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Application Number: 18585905

Document Date: 02/23/2024

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UTILITY PATENT APPLICATION TRANSMITTAL (Only for new nonprovisional applications under 37 CFR 1.53(b))	Attorney Docket No.	JHU-36631.304
	First Named Inventor	Xing Yang
	Title	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVA
	Priority Mail Express® Label No.	

APPLICATION ELEMENTS <i>See MPEP chapter 600 concerning utility patent application contents.</i>	ADDRESS TO: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
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1. ☐ Fee Transmittal Form (PTO/SB/17 or equivalent)	ACCOMPANYING APPLICATION PAPERS
2. ☒ Applicant asserts small entity status. See 37 CFR 1.27	
3. ☐ Applicant certifies micro entity status. See 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.	
4. ☒ Specification [Total Pages <u>77</u>] Both the claims and abstract must start on a new page. (See MPEP § 608.01(a) for information on the preferred arrangement)	
5. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets <u>9</u>]	
6. Inventor's Oath or Declaration [Total Pages <u>5</u>] (including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e)) a. ☐ Newly executed (original or copy) b. ☒ A copy from a prior application (37 CFR 1.63(d))	
7. ☒ Application Data Sheet * See note below. See 37 CFR 1.76 (PTO/AIA/14 or equivalent)	
8. CD-ROM or CD-R in duplicate, large table, or Computer Program (Appendix) ☐ Landscape Table on CD	
9. Nucleotide and/or Amino Acid Sequence Submission (if applicable, items a. – c. are required) a. ☐ Computer Readable Form (CRF) b. ☐ Specification Sequence Listing on: i. ☐ CD-ROM or CD-R (2 copies); or ii. ☐ Paper c. ☐ Statements verifying identity of above copies	
10. ☐ Assignment Papers (cover sheet & document(s)) Name of Assignee _____	
11. ☐ 37 CFR 3.73(c) Statement ☒ Power of Attorney (when there is an assignee)	
12. ☐ English Translation Document (if applicable)	
13. ☐ Information Disclosure Statement (PTO/SB/08 or PTO-1449) ☐ Copies of citations attached	
14. ☒ Preliminary Amendment	
15. ☐ Return Receipt Postcard (MPEP § 503) (Should be specifically itemized)	
16. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)	
17. ☐ Nonpublication Request Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.	
18. ☐ Other: _____ _____ _____ _____	

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

19. CORRESPONDENCE ADDRESS				
☒ The address associated with Customer Number: <u>101943</u> OR ☐ Correspondence address below				
Name				
Address				
City	State	Zip Code		
Country	Telephone	Email		

Signature	/Jeffrey W. Childers/	Date	February 23, 2024
Name (Print/Type)	Jeffrey W. Childers	Registration No. (Attorney/Agent)	58126

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 0651-0032. 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 UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.

Confirmation No.: TBD

Serial No.: TBD

Art Unit: TBD

Filed: herewith

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.

IN THE CLAIMS:

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

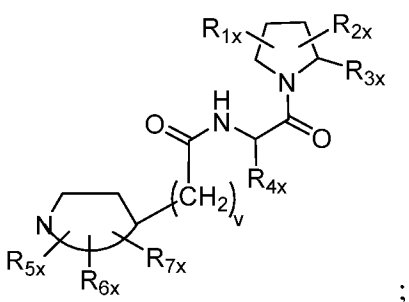
1-27. (Canceled)

28. (New) A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

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



wherein:

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

R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂, -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

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

v is 0; and



represents a quinolinyl ring having a point of attachment to a remainder of the FAP binding moiety at the 4-position of the 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.

29. (New) The compound of claim 28, wherein R_{1x} and R_{2x} are each independently selected from the group consisting of H and F.

30. (New) The compound of claim 29, wherein R_{3x} is -CN.

REMARKS

Original 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. New claims 28-30 have been added. Support for new claims 28-30 can be found in the claims and specification as originally filed. No new matter has been 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: February 23, 2024

/JEFFREY W. CHILDERS/
Jeffrey W. Childers, Ph.D.
Registration No. 58126
Customer No. 101943

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-36631.304
		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.)
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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 Residenceⁱ	US	
Mailing Address of Inventor:						
Address 1		c/o The Johns Hopkins University				
Address 2		3400 North Charles St.				
City	Baltimore	State/Province	MD			
Postal Code	21218	Countryⁱ	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 Residenceⁱ	US	
Mailing Address of Inventor:						
Address 1		c/o The Johns Hopkins University				
Address 2		3400 North Charles St.				
City	Baltimore	State/Province	MD			
Postal Code	21218	Countryⁱ	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						

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-36631.304
		Application Number	
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)		

City	Parkville	State/Province	MA	Country of Residence ⁱ	US
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Mailing Address of Inventor:

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

Mailing Address of Inventor:

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

Mailing Address of Inventor:

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

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

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence information of this application.	

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.304
		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-36631.304	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		

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.304
		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	18354282	2023-07-18
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
18354282	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).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Remove	Access Code ⁱ (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.304
		Application Number	
Title of Invention	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-ALPHA (FAP-ALPHA)		

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

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.	
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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.304
		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.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	JHU-36631.304
		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	
☐ 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. ☒			
Organization Name	The Johns Hopkins University		
Mailing Address Information For Applicant:			
Address 1	3400 North Charles St.		
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.

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-36631.304
		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 ⁱ			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)	2024-02-23
First Name	Jeffrey W.	Last Name	Childers	Registration Number	58126
Additional Signature may be generated within this form by selecting the Add button.					

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-36631.304
		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 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 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.

Doc Code: ECOMM.AUTH/ECOMM.WTDW

Doc Description: Internet Communications Authorization/Internet Communications Authorization Withdrawal

PTO/SB/439 (11-15)

**AUTHORIZATION FOR INTERNET
COMMUNICATIONS IN A PATENT
APPLICATION OR REQUEST TO
WITHDRAW AUTHORIZATION FOR
INTERNET COMMUNICATIONS**

Application No.	TBD
Filing Date	herewith
First Named Inventor	Xing Yang
Art Unit	TBD
Examiner Name	TBD
Practitioner Docket No.	JHU-36631.304

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

February 23, 2024

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.

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

First Named Inventor:	Xing Yang	Nonprovisional Application 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), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.
2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.
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 oath or declaration under 37 CFR 1.63 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).

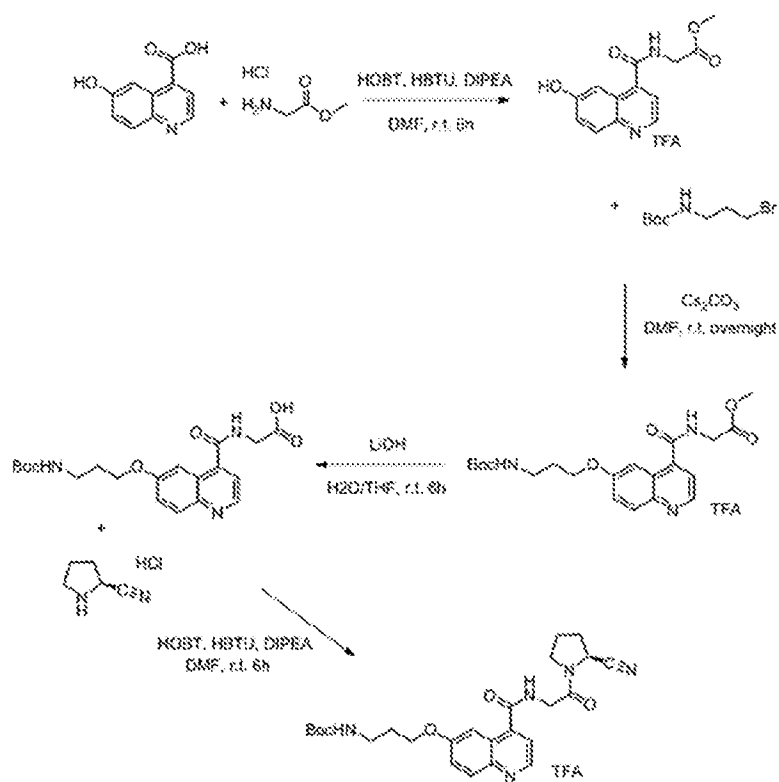
Signature	/Jeffrey W. Childers/	Date	February 23, 2024
Name (Print/Typed)	Jeffrey W. Childers	Practitioner Registration Number	58126
Note: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please 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 <u>1</u> forms are submitted.			

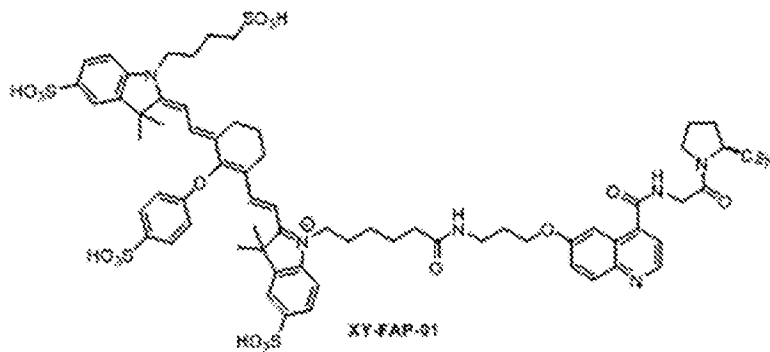
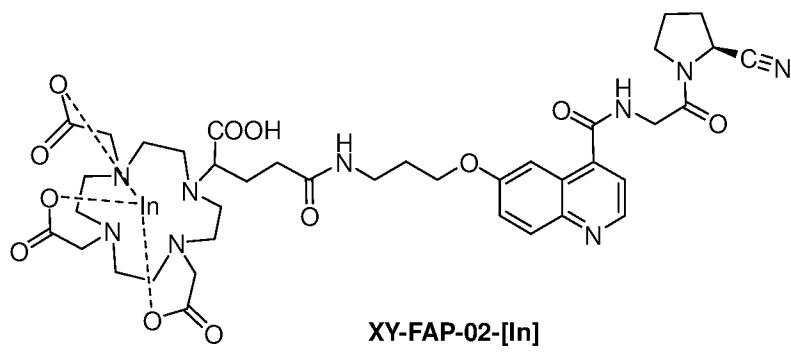
Privacy Act Statement

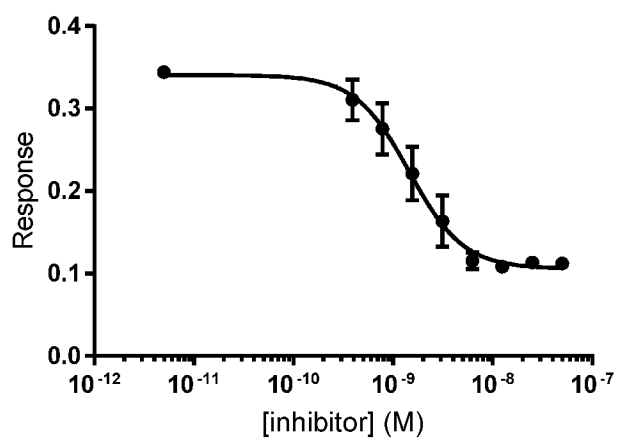
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**Fig. 1A**

**Fig. 1B****Fig. 1C**

FAP Binding***Fig. 2***

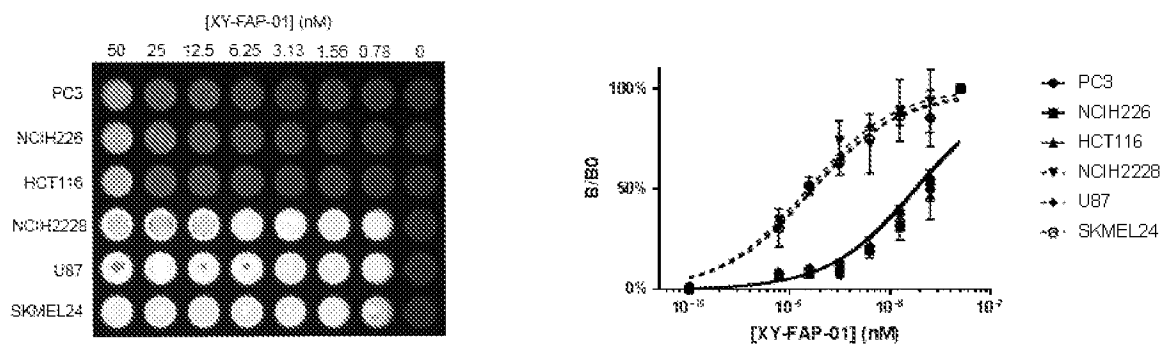


Fig. 3A

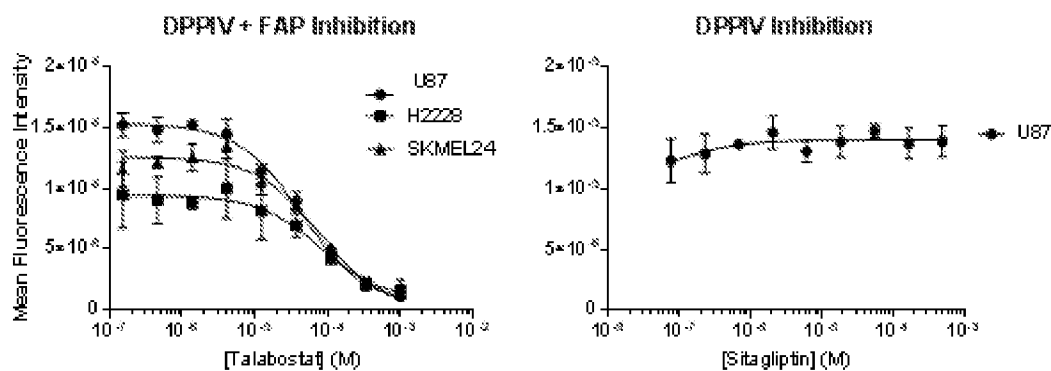


Fig. 3B

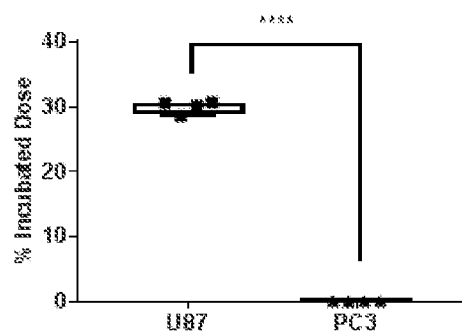


Fig. 3C

	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	6.88 ± 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	4.80 ± 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	0.46 ± 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	1.68 ± 0.22	0.09 ± 0.052	0.76 ± 0.14
lg. 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 ± 6.46	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	1.78 ± 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 ^b
PC3	2.20 ± 0.20	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 ± 0.26
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 ± 2.096	7.68 ± 0.97

Fig. 4

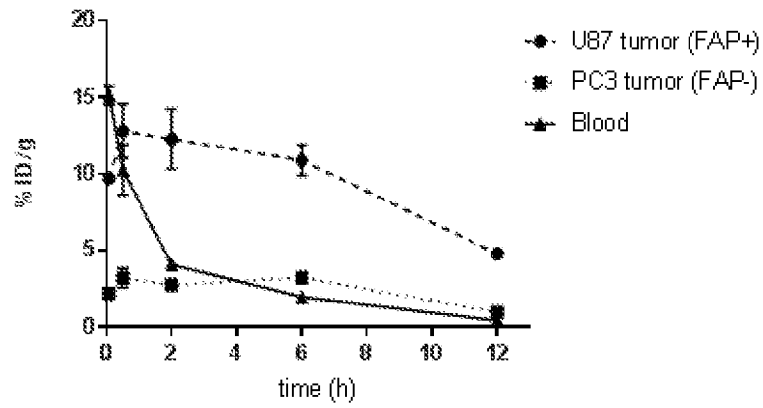


Fig. 5A

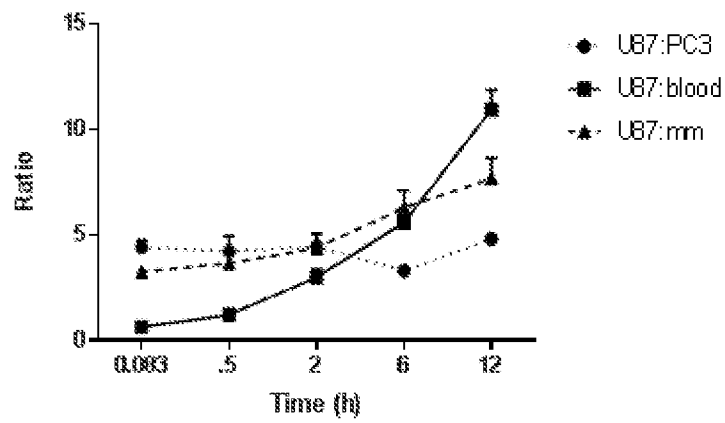


Fig. 5B

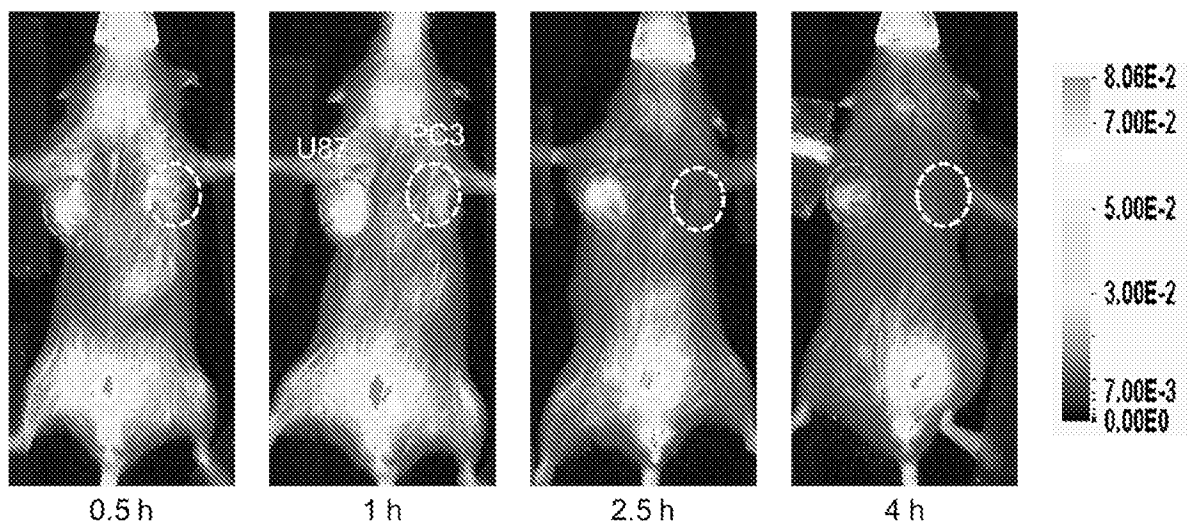


Fig. 6

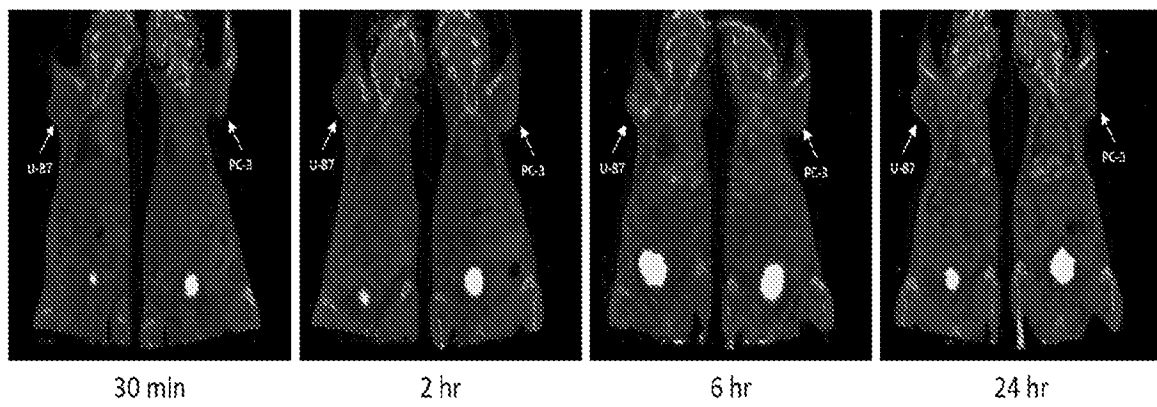


Fig. 7

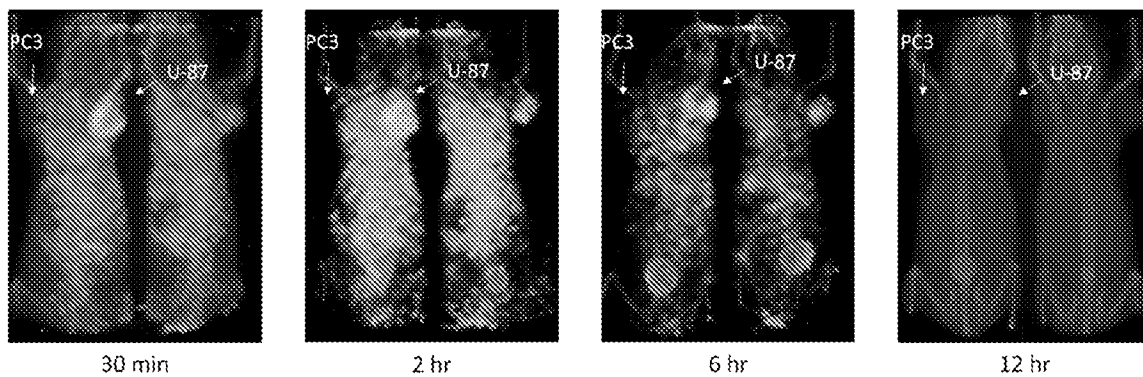


Fig. 8



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PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
02/23/2024 04:06:49 PM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 #	7296	FILED BY	Van Nguyen
PATENT CENTER #	64428723	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	-
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD CARD / 0638	PAYMENT TRANSACTION ID E20242MG08076277	PAYMENT AUTHORIZED BY Van Nguyen
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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.

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

Name

Title

Steven Kousouris

Executive Director, Johns Hopkins Technology Ventures, The Johns Hopkins University

Date (Optional)

5/8/2020

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.

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PATENT AND TRADEMARK OFFICE

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
02/23/2024 04:06:49 PM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 #	7296	FILED BY	Van Nguyen
PATENT CENTER #	64428723	FILING DATE	-
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 12

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-02- 23_36631.304_Preliminary Amendment.pdf	4	-	35 KB
2024-02- 23_36631.304_Preliminary Amendment-A.PE.pdf	(1-1) 1	Preliminary Amendment	15 KB
2024-02- 23_36631.304_Preliminary Amendment-CLM.pdf	(2-3) 2	Claims	25 KB
2024-02- 23_36631.304_Preliminary Amendment-REM.pdf	(4-4) 1	Applicant Arguments/Remarks Made in an Amendment	11 KB
2024-02-23 - JHU-36631.304	10	Application Data Sheet	245 KB

- ADS.pdf

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2024-02-23 - JHU-36631.304 - Auth for Internet Comm.pdf	2	Internet Communications Authorization	165 KB
2024-02-23 - JHU-36631.304 Transmittal of an Application .pdf	2	Transmittal of New Application	353 KB
2024-02-23 - JHU-36631.304 - Track 1 Request.pdf	2	Track One Request	160 KB
2023-07- 18_36631.303_EXEC_POA. pdf	1	Power of Attorney	842 KB
2024-02-23 - JHU-36631.304 - Figures.pdf	9	Drawings-only black and white line drawings	1283 KB
2023-07- 18_36631.303_ExecDecls_Al l.pdf	7	Oath or Declaration filed	3575 KB
2024-02-23 - JHU-36631.304 Application -APP.TEXT.docx	77	Application body structured text document	1274 KB
Warning: All artifacts (SmartArt, Drawings, Charts, etc) have been replaced with images. Bookmarks were found and have been removed. The abstract should be in narrative form and generally limited to a single paragraph preferably within the range of 50 to 150 words in length. See MPEP 608.01(b). Paragraph numbering is missing from the specification. Please review the specification and revise if necessary.			
2024-02-23 - JHU-36631.304 Application .pdf	77	Auxiliary PDF of Application	772 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-02- 23_36631.304_Preliminary Amendment.pdf	2DA705B392A7309517CA4C32C7AF9DB9B9A03736F6C3B8813 2B3BD393D17DA1F0E901CFBA53711B5E1BDAC1DDB25062F BA757EC607C3F951558783234640F155
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2024-02- 23_36631.304_Preliminary	2D2CA4511C8827BD64E919D57A9BBE07F529A7B6DE1E303B 9EDD14C0B05D252FC7B0AD90949334A9C366653EBC507D6E

Amendment-CLM.pdf	19CB7BD778FFB8306908F7489FC83782
2024-02-23_36631.304_Preliminary Amendment-REM.pdf	99F115794AA9D9CFF97975F2F86C200D6AF1153AE4092720765B63E69C3FEBD92610A26BA011D7E6718064C96AD90CFB4EA4DFF2CE9DE72125ED6C1BBA4118F7
2024-02-23 - JHU-36631.304 - ADS.pdf	063AF26EC22C356C4F5F7D806E896E2277B914B406B9BDDF40285BF9496CE06526BC7E375A8767DA8173240D855B5BCC39C4DEC9B629D8F78B533316833EC1E8
2024-02-23 - JHU-36631.304 - Auth for Internet Comm.pdf	FA48DCCF7640007966999E5334E4CBC4D715B786B6C07E93413A121DA56158B2AE7FE745DA204FBA87893DBFEB93388F761108168E65B377B7E66C76DF9B25A0
2024-02-23 - JHU-36631.304 Transmittal of an Application .pdf	D5FBFF1A20B1473C151B7E196584646F57080CFF98B02A826C42FF93665D7343F51E425810CF891FD9FE309B40C56DED4556A4CE2F639794D19AF5B77FB6EA611
2024-02-23 - JHU-36631.304 - Track 1 Request.pdf	89B38290A08BCCF85D0A9BDC0CD5D05A65BCCAF80FF066EEABD68063D20B9AF237BA34717FEF38C795C824AE35A7437844675030038B8B076C4B9D4D0FFC753D
2023-07-18_36631.303_EXEC_POA.pdf	64099E8B5B3623CDBC0D19368EFF9BB05C127C22F1473147C0CE0990CFD37787BA6DBEACE2EE4C94B44F97EE9C26F48AA3071A3A956F26924039FFBA17C730E
2024-02-23 - JHU-36631.304 - Figures.pdf	EEC9FACDF6290380DAA3BAF9F512913BEA72BBABC7E628CFF0588B57F78AA6643D46AF9037B8F8FC55572E3B7001F52FB00654D64701577EFBFACC24944F55AE
2023-07-18_36631.303_ExecDecls_All.pdf	71F5B35CDBE683B4AAF18EE60711C44AB1FFEE464AE7D04A153526EF437860995F7B8629133EF2EBF0DFFDD3E69FE18034EA1CCE79E6F8D92C2FFE263DB9401E
2024-02-23 - JHU-36631.304 Application -APP.TEXT.docx	CADC09C4D338BFAD0DA1330E24445B6E60213BC19091AE73FA677FA1975CCBC6BEB872D99F2F6D5E742EE40C6333A7C2678598C6FA9993E73466A49E2A8D461C
2024-02-23 - JHU-36631.304 Application .pdf	5DB93C779A26E58279A19992E6DCB4D89AE0B413AFAA62513C6FEF40D0EF2C3CCB34AD8AA23896244E2524DB33015EFE035CB1D0F88B26FA1CFEE09475EA8120

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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

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

New International Application Filed with the USPTO as a Receiving Office

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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.

