PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	26 AUG 2015
Applicant's or agent's file reference 48932-525001WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US15/32058	21 May 2015 (21.05.2015)	21 May 2014 (21.05.2014)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 38/00, 47/00 (2015.01)
CPC - A61K 38/00, 47/48238; C07K 7/06

Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	11 August 2015 (11.08.2015)	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a)).

3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established 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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ 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.

5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4-41, 45-85

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 4-41, 45-85 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4-41 and 45-85 are dependent claims which are not drafted in accordanc with Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 4-41, 45-85

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-3, 42-44	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	3/1, 3/2, 44/42, 44/43	YES
	Claims	1, 2, 42, 43	NO
Industrial applicability (IA)	Claims	1-3, 42-44	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 2, 42 and 43 lack an inventive step under PCT Article 33(3) as being obvious over US 2012/0329109 A1 to Chua, et al. (hereinafter 'Chua') in view of WO 2014/018552 A1 (BP CORPORATION NORTH AMERICA INC.) (hereinafter 'BP').

Regarding claim 1, Chua discloses a recombinant xylose transporter protein (genetically engineered xylose transporter; paragraphs [0018], [0054]) comprising a xylose transporter motif sequence (Candida intermedia GSX1 xylose transporter; paragraphs [0149], [0313]; SEQ ID NO: 39); and utilizing xylose as the sole carbon source in microbial growth media (paragraphs [0017], [0020], [0321]). Chua does not disclose a xylose transporter motif and a glucose mitigation mutation. BP discloses utilizing xylose media (abstract; paragraph [0019]) comprising a xylose transporter (paragraphs [0017], [0060]; C. intermedia GSX1, paragraph [0062]), further wherein the media has a glucose mitigation (using low glucose media in the presence of low-affinity hexose transporters, paragraph [0062]; which allows the microbe (genetically modified yeast) to exhibit decreased sensitivity to glucose catabolite repression; paragraphs [0069], [0079]) mutation (microbe mutated to increase xylose utilization; paragraph [0016]). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modifeid the previous disclosure of Chua, for integrating a recombinant xylose transporter protein having a xylose transporter motif sequence, further comprising a glucose mitigation mutation, since the mutation which confers decreased glucose sensitivity to enhance the transport of xylose in recombinant yeast, as previously disclosed by BP, would have augmented the ability of the GSX1 xylose transporter motif sequence, as previously disclosed by Chua, for efficiently transporting and utilizing xylose with decreased glucose interference (glucose mitigation), through routine experimentation and testing.

Regarding claim 2, Chua and BP, in combination, disclose the recombinant xylose transporter protein of claim 1, and Chua further discloses wherein said xylose transporter motif sequence (Candida intermedia GSX1 xylose transporter; paragraphs [0149], [0313]; SEQ ID NO: 39 of the Chua reference) corresponds to amino acid residue positions 36, 37, 38, 39, 40 and 41 of Candida intermedia GXS1 protein (complete polypeptide sequence of Candida intermedia GXS1; paragraph [0149]; SEQ ID NO 39 of the Chua reference).

Regarding claim 42, Chua discloses a method of transporting xylose (paragraphs [0062], [0149]) into a recombinant (genetically engineered; paragraphs [0017], [0020]) yeast cell (oleaginous yeast; paragraph [0016]), said method comprising: i) contacting a recombinant yeast cell (paragraph [0016]) with a xylose compound (incubating culture with xylose-containing media; paragraphs [0075], [0312]), wherein said recombinant yeast cell (paragraph [0016]) comprises a recombinant xylose transporter protein (genetically engineered xylose transporter; paragraphs [0018], [0054]), said recombinant xylose transporter protein comprising a xylose transporter motif sequence (Candida intermedia GSX1 xylose transporter; paragraphs [0149], [0313]; SEQ ID NO: 39); and ii) allowing said recombinant xylose transporter protein (genetically engineered xylose transporter; paragraphs [0018], [0054]) to transport said xylose compound (paragraphs [0062], [0149]) into said recombinant (genetically engineered; paragraphs [0017], [0020]) yeast cell (oleaginous yeast; paragraph [0016]); and utilizing xylose as the sole carbon source in microbial growth media (paragraphs [0017], [0020], [0321]). Chua does not disclose a glucose mitigation mutation. BP discloses utilizing xylose media (abstract; paragraph [0019]) comprising a xylose transporter (paragraphs [0017], [0060]; C. intermedia GSX1, paragraph [0062]), further wherein the media has a glucose mitigation (using low glucose media in the presence of low-affinity hexose transporters, paragraph [0062]; which allows the microbe (genetically modified yeast) to exhibit decreased sensitivity to glucose catabolite repression; paragraphs [0069], [0079]) mutation (microbe mutated to increase xylose utilization; paragraph [0016]). 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 Chua, for providing a recombinant xylose transporter protein having a xylose transporter motif sequence, further comprising a glucose mitigation mutation, since the mutation which confers decreased glucose sensitivity to enhance the transport of xylose into a recombinant yeast, as previously disclosed by BP, would have augmented the ability of the GSX1 xylose transporter motif sequence, as previously disclosed by Chua, for efficiently transporting and utilizing xylose with decreased glucose interference (glucose mitigation), through routine experimentation and testing.

