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(71) Applicants: **UNITED STATES GOVERNMENT AS REPRESENTED BY THE DEPARTMENT OF VETERANS AFFAIRS** [US/US]; 810 Vermont Avenue, Washington, D.C. 20420 (US). **UNIVERSITY OF MIAMI** [US/US]; 1951 NW 7th Avenue, Miami, FL 33166 (US).

(72) Inventors: **JACKSON, Andrew**; Miami Va Healthcare System, 1201 NW 19th St., Miami, FL 33125 (US). **SCHALLY, Andrew, V.**; 3801 Collins Avenue, #1506, Miami Beach, FL 33140 (US). **CAI, Renzhi**; Miami VA Healthcare System, 1201 Nw 19th St., Miami, FL 33125 (US). **CAI, Xianyang, Zhang**; 1200 Brickell Bay Drive #2109, Miami, FL 33131 (US). **WANG, Haibo**; 1441 NW 19th Street #127, Miami, FL 33135 (US). **SHA, Wei**; 1400 NW 10th Avenue #2009, Miami, FL 33136 (US).

(74) Agent: **MARTY, Scott, D.** et al.; Ballard Spahr LLP, 999 Peachtree Street, Suite 1000, Atlanta, GA 30309 (US).

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(54) Title: GROWTH HORMONE-RELEASING HORMONE ANTAGONISTS AND USES THEREOF

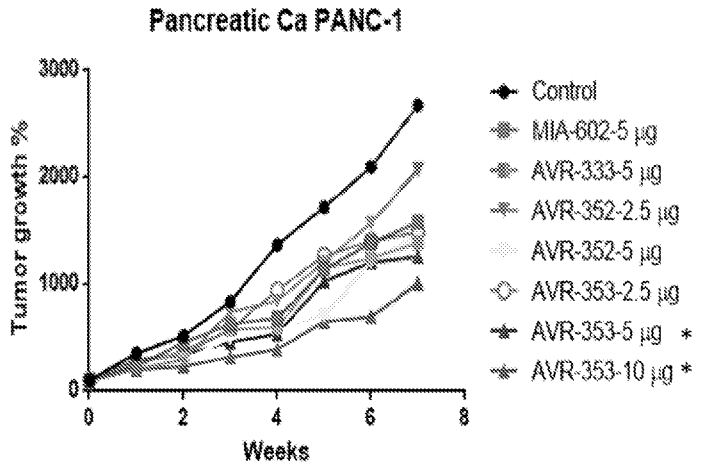

Fig. 1A

(57) Abstract: Described herein are compositions and methods for treating pulmonary fibrosis and cancer. The compositions include growth hormone releasing hormone peptides. The methods include reducing lung inflammation, lung scarring, reducing expression of T cell receptor complex genes as well as inhibiting tumor growth.

WO 2020/163833 A3

[Continued on next page]

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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))*

— *with sequence listing part of description (Rule 5.2(a))*

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/17375

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 38/25; C07K 14/60; G01N 33/74 (2020.01)

CPC - A61K 38/25; C07K14/60, 14/001; G01N 33/74

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 -- A	WO 2009/120831 A2 (THE UNIVERSITY OF MIAMI, et al.) 01 October 2009; abstract; paragraphs [0019], [0024], [0031], [0064], [0066], [0071], [0094]	10-11, 14-15, 18-19, 22-23, 27-28 ---------- 1, 5/1, 6/5/1, 7/5/1, 8/1, 9/8/1
A	US 2011/0066230 A1 (SCHALLY, A et al.) 17 March 2011; paragraph [0248]	1, 5/1, 6/5/1, 7/5/1, 8/1, 9/8/1
A	US 2018/0250358 A1 (UNIVERSITY OF MIAMI, et al.) 06 September 2018; abstract	1, 5/1, 6/5/1, 7/5/1, 8/1, 9/8/1
PX	(ZHANG, C et al.) Growth Hormone-Releasing Hormone Receptor Antagonist Modulates Lung Inflammation and Fibrosis due to Bleomycin. Lung. 07 August 2019; Vol. 197, No. 5; pages 541-549; entire document; DOI: 10.1007/s00408-019-00257-w	10-11, 14-15, 18-19, 22-23, 27-28

☐ 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	Date of mailing of the international search report
06 August 2020 (06.08.2020)	04 SEP 2020
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US20/17375

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.: 26, 31-35
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:

-***- Please See within the Next 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.:

Group 1+ Claims 1, 5-11, 14-15, 18-19, 22-23, 27-28; 5FPhAC-Ada-Tyr-DArg-Asp-Ala-Ile-5FPhe-Thr-Ala-Arg-Tyr (Me)-Arg-Lys-Val-Leu-Abu-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Nle-DArg-Har-Ada-NH2 (peptide sequence)

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.

-***-Continued from Box III Observations where unity of invention is lacking -***-

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 1-25, 27-30 and a peptide encompassing the sequence: 5FPhAC-Ada-Tyr-DArg-Asp-Ala-Ile-5FPhe-Thr-Ala-Arg-Tyr (Me)-Arg-Lys-Val-Leu-Abu-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Nle-DArg-Har-Ada-NH2 (peptide sequence) are directed toward peptides, and methods associated therewith.

