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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: PAK4 INHIBITORS AND METHODS OF USE

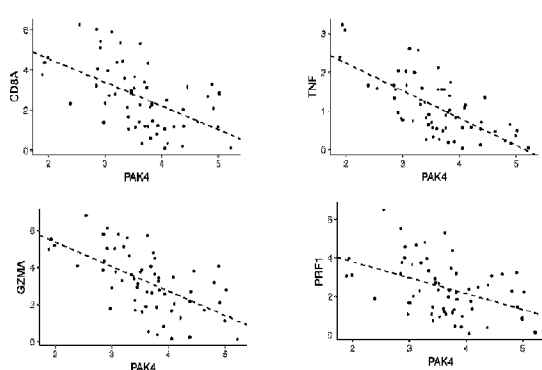


Figure 1

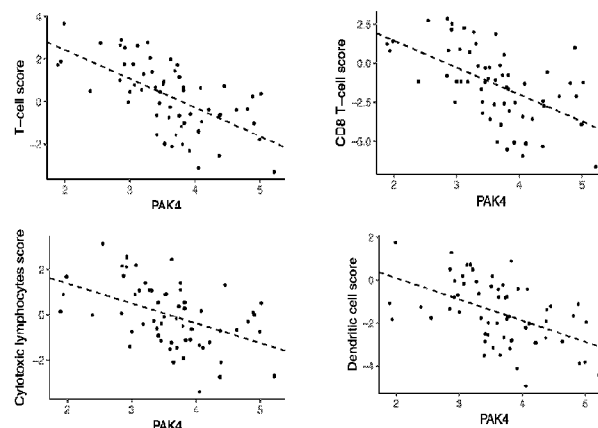


Figure 1 (continued)

(57) Abstract: Disclosed herein are methods of treating cancer in a subject, comprising: administering at least one PAK4 inhibitor to the subject; and in certain embodiments administering at least one immunostimulatory agent to the subject. In some aspects, the immunostimulatory agent can be a checkpoint inhibitor. In certain aspects the checkpoint inhibitor can be an anti-PD1 antibody.

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:

28 November 2019 (28.11.2019)

INTERNATIONAL SEARCH REPORT

International application No.

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Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

- a. ☐ forming part of the international application as filed:
☐ in the form of an Annex C/ST.25 text file.
☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☒ furnished subsequent to the international filing date for the purposes of international search only:
☒ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☒ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 14-28, 42-65
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-13, 29-41, 66-84, an antibody that inhibits binding between PD1 and PD-L1 (immunostimulatory agent), and KPT-9274 (Pak4 inhibitor) are directed toward methods of treating cancer in a subject, and a kit therefor.

---Continued on supplemental page---

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 4/2-3, 11, 12/1-2, 13/1-2, 29-31, 39-41, 66-68, 76-78; KPT-9274; an antibody that inhibits binding between PD1 and PD-L1 (immunostimulatory agent)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/53, 31/506, 31/519, 31/5377, 39/395; C12N 9/12, 9/99; A61P 35/02, 35/04 (2019.01)

