INITIAL filing of the application and either box A or B is not 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, **all** 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 **all** 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.

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

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.**

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 the Freedom of Information Act requires disclosure of these records.

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 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.

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 inspections 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.

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.

Petitioner GE Healthcare – Ex. 1031, p. 125

Attorney Docket No. JHU-36631.303

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.	Confirmation No.: TBD
Serial No.: TBD	Art Unit: TBD
Filed: July 18, 2023	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 Claims begin on page 2 of this paper.

Remarks begin on page 4 of this paper.

Petitioner GE Healthcare – Ex. 1031, p. 126

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 18354282 Document Date: 07/24/2023

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.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access SCORE content via DAV or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: March 1, 2019

Attorney Docket No. 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: TBD
Filed: July 18, 2023	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.

Petitioner GE Healthcare – Ex. 1031, p. 128

AMENDMENTS TO THE SPECIFICATION

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

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.

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 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.

SUMMARY

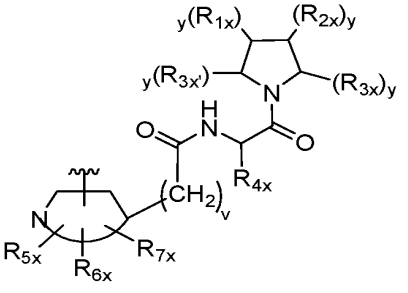
In some aspects, the presently disclosed subject matter provides a compound of Formula (I):



(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.

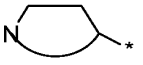
In particular aspects, A is an FAP-α targeting moiety having the structure of:



(X');

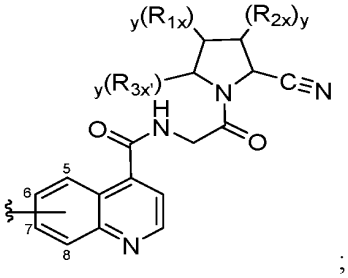
wherein each y is independently an integer selected from the group consisting of 0, 1, and 2; R_{1x}, R_{2x}, and $R_{3x'}$, are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl; R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$, -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl; R_{4x} is H; R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of $C_{1\text{-}6}$alkyl being optionally substituted with from 1 to 3 substituents

selected from -OH and halogen; R_{8x}, R_{9x}, and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and -Ar_3; R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; v is 0, 1, 2, or 3; and



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

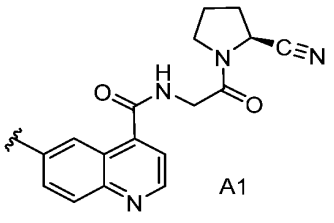
In more particular aspects, A is an FAP-α targeting moiety having the structure of:

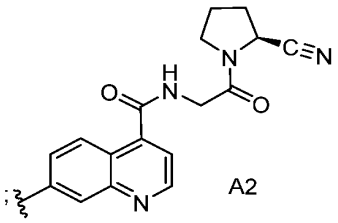


;

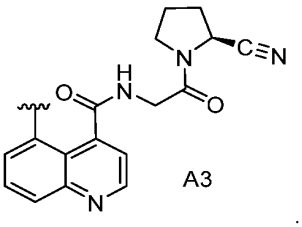
wherein ⟆ indicates a point of attachment of the FAP-α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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


A1


A2

; and


A3

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 ^{1}H 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, **[^{111}In]-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 ^{111}In and HPLC purification resulted in the radiolabeled product, **[^{111}In]-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 FAP-negative 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 **[^{111}In]-XY-FAP-02** in FAP-positive U87 and FAP-negative PC3 cell lines. Cells were incubated with 1 μCi **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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. [a]Student'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. [b]Student'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 ($p=0.0006$). [c]Student'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 **[^{111}In]-XY-FAP-02**. FIG. 5A shows tissue time activity curves (TACs) of **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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

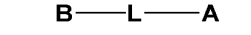
The highly potent and specific binding moiety targeting FAP-α enables its use in nuclear imaging and radiotherapy. The presently disclosed subject matter provides the first synthesis of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to FAP-α.

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, ^{68}Ga, ^{64}Cu, ^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{125}I, ^{124}I, 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, ^{90}Y, ^{177}Lu, ^{125}I, ^{131}I, ^{211}At, ^{111}In, ^{153}Sm, ^{186}Re, ^{188}Re, ^{67}Cu, ^{212}Pb, ^{225}Ac, ^{213}Bi, ^{212}Bi, ^{212}Pb, and ^{67}Ga, 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 ^{111}In labeled ligand (**XY-FAP-02-[^{111}In]**) 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):

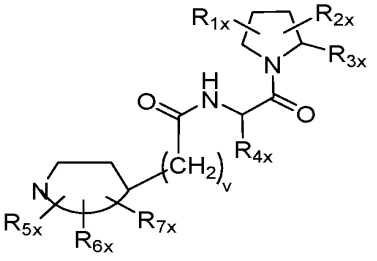


(I)

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:



(X);

wherein:

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

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

R_{4x} is H;

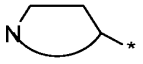
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH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

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

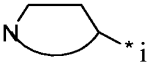
R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from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

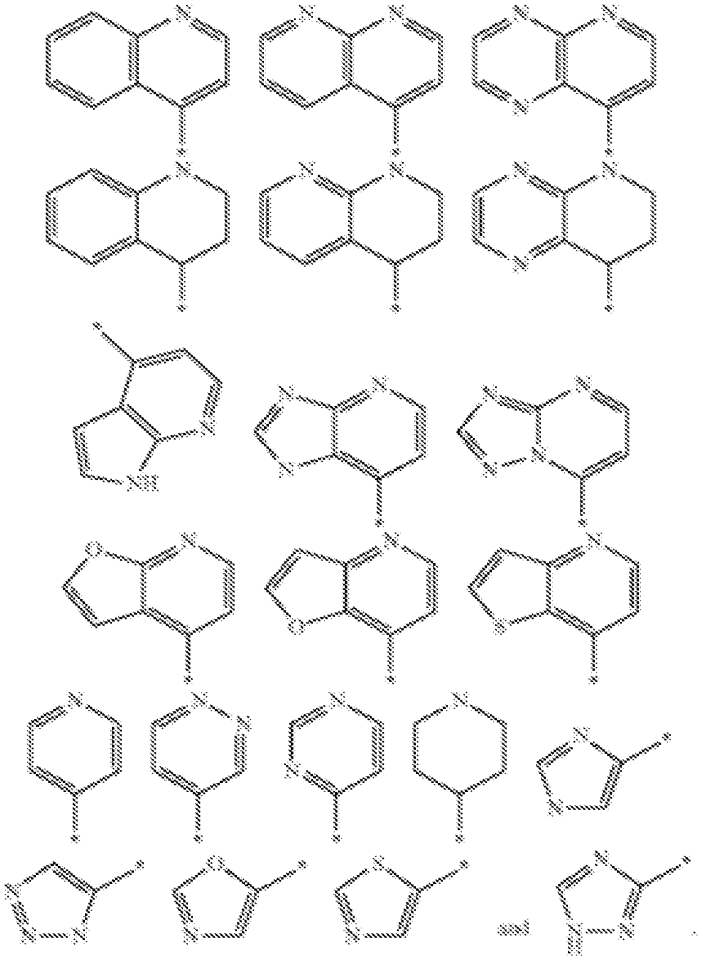
Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

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



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

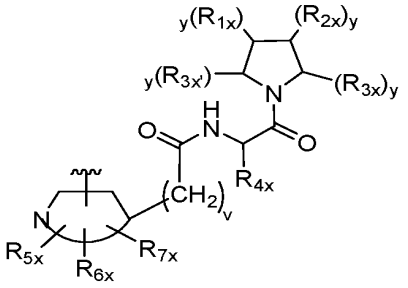
In particular embodiments,  is selected from the group consisting of:



;

wherein * indicates the point of attachment of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle to $-(CH_2)_v-$.

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



(X');

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

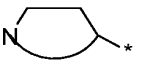
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH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

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

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

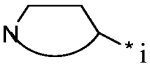
Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

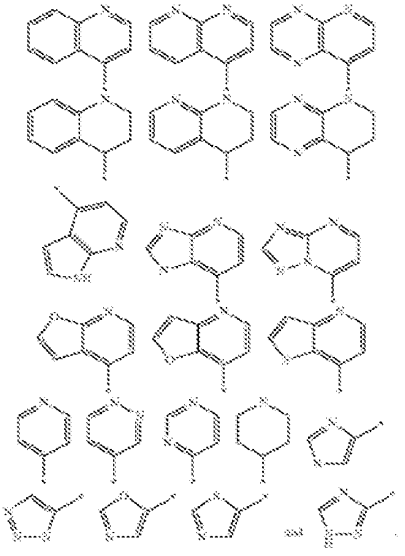
v is 0, 1, 2, or 3; and



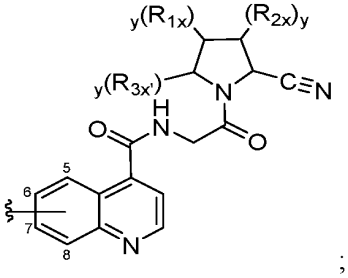
represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

wherein $\sim$— 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,  is selected from the group consisting of:



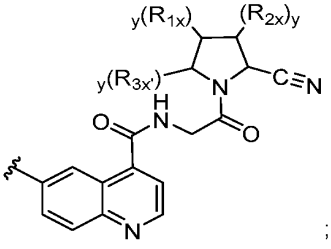
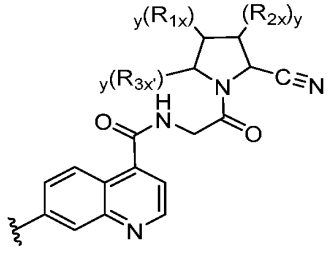
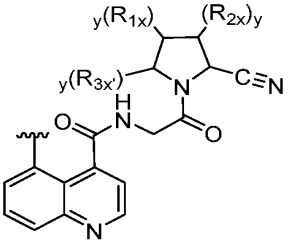
In some embodiments, A is an FAP-α targeting moiety having the structure of:



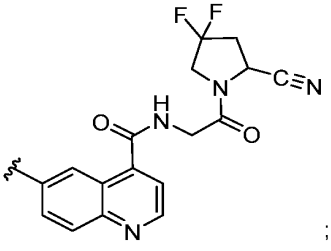
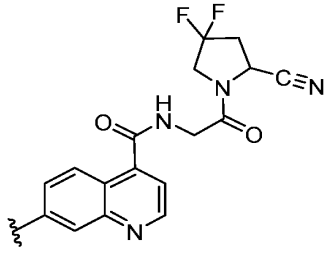
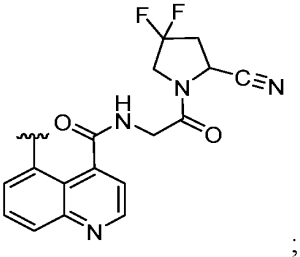
;

wherein y, R_{1x}, R_{2x} and $R_{3x'}$ are defined as hereinabove; ⟆ 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:

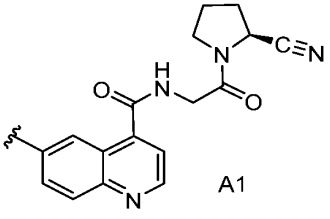
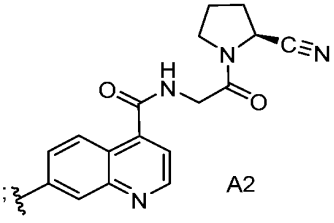
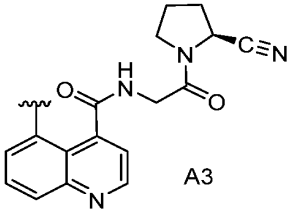

;

; and

.

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

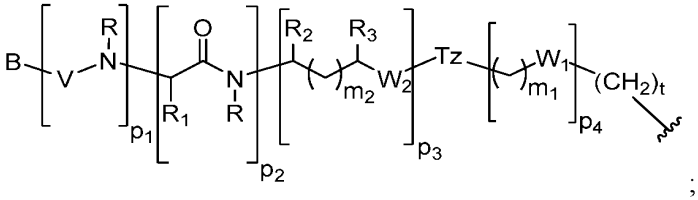

;

; and

;

and stereoisomers thereof.

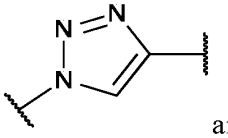
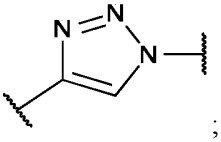
In yet more particular embodiments, A is selected from the group consisting of:


A1
;

A2
; and

A3
.

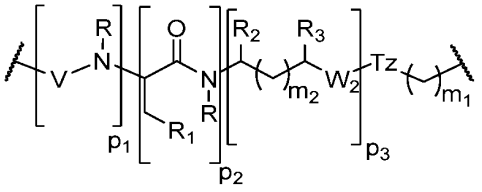
In some embodiments, the combination of L and B can be represented by:


;

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 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)–; W_2 is selected from the group consisting of a bond, -S-, -CH_2-C(=O)-NR-, –C(O)–, –NRC(O)–, –NR'C(O)NR–, –NRC(S)NR'$_2$–, –NRC(O)O–, –OC(O)NR–, –OC(O)–, –C(O)NR–, –NR–C(O)–, –C(O)O–, –(O–CH_2–CH_2)$_q$– and –(CH_2-CH_2-O)$_q$–, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and –OR_4, wherein R_4 is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove; Tz is a triazole group that can be present or absent and, if present, is selected from the group consisting of


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 $-L_1-$, $-L_2-L_3-$, and $-L_1-L_2-L_3-$, wherein:

L_1 is $-NR-(CH_2)_q-[O-CH_2-CH_2-O]_q-(CH_2)_q-C(=O)-$;

L_2 is $-NR-(CH_2)_q-C(COOR_5)-NR-$; and

L_3 is $-(O=)C-(CH_2)_q-C(=O)-$;

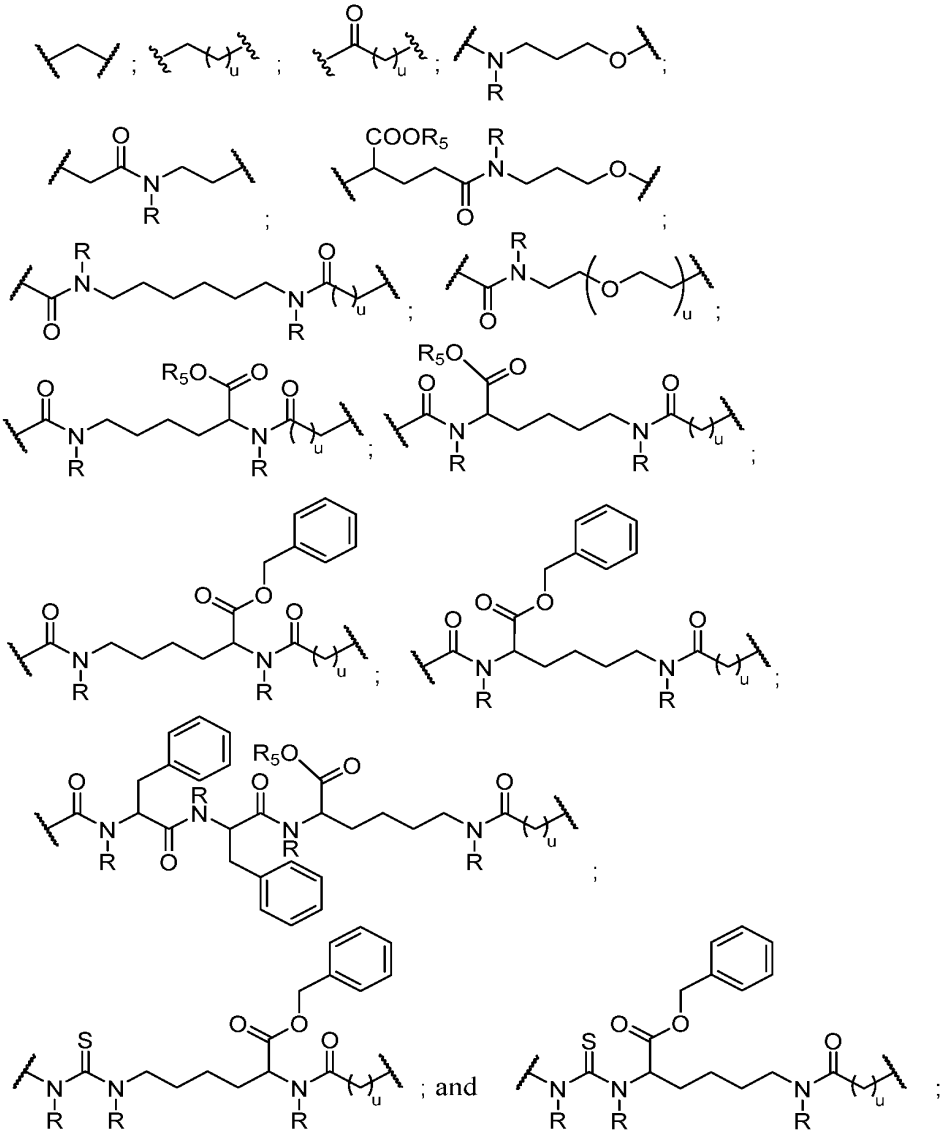
wherein each q is independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

In particular embodiments, L is:

$-(CR_6H)_q-(CH_2)_q-C(=O)-NR-(CH_2)_q-O-$ or $-NR-(CH_2)_q-O-$;

wherein each q and R is defined hereinabove; and R_6 is H or $-COOR_5$.

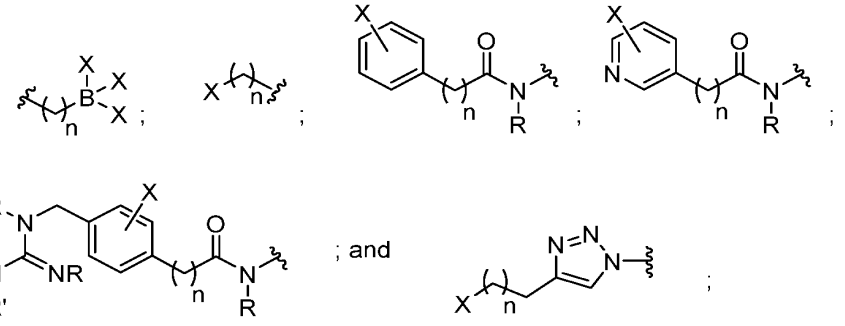
In yet more particular embodiments, L is selected from the group consisting of:



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.

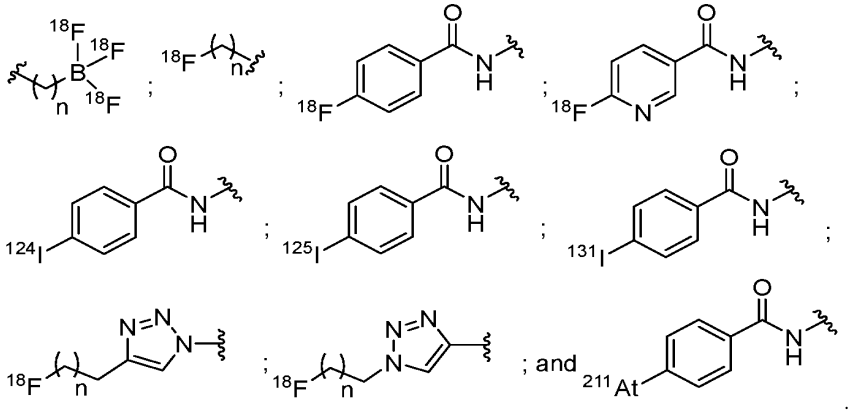
Suitable linkers are disclosed in U.S. Patent Application Publication No. US2011/0064657 A1, for "Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA), Biological Evaluation, and Use as Imaging Agents," published March 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. 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 ^{18}F, ^{124}I, ^{125}I, ^{131}I, and ^{211}At. Representative radiolabeled prosthetic groups include, but are not limited to:

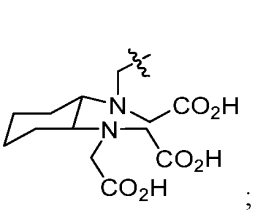
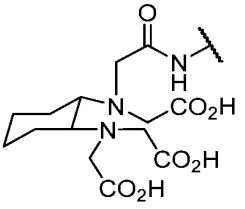
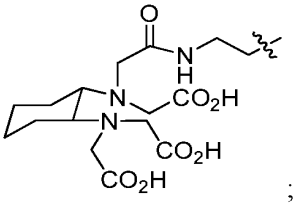
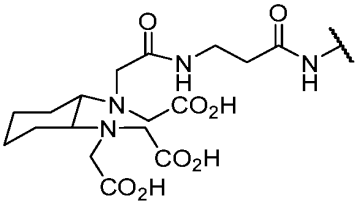
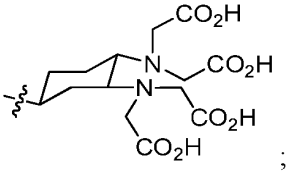
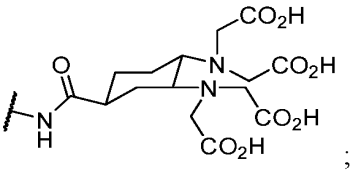
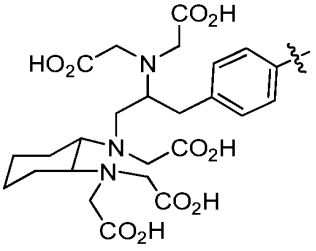
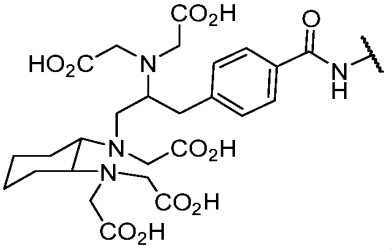
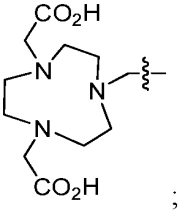
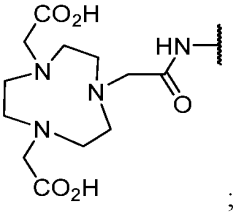
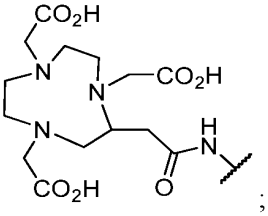
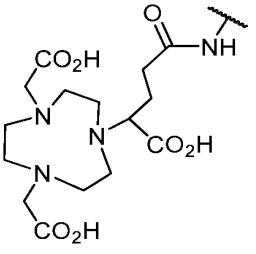
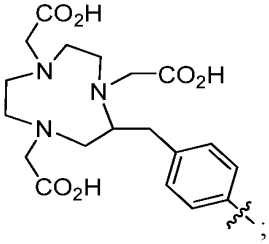
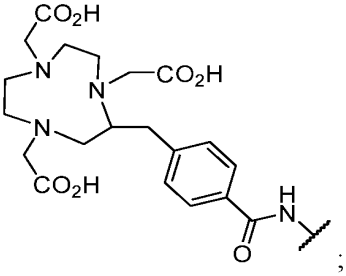
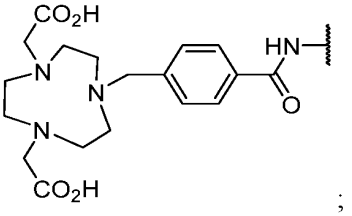
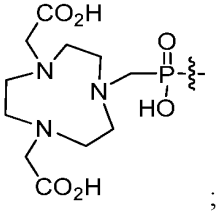
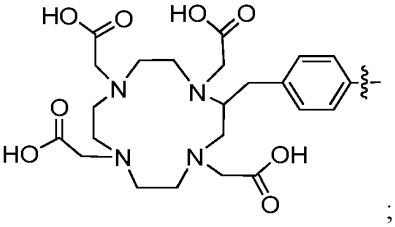
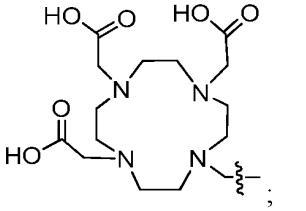


wherein each X is independently a radioisotope selected from the group consisting of ^{18}F, ^{124}I, ^{125}I, ^{131}I, and ^{211}At; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,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

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



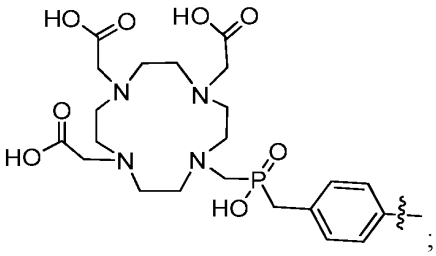
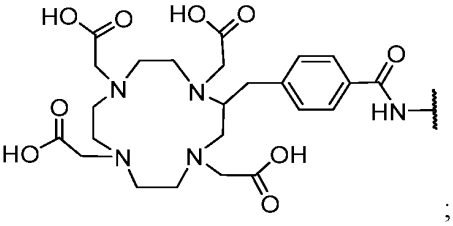
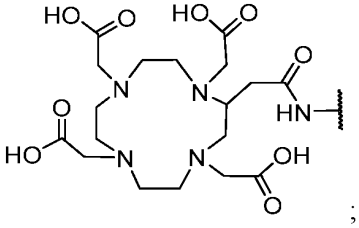
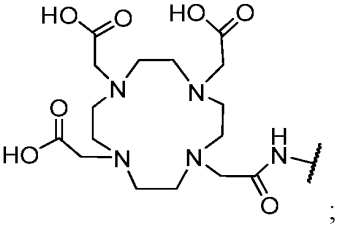
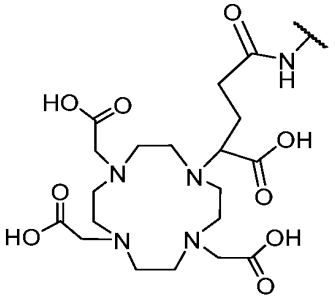
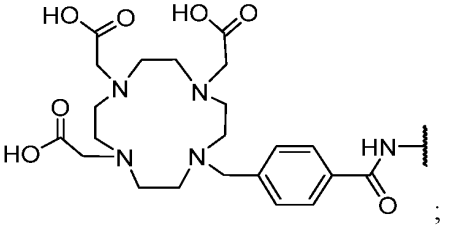
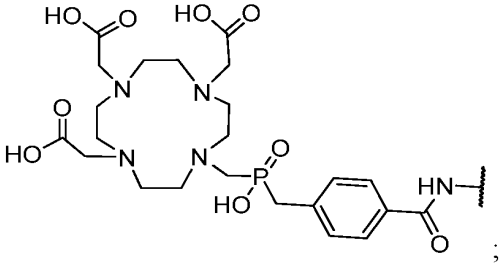
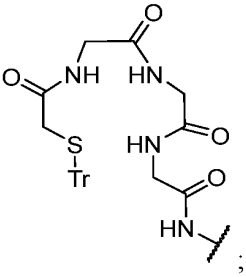
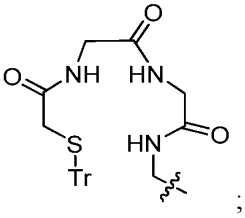
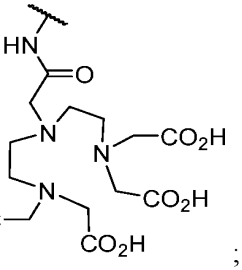
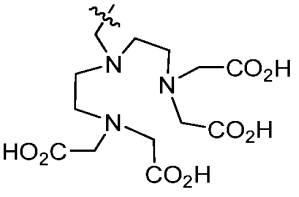
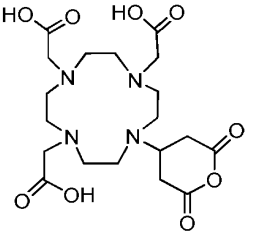
In other embodiments, B comprises a chelating agent. Representative chelating agents include, but are not limited to:

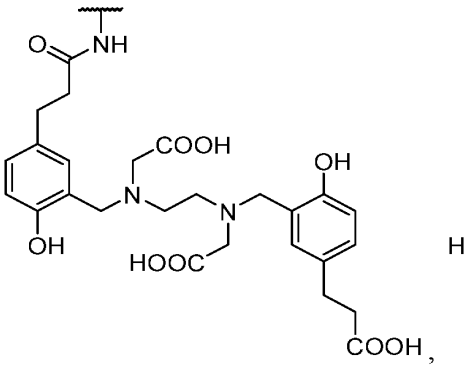

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

;

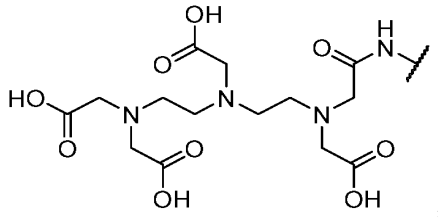
;

;

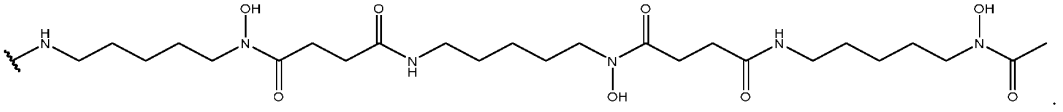
;


;

;

;

;

;

;

;

;

;

;

;

;





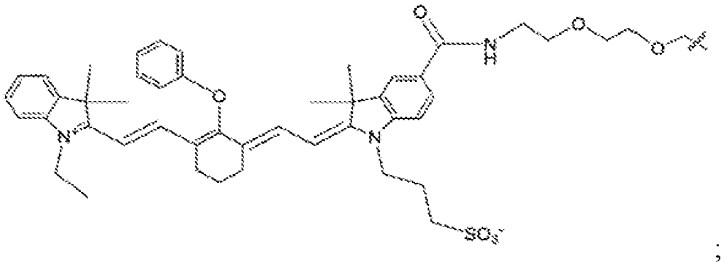
, and



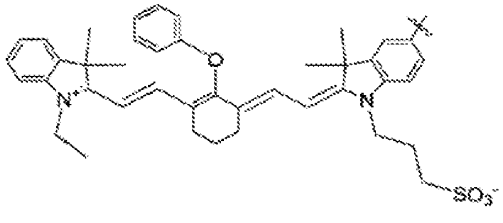
.

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, 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.

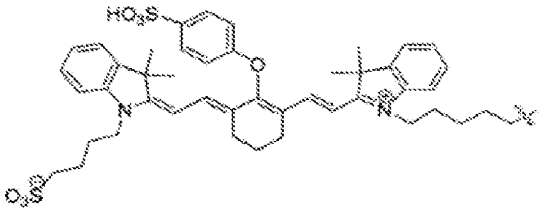
Representative optical dyes include, but are not limited to:



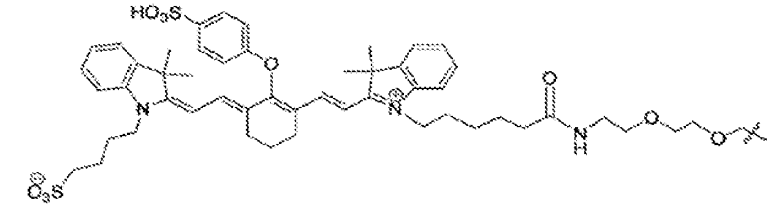
;



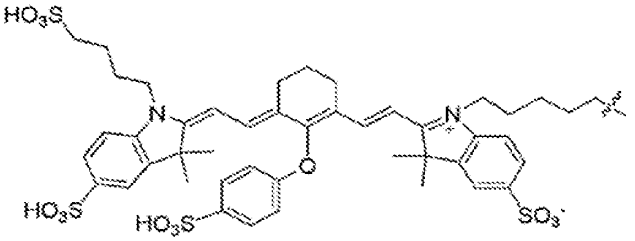
;



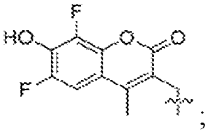
;



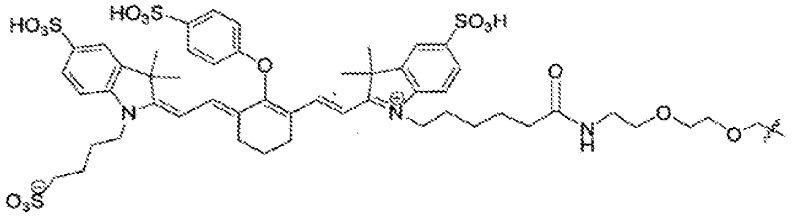
;



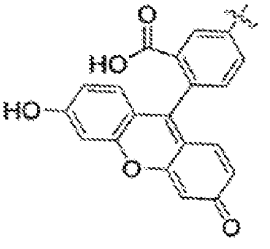
;



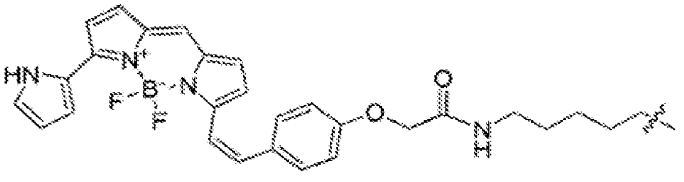
;



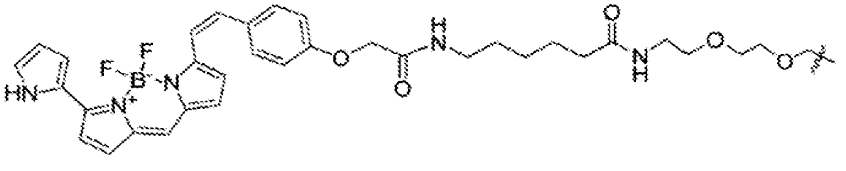
;



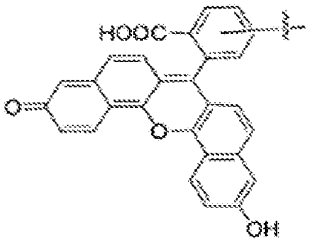
;

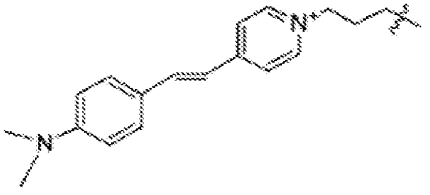


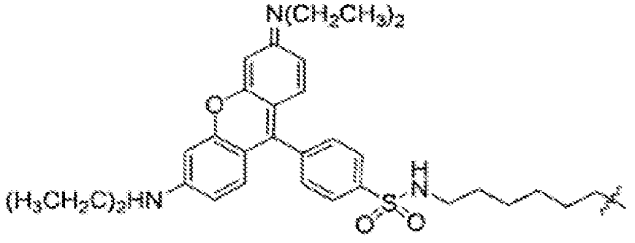
;



;

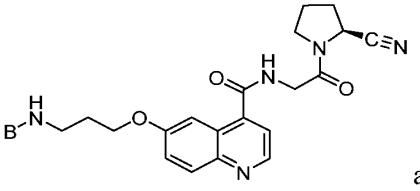


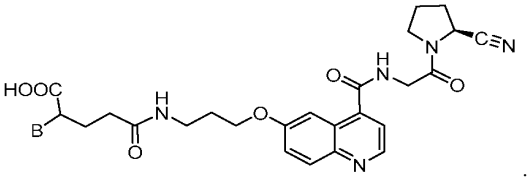
;


;


and .