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 <u>16/758,182</u> filed on <u>22-Apr-2020</u> The above-identified application was made or authorized to be made by me. I believe that I am the original inventor or an original joint inventor of a claimed invention in the application. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both. WARNING: 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: <u>Xing Yang</u> Date (Optional): <u>06/24/2020</u> Signature: <u>Xing Yang</u> Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.	

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**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
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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:

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LEGAL NAME OF INVENTOR

Inventor: Sridhar Nimmagadda

Date (Optional) _____

Signature: N. Sridhar

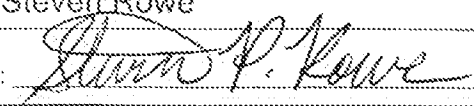
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**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
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LEGAL NAME OF INVENTOR Inventor: <u>Steven Rowe</u> Date (Optional): <u>9-25-2020</u> Signature: 	
Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.	

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As the below named inventor, I hereby declare that:

This declaration
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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.

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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.

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

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

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

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As the below named inventor, I hereby declare that:

This declaration
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United States application or PCT international application number 16/758,182

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

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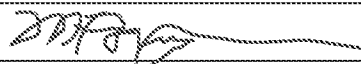
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LEGAL NAME OF INVENTOR

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.

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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 18/354,282, filed July 18, 2023, which is 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 .

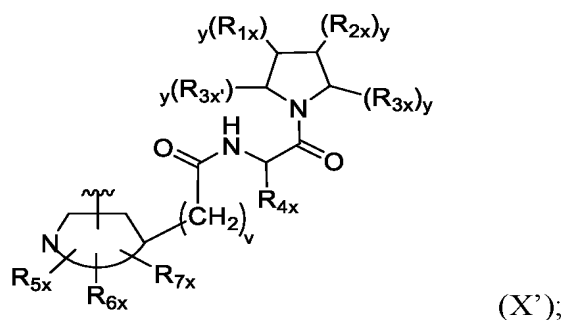
SUMMARY

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



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:



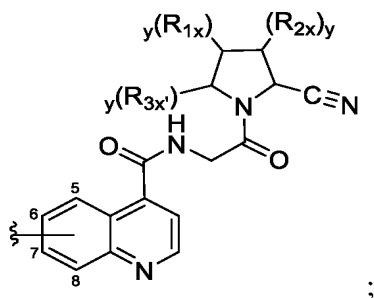
wherein each y is independently an integer selected from the group consisting of 0, 1, and 2; R_{1x} , R_{2x} , and $R_{3x'}$, are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl; R_{3x} is selected from the group consisting of H, $-CN$, $-B(OH)_2$, $-C(O)alkyl$, $-C(O)aryl$ -, $-C=C-C(O)aryl$, $-C=C-S(O)_2aryl$, $-CO_2H$, $-SO_3H$, $-SO_2NH_2$, $-PO_3H_2$, 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 -

Ar₂; each of C₁₋₆alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen; R_{8x}, R_{9x}, and R_{12x} are each independently selected from the group consisting of H, -OH, halo, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, and -Ar₃; R_{10x}, R_{11x}, R_{13x} and R_{14x} are each independently selected from the group consisting of H, -OH, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Ar₁, Ar₂ and Ar₃ are each independently a 5- or 6-membered aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; each of Ar₁, Ar₂ and Ar₃ being optionally and independently substituted with from 1 to 3 substituents selected from -NR_{10x}R_{11x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from -NR_{13x}R_{14x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl; v is 0, 1, 2, or 3; and



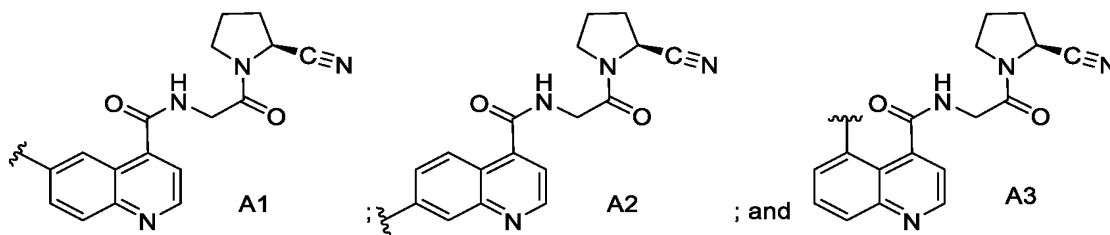
represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S; wherein $\frac{1}{2}$ — indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the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

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



wherein $\frac{1}{2}$ — indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable salts thereof.

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



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

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

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

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

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

Certain aspects of the presently disclosed subject matter having been stated hereinabove, which are addressed in whole or in part by the presently disclosed subject matter, other aspects will become evident as the description proceeds when

taken in connection with the accompanying Examples and Figures as best described herein below.

BRIEF DESCRIPTION OF THE FIGURES

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

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

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

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

FIG. 3A, FIG. 3B, and FIG. 3C show the assessment of the *in vitro* binding ability and specificity of **XY-FAP-01** and [¹¹¹In]-**XY-FAP-02**. FIG. 3A shows the concentration dependent uptake of **XY-FAP-01** in various cell lines. Cells incubated with various concentrations (range: 50 nM to 0.78 nM) of **XY-FAP-01** were imaged

with the LI-COR Pearl Impulse Imager to assess uptake of agent in various FAP-positive and FAP-negative cell lines (left). Dose-response curves of **XY-FAP-01** 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 [¹¹¹In]-**XY-FAP-02** in FAP-positive U87 and FAP-negative PC3 cell lines. Cells were incubated with 1 µCi [¹¹¹In]-**XY-FAP-02** and were washed with cold PBS. Radioactivity of the cell pellets was measured and normalized to the incubated dose;

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

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

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

FIG. 7 shows SPECT-CT images of [^{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 , $^{99\text{m}}\text{Tc}$, ^{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):

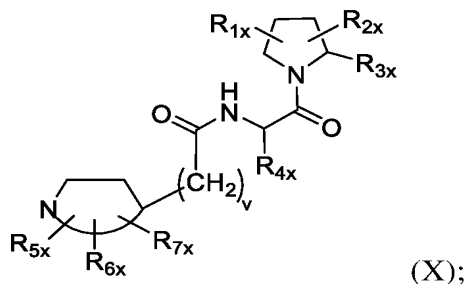


wherein: A is a targeting moiety for FAP- α ; B is any optical or radiolabeled functional group suitable for optical imaging, positron-emission tomography (PET) imaging, single-photon emission computed tomography (SPECT) imaging, or radiotherapy; and L is a linker having bi-functionalization adapted 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 incorporated by reference in their entirety.

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



wherein:

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

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

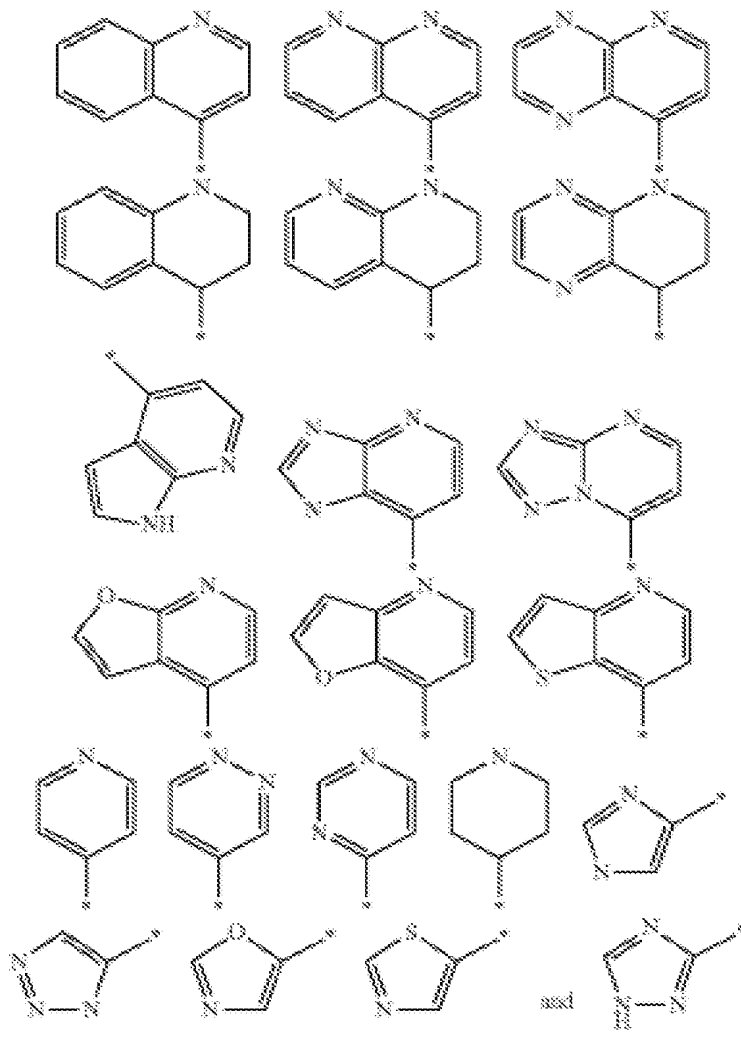
from 1 to 3 substituents selected from $-NR_{13x}R_{14x}$, $-C_{1-6}alkyl$, $-O-C_{1-6}alkyl$, and $-S-C_{1-6}alkyl$;

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



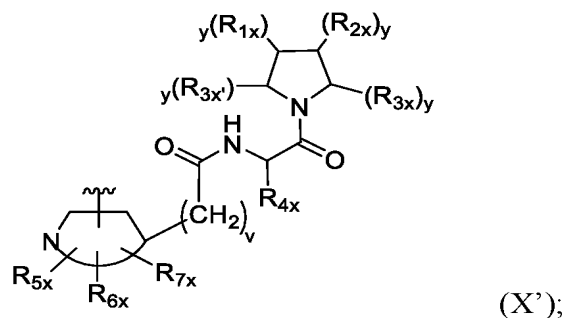
represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S.

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:



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

R_{1x} , R_{2x} , and $R_{3x'}$, are each independently selected from the group consisting of H, OH, halogen, C_{1-6} alkyl, $-O-C_{1-6}$ alkyl, and $-S-C_{1-6}$ alkyl;

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

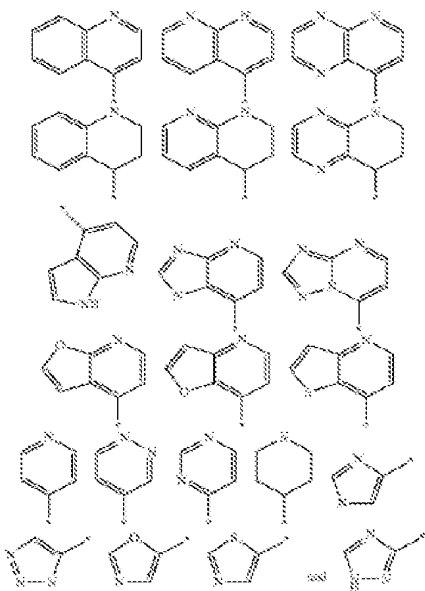
v is 0, 1, 2, or 3; and



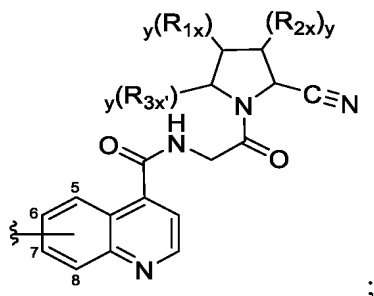
represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

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:



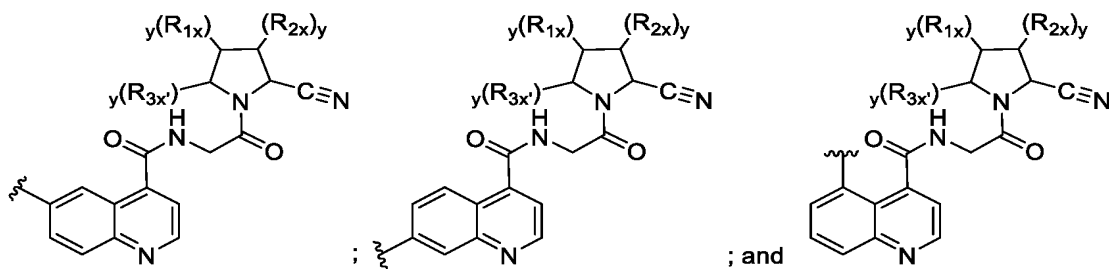
In some embodiments, A is an FAP- α targeting moiety having the structure of:



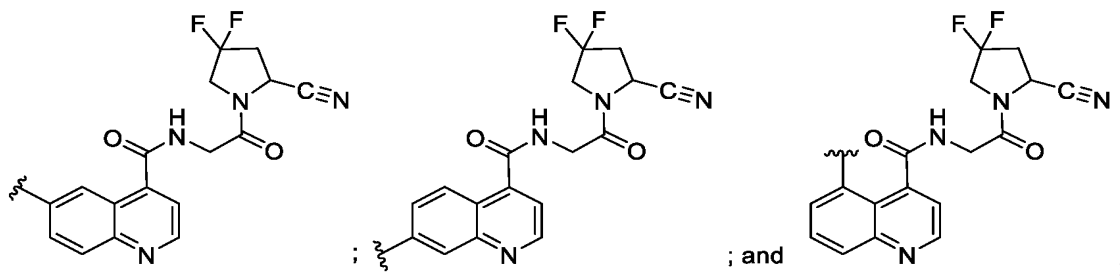
;

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

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

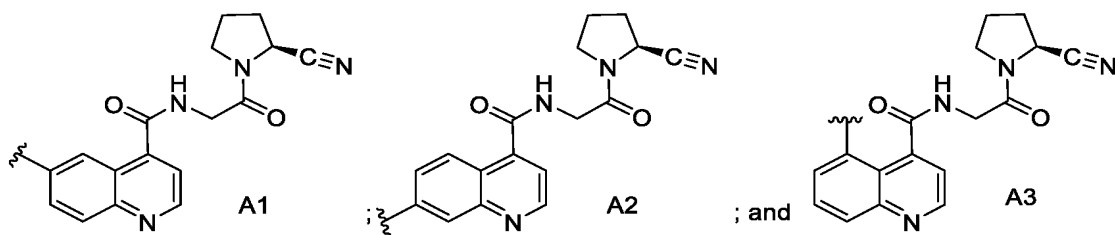


In more particular embodiments, A is selected from the group consisting of:

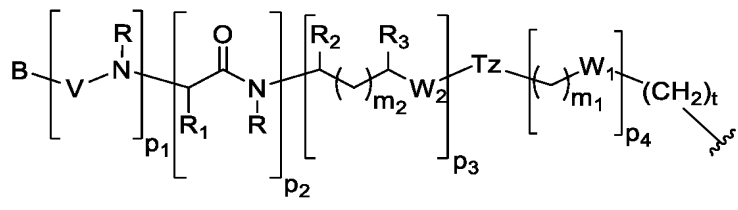


and stereoisomers thereof.

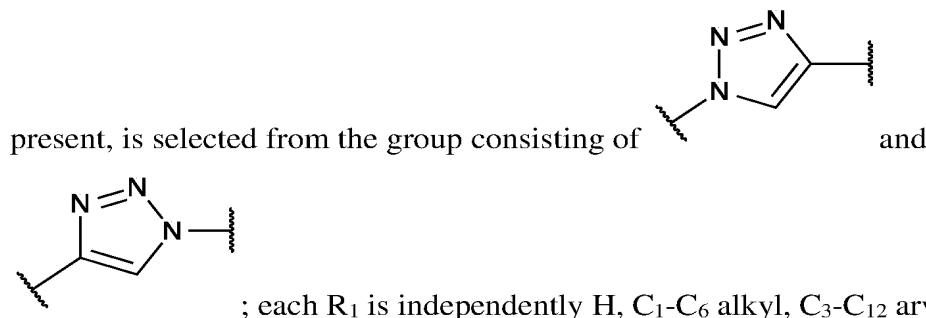
In yet more particular embodiments, A is selected from the group consisting of:



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

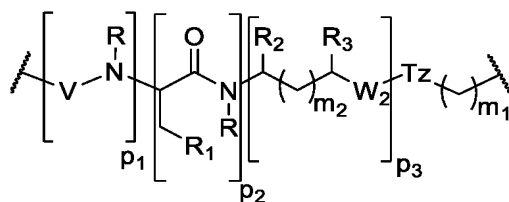


wherein the subunits associated with elements p_1 , p_2 , p_3 and p_4 may be in any order; t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; p_1 , p_3 , and p_4 are each independently 0 or 1; p_2 is an integer selected from the group consisting of 0, 1, 2, and 3, and when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



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 $-\text{NR}-(\text{CH}_2)_q-[\text{O}-\text{CH}_2-\text{CH}_2-\text{O}]_q-(\text{CH}_2)_q-\text{C}(=\text{O})-$;

L_2 is $-\text{NR}-(\text{CH}_2)_q-\text{C}(\text{COOR}_5)-\text{NR}-$; and

L_3 is $-(\text{O})\text{C}-(\text{CH}_2)_q-\text{C}(=\text{O})-$;

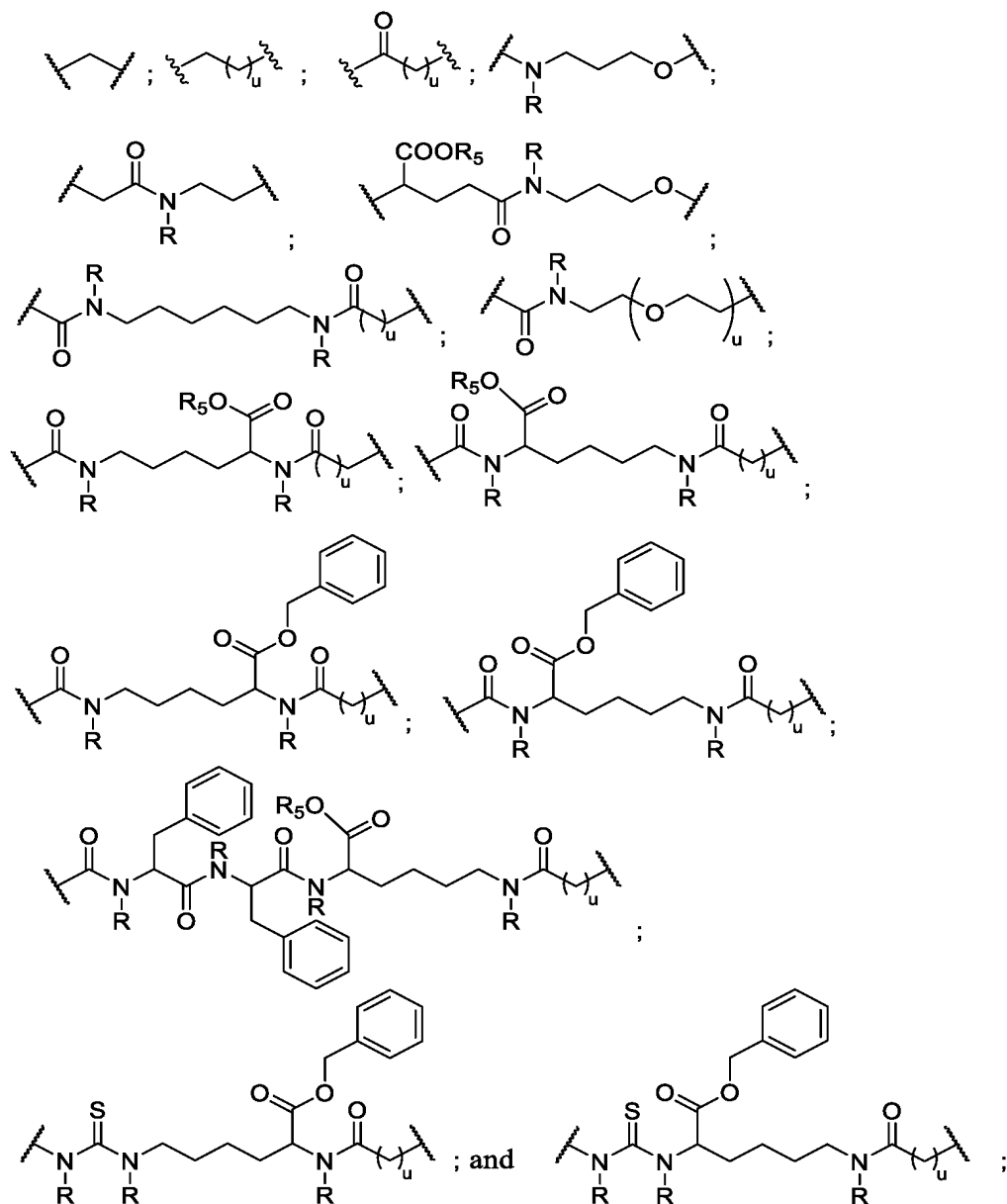
wherein each q is independently an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8; and R and R_5 are as defined hereinabove.

In particular embodiments, L is:

$-(\text{CR}_6\text{H})_q-(\text{CH}_2)_q-\text{C}(=\text{O})-\text{NR}-(\text{CH}_2)_q-\text{O}-$ or $-\text{NR}-(\text{CH}_2)_q-\text{O}-$;

wherein each q and R is defined hereinabove; and R_6 is H or $-\text{COOR}_5$.

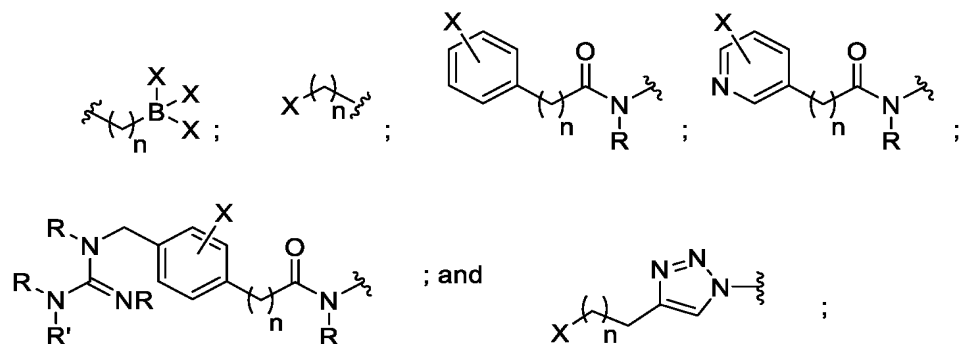
In yet more particular embodiments, L is selected from the group consisting of:



wherein u is an integer selected from 1, 2, 3, 4, 5, 6, 7, and 8; and R and R₅ are as defined hereinabove.

