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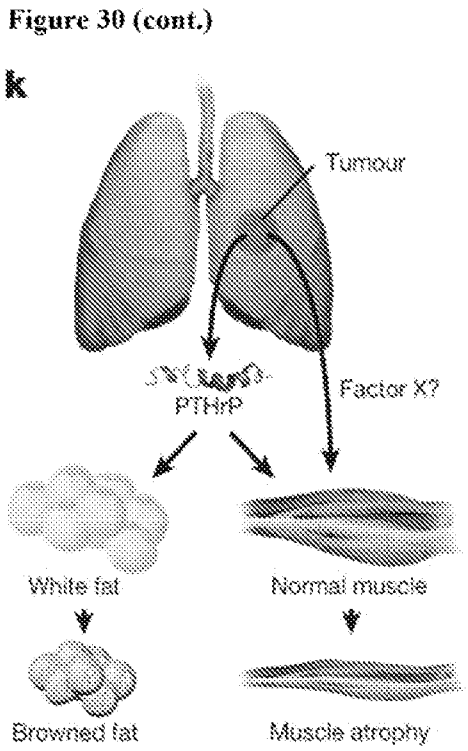
[Continued on next page]

(54) Title: COMPOSITIONS AND METHODS FOR MODULATING THERMOGENESIS USING PTH-RELATED AND EGF-RELATED MOLECULES



(57) Abstract: The present invention provides compositions and methods for modulating thermogenesis and related activities by modulating PTH-related and EGF-related expression and activity. Also provided are methods for preventing or treating metabolic disorders in a subject through modulation of PTH-related and EGF-related expression and activity.

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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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16 April 2015

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/48870

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 48/00; C07H 21/02 (2015.01)
CPC - A61K 48/00; C12N 15/63
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)
IPC(8): A61K 48/00; C07 H21/02 (2015.01)
CPC: A61K 48/00; C12N 15/63

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google; Google Scholar; NCBI/BLAST/PubMed; Dialog ProQuest; metabolic, biomarker, 'TGFA,' expression, level, 'NM_003236,' agent, adipose, insulin, glucose, obesity

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2013/090186 A1 (MODERNA THERAPEUTICS); June 20, 2013; paragraphs [0029], [00130], [00143], [00169], [00171], [00189], [00192], [00383], [00388], [00421], [00461], [00608]-[00616], [00628], [00824]; Table 1	79, 82, 87/79, 87/82 ----- 1, 2, 5-7, 12-14, 18-23, 26-27, 33-50, 53-54, 59-66, 69-70, 73-78, 81, 87/81
Y	US 2007/0037228 A1 (MOECKS, J et al.); February 15, 2007; paragraphs [0007]-[0009], [0017]-[0019], [0080]; SEQ ID NO:7; NCBI Reference Sequence: NM_003236	1, 2, 5-7, 12-14, 18-23, 26, 27, 33-50, 53, 54, 59-66, 69, 70, 73-78, 81, 87/81
Y	US 2013/0074199 A1 (SPIEGELMAN, BM et al.); March 21, 2013; paragraphs [0009], [0020]	21, 48, 76

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
16 January 2015 (16.01.2015)	09 FEB 2015
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. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/48870

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.: 17, 88-91
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 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.:

-***-Please See Supplemental Page-***-

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 No. 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 1-16 and 18-87 are directed toward methods of modulating a metabolic response, preventing or treating a metabolic disorder, and assessing the efficacy of an agent that modulates the expression or activity of a biomarker.

The methods of modulating a metabolic response, preventing or treating a metabolic disorder, and assessing the efficacy of an agent that modulates the expression or activity of a biomarker will be searched to the extent that the methods encompass a TGFA nucleic acid having a sequence at least 80% identical to SEQ ID NO: 1 (Homo sapiens DNA sequence). It is believed that Claims 1 (in-part), 2 (in-part), 5 (in-part), 6, 7, 12-14, 17-21, 22 (in-part), 23 (in-part), 26 (in-part), 27, 33 (in-part), 34 (in-part), 35 (in-part), 36 (in-part), 37 (in-part), 38 (in-part), 39 (in-part), 40 (in-part), 41 (in-part), 42 (in-part), 43 (in-part), 44 (in-part), 45 (in-part), 46 (in-part), 47 (in-part), 48 (in-part), 49 (in-part), 50 (in-part), 53 (in-part), 54, 59 (in-part), 60 (in-part), 61 (in-part), 62 (in-part), 63 (in-part), 64 (in-part), 65 (in-part), 66 (in-part), 69 (in-part), 70 (in-part), 73 (in-part), 74 (in-part), 75 (in-part), 76 (in-part), 77 (in-part), 78 (in-part), 79 (in-part), 81 (in-part), 82 (in-part) and 87 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NO: 1 (Homo sapiens DNA sequence). Additional nucleic acid and/or amino acid sequence(s) can be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected nucleic acid and/or amino acid 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: a TGFA amino acid sequence having a sequence at least 80% identical to SEQ ID NO: 2 (Homo sapiens amino acid sequence).