Regarding claim 43, Chua and BP, in combination, disclose the method of claim 42, and Chua further discloses wherein said xylose transporter motif sequence (Candida intermedia GSX1 xylose transporter; paragraphs [0149], [0313]; SEQ ID NO: 39 of the Chua reference) corresponds to amino acid residue positions 36, 37, 38, 39, 40 and 41 of Candida intermedia GXSI protein (complete polypeptide sequence of Candida intermedia GXS1; paragraph [0149]; SEQ ID NO 39 of the Chua reference).

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

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:

Box No. V:
-Continued from Citations and Explanations:

Claims 3/1 and 3/2 meet the criteria set-out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a xylose transporter motif sequence is -G-G/F-X1-X2-X3-G-; wherein, X1 is D, C, G, H, I, L, or F; X2 is A, D, C, E, G, H, or I; and X3 is N, C, Q, F, G, L, M, S, T, or P.

Chua discloses a xylose transporter motif sequence (Candida intermedia GSX1 xylose transporter; paragraphs [0149], [0313]; SEQ ID NO 39 of the Chua reference), wherein the motif comprises amino acid residues 36-41 is GGVLFG; SEQ ID NO: 39 of the Chua reference). Chua does not disclose wherein said xylose transporter motif sequence is -G-G/F-X1-X2-X3-G-; wherein, X1 is D, C, G, H, I, L, or F; X2 is A, D, C, E, G, H, or I; and X3 is N, C, Q, F, G, L, M, S, T, or P.

US2010/0017904 A1 to Abad, et al. (hereinafter 'Abad') discloses a hexapeptide motif of -G-G/F-X1-X2-X3-G-; wherein X1 is F; X2 is I; and X3 is M (GGFIMG at residues 73-78 of SEQ ID NO: 33569 of the Abad reference). However, the sequence previously disclosed by Abad is not a motif of a xylose transporter protein.

Although numerous sequences in the prior art disclose the sequence motif of -G-G/F-X1-X2-X3-G-; wherein, X1 is D, C, G, H, I, L, or F; X2 is A, D, C, E, G, H, or I; and X3 is N, C, Q, F, G, L, M, S, T, or P, it would not 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 Chua, for implementing a xylose transporter motif sequence which is -G-G/F-X1-X2-X3-G-; wherein, X1 is D, C, G, H, I, L, or F; X2 is A, D, C, E, G, H, or I; and X3 is N, C, Q, F, G, L, M, S, T, or P, since a hexapeptide motif residing within a polypeptide with 100% identity to -G-G/F-X1-X2-X3-G- with variable (X) residues, as defined above, but which is not a component of a xylose transporter protein, would not have taught or fairly suggested a xylose transporter comprising the -G-G/F-X1-X2-X3-G- sequence motif.

Claims 44/42 and 44/43 meet the criteria set-out in PCT Articles 33(2)-(3), because the prior art does not teach or fairly suggest a xylose transporter motif sequence is -G-G/F-X1-X2-X3-G-; wherein, X1 is D, C, G, H, I, L, or F; X2 is A, D, C, E, G, H, or I; and X3 is N, C, Q, F, G, L, M, S, T, or P.

Chua discloses a xylose transporter motif sequence (Candida intermedia GSX1 xylose transporter; paragraphs [0149], [0313]; SEQ ID NO 39 of the Chua reference), wherein the motif comprises amino acid residues 36-41 is GGVLFG; SEQ ID NO: 39 of the Chua reference). Chua does not disclose wherein said xylose transporter motif sequence is -G-G/F-X1-X2-X3-G-; wherein, X1 is D, C, G, H, I, L, or F; X2 is A, D, C, E, G, H, or I; and X3 is N, C, Q, F, G, L, M, S, T, or P.

Abad discloses a hexapeptide motif of -G-G/F-X1-X2-X3-G-; wherein X1 is F; X2 is I; and X3 is M (GGFIMG at residues 73-78 of SEQ ID NO: 33569 of the Abad reference). However, the sequence previously disclosed by Abad is not a motif of a xylose transporter protein.

Although numerous sequences in the prior art disclose the sequence motif of -G-G/F-X1-X2-X3-G-; wherein, X1 is D, C, G, H, I, L, or F; X2 is A, D, C, E, G, H, or I; and X3 is N, C, Q, F, G, L, M, S, T, or P, it would not 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 Chua, to have provided a xylose transporter motif sequence which is -G-G/F-X1-X2-X3-G-; wherein, X1 is D, C, G, H, I, L, or F; X2 is A, D, C, E, G, H, or I; and X3 is N, C, Q, F, G, L, M, S, T, or P, since a hexapeptide motif residing within a polypeptide with 100% identity to -G-G/F-X1-X2-X3-G- with variable (X) residues, as defined above, but which is not a component of a xylose transporter protein would not have taught or fairly suggested a method for producing a xylose transporter comprising the -G-G/F-X1-X2-X3-G- sequence motif.

Claims 1-3 and 42-44 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.