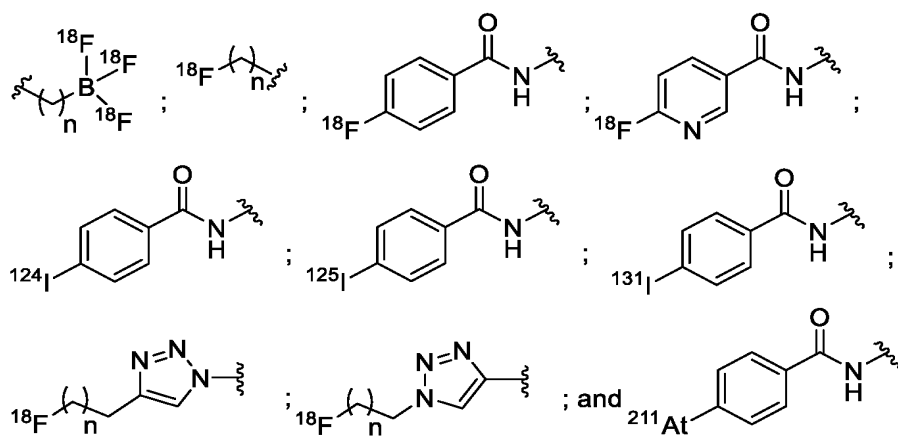
Suitable linkers are disclosed in U.S. Patent Application Publication No. US2011/0064657 A1, for "Labeled Inhibitors of Prostate Specific Membrane Antigen (PSMA), Biological Evaluation, and Use as Imaging Agents," published March 17, 2011, to Pomper et al., and U.S. Patent Application Publication No. 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:

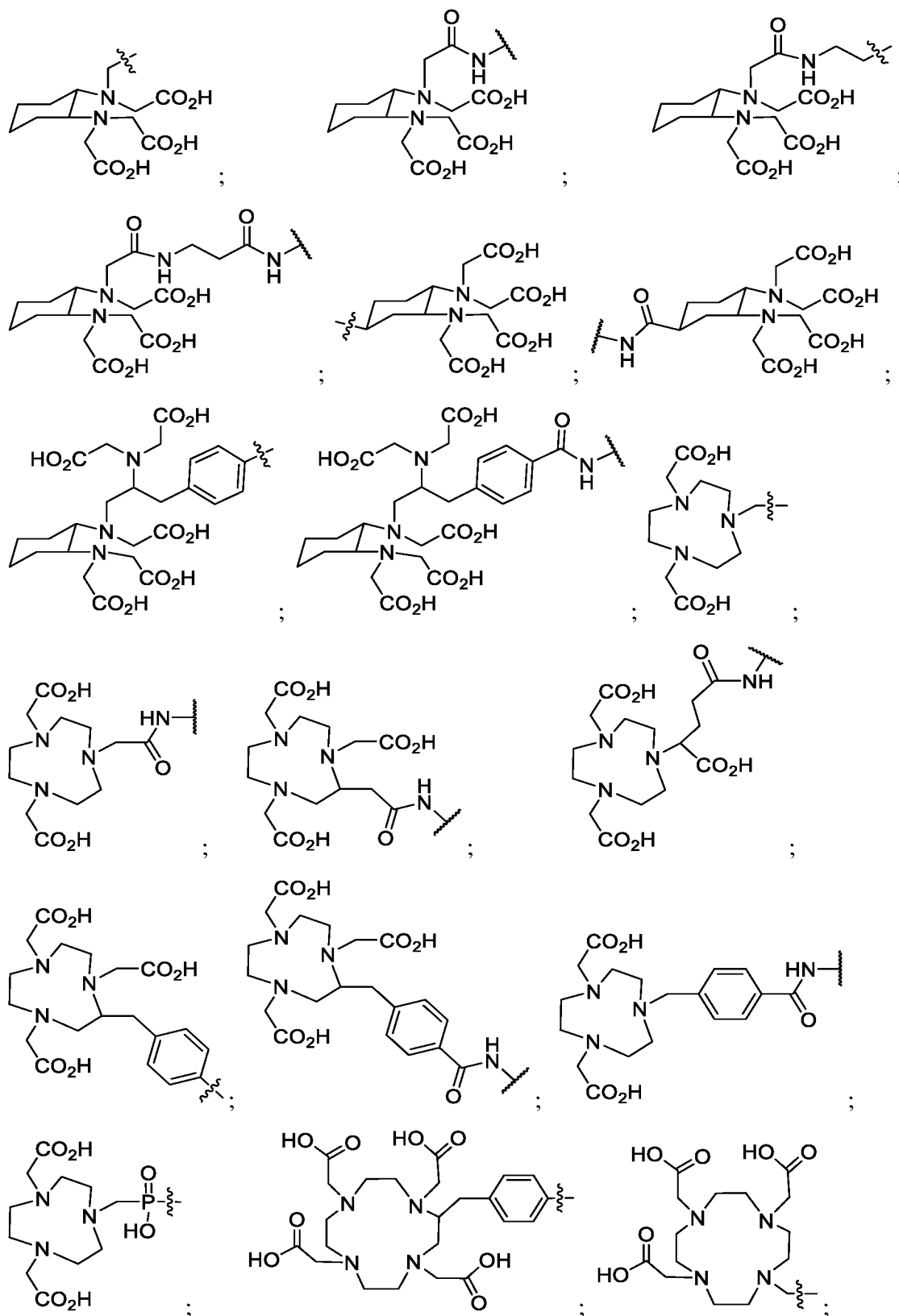


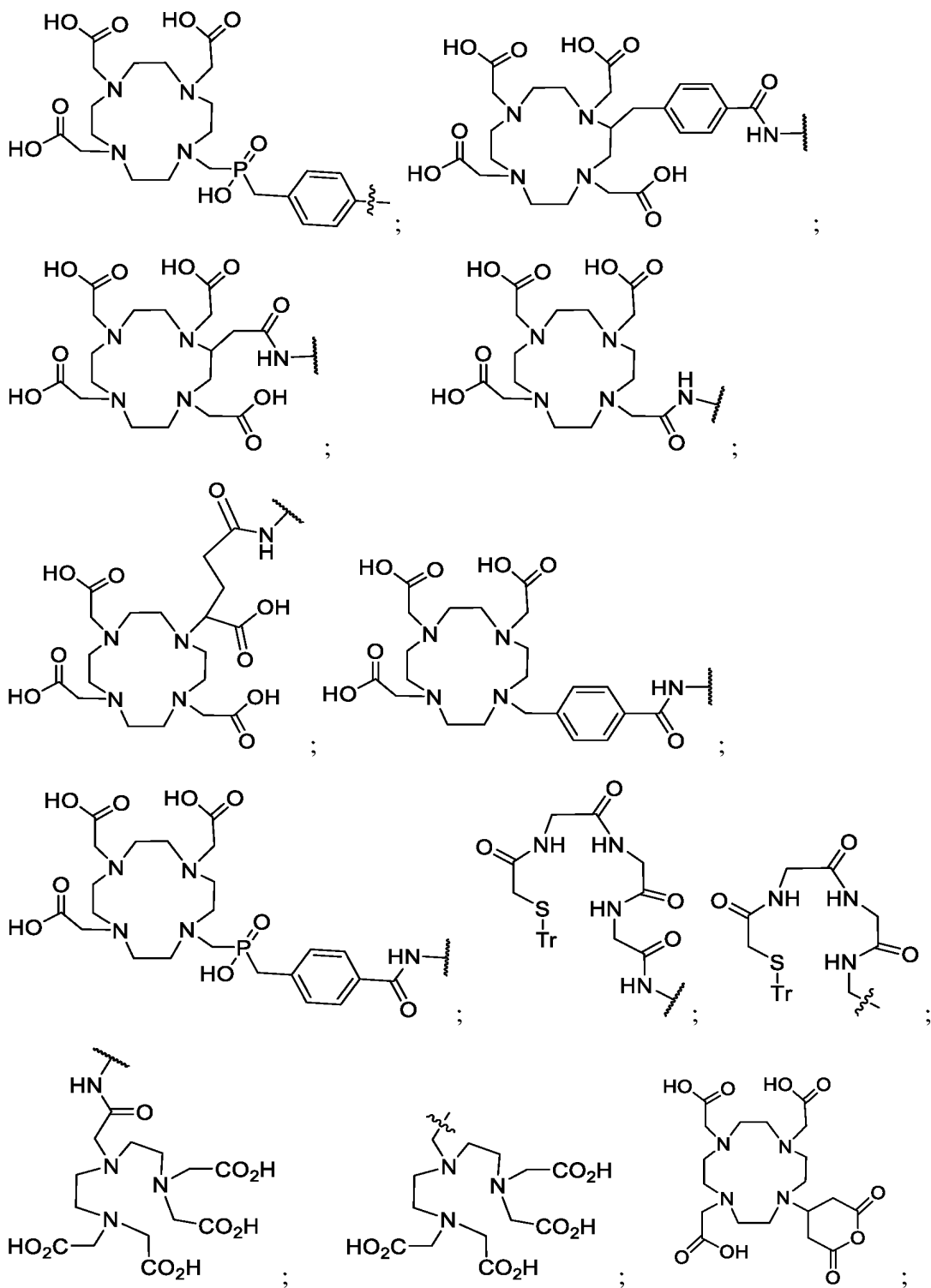
wherein each X is independently a radioisotope selected from the group consisting of ^{18}F , ^{124}I , ^{125}I , ^{131}I , and ^{211}At ; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,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

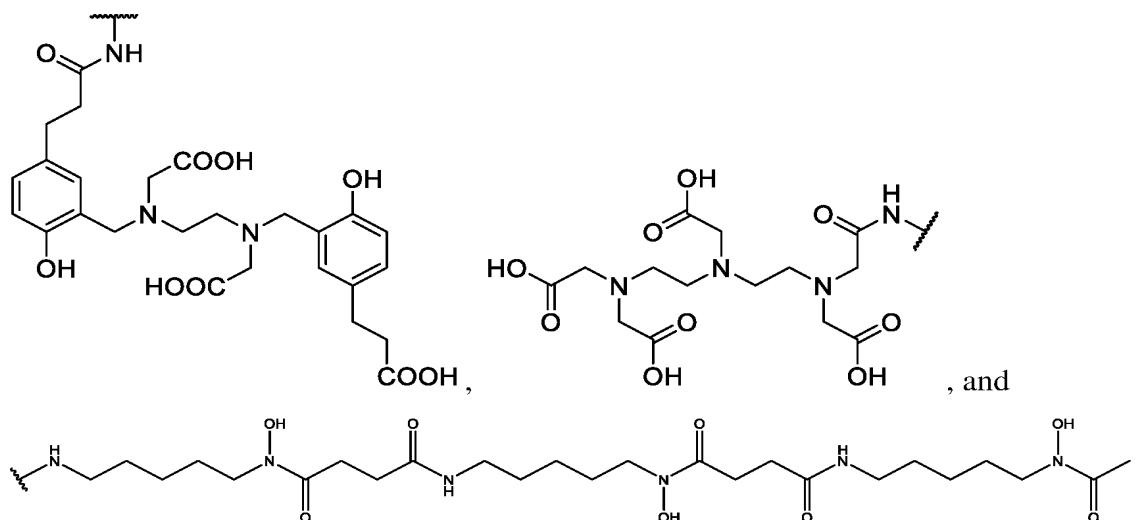
In more particular embodiments, the radiolabeled prosthetic group is selected from the group consisting of:



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

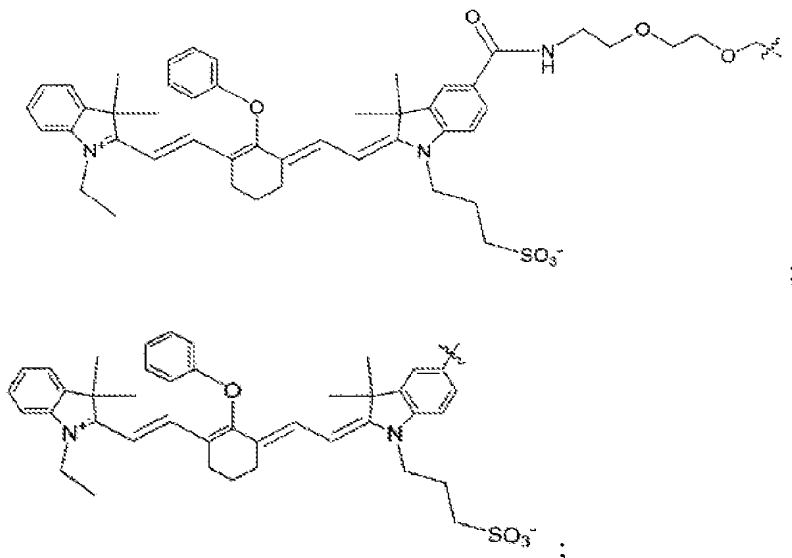


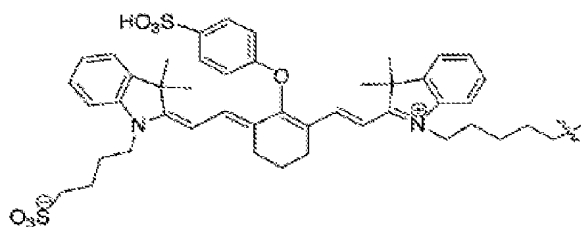




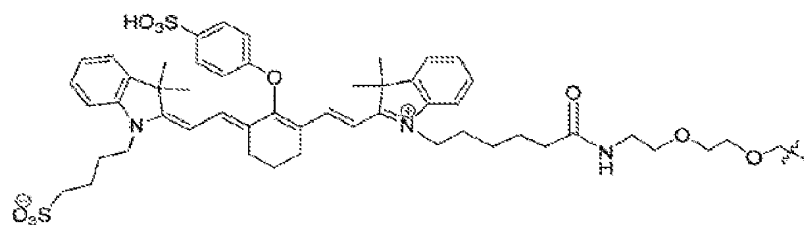
In some embodiments, B comprises an optical dye, e.g., in particular embodiments, a fluorescent dye. In some embodiments, the fluorescent dye moiety comprises carbocyanine, indocarbocyanine, oxacarbocyanine, thiocarbocyanine and merocyanine, polymethine, coumarine, rhodamine, xanthene, fluorescein, boron-dipyrromethane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

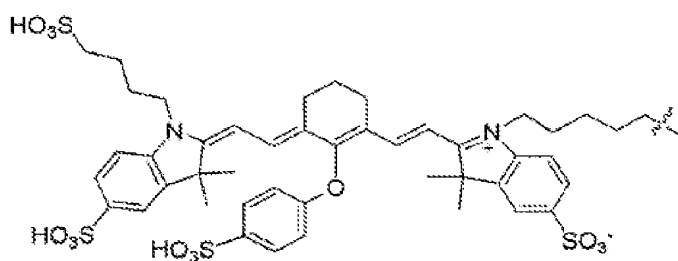




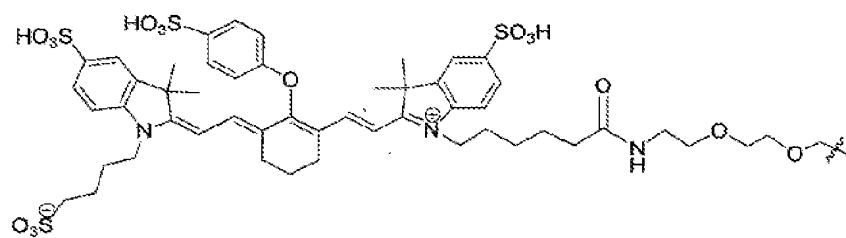
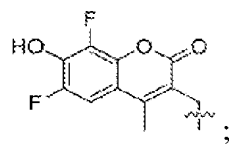
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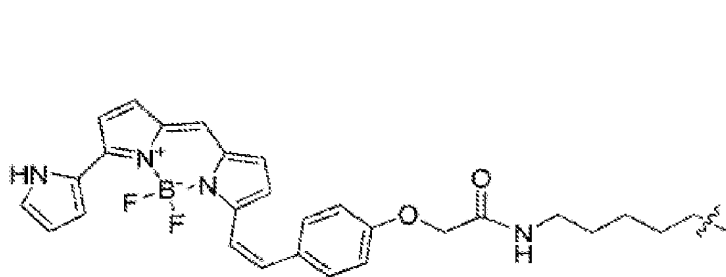
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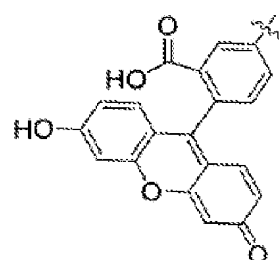
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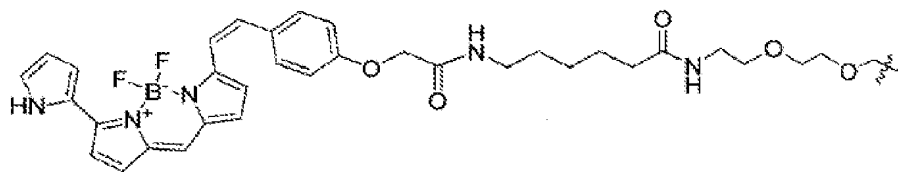
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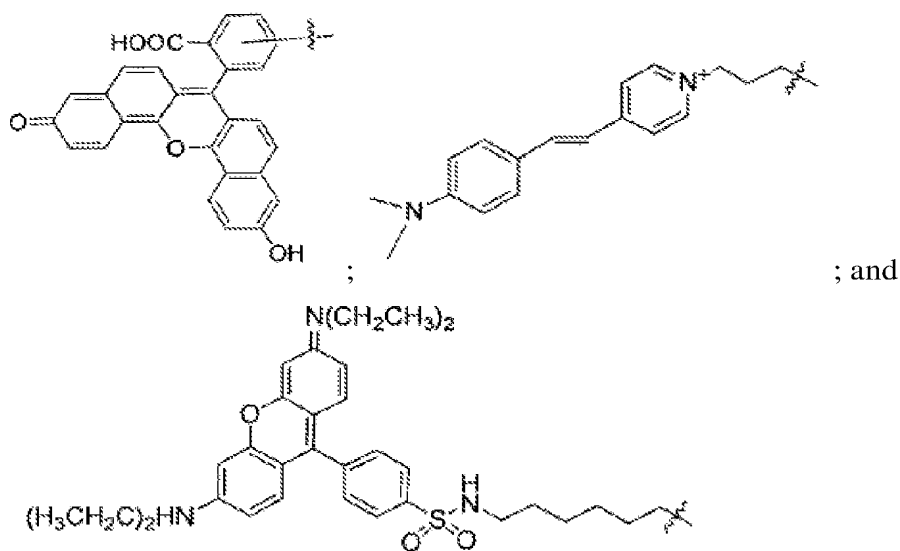
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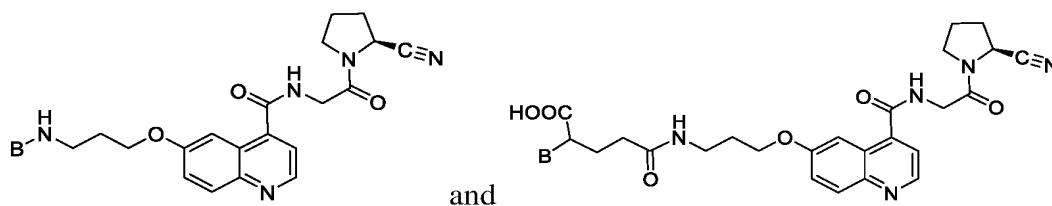
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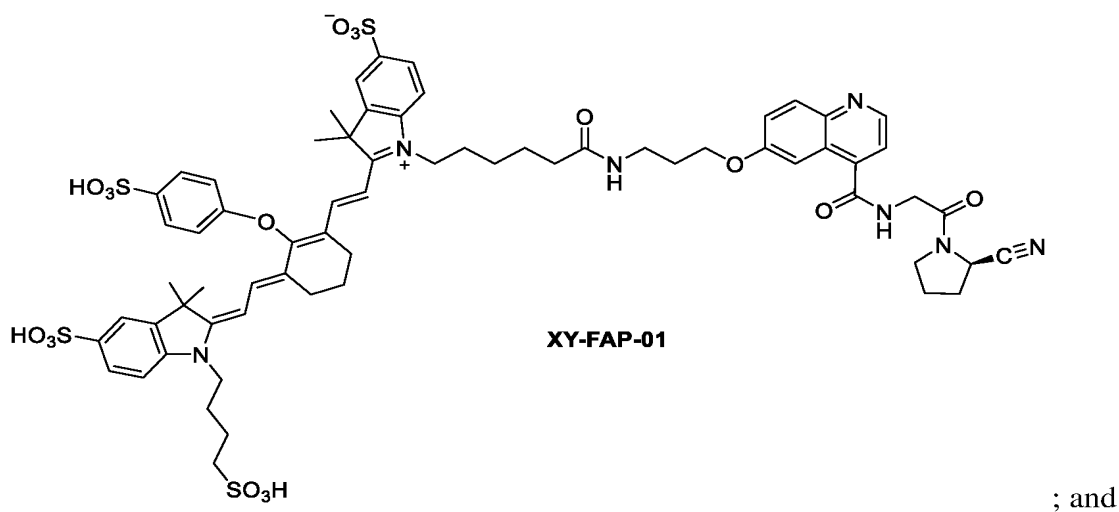
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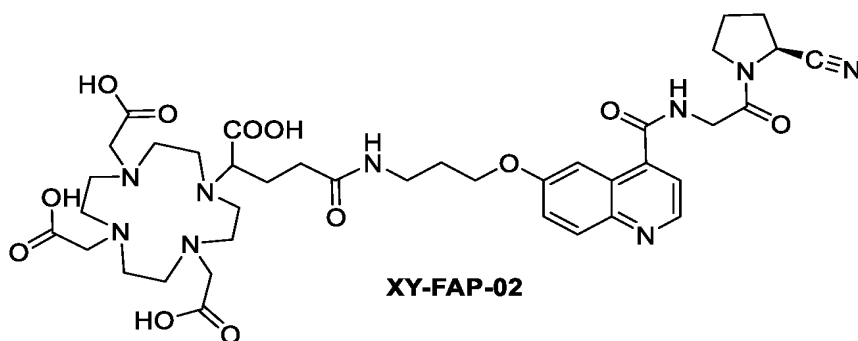


In some embodiments, the presently disclosed subject matter provides a compound selected from the group consisting of:



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





B. Pharmaceutical Compositions and Administration

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

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

When compounds of the present disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent or by ion exchange, whereby one acidic counterion (acid) in an ionic complex is substituted for another. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic,

benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, 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., $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$; $-\text{C}(=\text{O})\text{O}-$ is equivalent to $-\text{OC}(=\text{O})-$; $-\text{OC}(=\text{O})\text{NR}-$ is equivalent to $-\text{NRC}(=\text{O})\text{O}-$, 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., C₁-C₁₀ means one to ten carbons, including 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 carbons). In particular embodiments, the term “alkyl” refers to C₁₋₂₀ inclusive, including 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, and 20 carbons, linear (i.e., “straight-chain”), branched, or cyclic, saturated or at least partially and in some cases fully unsaturated (i.e., alkenyl and alkynyl) hydrocarbon radicals derived from a hydrocarbon moiety containing between one and twenty carbon atoms by removal of a single hydrogen atom.

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

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

Alkyl groups can optionally be substituted (a “substituted alkyl”) with one or more alkyl group substituents, which can be the same or different. The term “alkyl group substituent” includes but is not limited to alkyl, substituted alkyl, halo, alkylamino, arylamino, acyl, hydroxyl, aryloxy, alkoxy, alkylthio, arylthio, aralkyloxy, 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, alkoxy, 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, $-\text{CH}_2\text{-CH}_2\text{-O-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-NH-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N(CH}_3\text{)-CH}_3$, $-\text{CH}_2\text{-S-CH}_2\text{-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)}_2\text{-CH}_3$, $-\text{CH=CH-O-CH}_3$, $-\text{Si(CH}_3\text{)}_3$, $-\text{CH}_2\text{-CH=N-OCH}_3$, $-\text{CH=CH-N(CH}_3\text{)-CH}_3$, O-CH_3 , $-\text{O-CH}_2\text{-CH}_3$, and $-\text{CN}$. Up to two or three heteroatoms may be consecutive, such as, for example, $-\text{CH}_2\text{-NH-OCH}_3$ and $-\text{CH}_2\text{-O-Si(CH}_3\text{)}_3$.

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 $-\text{C(O)NR}'$, $-\text{NR}'\text{R}''$, $-\text{OR}'$, $-\text{SR}$, $-\text{S(O)R}$, and/or $-\text{S(O)}_2\text{R}'$. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as $-\text{NR}'\text{R}$ or the like, it will be understood that the terms heteroalkyl and $-\text{NR}'\text{R}$ 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 heterocyclic 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, imidazoliny, pyrazolidinyl, pyrazoliny, piperidyl, piperazinyl, indoliny, quinuclidinyl, morpholiny, thiomorpholiny, thiadiazinany, tetrahydrofurany, 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-morpholiny, 3-morpholiny, 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-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, 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 C₁₋₂₀ inclusive straight or branched hydrocarbon moiety having at least one carbon-carbon double bond by the removal of a single hydrogen molecule. Alkenyl groups include, for example, ethenyl (i.e., vinyl), propenyl, butenyl, 1-methyl-2-buten-1-yl, pentenyl, hexenyl, octenyl, allenyl, and butadienyl.