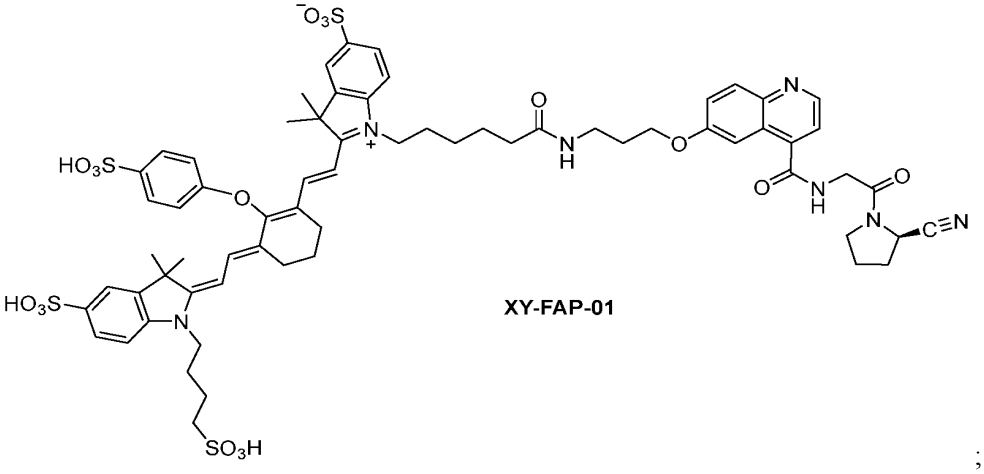
In some embodiments, the presently disclosed subject matter provides a compound selected from the group consisting of:



and


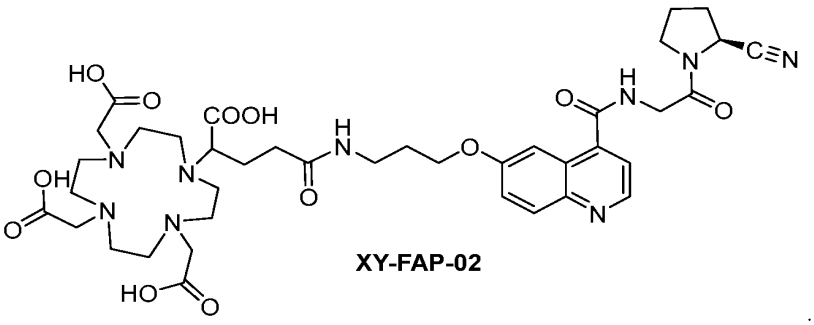
.

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



XY-FAP-01

; and



XY-FAP-02

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, p-toluenesulfonic, 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. Dye-stuffs 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 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.

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

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 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 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, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_{25}-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

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 10-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-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 7-membered 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, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(l,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 ($–CH_2–$); ethylene ($–CH_2–CH_2–$); propylene ($–(CH_2)_3–$); cyclohexylene ($–C_6H_{10}–$); $–CH=CH–CH=CH–$; $–CH=CH–CH_2–$; $-CH_2CH_2CH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CsCCH_2-$, $-CH_2CH_2CH(CH_2CH_2CH_3)CH_2-$, $-(CH_2)_q-N(R)-(CH_2)_r–$, 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 ($–O–CH_2–O–$); and ethylenedioxyl ($-O-(CH_2)_2–O–$). 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.

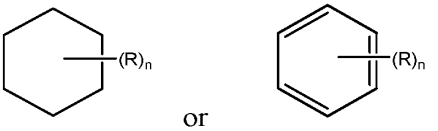
The term "heteroalkylene" by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (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, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-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-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., 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.

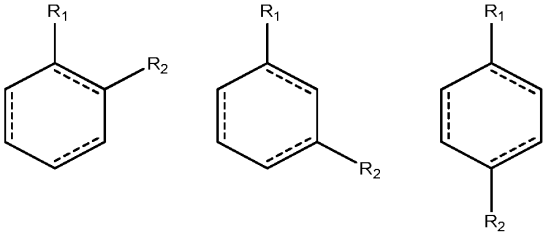
Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" refers to a carbon or heteroatom.

Further, a structure represented generally by the formula:



or

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', -CO_2R',-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', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2 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 4-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., -CF_3 and -CH_2CF_3) and acyl (e.g., -C(O)CH_3, -C(O)CF_3, -C(O)CH_2OCH_3, 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', -CO_2R', -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', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxo, and fluoro(C_1-C_4)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 cycloalkyl, substituted 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-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- 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 -$S(O)_2$NR'-. 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., C_6H_5-CH_2-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 $-(CH_2)_k-$ 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 $–NO_2$ 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 $–SO_4$ 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 $–NH—CO—NH_2$.

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.

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.

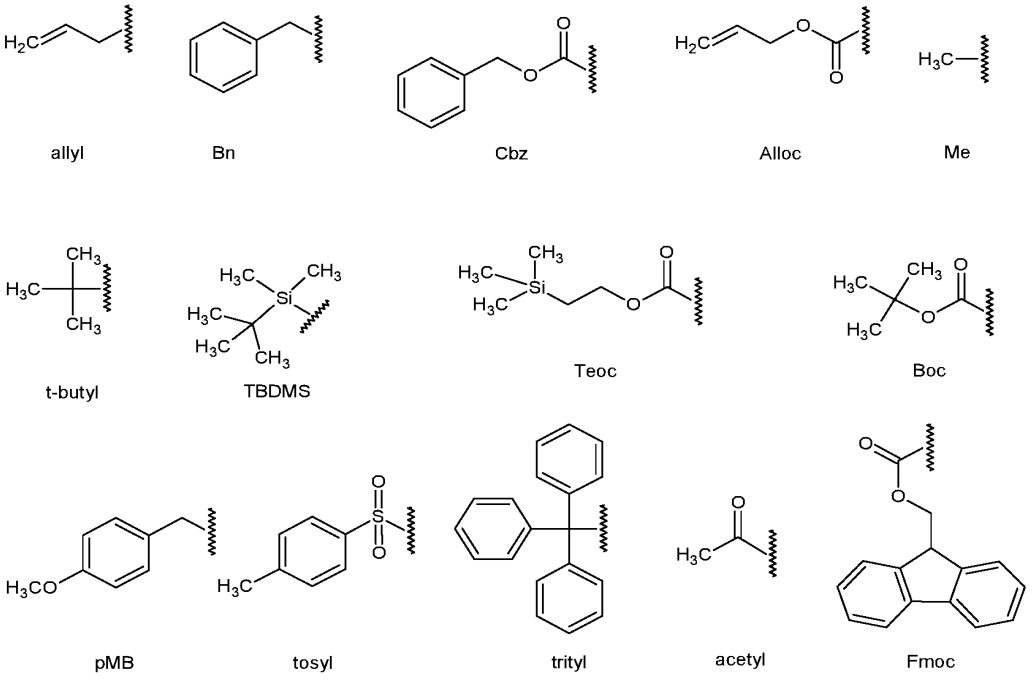
The term "protecting group" refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, Protective 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 co-existing 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:



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, ± 100% in some embodiments ± 50%, in some embodiments ± 20%, in some embodiments ± 10%, in some embodiments ± 5%, in some embodiments ±1%, in some embodiments ± 0.5%, and in some embodiments ± 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.

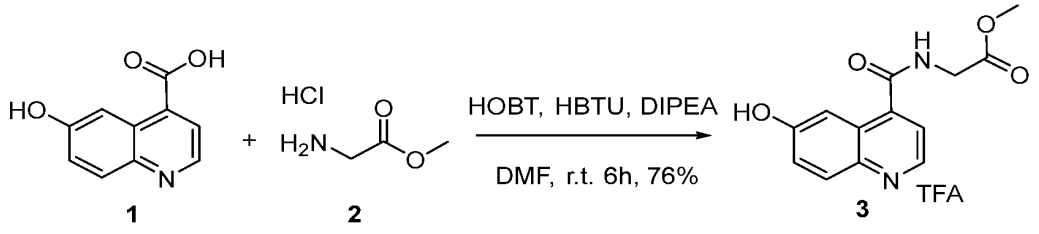
EXAMPLES

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

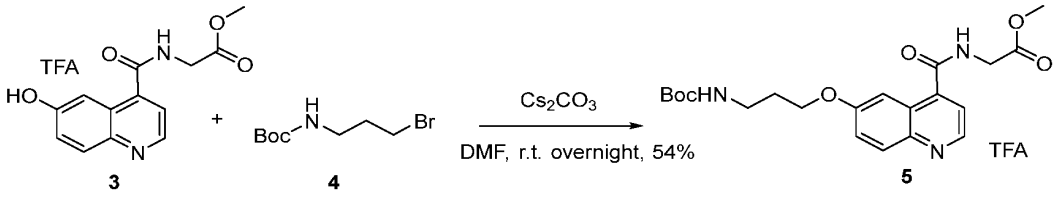
Experimental Procedures

*1.1 Synthesis of **XY-FAP-01**.*

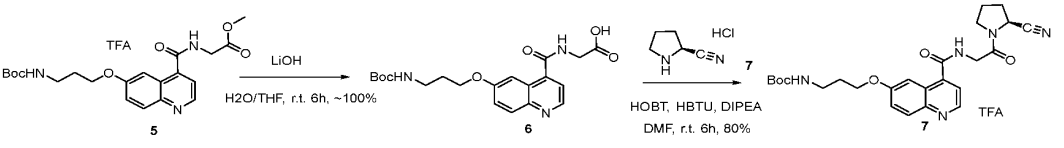


Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**): 6-Hydroxyquinoline-4-carboxylic acid (**1**) 210 mg (1.1 mmol), methyl glycinate HCl salt (**2**) 143 mg (1.1 mmol), HBTU 420 mg (1.1 mmol) and HOBt 170 mg (1.1 mmol) were dissolved in 12 mL dry DMF. To the solution, 0.77 mL of DIPEA (4.4 mmol) 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%. ^{1}H-NMR (400 MHz, CD_3OD): 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). ^{13}C-NMR (100 MHz, CD_3OD): 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.

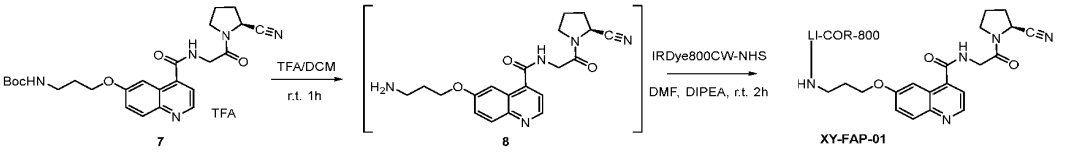


Methyl (6-(3-((tert-butoxycarbonyl)amino)propoxy)quinoline-4-carbonyl)glycinate (**5**): Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**) 360 mg (1.0 mmol), tert-butyl (3-bromopropyl)carbamate (**4**) 500 mg (2.1 mmol) were dissolved in 20 mL DMF. Cs_2CO_3 1 g (3.0 mmol) was added to the solution 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%. ^{1}H-NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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.



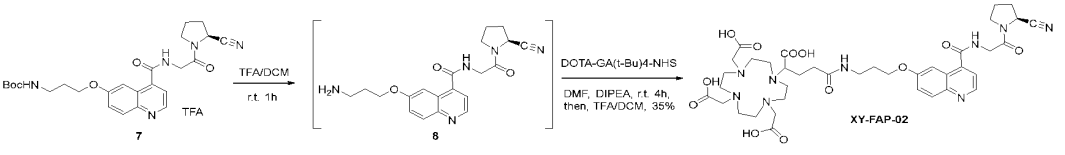
tert-Butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate (7): Compound **5** 110 mg (0.21 mmol) and LiOH 30 mg (1.2 mmol) was stirred in 4 mL of H_2O/THF (1/1) for 6 hours. After most of the THF was removed under vacuum, the mixture was loaded onto a 25 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%. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $[C_{25}H_{32}N_5O_5]^+$, 482.6 [M + H]$^+$; found 482.3.



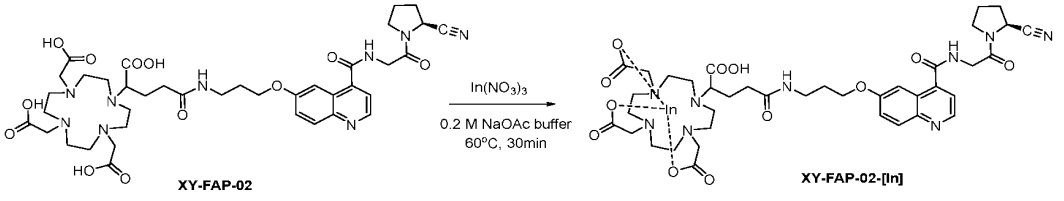
XY-FAP-01. Compound 7 (1 mg, 1.7 μmol) was treated with a 1 mL solution of TFA/methylene chloride (1/1) for 2 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMSO. To the solution, LICOR800CW-NHS ester 0.5 mg (0.43 μmol) and Et_3N 10 μL were added. After 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/H_2O/TFA to 80/20/0.1 MeCN/H_2O/TFA within 15 min at a flow of 3 mL/min. The product was eluted at 10.1 min. MS: Calculated for$[C_{66}H_{76}N_7O_{17}S_4]^+$, 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)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)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, H_2O 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 $In(NO_3)_3$ 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 $^{111}InCl_3$ 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 μm C_{18} Luna 4.6 x 250 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, **^{111}In-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, **^{111}In-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 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 IC_{50} 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).

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% penicillin-streptomycin, 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 (CO_2) 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% CO_2. 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% CO_2. 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 **^{111}In-XY-FAP-02** was also assessed in cells. Cell aliquots (1 million) were incubated with 1 μCi **^{111}In-XY-FAP-02** in saline for 30 minutes at 37 °C and 5% CO_2. 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 **^{111}In-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 μCi **^{111}In-XY-FAP-02** in 200 μL 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 CO_2 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 Wizard^2 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 μg per mouse) and 10 μCi **^{111}In-XY-FAP-02** in 200 μL saline. Mice (n=5) injected with 10 μCi **^{111}In-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

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 mm^3.

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, **^{111}In-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 **^{111}In-XY-FAP-02** in the engagement of FAP *in vitro*.

2.3 Ex-vivo Biodistribution. *Ex-vivo* biodistribution of **^{111}In-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 **^{111}In-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.

Allinen M, Beroukhim R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, Schnitt S, Sellers WR, Polyak K. Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004 Jul;6(1):17-32.

Bae S, Park CW, Son HK, Ju HK, Paik D, Jeon CJ, Koh GY, Kim J, Kim H. Fibroblast activation protein alpha identifies mesenchymal stromal cells from human bone marrow. Br J Haematol. 2008 Sep;142(5):827-30.

Chen ZY, Wang YX, Lin Y, Zhang JS, Yang F, Zhou QL, Liao YY. Advance of molecular imaging technology and targeted imaging agent in imaging and therapy. Biomed Res Int. 2014; 2014 : 819324. PMCID: PMC3943245.

Coenen HH, Elsinga PH, Iwata R, Kilbourn MR, Pillai MR, Rajan MG, Wagner HN Jr. Zaknun JJ. Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727–740.

Coenen HH, Elsinga PH, Iwata R, Kilbourn MR, Pillai MR, Rajan MG, Wagner HN Jr. Zaknun JJ. Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727–740. 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.

Edosada CY, Quan C, Tran T, Pham V, Wiesmann C, Fairbrother W, Wolf BB. 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 E, Chaitanya K, Wuest T, et al. Radioimmunotherapy of fibroblast activation protein positive tumors by rapidly internalizing antibodies. Clin Cancer Res. 2012;18:6208–6218.

Franco OE, Shaw AK, Strand DW, Hayward SW. Cancer associated fibroblasts in cancer pathogenesis. Semin Cell Dev Biol. 2010 Feb;21(1):33-9.

Garin-Chesa P, Old LJ, Rettig WJ. 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 K, Heirbaut L, Cheng JD, Joossens J, Ryabtsova O, Cos P, Maes L, Lambeir AM, De Meester I, Augustyns K, Van der Veken P. 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 K, Heirbaut L, Verkerk R, Cheng JD, Joossens J, Cos P, Maes L, Lambeir AM, De Meester I, Augustyns K, Van der Veken P. 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 T. 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.

Kraman M, Bambrough PJ, Arnold JN, Roberts EW, Magiera L, Jones JO, Gopinathan A, Tuveson DA, Fearon DT. Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. Science. 2010 Nov 5;330(6005):827-30.

Laverman P, van der Geest T, Terry SY, Gerrits D, Walgreen B, Helsen MM, Nayak TK, Freimoser-Grundschober A, Waldhauer I, Hosse RJ, Moessner E, Umana P, Klein C, Oyen WJ, Koenders MI, Boerman OC. 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.

Lo PC, Chen J, Stefflova K, Warren MS, Navab R, Bandarchi B, Mullins S, Tsao M, Cheng JD, Zheng G. Photodynamic molecular beacon triggered by fibroblast activation protein on cancer-associated fibroblasts for diagnosis and treatment of epithelial cancers. J Med Chem. 2009 Jan 22;52(2):358-68.

Poplawski SE, Lai JH, Li Y, Jin Z, Liu Y, Wu W, Wu Y, Zhou Y, Sudmeier JL, Sanford DG, Bachovchin WW. Identification of selective and potent inhibitors of fibroblast activation protein and prolyl oligopeptidase. J Med Chem. 2013 May 9;56(9):3467-77.

Reilly RM, Lam K, Chan C, Levine M. Advancing Novel Molecular Imaging Agents

from Preclinical Studies to First-in-Humans Phase I Clinical Trials in Academia-A Roadmap for Overcoming Perceived Barriers. Bioconjugate chemistry. 2015; 26:625–632.

Rettig WJ, Garin-Chesa P, Healey JH, Su SL, Ozer HL, Schwab M, Albino AP, Old LJ. Regulation and heteromeric structure of the fibroblast activation protein in normal and transformed cells of mesenchymal and neuroectodermal origin Cancer Res. 1993 Jul 15;53(14):3327-35.

Ryabtsova O, Jansen K, Van Goethem S, Joossens J, Cheng JD, Lambeir AM, De Meester I, Augustyns K, Van der Veken P. Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity. Bioorg Med Chem Lett. 2012 May 15;22(10):3412-7.

Scanlan MJ, Raj BK, Calvo B, Garin-Chesa P, Sanz-Moncasi MP, Healey JH, Old LJ, Rettig WJ. Molecular cloning of fibroblast activation protein alpha, a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. Proc Natl Acad Sci U S A. 1994 Jun 7;91(12):5657-61.

Scott AM, Wiseman G, Welt S, Adjei A, Lee FT, Hopkins W, Divgi CR, Hanson LH, Mitchell P, Gansen DN, Larson SM, Ingle JN, Hoffman EW, Tanswell P, Ritter G, Cohen LS, Bette P, Arvay L, Amelsberg A, Vlock D, Rettig WJ, Old LJ. A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res. 2003 May;9(5):1639-47.

Tsai TY, Yeh TK, Chen X, Hsu T, Jao YC, Huang CH, Song JS, Huang YC, Chien CH, Chiu JH, Yen SC, Tang HK, Chao YS, Jiaang WT. Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein. J Med Chem. 2010 Sep 23;53(18):6572-83.

Tuxhorn JA, Ayala GE, Smith MJ, Smith VC, Dang TD, Rowley DR. Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling. Clin Cancer Res. 2002 Sep;8(9):2912-23.

Welt S, Divgi CR, Scott AM, Garin-Chesa P, Finn RD, Graham M, Carswell EA, Cohen A, Larson SM, Old LJ, 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 H., Hong K. In vivo noninvasive small animal molecular imaging. Osong Public Health Res Perspect. 2012; 3 :48-59. PMCID: PMC3738683.

Yu DM, Yao TW, Chowdhury S, Nadvi NA, Osborne B, Church WB, McCaughan GW, Gorrell MD. The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J. 2010 Mar;277(5):1126-44.

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.

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.

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 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.

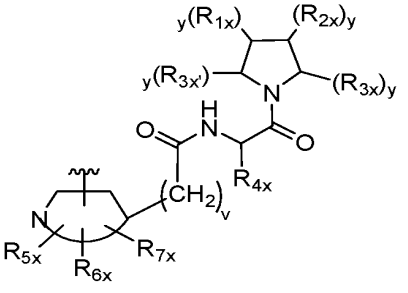
SUMMARY

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

(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.

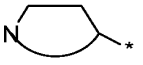
In particular aspects, A is an FAP-α targeting moiety having the structure of:



(X');

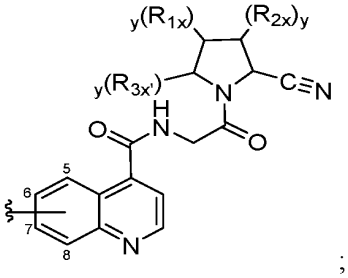
wherein each y is independently an integer selected from the group consisting of 0, 1, and 2; R_{1x}, R_{2x}, and $R_{3x'}$, are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl; R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$, -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl; R_{4x} is H; R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of $C_{1\text{-}6}$alkyl being optionally substituted with from 1 to 3 substituents

selected from -OH and halogen; R_{8x}, R_{9x}, and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, and -Ar_3; R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; v is 0, 1, 2, or 3; and



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

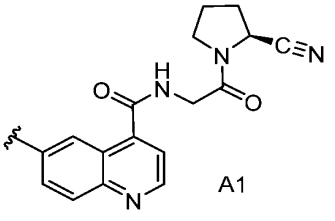
In more particular aspects, A is an FAP-α targeting moiety having the structure of:

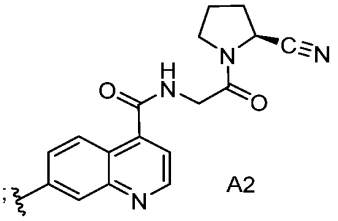


;

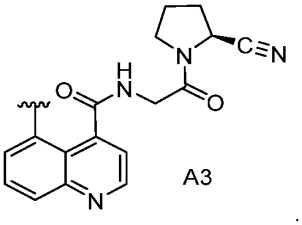
wherein ⟆ indicates a point of attachment of the FAP-α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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


A1


A2

; and


A3

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 ^{1}H 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, **[^{111}In]-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 ^{111}In and HPLC purification resulted in the radiolabeled product, **[^{111}In]-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 FAP-negative 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 **[^{111}In]-XY-FAP-02** in FAP-positive U87 and FAP-negative PC3 cell lines. Cells were incubated with 1 μCi **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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. [a]Student'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. [b]Student'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 ($p=0.0006$). [c]Student'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 **[^{111}In]-XY-FAP-02**. FIG. 5A shows tissue time activity curves (TACs) of **[^{111}In]-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 **[^{111}In]-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 **[^{111}In]-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

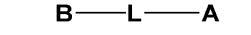
The highly potent and specific binding moiety targeting FAP-α enables its use in nuclear imaging and radiotherapy. The presently disclosed subject matter provides the first synthesis of nuclear imaging and radiotherapy agents based on this dual-targeting moiety to FAP-α.

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, ^{68}Ga, ^{64}Cu, ^{18}F, ^{86}Y, ^{90}Y, ^{89}Zr, ^{111}In, ^{99m}Tc, ^{125}I, ^{124}I, 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, ^{90}Y, ^{177}Lu, ^{125}I, ^{131}I, ^{211}At, ^{111}In, ^{153}Sm, ^{186}Re, ^{188}Re, ^{67}Cu, ^{212}Pb, ^{225}Ac, ^{213}Bi, ^{212}Bi, ^{212}Pb, and ^{67}Ga, 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 ^{111}In labeled ligand (**XY-FAP-02-[^{111}In]**) 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):

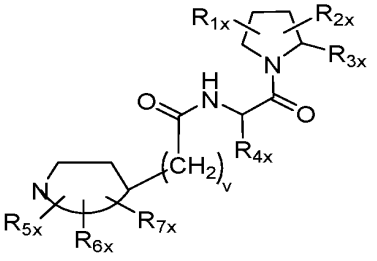


(I)

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:



(X);

wherein:

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

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

R_{4x} is H;

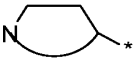
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH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

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

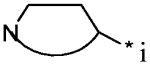
R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from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

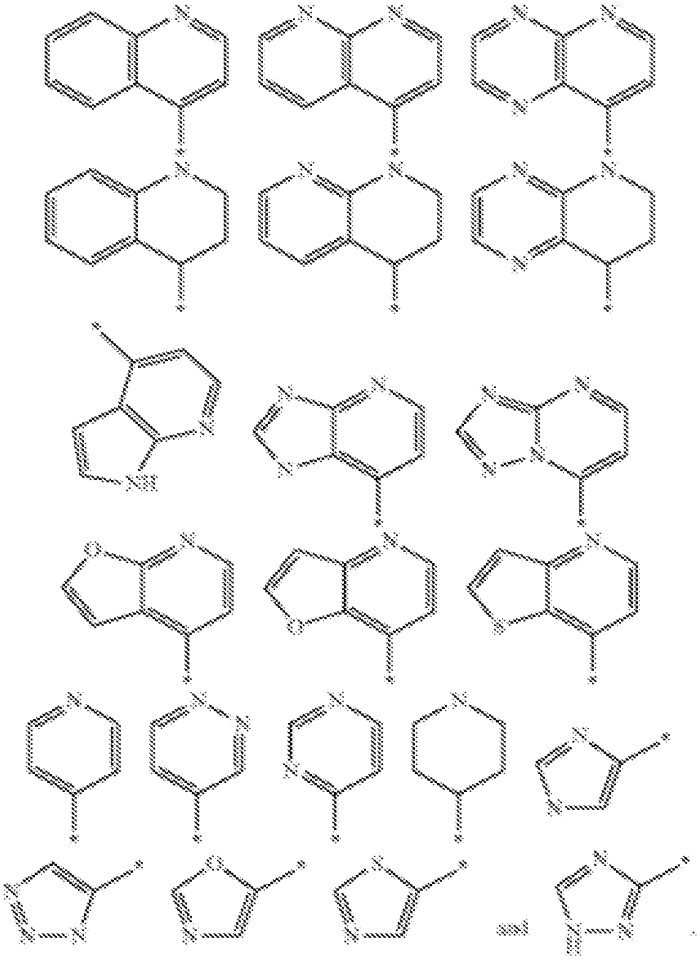
Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

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



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

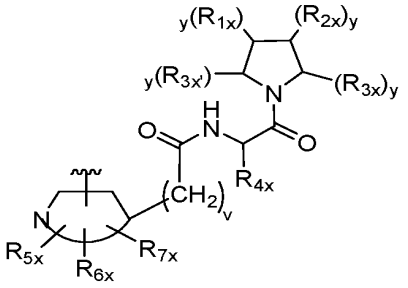
In particular embodiments,  is selected from the group consisting of:



;

wherein * indicates the point of attachment of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle to $-(CH_2)_v-$.

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



(X');

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

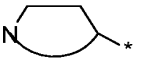
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH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

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

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

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

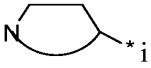
v is 0, 1, 2, or 3; and

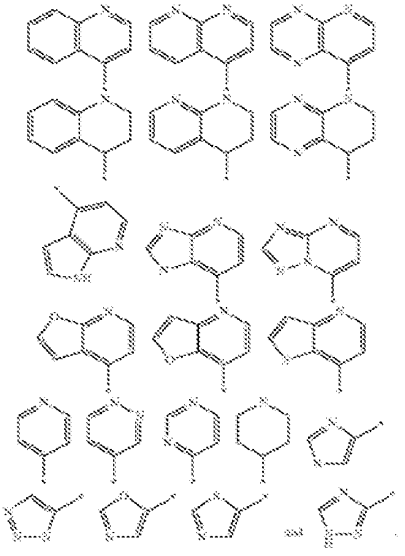


Petitioner GE Healthcare – Ex. 1031, p. 203

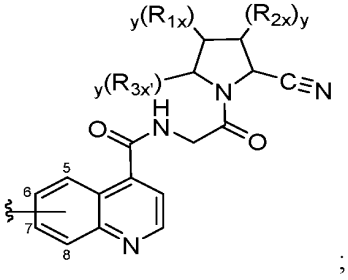
represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

wherein 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,  is selected from the group consisting of:



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

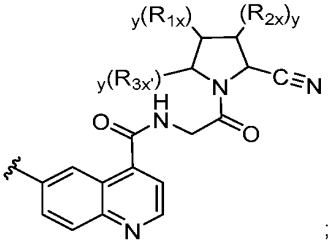
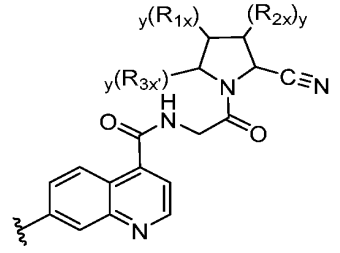
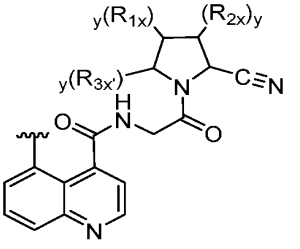


;

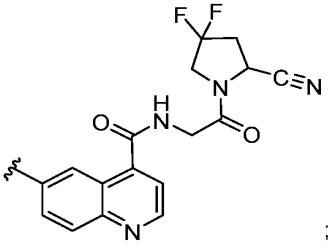
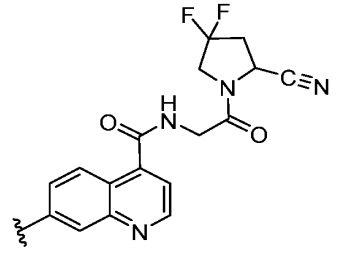
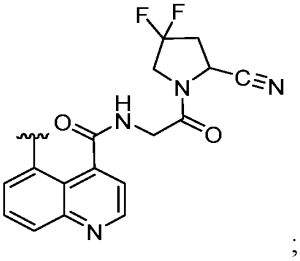
Petitioner GE Healthcare – Ex. 1031, p. 204

wherein y, R_{1x}, R_{2x} and $R_{3x'}$ are defined as hereinabove; ⟆ 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:

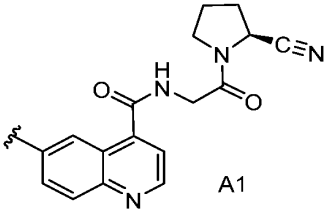
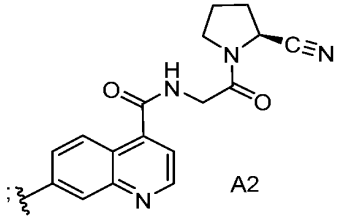
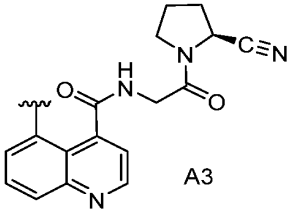

;

; and

.

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

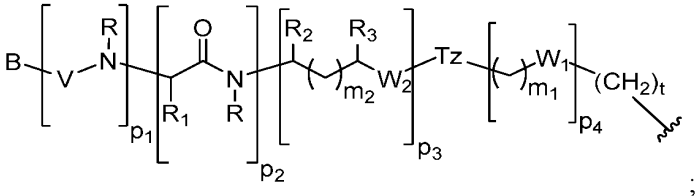

;

; and

;

and stereoisomers thereof.

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

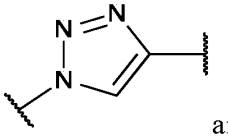
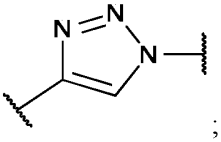

A1
;

A2
; and

A3
.