CPC - A61K 31/53, 31/506, 31/519, 31/5377, 39/395; C12N 9/12, 9/99; A61P 35/02, 35/04; C07D 401/14, 403/10, 403/14, 405/12, 405/14, 413/12, 413/14, 417/12, 471/08, 487/04, 487/08, 491/08, 495/04, 498/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/197036 A1 (C4 THERAPEUTICS, INC.) 16 November 2017; ; page 6, line 12; page 12, lines 4-5, 7; page 13, lines 26-28; page 27, line 28; page 79, lines 15-18; page 160, line 28;	1-3, 11, 12/1-2, 13/1-2, 66-67, 76-78
Y	page 161, line 8-13, 15; Figure 3PP, 8YY	4/2-3, 29-31, 39-41, 68
Y	~ (SENAPEDES, W et al.) Therapeutic Potential of Targeting PAK Signaling. Anti-Cancer Agents in Medicinal Chemistry. 2016, Vol. 16, No. 1; pages 75-88; abstract; page 76, 1st column, 3rd paragraph; page 80, 2nd column, 2nd paragraph; Figure 1; DOI: 10.2174/1871520615666150617111414	1-3, 4/2-3, 11, 12/1-2, 13/1-2, 29-31, 39-41, 66-68, 76-78
Y	~ (RANE, C et al.) A novel orally bioavailable compound KPT-9274 inhibits PAK4, and blocks triple negative breast cancer tumor growth. Scientific Reports. 15 February 2017, Vol. 7; pages 1-12; abstract; page 1, 2nd paragraph; Figure 1; DOI: 10.1038/srep42555	4/2-3, 29-31, 39-41, 68
A	WO 2007/023382 A2 (PFIZER INC.) 1 March 2007; entire document	1-3, 4/2-3, 11, 12/1-2, 13/1-2, 29-31, 39-41, 66-68, 76-78
A	~ (STABEN, ST et al.) Back Pocket Flexibility Provides Group II p21-Activated Kinase (PAK) Selectivity for Type I 1/2 Kinase Inhibitors. Journal of Medicinal Chemistry. 16 January 2014, Vol. 57, pages 1033-1045; DOI: 10.1021/jm401768t	1-3, 4/2-3, 11, 12/1-2, 13/1-2, 29-31, 39-41, 66-68, 76-78
A	~ (GUO, C et al.) Discovery of Pyrroloaminopyrazoles as Novel PAK Inhibitors. Journal of Medicinal Chemistry. 03 May 2012, Vol. 55, pages 4728-4739; DOI: 10.1021/jm300204j	1-3, 4/2-3, 11, 12/1-2, 13/1-2, 29-31, 39-41, 66-68, 76-78

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 September 2019 (12.09.2019)

Date of mailing of the international search report

22 OCT 2019

Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US19/27716

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	(KUZNAR, W) Research Update: Targets to Enhance Melanoma Anti-tumor Immune Response. MedPageToday. Webpage [online]. 23 February 2019 [Retrieved on 15 August 2019]. Retrieved from the Internet: <URL: https://www.medpagetoday.com/reading-room/asco/skin-cancer/78162 >; pages 1-5	1-3, 4/2-3, 11, 12/1-2, 13/1-2, 29-31, 39-41, 66-68, 76-78
P, X	WO 2019/033041 A1 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 14 February 2019; entire document	1-3, 4/2-3, 11, 12/1-2, 13/1-2, 29-31, 39-41, 66-68, 76-78

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-Continued from Box No. III: Observations where unity of invention is lacking-

The methods and kit will be searched to the extent they encompass an antibody that inhibits binding between PD1 and PD-L1 (first exemplary immunostimulatory agent), and KPT-9274 (first exemplary Pak4 inhibitor). Applicant is invited to elect additional immunostimulatory agent(s), and/or Pak4 inhibitor(s) with specified inhibitor name, or with fully specified inhibitor structure(s) (i.e. no optional or variable atoms, bonds, moieties or substituents), and/or Pak4 inhibitory system(s) (i.e. a CRISPR-Cas9 system with targeting sgRNAs encompassing SEQ ID NOs: 1 and 2), to be searched, where any elected species is available as an option within at least one searchable claim. Additional immunostimulatory agent(s) and/or Pak4 inhibitor(s) or inhibitory system(s) will be searched upon the payment of additional fees. It is believed that claims x1-3, 4 (in-part), 11-13 (each in-part), 29-31, 39-41 (each in-part), 66-68, and 76-78 (each in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass an antibody that inhibits binding between PD1 and PD-L1 (immunostimulatory agent), and KPT-9274 (Pak4 inhibitor). Applicants must specify the searchable claims that encompass any additionally elected immunostimulatory agent(s) and/or Pak4 inhibitor(s) or inhibitory system(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a Pak4 inhibitor encompassing PF-3758309 (Pak4 inhibitor).

No technical features are shared between the immunostimulatory agents and/or Pak4 inhibitors of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including the following claims:

1, a method of treating cancer in a subject, comprising: (1) administering at least one PAK4 inhibitor to the subject; and (2) administering at least one immunostimulatory agent to the subject.