No technical features are shared between nucleic acids and polypeptides of Table I, and, accordingly, these nucleic acids and polypeptides lack unity a priori.

Groups I+ share the technical features including: a method of modulating a metabolic response comprising contacting a cell with an agent that modulates the expression and/or activity of one or more biomarkers listed in Table 1, or orthologs and fragments thereof to thereby modulate the metabolic response; a method of assessing the efficacy of an agent that modulates the expression and/or activity of one or more biomarkers listed in Table 1, or orthologs and fragments thereof, for modulating a metabolic response in a subject, comprising: a) detecting in a subject sample at a first point in time, the expression and/or activity of the expression and/or activity of the one or more biomarkers: b) repeating step a) during at least one subsequent point in time after administration of the agent and c) comparing the expression and/or activity detected in steps a) and b), wherein a significantly lower biomarker expression and/or activity in the first subject sample relative to at least one subsequent subject sample, indicates that the agent increases the metabolic response in the subject and/or wherein a significantly higher biomarker expression and/or activity in the first subject sample relative to at least one subsequent subject sample indicates that the test agent decreases the metabolic response in the subject; a method for preventing or treating a metabolic disorder in a subject comprising administering to the subject an agent that promotes expression and/or activity of one or more biomarkers listed in Table 1 or orthologs and fragments thereof, in the subject, thereby preventing or treating the metabolic disorder in the subject; a method for preventing or treating a metabolic disorder in a subject comprising administering to the subject an agent that inhibits expression and/or activity of one or more biomarkers listed in Table 1, or orthologs and fragments thereof, in the subject, thereby preventing or treating the metabolic disorder in the subject; a method for preventing or treating a metabolic disorder in a subject comprising administering to the subject an agent that increases expression and/or activity of one or more of PTHrP, PTH, BTC, EREG, HBEGP, AREG, EGF, EPGN, and TGFA, and orthologs and fragments thereof in the subject, thereby preventing or treating the metabolic disorder in the subject.

However, these shared technical features are previously disclosed by US 2005/0113303 A1 to Karaplis, et al. (hereinafter 'Karaplis') and further in view of US 2011/0195422 A1 to Selinfreund, et al. (hereinafter 'Selinfreund') and the publication entitled 'The Effect Of Obesity On The Relationship Between Serum Parathyroid Hormone And 25-Hydroxyvitamin D In Women: NCBI Reference Sequence: NP_000306.1' by Shapses, et al. (hereinafter 'Shapses').

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from Previous Supplemental Page:

Karaplis discloses a method of modulating a metabolic response (a method of treating metabolic bone disease; abstract) comprising contacting a cell with an agent (comprising administering to a patient a compound; paragraph [0013]) that modulates the expression and/or activity of one or more biomarkers (that modulates PEX enzymatic activity which modulates PTH and/or PTHrP levels; paragraphs [0013], [0022]) listed in Table 1 (listed in Table 1; PTH, PTHrP), or orthologs and fragments thereof, to thereby modulate the metabolic response (to thereby treat the metabolic bone disease; abstract, paragraph [0013]); a method for preventing or treating a metabolic disorder in a subject (method for preventing or treating a metabolic bone disorder in a subject; abstract; paragraph [0013]) comprising administering to the subject an agent (comprising administering to the subject a compound; paragraph [0013]) that promotes expression and/or activity (comprising an increase in PTH/PTHrP levels; paragraph [0022]) of one or more biomarkers listed in Table 1 (of PTH and/or PTHrP (of one or more biomarkers listed in Table 1); paragraph [0022]) or orthologs and fragments thereof, in the subject (paragraphs [0013], [0022]), thereby preventing or treating the metabolic disorder in the subject (abstract, paragraph [0013]); a method for preventing or treating a metabolic disorder in a subject (abstract; paragraph [0013]) comprising administering to the subject an agent (comprising administering to the subject a compound; paragraph [0013]) that inhibits expression and/or activity (that decreases PTH/PTHrP levels (that inhibits expression and/or activity); abstract, paragraph [0157]) of one or more biomarkers listed in Table 1 (of PTH and/or PTHrP (of one or more biomarkers listed in Table 1); paragraph [0022]) or orthologs and fragments thereof, in the subject (paragraphs [0013], [0022]), thereby preventing or treating the metabolic disorder in the subject (abstract, paragraph [0013]); a method for preventing or treating a metabolic disorder in a subject (abstract; paragraph [0013]) comprising administering to the subject an agent (comprising administering to the subject a compound; paragraph [0013]) that increases expression and/or activity (paragraph [0022]) of one or more of PTHrP, PTH, BTC, EREG, HBEGP, AREG, EGF, EPGN, and TGFA (of one or more of PTHrP and/or PTH; paragraph [0022]), or orthologs and fragments thereof, in the subject (paragraphs [0013], [0022]), thereby preventing or treating the metabolic disorder in the subject (abstract, paragraph [0013]); and a method of identifying a compound that modulates the expression and/or activity of PTH and/or PTHrP (a method of identifying a compound that modulates the expression and/or activity of PTH and/or PTHrP; paragraph [0039]).