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

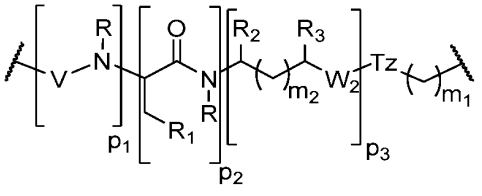

;

Petitioner GE Healthcare – Ex. 1031, p. 205

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 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)–; W_2 is selected from the group consisting of a bond, -S-, -CH_2-C(=O)-NR-, –C(O)–, –NRC(O)–, –NR'C(O)NR–, –NRC(S)NR'$_2$–, –NRC(O)O–, –OC(O)NR–, –OC(O)–, –C(O)NR–, –NR–C(O)–, –C(O)O–, –(O–CH_2–CH_2)$_q$– and –(CH_2-CH_2-O)$_q$–, wherein q is selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and –OR_4, wherein R_4 is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, and substituted heterocycloalkyl, wherein q is defined as immediately hereinabove; Tz is a triazole group that can be present or absent and, if present, is selected from the group consisting of


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:



Petitioner GE Healthcare – Ex. 1031, p. 206

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 $-L_1-$, $-L_2-L_3-$, and $-L_1-L_2-L_3-$, wherein:

L_1 is $-NR-(CH_2)_q-[O-CH_2-CH_2-O]_q-(CH_2)_q-C(=O)-$;

L_2 is $-NR-(CH_2)_q-C(COOR_5)-NR-$; and

L_3 is $-(O=)C-(CH_2)_q-C(=O)-$;

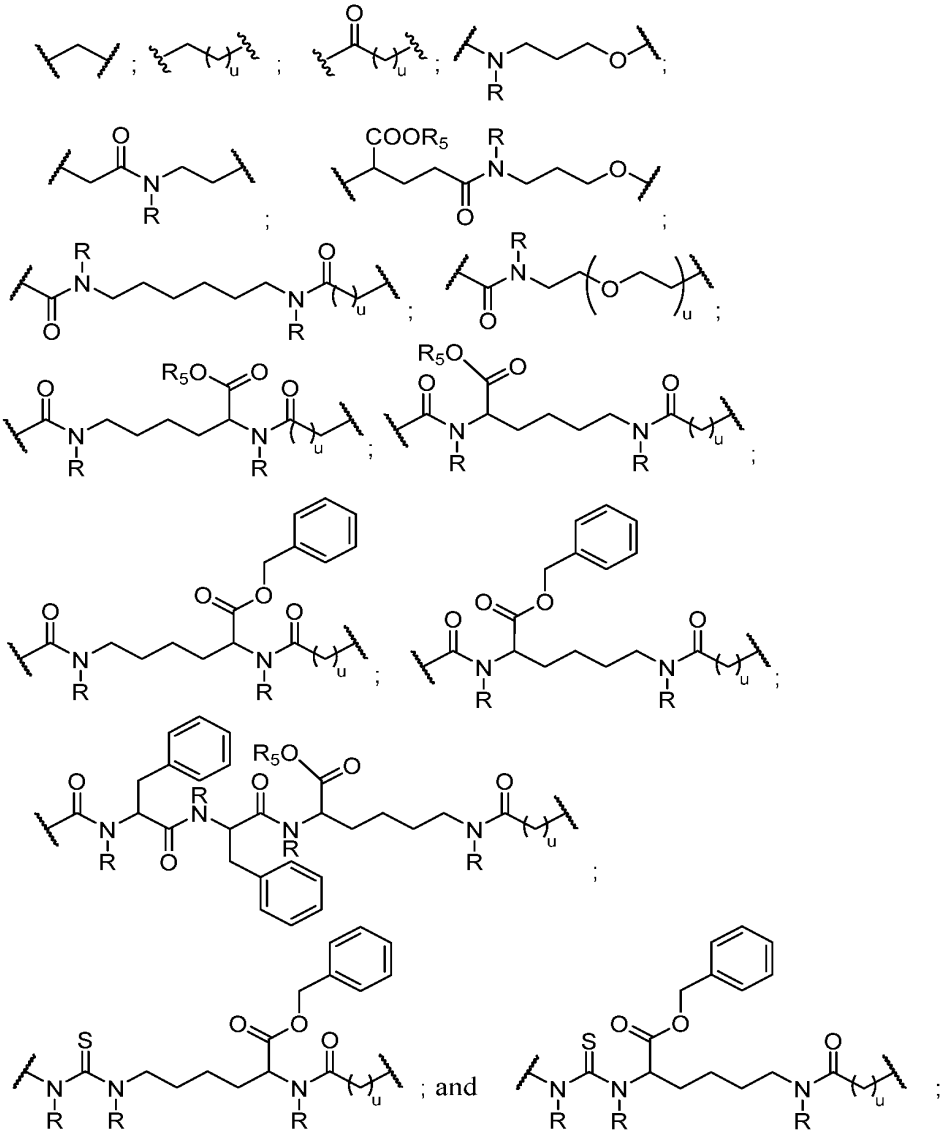
wherein each q is independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

In particular embodiments, L is:

$-(CR_6H)_q-(CH_2)_q-C(=O)-NR-(CH_2)_q-O-$ or $-NR-(CH_2)_q-O-$;

wherein each q and R is defined hereinabove; and R_6 is H or $-COOR_5$.

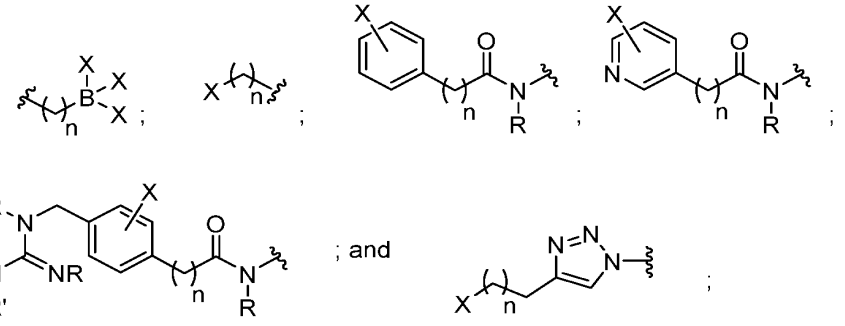
In yet more particular embodiments, L is selected from the group consisting of:



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.

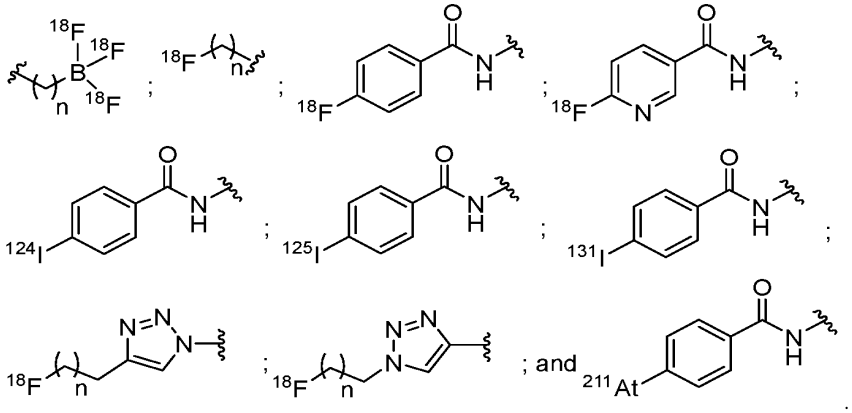
Suitable linkers are disclosed in U.S. Patent Application Publication No. US2011/0064657 A1, for "Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA), Biological Evaluation, and Use as Imaging Agents," published March 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. 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 ^{18}F, ^{124}I, ^{125}I, ^{131}I, and ^{211}At. Representative radiolabeled prosthetic groups include, but are not limited to:



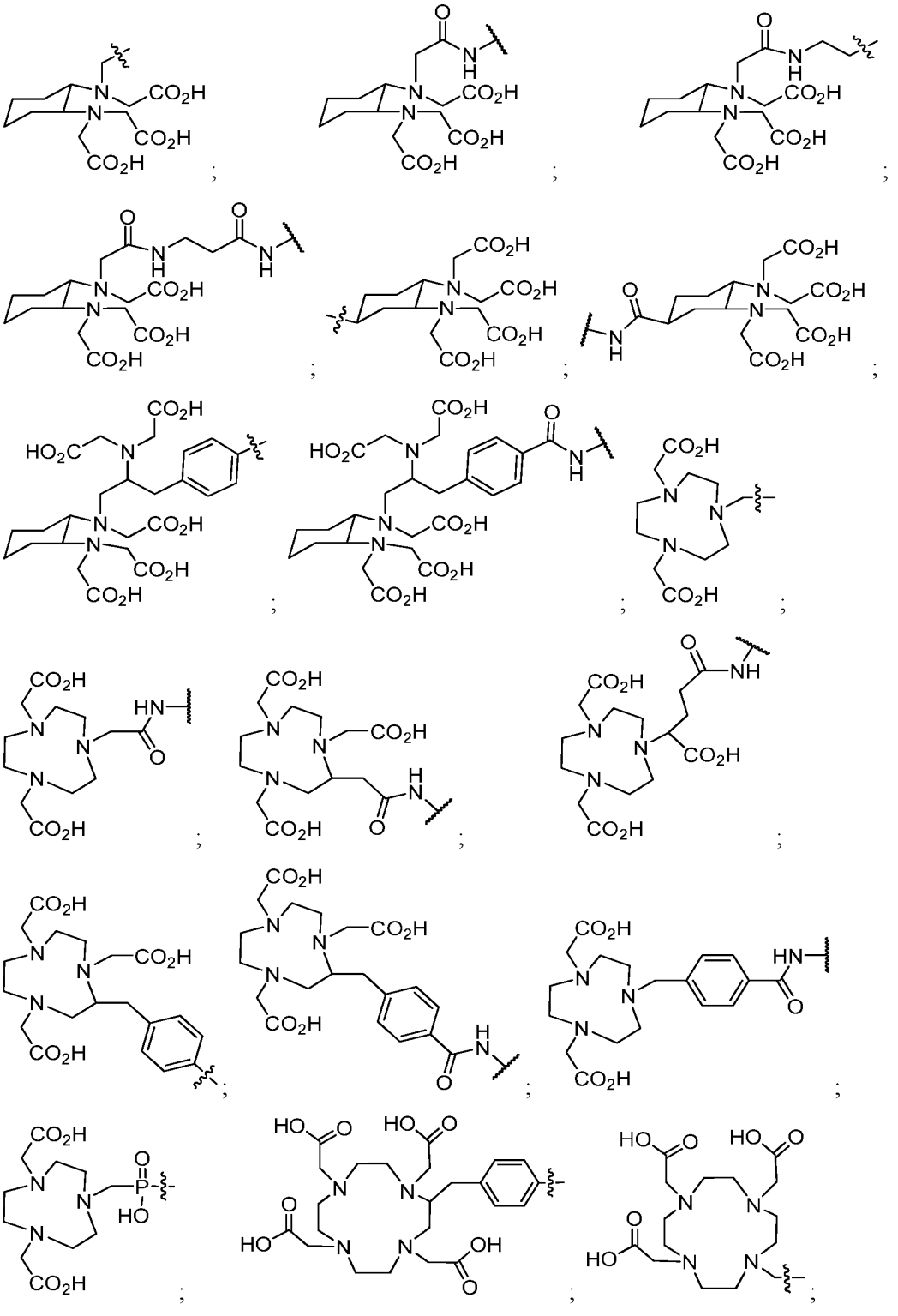
wherein each X is independently a radioisotope selected from the group consisting of ^{18}F, ^{124}I, ^{125}I, ^{131}I, and ^{211}At; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,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

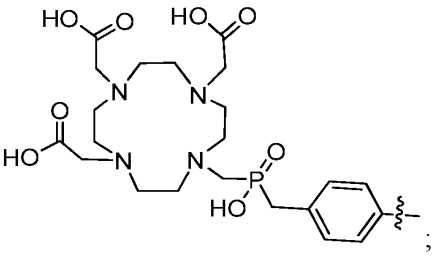
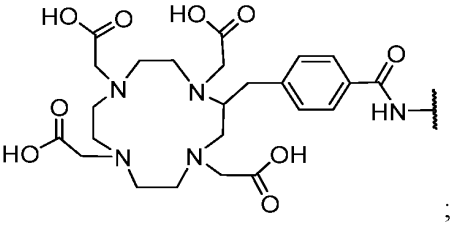
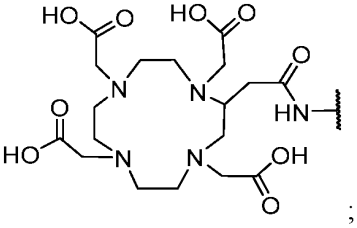
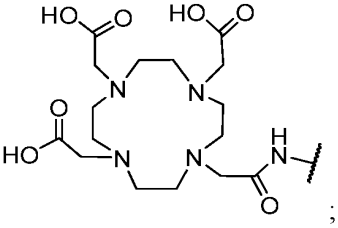
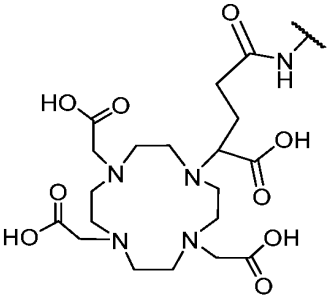
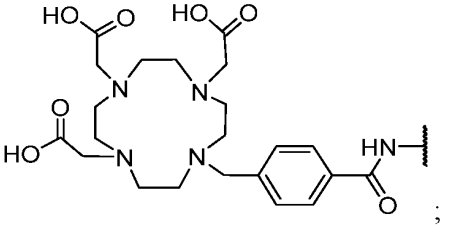
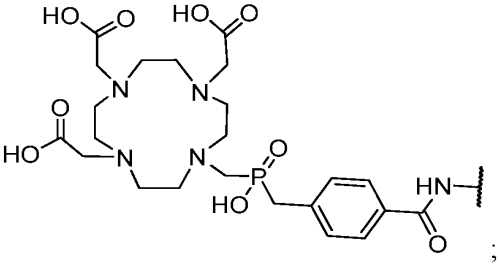
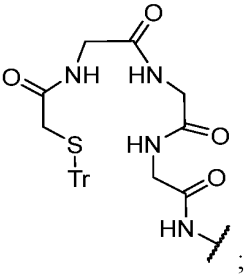
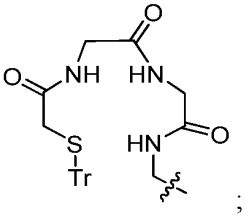
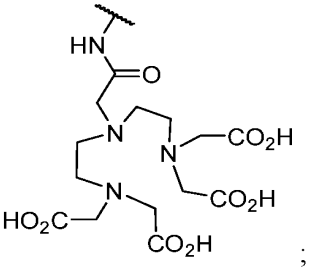
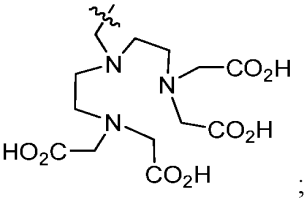
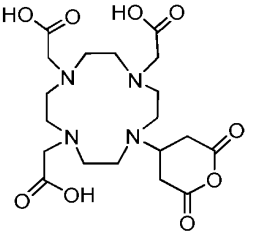
In more particular embodiments, the radiolabeled prosthetic group is selected from the group consisting of:

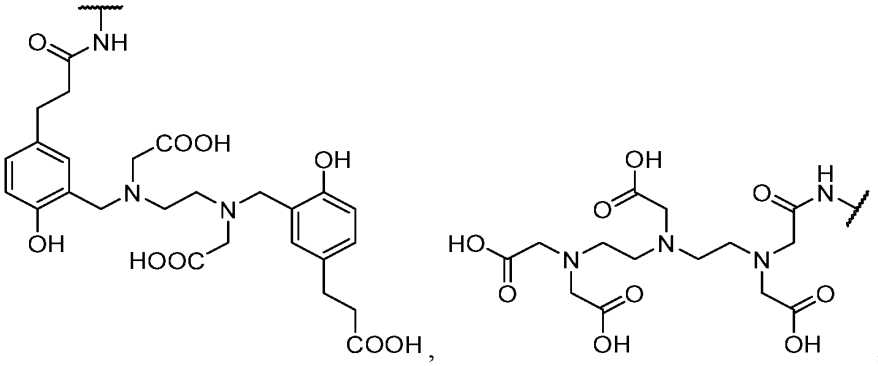


In other embodiments, B comprises a chelating agent. Representative chelating agents include, but are not limited to:

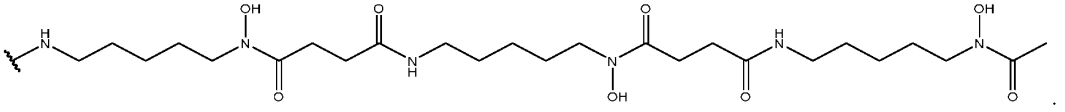
Petitioner GE Healthcare – Ex. 1031, p. 209




;

;

;

;

;

;

;

;

;

;

;

;



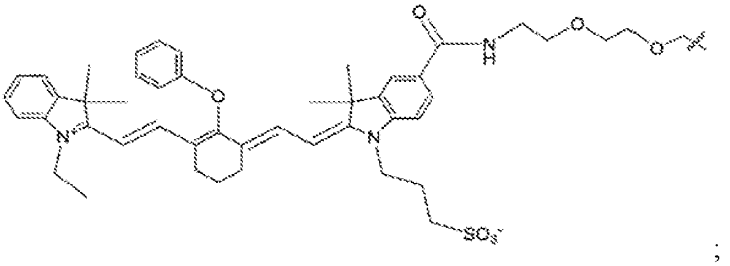
, and



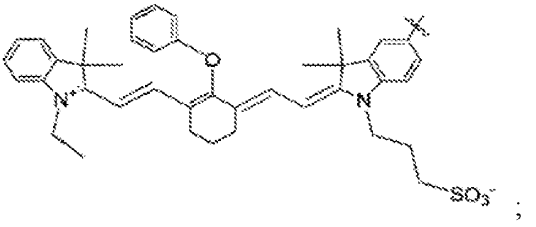
.

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, 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.

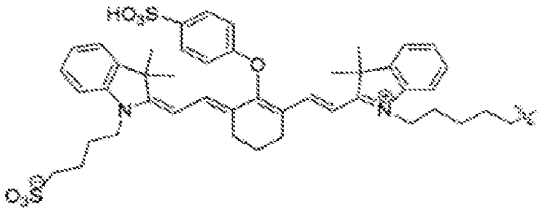
Representative optical dyes include, but are not limited to:



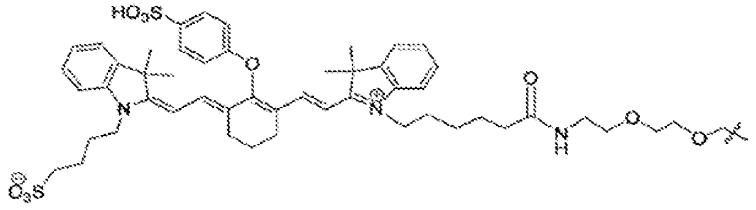
;



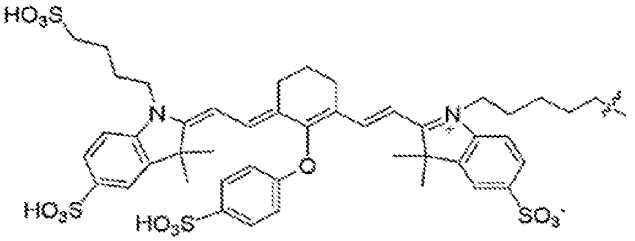
;



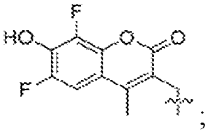
;



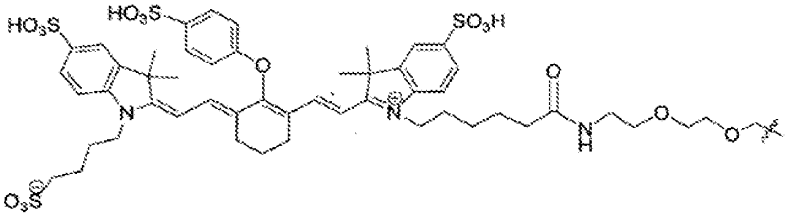
;



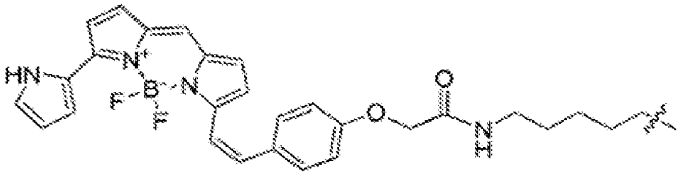
;



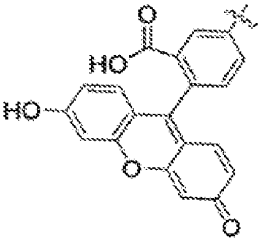
;



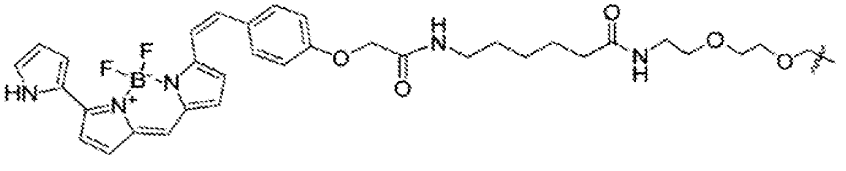
;



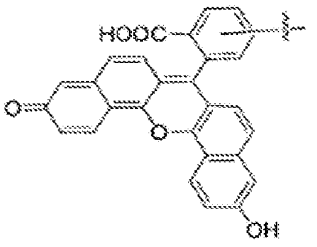
;

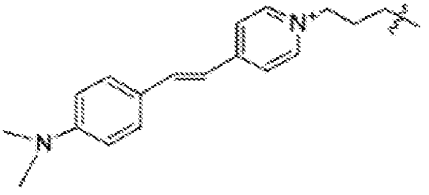


;

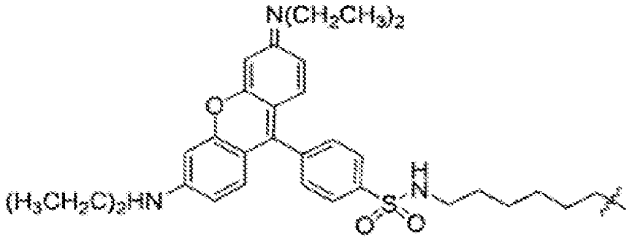


;



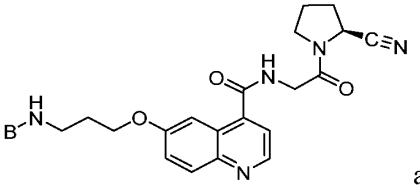
;


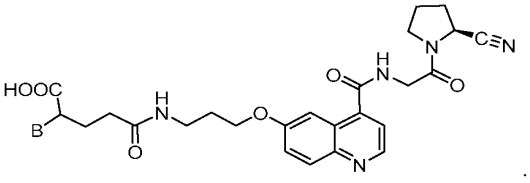
;

and


.

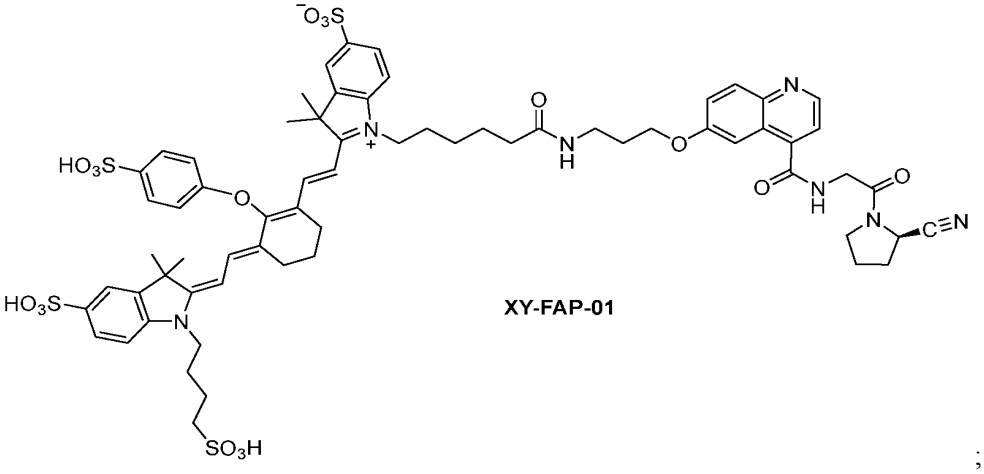
In some embodiments, the presently disclosed subject matter provides a compound selected from the group consisting of:



and


.

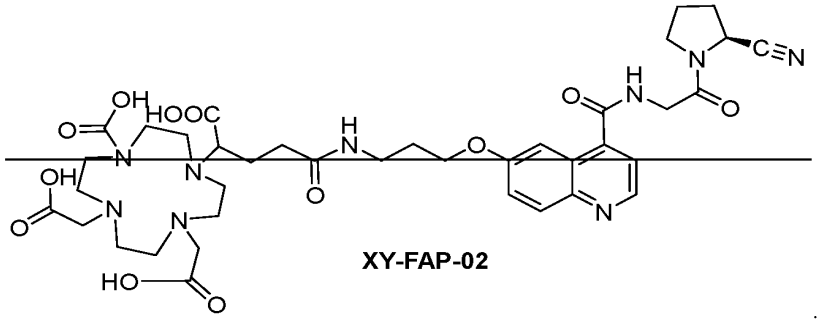
In particular embodiments, the compound is selected from the group consisting of:



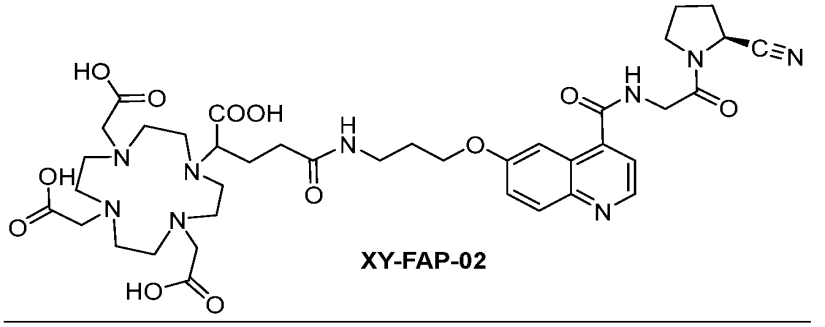
XY-FAP-01

; and

Petitioner GE Healthcare – Ex. 1031, p. 214



XY-FAP-02



XY-FAP-02

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, p-toluenesulfonic, 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, camsylate, 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. Dye-stuffs 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 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.

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 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 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

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 $C_{1\text{-}20}$ 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 $C_{1\text{-}8}$ 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, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_{25}-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

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 10-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-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 7-membered 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, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(l,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 $C_{1\text{-}20}$ 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 ($–CH_2–$); ethylene ($–CH_2–CH_2–$); propylene ($–(CH_2)_3–$); cyclohexylene ($–C_6H_{10}–$); $–CH=CH–CH=CH–$; $–CH=CH–CH_2–$; $-CH_2CH_2CH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CsCCH_2-$, $-CH_2CH_2CH(CH_2CH_2CH_3)CH_2-$, $-(CH_2)_q-N(R)-(CH_2)_r–$, 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 ($–O–CH_2–O–$); and ethylenedioxyl ($-O-(CH_2)_2–O–$). 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, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (e.g., alkyleneoxo,

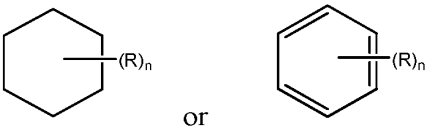
alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula -C(O)OR'- represents both -C(O)OR'- 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, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-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-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., 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.

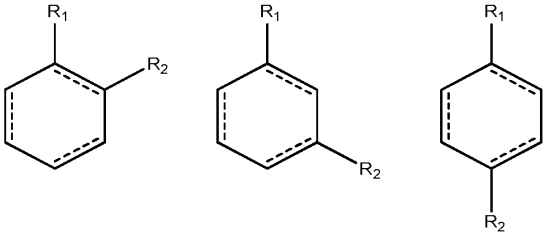
Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" refers to a carbon or heteroatom.

Further, a structure represented generally by the formula:



or

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', -CO_2R',-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', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2 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 4-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., -CF_3 and -CH_2CF_3) and acyl (e.g., -C(O)CH_3, -C(O)CF_3, -C(O)CH_2OCH_3, 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', -CO_2R', -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', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxo, and fluoro(C_1-C_4)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 cycloalkyl, substituted 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-$(CH_2)_r$-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- 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 -$S(O)_2$NR'-. 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., C_6H_5-CH_2-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 $-(CH_2)_k-$ 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 $–NO_2$ 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 $–SO_4$ 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 $–NH—CO—NH_2$.

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.

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.

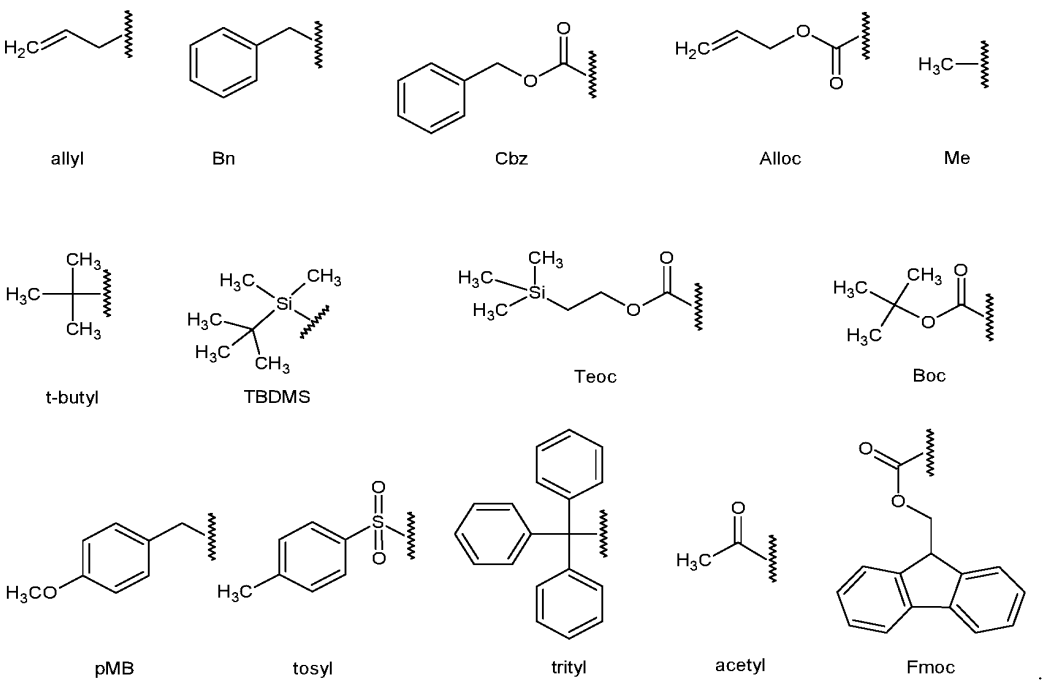
The term "protecting group" refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, Protective 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 co-existing 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:



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, ± 100% in some embodiments ± 50%, in some embodiments ± 20%, in some embodiments ± 10%, in some embodiments ± 5%, in some embodiments ±1%, in some embodiments ± 0.5%, and in some embodiments ± 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.

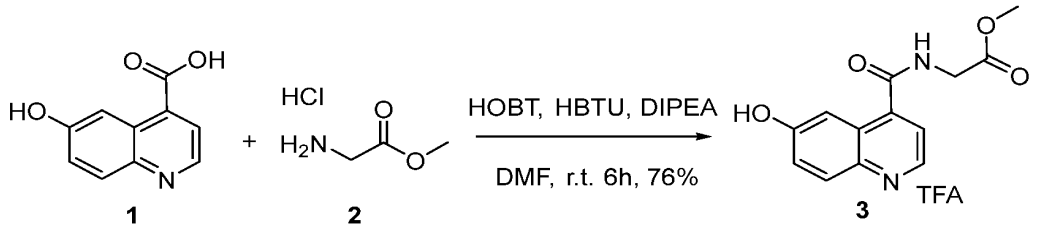
EXAMPLES

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.

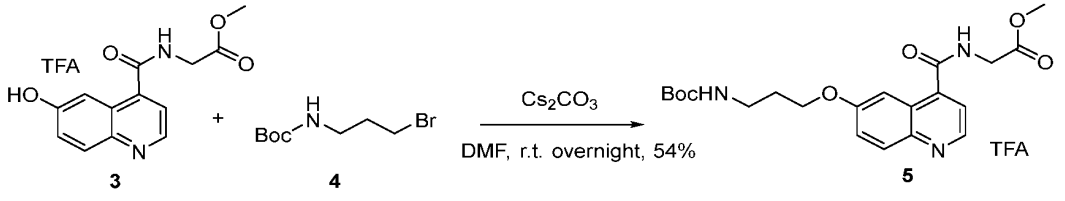
EXAMPLE 1

Experimental Procedures

1.1 Synthesis of ***XY-FAP-01.***

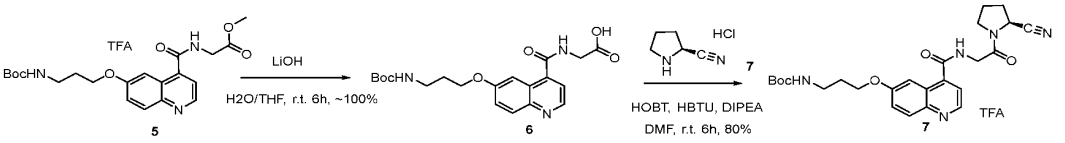


Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**): 6-Hydroxyquinoline-4-carboxylic acid (**1**) 210 mg (1.1 mmol), methyl glycinate HCl salt (**2**) 143 mg (1.1 mmol), HBTU 420 mg (1.1 mmol) and HOBt 170 mg (1.1 mmol) were dissolved in 12 mL dry DMF. To the solution, 0.77 mL of DIPEA (4.4 mmol) 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%. ^{1}H-NMR (400 MHz, CD_3OD): 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). ^{13}C-NMR (100 MHz, CD_3OD): 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.

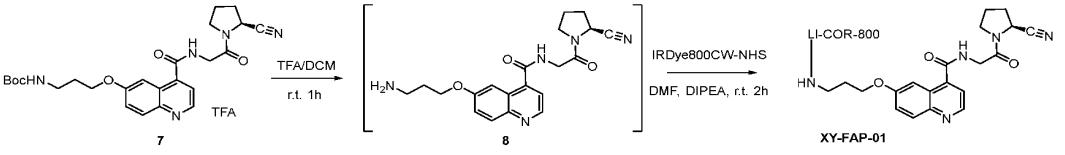


Methyl (6-(3-((tert-butoxycarbonyl)amino)propoxy)quinoline-4-carbonyl)glycinate (**5**): Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**) 360 mg (1.0 mmol), tert-butyl (3-bromopropyl)carbamate (**4**) 500 mg (2.1 mmol) were dissolved in 20 mL DMF. Cs_2CO_3 1 g (3.0 mmol) was added to the solution 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%. ^{1}H-NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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.



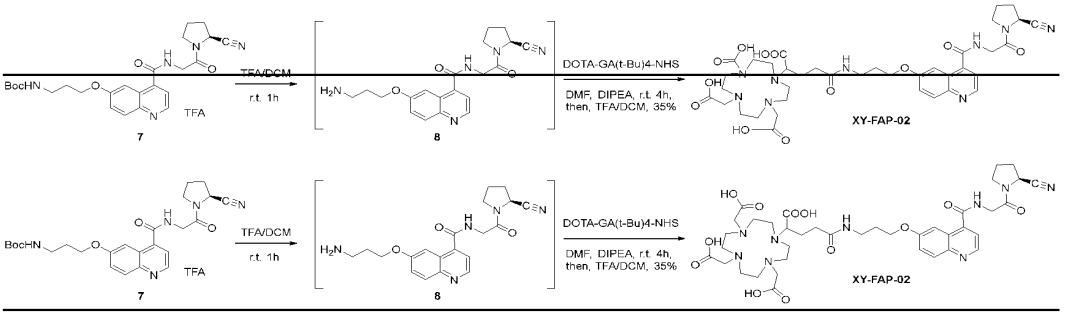
tert-Butyl(S)-(3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate (7): Compound **5** 110 mg (0.21 mmol) and LiOH 30 mg (1.2 mmol) was stirred in 4 mL of H_2O/THF (1/1) for 6 hours. After most of the THF was removed under vacuum, the mixture was loaded onto a 25 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%. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $[C_{25}H_{32}N_5O_5]^+$, 482.6 $[M + H]^+$; found 482.3.