The peptides and methods will be searched to the extent they encompass the sequence: 5FPhAC-Ada- Tyr-DArg-Asp-Ala-Ile-5FPhe-Thr-Ala-Arg-Tyr-(Me)-Arg-Lys-Val-Leu-Abu-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Nle-DArg-Har-Ada-NH2 (first exemplary peptide sequence). Applicant is invited to elect additional peptide(s), with specified SEQ ID NO: for each, or with specified substitution(s) at specified site(s) of a SEQ ID NO:, such that the sequence of each elected species is fully specified (i.e. no optional or variable residues or substituents), and where available as an option within at least one searchable claim, to be searched. Additional peptide sequence(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 5-9 (each in-part), 10, 11, 14, 15, 18, 19, 22, 23, 27, and 28 encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass the sequence: 5FPhAC-Ada- Tyr-DArg-Asp-Ala-Ile-5FPhe-Thr-Ala-Arg-Tyr (Me)-Arg-Lys-Val-Leu-Abu-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln- Asp-Ile-Nle-DArg-Har-Ada-NH2 (peptide sequence). Applicants must specify the searchable claims that encompass any additionally elected peptide sequence(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 p-cePhAC-Tyr-DArg-Asp-Ala-Ile-5FPhe-Thr-Ala-Arg-Tyr (Me)-Arg-Lys-Val-Leu-Abu-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Nle- DArg-Har-Ada-NH2 (peptide sequence).

No technical features are shared between the GHRH receptor antagonists of Groups I+ and, accordingly, these groups lack unity a priori.

Groups I+ share the technical features including: a peptide comprising Formula I: X0-Tyr-DArg-Asp-Ala-Ile-X6-Thr-X8-X9-X10-X11-X12-Val-Leu-Abu-Gln-Leu-Ser-Ala-X20-X21-Leu-Leu-Gln-Asp-Ile-Nle-DArg-X29-X30 (SEQ ID NO: 1), wherein X30 is present or absent, or a pharmaceutically acceptable salt thereof: a method of inhibiting tumor growth, and treating cancer, the method comprising administering to a subject an effective amount of the peptide; a method of treating pulmonary fibrosis or ameliorating one or more symptoms thereof, and reducing lung inflammation and scarring, the method comprising: administering to a subject with pulmonary fibrosis a therapeutically effective amount of a growth hormone releasing hormone (GHRH) receptor antagonist; and a method of reducing expression of one or more T cell receptor complex genes, the method comprising administering to a subject with pulmonary fibrosis a therapeutically effective amount of a growth hormone releasing hormone (GHRH) receptor antagonist.

However, these shared technical features are previously disclosed by WO 2009/120831 A2 to The University of Miami (hereinafter 'Miami').

Miami discloses a peptide comprising Formula I: X0-Tyr-DArg-Asp-Ala-Ile-X6-Thr-X8-X9-X10-X11-X12-Val-Leu-Abu-Gln-Leu-Ser-Ala-X20-X21-Leu-Leu-Gln-Asp-Ile-Nle-DArg-X29-X30 (SEQ ID NO: 1) wherein X30 is present or absent, or a pharmaceutically acceptable salt thereof (a peptide comprising Formula I: X0-Tyr-DArg-Asp-Ala-Ile-X6-Thr X8-X9-X10-X11-X12-Val-Leu-Abu-Gln-Leu-Ser-Ala-X20-X21- Leu-Leu-Gln-Asp-Ile-Nle-DArg-X29-X30. wherein X30 is present or absent, or a pharmaceutically acceptable salt thereof [SEQ ID NO: 99] (SEQ ID NO: 1); paragraph [0024], SEQ ID NO: 99), a method of inhibiting tumor growth, and treating cancer, the method comprising administering to a subject an effective amount of the peptide (a method of inhibiting tumor growth, and treating cancer, the method comprising administering to a subject an effective amount of the peptide; paragraph [0031]); a method of treating pulmonary fibrosis or ameliorating one or more symptoms thereof, and reducing lung inflammation and scarring, the method comprising: administering to a subject with pulmonary fibrosis a therapeutically effective amount of a growth hormone releasing hormone (GHRH) receptor antagonist (a method of controlling or slowing the progression of (treating or ameliorating one or more symptoms thereof, and reducing lung inflammation and scarring) pulmonary fibrosis, the method comprising: administering to a subject with pulmonary fibrosis a therapeutically effective amount of a growth hormone releasing hormone (GHRH) receptor antagonist; paragraphs [0031], [0071]); and a method of reducing expression of one or more T cell receptor complex genes, the method comprising administering to a subject with pulmonary fibrosis a therapeutically effective amount of a growth hormone releasing hormone (GHRH) receptor antagonist (a method of controlling or slowing the progression of pulmonary fibrosis (a method of reducing expression of one or more T cell receptor complex genes), the method comprising administering to a subject with pulmonary fibrosis a therapeutically effective amount of a growth hormone releasing hormone (GHRH) receptor antagonist; paragraphs [0031], [0071]; wherein, absent evidence to the contrary, the reduced expression of one or more T cell receptor complex genes occurs as a natural response of the body to the administration of the GHRH receptor antagonist).

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 Miami reference, unity of invention is lacking.