

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: see form PCT/ISA/220		PCT WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43 <i>bis</i> .1)	
		Date of mailing (day/month/year) see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220		FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US2024/048763	International filing date (day/month/year) 27.09.2024	Priority date (day/month/year) 02.10.2023	
International Patent Classification (IPC) or both national classification and IPC INV. C12N15/13			
Applicant ELI LILLY AND COMPANY			
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<i>bis</i>.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 usually 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<i>bis</i>(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:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040		Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Romano, Alper Telephone No. -0



Box No. I Basis of the 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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

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. 10, 35(completely); 1-9, 11-34, 36-50(partially)

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. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ 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 the whole application or for said claims Nos. 10, 35(completely); 1-9, 11-34, 36-50(partially)
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13~~ter~~.1(a).
- ☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-9, 11-34, 36-50(all partially)

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

1. Statement

Novelty (N)	Yes: Claims	<u>1-9, 11-34, 36-50(all partially)</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-9, 11-34, 36-50(all partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>1-9, 11-34, 36-50(all partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

- D1 ABDULKARIM BAROJ ET AL: "A Missense Mutation in PPP1R15B Causes a Syndrome Including Diabetes, Short Stature, and Microcephaly", DIABETES, vol. 64, no. 11, 1 November 2015, pages 3951-3962, DOI: 10.2337/db15-0477;
-& Abdulkarim Baroj ET AL: "Supplementary Data: A Missense Mutation in PPP1R15B Causes a Syndrome Including Diabetes, Short Stature, and Microcephaly", Diabetes, 9 July 2015, pages 1-7, DOI: 10.2337/db15-0477
Retrieved from the Internet:
URL: https://ada.silverchair-cdn.com/ada/content_public/journal/diabetes/64/11/10.2337_db15-0477/3/db150477supplementarydata.pdf
- D2 MARIA SHAHMORADGOLI ET AL: "Protein phosphatase 1, regulatory subunit 15B is a survival factor for ER[alpha]-positive breast cancer", INTERNATIONAL JOURNAL OF CANCER, vol. 132, no. 11, 27 December 2012, pages 2714-2719, DOI: 10.1002/IJC.27945
- D3 KHAN RUKSHAR ET AL: "mir-98-5p regulates gluconeogenesis and lipogenesis by targeting PPP1R15B in hepatocytes", JOURNAL OF CELL COMMUNICATION AND SIGNALING, vol. 17, no. 3, 14 March 2023, pages 881-895, DOI: 10.1007/s12079-023-00735-0
- D4 WO 2022/271806 A1 (LILLY CO ELI [US]) 29 December 2022

Re Item IV

Lack of unity of invention

- 1 Present claims lack unity of invention:
- 1.1 Claim 1 is directed to PPP1R15B RNAi agents selected from SEQ ID NOs: 81-238. Claim 6 is directed to PPP1R15B RNAi agents linked to a GalNAc moiety.
- 1.2 The common matter which can be identified a priori is:
RNAi agent targeting PPP1R15B.

- This common matter is not novel over the prior art:
D1-D3, all disclose siRNAs targeting PPP1R15B.
- 2 In view of the above, the common matter does not comprise any same or corresponding special technical features and there is consequently not a single general inventive concept.
- 2.1 Starting from the common matter, the following groups of inventions are identified:
1. claims 1-9,11-34,36-50 (partially): RNAi agent targeting PPP1R15B wherein the sense strand comprises SEQ ID NO:81 and antisense strand comprises SEQ ID NO:160.
- 2.-79. claims 1-50 (partially) RNAi agents targeting PPP1R15B wherein the sense strand comprises SEQ ID NO:82-159 and antisense strand comprises SEQ ID NO:161-238
- 2.2 Starting from the common matter inventions 1-79 comprise the additional features of sense and antisense sequences due to different target regions.
- Consequently, the features of inventions 1-79 which make a contribution over the common matter are different:
- 2.3 The problem they solve are known from D1-D3: providing further RNAi agents targeting PPP1R15B. Since D1-D3 also disclose solutions to this problem, the features are not corresponding either.
- 2.4 There is thus no relationship among these inventions which would involve the same or corresponding special technical features, such that the requirement of unity of invention is not met (Rule 13.1 PCT in conjunction with Rule 13.2 PCT).
- 2.5 In case of payment of additional search fees, the siRNAs to be searched could be grouped according to their overlapping or close adjacency of their targeted region.
- The present opinion relates only to invention 1.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INVENTION 1

- 3 Claims 38-43 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.
- The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.
- 4 Present claims directed to SEQ ID NOs:81/160 are novel (Art. 33(2) PCT).
- 5 D1 is considered as the most suitable closest prior art because it discloses the sequences of the siRNAs used in the publication (D1: supplementary table 2). The subject matter of invention 1 differs from this disclosure of D1 in that another siRNA targeting PPP1R15B is claimed. There is no effect due to this difference because no comparison has been made.
- 5.1 In view of D1, the problem underlying invention 1 is the provision of alternative siRNAs targeting PPP1R15B.
- 5.2 The solution is an siRNA having SEQ ID NOs:81/160
- 5.3 According to table 8 which shows in vitro knock-down of PPP1R15B in human Hep3b cells, modified form of siRNA SEQ ID NOs:81/160 didn't have any knock-down at 500 nM and was not selected for further experiments. In the absence of any surprising or unexpected effect, provision of further siRNAs cannot be considered inventive because the skilled person doesn't require any inventive skills to design functional siRNAs of a known gene.
- 5.4 Claims 5 and 6 refer to specific GalNAc moieties as conjugates. D4 already discloses this specific GalNAc moiety as a conjugate for siRNAs. When looking for GalNAc targeting moieties the skilled person would consider the teaching of D4, apply it to the siRNAs of the application. Therefore this feature also cannot be considered inventive. The reasoning also applies to the linkers of claim 36.
- 5.5 Regarding the modification patterns of claims 11-33, the teaching of D4 is also applicable. D4 discloses in example 3 very similar or identical modification pattern composed of 2'-OMe and 2'-fluoro like those of said claims. Since no (surprising) activity is associated with the claimed siRNA of invention 1, said claims 11-23 related to specific modification patterns are not inventive either.
- 5.6 No other feature could be found which would render present claimed invention inventive. Claims 1-9,11-34,36-50 do not involve an inventive step (Art. 33(3) PCT).

- 6 Claims 1-9,11-34,36-50 of invention 1 are industrially applicable (Art. 33(4) PCT).