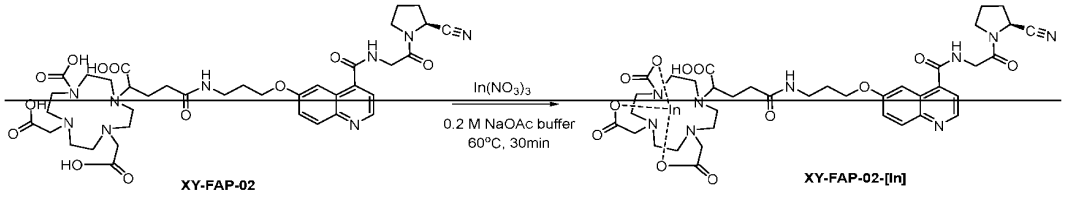
XY-FAP-01. Compound 7 (1 mg, 1.7 μmol) was treated with a 1 mL solution of TFA/methylene chloride (1/1) for 2 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMSO. To the solution, LICOR800CW-NHS ester 0.5 mg (0.43 μmol) and Et_3N 10 μL were added. After 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

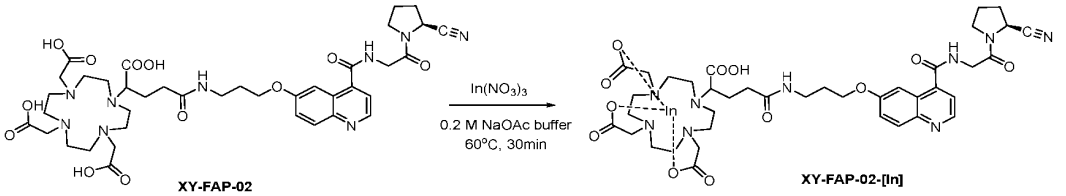
Phenomenex, Luna 10 x 250 mm, 10 u. Gradient 10/90/0.1 MeCN/H_2O/TFA to 80/20/0.1 MeCN/H_2O/TFA within 15 min at a flow of 3 mL/min. The product was eluted at 10.1 min. MS: Calculated for$[C_{66}H_{76}N_7O_{17}S_4]^+$, 1366.4$[M+H]^+$; found 1366.8.

*1.2 Synthesis of **XY-FAP-02***



2,2',2''-(10-(1-Carboxy-4-((3-((4-((2-((S)-2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)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, H_2O 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 $In(NO_3)_3$ 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 $^{111}InCl_3$ 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 μm C_{18} Luna 4.6 x 250 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, **^{111}In-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, **^{111}In-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 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 IC_{50} 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).

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% penicillin-streptomycin, 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 (CO_2) 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% CO_2. 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% CO_2. 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 **^{111}In-XY-FAP-02** was also assessed in cells. Cell aliquots (1 million) were incubated with 1 µCi **^{111}In-XY-FAP-02** in saline for 30 minutes at 37 °C and 5% CO_2. 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 **^{111}In-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 μCi **^{111}In-XY-FAP-02** in 200 μL 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 CO_2 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 Wizard^2 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 μg per mouse) and 10 μCi **^{111}In-XY-FAP-02** in 200 μL saline. Mice (n=5) injected with 10 μCi **^{111}In-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 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 mm^3.

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, **^{111}In-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 **^{111}In-XY-FAP-02** in the engagement of FAP *in vitro*.

2.3 Ex-vivo Biodistribution. *Ex-vivo* biodistribution of **^{111}In-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 **^{111}In-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.

Allinen M, Beroukhim R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, Schnitt S, Sellers WR, Polyak K. Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004 Jul;6(1):17-32.

Bae S, Park CW, Son HK, Ju HK, Paik D, Jeon CJ, Koh GY, Kim J, Kim H. Fibroblast activation protein alpha identifies mesenchymal stromal cells from human bone marrow. Br J Haematol. 2008 Sep;142(5):827-30.

Chen ZY, Wang YX, Lin Y, Zhang JS, Yang F, Zhou QL, Liao YY. Advance of molecular imaging technology and targeted imaging agent in imaging and therapy. Biomed Res Int. 2014; 2014 : 819324. PMCID: PMC3943245.

Coenen HH, Elsinga PH, Iwata R, Kilbourn MR, Pillai MR, Rajan MG, Wagner HN Jr. Zaknun JJ. Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727–740.

Coenen HH, Elsinga PH, Iwata R, Kilbourn MR, Pillai MR, Rajan MG, Wagner HN Jr. Zaknun JJ. Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727–740. 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.

Edosada CY, Quan C, Tran T, Pham V, Wiesmann C, Fairbrother W, Wolf BB. 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 E, Chaitanya K, Wuest T, et al. Radioimmunotherapy of fibroblast activation protein positive tumors by rapidly internalizing antibodies. Clin Cancer Res. 2012;18:6208–6218.

Franco OE, Shaw AK, Strand DW, Hayward SW. Cancer associated fibroblasts in cancer pathogenesis. Semin Cell Dev Biol. 2010 Feb;21(1):33-9.

Garin-Chesa P, Old LJ, Rettig WJ. 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 K, Heirbaut L, Cheng JD, Joossens J, Ryabtsova O, Cos P, Maes L, Lambeir AM, De Meester I, Augustyns K, Van der Veken P. 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 K, Heirbaut L, Verkerk R, Cheng JD, Joossens J, Cos P, Maes L, Lambeir

AM, De Meester I, Augustyns K, Van der Veken P. 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 T. 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.

Kraman M, Bambrough PJ, Arnold JN, Roberts EW, Magiera L, Jones JO, Gopinathan A, Tuveson DA, Fearon DT. Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. Science. 2010 Nov 5;330(6005):827-30.

Laverman P, van der Geest T, Terry SY, Gerrits D, Walgreen B, Helsen MM, Nayak TK, Freimoser-Grundschober A, Waldhauer I, Hosse RJ, Moessner E, Umana P, Klein C, Oyen WJ, Koenders MI, Boerman OC. 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.

Lo PC, Chen J, Stefflova K, Warren MS, Navab R, Bandarchi B, Mullins S, Tsao M, Cheng JD, Zheng G. Photodynamic molecular beacon triggered by fibroblast activation protein on cancer-associated fibroblasts for diagnosis and treatment of epithelial cancers. J Med Chem. 2009 Jan 22;52(2):358-68.

Poplawski SE, Lai JH, Li Y, Jin Z, Liu Y, Wu W, Wu Y, Zhou Y, Sudmeier JL, Sanford DG, Bachovchin WW. Identification of selective and potent inhibitors of fibroblast activation protein and prolyl oligopeptidase. J Med Chem. 2013 May 9;56(9):3467-77.

Reilly RM, Lam K, Chan C, Levine M. Advancing Novel Molecular Imaging Agents from Preclinical Studies to First-in-Humans Phase I Clinical Trials in Academia-A Roadmap for Overcoming Perceived Barriers. Bioconjugate chemistry. 2015; 26:625–632.

Rettig WJ, Garin-Chesa P, Healey JH, Su SL, Ozer HL, Schwab M, Albino AP, Old LJ. Regulation and heteromeric structure of the fibroblast activation protein in normal and transformed cells of mesenchymal and neuroectodermal origin Cancer Res. 1993 Jul 15;53(14):3327-35.

Ryabtsova O, Jansen K, Van Goethem S, Joossens J, Cheng JD, Lambeir AM, De

Meester I, Augustyns K, Van der Veken P. Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity. Bioorg Med Chem Lett. 2012 May 15;22(10):3412-7.

Scanlan MJ, Raj BK, Calvo B, Garin-Chesa P, Sanz-Moncasi MP, Healey JH, Old LJ, Rettig WJ. Molecular cloning of fibroblast activation protein alpha, a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. Proc Natl Acad Sci U S A. 1994 Jun 7;91(12):5657-61.

Scott AM, Wiseman G, Welt S, Adjei A, Lee FT, Hopkins W, Divgi CR, Hanson LH, Mitchell P, Gansen DN, Larson SM, Ingle JN, Hoffman EW, Tanswell P, Ritter G, Cohen LS, Bette P, Arvay L, Amelsberg A, Vlock D, Rettig WJ, Old LJ. A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res. 2003 May;9(5):1639-47.

Tsai TY, Yeh TK, Chen X, Hsu T, Jao YC, Huang CH, Song JS, Huang YC, Chien CH, Chiu JH, Yen SC, Tang HK, Chao YS, Jiaang WT. Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein. J Med Chem. 2010 Sep 23;53(18):6572-83.

Tuxhorn JA, Ayala GE, Smith MJ, Smith VC, Dang TD, Rowley DR. Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling. Clin Cancer Res. 2002 Sep;8(9):2912-23.

Welt S, Divgi CR, Scott AM, Garin-Chesa P, Finn RD, Graham M, Carswell EA, Cohen A, Larson SM, Old LJ, 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 H., Hong K. In vivo noninvasive small animal molecular imaging. Osong Public Health Res Perspect. 2012; 3 :48-59. PMCID: PMC3738683.

Yu DM, Yao TW, Chowdhury S, Nadvi NA, Osborne B, Church WB, McCaughan GW, Gorrell MD. The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J. 2010 Mar;277(5):1126-44.

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.

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.

REMARKS

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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**07/24/2023 02:23:01 PM ET**	**JHU-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	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-SA...pdf	(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

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_ReplcementFigures.pdf		9	Drawings-only black and white line drawings	3020 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2023-07-24_36631.303_PA2.pdf	F39DF42D8DB3AF2782DDD73663E9CDDE163E90E4BA63D1449A73D8EFE5F89BD76735A8C100D5EA658794A10193B010E108EFEFB0091C3B4044D62010CDA6A24B
2023-07-24_36631.303_PA2-SA...pdf	10FB294B23D744BC60F9831AC47A001EAEADFB8B4963B5FFCFF379E47E6C44F42AA1159EF3B28664E32E519C4D051C79A4871DC6368DCFEC3525E8E1AF1E1062
2023-07-24_36631.303_PA2-SPEC.pdf	DCF1D119222C82BE271A6609AABE7B9F7B66F5D58F840B13ED5DB584B4205C001EED36D96C79D4A27405B064D45C0685BDEA3688FC094C361541D4746A61675B
2023-07-24_36631.303_PA2-DRW.pdf	47BAABA42FC99C3AF8EB12C7FB0A3A7C5A86B8C6B1D79961795029404F99C30C49135BDC6608A06EF4E434DA766FB6A34

	C4AC33AA9A26E8950ACF36E880A7C5D
2023-07-24_36631.303_PA2-CLM.pdf	B357F341D488E935AFDF5D6A4521DB655EF39F414FA50A4AAF822D083DB98530192BAD8279248C4A95B97A0EA5B1BF55DAE8902BDB16799E27206F82AFF127A6
2023-07-24_36631.303_PA2-REM.pdf	FAFD657DF82965DE22682CA1402DB963566CF22409FD8DF8C53A87790108A1B10A540E923F77F09387AE7F0D41AE99E32BAE136AFA9EB20FAF0D0A531E2BD7EA
2023-07-24_36631.303_SubSpec-marked.pdf	60FB1A3ABF7C34BD3E82821118D3A2EC89538474EA6697CAF9D34917EA372F17B6ED1BBC49CE0E536B4F94C3AA7E87644AC68AA47068A9D26AC9FB858A87BDBB
2023-07-24_36631.303_SubSpec-clean.pdf	A25B955AE4838D0E364AF869FC429612CD956EE38B2B0BC20BE4E42F211994B136CCDF47AAF07CFD7C206D88CD60A1D157FEECCCA40B88D9698D1844903DA416
2023-07-24_36631.303_ReplcementFigures.pdf	ED37576B13EBCB8D0AE3BE72252E5E23645B4C696C299D04E8556FA0EA84847CB5616806B97D5FC8A8A2DA930E625A631AF7FDDEFE6DBE9BBA755F4C9BCB4759

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.

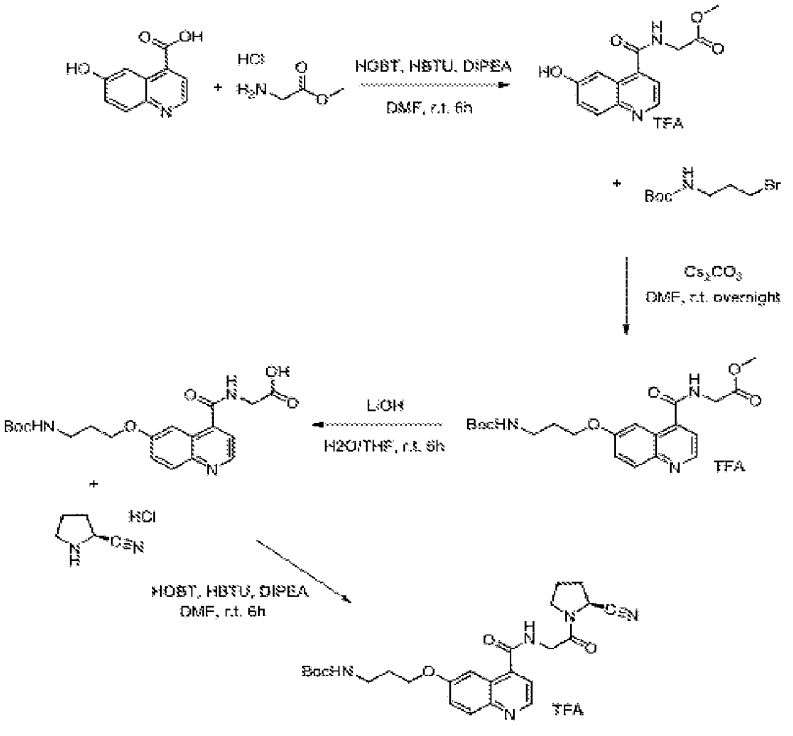

HCl
NOBT, HBTU, DIPEA
DMF, r.t. 6h
TFA
Cs2CO3
DMF, r.t. overnight
LiOH
H2O/THF, r.t. 6h
HCl
NOBT, HBTU, DIPEA
DMF, r.t. 6h
TFA

Fig. 1A

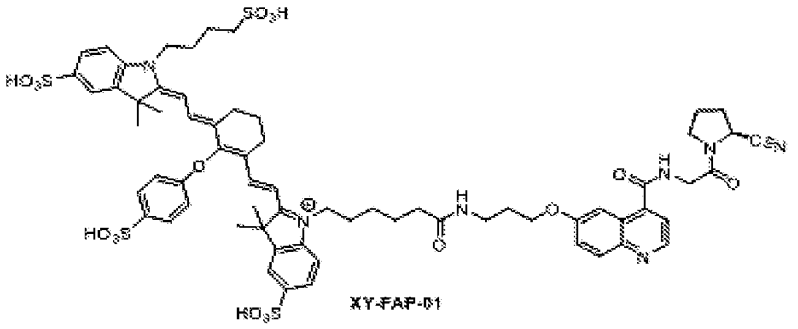


Fig. 1B

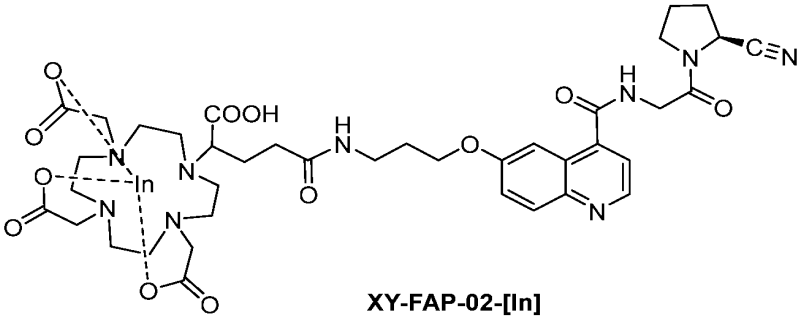


Fig. 1C

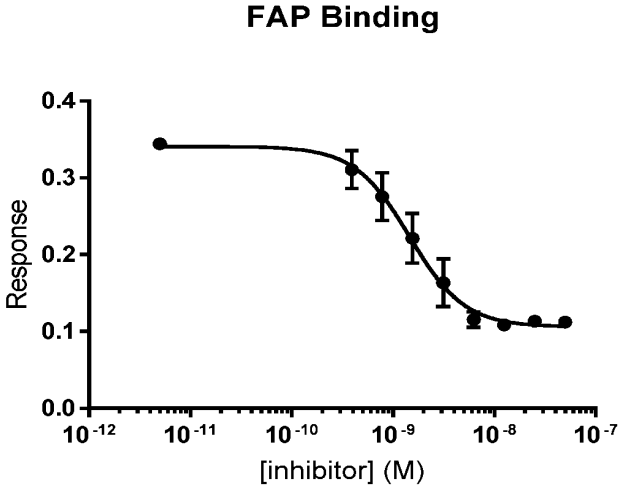

FAP Binding
Response
0.4
0.3
0.2
0.1
0.0
10-12
10-11
10-10
10-9
10-8
10-7
[inhibitor] (M)

Fig. 2

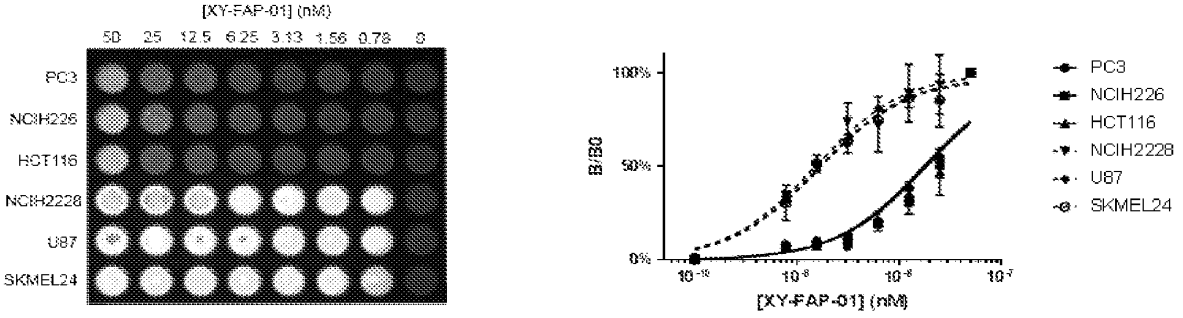


Fig. 3A

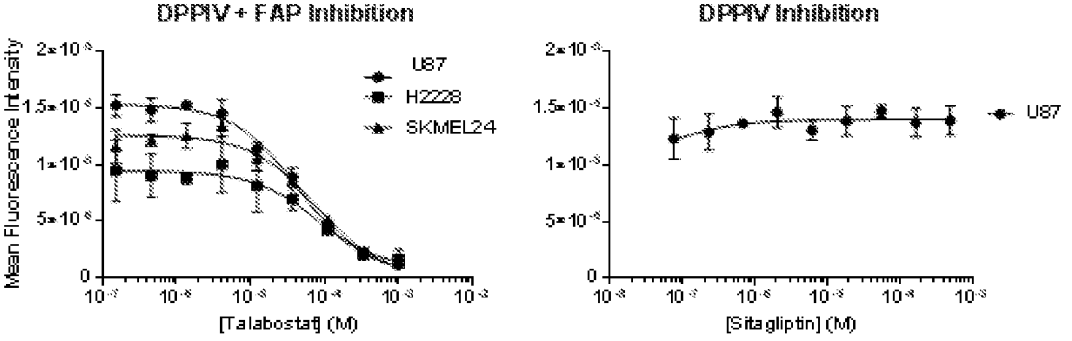


Fig. 3B

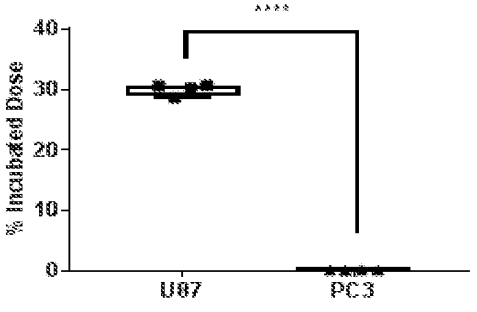


Fig. 3C

	5 min (n= 3)	0.5 h (n= 4)	2 h (n= 3)	6 hr (n= 4)	6 h - blocking (n=4)	12 h (n= 4)
blood	15.13 ± 0.62	10.64 ± 1.54	4.10 ± 0.39	2.01 ± 0.18	0.02 ± 0.001	0.42 ± 0.04
heart	6.68 ± 0.99	4.98 ± 0.71	2.61 ± 0.09	1.07 ± 0.09	0.02 ± 0.002	0.46 ± 0.04
lungs	6.99 ± 1.37	5.60 ± 0.89	2.59 ± 0.32	1.36 ± 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 ± 0.20	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	0.45 ± 0.16	0.02 ± 0.017	0.15 ± 0.08
kidney	4.80 ± 0.57	3.56 ± 0.18	1.95 ± 0.06	1.79 ± 0.21	1.16 ± 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
lrg. 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	2.96 ± 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	0.02 ± 0.005	0.60 ± 0.03
femur	4.76 ± 0.12	5.83 ± 0.72	4.95 ± 0.69	3.91 ± 0.70	0.08 ± 0.021	1.38 ± 0.20
U87	9.71 ± 0.24[a]	12.89 ± 1.45[a]	12.28 ± 1.95[a]	11.20 ± 1.03[a]	0.27 ± 0.019[a]	4.57 ± 0.54[a]
PC3	2.20 ± 0.29	3.10 ± 0.57	2.75 ± 0.11	3.40 ± 0.34	0.11 ± 0.024[a]	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 ± 0.36	18.07 ± 1.197	10.94 ± 0.93
U87:mm	3.25 ± 0.26	3.68 ± 0.44	4.38 ± 0.66	6.29 ± 0.82	11.81 ± 2.086	7.68 ± 0.97

Fig. 4

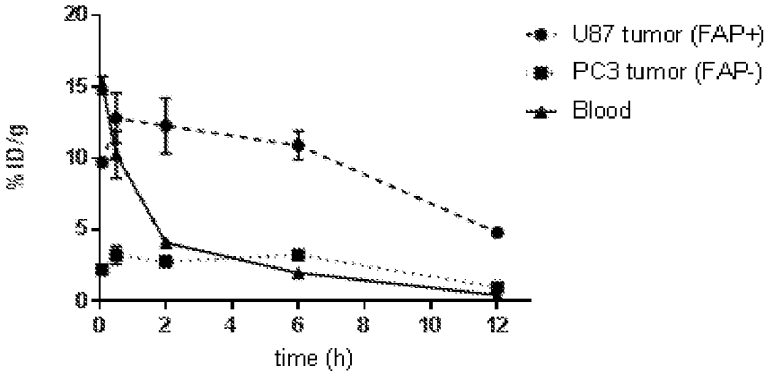

U87 tumor (FAP+)
PC3 tumor (FAP-)
Blood
%ID/g
time (h)
0
5
10
15
20
0
2
4
6
8
10
12

Fig. 5A

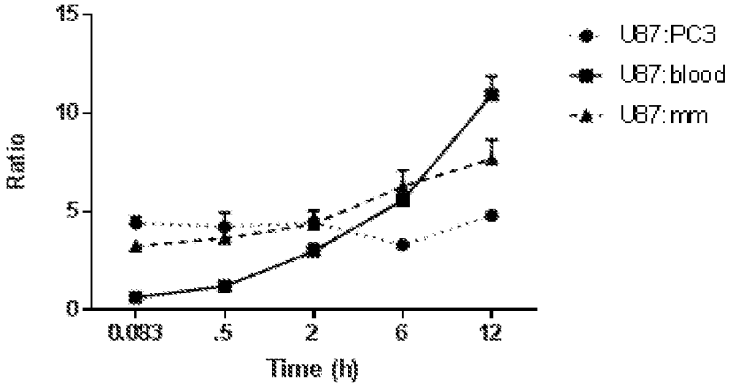

U87:PC3
U87:blood
U87:mm
Ratio
Time (h)
0
5
10
15
0.083
.5
2
6
12

Fig. 5B

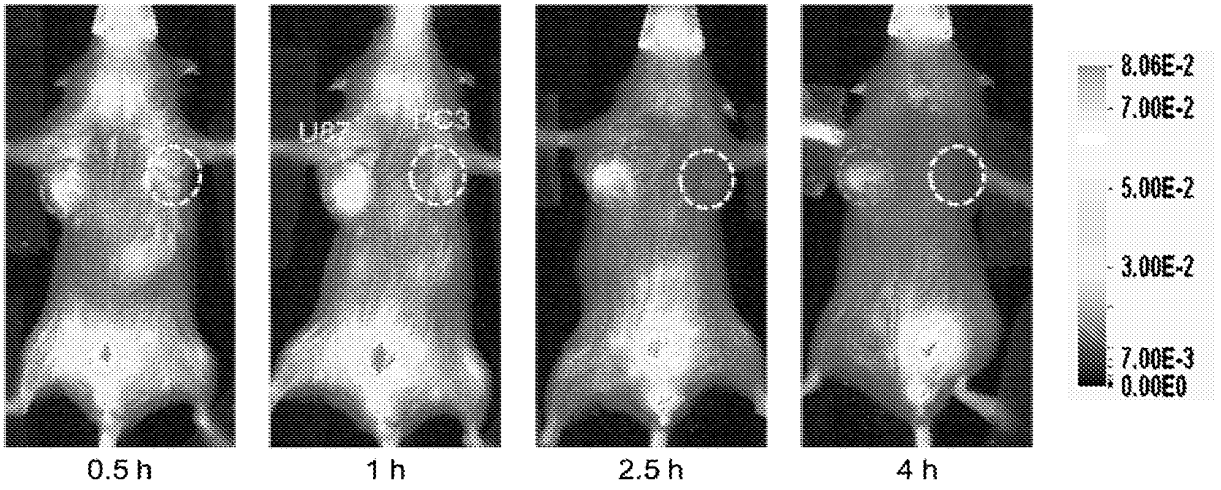


Fig. 6

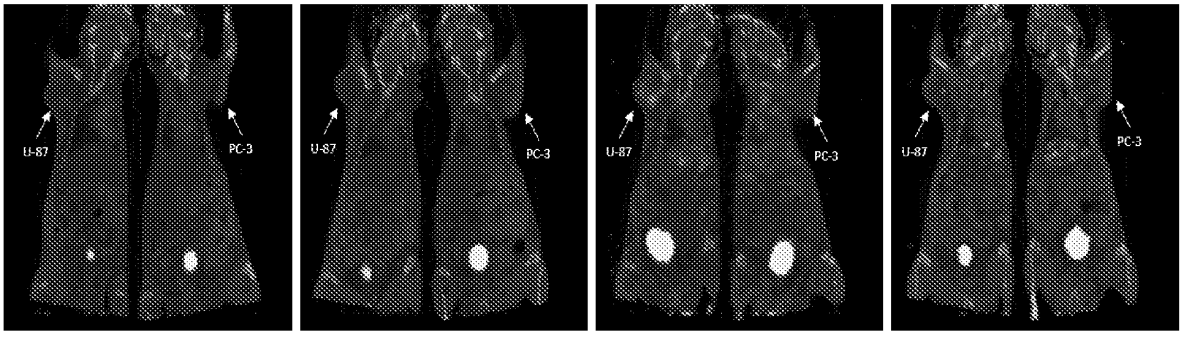


Fig. 7

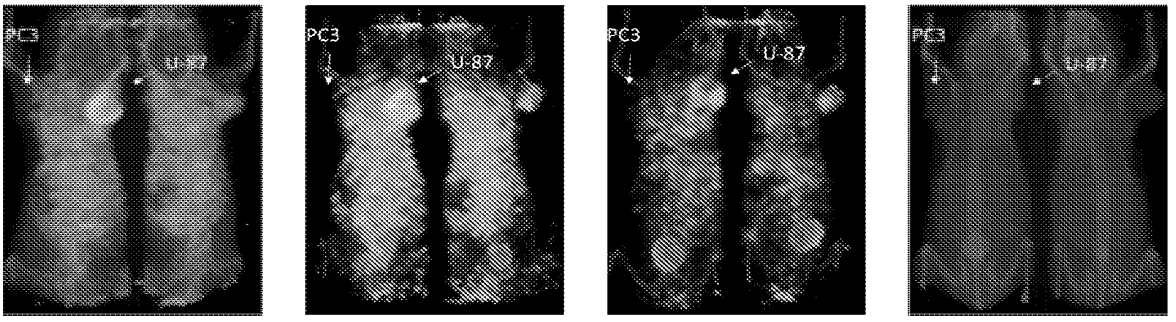


Fig. 8

AMENDMENTS TO THE CLAIMS:

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

1.-27. (Canceled)

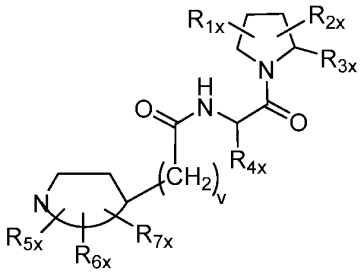
28. (Canceled)

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

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

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

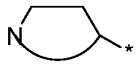
R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from

Petitioner GE Healthcare – Ex. 1031, p. 267

O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from $-NR_{10x}R_{11x}$, $-C_{1-6}$alkyl, $-O-C_{1-6}$alkyl, and $-S-C_{1-6}$alkyl;

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

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



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

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

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/354,282

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	64		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	280		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	320		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	1 minus 20 =	* 0	x =	0	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x =	0			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	664		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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 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

CONFIRMATION NO. 7536

FILING RECEIPT

101943
The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

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.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

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 http://www.uspto.gov 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

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

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

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative,

Petitioner GE Healthcare – Ex. 1031, p. 271

this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

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 U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop

technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

Petitioner GE Healthcare – Ex. 1031, p. 273

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 with 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) Form (SB08)	2023-08-08_36631-303-IDS_SB08.pdf	46022 247bb7f5587f230539953ed88b79c5bcca89799d	no	4

Warnings:

Information:					
This is not an USPTO supplied IDS fillable form					
2	Foreign Reference	EP18199641.pdf	17148949 f3a2a5725fd108ce02d07d18f88e834bd4100292	no	149
Warnings:					
Information:					
3	Foreign Reference	JP2021512949A.pdf	23045549 f5c29b108e53b17139acba43921c6ac626a69396	no	171
Warnings:					
Information:					
4	Foreign Reference	WO2010014933A2.pdf	3823640 1ec298234312be44fa6893719216d196d728435d	no	64
Warnings:					
Information:					
5	Foreign Reference	WO2010108125A2.pdf	8515844 506ba62b29e0bfb5e34964a46e1bfb51b26eddb2	no	159
Warnings:					
Information:					
6	Foreign Reference	WO2016065142A2.pdf	5159352 3b4a125bb48b122831526d523b31ae79aac5be79	no	128
Warnings:					
Information:					
7	Foreign Reference	WO2019154886A1_Original_document.pdf	18470573 440e432818dd839dc9f75574695f4559cae55b8f	no	195
Warnings:					
Information:					
8	Other reference-Patent/Application/ Search Documents	ThirdPartyPreissuance-16-758-182.pdf	384520 a06781ffdfe7e7ea44486db2b2dc7aae390ccfbf	no	6
Warnings:					
Information:					

9	Other reference-Patent/Application/ Search Documents	ThirdPartyObservation_JP2020-523010.pdf	281640 82e6ab8429dc3a5a5be498e97e6ef3ac1b4d40cf	no	7
Warnings:					
Information:					
10	Other reference-Patent/Application/ Search Documents	ThirdPartyObservation_EP2018-0871298.pdf	334885 f338935e84831506137afdea18cbccde0cf47493	no	7
Warnings:					
Information:					
11	Non Patent Literature	BERNHARD_2012.pdf	8749380 03284bc7c67fcc802ef3b247219049176ad023bf	no	8
Warnings:					
Information:					
12	Non Patent Literature	JAMOUS_2013.pdf	23794390 965b6f4ed231bfbd3c07a80c833b475d0dbae8c9	no	31
Warnings:					
Information:					
			Total Files Size (in bytes):	109754744	

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 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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] (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

U.S. PUBLISHED PATENT APPLICATIONS					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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
	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] (if known)	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		X
	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	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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		Date 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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).

☐ 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

.

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 7590 08/30/2023

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
CENTRAL, DOCKET	

ART UNIT	PAPER NUMBER
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

Decision Granting Request for Prioritized Examination (Track I)	**Application No.** 18/354,282	**Applicant(s)** Yang et al.	
	Examiner CHERYL P GIBSON BAYLOR	**Art Unit** OPET	**AIA (FITF) Status** Yes

1. THE REQUEST FILED 18 July 2023 IS **GRANTED** .

   The above-identified application has met the requirements for prioritized examination
   - A. ☑ for an original nonprovisional application (Track I).
   - B. ☐ for an application undergoing continued examination (RCE).

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:
   - A. filing a **petition for extension of time** to extend the time period for filing a reply;
   - 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. 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;
   - H. completion of examination as defined in 37 CFR 41.102; or
   - I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to CHERYL GIBSON BAYLOR at (571)272-3213. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.

/CHERYL GIBSON BAYLOR/ Paralegal Specialist, OPET	

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 cy5.5	(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

Petitioner GE Healthcare – Ex. 1031, p. 283

			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)				
L6	58	L4 AND L5	(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; JPO; DERWENT)	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.