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

The term “alkynyl” as used herein refers to a monovalent group derived from a straight or branched C₁₋₂₀ hydrocarbon of a designed number of carbon atoms containing at least one carbon-carbon triple bond. Examples of “alkynyl” include ethynyl, 2-propynyl (propargyl), 1-propynyl, pentynyl, hexynyl, and heptynyl groups, and the like.

The term “alkylene” by itself or a part of another substituent refers to a straight or branched bivalent aliphatic hydrocarbon group derived from an alkyl group having from 1 to about 20 carbon atoms, e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 carbon atoms. The alkylene group can be straight, branched or cyclic. The alkylene group also can be optionally unsaturated and/or substituted with one or more “alkyl group substituents.” There can be optionally inserted along the alkylene group one or more oxygen, sulfur or substituted or unsubstituted nitrogen atoms (also referred to herein as “alkylaminoalkyl”), wherein the nitrogen substituent is alkyl as previously described. Exemplary alkylene groups include methylene (–CH₂–); ethylene (–CH₂–CH₂–); propylene (–(CH₂)₃–); cyclohexylene (–C₆H₁₀–); –CH=CH–CH=CH–; –CH=CH–CH₂–; –CH₂CH₂CH₂CH₂–, –CH₂CH=CHCH₂–, –CH₂CsCCH₂–, –CH₂CH₂CH(CH₂CH₂CH₃)CH₂–, –(CH₂)_q–N(R)–(CH₂)_r–, wherein each of q and r is independently an integer from 0 to about 20, e.g., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, and R is hydrogen or lower alkyl; methylenedioxy (–O–CH₂–O–); and ethylenedioxy (–O–(CH₂)₂–O–). An alkylene group can have about 2 to about 3 carbon atoms and can further have 6-20 carbons. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being some embodiments of the present disclosure. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

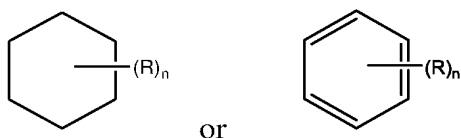
The term “heteroalkylene” by itself or as part of another substituent means a divalent group derived from heteroalkyl, as exemplified, but not limited by, –CH₂–CH₂–S–CH₂–CH₂– and –CH₂–S–CH₂–CH₂–NH–CH₂–. For heteroalkylene groups, heteroatoms also can occupy either or both of the chain termini (e.g.,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

The term “aryl” means, unless otherwise stated, an aromatic hydrocarbon substituent that can be a single ring or multiple rings (such as from 1 to 3 rings), which are fused together or linked covalently. The term “heteroaryl” refers to aryl groups (or rings) that contain from one to four heteroatoms (in each separate ring in the case of multiple rings) selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 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-quinoxalyl, 5-quinoxalyl, 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.

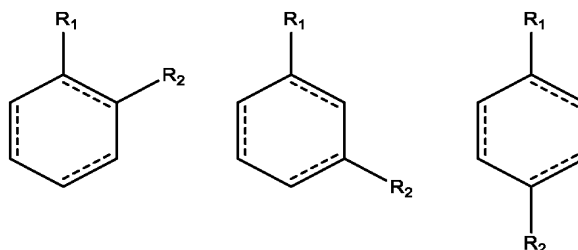
For brevity, the term “aryl” when used in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the terms “arylalkyl” and “heteroarylalkyl” are meant to include those groups in which an aryl or heteroaryl group is attached 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-(1-naphthyloxy)propyl, and the like). However, the term “haloaryl,” as used herein is meant to cover only aryls substituted with one or more halogens.

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

Further, a structure represented generally by the formula:



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



and the like.

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

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

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

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

Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent

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

Similar to the substituents described for alkyl groups above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, -OR', -NR'R'', -SR', -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -C(O)NR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)OR', -NR-C(NR'R'')=NR'', -NR-C(NR'R'')=NR'' -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxo, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R'', R''' and R'''' may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted 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 $-CRR'-$, $-O-$, $-NR-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-S(O)_2NR'-$ or a single bond, and r is an integer of from 1 to 4.

One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C''R'')_d-$, where s and d are independently integers of from 0 to 3, and X' is $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituents R, R', R'' and R''' may be independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

As used herein, the term “acyl” refers to an organic acid group wherein the $-OH$ of the carboxyl group has been replaced with another substituent and has the general formula $RC(=O)-$, wherein R is an alkyl, alkenyl, alkynyl, aryl, carbocyclic, 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 alkoxy 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.

“Alkoxy carbonyl” refers to an alkyl-O-C(=O)- group. Exemplary alkoxy carbonyl groups include methoxy carbonyl, ethoxy carbonyl, butyloxy carbonyl, and *tert*-butyloxy carbonyl.

“Aryloxy carbonyl” refers to an aryl-O-C(=O)- group. Exemplary aryloxy carbonyl groups include phenoxy- and naphthoxy-carbonyl.

“Aralkoxy carbonyl” refers to an aralkyl-O-C(=O)- group. An exemplary aralkoxy carbonyl group is benzyloxy carbonyl.

“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 $\text{-(CH}_2\text{)}_k$ 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($\text{C}_1\text{-C}_4$)alkyl” is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term “hydroxyl” refers to the –OH group.

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

The term “mercapto” refers to the –SH group.

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

The term “nitro” refers to the –NO₂ group.

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

The term “sulfate” refers to the –SO₄ group.

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

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

The term “sulfone” refers to compound having a sulfonyl group –S(O)₂R.

The term “sulfoxide” refers to a compound having a sulfinyl group –S(O)R

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

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

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

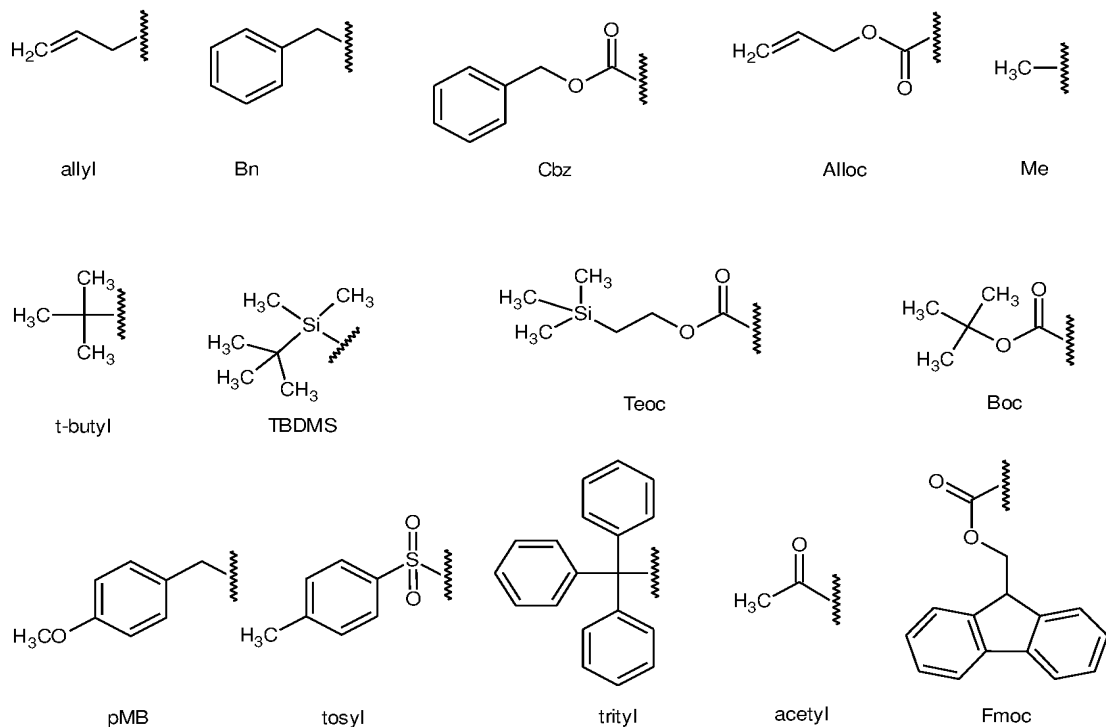
The term “protecting group” refers to chemical moieties that block some or all reactive moieties of a compound and prevent such moieties from participating in chemical reactions until the protective group is removed, for example, those moieties listed and described in T. W. Greene, P.G.M. Wuts, *Protective 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, $\pm 100\%$ in some embodiments $\pm 50\%$, in some embodiments $\pm 20\%$, in some embodiments $\pm 10\%$, in some embodiments $\pm 5\%$, in some embodiments $\pm 1\%$, in some embodiments $\pm 0.5\%$, and in some embodiments $\pm 0.1\%$ from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

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

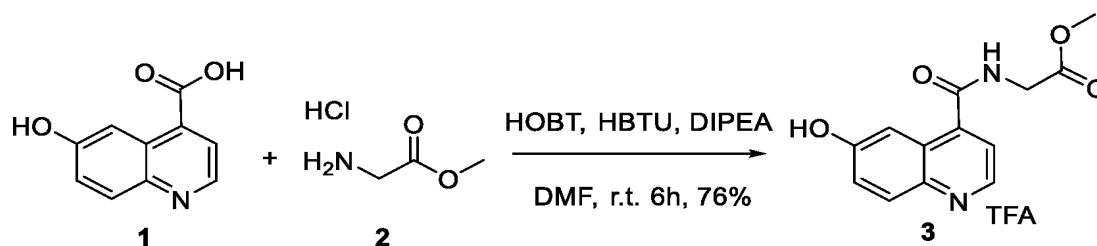
EXAMPLES

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

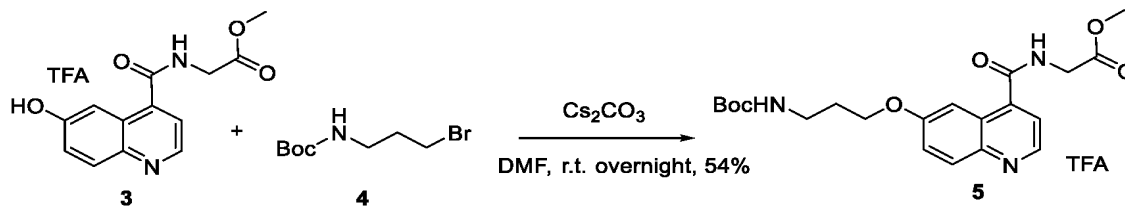
EXAMPLE 1

Experimental Procedures

1.1 Synthesis of XY-FAP-01.

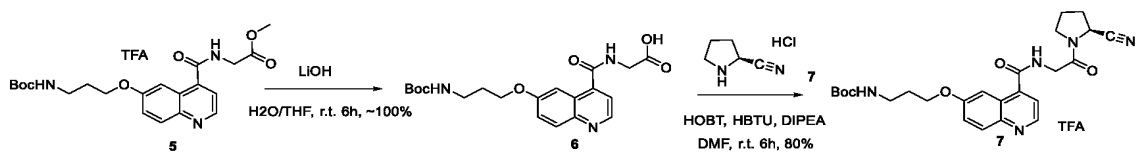


Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**): 6-Hydroxyquinoline-4-carboxylic acid (**1**) 210 mg (1.1 mmol), methyl glycinate HCl salt (**2**) 143 mg (1.1 mmol), HBTU 420 mg (1.1 mmol) and HOBt 170 mg (1.1 mmol) were dissolved in 12 mL dry DMF. To the solution, 0.77 mL of DIPEA (4.4 mmol) 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%. ¹H-NMR (400 MHz, CD₃OD): δ 8.69 (s, 1H), 7.94 (d, J = 7.92 Hz, 1H), 7.57–7.51 (m, 3H), 7.42–7.37 (m, 1H), 4.21 (s, 2H), 3.81 (s, 3H). ¹³C-NMR (100 MHz, CD₃OD): δ 172.4, 160.9, 145.1, 143.7, 129.7, 129.4, 128.3, 121.8, 119.6, 112.4, 109.1, 56.8, 44.8. MS: calculated for [C₁₃H₁₃N₂O₄]⁺, 261.3 [M + H]⁺; found 261.1.

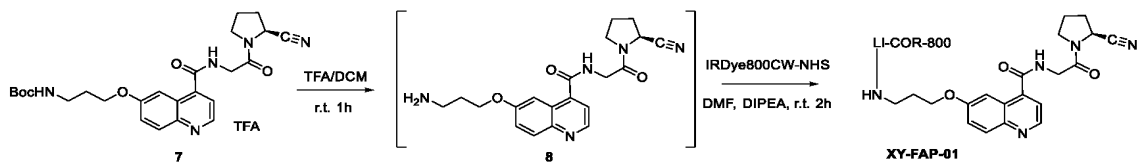


Methyl (6-(3-((tert-butoxycarbonyl)amino)propoxy)quinoline-4-carbonyl)glycinate (**5**): Methyl (6-hydroxyquinoline-4-carbonyl)glycinate (**3**) 360 mg (1.0 mmol), tert-butyl (3-bromopropyl)carbamate (**4**) 500 mg (2.1 mmol) were dissolved in 20 mL DMF. Cs₂CO₃ 1 g (3.0 mmol) was added to the solution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

128.4, 126.1, 124.7, 119.1, 103.7, 79.5, 60.4, 52.5, 41.4, 37.7, 29.3, 28.4. MS: calculated for $[C_{21}H_{28}N_3O_6]^+$, 418.5 $[M + H]^+$; found 418.3.



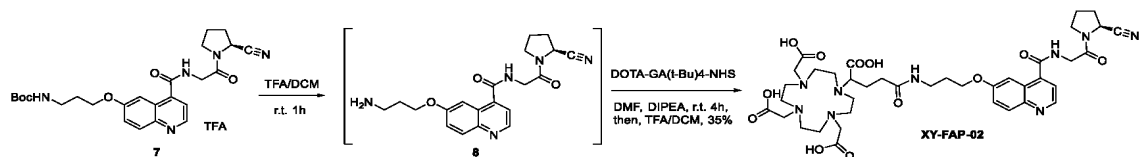
tert-Butyl(S)-3-((4-((2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamoyl)quinolin-6-yl)oxy)propyl)carbamate (**7**): Compound **5** 110 mg (0.21 mmol) and LiOH 30 mg (1.2 mmol) was stirred in 4 mL of H₂O/THF (1/1) for 6 hours. After most of the THF was removed under vacuum, the mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada) and eluted with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1) to remove the salts. The product **6** obtained was mixed with (S)-pyrrolidine-2-carbonitrile 53 mg (0.4 mmol), HOBT 68 mg (0.4 mmol), HBTU 152 mg (0.4 mmol) and DIPEA 0.56 mL (1.6 mmol) in dry 10 mL DMF. After 6 hours, the solvent was removed under vacuum and the remaining mixture was loaded onto a 25 g C18 cartridge (Silicycle, Canada). The product was purified with a MeCN/water/TFA gradient (0/100/0.1 to 90/10/0.1). 99 mg of **7** was obtained with a yield of 80%. ¹H NMR (400 MHz, CDCl₃): δ 8.73 (s, 1H), 7.95 (d, J = 10.2 Hz, 1H), 7.68 (br s, 1H), 7.63–7.56 (m, 1H), 7.56–7.48 (m, 1H), 7.38–7.29 (m, 1H), 5.27 (br s, 1H), 4.84–4.72 (m, 1H), 4.46–4.35 (m, 1H), 4.33–4.20 (m, 1H), 4.17–4.09 (m, 2H), 3.78–3.64 (m, 1H), 3.59–3.46 (m, 1H), 3.36 (s, 2H), 2.38–2.17 (m, 4H), 1.42 (s, 9H), 1.35–1.27 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 167.6, 167.5, 157.9, 156.2, 146.3, 130.2, 125.7, 123.7, 119.3, 118.0, 103.3, 79.0, 65.9, 46.8, 45.7, 42.2, 37.6, 29.8, 29.3, 28.4, 25.1. MS: calculated for $[C_{25}H_{32}N_5O_5]^+$, 482.6 $[M + H]^+$; found 482.3.



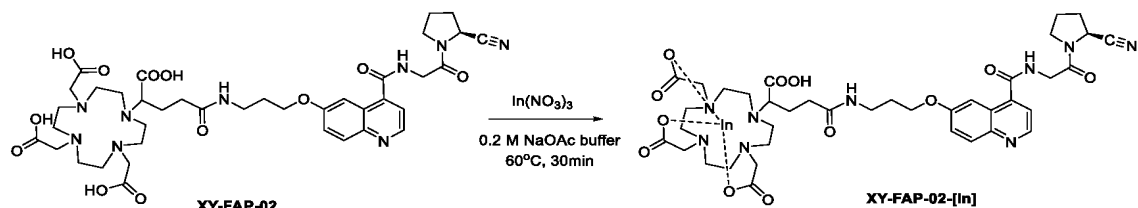
XY-FAP-01. Compound **7** (1 mg, 1.7 μmol) was treated with a 1 mL solution of TFA/methylene chloride (1/1) for 2 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMSO. To the solution, LICOR800CW-NHS ester 0.5 mg (0.43 μmol) and Et₃N 10 μL were added. After 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 μ m. Gradient 10/90/0.1 MeCN/H₂O/TFA to 80/20/0.1 MeCN/H₂O/TFA within 15 min at a flow of 3 mL/min. The product was eluted at 10.1 min. MS: Calculated for [C₆₆H₇₆N₇O₁₇S₄]⁺, 1366.4[M+H]⁺; found 1366.8.

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



2,2',2''-(10-(1-Carboxy-4-((3-((4-((2-((S)-2-cyanopyrrolidin-1-yl)-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 μ mol) was treated with a 1-mL solution of TFA/methylene chloride (1/1) for 1 h. The solvent was removed under vacuum, and the remaining material re-dissolved in 0.5 mL of DMF. To the solution, DIPEA (27 μ L, 156.5 μ mol) was added, followed by dropwise addition of a solution of DOTA-GA(t-Bu)₄-NHS (25 mg, 31.3 μ L) in 0.5 mL of DMF. The reaction mixture was stirred for 4 h at ambient temperature and then concentrated under vacuum. The t-Bu-protected intermediate was deprotected in situ without further purification using a 1 mL mixture of TFA, H₂O and triethylsilane (TES) (95:2.5:2.5). Reaction mixture was then concentrated and purified by semipreparative HPLC, to afford the product as a white solid (8.5 mg, 33% yield). MS: calculated for [C₃₉H₅₄N₉O₁₂]⁺, 840.9 [M + H]⁺; found 840.5. HPLC (10 mm x 250 mm Phenomenex Luna C18 column, 10 μ m, 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 μ mol) of **XY-FAP-02** in 1 mL of 0.2M AcONa, a solution of 1.4 mg (4.6 μ mol) of In(NO₃)₃ in 0.5 mL water is added and warmed in a 60 °C

bath for 30 min. After cooling to ambient temperature, the mixture was purified by semipreparative HPLC. The product was obtained as a white solid (1.8 mg, 79% yield). MS: calculated for $[C_{39}H_{51}N_9O_{12}In]^+$, 951.7 $[M + H]^+$; found 952.5. HPLC (10 mm x 250 mm Phenomenex Luna C18 column, 10 μ m, 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 μ m C₁₈ Luna 4.6 x 250 mm² column (Torrance, CA) with a flow rate of 0.6 mL/min with water (0.1% TFA) (A) and MeCN (0.1% TFA) (B) as the eluting solvents. An isocratic 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 N₂ (to a total volume of < 50 μ L). The resulting solution was formulated in saline for the imaging and biodistribution studies.

1.4 FAP Inhibition Assay. The inhibitory activity of **XY-FAP-01** was determined using a fluorogenic FAP Assay Kit (BPS Bioscience, San Diego, CA). Briefly, **XY-FAP-01**, DPP substrate, and human recombinant FAP were loaded into a 96 well plate to initiate the enzyme reaction. The reaction was left for 10 minutes at room temperature before fluorescence was measured with a VICTOR3 V multilabel plate reader (PerkinElmer Inc., Waltham, MA). Data was normalized and semi-log inhibition curves were generated in order to determine the IC₅₀ value (concentration of **XY-FAP-01** where the enzyme activity is 50% inhibited) for **XY-FAP-01** and subsequent enzyme inhibition 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 (CO₂) in a humidified incubator.

1.6 Cellular Uptake Studies. All cellular uptake and specific binding studies were performed in triplicate to ensure reproducibility. Cells were detached using 0.05% trypsin (Corning), resuspended in 1 million cell aliquots in binding buffer, and incubated with various concentrations (range, 50 nM to 0.78 nM) of **XY-FAP-01** for 1 hour at 37 °C and 5% CO₂. To assess the specific uptake of **XY-FAP-02**, cells were preblocked with a FAP and DPP-IV specific inhibitor (Val-boroPro, MilliporeSigma, Burlington, MA) or a DPP-IV specific inhibitor (Sitagliptin, Santa Cruz Biotechnology, Inc., Dallas, TX) at various concentrations (range, 10⁻¹⁰ M to 10⁻⁴ M) prior to incubation with 25 nM **XY-FAP-02** solution in binding buffer for 1 hour at 37 °C and 5% CO₂. Cellular uptake was terminated by washing cells with ice cold PBS (1x) three times. Cells were resuspended in binding buffer and transferred to a

96-well plate for imaging. Images were acquired on the LI-COR Pearl Impulse Imager (Lincoln, NE) using an excitation wavelength of 785 nm and detection of the emission wavelength at 800 nm. Images were analyzed using the LI-COR Pearl Impulse Software (Version 2.0) and fluorescence intensity was corrected for background signal and normalized to well area.

Cellular Uptake of ¹¹¹In-XY-FAP-02 was also assessed in cells. Cell aliquots (1 million) were incubated with 1 µCi ¹¹¹In-XY-FAP-02 in saline for 30 minutes at 37 °C and 5% CO₂. Cells were washed three times with cold PBS (1x) and activity of the cell pellets was measured with the 1282 CompuGamma CS gamma well counter (Pharmacia/LKB Nuclear, Inc., Gaithersburg, MD). The percent uptake of the 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% isoflurane (v/v) and maintained at 1.5% isoflurane for the imaging procedure. NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts were injected with 10 nmol of XY-FAP-01 via tail vein injection and images were acquired at 30 min, 1 h, 2 h, 2.5 h, and 4 h after injection of tracer. Data were displayed and analyzed using the LI-COR Pearl Impulse Software (Version 2.0).

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

1.9 Ex-vivo Biodistribution. NOD/SKID mice bearing FAP+ U-87-MG and FAP- PC-3 tumor xenografts were injected with 10 µCi ¹¹¹In-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 CO₂ asphyxiation and blood was immediately collected by cardiac puncture. Additionally, the heart, lungs, liver, stomach, pancreas, spleen, fat, kidney, small intestine, large intestine, bladder, muscle, femur, FAP+ U-87-MG xenograft, and FAP- PC-3 xenograft were collected for biodistribution analysis. Each tissue was weighed and radioactivity was measuring using a 2480 Wizard² automated gamma counter (PerkinElmer, Waltham, MA). Radioactivity measurements were corrected for decay and compared with samples of a standard dilution of the initial dose to calculated percent injected dose per gram (%ID/g).

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

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

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

EXAMPLE 2

Representative Results

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

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

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

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

2.3 Ex-vivo Biodistribution. *Ex-vivo* biodistribution of **¹¹¹In-XY-FAP-02** results correlated with the observed imaging results (FIG. 4). Initially, the blood pool activity is very high, with over 10% %ID/g at 30 minutes post injection. With clearance of the compound, we see the blood pool activity drop significantly after 2 hours of distribution and remained less than 5% %ID/g from 2 hours post injection (FIG. 5A). High activity was also observed in pancreas, small intestines, and bladder until 2 hours post injection. Positive tumor uptake peaked at 30 minutes post injection and remained between 13-11% %ID/g up to 6 hours. Washout of tumor was observed at 12 hours post injection, with %ID/g dropping to below 5%. The PC-3, FAP negative xenograft had less than 3.5% %ID/g for all timepoints.

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

2.4 Small-Animal Near Infrared Fluorescence (NIRF) Imaging. NIRF imaging of **XY-FAP-01** demonstrated specific uptake of tracer in the U-87-MG xenograft as early as 30 minutes post injection (FIG. 6). After one hour of distribution, tracer clearance via the bladder was observed with retained tracer uptake in the FAP positive xenograft. Tracer uptake was retained in the positive xenograft

after four hours of distribution. In contrast, no significant uptake of tracer was observed in the FAP negative tumor at all imaging time points.

REFERENCES

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

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- 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.