Karaplis does not disclose a biomarker having any of the sequences disclosed in Table 1; or a method of assessing the efficacy of an agent that modulates the expression and/or activity of one or more biomarkers listed in Table 1, or orthologs and fragments thereof, for modulating a metabolic response in a subject, comprising: a) detecting in a subject sample at a first point in time, the expression and/or activity of the expression and/or activity of the one or more biomarkers: b) repeating step a) during at least one subsequent point in time after administration of the agent and c) comparing the expression and/or activity detected in steps a) and b), wherein a significantly lower biomarker expression and/or activity in the first subject sample relative to at least one subsequent subject sample, indicates that the agent increases the metabolic response in the subject and/or wherein a significantly higher biomarker expression and/or activity in the first subject sample relative to at least one subsequent subject sample indicates that the test agent decreases the metabolic response in the subject.

Selinfreund discloses a method of assessing the efficacy of an agent (a method of assessing the efficacy of a therapeutic (an agent); abstract) by assessing the expression and/or activity of one or more biomarkers (that by assessing the expression and/or activity of one or more diagnostic biomarkers; abstract) for a metabolic disease in a subject (for a metabolic disease (metabolic disease in a subject); paragraph [0072]), comprising: a) detecting in a subject sample at a first point in time (detecting a previous marker profile from a subject (detecting in a subject sample at a first point in time); paragraph [0006]), the expression and/or activity of the expression and/or activity of the one or more biomarkers (a marker profile; paragraph [0006]): b) repeating step a) during at least one subsequent point in time after administration of the agent (treating a subject having a disease state with a therapeutic compound and analyzing a sample from the subject for at least one diagnostic marker (repeating step a) during at least one subsequent point in time after administration of the agent); paragraph [0006]) and c) comparing the expression and/or activity detected in steps a) and b) (comparing the marker profiles (comparing the expression and/or activity detected in steps a) and b)); paragraph [0006]).

Shapses discloses a sequence disclosed in Table 1, in particular, the sequence of human PTH (human PTH amino acid sequence (a sequence disclosed in Table 1, in particular, the sequence of human PTH); page 2).

It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the previous disclosure of Karaplis, for including the assessment of efficacy of an agent that modulates the expression and/or activity of a biomarker, as prevoiusly disclosed by Selinfreund, such as PTH, or PTHrP, as previously disclosed by Karaplis, wherein a significantly lower biomarker expression and/or activity in the first subject sample relative to at least one subsequent subject sample indicates that the agent increases the metabolic response in the subject, and thereby provides an effective treatment, provided the previous disclosure of Karaplis, for ensuring that the treatment prevoiusly disclosed by Karaplis would have utilized a highly efficacious treatment agent that was both effective, and which demonstrated a minimal amount of side-effects in a subject. Furthermore, it would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified modified the previous disclosure of Karaplis, for including the assessment of the levels of a polypeptide having the sequence previously disclosed by Shapses, for ensuring the modulation of PTH levels in a subject administered a treatment, for improving the efficacy and specificity of treatment, based on the disclosure of Karaplis.

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 a combination of the Karaplis, Selinfreund and Shapses references, unity of invention is lacking.