Petitioner GE Healthcare – Ex. 1031, p. 285

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
9/19/2023 8:55:37 PM	Google	cyanoproline fap cyanine dye
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

```
* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1  MAR 25  New Get Prior Art Analysis Feature in CA/CAplus Provides
                  an Efficient Means to Expand Search Results
 NEWS  2  MAR 25  Searching Chemical Compounds with Fragmentation Codes in
                  Derwent World Patents Index (R) Subscriber Files
 NEWS  3  MAR 30  New Projects Feature Allows STNext Users to Define and
                  Manage Search Projects
 NEWS  4  APR  4  The enhanced Derwent World Patents Index(R) is now
                  available on STNext
 NEWS  5  APR  4  The Derwent Chemistry Resource (DCR) is now available as
                  a standalone database on STNext
 NEWS  6  JUN 22  Claims for Four Additional Patent Authorities Added to
                  CA/CAplus
 NEWS  7  JUN 24  SMARTracker SDI Option Now Supported in Derwent Files
 NEWS  8  JUN 24  Expanded Claims Coverage and Enhanced HIT Displays of
                  Claims Data in Derwent World Patents Index(R)
 NEWS  9  SEP  9  Enhanced Coverage of Malaysia, Saudi Arabia, and
                  Georgia Increases Comprehensiveness of INPADOC
 NEWS 10  SEP 14  New Preference Setting for Transcript Options Helps
                  Better Manage Transcripts, Increase Their Efficiency
 NEWS 11  SEP 22  CAS STNext Structure Editor Update Preserves Functionality,
                  Increases Flexibility
 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
                  Claims and Assignee Searching Enhancements
 NEWS 14  NOV  7  EPFULL Reload on STNext Features New Independent Claims
                  Searching Capabilities
 NEWS 15  NOV 10  PS (Pharmaceutical Substances) Database Reloaded
 NEWS 16  DEC 05  Expanded access to Taiwanese patent information provided
                  by new full text database TWFULL and claims coverage
                  in CAplus(SM)
 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
                  Makes Claim Analysis More Efficient
 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
                  2023 on STNext
 NEWS 22  MAR 23  Expanded Patent Authority Coverage in CA/CAplus Means
                  Access to More Inventions, More Complete Patent
                  Families
 NEWS 23  MAY 12  Claim Tags Enhancement Extended to Include WO Patents
 NEWS 24  JUL 05  Reloaded Japanese Patent Full-Text Database JPFULL Provides
                  Expanded Content, New Search Options
 NEWS 25  JUL 06  Interactive Claims Viewer Enhancements: JPFULL Now Supported,
                  Links to the Interactive Claims Viewer Now Available in
                  Reports and Transcripts
 NEWS 26  SEP 04  September 2023 Update to Emtree(R) Provides Latest Biomedical
                  Terminology for Searching
 NEWS 27  SEP 08  Ultimate Owner Information Included in CA/CAplus Aids
                  in Determining Current IP Rights Owners

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items
 NEWS TRAINING Find instructor-led and self-directed training opportunities

Enter NEWS followed by the item number or name to see news on that
specific topic.

For pricing information enter HELP PRICE or HELP COST at any arrow prompt.

  All access and use of STNext (the "Product") is subject to the applicable
  Product Terms of Use at www.cas.org/legal.  The Product may be used by
  Named Users solely for private, internal scientific research related to
  Licensee's business.  It is your obligation to review the Product Terms of
  Use "Prohibited Uses" list.  If your organization has a separate Product
  agreement with CAS, then the terms of that agreement shall supersede the
```

Terms of Use at www.cas.org/legal to the extent they conflict.

Access the latest version of STN.
Log into STNext with your STN login ID at https://www.stn.org

STNext is updated frequently. To see the latest STNext Release Notes, click
https://www.stn.org/help/stnext/ReleaseNotes.htm

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:53:20 ON 20 SEP 2023

=> Fil BIOSIS BIOTECHNO CAPLUS CHEMCATS CHEMLIST EMBASE ESBIOBASE HCAPLUS
HCHEMLIST KOSMET LEMBASE MEDLINE REGISTRY SCISEARCH ZCAPLUS ZREGISTRY

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.28	0.28

FILE 'BIOSIS' ENTERED AT 10:53:44 ON 20 SEP 2023
Copyright (c) 2023 Clarivate Analytics

FILE 'BIOTECHNO' ENTERED AT 10:53:44 ON 20 SEP 2023
COPYRIGHT (C) 2023 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'CAPLUS' ENTERED AT 10:53:44 ON 20 SEP 2023
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2023 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'CHEMCATS' ENTERED AT 10:53:44 ON 20 SEP 2023
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2023 American Chemical Society (ACS)

FILE 'CHEMLIST' ENTERED AT 10:53:44 ON 20 SEP 2023
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2023 American Chemical Society (ACS)

FILE 'EMBASE' ENTERED AT 10:53:44 ON 20 SEP 2023
Copyright (c) 2023 Elsevier B.V. All rights reserved.

FILE 'ESBIOBASE' ENTERED AT 10:53:44 ON 20 SEP 2023
COPYRIGHT (C) 2023 Elsevier Science B.V., Amsterdam. All rights reserved.

FILE 'HCAPLUS' ENTERED AT 10:53:44 ON 20 SEP 2023
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2023 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'HCHEMLIST' ENTERED AT 10:53:44 ON 20 SEP 2023
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2023 American Chemical Society (ACS)

FILE 'KOSMET' ENTERED AT 10:53:44 ON 20 SEP 2023
COPYRIGHT (C) 2023 International Federation of the Societies of Cosmetics
Chemists

FILE 'LEMBASE' ENTERED AT 10:53:44 ON 20 SEP 2023
Copyright (c) 2023 Elsevier B.V. All rights reserved.

FILE 'MEDLINE' ENTERED AT 10:53:44 ON 20 SEP 2023

FILE 'REGISTRY' ENTERED AT 10:53:44 ON 20 SEP 2023
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2023 American Chemical Society (ACS)

FILE 'SCISEARCH' ENTERED AT 10:53:44 ON 20 SEP 2023
Copyright (c) 2023 Clarivate Analytics

FILE 'ZCAPLUS' ENTERED AT 10:53:44 ON 20 SEP 2023
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2023 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'ZREGISTRY' ENTERED AT 10:53:44 ON 20 SEP 2023

```
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
COPYRIGHT (C) 2023 American Chemical Society (ACS)

=>

 * * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'BIOSIS, BIOTECHNO, CAPLUS, CHEMCATS, CHEMLIST, EMBASE,
ESBIOBASE, HCAPLUS, HCHEMLIST, KOSMET, LEMBASE, MEDLINE, REGISTRY, SCISEARCH,
ZCAPLUS, ZREGISTRY' AT 11:09:06 ON 20 SEP 2023
FILE 'BIOSIS' ENTERED AT 11:09:06 ON 20 SEP 2023
Copyright (c) 2023 Clarivate Analytics
FILE 'BIOTECHNO' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 Elsevier Science B.V., Amsterdam. All rights reserved.
FILE 'CAPLUS' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'CHEMCATS' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 American Chemical Society (ACS)
FILE 'CHEMLIST' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 American Chemical Society (ACS)
FILE 'EMBASE' ENTERED AT 11:09:06 ON 20 SEP 2023
Copyright (c) 2023 Elsevier B.V. All rights reserved.
FILE 'ESBIOBASE' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 Elsevier Science B.V., Amsterdam. All rights reserved.
FILE 'HCAPLUS' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'HCHEMLIST' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 American Chemical Society (ACS)
FILE 'KOSMET' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 International Federation of the Societies of Cosmetics
Chemists
FILE 'LEMBASE' ENTERED AT 11:09:06 ON 20 SEP 2023
Copyright (c) 2023 Elsevier B.V. All rights reserved.
FILE 'MEDLINE' ENTERED AT 11:09:06 ON 20 SEP 2023
FILE 'REGISTRY' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 American Chemical Society (ACS)
FILE 'SCISEARCH' ENTERED AT 11:09:06 ON 20 SEP 2023
Copyright (c) 2023 Clarivate Analytics
FILE 'ZCAPLUS' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 AMERICAN CHEMICAL SOCIETY (ACS)
FILE 'ZREGISTRY' ENTERED AT 11:09:06 ON 20 SEP 2023
COPYRIGHT (C) 2023 American Chemical Society (ACS)
COST IN U.S. DOLLARS                          SINCE FILE            TOTAL
                                                   ENTRY          SESSION
FULL ESTIMATED COST                               113.84           114.12

=> s "Fibroblast activation protein .alpha." OR "Fibroblast-activating protein
.alpha." OR "Fibroblast activation protein" OR "FAP.alpha." OR "FAP alpha" OR
"Proteins, FAP.alpha." OR "Fibroblast activation protein FAP.alpha." OR "FAP" OR
"Fibroblast activation protein alpha" OR "Proteins, FAP"

L1         5762 FILE BIOSIS
L2          579 FILE BIOTECHNO
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

TOTAL FOR ALL FILES
L17       58584 "FIBROBLAST ACTIVATION PROTEIN A" OR "FIBROBLAST-ACTIVATIN
                G PROTEIN A" OR "FIBROBLAST ACTIVATION PROTEIN" OR "FAP.AL
                PHA." OR "FAP ALPHA" OR "PROTEINS, FAPA" OR "FIBROBLAST
                ACTIVATION PROTEIN FAPA" OR "FAP" OR "FIBROBLAST ACTIVATIO
```

```
               N PROTEIN ALPHA" OR "PROTEINS, FAP"

=> 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
L27         23 FILE KOSMET
L28         35 FILE LEMBASE
L29     284572 FILE MEDLINE
L30          0 FILE REGISTRY
L31      70891 FILE SCISEARCH
L32     141489 FILE ZCAPLUS
L33          0 FILE ZREGISTRY

TOTAL FOR ALL FILES
L34     917049 RADIONUCLIDE OR "RADIOACTIVE SUBSTANCES" OR "RADIOISOTOPES" OR
               "ISOTOPIC RADIOELEMENTS" OR "RADIOELEMENT" OR "RADIOELEMENT ISOT
               OPES" OR "RADIOACTIVE ELEMENTS" OR "RADIOACTIVE NUCLIDES" OR
               "RADIOACTIVE ISOTOPES" OR "RADIOELEMENT COMPLEXES" OR "RADIOELEM
               ENT CONJUGATES"

=> s l17 and l34

L35         38 FILE BIOSIS
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
L50          0 FILE ZREGISTRY

TOTAL FOR ALL FILES
L51        999 L17 AND L34

=> s ibody or ibodies

L52         16 FILE BIOSIS
L53          1 FILE BIOTECHNO
L54         15 FILE CAPLUS
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
```

```
TOTAL FOR ALL FILES
L68        109 IBODY OR IBODIES

=> l51 and l68

L51 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l51 and l68

L69          0 FILE BIOSIS
L70          0 FILE BIOTECHNO
L71          0 FILE CAPLUS
L72          0 FILE CHEMCATS
L73          0 FILE CHEMLIST
L74          0 FILE EMBASE
L75          0 FILE ESBIOBASE
L76          0 FILE HCAPLUS
L77          0 FILE HCHEMLIST
L78          0 FILE KOSMET
L79          0 FILE LEMBASE
L80          0 FILE MEDLINE
L81          0 FILE REGISTRY
L82          0 FILE SCISEARCH
L83          0 FILE ZCAPLUS
L84          0 FILE ZREGISTRY

TOTAL FOR ALL FILES
L85          0 L51 AND L68

=> s cyanoproline

L86          1 FILE BIOSIS
L87          0 FILE BIOTECHNO
L88          3 FILE CAPLUS
L89          3 FILE CHEMCATS
L90          0 FILE CHEMLIST
L91          3 FILE EMBASE
L92          0 FILE ESBIOBASE
L93          3 FILE HCAPLUS
L94          0 FILE HCHEMLIST
L95          0 FILE KOSMET
L96          0 FILE LEMBASE
L97          2 FILE MEDLINE
L98         16 FILE REGISTRY
L99          0 FILE SCISEARCH
L100         3 FILE ZCAPLUS
L101        16 FILE ZREGISTRY

TOTAL FOR ALL FILES
L102        50 CYANOPROLINE

=> s l51 and l102

L103         0 FILE BIOSIS
L104         0 FILE BIOTECHNO
L105         0 FILE CAPLUS
L106         0 FILE CHEMCATS
L107         0 FILE CHEMLIST
L108         0 FILE EMBASE
L109         0 FILE ESBIOBASE
L110         0 FILE HCAPLUS
L111         0 FILE HCHEMLIST
L112         0 FILE KOSMET
L113         0 FILE LEMBASE
L114         0 FILE MEDLINE
L115         0 FILE REGISTRY
L116         0 FILE SCISEARCH
L117         0 FILE ZCAPLUS
L118         0 FILE ZREGISTRY
```

```
TOTAL FOR ALL FILES
L119         0 L51 AND L102

=> s 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"

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

TOTAL FOR ALL FILES
L153      5482 L17 AND L136

=> s l153 and l102

L154         0 FILE BIOSIS
L155         0 FILE BIOTECHNO
L156         0 FILE CAPLUS
L157         0 FILE CHEMCATS
L158         0 FILE CHEMLIST
L159         1 FILE EMBASE
L160         0 FILE ESBIOBASE
L161         0 FILE HCAPLUS
L162         0 FILE HCHEMLIST
L163         0 FILE KOSMET
L164         0 FILE LEMBASE
L165         1 FILE MEDLINE
L166         0 FILE REGISTRY
L167         0 FILE SCISEARCH
L168         0 FILE ZCAPLUS
L169         0 FILE ZREGISTRY

TOTAL FOR ALL FILES
```

L170 2 L153 AND L102

=> d bib l179 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 l170 1-2

L170 ANSWER 1 OF 2 EMBASE COPYRIGHT (c) 2023 Elsevier B.V. All rights reserved on STN
AN 20230385996 EMBASE Full-text
DN 2024158278 PMID: 37117123
TI Advanced Fibroblast Activation Protein-Ligand Developments: FAP Imaging Agents: A Review of the Structural Requirements.
AU DiMagno, Stephen G.; Babich, John W., PhD (correspondence)
CS Ratio Therapeutics, Inc., One Design Center Place, Suite# 19-601, Boston, MA, 02210, United States. jbabich@ratiotx.com
SO PET Clinics, (July 2023) Vol. 18, No. 3, pp. 287-294.
Refs: 55
ISSN: 1556-8598; E-ISSN: 1879-9809
DOI 10.1016/j.cpet.2023.03.002
PB W.B. Saunders.
PUI S 1556-8598(23)00028-7
CY United States
DT Journal; General Review; (Review)
FS Intellectual Indexing
016 Cancer
023 Nuclear Medicine
037 Drug Literature Index
FS ClinicalTrials.gov
NCT NCT04939610
LA English
ED Entered 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
DN PubMed ID: 37117123
TI Advanced Fibroblast Activation Protein-Ligand Developments: FAP 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
CS Ratio Therapeutics, Inc., One Design Center Place, Suite# 19-601, Boston, MA 02210, USA. jbabich@ratiotx.com
SO PET clinics, (2023 Jul) Vol. 18, No. 3, pp. 287-294. Electronic 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
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS MEDLINE; Priority Journals
FS Print; Electronic
EM 202306
ED Entered STN: 30 Apr 2023
Last Updated on STN: 2 Jun 2023
Indexing Added: 2 Jun 2023
Entered Medline: 2 Jun 2023