THAT WHICH IS CLAIMED:

1. A compound of Formula (I):



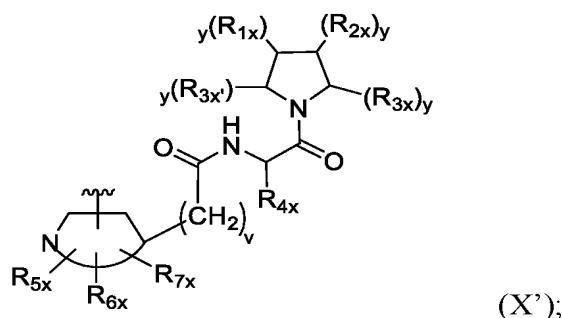
wherein:

A is a targeting moiety for FAP- α ;

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

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

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



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

R_{1x}, R_{2x}, and R_{3x'}, are each independently selected from the group consisting of H, OH, halogen, C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂, -C(O)alkyl, -C(O)aryl-, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

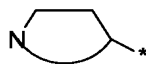
R_{5x}, R_{6x}, and R_{7x} are each independently selected from the group consisting of H, -OH, oxo, halogen, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -S-C₁₋₆alkyl, -NR_{8x}R_{9x}, -OR_{12x}, -Het₂ and -Ar₂; each of C₁₋₆alkyl being optionally substituted with from 1 to 3 substituents selected from -OH and halogen;

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

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

Het₂ is a 5- or 6-membered non-aromatic monocycle optionally comprising 1 or 2 heteroatoms selected from O, N and S; Het₂ being optionally substituted with from 1 to 3 substituents selected from -NR_{13x}R_{14x}, -C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

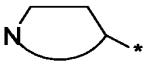
v is 0, 1, 2, or 3; and

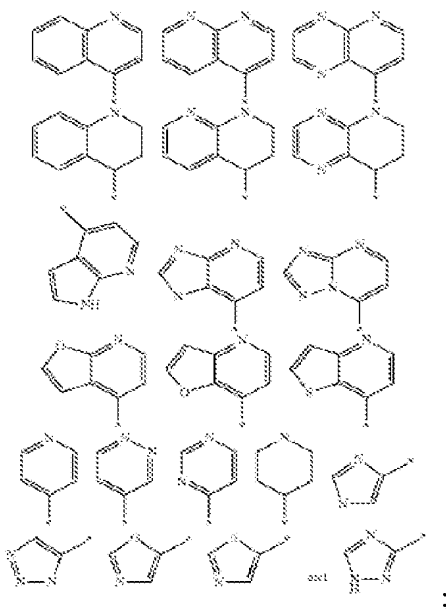


represents a 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle, said heterocycle optionally further comprising 1, 2 or 3 heteroatoms selected from O, N and S;

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;

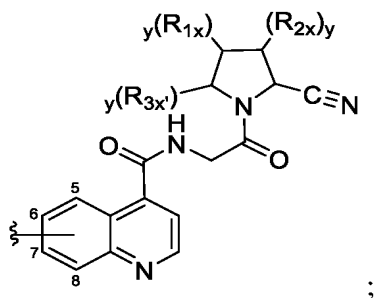
and stereoisomers and pharmaceutically acceptable salts thereof.

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



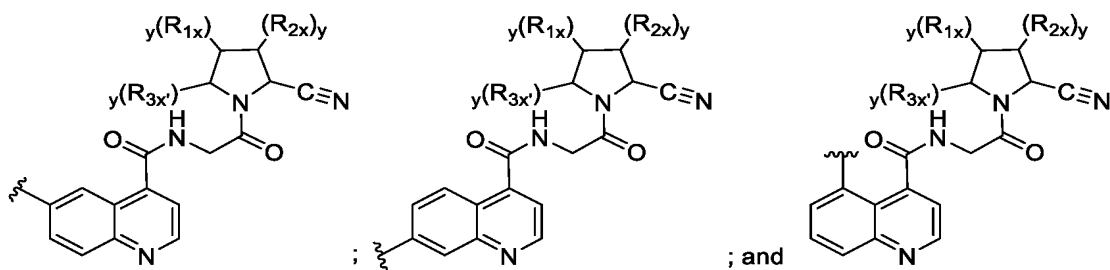
wherein * indicates the point of attachment of the 5 to 10-membered N-containing aromatic or non-aromatic mono- or bicyclic heterocycle to $-(CH_2)_v-$.

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

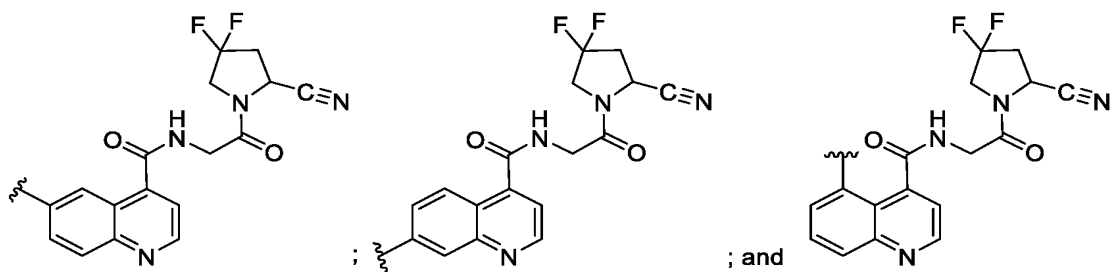


wherein $\text{---}\text{X}\text{---}$ indicates a point of attachment of the FAP- α binding ligand to the linker, L, or the reporter moiety, B, wherein the point of attachment can be through any of carbon atoms 5, 6, 7, or 8 of the quinolinyl ring thereof; and stereoisomers and pharmaceutically acceptable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

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

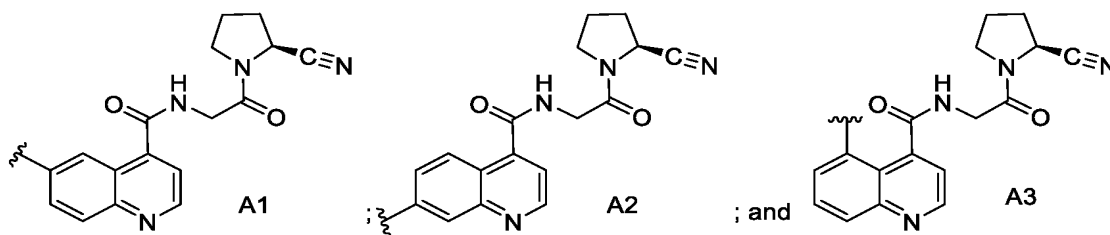


6. The compound of claim 5, wherein A is selected from the group consisting of:

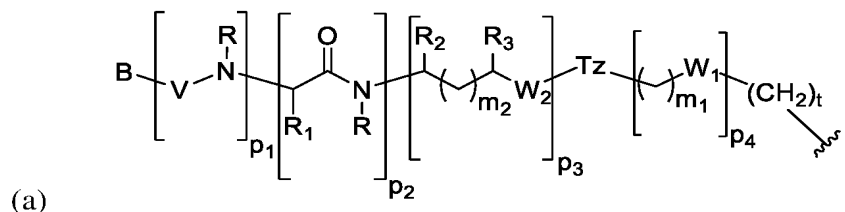


and stereoisomers thereof.

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



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



wherein:

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

t is an integer selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, and 8;

p₁, p₃, and p₄ are each independently 0 or 1;

p₂ is an integer selected from the group consisting of 0, 1, 2, and 3, and when p₂ is 2 or 3, each R₁ is the same or different;

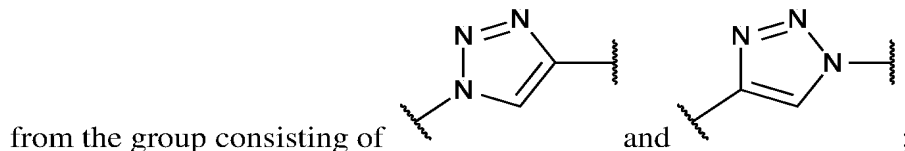
m₁ and m₂ are each an integer independently selected from the group consisting of 0, 1, 2, 3, 4, 5, and 6;

W₁ is selected from the group consisting of a bond, -S-, -C(=O)-NR-, and -NR-C(=O)-;

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

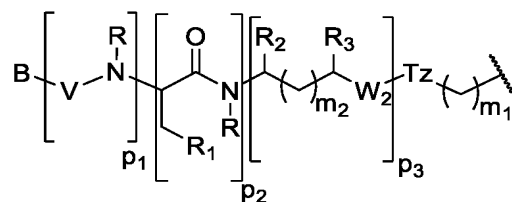
each R or R' is independently H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, and -OR₄, wherein R₄ is selected from the group consisting of H, alkyl, substituted alkyl, cycloalkyl,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

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



each R₁ is independently H, C₁-C₆ alkyl, C₃-C₁₂ aryl, -(CH₂)_q-C₃-C₁₂ aryl, -C₄-C₁₆ alkylaryl, or -(CH₂)_q-C₄-C₁₆ alkylaryl; R₂ and R₃ are each independently H and -CO₂R₅, wherein R₅ is selected from the group consisting of H, C₁-C₆ alkyl, C₃-C₁₂ aryl, and C₄-C₁₆ alkylaryl, wherein when one of R₂ or R₃ is CO₂R₅, then the other is H;

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



(b)

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 $-\text{NR}-(\text{CH}_2)_q-[\text{O}-\text{CH}_2-\text{CH}_2-\text{O}]_q-(\text{CH}_2)_q-\text{C}(=\text{O})-$;

L_2 is $-\text{NR}-(\text{CH}_2)_q-\text{C}(\text{COOR}_5)-\text{NR}-$; and

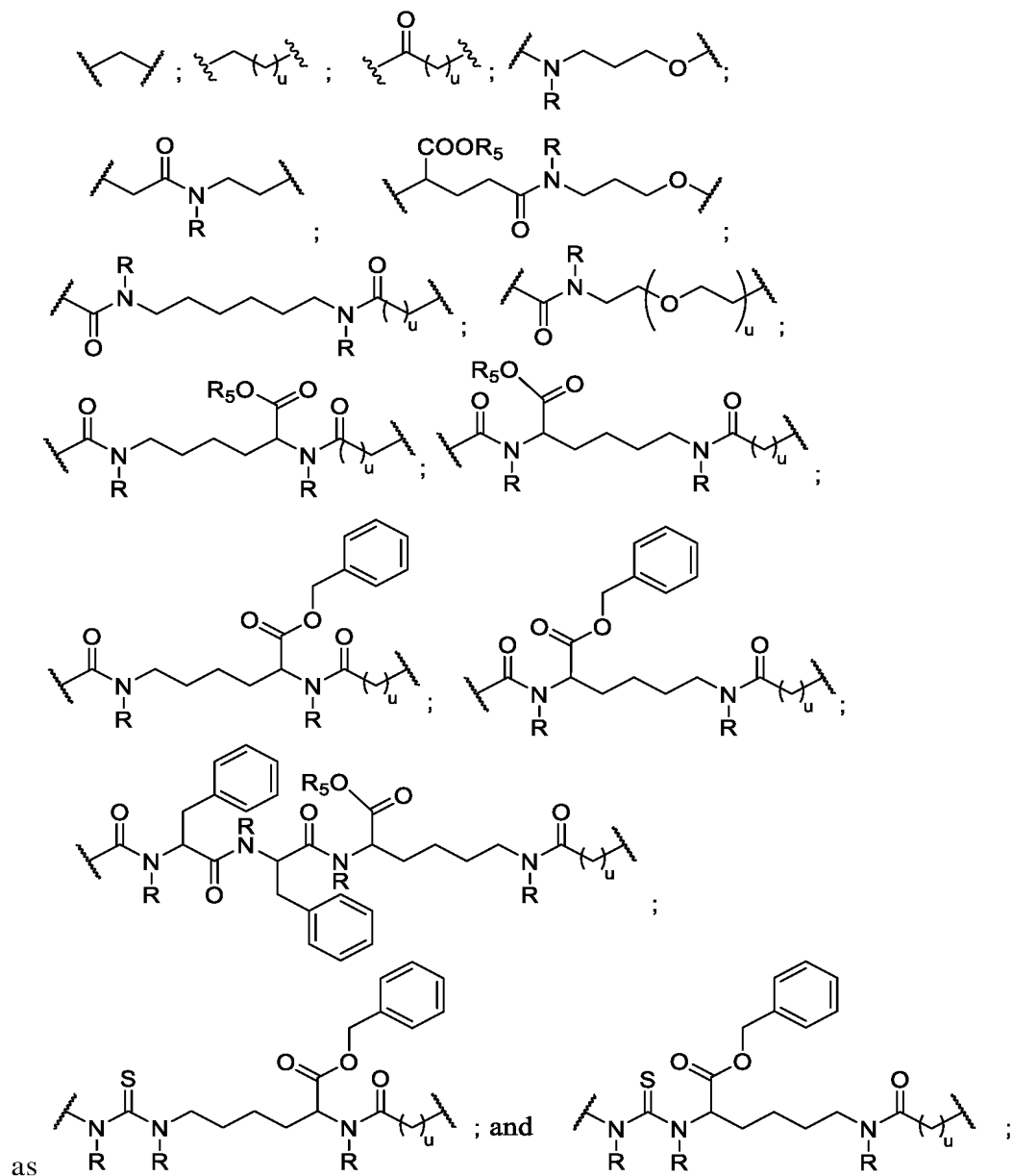
L_3 is $-(\text{O}=\text{C})-(\text{CH}_2)_q-\text{C}(=\text{O})-$;

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) $\text{B}-(\text{CR}_6\text{H})_q-(\text{CH}_2)_q-\text{C}(=\text{O})-\text{NR}-(\text{CH}_2)_q-\text{O}-$ or $\text{B}-\text{NR}-(\text{CH}_2)_q-\text{O}-$; wherein each q and R is defined hereinabove; and R_6 is H or $-\text{COOR}_5$; and

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

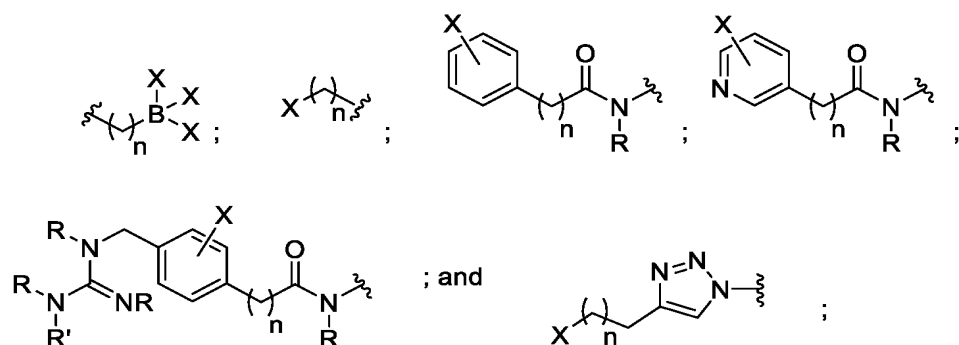
9. The compound of any of claims 1-8, wherein L is selected from the group consisting of:



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

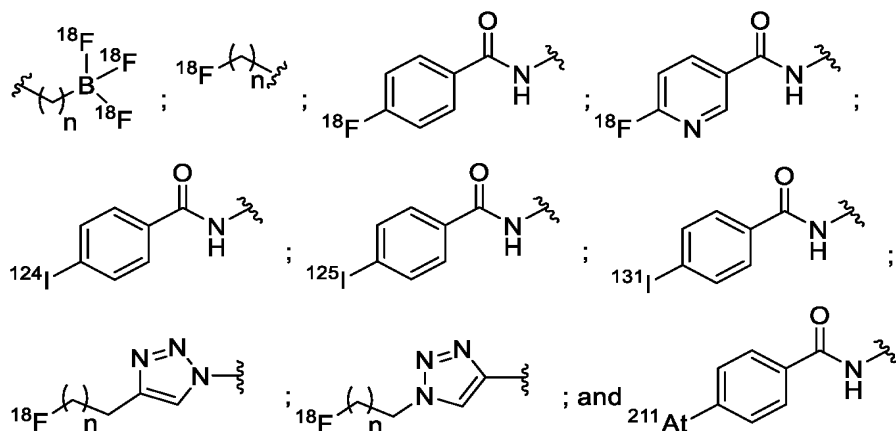
10. The compound of any of claims 1-9, wherein B is a radiolabeled prosthetic group comprising a radioisotope selected from the group consisting of ^{18}F , ^{124}I , ^{125}I , ^{131}I , and ^{211}At .

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



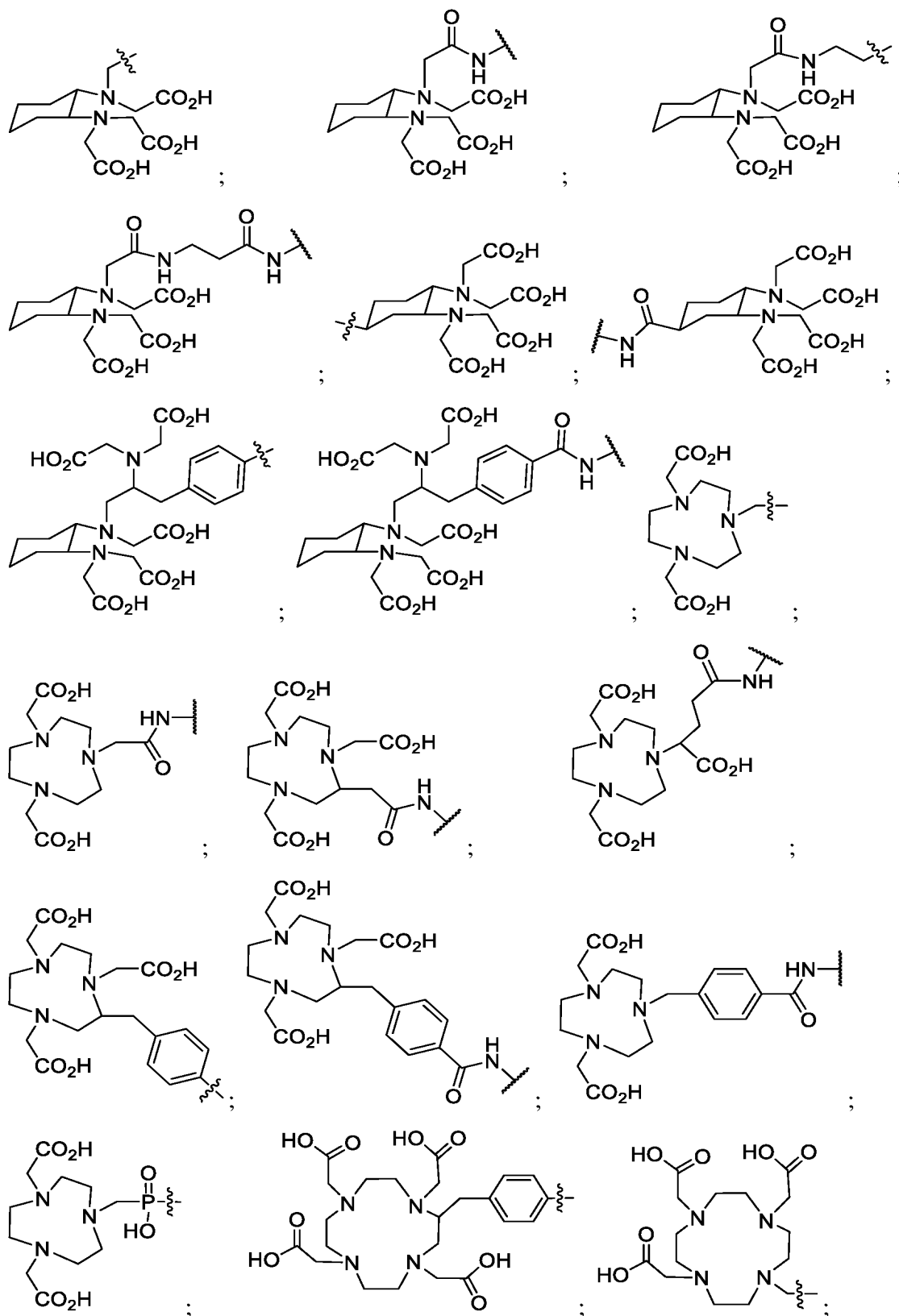
wherein each X is independently a radioisotope selected from the group consisting of ^{18}F , ^{124}I , ^{125}I , ^{131}I , and ^{211}At ; each R and R' is defined hereinabove; and each n is independently an integer selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,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

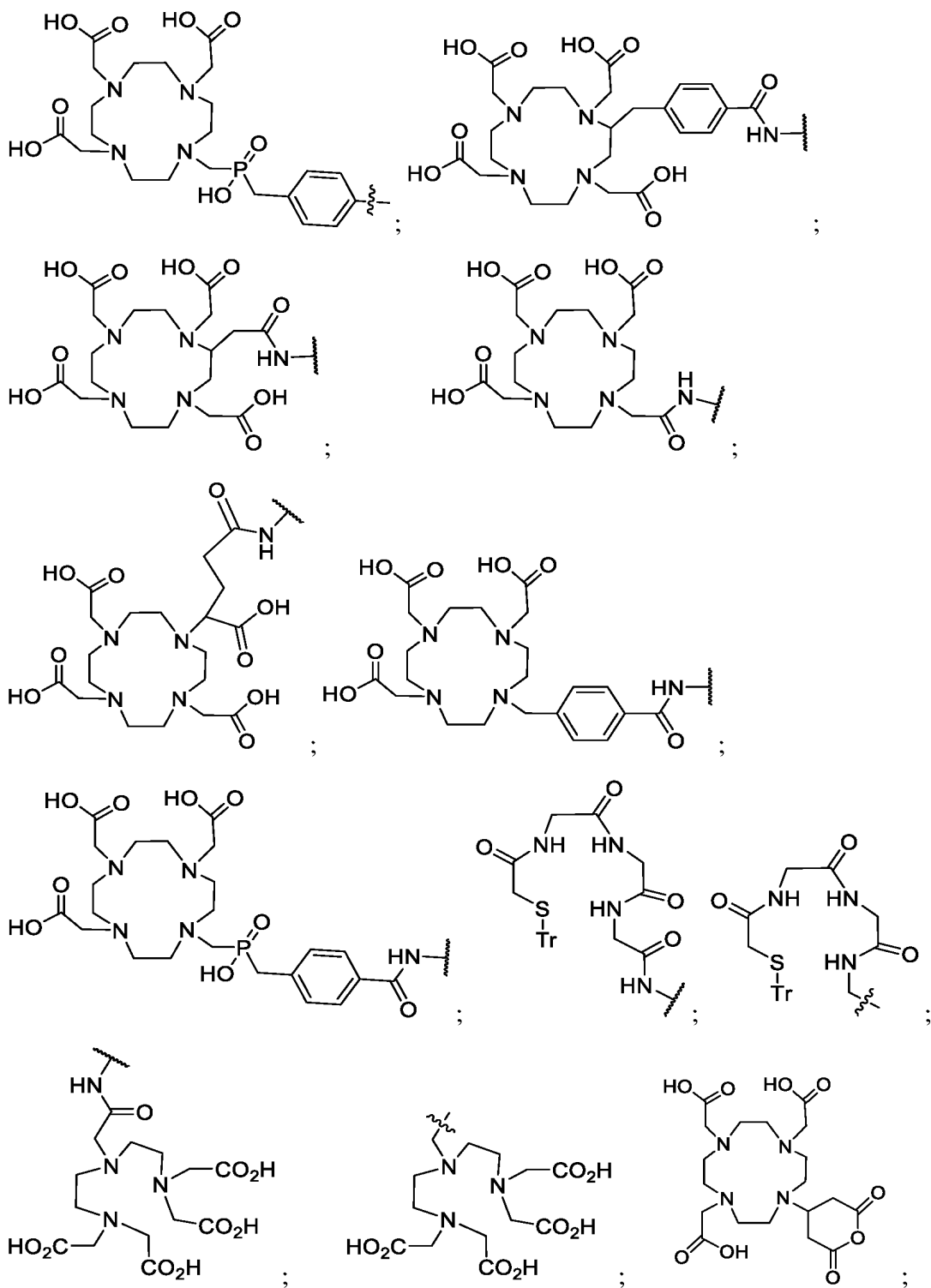
12. The compound of claim 11, wherein the radiolabeled prosthetic group is selected from the group consisting of:

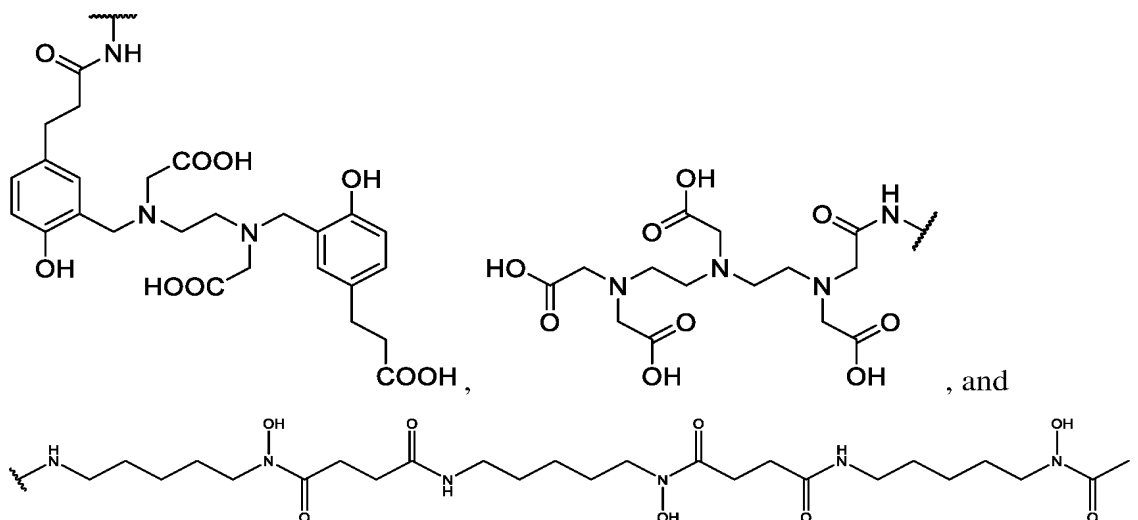


13. The compound of any of claims 1-9, wherein B comprises a chelating agent.

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





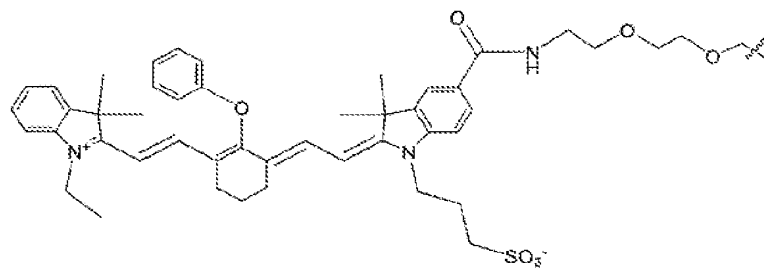


15. The compound of any of claims 1-9, wherein B comprises an optical dye.

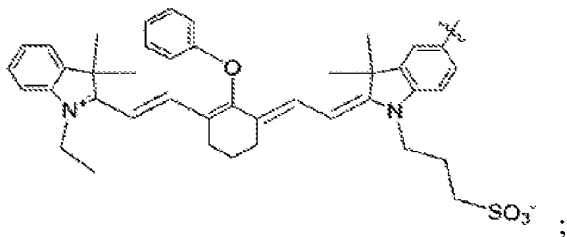
16. The compound of claim 15, wherein the optical dye comprises a fluorescent dye.

