Provided herein is a pathway for adipocyte energy consumption regulation involving ARID5B, genetic variant rs421085, IRX3, and IRX5. Compositions and methods for modulating the pathway in vitro and in vivo for anti-cachectic and anti-obesity effects are provided. Methods of identifying subjects at risk of developing a disorder mediated by a dysregulation of the energy consumption pathway are also provided.
## INTERNATIONAL SEARCH REPORT

### Box No. 1 Nucleotide and/or amino acid sequence(s) (Continuation of Item 1c 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 131(a) for the purposes of international search only in the form of an Annex C/ST.2S 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.2S text file (Rule 131er.1(a)).
   - on paper or in the form of an image file (Rule 131er.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:

   An Invitation to Furnish Nucleotide and/or Amino Acid Sequence Listing and to Pay, Where Applicable, Late Furnishing Fee ("ISA/225") was mailed on 28 January 2016 (28.01.2016). The electronic sequence listing submitted on 26 February 2016 (26.02.2016) in response to the ISA/225 is acknowledged, however it contains errors and does not comply with the standard provided for in Annex C of the Administrative Instructions. Therefore, the international search has been carried out only to the extent possible.
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/0031

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.: 9-28, 30
   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.:
   1-8, 29, 35-40

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.

Form PCT/ISA/2 10 (continuation of first sheet (2)) (January 2015)
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.

Group I, Claims 1-8, 29 and 35-40 are directed toward methods of modulating energy consumption or treating a disorder in a patient, comprising contacting an adipocyte with an effective amount of one or more agents that modulate one or more of Iroquois homeobox protein 3 (IRX3) function, Iroquois homeobox protein 5 (IRX5) function, AT-rich interactive domain-containing protein 5B (ARID5B) function, or obesity browning enhancer 1 (OBE1) function; and methods of identifying a patient with an increased risk of developing a disorder associated with dysregulation of energy.

Group II, Claims 31-34 are directed toward a method of modulating energy consumption in a cell, comprising contacting the cell with an effective amount of a genome editing system that modifies genetic variant rs1421085.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include Iroquois homeobox protein 3 (IRX3), not present in Group II; the special technical features of Group II include genetic variant rs1421085, not present in Group I.

Groups I and II share the technical features including: a method of modulating energy consumption in a cell, comprising contacting the cell with an effective amount.

However, these shared technical features are previously disclosed by US 2014/0148383 A1 to National Institute of Biological Sciences, Beijing (hereinafter 'Beijing'), in view of the article 'β hex : a key regulator of energy balance in the single cell and the whole organism' (hereinafter 'Hardie').

Beijing discloses a method comprising contacting a cell with an effective amount (a method comprising administering to a person (contacting a cell with) an effective amount; paragraph [0003]); for inhibiting weight gain (for inhibiting weight gain; paragraph [0005]); wherein the contacting inhibits triglyceride synthesis (wherein the administration (contacting) inhibits triglyceride synthesis; paragraphs [0016], [0047]).

Beijing does not disclose modulating energy consumption in a cell.

Hardie discloses wherein anabolic cellular process consume ATP, and include the synthesis of triglycerides (wherein anabolic cellular process consume ATP, and include the synthesis of triglycerides; page 59, column 2, paragraph 2).

It would have been obvious to a person of ordinary skill in the art at the time of the invention was made to have modified the disclosure of Beijing to have included wherein the energy consumption in a cell is modulated, based on the modulation of the consumption of ATP by cells in which triglyceride synthesis is inhibited, based on the disclosure of Hardie, in order to determine the effects of the treatment disclosed by Beijing on the energy consumption of individual cells, and the contributions of said individual cells to the inhibition of weight gain in an individual, as treated using the method of Beijing.

Since none of the special technical features of the Groups I and II 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 Beijing and Hardie references, unity of invention is lacking.