=> s l153 and l68

```
L171          1 FILE BIOSIS
L172          0 FILE BIOTECHNO
L173          1 FILE CAPLUS
L174          0 FILE CHEMCATS
L175          0 FILE CHEMLIST
L176          0 FILE EMBASE
L177          0 FILE ESBIOBASE
L178          1 FILE HCAPLUS
L179          0 FILE HCHEMLIST
L180          0 FILE KOSMET
L181          0 FILE LEMBASE
L182          0 FILE MEDLINE
L183          0 FILE REGISTRY
L184          0 FILE SCISEARCH
L185          1 FILE ZCAPLUS
L186          0 FILE ZREGISTRY

TOTAL FOR ALL FILES
L187          4 L153 AND L68

=> d bib l187 1-4


L187 ANSWER 1 OF 4  BIOSIS  COPYRIGHT (c) 2023 Clarivate Analytics  on STN
AN   2018:61517  BIOSIS Full-text
DN   PREV201800061517
TI   Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation
     Protein.
AU   Dvorakova, Petra [Reprint Author]; Busek, Petr; Knedlik, Tomas; Schimer,
     Jiri; Etrych, Tomas; Kostka, Libor; Sromova, Lucie Stollinova; Subr,
     Vladimir; Sacha, Pavel [Reprint Author]; Sedo, Aleksi [Reprint Author];
     Konvalinka, Jan [Reprint Author]
CS   Czech Acad Sci, Inst Organ Chem and Biochem, Flemingovo Nam 2, Prague
     16610 6, Czech Republic
     pavelsacha@gmail.com; aleksi@cesnet.cz; jan.konvalinka@uochb.cas.cz
SO   Journal of Medicinal Chemistry, (OCT 26 2017) Vol. 60, No. 20, pp.
     8385-8393.
     CODEN: JMCMAR. ISSN: 0022-2623. E-ISSN: 1520-4804.
DOI  10.1021/acs.jmedchem.7b00767
DT   Article
LA   English
ED   Entered STN: 27 Dec 2017
     Last Updated on STN: 17 Jan 2018

L187 ANSWER 2 OF 4  CAPLUS  COPYRIGHT 2023 ACS on STN
AN   2017:1570779  CAPLUS Full-text
DN   169:205864
TI   Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation
     Protein
AU   Dvorakova, Petra; Busek, Petr; Knedlik, Tomas; Schimer, Jiri; Etrych,
     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.
SO   Journal of Medicinal Chemistry (2017), 60(20), 8385-8393
     CODEN: JMCMAR; ISSN: 0022-2623
DOI  10.1021/acs.jmedchem.7b00767
PB   American Chemical Society
DT   Journal; (online computer file)
LA   English
OS   CASREACT 169:205864
OSC.G   16    THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
RE.CNT  52    THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L187 ANSWER 3 OF 4  HCAPLUS  COPYRIGHT 2023 ACS on STN
AN   2017:1570779  HCAPLUS Full-text
DN   169:205864
TI   Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation
     Protein
AU   Dvorakova, Petra; Busek, Petr; Knedlik, Tomas; Schimer, Jiri; Etrych,
     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.
SO Journal of Medicinal Chemistry (2017), 60(20), 8385-8393
CODEN: JMCMAR; ISSN: 0022-2623
DOI 10.1021/acs.jmedchem.7b00767
PB American Chemical Society
DT Journal; (online computer file)
LA English
OS CASREACT 169:205864
OSC.G 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L187 ANSWER 4 OF 4 ZCAPLUS COPYRIGHT 2023 ACS on STN
AN 2017:1570779 ZCAPLUS Full-text
DN 169:205864
TI Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein
AU Dvorakova, Petra; Busek, Petr; Knedlik, Tomas; Schimer, Jiri; Etrych, 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.
SO Journal of Medicinal Chemistry (2017), 60(20), 8385-8393
CODEN: JMCMAR; ISSN: 0022-2623
DOI 10.1021/acs.jmedchem.7b00767
PB American Chemical Society
DT Journal; (online computer file)
LA English
OS CASREACT 169:205864
OSC.G 16 THERE ARE 16 CAPLUS RECORDS THAT CITE THIS RECORD (16 CITINGS)
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	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
PE2E search	09/19/2023	MP
STNext	09/20/2023	MP

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

Petitioner GE Healthcare – Ex. 1031, p. 296

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	Art Unit
	MELISSA J PERREIRA	1618

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/20/2023								
	1	-								
	2	-								
	3	-								
	4	-								
	5	-								
	6	-								
	7	-								
	8	-								
	9	-								
	10	-								
	11	-								
	12	-								
	13	-								
	14	-								
	15	-								
	16	-								
	17	-								
	18	-								
	19	-								
	20	-								
	21	-								
	22	-								
	23	-								
	24	-								
	25	-								
	26	-								
	27	-								
	28	-								
	29	✓								

Petitioner GE Healthcare – Ex. 1031, p. 297

Notice of References Cited	Application/Control No. 18/354,282	Applicant(s)/Patent Under Reexamination Yang et al.	
	Examiner MELISSA J PERREIRA	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20100098633-A1	04-2010	ZIMMERMAN; Craig	C07D401/14	424/1.85
	B					
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

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)
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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

U.S. PATENTS					
Examiner 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					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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
		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						
Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[5] Number[6] Kind Code[7] (if known)	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]
		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

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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				Art Unit	
				Examiner Name	
Sheet	2	of	4	Attorney Docket Number	JHU-36631.303

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]
		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

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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				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.	
		LI et al., Activatable Near-Infrared Fluorescent Probe for In Vivo Imaging of Fibroblast Activation Protein-alpha. Bioconjugate Chem. 2012 Jul. 19;23:1704-11	
		LO et al., Photodynamic molecular beacon triggered by fibroblast activation protein on cancer-associated fibroblasts for diagnosis and treatment of epithelial cancers. J Med Chem. 2009 Jan 22;52(2):358-68.	
		POPLAWSKI et al., Identification of selective and potent inhibitors of fibroblast activation protein and prolyl oligopeptidase. J Med Chem. 2013 May 9;56(9):3467-77.	
		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 Perceived Barriers. Bioconjugate chemistry. 2015; 26:625–632.	
		RETTIG et al., Regulation and heteromeric structure of the fibroblast activation protein in normal and transformed cells of mesenchymal and neuroectodermal origin Cancer Res. 1993 Jul 15;53(14):3327-35.	
		RYABTSOVA et al., Acylated Gly-(2-cyano)pyrrolidines as inhibitors of fibroblast activation protein (FAP) and the issue of FAP/prolyl oligopeptidase (PREP)-selectivity. Bioorg Med Chem Lett. 2012 May 15;22(10):3412-7.	
		SCANLAN et al., Molecular cloning of fibroblast activation protein alpha, a member of the serine protease family selectively expressed in stromal fibroblasts of epithelial cancers. Proc Natl Acad Sci U S A. 1994 Jun 7;91(12):5657-61.	
		SCOTT et al., A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer. Clin Cancer Res. 2003 May;9(5):1639-47.	
		TSAI et al., Substituted 4-carboxymethylpyroglutamic acid diamides as potent and selective inhibitors of fibroblast activation protein. J Med Chem. 2010 Sep 23;53(18):6572-83.	
		TUXHORN et al., Reactive stroma in human prostate cancer: induction of myofibroblast phenotype and extracellular matrix remodeling. Clin Cancer 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 Signature	/MELISSA J PERREIRA/	Date Considered	09/20/2023

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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				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

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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	
				Filing Date	
				First Named Inventor	YANG
				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.

☐ 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)	2023-07-18
Printed Name	Jeffrey W. Childers	Registration Number	58126

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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**.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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] (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

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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
	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] (if known)	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		X
	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

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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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

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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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).

☐ 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

.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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**.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
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

Office Action Summary	Application No. 18/354,282	Applicant(s) Yang et al.	
	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 --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 7/24/23.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(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 response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 29 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 29 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, 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/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 7/18/23 is/are: a)☐ accepted or b)☑ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

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

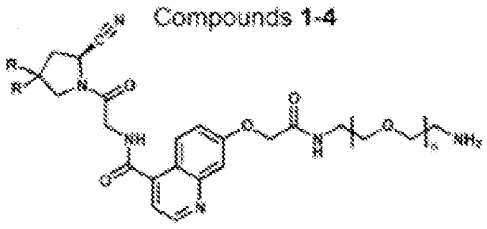
In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory

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:

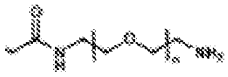
> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.

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.

The  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

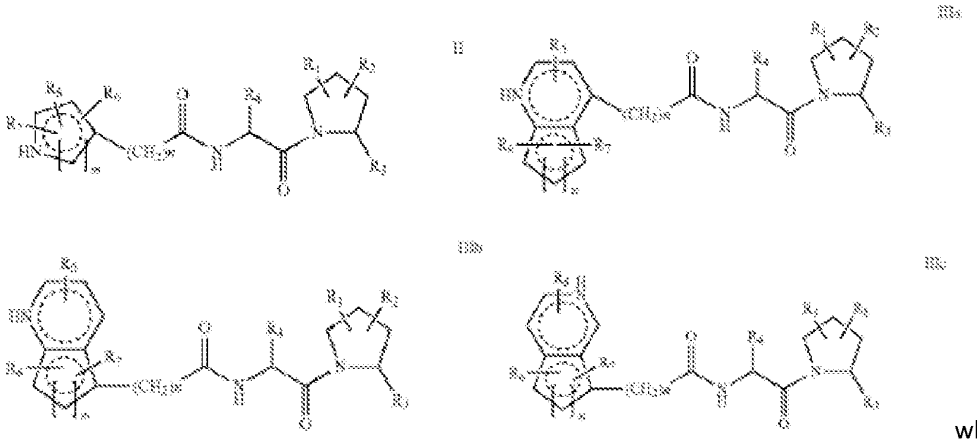
In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis (i.e., changing from AIA to pre-AIA) for the rejection will not be considered a new ground of rejection 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).

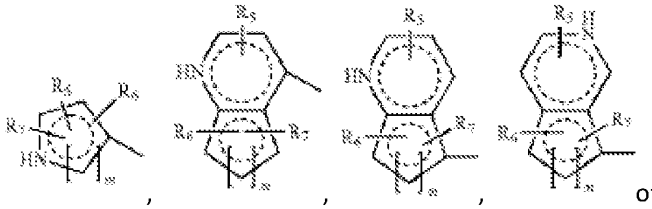
Jansen et al. (US2014/0357650A1) discloses the FAP inhibitors



wherein R_1 and R_2 are H, -OH, halogen, etc. and encompass the corresponding R_{1x} and R_{2x} are H, -OH, halogen, etc. of the instant claims.

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.

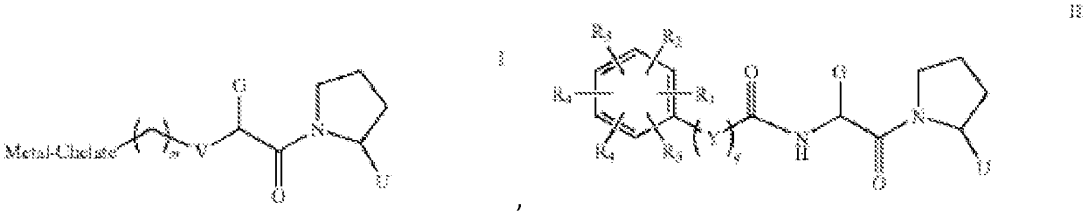
The  of the disclosure encompasses the corresponding  5 to 10-membered N-containing aromatic mono- or bicyclic heterocycle of the instant claims.

The R_5-R_7 are H, -OH, oxo, -halo, C_{1-6}alkyl, -O-C_{1-6}alkyl 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, C_{1-6}alkyl, -O-C_{1-6}alkyl, 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.

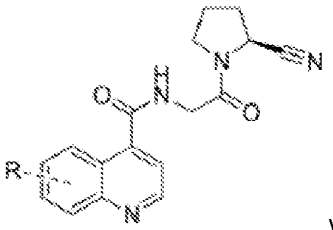
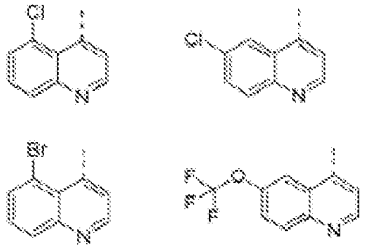
Jansen et al. (US2014/0357650A1) does not disclose an optical or radiolabeled functional group suitable for optical imaging, PET, SPECT or radiotherapy.

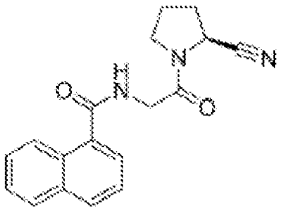
Zimmerman et al. (US2010/0098633A1) discloses radiopharmaceuticals useful in diagnostic imaging and therapeutic treatment of disease comprising



,

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 R_1-R_5 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  wherein R comprises  , etc. (abstract; 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 C_{1-6}alkyl, -O-C_{1-6}alkyl 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 ^{111}In-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 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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**10/30/2023 10:53:51 AM ET**	**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	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	**E20230TA54136455**	**Van Nguyen**

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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**10/30/2023 10:53:51 AM ET**	**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	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)
2023-10-30 - Supp IDS.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	33 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
Azhdarinia et.pdf	8	Non Patent Literature	770 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)

2023-10-30 - Supp IDS.pdf	B954EE41A724E80D01515F926EB742F932937B05159CCC85A2 B3F397DC116FB6E53DB13026C69212CCCAEDC7FBD8CAD05 3AAC6C631B88AA045426ACDDA862DCD
Azhdarinia et.pdf	8B7C1ADD1C50CB3D987C4734551ABC0BA7E98B1323C365DE 3EE3666F6597E2545B89A712F029C6D0B76FC38D320911D3AF DA48070DE05458F726CF6D3A1620C0

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				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] (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

U.S. PUBLISHED PATENT APPLICATIONS						
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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	

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	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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.

☒ 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).
[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

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
The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

PUBLICATION NOTICE

OC00000006463215 3

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/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Petitioner GE Healthcare – Ex. 1031, p. 326

Status

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.

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 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

Petitioner GE Healthcare – Ex. 1031, p. 327

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-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.

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

Petitioner GE Healthcare – Ex. 1031, p. 328

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/small-molecules/ ("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.

Petitioner GE Healthcare – Ex. 1031, p. 329

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

Petitioner GE Healthcare – Ex. 1031, p. 330

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 modify any compounds of Jansen I and Jansen II to arrive at the claimed 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. 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-C_{1-6}alkyl 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 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.

Petitioner GE Healthcare – Ex. 1031, p. 331

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 IC_{50} 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 IC_{50} 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-

Petitioner GE Healthcare – Ex. 1031, p. 332

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 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. IC_{50} for FAP (an indicator of the FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM for the unsubstituted FAP inhibitor; selectivity index is 59 versus 83.

Petitioner GE Healthcare – Ex. 1031, p. 333

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 $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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

Petitioner GE Healthcare – Ex. 1031, p. 334

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 [^{125}I]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 [^{125}I]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.

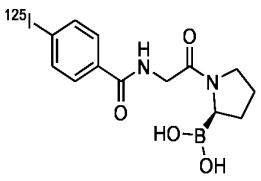
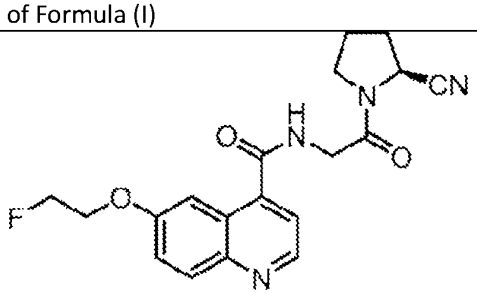
iii. <u>There are unexpected results associated with the claimed compounds to rebut any showing of prima facie obviousness</u>

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

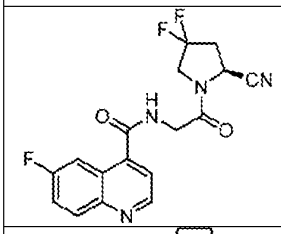
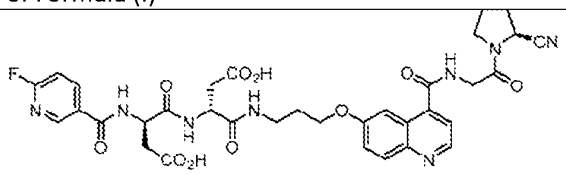
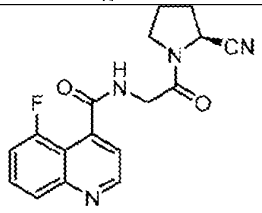
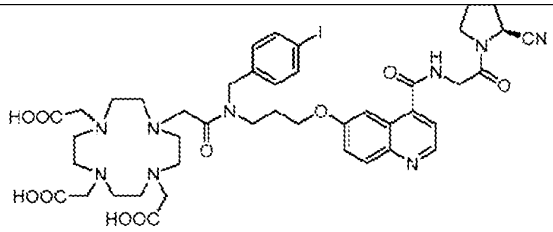
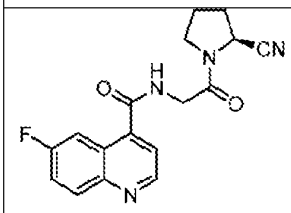
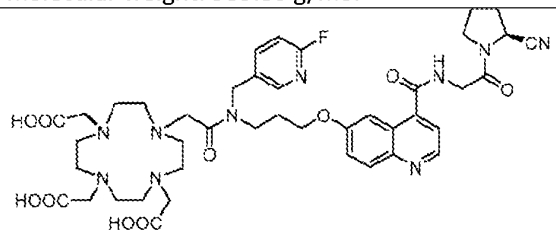
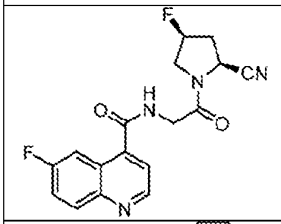
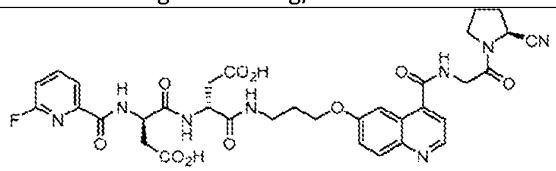
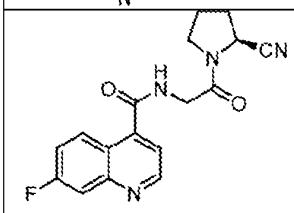
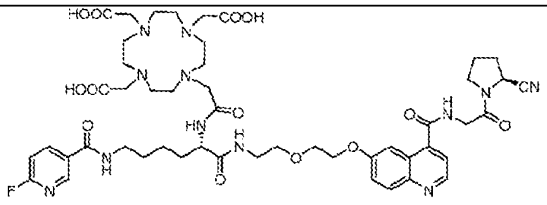
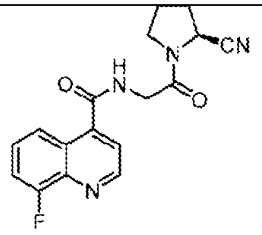
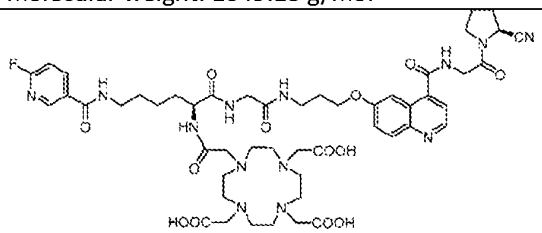
selectively bind to the target protein associated with a disease, therefore enabling the imaging agent to diagnose the disease more accurately.

In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]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.

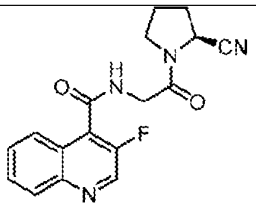
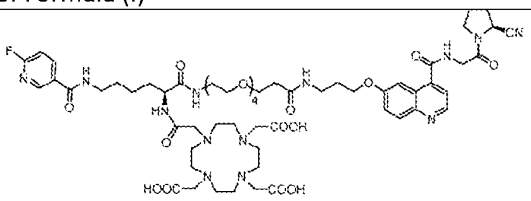
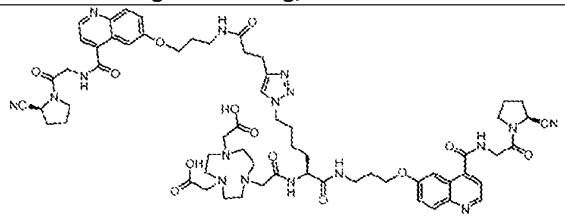
Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase (PREP) versus FAP. Pomper Affidavit, Para. 41. In fact, Jansen I uses such a PREP/FAP ratio as a "selectivity index" for the compounds 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 falling under the scope of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. 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 Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	32 *	 molecular weight: 370.38 g/mol	4,111

Petitioner GE Healthcare – Ex. 1031, p. 336

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	152	 molecular weight: 734.70 g/mol	66,084
	20	 molecular weight: 983.86 g/mol	>1,418,440
	403	 molecular weight: 876.94 g/mol	10,502
	15.7	 molecular weight: 734.70 g/mol	5,807
	241	 molecular weight: 1049.13 g/mol	779
	17	 molecular weight: 1073.15 g/mol	1,693

Petitioner GE Healthcare – Ex. 1031, p. 337

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	3	 molecular weight: 1266.39 g/mol	407
		molecular weight: 889.39 g/mol	10,694
		molecular weight: 761.39 g/mol	11,893
		 molecular weight: 1282.43 g/mol	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

Petitioner GE Healthcare – Ex. 1031, p. 338

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

Petitioner GE Healthcare – Ex. 1031, p. 339

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

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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	12/13/2023 03:39:21 PM Z ET	JHU-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 #	63593228	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	E2023BCF40079520	Van Nguyen

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	1	170.00
			TOTAL AMOUNT:	$330.00

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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**12/13/2023 03:39:21 PM Z ET**	**JHU-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 #	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 supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
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

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 RNFOApdf.pdf		17	-	442 KB
2023-12-13 - 36631_303 RNFOApdf-A....pdf	(1-1)	1	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
Small molecules _ Metabolomics.pdf	F1E4BC35DAD24CA1195511593AEDBADE15BEEE47DDEF0C6 5677347D7A28D6DC39F309F28E8C3BDB0E99740D1D838D59C 134487CF7BA459F55C0511A860A4B85B

Meletta artic.pdf	D456F58C8A7D72914094CCE81B77A15D15C10AC5AD1AEF28A6C06EA5D4CFD9C7DFCCBB95D3E2A6A33FC0CB45847D675FB59EB895A581C561E43D3B7DDC69B1A0
Beebe 2014.pdf	804E6BB35A8916C251CE8135A1AE191E889394554764C66C9355FFE4623B3400384BE589C168B94AB053550BD2D702646871C736144802E75BB3B229AAA29F38
Ferreira2014.pdf	AED72385E725334E81A6289E61A70112F2789F38DC7BD68E888006D2036E622176E812B226D3A1C3DDF2DEFF587EF30F51CDE1CEC9DF34478E89F6A81F43C6BD
Llewellyn 201.pdf	3C70B8B79100C9D2D063F62AA707F2DEC425A1B9C9A7D25F5E858E61FCDD3BA45A29913A9AF7C5F764E75DF0D3CDC4FE60ACA9E84917362472699AFF5202D350
2023-12-13 - JHU-36631.303 TD.pdf	02A1FAD0F627ADE1FE89ABA642A3436736D6A800541C87668FB94ED8C0499E7DE58E56BA018B7ED059B5D29E49973E1DCDE532300244A7E93DE75C23F547C8F0
2023-12-13 - 36631_303 RNFOApdf.pdf	B91DCF3CBC4BB5F3CC45181CDE559C67779D7C1060FA77E4B24CA7B7D156406D3E1DAD0844F8B1A5E426E9E2AA2CCF5354FBB7A923E4F536D69B1FE3EA033EC3
2023-12-13 - 36631_303 RNFOApdf-A....pdf	1AD2AA341DCF1F97E5144FE4CBD14C78AB0CF67C19674703B26069FA3874BADDE7953D147F4D76D4E93CE4CAFF2A3480FCEC15B70DF1543416EDB6DBD92C1861
2023-12-13 - 36631_303 RNFOApdf-CLM.pdf	1163861942153 98C9F8A60C2F2532272035F3305095B44AA38F43B52941177A0891AF2289D4BB1B2D6672228F1D3DBD2E299427256BC99D6DAD538746E67FFB2
2023-12-13 - 36631_303 RNFOApdf-REM.pdf	34D3B3FBE8C6834DB88450784B545EBCA964B9290FF65C8A969B4BC658D620A64C54B2EBC9F8D23C102381300A286AE7790867BC1AEAB86B2FD19BBFA9F9D9C3
2023-12-13 - 36631_303 Declaration 1.132.pdf	F3993FEF9318D0397B2409722BCDC279406FA612A0A350E24C715DADAAE459ADC65978ABEAA7A54F502AFB9B1109522113EC3189F5D4D388A94A0430CDD37D80

2023-12-13 -36631.303 Petition 1.84.pdf	B0699024CBFC974BCCF60C1AFB52FB7C00CD3A1DC93620FB F2DBB15AB984DA174FDFFE51A46F4D210C138176C38F48AD A29A88875B1B7E075997BC87B4994A9F

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				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] *(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

U.S. PUBLISHED PATENT APPLICATIONS						
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(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	

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]
		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	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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.

☒ 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.

.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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

.

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.

PTO/AIA/25 (04-13)
Approved for use through 05/31/2024. OMB 0651-0031
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.

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 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 of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 16/758,182, filed, April 22, 2020, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, 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 on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** 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 jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated 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.

1. ☐ 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 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

/Jeffrey W. Childers/	December 13, 2023
Signature	Date
Jeffrey W. Childers	
Typed or printed name	
Attorney of Record	608.662.1277
Title	Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WARNING: Information 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.

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 information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **If filing this completed form by mail, 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. 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; 6) 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 9) 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.

Additional Uses

Additional USPTO uses of the information in this record may include disclosure to: 1) the International Bureau of the World Intellectual Property Organization, if the record is related to an international application filed under the Patent Cooperation Treaty; 2) the public i) after publication of the application pursuant to 35 U.S.C. 122(b), ii) after issuance of a patent pursuant to 35 U.S.C. 151, iii) 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 inspections, or an issued patent, or iv) without publication of the application or patent under the specific circumstances provided for by 37 CFR 1.14(a)(1)(v)-(vii); and/or 3) the National Archives and Records Administration, for inspection of records.

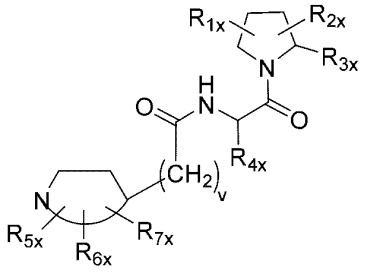
IN THE CLAIMS:

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

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

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

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

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

Petitioner GE Healthcare – Ex. 1031, p. 354

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;

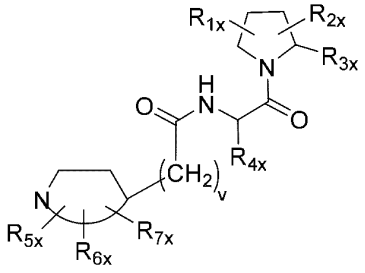
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

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

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

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

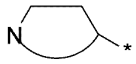
Petitioner GE Healthcare – Ex. 1031, p. 355

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

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

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

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



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

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

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

Petitioner GE Healthcare – Ex. 1031, p. 356

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

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.

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.

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-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 [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 **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.

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/small-molecules/ ("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).")

18. 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 $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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.

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 $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl group disclosed in Jansen I may serve as the linker when the compounds containing the $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl of Jansen I are modified with a radiohalogen.

23. I observed that $C_{1\text{-}6}$alkyl and the -O-$C_{1\text{-}6}$alkyl 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, —$C_{1\text{-}6}$alkyl, —O—$C_{1\text{-}6}$alkyl, —S—$C_{1\text{-}6}$alkyl, —NR_8R_9, —OR_{12}, —Het_2 and —Ar_2, wherein the $C_{1\text{-}6}$alkyl 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 $C_{1\text{-}6}$alkyl substitution. Out of 43 representative FAP inhibitors in Jansen I, only one of them is substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl. *See* Jansen I, Table 4, Example 11. The same compound is also the only FAP inhibitor substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl out of 39 representative FAP inhibitors in Jansen II. *See* Jansen II, Table 3, Compound 28.

25. FAP inhibitors substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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 $C_{1\text{-}6}$alkyl should be selected for modification with a radiohalogen.

26. I notice that the single FAP inhibitor substituted with the halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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