17. The compound of claim 16, wherein the fluorescent dye is selected from the group consisting of carbocyanine, indocarbocyanine, oxacarbocyanine, thiocarbocyanine 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.

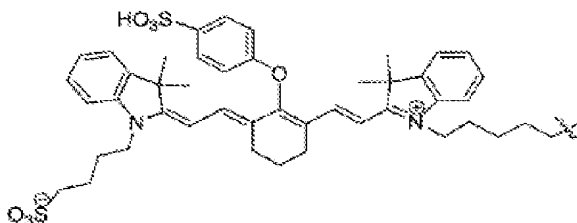
18. The compound of claim 15, wherein the optical dye is selected from the group consisting of:



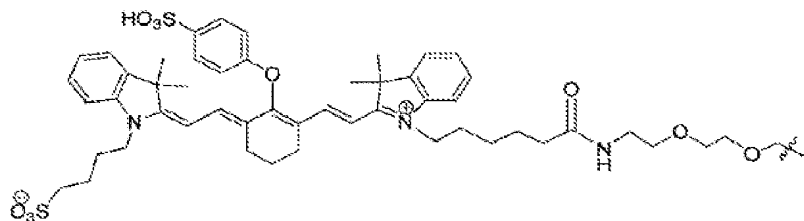
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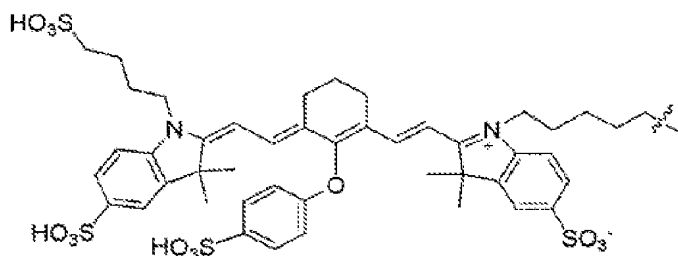
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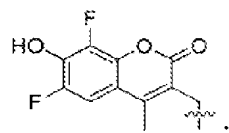
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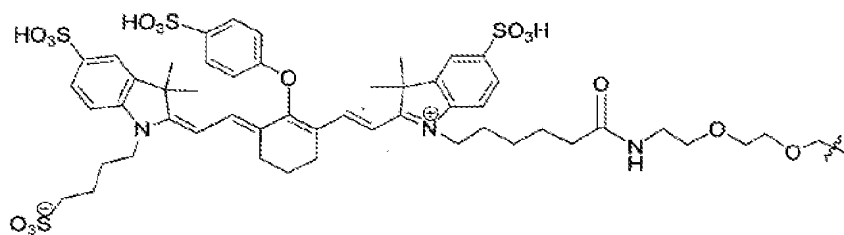
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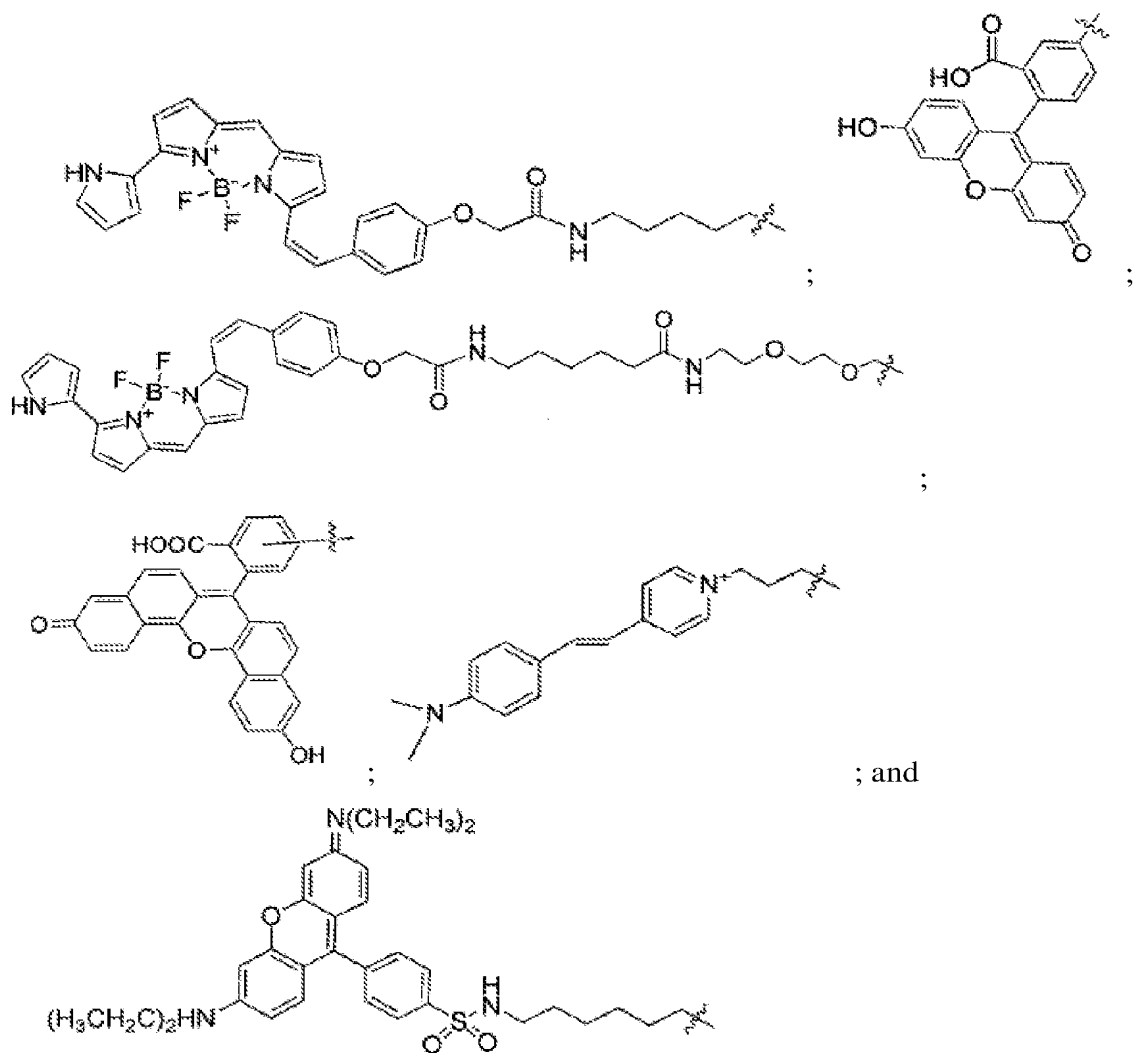
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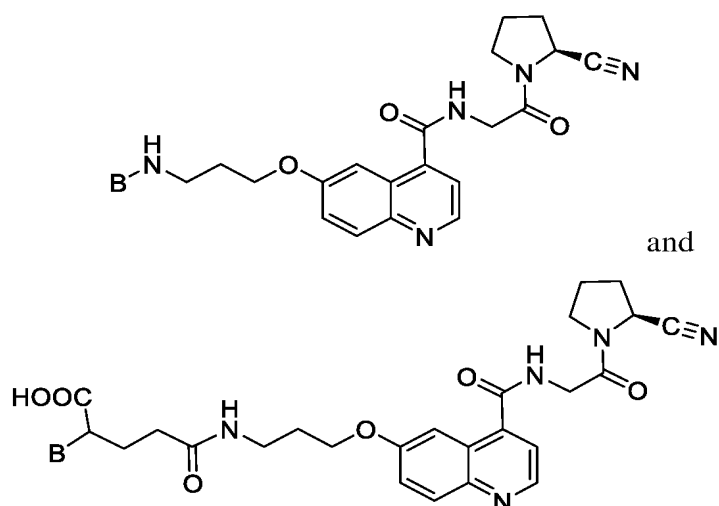
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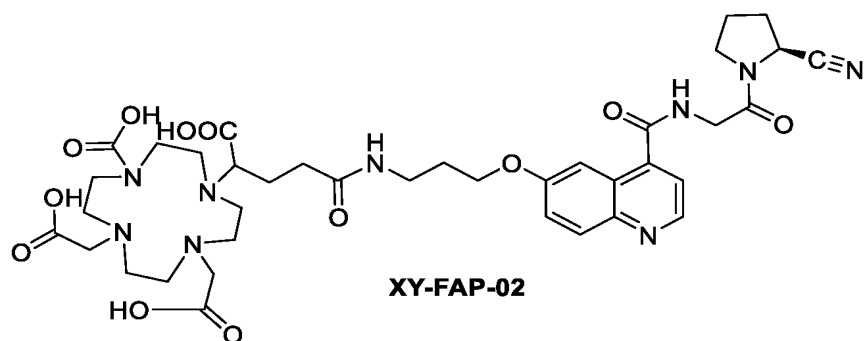
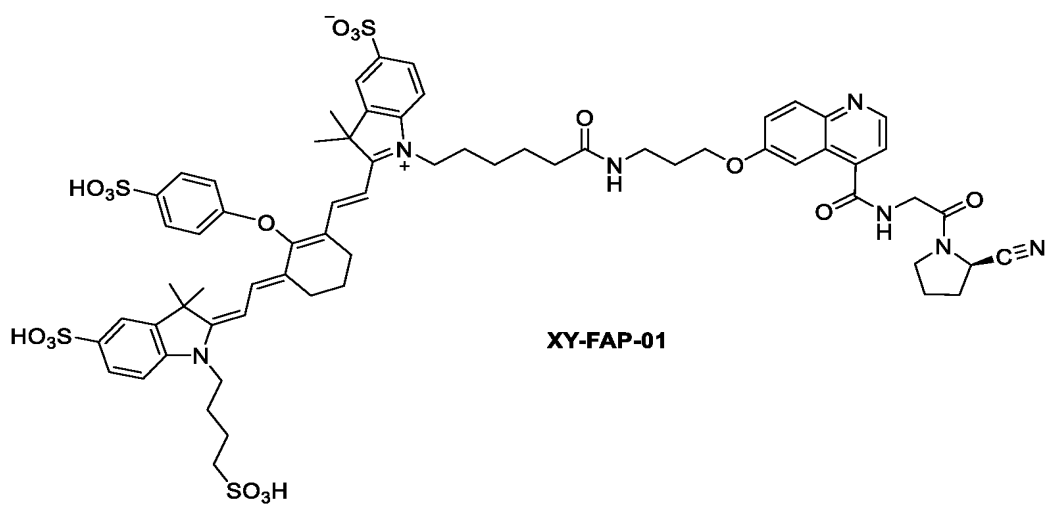
;



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



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



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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
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				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
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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
	1.	9346814	2016-05-24	JANSEN et al.	

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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.	2008/0280856	2008-11-13	COHEN et al.	
	2.	20100098633 A1	2010-04-22	ZIMMERMAN et al.	
	3.	20140357650	2014-12-04	JANSEN et al.	
	4.	2020/0237936	2020-07-30	LOW et al.	
	5.	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.

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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 2010/014933	2010-02-04	THE JOHNS HOPKINS UNIVERSITY		
	2.	WO 2010/108125	2010-09-23	THE JOHNS HOPKINS UNIVERSITY		

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	5.	WO 2015/114166	2015-08-06	PHILOCHEM AG		
	6.	WO 2016/065142	2016-04-28	THE JOHNS HOPKINS UNIVERSITY		
	7.	WO 2016/149188	2016-09-22	THE JOHNS HOPKINS UNIVERSITY		
	8.	WO 2016/196628 A1	2016-12-08	THE JOHNS HOPKINS UNIVERSITY		
	9.	EP 18199641.4	2018-10-10	UNIV HEIDELBERG		
	10	WO 2019/154886	2019-08-15	UNIV HEIDELBERG		
	11	JP2021-512949A	2021-05-20	UNIV HEIDELBERG		X

NONPATENT LITERATURE DOCUMENTS			
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	1.	ALLINEN et al., Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004 Jul;6(1):17-32.	
	2.	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.	
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	42	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.			
	43	YOUN et al., In vivo noninvasive small animal molecular imaging. Osong Public Health Res Perspect. 2012; 3 :48-59.			
	44	YU et al., The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J. 2010 Mar;277(5):1126-44.			

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 <i>(Use as many sheets as necessary)</i>				Complete if Known	
				<i>Application Number</i>	18/585,905
				<i>Filing Date</i>	23-Feb-2024
				<i>First Named Inventor</i>	Yang
				<i>Art Unit</i>	
				<i>Examiner Name</i>	
Sheet	6	of	3	<i>Attorney Docket Number</i>	JHU-36631.304

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 18/354,282 filed on July 18, 2023. 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 <i>(Use as many sheets as necessary)</i>				Complete if Known	
				<i>Application Number</i>	18/585,905
				<i>Filing Date</i>	23-Feb-2024
				<i>First Named Inventor</i>	Yang
				<i>Art Unit</i>	
				<i>Examiner Name</i>	
Sheet	7	of	3	<i>Attorney Docket Number</i>	JHU-36631.304

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-02-26
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.**



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
02/26/2024 02:34:06 PM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 #	7296	FILED BY	Van Nguyen
PATENT CENTER #	64439913	FILING DATE	-
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-02-26 - JHU-36631.304 IDS_SB08.pdf	8	Information Disclosure Statement (IDS) Form (SB08)	100 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)
2024-02-26 - JHU-36631.304 IDS_SB08.pdf	1F6A827E2DA92B86059C3D6F71E37677FAFC32FA87EDF9F3 C24833A1920E39AD29129FF5FA9D1669C9A4ED8D51CB490A A73B16A8CAA0E355CC5F75CDCF82FB38

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, et al.

Confirmation No.: 7296

Serial No.: 18/585,905

Art Unit: TBD

Filed: February 23, 2024

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

SECOND 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.

IN THE CLAIMS:

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

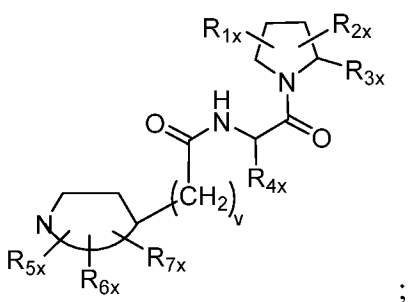
1-27. (Canceled)

28. (Previously Presented) A low molecular weight compound of Formula (I):

B-L-A (I)

wherein:

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



wherein:

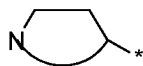
R_{1x} and R_{2x} are each independently selected from the group consisting of H, OH, halogen, C₁₋₆alkyl, -O-C₁₋₆alkyl, and -S-C₁₋₆alkyl;

R_{3x} is selected from the group consisting of H, -CN, -B(OH)₂, -C(O)alkyl, -C(O)aryl, -C=C-C(O)aryl, -C=C-S(O)₂aryl, -CO₂H, -SO₃H, -SO₂NH₂, -PO₃H₂, and 5-tetrazolyl;

R_{4x} is H;

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

v is 0; and



represents a quinolinyl ring having a point of attachment to a remainder of the FAP binding moiety at the 4-position of the 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.

29. (Previously Presented) The compound of claim 28, wherein R_{1x} and R_{2x} are each independently selected from the group consisting of H and F.

30. (Previously Presented) The compound of claim 29, wherein R_{3x} is -CN.

31. (New) The compound of claim 30, wherein B comprises a chelating agent.

REMARKS

New claim 31 has been added. Support for new claim 31 can be found in the claims and specification as originally filed. No new matter has been added.

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.

Respectfully Submitted,

CASIMIR JONES, S.C.

Date: February 26, 2024

/JEFFREY W. CHILDERS/

Jeffrey W. Childers, Ph.D.

Registration No. 58126

Customer No. 101943



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
02/26/2024 02:36:07 PM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 # 7296

FILED BY Van Nguyen

PATENT CENTER # 64444547

FILING DATE -

CUSTOMER # 101943

FIRST NAMED
INVENTOR Xing Yang

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Jeffrey Childers

Documents

TOTAL DOCUMENTS: 3

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
2024-02- 26_36631.304_Second Preliminary Amendment.pdf		4	-	35 KB
2024-02- 26_36631.304_Second Preliminary Amendment- A.PE.pdf	(1-1)	1	Preliminary Amendment	15 KB
2024-02- 26_36631.304_Second Preliminary Amendment- CLM.pdf	(2-3)	2	Claims	25 KB
2024-02- 26_36631.304_Second	(4-4)	1	Applicant Arguments/Remarks Made in an Amendment	11 KB

Preliminary Amendment-
REM.pdf

Digest

DOCUMENT

MESSAGE DIGEST(SHA-512)

2024-02-
26_36631.304_Second
Preliminary Amendment.pdf

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2024-02-
26_36631.304_Second
Preliminary Amendment-
A.PE.pdf

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2024-02-
26_36631.304_Second
Preliminary Amendment-
CLM.pdf

0908B2721A09EB9CF993607430ECC4A608615407A3776E37E3
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2024-02-
26_36631.304_Second
Preliminary Amendment-
REM.pdf

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E75A593FCA04307C081AAA0669F2C17C

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

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

New International Application Filed with the USPTO as a Receiving Office

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



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APPLICATION NUMBER	FILING of 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
18/585,905	02/23/2024		664	JHU-36631.304	4	1

CONFIRMATION NO. 7296

101943

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

FILING RECEIPT



00000000/0926101

Date Mailed: 04/10/2024

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, Baltimore, 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 18/354,282 07/18/2023 PAT 11,938,201
which 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: 04/09/2024

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/585,905**

Projected Publication Date: To Be Determined - pending completion of Missing Parts.

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,

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).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
18/585,905

APPLICATION AS FILED - PART I

(Column 1)		(Column 2)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	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), (l), 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))	4 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)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT A	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
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))						OR		
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						OR		
				TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT B	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
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))						OR		
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.



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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/585,905	02/23/2024	Xing Yang	JHU-36631.304

CONFIRMATION NO. 7296

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

FORMALITIES LETTER



OC000000070926103

Date Mailed: 04/10/2024

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to the above-identified nonprovisional application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The fee set forth in 37 CFR 1.16(u) for submitting documents not in DOCX format has not been received.

The fee is due because:

- the claims were not submitted in DOCX format.

Note: The fee set forth in 37 CFR 1.16(u) is required if the specification, claims, and/or abstract do not conform to the USPTO requirements for submission in DOCX format. In addition, if applicants submit a PDF version of the specification, claims, and/or abstract that is not generated by the USPTO filing system and also includes a DOCX version of the specification, claims, and/or abstract, then the surcharge is required for the version of the specification, claims, and/or abstract that were submitted in PDF format. However, the fee set forth in 37 CFR 1.16(u) will not be required if applicant submitted an Auxiliary PDF in compliance with the USPTO process for submitting an Auxiliary PDF that was automatically assigned the document code AUX.PDF.

SUMMARY OF FEES DUE:

The fee(s) required (including the fees noted above) are as follows. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- **\$160** non-DOCX fee.
- **\$(0)** previous unapplied payment amount.
- **\$160** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be addressed to:

Mail Stop Missing Parts
Commissioner for Patents
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REPLY VIA ELECTRONIC FILING

A reply may be submitted via electronic filing only by registered users of the appropriate USPTO patent electronic filing system and must include:

- A separate document having the document description, "**Applicant response to Pre-Exam Formalities Notice**"; and
- the item(s) for which a reply period is set forth above.

For more information about electronic filing, contact the Patent Electronic Business Center (EBC) 1-866-217-9197 or visit <https://www.uspto.gov/ebc>

NOTE: If the reply is not being submitted electronically, a copy of this notice must be included.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/ktesfaye/



United States Patent and Trademark Office

Under Secretary of Commerce for Intellectual Property and
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Kathi Vidal

Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office

Derrick Brent

Deputy Under Secretary of Commerce for Intellectual Property and
Deputy Director of the United States Patent and Trademark Office



UNITED STATES
PATENT AND TRADEMARK OFFICE

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

ELECTRONIC PAYMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
05/20/2024 03:01:30 PM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 #	7296	FILED BY	Van Nguyen
PATENT CENTER #	65595195	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	02/23/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD CARD / 0638	PAYMENT TRANSACTION ID E20245JF01596709	PAYMENT AUTHORIZED BY Van Nguyen
-------------------------------	--	-------------------------------------

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2054	Non-DOCX Filing Surcharge	160.00	1	160.00
TOTAL AMOUNT:				\$160.00

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.

Confirmation No.: 7296

Serial No.: 18/585,905

Art Unit: TBD

Filed: February 23, 2024

Examiner: TBD

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

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO FILE MISSING PARTS

Dear Sir or Madam:

This is responsive to the Notice to File Missing Parts mailed April 10, 2024. Such notice indicates that a \$160 non-DOCX fee is due. Applicant submits herewith \$160 for a non-DOCX fee.

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.

The Commissioner is hereby authorized to charge any underpayment or credit any overpayment associated with this filing to Deposit Account Number 50-4302.

Respectfully Submitted,

CASIMIR JONES, S.C.

Date: May 20, 2024

/JEFFREY W. CHILDERS/
Jeffrey W. Childers, Ph.D.
Registration No. 58126
Customer No. 101943



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
05/20/2024 03:01:30 PM Z ET

ATTORNEY DOCKET #
JHU-36631.304

Title of Invention

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

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PATENT CENTER #	65595195	FILING DATE	02/23/2024
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-05-20 - JHU-36631.304 - RNTFMP.pdf	1	Applicant Response to Pre- Exam Formalities Notice	17 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-05-20 - JHU-36631.304 - RNTFMP.pdf	03DE2F70D7793221343C2C234EF43DA12942F9AC9A6F488F8 A90A861F498D2F261FE51CE8F4C601F610280B38DF913B56EB 9FEFC659AC91E1EC04E5833AC2672

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.



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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
18/585,905	02/23/2024		824	JHU-36631.304	4	1

101943

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

CONFIRMATION NO. 7296
UPDATED FILING RECEIPT



0000000073028539

Date Mailed: 05/24/2024

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, Baltimore, 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 18/354,282 07/18/2023 PAT 11,938,201
which 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: 04/09/2024

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/585,905**

Projected Publication Date: 08/29/2024

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

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

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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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,

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).

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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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).

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number
18/585,905

APPLICATION AS FILED - PART I

(Column 1)		(Column 2)		SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)	RATE(\$)		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), (l), 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))	4	minus 20 =	*	0	x	=	0	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1	minus 3 =	*	0	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).							
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))								
				0				
				TOTAL	664			

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED - PART II

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

AMENDMENT B	(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	CLAIMS REMAINING AFTER AMENDMENT	HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)	RATE(\$)	ADDITIONAL FEE(\$)				
Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	x	=	OR	x	=
Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	x	=	OR	x	=
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.

