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(71) Applicants: **SANFORD BURNHAM PREBYS MEDICAL DISCOVERY INSTITUTE** [US/US]; 10901 North Torrey Pines Road, La Jolla, California 92037 (US). **THE REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, Michigan 48109-2590 (US).

(72) Inventors: **KAUFMAN, Randal J.**; 10901 North Torrey Pines Road, La Jolla, California 92037 (US). **ARVAN, Peter**; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, Michigan 48109-2590 (US).

(74) Agent: **LEACHMAN, Nathaniel T.**; WILSON SONSINI, 650 Page Mill Road, Palo Alto, California 94304 (US).

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(54) Title: CORRECTING PROTEIN MISFOLDING IN DIABETES

(57) Abstract: The present disclosure relates to proinsulin misfolding in beta cells as it relates to glucose intolerance associated with type 2 diabetes (T2D).

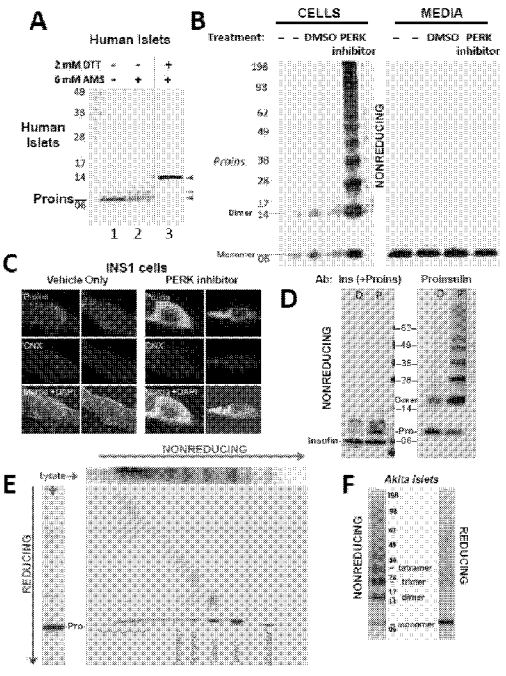

Fig. 1

[Continued on next page]

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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))*

(88) Date of publication of the international search report:
28 January 2021 (28.01.2021)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/36835

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07K 14/62; G01N 33/483; A61P 5/48 (2020.01)

CPC - C07K 14/62; G01N 33/483; A61P 5/48

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	SUN et al. Proinsulin misfolding and endoplasmic reticulum stress during the development and progression of diabetes. Mol Aspects Med, April 2015, Vol 42, Pages 105-118. Especially abstract, pg 107 col 2 para 2, pg 109 col 2 para 1, pg 109 fig 3, pg 112 col 2 para 3, pg 113 col 1 para 2-4.	1-4
A	WO 2012/152439 A1 (GLUCOMETRIX AG) 15 November 2012 (15.11.2012) claim 1.	1-4

☐ 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
21 October 2020	18 DEC 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 Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/36835

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.: 5-18, 23-31, 36-39
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:
-----Go to Extra Sheet for continuation------

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.:
Claims 1-4

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
Information on patent family members

International application No.
PCT/US 20/36835

Continuation of 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 searched, the appropriate additional search fees must be paid.

Group I: Claims 1-4, drawn to a method of detecting aberrant, misfolded proinsulin.

Group II: Claims 19-22, drawn to a method of detecting an abnormality of an ER oxidoreductase in a sample.

Group III: Claims 32-35, drawn to a method of suppressing the formation of an aberrant proinsulin complex by facilitating an activity of an ER oxidoreductase.

The inventions listed as Groups I-III 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:

Special Technical Features:

Group I has the special technical feature of a specific method step in detecting aberrant, misfolded proinsulin, not required by Groups II or III.

Group II has the special technical feature of a specific method step in detecting an abnormality in an ER oxidioreductase, not required by Groups I or III.

Group III has the special technical feature of facilitating an activity of an ER oxidoreductase (e.g., overexpression), not required by Groups I or II.

Common Technical Features:

1. Groups I-III share the common technical feature of an aberrant proinsulin complex.

2. Groups II-III share the common technical feature of ER oxidoreductases.

However, said common technical features do not represent a contribution over the prior art, and is disclosed by the publication "Proinsulin misfolding and endoplasmic reticulum stress during the development and progression of diabetes" by Sun et al. (hereinafter "Sun")[published in Mol Aspects Med April 2015, Vol 42, Pages 105-118].

As to common technical feature #1, Sun discloses an aberrant proinsulin complex (pg 109 col 2 para 1; "When newly synthesized preproinsulin and proinsulin are analyzed under nonreducing conditions such that preformed disulfide bonds in the cells are preserved, this gel system can discriminate between native proinsulin and misfolded disulfide isomers"; pg 109 fig 3).

As to common technical feature #2, Sun discloses an ER oxidoreductase (pg 112 col 2 para 2; "Recently, increased wild type proinsulin misfolding was also found in defective ER folding environments caused by defects in ER oxidoreductases").

As the common technical features were known in the art at the time of the invention, they cannot be considered common special technical features that would otherwise unify the groups. The inventions lack unity with one another.

Therefore, Groups I-III lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Item 4 (cont.): Claims 5-18, 23-31, 36-39 are held unsearchable because they are not drafted according to the second and third sentences of PCT Rule 6.4(a).