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 $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$ 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 $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$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, IC_{50} for FAP (an indicator of the FAP affinity; a higher value means a lower FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM 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.

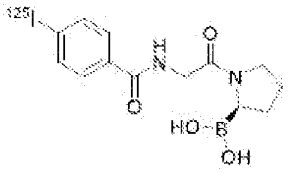
29. Accordingly, the cited references not only fail to suggest selecting and modifying FAP inhibitors, but also may discourage one of ordinary skill in the art to substitute the FAP inhibitors with any functional groups, including the C_{1-6}alkyl or -O-C_{1-6}alkyl.

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



[^{125}I]MIP-1232

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

34. As provided on page 2089 of Meletta, while pronounced binding of [^{125}I]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 [^{125}I]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.

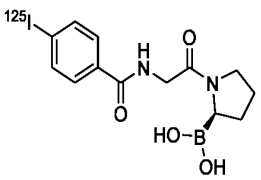
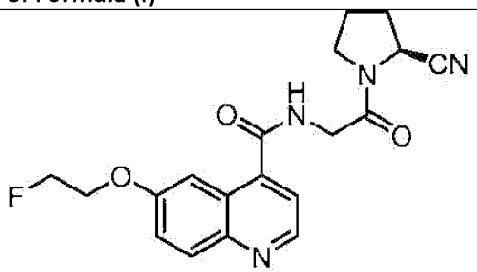
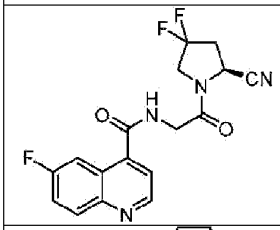
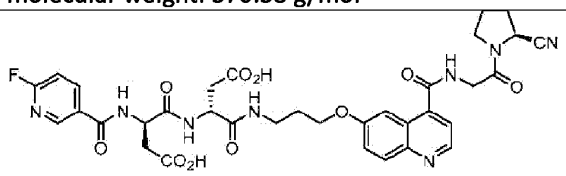
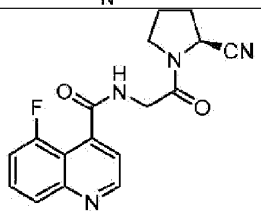
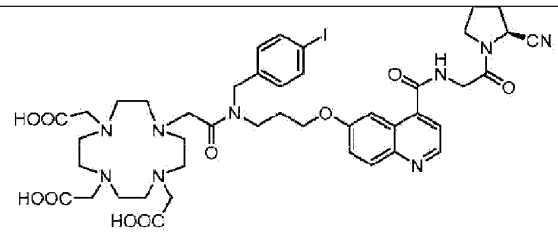
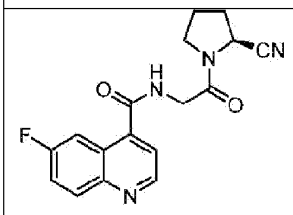
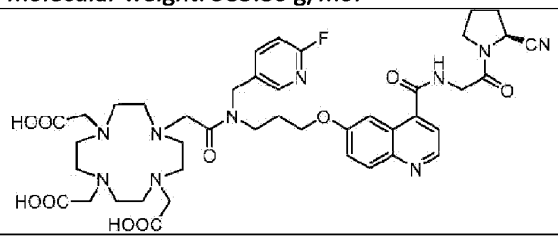
39. Specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a medical condition, therefore enabling the imaging agent to diagnose the medical condition more accurately.

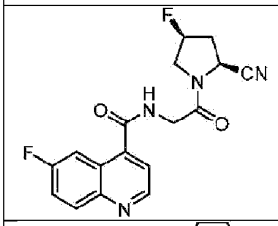
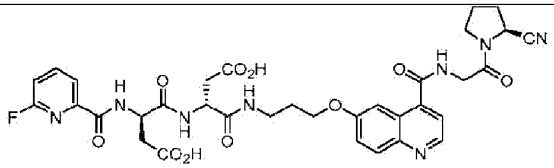
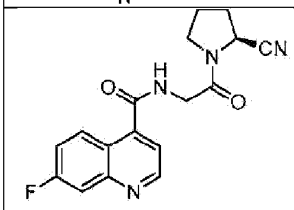
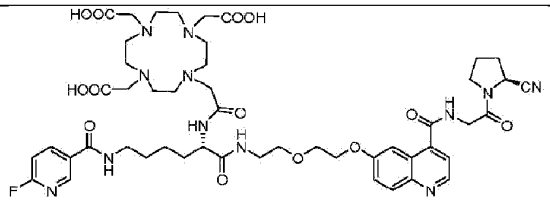
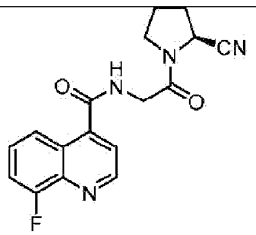
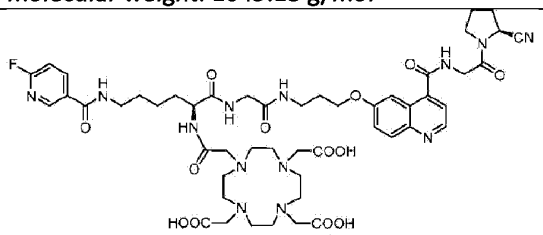
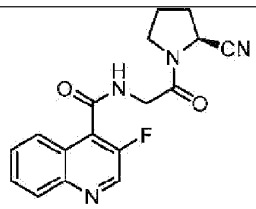
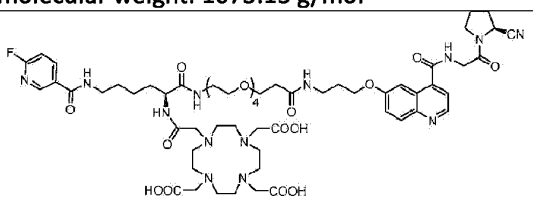
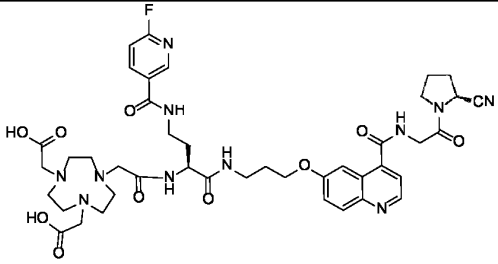
40. While Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]MIP-1232 for FAP (above), we found the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents as shown in the current application US 2020/0330624 A1 for the selectivity for FAP over dipeptidyl peptidase 4 (DPPIV), a related serine protease (Paragraphs [0019], [0020], [0244]-[0245], and Figures 2, 3A, 3B, and 3C).

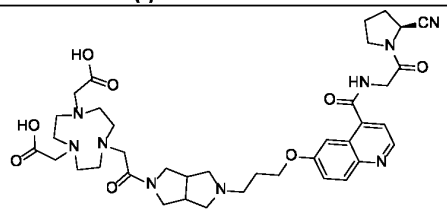
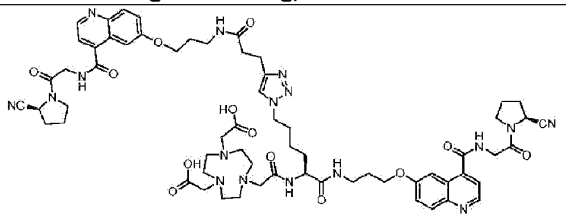
41. Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase

(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.

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	32 *	 molecular weight: 370.38 g/mol	4,111
	152	 molecular weight: 734.70 g/mol	66,084
	20	 molecular weight: 983.86 g/mol	>1,418,440
	403		10,502

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
		molecular weight: 876.94 g/mol	
	15.7	 molecular weight: 734.70 g/mol	5,807
	241	 molecular weight: 1049.13 g/mol	779
	17	 molecular weight: 1073.15 g/mol	1,693
	3	 molecular weight: 1266.39 g/mol	407
		 molecular weight: 889.39 g/mol	10,694

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
		 molecular weight: 761.39 g/mol	11,893
		 molecular weight: 1282.43 g/mol	1,313

* 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.

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.	Confirmation No.: 7536
Serial No.: 18/354,282	Art Unit: 1618
Filed: July 18, 2023	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.

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

Remarks begin on page 5 of this paper.

Petitioner GE Healthcare – Ex. 1031, p. 369

FOR PURPOSES OF INTERVIEW ONLY – DO NOT ENTER

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

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.

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 $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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:

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 $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl group disclosed in Jansen I may serve as the linker when the compounds containing the $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl of Jansen I are modified with a radiohalogen.

14. I observed that $C_{1\text{-}6}$alkyl and the -O-$C_{1\text{-}6}$alkyl 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, —$C_{1\text{-}6}$alkyl, —O—$C_{1\text{-}6}$alkyl, —S—$C_{1\text{-}6}$alkyl, —NR_8R_9, —OR_{12}, —Het_2 and —Ar_2, wherein the $C_{1\text{-}6}$alkyl 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 $C_{1\text{-}6}$alkyl substitution. Out of 43 representative FAP inhibitors in Jansen I, only one of them is substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl. *See* Jansen I, Table 4, Example 11. The same compound is also the only FAP inhibitor substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$alkyl out of 39 representative FAP inhibitors in Jansen II. *See* Jansen II, Table 3, Compound 28.

16. FAP inhibitors substituted with a halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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 $C_{1\text{-}6}$alkyl should be selected for modification with a radiohalogen.

17. I notice that the single FAP inhibitor substituted with the halogenated $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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 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.

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 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.

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, IC_{50} for FAP (an indicator of the FAP affinity; a higher value means a lower FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM 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.

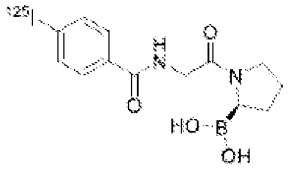
20. Accordingly, the cited references not only fail to suggest selecting and modifying FAP inhibitors, but also may discourage one of ordinary skill in the art to substitute the FAP inhibitors with any functional groups, including the C_{1-6}alkyl or -O-C_{1-6}alkyl.

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 from interfering with the binding between the imaging agent and the target protein. 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



[^{125}I]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").

25. As provided on page 2089 of Meletta, while pronounced binding of [^{125}I]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 [^{125}I]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.

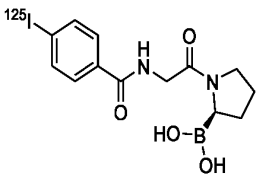
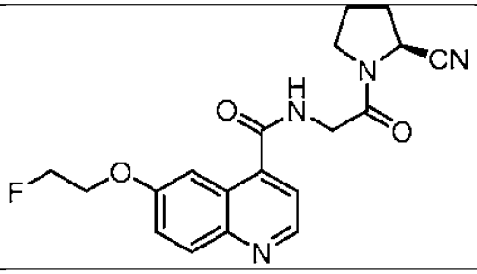
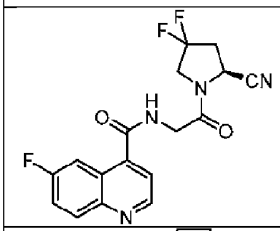
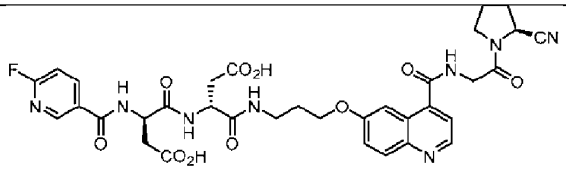
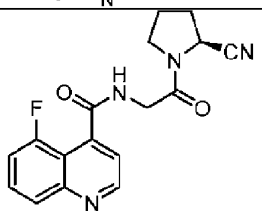
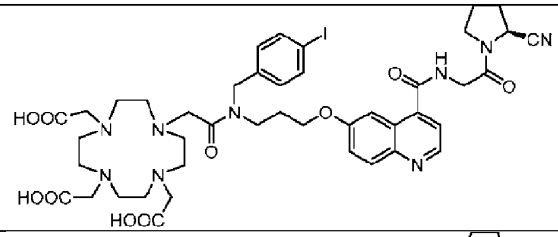
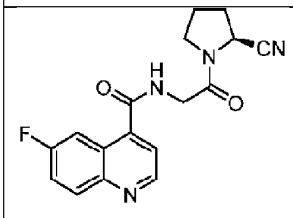
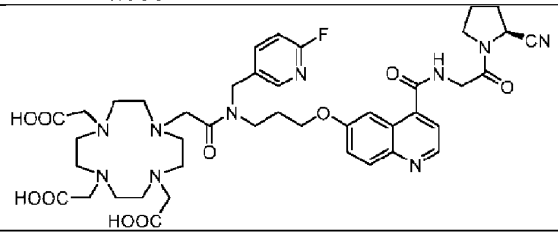
29. Further, I am of the opinion that there are unexpectedly superior FAP specificity associated with the compounds of the pending claims based on the testing results from my lab.

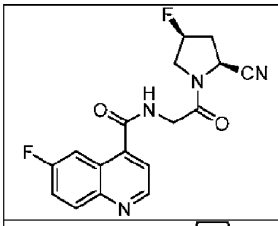
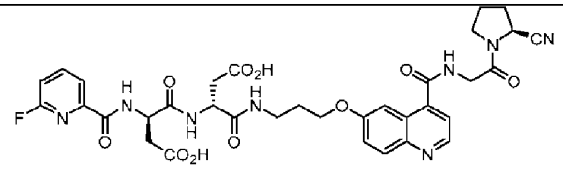
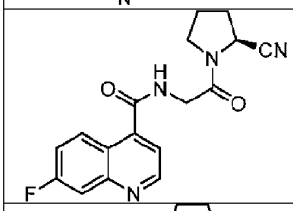
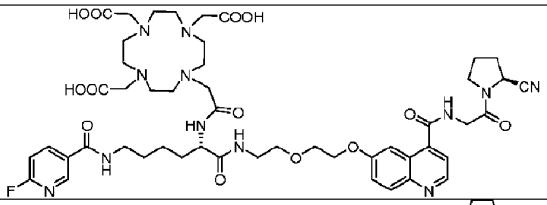
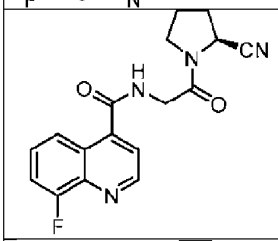
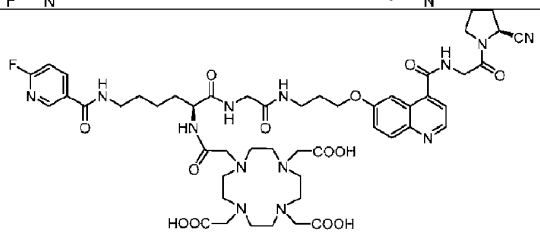
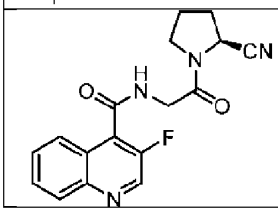
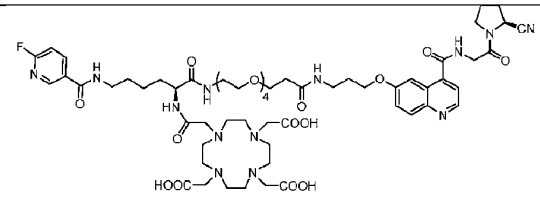
30. Specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a medical condition, therefore enabling the imaging agent to diagnose the medical condition more accurately.

31. While Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]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.

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.

Reference Compound Molecular Structure	PREP/FAP Ratio	Claimed Compound Molecular structure	PREP/FAP Ratio
	32 *		4,111
	152		66,084
	20		>1,418,440
	403		10,502

	15.7		5,807
	241		779
	17		1,693
	3		407

* 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.

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

FOR THE PURPOSES OF INTERVIEW ONLY – DO NOT ENTER

INTERVIEW AGENDA

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
Attorney Docket No.: JHU-36631.303	

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.

FOR THE PURPOSES OF INTERVIEW ONLY – DO NOT ENTER

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

FOR THE PURPOSES OF INTERVIEW ONLY – DO NOT ENTER

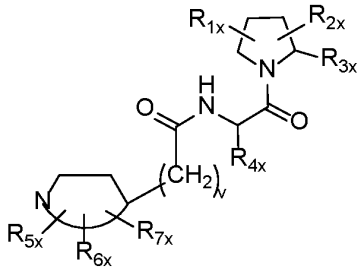
Proposed Claim Amendments

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, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

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

R_{4x} is H;

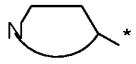
R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of $C_{1\text{-}6}$alkyl being optionally substituted with from 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, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, -S-$C_{1\text{-}6}$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, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$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 -$NR_{10x}R_{11x}$, -$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

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

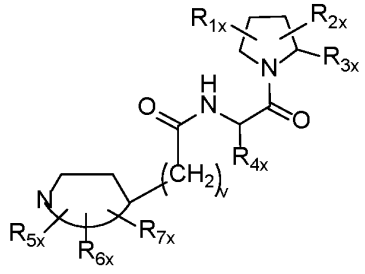
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

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

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$(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

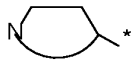
R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH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

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

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

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

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



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

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

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

FOR THE PURPOSES OF INTERVIEW ONLY – DO NOT ENTER

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-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.

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-

molecules/ ("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 modify any compounds of Jansen I and Jansen II to arrive at the claimed 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 IC_{50} of 0.012μm and a selectivity index of 59, which do not compare favorably to a number of compounds including compound Example 15, which has a IC_{50} 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. 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 I or Jansen II, any

[1] *See* Jansen I, Table 4. IC_{50} for FAP (an indicator of the FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM 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 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 $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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 [^{125}I]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 [^{125}I]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.

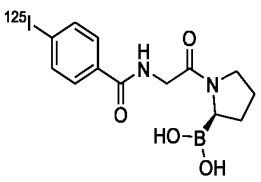
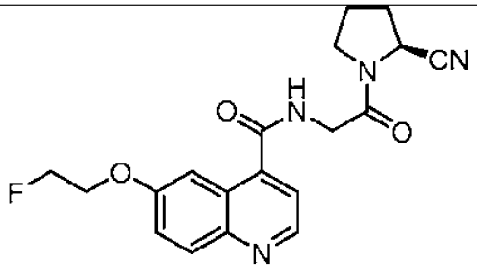
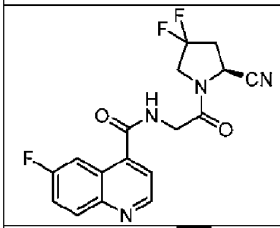
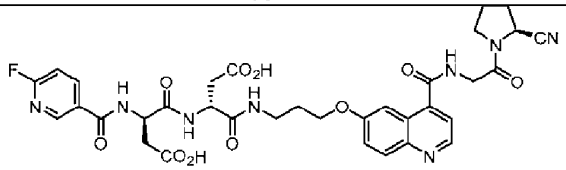
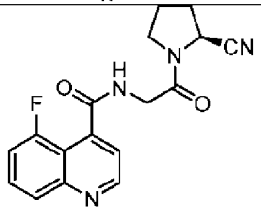
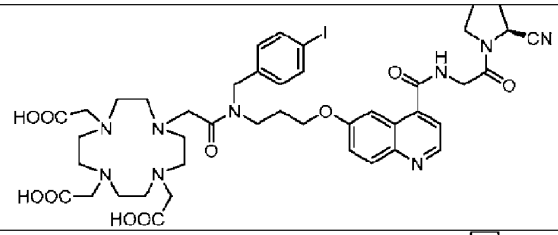
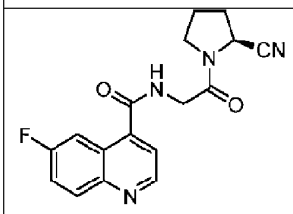
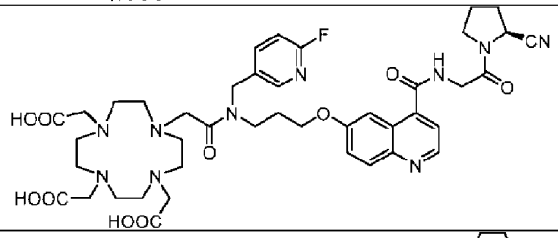
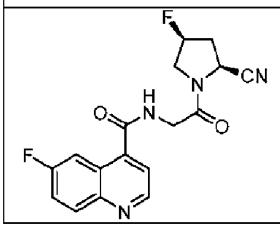
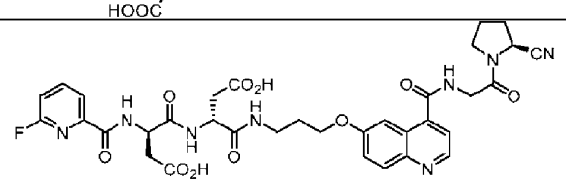
iii. <u>There are unexpected results associated with the claimed compounds to rebut any showing of prima facie obviousness</u>

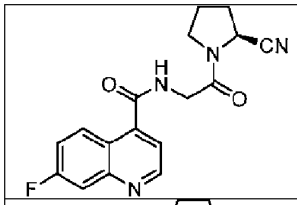
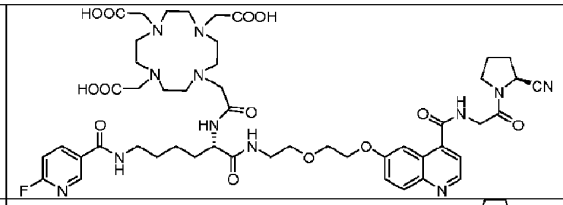
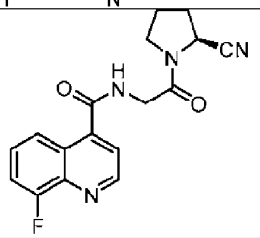
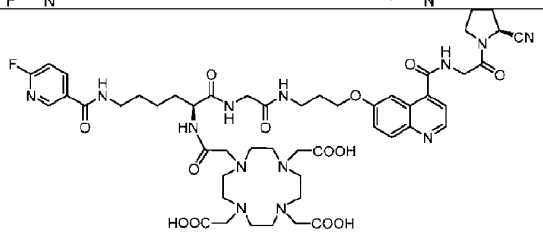
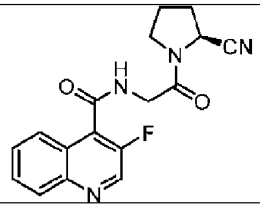
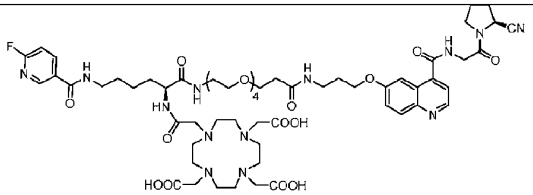
The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Dr. Pomper's Rule 132 Declaration (hereinafter "the Pomper Declaration"), Paragraphs 28-30. As provided in the Pomper Affidavit, specificity is an important 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 [^{125}I]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 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.

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	32 *		4,111
	152		66,084
	20		>1,418,440
	403		10,502
	15.7		5,807

	241		779
	17		1,693
	3		407

* 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 Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
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

Applicant-Initiated Interview Summary	**Application No.** 18/354,282	**Applicant(s)** Yang et al.		
	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**	**Type**
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 substance of the interview must be made of record in the application file. It is the applicants responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04
Please further see:
MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

Applicant-Initiated Interview Summary	**Application No.** 18/354,282	**Applicant(s)** Yang et al.		
	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.

Petitioner GE Healthcare – Ex. 1031, p. 397

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
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 18/354,282	Filing Date 07/18/2023	☐ To be Mailed

ENTITY: ☐ LARGE ☑ SMALL ☐ MICRO

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A		N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A		N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*		x $40 =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*		x $ 192 =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).				
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))					
* If the difference in column 1 is less than zero, enter "0" in column 2.				TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT	12/18/2023	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 3	Minus	** 20	= 0		x $40 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0		x $ 192 =	0
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)			
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=		x $0 =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=		x $0 =	
	☐ Application Size Fee (37 CFR 1.16(s))							
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							
							TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.	LIE
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".	/MARISSA R BLYTHER/
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".	
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.	

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, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Attorney Docket No. 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

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.

Status

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 10-membered 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

Petitioner GE Healthcare – Ex. 1031, p. 400

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-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.

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,

Petitioner GE Healthcare – Ex. 1031, p. 401

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/small-molecules/ ("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

Petitioner GE Healthcare – Ex. 1031, p. 402

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.

Petitioner GE Healthcare – Ex. 1031, p. 403

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 modify any compounds of Jansen I and Jansen II to arrive at the claimed 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. 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-C_{1-6}alkyl 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 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

Petitioner GE Healthcare – Ex. 1031, p. 404

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 IC_{50} 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 IC_{50} 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.

Petitioner GE Healthcare – Ex. 1031, p. 405

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 in Jansen I or Jansen II to arrive at the compounds of the pending claims</u>

[1] *See* Jansen I, Table 4. IC_{50} for FAP (an indicator of the FAP affinity) is 0.012 μM for the FAP inhibitor substituted with a trifluomethoxy substitution versus 0.010 μM for the unsubstituted FAP inhibitor; selectivity index is 59 versus 83.

Petitioner GE Healthcare – Ex. 1031, p. 406

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 $C_{1\text{-}6}$alkyl or -O-$C_{1\text{-}6}$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

Petitioner GE Healthcare – Ex. 1031, p. 407

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 [^{125}I]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 [^{125}I]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 rebut any showing of prima facie obviousness</u>

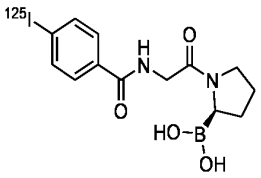
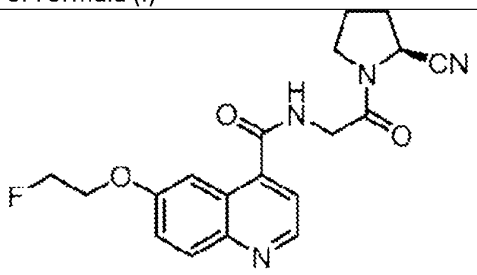
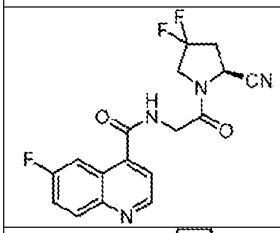
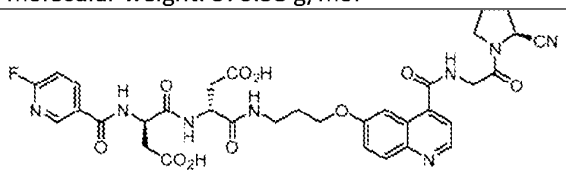
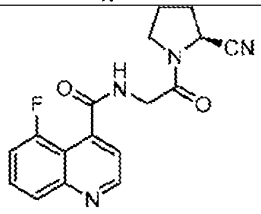
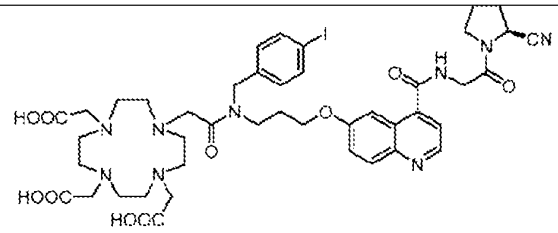
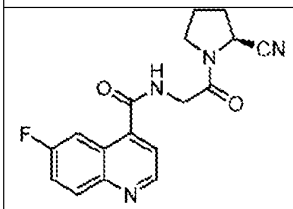
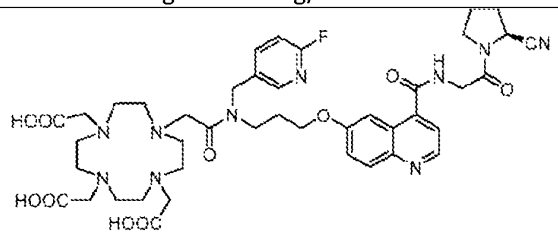
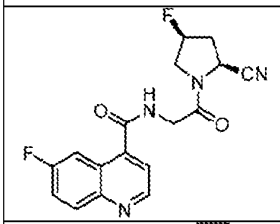
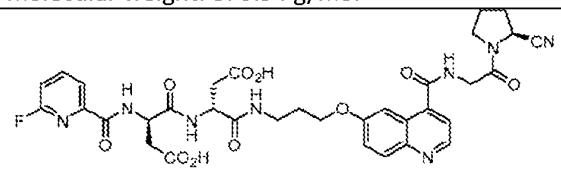
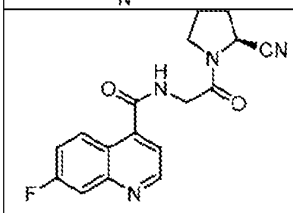
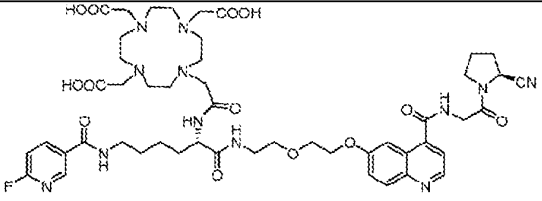
The strong showing of unexpected results associated with the claimed compounds further demonstrates the non-obviousness of the pending claims. *See* Pomper Affidavit, Paras. 38-42.

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.

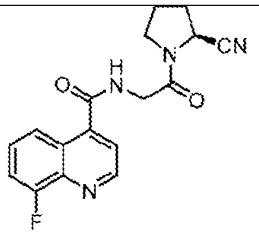
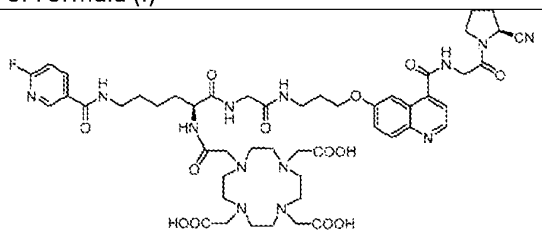
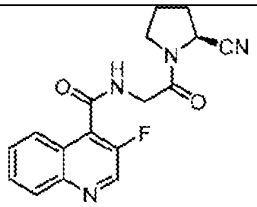
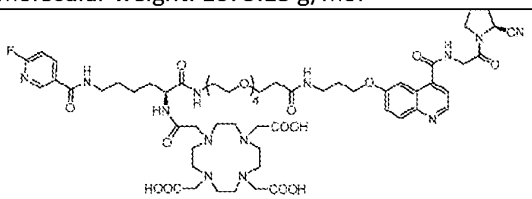
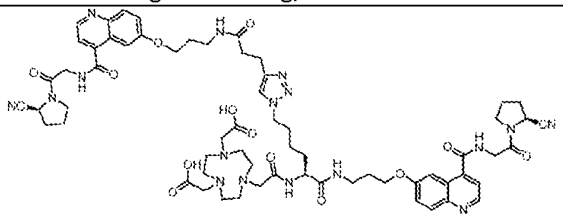
In particular, while Meletta could not conclude on the selectivity of the compound of Zimmerman [^{125}I]MIP-1232 for FAP (above section ii), the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents is shown in the current application US 2020/0330624 for the selectivity for FAP over dipeptidyl 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 falling under the scope of the pending claims for FAP is generally several orders of magnitude higher than that of other small molecule FAP inhibitors. 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.

Petitioner GE Healthcare – Ex. 1031, p. 409

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	32 *	 molecular weight: 370.38 g/mol	4,111
	152	 molecular weight: 734.70 g/mol	66,084
	20	 molecular weight: 983.86 g/mol	>1,418,440
	403	 molecular weight: 876.94 g/mol	10,502
	15.7	 molecular weight: 734.70 g/mol	5,807
	241	 molecular weight: 1049.13 g/mol	779

Petitioner GE Healthcare – Ex. 1031, p. 410

Reference Compound Molecular Structure	PREP/FAP Ratio	Molecular structure of Representative Compounds of Formula (I)	PREP/FAP Ratio
	17	 molecular weight: 1073.15 g/mol	1,693
	3	 molecular weight: 1266.39 g/mol	407
		molecular weight: 889.39 g/mol	10,694
		molecular weight: 761.39 g/mol	11,893
		 molecular weight: 1282.43 g/mol	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

Petitioner GE Healthcare – Ex. 1031, p. 411

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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**12/18/2023 01:35:41 PM Z ET**	**JHU-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 #	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-SA...pdf	(1-1)	1	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-A....pdf	(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	A243C9BC115DAA8E31970D3E00A50693D766640C629D4D6F46257C622266E34EF3AA5EAE3250A1AE87C73E3217F86827B73589316A7F33472A0B7D598EA42578
2023-12-18 - 36631.303 Supp Amendment NFOA-SA...pdf	17956623C7889FECDEEF508489336787770BA4459EEC754E3C95A9F2C5A2318B6829CF9C26419249DA5C0E8F027BA36FA0408D264F69F7F5E3ED4D763DE203500
2023-12-18 - 36631.303 Supp Amendment NFOA-CLM.pdf	B60C1AE0EBF4246B30CEEB95A807336E01ABF9E0322E79B743B5E860596DBE7A584DD90617C7754EFB83065234FED26592DD937821DCC48F655022B8CB525253
2023-12-18 - 36631.303 Supp Amendment NFOA-A...pdf	C7A6DD5081F86ABAB3900C09D15F01C3AC1A6DBABCACD75108CBAD2A64F668838A623DE25DCF3F9E0C5BDBCD3454B3E4A288DDF195BDA84B9F65417797E7C126

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.

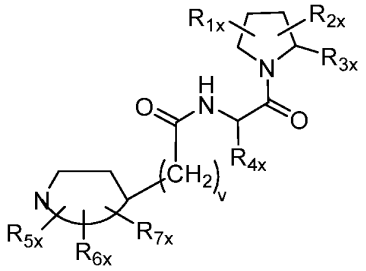
IN THE CLAIMS:

29. (Presently Amended) A 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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

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

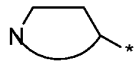
~~R_{8x}, R_{9x} and R_{12x} are each independently selected from the group consisting of H, OH, halo, C_{1-6}alkyl, O-C_{1-6}alkyl, S-C_{1-6}alkyl, and Ar_3;~~

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

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

Petitioner GE Healthcare – Ex. 1031, p. 415

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



represents a quinolinyl ring~~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;~~

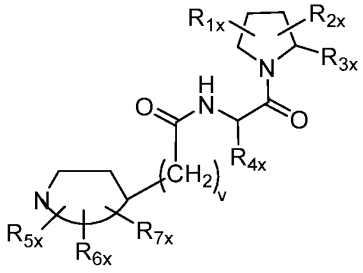
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

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

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, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

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

R_{4x} is H;

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

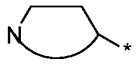
Petitioner GE Healthcare – Ex. 1031, p. 416

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

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

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

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



represents a quinolinyl ring ~~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.

Petitioner GE Healthcare – Ex. 1031, p. 417

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
* 18/354,282 *	18/354,282	Yang et al.	
	Examiner	Art Unit	
	PERREIRA, MELISSA JEAN	1618	

Document Code - DISQ	Internal Document - DO NOT MAIL

TERMINAL DISCLAIMER	☑ APPROVED	☐ DISAPPROVED
Date Filed: **13 December 2023**	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

/KIMBERLY R WHITE/

Technology Center: OPLC

Telephone: (571)272-6179

_____

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 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
12/19/2023 10:20:13 AM	Google Scholar	[after:2000] [before:2017] proline quinoline FAP DOTA
12/19/2023 10:21:21 AM	Google Scholar	[after:2000] [before:2017] proline quinoline FAP radiolabeling
12/19/2023 10:25:23 AM	Google Scholar	proline quinoline FAP radiolabeling [after:2000] [before:2017]
12/19/2023 10:28:12 AM	Google Scholar	[after:2000] [before:2017] radiolabeled proline FAP
12/19/2023 10:29:44 AM	Google Scholar	radiolabeled proline FAP [after:2000] [before:2017]
12/19/2023 10:30:54 AM	Google Scholar	[after:2000] [before:2017] quinoline proline FAP PET
12/19/2023 10:31:03 AM	Google Scholar	quinoline proline FAP PET [after:2000] [before:2017]
12/19/2023 10:35:01 AM	Google Scholar	[after:2000] [before:2017] proline FAP PET
12/19/2023 10:35:25 AM	Google Scholar	proline FAP PET [after:2000] [before:2017]
12/19/2023 10:40:39 AM	Google Scholar	[after:2000] [before:2017] proline FAP SPECT
12/19/2023 11:00:22 AM	Google Scholar	[after:2000] [before:2017] proline FAP cyanine dye
12/19/2023 11:48:35 AM	Google Scholar	proline FAP cyanine dye [after:2000] [before:2017]
12/19/2023 11:49:30 AM	Google Scholar	[after:2000] [before:2017] cyanoproline FAP PET
12/19/2023 11:49:32 AM	Google Scholar	[after:2000] [before:2017] cyanoproline FAP cyanine dye
12/19/2023 11:50:09 AM	Google Scholar	[after:2000] [before:2017] cyanoproline FAP imaging

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	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
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

Petitioner GE Healthcare – Ex. 1031, p. 422

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	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

Petitioner GE Healthcare – Ex. 1031, p. 423

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.	Confirmation No.: 7536
Serial No.: 18/354,282	Art Unit: 1618
Filed: July 18, 2023	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.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/354,282	Yang et al.
	Examiner	**Art Unit**
	MELISSA J PERREIRA	1618

CPC								
Symbol							**Type**	**Version**
A61K	/	51	/	0485			F	2013-01-01
A61K	/	47	/	545			I	2017-08-01
A61K	/	51	/	0478			I	2013-01-01
A61K	/	51	/	0482			I	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**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 — Part of Paper No.: 20240105

Petitioner GE Healthcare – Ex. 1031, p. 425

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	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 REFERENCES(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 — Part of Paper No.: 20240105

Petitioner GE Healthcare – Ex. 1031, p. 426

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	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

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.: 20240105

Petitioner GE Healthcare – Ex. 1031, p. 427

Bibliographic Data

Application No: 18/354,282

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☐ No ☐ Met After Allowance

Verified and Acknowledged: /MELISSA J PERREIRA/ (Examiner's Signature) | (Initials)

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

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
07/18/2023	424	1618	JHU-36631.303
RULE			

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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				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] (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

U.S. PUBLISHED PATENT APPLICATIONS						
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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	

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]
		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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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.

☒ 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.

.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				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] (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

U.S. PUBLISHED PATENT APPLICATIONS						
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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	

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

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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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.

☒ 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

.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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 7590 01/10/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER
PERREIRA, MELISSA JEAN

ART UNIT	PAPER NUMBER
1618	

DATE MAILED: 01/10/2024

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. PROSECUTION ON THE MERITS IS CLOSED. 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 THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. 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: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

101943 7590 01/10/2024
The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

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

EXAMINER	ART UNIT	CLASS-SUBCLASS
PERREIRA, MELISSA JEAN	1618	424-001890

1. 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/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Petitioner GE Healthcare – Ex. 1031, p. 438