** 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.



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United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296
101943	7590	06/14/2024	EXAMINER	
The Johns Hopkins University c/o Casimir Jones 2275 Deming Way Suite 310 Middleton, WI 53562			CENTRAL, DOCKET	
			ART UNIT	PAPER NUMBER
			1618	
			NOTIFICATION DATE	DELIVERY MODE
			06/14/2024	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

<i>Decision Granting Request for Prioritized Examination (Track I)</i>	Application No. 18/585,905	Applicant(s) Yang et al.	
	Examiner FIKIRTE A GEREMEW	Art Unit OMBL	AIA (FITF) Status Yes
1. THE REQUEST FILED <u>23 February 2024</u> 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 <u>petition for extension of time</u> to extend the time period for filing a reply; B. filing an <u>amendment to amend the application to contain more than four independent claims, more than thirty total claims</u>, or a multiple dependent claim; C. filing a <u>request for continued examination</u> ; 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 FIKIRTE GEREMEW at (703) 756-1930. In his/her absence, calls may be directed to Petition Help Desk at (571) 272-3282.			
/FIKIRTE A GEREMEW/ PROGRAM SUPPORT SPECIALIST, OMBL			



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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

APPLICATION #	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET #
18585905	02/23/2024	Xing Yang	JHU-36631.304

Title of Invention

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



Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action



This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent interest
The Johns Hopkins University	100%
Total	100%

The owner(s) of percent interest listed above 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(s)

Application #	Filing Date
---------------	-------------

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 owner 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 owner 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.

The owner(s) of percent interest listed above 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 prior patent number(s)

Patent #

11938201

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent 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 owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:

- 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 presently shortened by any terminal disclaimer.



Terminal disclaimer fee under 37 CFR 1.20(d) included with Electronic Terminal Disclaimer request.

Applicant claims the following entity status:

Small

I hereby declare that all statements made herein of my own 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.

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 is of record in this application

Signature	Name	Registration #
/Jeffrey Childers/	Jeffrey Childers	58126

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP 324.



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APPROVAL LETTER

APPLICATION #
18/585,905

FILING DATE
02/23/2024

APPLICANT/PATENT UNDER REEXAMINATION
Xing Yang

Title of Invention

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

Electronic terminal disclaimer filed on 08/06/2024



Approved

This patent is subject to a Terminal Disclaimer

Approved / Disapproved by: Electronic Terminal Disclaimer automatically approved



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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/585,905	08/06/2024 10:58:40 AM Z ET	JHU-36631.304

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 #	7296	FILED BY	Van Nguyen
PATENT CENTER #	66665377	AUTHORIZED BY	Jeffrey Childers
CUSTOMER #	101943	FILING DATE	02/23/2024
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Xing Yang

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
CARD / 0638	E202486B14238340	Jeffrey Childers

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
TOTAL AMOUNT:				\$170.00

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.



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
08/06/2024 10:58:40 AM Z ET

ATTORNEY DOCKET #
JHU-36631.304

Title of Invention

IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION
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PATENT CENTER #	66665377	FILING DATE	02/23/2024
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	3	Terminal Disclaimer-Filed (Electronic)	44 KB
grantLetter.pdf	1	Terminal Disclaimer-Electronic- Approved	18 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	AFA262A3E83BED96FDD59B36881646E0EB6615FA146BE8FD 999139AA4C851DB6C3F2B894ABFB72249AC4A9821F3B0CB9 AB066E31CD07CA93B7749E86208110A0

grantLetter.pdf

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New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: YANG, et al.

Confirmation No.: 7296

Serial No.: 18/585,905

Art Unit: 1618

Filed: February 23, 2024

Examiner: Perreira, Melissa Jean

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

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

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

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

Examiner Perreira:

1. I, Martin Pomper, am the Principal Investigator and co-inventor of the subject matter described and claimed in the above-referenced patent application (the “Application”). The research leading to the subject matter of the Application was conducted in my laboratory.

2. I am currently Chair of the Department of Radiology at University of Texas Southwestern Medical Center. Previously, I was Professor of Radiology and Radiological Science, Professor of Oncology and Radiation Oncology and Molecular Radiation Services, Research Chief of Nuclear Medicine, Director of the Division of Nuclear Medicine and Molecular Imaging, Associate Dean of Entrepreneurship and Technology Development, and Director of the Johns Hopkins Center for Translational Molecular Imaging at the Johns Hopkins School of Medicine.

3. I received my B.Sc. degree, Ph.D. degree, and MD degrees all from the University of Illinois at Urbana-Champaign.

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4. I completed my postgraduate medical training at Johns Hopkins that included a medical internship, residencies in diagnostic radiology and nuclear medicine, and a fellowship in neuroradiology, before I joined the Johns Hopkins faculty in 1996.

5. I have authored hundreds scientific articles and am inventor of numerous issued patents or patent applications in the field of medical diagnostic imaging.

6. I have read the non-final Office Action dated September 26, 2023, in the subject Application and the references cited therein.

7. I understand the Office Action rejected claim 29 on numerous grounds, including anticipation under 35 U.S.C. § 102(a) and obviousness under 35 U.S.C. § 103.

8. I understand that the pending claims are directed to a low molecular weight compound of Formula (I):

B-L-A

wherein A is a targeting moiety for FAP- α defined by a specific structure, B is an optical or radiolabeled functional group, and L is a linker having bi-functionalization adapted to form a chemical bond with B and A.

9. The office action asserts that prior claim 29 is anticipated under 35 U.S.C. § 102(a)(1) by Dvořáková et al. (J. Med. Chem. 2017, 60, 8385-8393) (hereinafter “Dvořáková”).

10. Claim 29 is amended and further defines the compound of formula (I) as being “low molecular weight” (“LMW”). I distinguish the LMW compound of the pending claims from large molecule imaging agents containing anti-FAP moieties. In particular, I characterize large molecule imaging agents as having numerous disadvantages, including pharmacokinetic limitations, including slow blood and non-target tissue clearance and non-specific organ uptake. Page 1, lines 28-34; page 2, lines 1-7. In contrast, the LMW imaging agents of the instant application possess numerous advantages compared with the large molecule imaging agents. *Id.* Specifically, LMW imaging agents demonstrate faster pharmacokinetics and a higher specific signal within clinically convenient times after administration. *Id.* They also can be synthesized in radiolabeled form more easily and may offer a shorter path to regulatory approval.

11. I distinguish between the LMW compounds of the pending claims and larger biologic compounds such as antibodies and high relative molecule mass polymers, as cited below.

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 C₁₋₆alkyl or -O-C₁₋₆alkyl 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 C₁₋₆alkyl or -O-C₁₋₆alkyl group disclosed in Jansen I may serve as the linker when the compounds containing the C₁₋₆alkyl or -O-C₁₋₆alkyl of Jansen I are modified with a radiohalogen.

23. I observed that C₁₋₆alkyl and the -O-C₁₋₆alkyl are among a variety of functional groups that may be attached to the heterocyclic group of the FAP inhibitor compounds disclosed in Jansen I, including —H, —OH, —oxo, —halo, —C₁₋₆alkyl, —O—C₁₋₆alkyl, —S—C₁₋₆alkyl, —NR₈R₉, —OR₁₂, —Het₂ and —Ar₂, wherein the C₁₋₆alkyl may be optionally substituted with —OH and —halo.

24. Further, I observed that the vast majority of the representative compounds disclosed in either Jansen I or Jansen II do not contain a halogenated C₁₋₆alkyl substitution. Out of 43 representative FAP inhibitors in Jansen I, only one of them is substituted with a halogenated C₁₋₆alkyl or -O-C₁₋₆alkyl. *See* Jansen I, Table 4, Example 11. The same compound is also the only FAP inhibitor substituted with a halogenated C₁₋₆alkyl or -O-C₁₋₆alkyl out of 39 representative FAP inhibitors in Jansen II. *See* Jansen II, Table 3, Compound 28.

25. FAP inhibitors substituted with a halogenated C₁₋₆alkyl or -O-C₁₋₆alkyl 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 C₁₋₆alkyl should be selected for modification with a radiohalogen.

26. I notice that the single FAP inhibitor substituted with the halogenated C₁₋₆alkyl or -O-C₁₋₆alkyl disclosed in Jansen I and Jansen II has worse bioactivities compared with the other compounds disclosed in the prior art. In particular, many FAP inhibitors of Jansen I and Jansen II have more favorable affinity and specificity properties than Example 11 of Jansen I or Compound 28 of Jansen II which is substituted with a trifluoromethoxy group. *See* Example 11, Table 4, Jansen I; Compound No. 28, Table 3, Jansen II. For example, compound Example 11 of

Jansen I with the trifluoromethoxy substitution has a IC_{50} of 0.012 μ M 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 μ M and a selectivity index of 193. Accordingly, one of ordinary skill in the art would not select the FAP inhibitor substituted with a trifluoromethoxy group for modification.

27. The Office Action appeared to correlate the substitution of a C_{1-6} alkyl or -O- C_{1-6} alkyl on the quinoline ring of the FAP inhibitors as a “linker” to the fact the quinoline containing FAP inhibitors have 60 times more FAP-affinity than N-(1-naphthoyl) FAP inhibitors:

It would have been obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to substitute the heteroaromatic FAP inhibitors of [Jansen I] with a radiohalogen via a linker, such as a C_{1-6} alkyl, -O- C_{1-6} alkyl as [Jensen II] teaches that the quinoline containing FAP inhibitors have 60 times more FAP-affinity than the N-(1-naphthoyl) FAP inhibitors and can be halogenated on the quinoline, such as via trifluoromethoxy. [Office Action dated September 26, 2023, pages 6-7].

I would point out that Jansen II merely discloses that quinoline containing FAP inhibitors have 60 times higher FAP-affinity than the N-(1-naphthoyl) FAP inhibitors. Jansen II does not suggest that substitution of the quinoline ring of the quinoline containing FAP inhibitors will improve the FAP-affinity or selectivity of the FAP inhibitors.

28. On the contrary, Jansen II observed that substitution of the quinoline ring has little or negative effects on the FAP-affinity of the quinoline containing FAP inhibitors:

Next, we turned our attention to the effect of substituting the N-(4-quinolinoyl) ring in 7 (Table 3). Overall, none of the evaluated substituents was able to improve FAP potency significantly, with substituents in the 2- and 3-position of the quinoline ring as in compounds 19–24, having a clearly negative effect on this parameter. [Janssen II, page 493, left column].

In particular, the only FAP inhibitor with a trifluoromethoxy substitution, i.e., Example 11 of Jansen I or Compound 28 of Jansen II, has an inferior FAP-affinity 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 μ M for the FAP inhibitor substituted with a trifluoromethoxy substitution versus 0.010 μ M for the unsubstituted FAP inhibitor. Selectivity index (a higher selectivity index means a higher selectivity) is 59 for the former versus 83 for the latter. *See* Jansen I, Table 4.

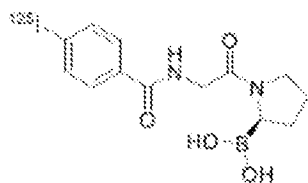
29. Accordingly, the cited references not only fail to suggest selecting and modifying FAP inhibitors, but also may discourage one of ordinary skill in the art to substitute the FAP inhibitors with any functional groups, including the C₁₋₆alkyl or -O-C₁₋₆alkyl.

30. Further, due to the high unpredictability of the medical imaging art, I believe one of ordinary skill in the art would not reasonably expected success in modifying the cited prior art to arrive at the compounds of the pending claims for medical imaging applications.

31. There are numerous important parameters which need to be taken into consideration for successfully developing a FAP imaging agent. Those parameters include, for example, affinity for FAP, selectivity (specificity) for FAP, ease of synthesis, and biodistribution, and the like. It is important for the agent to have both high affinity and high specificity to bind to the target protein that is associated with a medical condition. The high specificity allows the imaging agent to bind selectively to the target protein associated with the medical condition but not other proteins unrelated to the medical condition. A high specificity is important for a medical imaging agent because it prevents proteins unrelated to the medical condition from interfering with the binding between the imaging agent and the target protein. The affinity and specificity of the medical imaging agent are highly dependent on the molecular structure of the agent. Accordingly, the art of developing a medical imaging agent is highly unpredictable as it involves optimizing numerous parameters including the specificity of the compound.

32. The unpredictability of the art is clearly manifested by the documented failure of a compound disclosed in Zimmerman.

33. In particular, a representative compound disclosed in Zimmerman, namely MIP-1232, was extensively investigated as a potential medical imaging agent for atherosclerotic



[¹²⁵I]MIP-1232

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

34. As provided on page 2089 of Meletta, while pronounced binding of [¹²⁵I]MIP-1232 to carotid plaques was observed, Meletta did not observe, however, any difference in average specific binding between stable and vulnerable plaques and between plaques and normal arteries. Based on these data, Meletta could not conclude on the selectivity of [¹²⁵I]MIP-1232 for FAP.

35. Accordingly, because of the low specificity MIP-1232 displayed in the testing, Meletta concluded that MIP-1232 was not suitable for the medical imaging application for the particular medical condition being tested in Meletta. *Id.* at 2095.

36. Based on my review, I am not aware of any other compounds disclosed in Zimmerman that fared better than MIP-1232 and that was developed successfully as a medical imaging agent.

37. The failure of investigations with MIP-1232, which is a compound disclosed in the cited prior art, is especially telling as it demonstrates the high unpredictability of the art and lack of reasonable expectation of success by combining the prior art to arrive at the compounds of the pending claims for medical imaging applications.

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

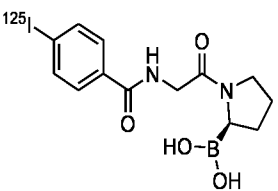
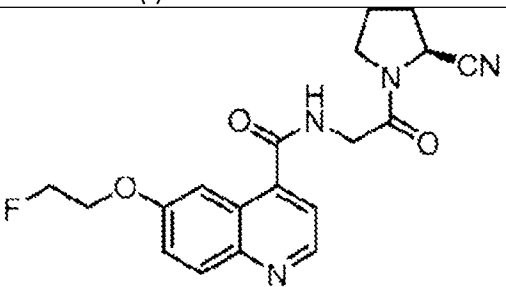
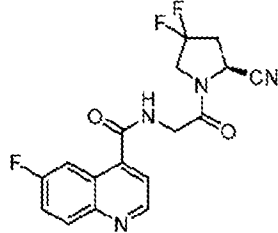
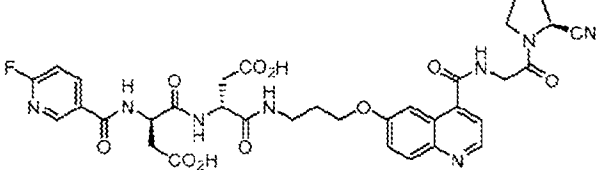
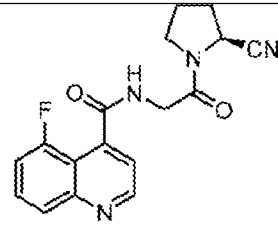
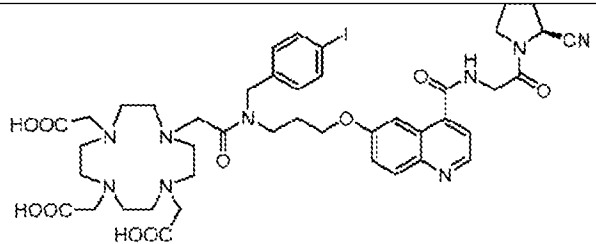
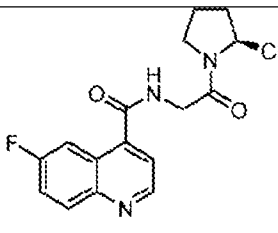
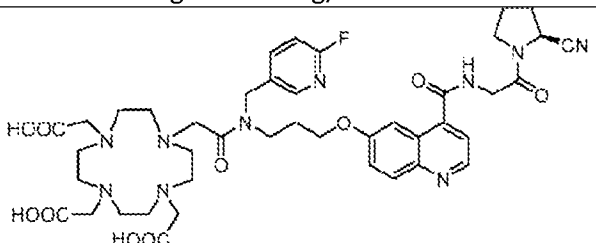
39. Specificity is an important parameter for developing a medical imaging agent because a high specificity of the compound allows the imaging agent to selectively bind to the target protein associated with a medical condition, therefore enabling the imaging agent to diagnose the medical condition more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

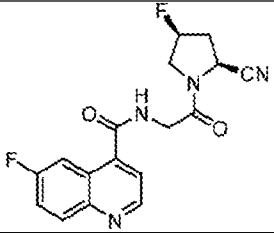
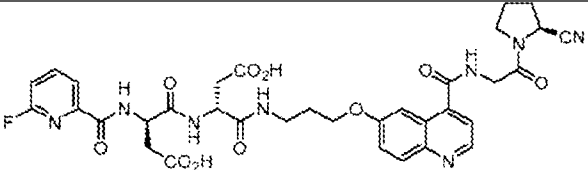
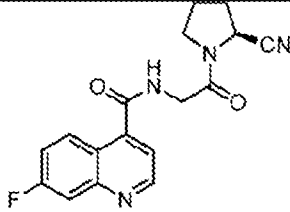
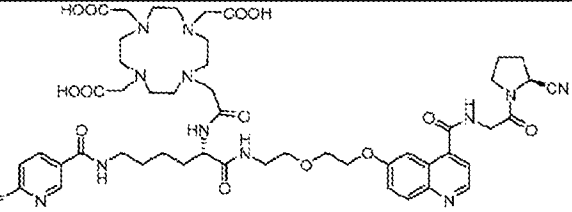
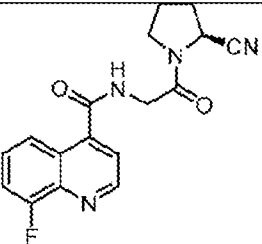
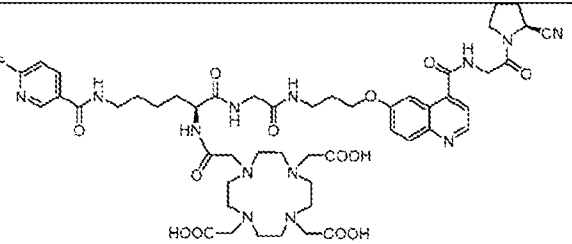
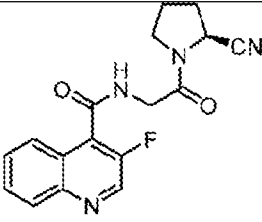
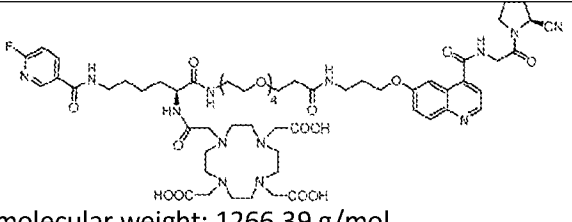
40. While Meletta could not conclude on the selectivity of the compound of Zimmerman [¹²⁵I]MIP-1232 for FAP (above), we found the specificity/selectivity of XY-FAP-01 and XY-FAP-02 imaging agents as shown in the current application US 2020/0330624 A1 for the selectivity for FAP over dipeptidyl peptidase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

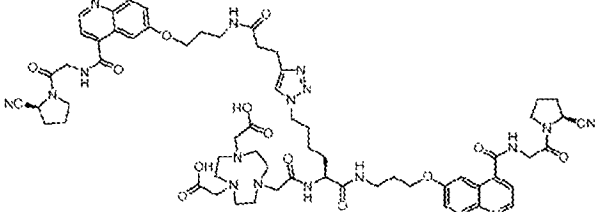
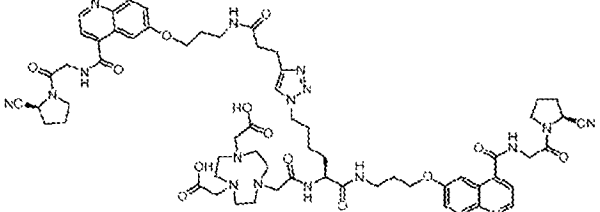
41. Further, a well-accepted indicator of the specificity/selectivity of the FAP imaging agent is ratio of the amounts taken for the FAP imaging agent to inhibit prolyl peptidase

(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	 molecular weight: 983.86 g/mol	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,

A handwritten signature in black ink, appearing to read 'Martin Pomper', written over a horizontal line.

August 6, 2024_

Martin Pomper

Date



UNITED STATES
PATENT AND TRADEMARK OFFICE

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

ELECTRONIC PAYMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
08/06/2024 11:25:07 AM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 # 7296

FILED BY Van Nguyen

PATENT CENTER # 66665415

AUTHORIZED BY Jeffrey Childers

CUSTOMER # 101943

FILING DATE 02/23/2024

CORRESPONDENCE
ADDRESS -

FIRST NAMED
INVENTOR Xing Yang

Payment Information

PAYMENT METHOD
CARD / 0638

PAYMENT TRANSACTION ID
E202486B25539003

PAYMENT AUTHORIZED BY
Van Nguyen

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
TOTAL AMOUNT:				\$56.00

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
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
08/06/2024 11:25:07 AM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 #	7296	FILED BY	Van Nguyen
PATENT CENTER #	66665415	FILING DATE	02/23/2024
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-08-06 - JHU-36631.304_Petition-Color-Drawings.pdf	2	A petition from Applicant to accept Color Drawings or Color Photographs	28 KB
2024-08-06 - JHU-36631.304 Pomper Affidavit - signed.pdf	12	Affidavit-traversing rejections or objections rule 132	464 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-08-06 - JHU-36631.304_Petition-Color-Drawings.pdf	B8EEABF1BDE215FEFC111B04373A7265C6F57CA2034303AB 2DF481986FED7838248FC87EC4A977EB2DD672D399AB9468A 70F239A6D093C876F288637ECAD2F98

2024-08-06 - JHU-36631.304
Pomper Affidavit - signed.pdf

B073BE65D3D73965683500A861819BDDBC909725D4C2DF233
1D0E0474DA2A21C01C113EF1B1942C2C2118B232696B91C16
8E2ABB650029B27607B6D13B463396

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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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, et al.

Confirmation No.: 7296

Serial No.: 18/585,905

Art Unit: 1618

Filed: February 23, 2024

Examiner: Perreira, Melissa Jean

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

Mailstop: Office of Petitions
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: August 6, 2024

/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

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296
101943	7590	08/14/2024		
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
			08/14/2024	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



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.
Application No. 18/585,905
Filed: 02/23/2024
Attorney Docket No. JHU-36631.304

:
: **DECISION ON PETITION**
: **UNDER 37 CFR 1.84(a)(2)**
:
:

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 August 6, 2024.

37 CFR 1.84(a)(2) in relevant part states:

On rare occasions, color drawings may be necessary as the only practical medium by which to disclose the subject matter sought to be patented in a utility patent application. ... The Office will accept color drawings in utility patent applications only after granting a petition filed under this paragraph explaining why the color drawings are necessary. Any such petition must include the following:

- (i) Payment of the fee set forth under 37 CFR 1.17(h),
- (ii) Submission of three (3) sets of color drawings, or one (1) set of color drawings if filed by EFS-Web, and
- (iii) An amendment to the specification to insert (unless the specification contains or has been previously amended to contain) the following language as the first paragraph of the brief description of the drawings:

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

MPEP § 608.02(VIII) COLOR DRAWINGS OR COLOR PHOTOGRAPHS states in relevant part:

It is anticipated that such a petition will be granted only when the U.S. Patent and Trademark Office has determined that a color drawing or color photograph is the only practical medium by which to disclose in a printed utility patent the subject matter to be patented.

A review of U.S. Patent and Trademark records indicates that all the criteria set forth in 37 CFR 1.84(a)(2) and MPEP § 608.02(VIII) have been satisfied. Accordingly, the petition under 37 CFR 1.84(a)(2) is **GRANTED**.

Petitioner is advised that this decision grants the petition to accept color drawing(s) or photograph(s) because the requirements of 37 CFR 1.84(a)(2) or (b)(2) have been met. The initial review undertaken for purposes of the petition did not identify new matter in the color drawing(s) or photograph(s). However, the grant of this

petition should not be construed as a determination that should the color drawing(s) be entered the application would be free of statutory and/or formal defects. See MPEP § 608.02(VIII) and 608.02(b). The examiner is charged with determining whether applicant's nonprovisional application as amended to include the replacement drawings complies with all statutory requirements (e.g., enablement under 35 U.S.C. 112) and other applicable requirements (e.g., other formal requirements under 37 CFR 1.84). Further, the determination of whether a petition establishes a sufficient basis to accept color drawings or photographs is separate from the examiner's ultimate determination as to whether an amendment to the drawings should be entered (e.g., based on the prohibition under 35 U.S.C. 132 against introducing new matter). See MPEP § 608.04(a), 608.02 (h), and 2163.06(l).

Should there be any questions about this decision, please contact BENNETT M CELSA, by letter addressed to Director, TC 1600, at the address listed above, or by telephone at (571)272-0807, or by facsimile sent to the general Office facsimile number, 571-273-8300.