66, a kit comprising at least one PAK4 inhibitor, at least one immunostimulatory agent, and instructions for use.

However, these shared technical features are previously disclosed by US 2012/0264751 A1 to Zhang et al. (hereinafter 'Zhang').

As per Claim 1, Zhang discloses a method of treating cancer in a subject (a method of treating tumor growth or abnormal cell proliferation (cancer) in a subject; paragraph [0107]), comprising: (1) administering at least one PAK4 inhibitor to the subject ((1) administering at least one PAK4 inhibitor to the subject; abstract, paragraphs [0107], [0108]); and (2) administering at least one immunostimulatory agent to the subject (administering in combination agents capable of enhancing antitumor immune responses, such as CTLA4 antibodies (at least one immunostimulatory agent) to the subject; paragraph [0121]).

As per Claim 66, Zhang discloses a kit (a kit; paragraphs [0246], [0247]) comprising at least one PAK4 inhibitor (comprising at least one Pak4 inhibitor; abstract, paragraphs [0107], [0108], [0246]), at least one immunostimulatory agent (agents capable of enhancing antitumor immune responses, such as CTLA4 antibodies (at least one immunostimulatory agent); paragraphs [0121], [0246]), and instructions for use (instructions for use; paragraph [0247]).

Groups I+ share the further technical features including the following Claim:

29, a method of treating cancer in a subject, comprising administering a PAK4 inhibitor to the subject, wherein the cancer (1) has been determined to be substantially free or have a low baseline level of tumor-infiltrating T cells defined by having a density of less than 500 CD3+ or CD8+ T cells per mm square inside the tumor or at the invasive margin of the tumor when analyzed by immunohistochemistry or by mRNA expression of T cell genes or interferon gamma signaling genes or an equivalent T cell quantitation method; or (2) has been determined to have increased PAK4 expression relative to control, defined by measuring PAK4 protein expression by immunohistochemistry or an equivalent protein quantitation method or PAK4 mRNA expression by RNASeq, Nanostring, or an equivalent mRNA quantitation method.

However, these shared technical features are previously disclosed by Zhang, in view of US 2012/0045775 A1 to Smeal et al. (hereinafter 'Smeal').

As per Claim 29, Zhang, as above, discloses a method of treating cancer in a subject, (a method of treating tumor growth or abnormal cell proliferation (cancer) in a subject; paragraph [0107]), comprising: (1) administering at least one PAK4 inhibitor to the subject (1. administering at least one PAK4 inhibitor to the subject; abstract, paragraphs [0107], [0108]). Zhang does not disclose wherein the cancer (1) has been determined to be substantially free or have a low baseline level of tumor-infiltrating T cells defined by having a density of less than 500 CD3+ or CD8+ T cells per mm square inside the tumor or at the invasive margin of the tumor when analyzed by immunohistochemistry or by mRNA expression of T cell genes or interferon gamma signaling genes or an equivalent T cell quantitation method; or (2) has been determined to have increased PAK4 expression relative to control, defined by measuring PAK4 protein expression by immunohistochemistry or an equivalent protein quantitation method or PAK4 mRNA expression by RNASeq, Nanostring, or an equivalent mRNA quantitation method. Smeal discloses the use of Pak4 as a biomarker for tumorigenesis (use of Pak4 as a biomarker for tumorigenesis; abstract), including the use of Pak4 antibodies for immunohistochemistry (use of Pak4 antibodies for immunohistochemistry; paragraph [0053], [0054]) for the determination of total Pak4 and phosphorylated Pak4 in a biopsy sample (for the determination of total Pak4 and phosphorylated Pak4 in a biopsy sample; paragraph [0018]). It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have modified the disclosure of Zhang to have included the immunohistochemical determination of Pak4 levels in a biopsy sample from a subject's tissue or tumor in order to determine whether the tumor expressed high levels of Pak4 or phosphorylated Pak4, as disclosed by Smeal, as a means of screening for patients in whom the Pak4 inhibitors, as disclosed by Zhang, would have been a useful therapeutic regimen for the treatment of cancer.

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Zhang and Smeal references, unity of invention is lacking.