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 01/10/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

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 with the Issue Notification 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;
6) 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.

Notice of Allowability	Application No. 18/354,282	Applicant(s) Yang et al.	
	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 12/18/23.
   ☐ 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/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☑ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

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

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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	01/16/2024 05:15:59 PM Z ET	JHU-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 #	63968554	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	E20241FN16479846	Van Nguyen

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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**01/16/2024 05:15:59 PM Z ET**	**JHU-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 #	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

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
WO2016196628A1.pdf	515E343648E2878B7A59FC35ECD8E7564DDC2D9AF7A6E4943ED650ABB977B3C0CCF2B3E57D934968296ED6542E7122943904B0013C234888C773A934472A23C9
2024-01-16 - JHu-36631.303 - Supp IDS.pdf	91A5DF33719D461247F422010D6C4620CC167D3FB4C8B575CB5C14834F5D1FF57A921C469D75C560C30C4BFEFC83896F9A3A16ADE638DE1A916D89C64AA059B6
Third Party Observations.pdf	9D1A24255E793F435B294816D357B4D479584A3CF45672812C46E3D0990121E8D082B3C39584A6CE8DEF76F42207F9DAC0746F58D55F3C30EBB28133A63F0084

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				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] (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

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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

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] (if known)	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.	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 Signature		Date 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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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.

☒ 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**.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	01/16/2024 05:18:26 PM Z ET	JHU-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 #	63968988	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	E20241FH19045329	Van Nguyen

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
504302	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL 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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**01/16/2024 05:18:26 PM Z ET**	**JHU-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 #	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 - Issue Fee Transmittal.pdf	4C775A38FA3EE63915A9CD7D2ED24BB19220A3B56F1B33AF238528BD37BC6B673A254D61E31B936A6E9D913402589A623F4AF522073AF44203CE6D7D341A7A5F

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

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

101943 7590 01/10/2024
The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

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

EXAMINER	ART UNIT	CLASS-SUBCLASS
PERREIRA, MELISSA JEAN	1618	424-001890

1. 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/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Casimir Jones, SC
2 Jeffrey W. Childers
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: The Johns Hopkins University

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Baltimore, MD

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 504302

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Jeffrey W. Childers/ Date January 16, 2024

Typed or printed name Jeffrey W. Childers Registration No. 58126

PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Petitioner GE Healthcare – Ex. 1031, p. 455

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**01/22/2024 01:37:02 PM Z ET**	**JHU-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	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_36631-303_SUPPL_IDS_SB08.pdf	52AC7B410E60580F35A2549C9975CA6DE0CDEBE91092F6D89CCF86F79E045BE686845BE62033CFC445D59F1A75D624E8CC

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

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18 Jul 2023
				First Named Inventor	Yang
				Art Unit	1618
				Examiner Name	Melissa Jean Perreira
Sheet	1	of	2	*Attorney Docket Number*	JHU-36631.303

U.S. PATENTS					
Examiner 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

U.S. PUBLISHED PATENT APPLICATIONS					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] *(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
	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 Country Code[5] Number[6] Kind Code[7] *(if known)*	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]

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	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18 Jul 2023
				First Named Inventor	Yang
				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).

☐ 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)	2024-01-22
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 7590 01/23/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
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(I).

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

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

7590 01/30/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	
NOTIFICATION DATE	DELIVERY MODE
01/30/2024	ELECTRONIC

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. Horne, for

571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management

FORM PTOM327-B (Rev. 02/08)

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

7590 01/30/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	
NOTIFICATION DATE	DELIVERY MODE
01/30/2024	ELECTRONIC

NOTICE OF NON-COMPLIANT INFORMATION DISCLOSURE STATEMENT

An Information Disclosure Statement (IDS) filed 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).

☒ 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. Horne, for

571-272-4200 or 1-888-786-0101
Application Assistance Unit
Office of Data Management

FORM PTOM327-B (Rev. 02/08)

Petitioner GE Healthcare – Ex. 1031, p. 465

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

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

Doc Code: QPIDS.REQ
Document Description: QuickPath Information Disclosure Statement

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 PROTEI

THE UNDERSIGNED HEREBY CERTIFIES AND REQUESTS THE FOLLOWING FOR THE ABOVE-IDENTIFIED APPLICATION.

1. Consideration is requested of the information disclosure statement (IDS) submitted herewith, which is being filed after payment of the issue fee.
2. 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).
3. Please charge the IDS fee set forth in 37 CFR 1.17(p) to Deposit Account No. 504302.
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 **Web-based ePetition**. **WARNING:** 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 37 CFR 1.114 and the RCE fee under 37 CFR 1.17(e) are submitted herewith.
6. 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.
7. This certification and request is being filed as a **Web-based ePetition** and is not accompanied by an amendment to the application. Inclusion of an amendment will result in automatic entry of the RCE.

Signature /Jeffrey W. Childers/	Date February 2, 2024
Name (Print/Typed) Jeffrey W. Childers	Practitioner Registration Number (If applicable) 58126

Note: *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 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.

Doc code : PET.DEC.AUTO
Description : ePetition Grant Letter

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

GRANT LETTER

APPLICATION #	DECISION DATE	DECISION ON PETITION #	ATTORNEY DOCKET NUMBER
18/354,282	02/02/2024		JHU-36631.303

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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**02/02/2024 05:07:17 PM Z ET**	**JHU-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	Jeffrey Childers
PATENT CENTER #	64194803	AUTHORIZED BY	-
CUSTOMER #	101943	FILING DATE	07/18/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	**E202422H07588108**	**Jeffrey Childers**

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
504302	**37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)**

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2464	PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III)	56.00	1	56.00
2801	REQUEST FOR CONTINUED EXAMINATION (RCE) - 1ST REQUEST (SEE 37 CFR 1.114)	544.00	1	544.00
			TOTAL AMOUNT:	**$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.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**02/02/2024 05:07:17 PM Z ET**	**JHU-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	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 fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
2024-02-02 - JHU-36631.303 - RCE.pdf	3	Request for Continued Examination (RCE)	131 KB
Warning: This is not a USPTO supplied RCE fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
2024-02-01 - JHU-36631.303 - QPIDS.pdf	2	Quick Path Information Disclosure Statement	151 KB

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	24A562B12BC7CF67E5C6722EA0826261D028C88AC39617E8EB3A682E5A1A0DA48402AE7E0947487559C69E462816E3EFDD74DF1E035F7D3FD596FC159EB63ED0
2024-02-02 - JHU-36631.303 - Supp IDSpdf.pdf	8DD1BB24F49C8A9DADA5B5A745DF6FD51DBD47EE1DD6AC77F320ADA0C471DB22799B873A9DE73C38311DEC1657DDDE772C7A82E22C924D6856B7EC460C755CDB
2024-02-02 - JHU-36631.303 - RCE.pdf	3FC1787EC432E484337EA03713EF5FF6BA594D11702F21CBA7DC15E89F54560B433A2564F6752CE61FCAB1000AAFDA21A670EB00EFA2D2D6EF30F77784DDEF57
2024-02-01 - JHU-36631.303 - QPIDS.pdf	F01234071E6EE3FB329DAE476CC39D1A7CB244D0B99A0768B1BD9574470652397488FBCF72113E283C8184CEEACA897A0E2F89C07A83C048E88A892E65BAB370
WO2016196628A1.pdf	515E343648E2878B7A59FC35ECD8E7564DDC2D9AF7A6E4943ED650ABB977B3C0CCF2B3E57D934968296ED6542E7122943904B0013C234888C773A934472A23C9
Third Party Observations.pdf	9D1A24255E793F435B294816D357B4D479584A3CF45672812C46E3D0990121E8D082B3C39584A6CE8DEF76F42207F9DAC0746F58D55F3C30EBB28133A63F0084
2024-02-02 - JHU-36631.303 - IDS Certification Statement.pdf	4CB170D87AAB22FCA3F32AC3032D81F30C1172BA26BE1A0C1C963BB4FCACBB84FDBDD80FA8769827F7FD50D32BA1E345FE1CCF03FC5AA795E2CD9EB334BDA982

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				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] (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

U.S. PUBLISHED PATENT APPLICATIONS					
Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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
	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 Country Code[5] Number[6] Kind Code[7] (if known)	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]
	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	

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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.

☐ 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	Fee Code	Fee Code Description	Amount Paid	Payment Method
I202425J43169200	2806	SUBMISSION- INFORMATION DISCLOSURE STMT	$104.00	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 7590 02/14/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
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

Notice of Allowability	Application No. 18/354,282	Applicant(s) Yang et al.	
	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/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   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)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

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. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618	/MELISSA J PERREIRA/ Examiner, Art Unit 1618

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				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] (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

U.S. PUBLISHED PATENT APPLICATIONS

Examiner Initials*	Cite No.[3]	Document Number Number-Kind Code[4] (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
	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 Country Code[5] Number[6] Kind Code[7] (if known)	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]
	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

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/

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Complete if Known	
				Application Number	18/354,282
				Filing Date	18-Jul-2023
				First Named Inventor	Yang
				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.

☐ 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

.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

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**.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /M.J.P/

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sengpheth Sandara

Refund Accounting Date:02/22/2024

Effective Date	Sale Item Reference Number	Refund Total
02/22/2024	18354282	$544.00

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method	Account Number
I20242LE59085803	2801	RCE- 1ST REQUEST	$544.00	Visa	**********0638

United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Sengpheth Sandara

Sale Adjustment Accounting Date:02/22/2024

Effective Date	Sale Accounting Date	Sale Item Reference Number
02/22/2024	02/22/2024	18354282

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20242LE59085803	2801	RCE- 1ST REQUEST	$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 7590 03/06/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
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 SelectUSA.gov.

DocCode - PATENT.GRANT

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

At the time of document entry (noted above):

- USPTO employees may access SCORE content via DAV or via the SCORE web page.
- External customers may access SCORE content via PAIR using the Supplemental Content tab.

Form Revision Date: March 1, 2019

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 03/26/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**08/22/2024 05:18:06 PM Z ET**	**JHU-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 #	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	53EE3AE1AE5E327A58F848D02BBF60B33259B1A4974B218F360F7EBDAF72A7B7F5B61204BFCD83910B0B90047E18CF20FA9CC0BFC094D0A13043C223AC837C44

2024-08-22_36631.303_CoC.pdf

F43EFA29A4425069313B778D9162E39E218B14D94D5BA1FAC5AF200E49C0CE90D07D8ACDAC1E976FDE5947CBF8AF5B4D34F1393C3B81B30F95126567C4499A67

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 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 RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (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.

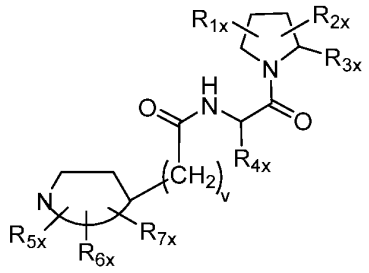
In the Letters Patent, Claim 1, Column 64, lines 47-67, Column 65, lines 1-62:

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

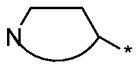
R_{5x}, R_{6x} and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -$NR_{8x}R_{9x}$, -OR_{12x}, -Het_2 and -Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH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

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

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

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

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



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

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

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

Petitioner GE Healthcare – Ex. 1031, p. 496

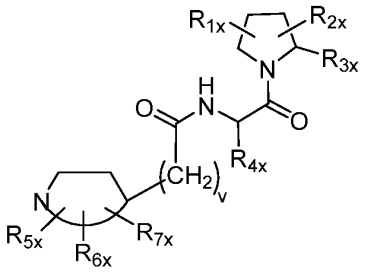
Whereas it should read:

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

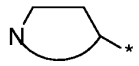
R_{5x}, R_{6x} and R_{7x} are each ~~independently selected from the group consisting of~~ H~~, OH, oxo, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, $NR_{8x}R_{9x}$, OR_{12x}, Het_2 and Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH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

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

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

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

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



represents a quinolinyl ring~~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~~;

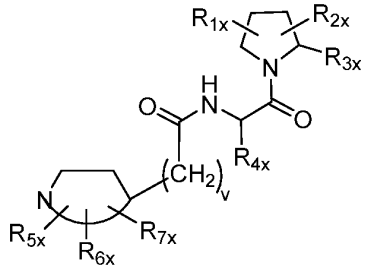
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

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

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;

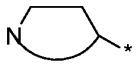
R_{3x} is selected from the group consisting of H, -CN, -$B(OH)_2$ -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

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

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

R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl; Ar_1, Ar_2 and Ar_3 are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar_1, Ar_2 and Ar_3 being optionally and independently substituted with from 1 to 3 substituents selected from -$NR_{10x}R_{11x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;
Het_2 is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het_2 being optionally substituted with from 1 to 3 substituents selected from -$NR_{13x}R_{14x}$, -C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;
v is 0, 1, 2, or 3; and

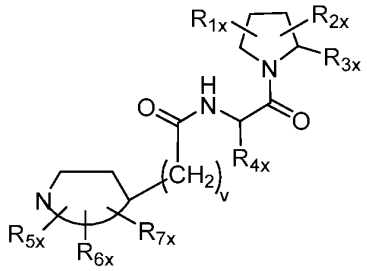


represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or
a stereoisomer, tautomer, racemate, salt, hydrate, or solvate thereof.-

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

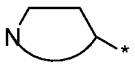
R_{5x}, R_{6x} and R_{7x} are each ~~independently selected from the group consisting of H, -OH, oxo, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, $NR_{8x}R_{9x}$, OR_{12x}, Het_2 and Ar_2; each of C_{1-6}alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and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

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

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

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

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



represents a quinolinyl ring ~~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.

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

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:

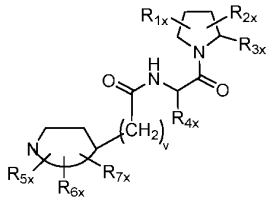
In the Letters Patent, Claim 1, Column 64, lines 47-67, Column 65, lines 1-62:

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:

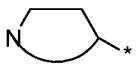
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, and -S-C_{1-6}alkyl;

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

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

v is 0;



represents a quinolinyl ring;

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 CFR 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 CFR 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, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 11,938,201
APPLICATION NO.: 18/354,282
ISSUE DATE : 26-Mar-2024
INVENTOR(S) : YANG, Xing, et al.

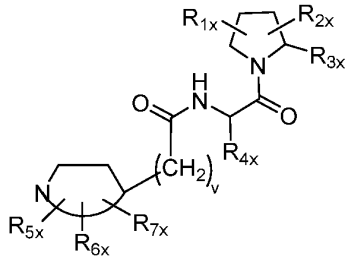
B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted to form a chemical bond with B and A; or

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

In the Letters Patent, Claim 3, Column 66, lines 1-67, 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, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):
Casimir Jones, S.C.
2275 Deming Way, Suite 310
Middleton, WI 53562

This collection of information is required by 37 CFR 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 CFR 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, Alexandria, VA 22313-1450.

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
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

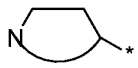
PATENT NO. : 11,938,201
APPLICATION NO.: 18/354,282
ISSUE DATE : 26-Mar-2024
INVENTOR(S) : YANG, Xing, et al

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-$S(O)_2$aryl, -CO_2H, -SO_3H, -SO_2NH_2, -PO_3H_2, and 5-tetrazolyl;

R_{4x} is H;

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

v is 0;



represents a quinolinyl ring;

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

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

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 CFR 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 CFR 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, 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.

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 7590 09/24/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
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

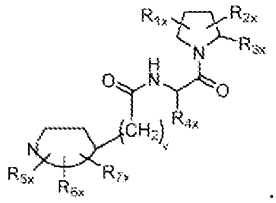
Claim 1, Column 64, Lines 47-67, Column 65, Lines 1-62 should read:

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

B-L-A (I)

wherein:

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



;

wherein:

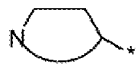
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

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

R_{4x} is H;

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

v is 0;



represents a quinolinyl ring;

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

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

Signed and Sealed this
Twenty-fourth Day of September, 2024

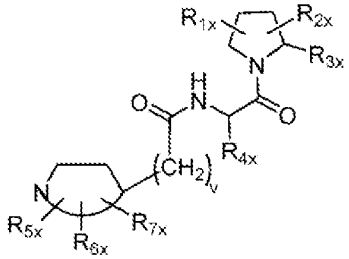
Katherine Kelly Vidal

Katherine Kelly Vidal
Director of the United States Patent and Trademark Office

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, $C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, and -S-$C_{1\text{-}6}$alkyl;

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

R_{4x} is H;

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

v is 0;



represents a quinolinyl ring;

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

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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

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:

	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

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

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/354,282	**11/19/2024 01:47:17 PM Z ET**	**JHU-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 #	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 Number	Effective Date
18354282	11/19/2024

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I2024BBB28079303	1461	1.28(C) SUBMISSIONS - APPLIC FILE FEE	$5,272.00	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 7590 12/23/2024

The Johns Hopkins University
c/o Casimir Jones
2275 Deming Way
Suite 310
Middleton, WI 53562

EXAMINER	
PERREIRA, MELISSA JEAN	

ART UNIT	PAPER NUMBER
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

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

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 **ACCEPTED**. 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

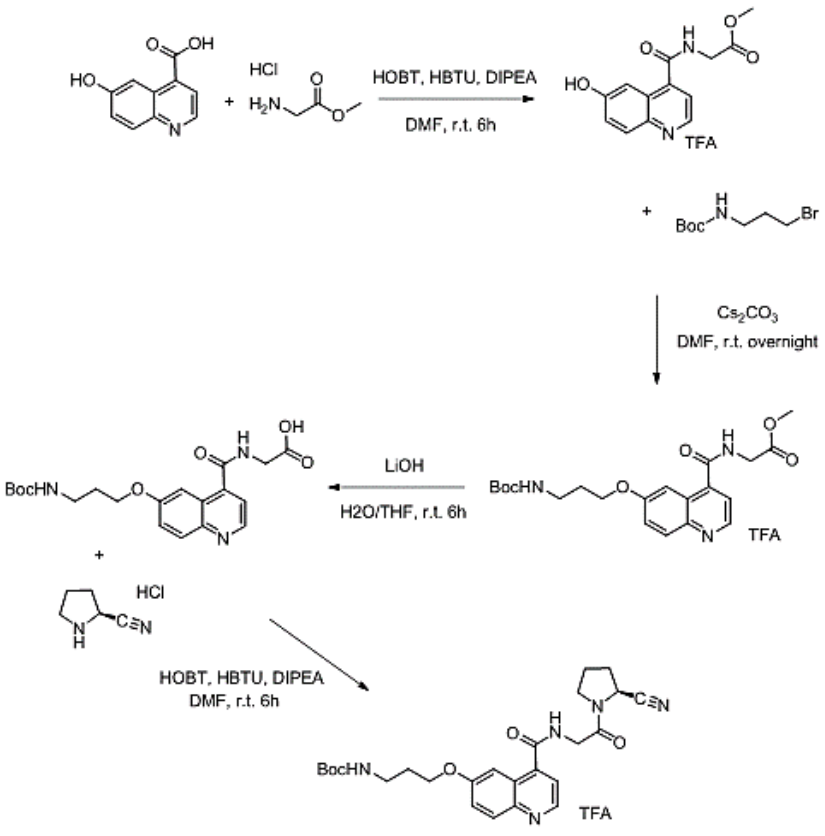

HCl
HOBT, HBTU, DIPEA
DMF, r.t. 6h
TFA
Boc
Br
Cs_2CO_3
DMF, r.t. overnight
LiOH
H2O/THF, r.t. 6h
BocHN
HCl
HOBT, HBTU, DIPEA
DMF, r.t. 6h
TFA

Fig. 1A

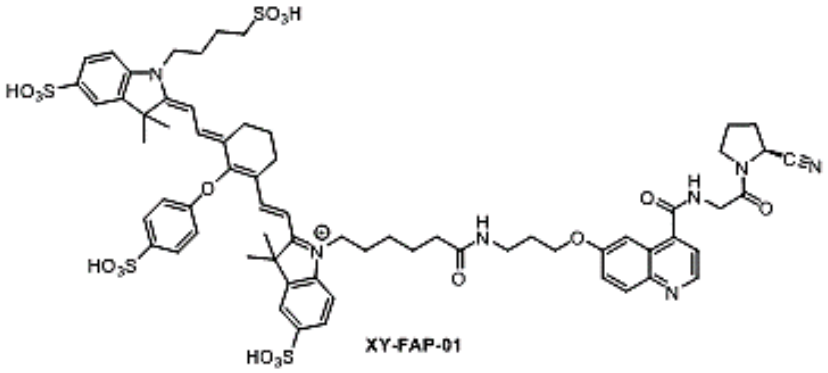


Fig. 1B

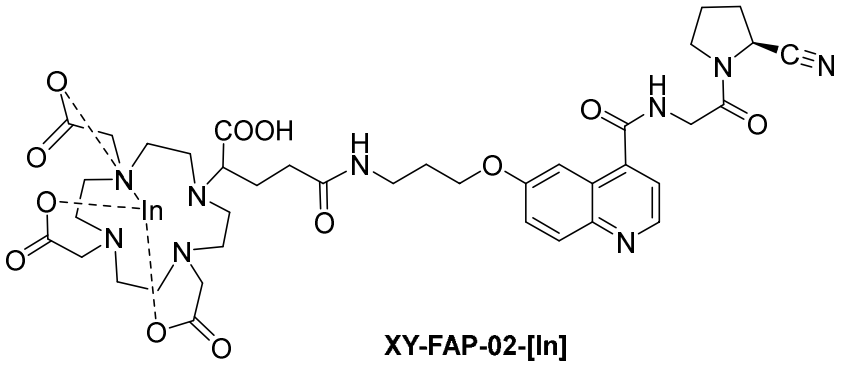


Fig. 1C

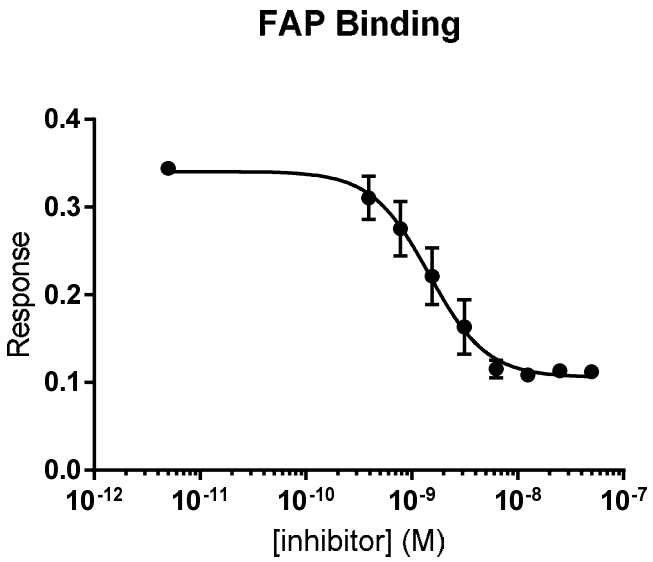

FAP Binding
Response
0.4
0.3
0.2
0.1
0.0
10-12
10-11
10-10
10-9
10-8
10-7
[inhibitor] (M)

Fig. 2

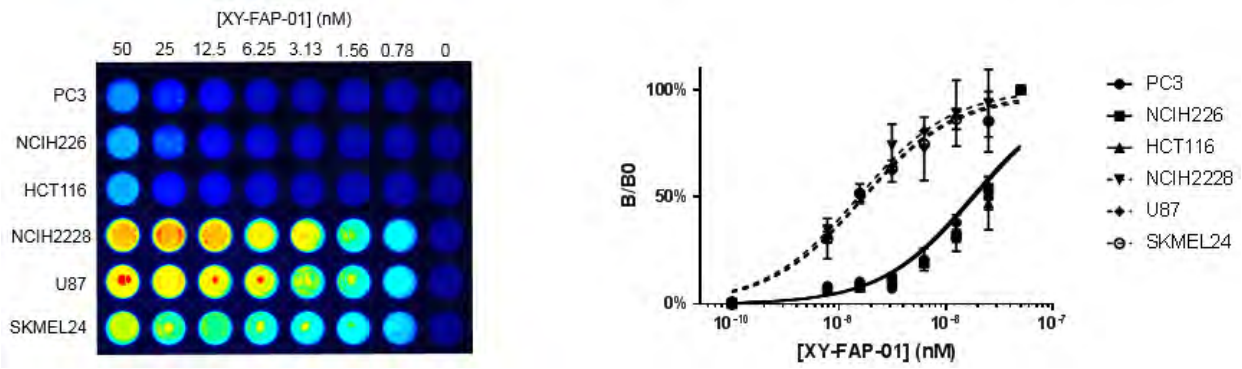


Fig. 3A

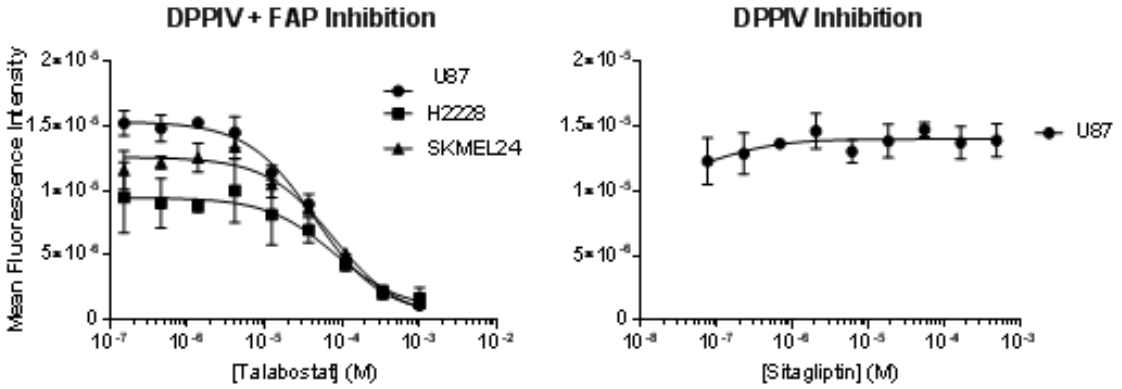


Fig. 3B

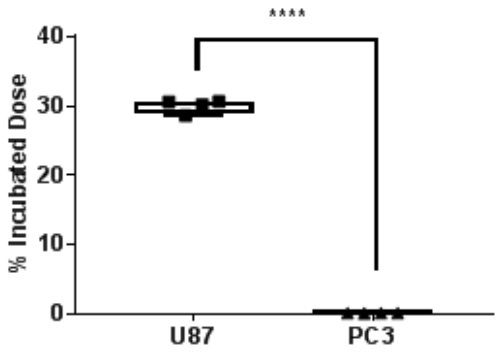


Fig. 3C

	5 min (n= 3)	0.5 h (n= 4)	2 h (n= 3)	6 hr (n= 4)	6 h - blocking (n=4)	12 h (n= 4)
blood	15.13 ± 0.62	10.64 ± 1.54	4.10 ± 0.39	2.01 ± 0.18	0.02 ± 0.001	0.42 ± 0.04
heart	6.68 ± 0.99	4.98 ± 0.71	2.61 ± 0.09	1.07 ± 0.09	0.02 ± 0.002	0.46 ± 0.04
lungs	6.99 ± 1.37	5.60 ± 0.89	2.59 ± 0.32	1.36 ± 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 ± 0.20	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	0.45 ± 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	1.16 ± 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
lrg. 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	2.96 ± 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	0.02 ± 0.005	0.60 ± 0.03
femur	4.76 ± 0.12	5.83 ± 0.72	4.95 ± 0.60	3.91 ± 0.70	0.08 ± 0.021	1.38 ± 0.20
U87	9.71 ± 0.24[a]	12.89 ± 1.45[a]	12.28 ± 1.95[a]	11.20 ± 1.03[a]	0.27 ± 0.019[c]	4.57 ± 0.54[b]
PC3	2.20 ± 0.20	3.10 ± 0.57	2.75 ± 0.11	3.40 ± 0.34	0.11 ± 0.024[c]	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 ± 0.36	18.07 ± 1.197	10.94 ± 0.93
U87:mm	3.25 ± 0.26	3.66 ± 0.44	4.38 ± 0.66	6.29 ± 0.82	11.81 ± 2.086	7.68 ± 0.97

Fig. 4

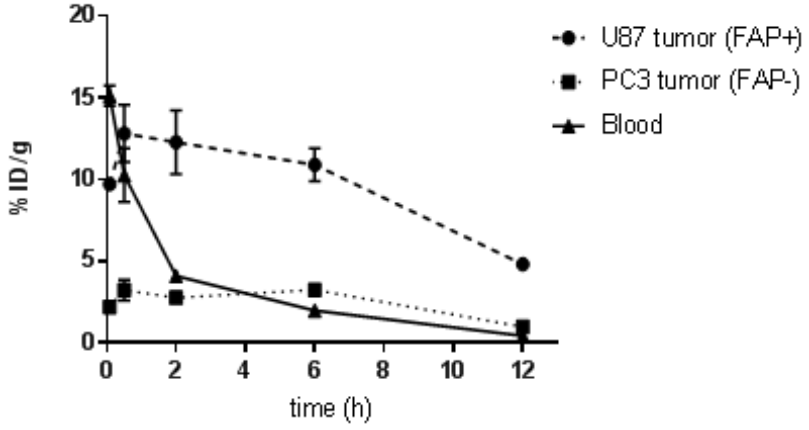

U87 tumor (FAP+)
PC3 tumor (FAP-)
Blood
% ID/g
time (h)
0
5
10
15
20
0
2
4
6
8
10
12

Fig. 5A

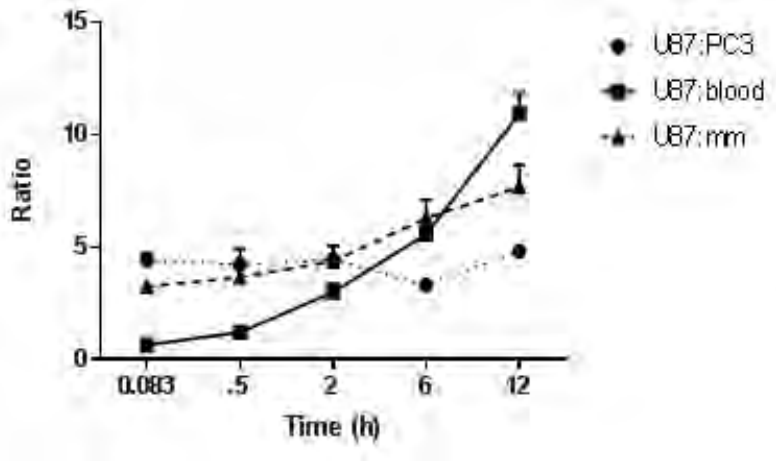

U87:PC3
U87:blood
U87:mm
Ratio
Time (h)
0
5
10
15
0.083
.5
2
6
12

Fig. 5B

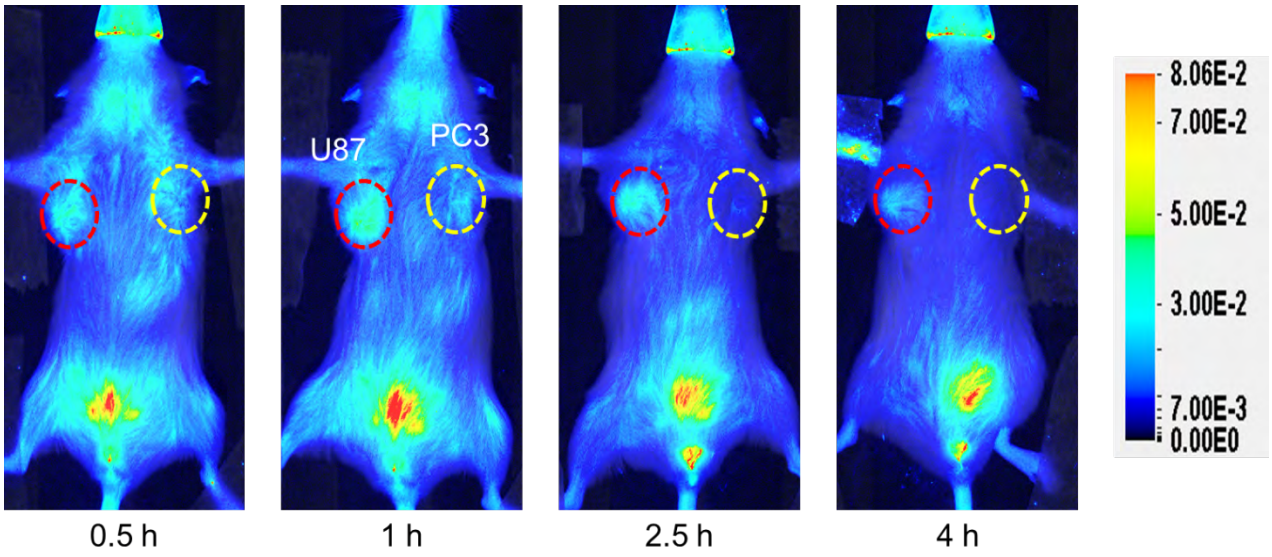


Fig. 6

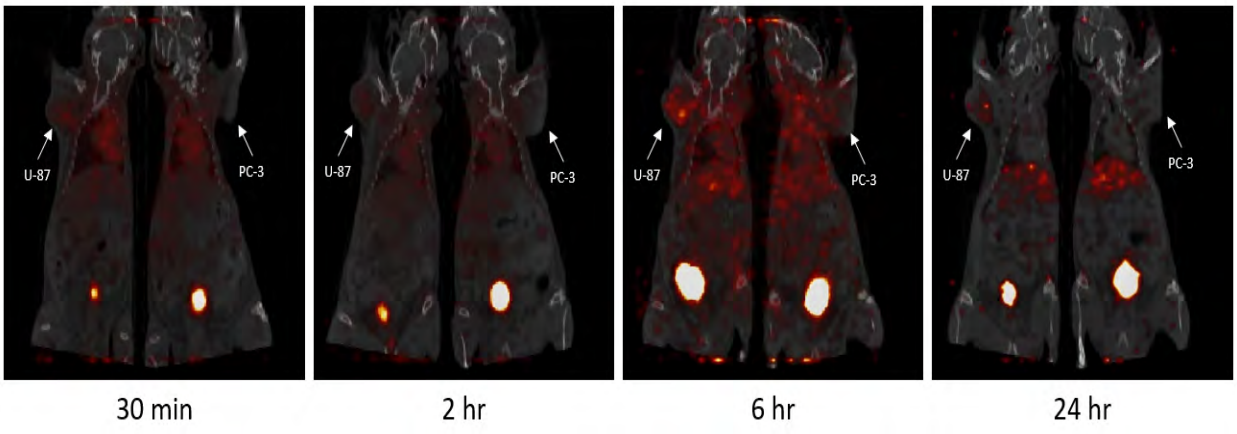


Fig. 7

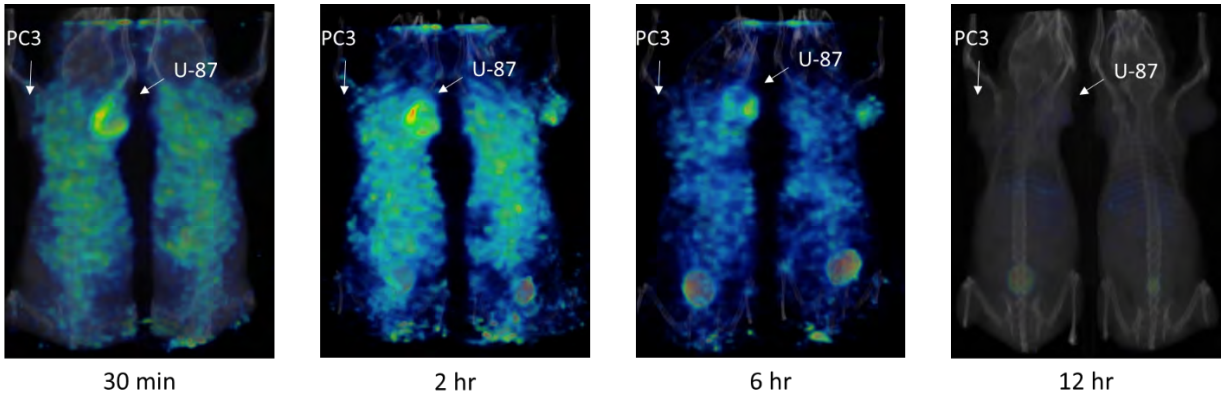


Fig. 8

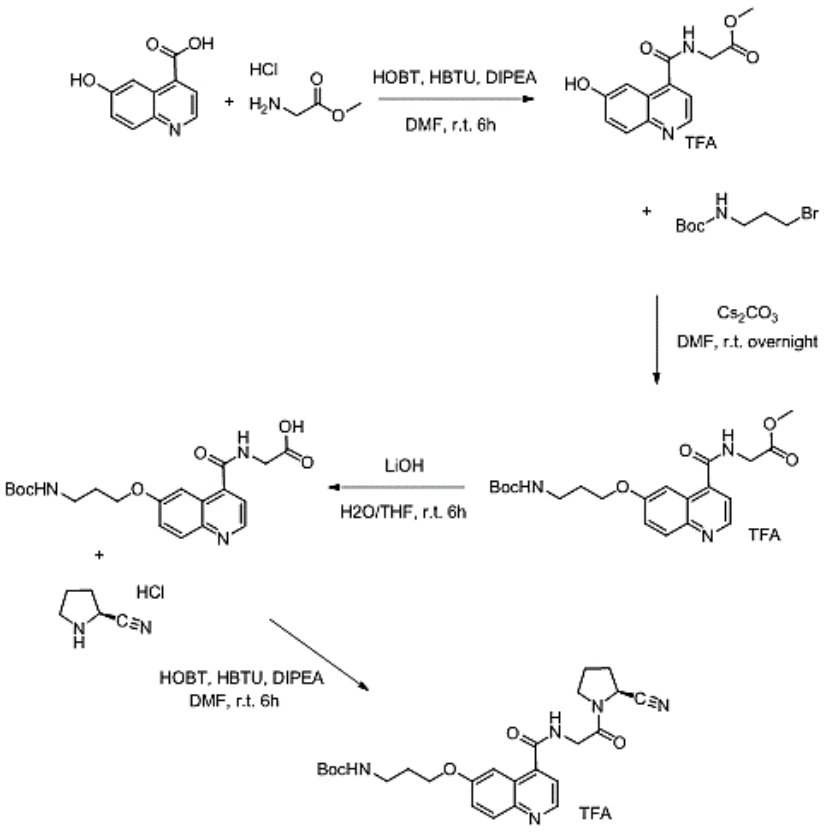

HCl
HOBT, HBTU, DIPEA
DMF, r.t. 6h
TFA
Boc
Br
Cs_2CO_3
DMF, r.t. overnight
LiOH
H2O/THF, r.t. 6h
BocHN
HCl
HOBT, HBTU, DIPEA
DMF, r.t. 6h
TFA

Fig. 1A

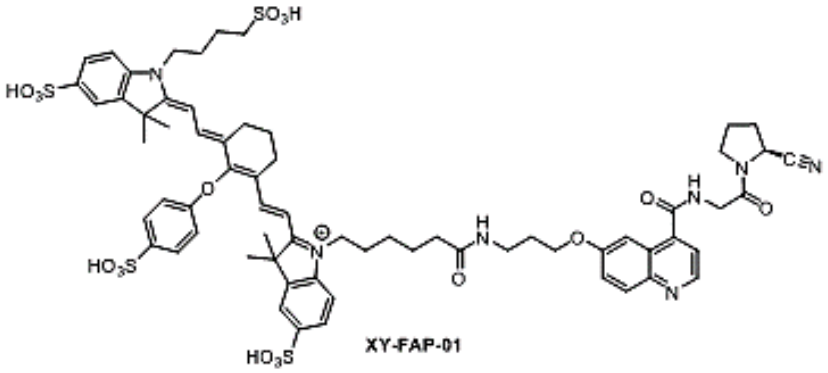


Fig. 1B

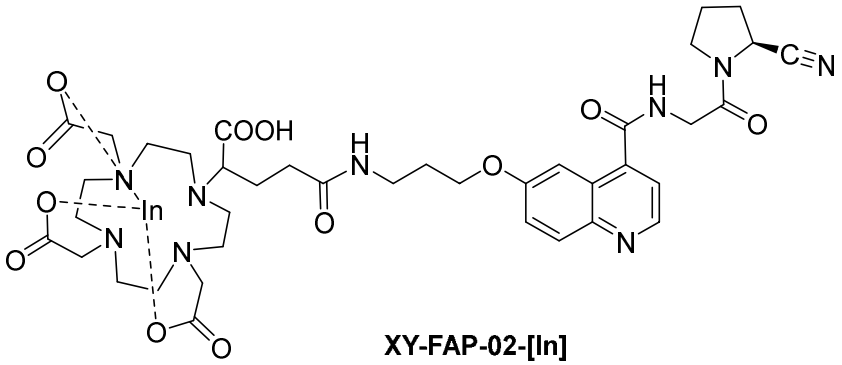


Fig. 1C

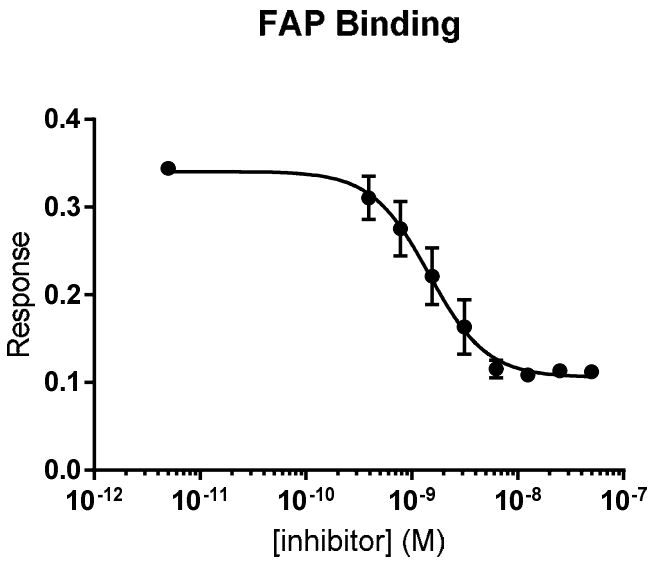

FAP Binding
Response
0.4
0.3
0.2
0.1
0.0
10-12
10-11
10-10
10-9
10-8
10-7
[inhibitor] (M)

Fig. 2

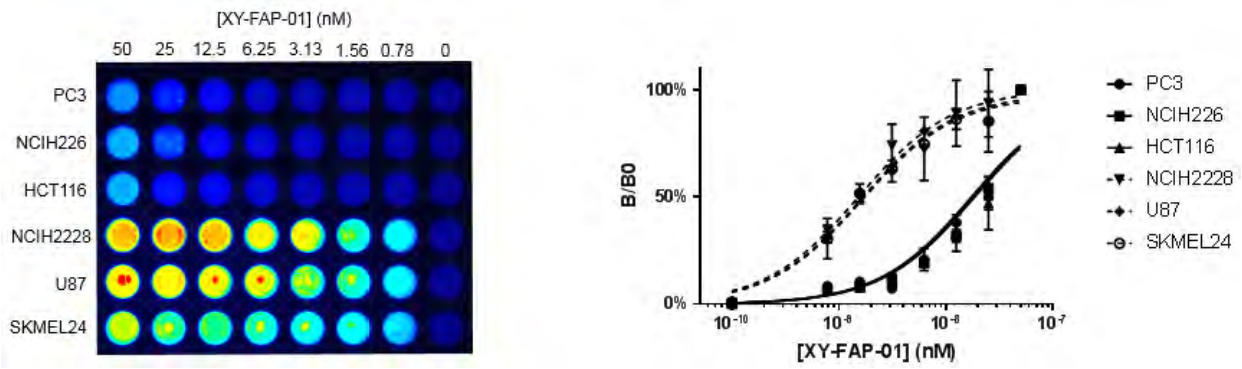


Fig. 3A

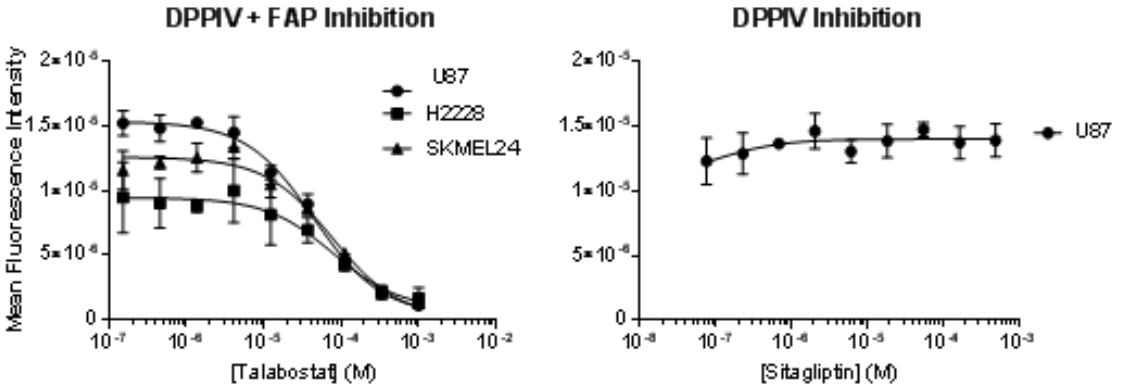


Fig. 3B

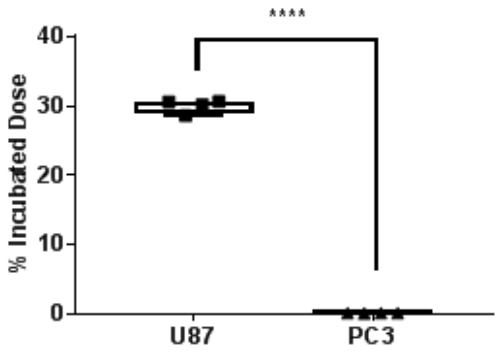


Fig. 3C

	5 min (n= 3)	0.5 h (n= 4)	2 h (n= 3)	6 hr (n= 4)	6 h - blocking (n=4)	12 h (n= 4)
blood	15.13 ± 0.62	10.64 ± 1.54	4.10 ± 0.39	2.01 ± 0.18	0.02 ± 0.001	0.42 ± 0.04
heart	6.68 ± 0.99	4.98 ± 0.71	2.61 ± 0.09	1.07 ± 0.09	0.02 ± 0.002	0.46 ± 0.04
lungs	6.99 ± 1.37	5.60 ± 0.89	2.59 ± 0.32	1.36 ± 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 ± 0.20	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	0.45 ± 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	1.16 ± 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
lrg. 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	2.96 ± 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	0.02 ± 0.005	0.60 ± 0.03
femur	4.76 ± 0.12	5.83 ± 0.72	4.95 ± 0.60	3.91 ± 0.70	0.08 ± 0.021	1.38 ± 0.20
U87	9.71 ± 0.24[a]	12.89 ± 1.45[a]	12.28 ± 1.95[a]	11.20 ± 1.03[a]	0.27 ± 0.019[c]	4.57 ± 0.54[b]
PC3	2.20 ± 0.20	3.10 ± 0.57	2.75 ± 0.11	3.40 ± 0.34	0.11 ± 0.024[c]	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 ± 0.36	18.07 ± 1.197	10.94 ± 0.93
U87:mm	3.25 ± 0.26	3.66 ± 0.44	4.38 ± 0.66	6.29 ± 0.82	11.81 ± 2.086	7.68 ± 0.97

Fig. 4

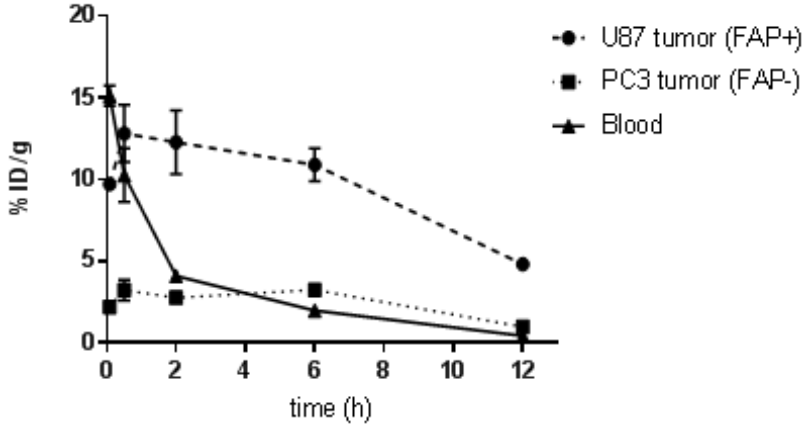

20
15
10
5
0
% ID/g
0
2
4
6
8
10
12
time (h)
U87 tumor (FAP+)
PC3 tumor (FAP-)
Blood

Fig. 5A

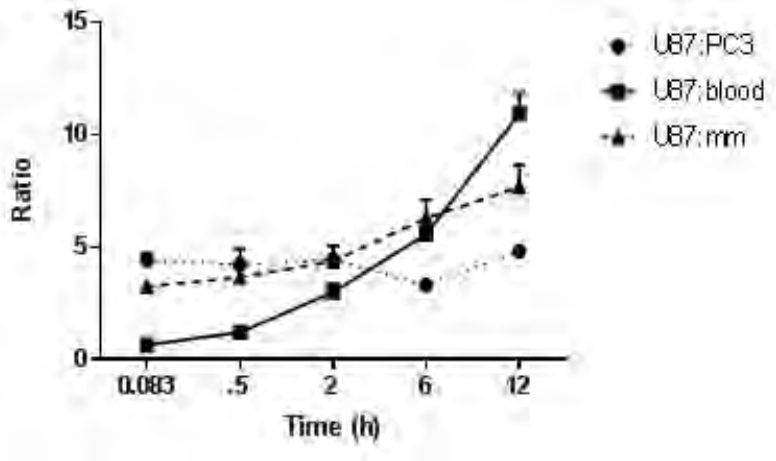

15
10
5
0
Ratio
0.083
.5
2
6
12
Time (h)
U87:PC3
U87:blood
U87:mm

Fig. 5B

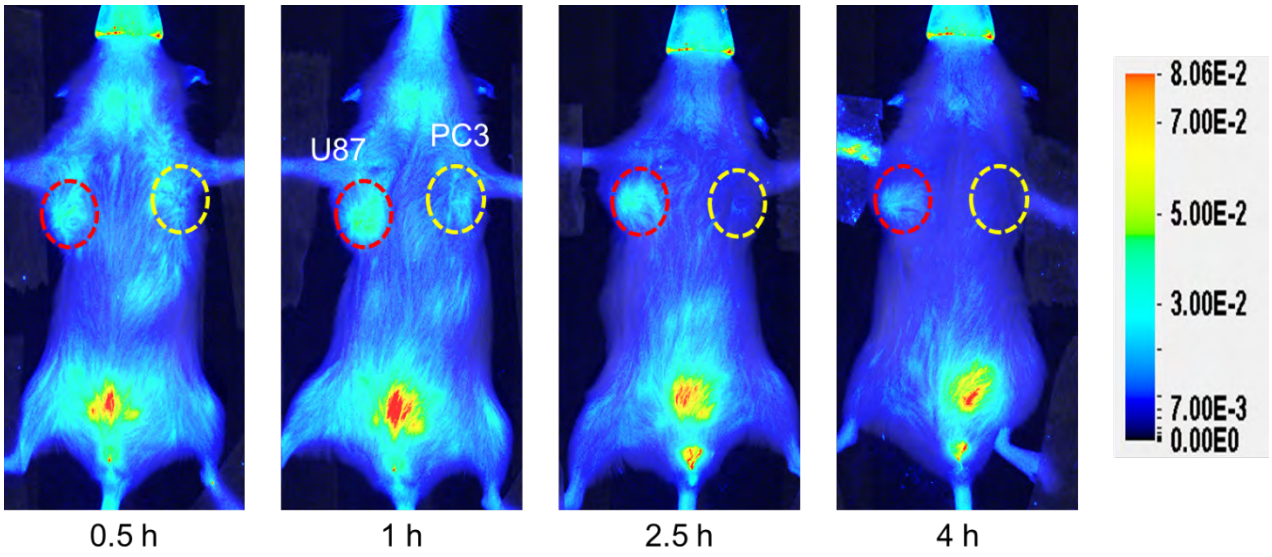


Fig. 6

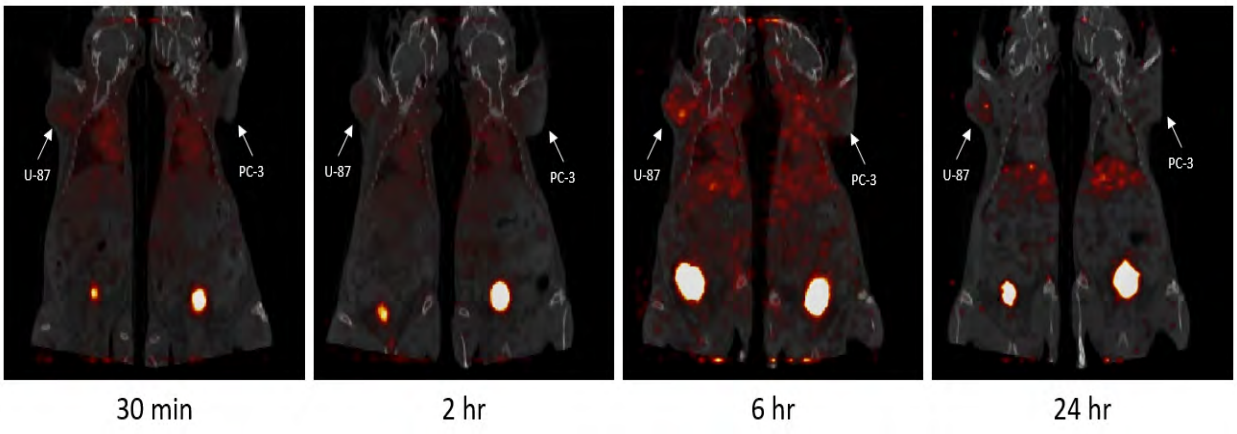


Fig. 7

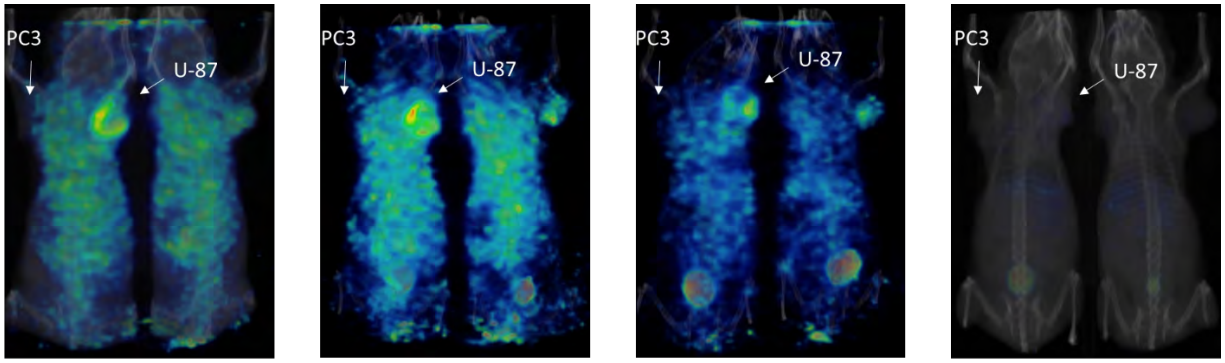


Fig. 8