/BRANDON J FETTEROLF/
Supervisory Patent Examiner, Technology
Center 1600

/BENNETT M CELSA/
Quality Assurance Specialist , Technology
Center 1600

Issue Classification 	Application/Control No. 18/585,905	Applicant(s)/Patent Under Reexamination Yang et al.
	Examiner MELISSA J PERREIRA	Art Unit 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
	/		/		

/MELISSA J PERREIRA/ Examiner, Art Unit 1618 (Assistant Examiner)	07 August 2024 (Date)	Total Claims Allowed: 4	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618 (Primary Examiner)	14 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 18/585,905	Applicant(s)/Patent Under Reexamination Yang et al.
	Examiner MELISSA J PERREIRA	Art Unit 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 (Assistant Examiner)	07 August 2024 (Date)	Total Claims Allowed: 4	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618 (Primary Examiner)	14 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Issue Classification 	Application/Control No. 18/585,905	Applicant(s)/Patent Under Reexamination Yang et al.
	Examiner MELISSA J PERREIRA	Art Unit 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	1	28								
	2		11		20	2	29								
	3		12		21	3	30								
	4		13		22	4	31								
	5		14		23										
	6		15		24										
	7		16		25										
	8		17		26										
	9		18		27										

/MELISSA J PERREIRA/ Examiner, Art Unit 1618 (Assistant Examiner)	07 August 2024 (Date)	Total Claims Allowed: 4	
/Michael G. Hartley/ Supervisory Patent Examiner, Art Unit 1618 (Primary Examiner)	14 August 2024 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Search Notes 	Application/Control No. 18/585,905	Applicant(s)/Patent Under Reexamination Yang et al.
	Examiner MELISSA J PERREIRA	Art Unit 1618

CPC - Searched*		
Symbol	Date	Examiner
A61K51/0485 or A61K47/545 or A61K51/0478 or A61K51/0482	07/29/2024	MP

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
filing receipt	07/29/2024	MP
continuity data map	07/29/2024	MP
allowability conference (SPE Mike Hartley)	07/31/2024	MP
google scholar	07/29/2024	MP
PE2E search and inventor search	07/29/2024	MP
DAV inventor search	07/29/2024	MP

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618
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<i>Search Notes</i> 	Application/Control No. 18/585,905	Applicant(s)/Patent Under Reexamination Yang et al.
	Examiner MELISSA J PERREIRA	Art Unit 1618

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	51/0485	07/29/2024	MP
A61K	47/545	07/29/2024	MP
A61K	51/0478	07/29/2024	MP
A61K	51/0482	07/29/2024	MP

	/MELISSA J PERREIRA/ Examiner, Art Unit 1618
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Web Search History

date, time	web site	search string
7/29/2024 4:43:20 PM	Google Scholar	FAP quinolinyly compounds
7/29/2024 4:44:20 PM	Google Scholar	FAP cyanoproline chelators
7/29/2024 4:44:30 PM	Google Scholar	FAP cyanoproline quinolinyly compounds
7/29/2024 4:44:37 PM	Google Scholar	FAP fluorinated quinolinyly compounds
7/29/2024 4:47:19 PM	Google Scholar	FAP quinolinyly compounds chelators
7/29/2024 4:47:48 PM	Google Scholar	FAP dye compounds
7/29/2024 4:48:39 PM	Google Scholar	cyano proline compounds
7/29/2024 4:48:51 PM	Google Scholar	fluorinated cyano proline compounds
7/29/2024 4:49:06 PM	Google Scholar	cyano proline compounds PET
7/29/2024 4:49:45 PM	Google Scholar	radiolabeled fibroblast activation protein inhibitor
7/29/2024 4:49:53 PM	Google Scholar	infrared fibroblast activation protein inhibitor
7/29/2024 4:50:16 PM	Google Scholar	metal chelator fibroblast activation protein inhibitor

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	18/585,905
				Filing Date	23-Feb-2024
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	1	of	3	Attorney Docket Number	JHU-36631.304

U.S. PATENTS					
Examine r 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
	1.	9346814	2016-05-24	JANSEN et al.	

U.S. PUBLISHED PATENT APPLICATIONS					
Examine r 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.	2008/0280856	2008-11-13	COHEN et al.	
	2.	20100098633 A1	2010-04-22	ZIMMERMAN et al.	
	3.	20140357650	2014-12-04	JANSEN et al.	
	4.	2020/0237936	2020-07-30	LOW et al.	
	5.	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	Translatio n ⁸
	1.	WO 2010/014933	2010-02-04	THE JOHNS HOPKINS UNIVERSITY		
	2.	WO 2010/108125	2010-09-23	THE JOHNS HOPKINS UNIVERSITY		

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	08/07/2024
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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 <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	18/585,905
				Filing Date	23-Feb-2024
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	2	of	3	Attorney Docket Number	JHU-36631.304

FOREIGN PATENT DOCUMENTS						
	3.	WO 2013/107820	2013-07-25	UNIVERSITEIT ANTWERPEN et al		
	4.	WO 2014 /001538	2014-01-03	GE HEALTHCARE LTD		
	5.	WO 2015/114166	2015-08-06	PHILOCHEM AG		
	6.	WO 2016/065142	2016-04-28	THE JOHNS HOPKINS UNIVERSITY		
	7.	WO 2016/149188	2016-09-22	THE JOHNS HOPKINS UNIVERSITY		
	8.	WO 2016/196628 A1	2016-12-08	THE JOHNS HOPKINS UNIVERSITY		
	9.	EP 18199641.4	2018-10-10	UNIV HEIDELBERG		
	10	WO 2019/154886	2019-08-15	UNIV HEIDELBERG		
	11	JP2021-512949A	2021-05-20	UNIV HEIDELBERG		X

NONPATENT LITERATURE DOCUMENTS				
Examiner Initials ⁷	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and-or country where published.		Translatio n ⁶
	1.	ALLINEN et al., Molecular characterization of the tumor microenvironment in breast cancer. Cancer Cell. 2004 Jul;6(1):17-32.		
	2.	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.		
	3.	BAE et al., Fibroblast activation protein alpha identifies mesenchymal stromal cells from human bone marrow. Br J Haematol. 2008 Sep;142(5):827-30.		
	4.	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.		
	5.	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.		

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	08/07/2024
-----------------------	----------------------	--------------------	------------

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.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	18/585,905
				Filing Date	23-Feb-2024
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	3	of	3	Attorney Docket Number	JHU-36631.304

NONPATENT LITERATURE DOCUMENTS					
	6.	CHEN et al., Advance of molecular imaging technology and targeted imaging agent in imaging and therapy. Biomed Res Int. 2014; 2014 : 819324. PMCID: PMC3943245.			
	7.	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.			
	8.	COENEN et al., Fluorine-18 radiopharmaceuticals beyond [18F]FDG for use in oncology and neurosciences. Nuclear medicine and biology. 2010; 37:727-740.			
	9.	DVORAKOVA et al., Inhibitor-Decorated Polymer Conjugates Targeting Fibroblast Activation Protein. J Med Chem. 2017;60:8385-8393.			
	10	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.			
	11	Extended EP Search Report for EP 18871298.8, mailed May 20, 2021, 7 pages			
	12	FERREIRA et al., "Monitoring Alcoholic Fermentation: An Untargeted Approach". Journal of Agricultural and Food Chemistry, 2014,62, 6784-6793.			
	13	FISCHER et al., Radioimmunotherapy of fibroblast activation protein positive tumors by rapidly internalizing antibodies. Clin Cancer Res. 2012;18:6208-6218.			
	14	FRANCO et al., Cancer associated fibroblasts in cancer pathogenesis. Semin Cell Dev Biol. 2010 Feb;21(1):33-9.			
	15	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.			
	16	International Search Report and Written Opinion for PCT/US2018/057086, mailed May 10, 2019, 12 pages			
	17	JAMOUS et al., Synthesis of peptide radiopharmaceuticals for the therapy and diagnosis of tumor diseases. Molecules. 2013 Mar 14;18(3):3379-409.			
	18	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.			
	19	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.			
	20	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 FERREIRA/	Date Considered	08/07/2024
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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 <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	18/585,905
				Filing Date	23-Feb-2024
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	4	of	3	Attorney Docket Number	JHU-36631.304

NONPATENT LITERATURE DOCUMENTS					
	21	KRAMAN et al., Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. Science. 2010 Nov 5;330(6005):827-30.			
	22	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.			
	23	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			
	24	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.			
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	26	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.			
	27	METABOLOMICS - EMBL-EBI,ht , ://www.ebi.ac.uk/traininalonlineicaffsesimetabolomics- introduction/what-is/rnall-molecules/, retrieved on 2023-12-12.5 pages.			
	28	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.			
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	32	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.			
	33	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.			

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	07/29/2024
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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 <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	18/585,905
				Filing Date	23-Feb-2024
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	5	of	3	Attorney Docket Number	JHU-36631.304

NONPATENT LITERATURE DOCUMENTS					
	34	TAHTIS et al., Expression and Targeting of Human Fibroblast Activation Protien in a Human Skin/Severe Combined Immunodeficient Mouse Breast Cancer Xenograft Model. Mol. Cancer Therap. 2003 August, Vol. 2: 729-737.			
	35	TERRY et al., Monitoring Therapy Response of Expiemental Arthritis with Radiolabeled Tracers Targeting Fibroblasts, Macrophages, or Integrin $\alpha\beta 3$. J. Nucl. Med. 2016 March, 57(3): 467-472.			
	36	Third Party Observations for application number EP18871298.8 Dated January 10, 2024. 553 pages			
	37	Third Party Observations for application number EP20180871298. Dated 04/03/2022. 7 pages.			
	38	Third Party Observations Japanese Patent Application no. 2020-523010. Dated 24 Oct 2022. 7 pages.			
	39	Third Party Preissuance Submission filed in USSN 16/758, 182, filed February 23, 2022, 6 pages.			
	40	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.			
	41	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.			
	42	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.			
	43	YOUN et al., In vivo noninvasive small animal molecular imaging. Osong Public Health Res Perspect. 2012; 3 :48-59.			
	44	YU et al., The dipeptidyl peptidase IV family in cancer and cell biology. FEBS J. 2010 Mar;277(5):1126-44.			

Examiner Signature	/MELISSA J PERREIRA/	Date Considered	07/29/2024
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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 <i>(Use as many sheets as necessary)</i>				Complete if Known	
				<i>Application Number</i>	18/585,905
				<i>Filing Date</i>	23-Feb-2024
				<i>First Named Inventor</i>	Yang
				<i>Art Unit</i>	
				<i>Examiner Name</i>	
Sheet	6	of	3	<i>Attorney Docket Number</i>	JHU-36631.304

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 18/354,282 filed on July 18, 2023. 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	18/585,905
				Filing Date	23-Feb-2024
				First Named Inventor	Yang
				Art Unit	
				Examiner Name	
Sheet	7	of	3	Attorney Docket Number	JHU-36631.304

Signature	/Jeffrey W. Childers/	Date (YYYY-MM-DD)	2024-02-26
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.

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⁵ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3).

⁶ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document.

⁷ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible.

⁸ Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

REMARKS

New claim 31 has been added. Support for new claim 31 can be found in the claims and specification as originally filed. No new matter has been added.

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.

Respectfully Submitted,

CASIMIR JONES, S.C.

Date: February 26, 2024

/JEFFREY W. CHILDERS/

Jeffrey W. Childers, Ph.D.

Registration No. 58126

Customer No. 101943

Bibliographic Data

Application No: 18/585,905

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.
02/23/2024	424	1618	JHU-36631.304
RULE			

APPLICANTS

The Johns Hopkins University, Baltimore, MD, UNITED STATES

INVENTORS

Xing Yang,

Sridhar Nimmagadda,

Steven Rowe,

Stephanie Slania,

Martin G. Pomper,

CONTINUING DATA

This application is a CON of 18354282 07/18/2023 PAT 11938201

18354282 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**

04/09/2024

** SMALL ENTITY **

STATE OR COUNTRY

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The Johns Hopkins University

c/o Casimir Jones

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UNITED STATES
FILING FEE RECEIVED
\$2,400

PE2E SEARCH - Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
L1	83739	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	2024/07/29 03:55 PM
L2	28270693	radioisotop\$6 OR radionuclide OR radiolabel\$3 OR dye OR optical OR cyanine OR chelator OR DOTA OR IRDye	(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	2024/07/29 03:56 PM
L3	52222	L1 AND L2	(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	2024/07/29 03:57 PM
L4	830266	proline OR (cyano near2 proline)	(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,	OR	ON	ON	2024/07/29 03:57 PM

L5	19977	L3 AND L4	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) (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	2024/07/29 03:57 PM
L6	1232323	quinolin\$4	(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	2024/07/29 03:58 PM
L7	4399	L5 AND L6	(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	2024/07/29 03:58 PM
L8	1892	L7 AND ((@py<="2017"))	(US-PGPUB; USPAT; USOCR; FIT (AU, AP,	OR	ON	ON	2024/07/29 03:58 PM

L9	132460800	CN OR cyanine	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	2024/07/29 03:59 PM
L10	1399	L8 AND L9	(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	2024/07/29 03:59 PM
L11	584	((("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	2024/07/29 04:38 PM
L12	9	L1 AND L11	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/07/29 04:39 PM

L13	6777	(A61K51/0485 OR A61K47/545 OR A61K51/0478 OR A61K51/0482).cpc.	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/07/29 04:40 PM
L14	197	L3 AND L13	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/07/29 04:40 PM
L15	1	L8 AND L13	(US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT)	OR	ON	ON	2024/07/29 04:40 PM

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	22617	FAP OR (fibroblast near2 activation)	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:41 PM
N2	5713814	radioisotop\$6 OR radionuclide OR radiolabel\$3 OR dye OR optical OR cyanine OR chelator OR DOTA OR IRDye	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:41 PM
N3	16524	N1 AND N2	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:41 PM
N4	14480503	N1 same' N2	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:41 PM
N5	977	N1 SAME N2	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:41 PM
N6	225286	proline OR (cyano near2 proline)	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:42 PM
N7	262	N5 AND N6	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:42 PM
N8	507	((("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	2024/07/29 04:42 PM
N9	8	N1 AND N8	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:42 PM
N10	3918	(A61K51/0485 OR A61K47/545 OR A61K51/0478 OR A61K51/0482).cpc.	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:42 PM
N11	207	N1 AND N10	(US-PGPUB; USPAT)	OR	ON	ON	2024/07/29 04:42 PM



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NOTICE OF ALLOWANCE AND FEE(S) DUE

101943 7590 08/20/2024
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: 08/20/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296

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	11/20/2024

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.

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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)

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.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296

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	11/20/2024

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,

1 _____

(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.

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

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

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.

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.

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. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296
101943	7590	08/20/2024	EXAMINER	
The Johns Hopkins University c/o Casimir Jones 2275 Deming Way Suite 310 Middleton, WI 53562			PERREIRA, MELISSA JEAN	
			ART UNIT	PAPER NUMBER
			1618	
DATE MAILED: 08/20/2024				

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. 18/585,905	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 8/6/24.
☐ 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 28-31 . 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

Art Unit: 1618

<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

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.**

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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.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296

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	11/20/2024

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

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

The Johns Hopkins University

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. 50-4302

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

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

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.

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.

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 August 26, 2024

Typed or printed name Jeffrey W. Childers

Registration No. 58126



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
08/26/2024 10:17:44 AM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 # 7296

FILED BY Van Nguyen

PATENT CENTER # 66920864

FILING DATE 02/23/2024

CUSTOMER # 101943

FIRST NAMED
INVENTOR Xing Yang

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Jeffrey Childers

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-08-26 - JHU-36631.304 - Issue Fee Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	109 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-08-26 - JHU-36631.304 - Issue Fee Transmittal.pdf	2F04A931D5EDC194C2B216E2D9D042FB7519B078407004E5E 77241A292D190FCC2135476C6C34F24EA2172B72246E566004 5F713558CF8B60F1EB4C8E3B53EAE

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.



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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
08/26/2024 10:17:44 AM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 # 7296

FILED BY Van Nguyen

PATENT CENTER # 66920864

AUTHORIZED BY Jeffrey Childers

CUSTOMER # 101943

FILING DATE 02/23/2024

CORRESPONDENCE
ADDRESS -

FIRST NAMED
INVENTOR Xing Yang

Payment Information

PAYMENT METHOD
CARD / 0638

PAYMENT TRANSACTION ID
E20248PA18438687

PAYMENT AUTHORIZED BY
Van Nguyen

PRE-AUTHORIZED ACCOUNT
504302

PRE-AUTHORIZED CATEGORY
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.

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New International Application Filed with the USPTO as a Receiving Office

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/585,905	02/23/2024	Xing Yang	JHU-36631.304

CONFIRMATION NO. 7296

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

PUBLICATION NOTICE



OC000000077448102

Date Mailed: 09/05/2024

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

Publication No.US-2024-0293584-A1

Publication Date:09/05/2024

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 viewed using the USPTO's publicly available Searchable Databases via the Patent Public Search tool at www.uspto.gov. The direct link to access the Patent Public Search tool is currently <https://ppubs.uspto.gov/pubwebapp/static/pages/ppubsbasic.html>.

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 Patent Center, the USPTO's electronic patent application filing and management system. The direct link to access this status information is currently <https://patentcenter.uspto.gov/>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of Patent Center.

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

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



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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/585,905	10/15/2024	12115233	JHU-36631.304	7296

101943 7590 09/25/2024
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, Baltimore, 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](https://selectusa.gov).

Placeholder Sheet for Supplemental Content

Application Number: 18585905

Document Date: 10/15/2024

The presence of this form indicates that the following document type was received in electronic format on the date identified above. This document is stored separately from the typical case contents which are stored in image format.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296
101943	7590	10/15/2024		
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
			10/15/2024	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.
18/585,905	15-Oct-2024	12115233

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
CERTIFICATE OF CORRECTIONPage 1 of 1

PATENT NO. : 12,115,233
APPLICATION NO.: 18/585,905
ISSUE DATE : 15-Oct-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, column 64, claim 1, line 32-33 reads:

- -B (OH)₂ -C(O) alkyl, -C(O)aryl-, -C-C-C(O) aryl, -C-C-S(O)₂aryl, - CO₂H, -SO₃H, -

Whereas it should read:

- -B (OH)₂ -C(O) alkyl, -C(O)aryl-, -C=C-C(O) aryl, -C=C-S(O)₂aryl, - CO₂H, -SO₃H, -

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.

Petitioner GE Healthcare – Ex. 1002, p. 226

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

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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.
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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.
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.:	12,115,233	Issued: 15-Oct-2024
Application No.:	18/585,905	Filing Date: 23-Feb-2024
Examiner:	MELISSA JEAN PERREIRA	Art Unit: 1618
Inventors:	YANG, Xing, et al.	
Title of Invention:	IMAGING AND RADIOTHERAPEUTICS AGENTS TARGETING FIBROBLAST-ACTIVATION PROTEIN-alpha (FAP-alpha)	

REQUEST FOR CERTIFICATE OF CORRECTION OF PATENT

Attention Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 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. Applicants submit herewith Form PTO/SB/44 showing the correction that is requested.

In the Letters Patent, column 64, claim 1, line 32-33 reads:

- -B (OH)₂ -C(O) alkyl, -C(O)aryl-, -C-C-C(O) aryl, -C-C-S(O)₂aryl, - CO₂H, -SO₃H, -

Whereas it should read:

- -B (OH)₂ -C(O) alkyl, -C(O)aryl-, -C=C-C(O) aryl, -C=C-S(O)₂aryl, - CO₂H, -SO₃H, -

The correct text of claim 1 can be found in the Preliminary Amendment filed on February 23, 2024 and within the second Preliminary Amendment filed February 26, 2024. Because the error in the patent is a result of the Office's mistake, applicants believe 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-36631.304**

Respectfully submitted,

Dated: November 14, 2024

/Jeffrey W. Childers/

Jeffrey W. Childers

CASIMIR JONES, S.C.

Reg. No. 58,126

2275 Deming Way, Suite 310

Middleton, WI 53562

608 662 1277



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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
11/14/2024 04:05:22 PM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 #	12115233
CONFIRMATION #	7296	FILED BY	Jeremiah Gile
PATENT CENTER #	67963909	FILING DATE	02/23/2024
CUSTOMER #	101943	FIRST NAMED INVENTOR	Xing Yang
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Jeffrey Childers

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
2024-11-14_36631.304_Request for CoC.pdf	2	Request for Certificate of Correction	108 KB
2024-11-14_36631.304_CoC.pdf	2	Request for Certificate of Correction	88 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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2024-11-
14_36631.304_CoC.pdf

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86521B0E8696C614C63B7BD75745B4EE5B07A3E8961A868C7
9B2D25AF5978FD311626AFE2CB1BF6

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.

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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.



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ACKNOWLEDGEMENT OF LOSS OF ENTITLEMENT TO ENTITY STATUS DISCOUNT

APPLICATION #	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET #	REQUEST ID
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	305752

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



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PATENT AND TRADEMARK OFFICE

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Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/585,905

RECEIPT DATE / TIME
11/19/2024 01:46:07 PM Z ET

ATTORNEY DOCKET #
JHU-36631.304

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 # 12115233

CONFIRMATION # 7296

FILED BY Van Nguyen

PATENT CENTER # 68018088

FILING DATE 02/23/2024

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- 36631.304_Petition-Pay-LE- Fee.pdf	3	Petition for review by the Office of Petitions	28 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
2024-11-19 - JHU- 36631.304_Petition-Pay-LE- Fee.pdf	63960AC206DF3E8236D2FB8B3DDC5D6C76A4180F713411FD 517FFDA33B2DCBF5A4D72FAE0DFF1C6EBF7B728B5E166E1 E4E170E5A1DA36F50A85EBF547448B080

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

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

New International Application Filed with the USPTO as a Receiving Office

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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent Application No.: 18/585,905
Filed: 23-February-2024
Applicant: Xing Yang, et al.
Art Unit: 1618
Examiner: MELISSA JEAN PERREIRA
Confirmation No.: 7296
Docket No.: JHU-36631.304
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)
Utility Issue Fee	1501	\$1,200.00	2501	\$480.00	08/26/2024	\$720.00
Statutory or Terminal Disclaimer	1814	\$170.00	2814	\$170.00	08/06/2024	\$0.00
Petition Fee-37CFR 1.17(H) (Group III)	1464	\$140.00	2464	\$56.00	08/06/2024	\$84.00
Non-DOCX Filing Surcharge	1054	\$400.00	2054	\$160.00	05/20/2024	\$240.00
Processing Fee, Except Prov. Appls	1830	\$140.00	2830	\$56.00	02/23/2024	\$84.00
Request for Prioritized Exam	1817	\$4,200	2817	\$1,680	02/23/2024	\$2,520
Utility Filing Fee	1011	\$ 320.00	4011	\$ 64.00	02/23/2024	\$256.00
Utility Exam Fee	1311	\$ 800.00	2311	\$ 320.00	02/23/2024	\$480.00
Utility Search Fee	1111	\$ 700.00	2111	\$ 280.00	02/23/2024	\$420.00
TOTALS:		\$ 8,070.00		\$3,266.00		\$4,804.00

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

U.S. Patent Application No. 18/585,905
Attorney Docket No. JHU-36631.304

CASIMIR JONES, S.C.
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Phone: 608.662.1277
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296
101943	7590	12/31/2024		
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
			12/31/2024	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.
18/585,905	31-Dec-2024	12115233

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. : 12,115,233 B2
APPLICATION NO. : 18/585905
DATED : October 15, 2024
INVENTOR(S) : Xing Yang et al.

Page 1 of 1

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

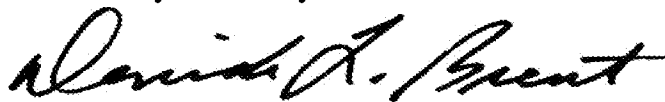
Column 64, Claim 1, Line 32-33 reads:

- -B (OH)₂ -C(O) alkyl, -C(O)aryl-, -C-C-C(O) aryl, -C-C-S(O)₂aryl, - CO₂H, -SO₃H, -

Whereas it should read:

- -B (OH)₂ -C(O) alkyl, -C(O)aryl-, -C=C-C(O) aryl, -C=C-S(O)₂aryl, - CO₂H, -SO₃H, -

Signed and Sealed this
Thirty-first Day of December, 2024



Derrick Brent
Acting Director of the United States Patent and Trademark Office



United States Patent and Trademark Office

Office of the Chief Financial Officer

Document Code:WFEE

User :Suad Mohammed

Sale Accounting Date:01/21/2025

Sale Item Reference Number

18585905

Effective Date

11/19/2024

Document Number	Fee Code	Fee Code Description	Amount Paid	Payment Method
I20251KF02526465	1461	1.28(C) SUBMISSIONS - APPLIC FILE FEE	\$4,804.00	Deposit Account



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/585,905	02/23/2024	Xing Yang	JHU-36631.304	7296
101943	7590	01/28/2025		
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
			01/28/2025	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
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In re Patent No. 12,115,233
Issue Date: October 15, 2024
Application No. 18/585,905
Filing or 371(c) Date: February 23, 2024
Attorney Docket No. JHU-36631.304

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DECISION ON PETITION

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 hereby **ACCEPTED**.

This patent is no longer entitled to small entity status. Accordingly, all future fees paid in this patent must be paid at the undiscounted entity status rate.

Inquiries related to this communication should be directed to Tamie Jarrett at (571) 270-1309.

/Irvin Dingle/
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