

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year) FEB 21 2024		
Applicant's or agent's file reference 30369	FOR FURTHER ACTION See paragraph 2 below	
International application No. PCT/US 23/71755	International filing date (day/month/year) 07 August 2023 (07.08.2023)	Priority date (day/month/year) 08 August 2022 (08.08.2022)
International Patent Classification (IPC) or both national classification and IPC IPC - INV. A61K 39/395 (2023.01) ADD. C07K 14/705 (2023.01) CPC - INV. A61K 47/6883, C07K 16/2881 ADD. C07K 17/06, C07K 2317/565, C07K 2317/56, A61K 47/6849		
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 43bis.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 66.1bis(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/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Date of completion of this opinion 27 December 2023	Authorized officer Kari Rodriguez PCT Help Desk Telephone No. 571-272-4300
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**WRITTEN OPINION OF THE
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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(b)).

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:



forming part of the international application as filed.



furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.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:

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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. 4-26, 31-41 and 48-128

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. 4-26, 31-41 and 48-128 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 said claims Nos. 4-26, 31-41 and 48-128

- ☐ 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. 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:

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 1-3 and 28-30 directed to a composition comprising an isolated protein comprising one monovalent human/mouse transferrin receptor (TfR) binding domain that comprises a heavy chain variable region (VH) and a light chain variable region (VL), the VH comprising complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprising LCDR1, LCDR2, and LCDR3. The transferrin receptor (TfR) binding domain composition will be searched to the extent that binding domain (TBD1- see applicant instant specification Tables 1-3) VH and VL comprise SEQ ID NOs: 27 and 28, respectively, and:

(1) HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 1 (SYSMN), 21 and 22, wherein, for SEQ ID NO: 21, Xaa1 = R, or SISRSSSYIYYADSVKVG (SEQ ID NO: 2), and for SEQ ID NO: 22, Xaa1 = E and Xaa2 = I, or EHGYSNSDAFDI (SEQ ID NO: 3), and: (2) LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 23, 5 (AASSLQS) and 24, wherein, for SEQ ID NO: 23, Xaa1 = N and Xaa2 = A or RASQGISNYLA (SEQ ID NO: 4), and for SEQ ID NO: 24, Xaa1 = R, or LQHNSYPRT (SEQ ID NO: 6), thus, HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 1-3, and LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 4-6. The first named invention was determined based on alternate VH, VL, HCDR1-3 and LCDR1-3 amino acid sequences in claims 1-3. This first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. It is believed that claims 1-3 limited to said TfR binding domain encompass this first named invention, and thus these claims will be searched without fee to the extent that the TfR binding domain encompasses said sequence features. Additional TfR binding domains will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected TfR binding domains. 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. An exemplary election would be an isolated human TfR binding domain (TBD5- see applicant instant specification Tables 1-3) wherein the VH and VL comprise SEQ ID NOs: 34 and 35, respectively, and:

(1) HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 13 (TYWMH) -15, 25 and 26, wherein, for SEQ ID NO: 25, Xaa1 = G, or RINGDGSRTNYADSVKVG (SEQ ID NO: 14), and for SEQ ID NO: 26, Xaa1 = D, or SSYAFDV (SEQ ID NO: 15), and: (2) LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 16-18, thus, HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 13-15, and LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 16-18 (claims 1-3). Another exemplary election would be an isolated mouse TfR binding domain comprising a Heavy chain and a light chain comprising SEQ ID NOs: 79 and 80, respectively, a VH and a VL comprising SEQ ID NOs: 77 and 78, respectively, and: (1) HCDR1, HCDR2, and HCDR3 that comprise SEQ ID NOs: 71-73, and (2) LCDR1, LCDR2, and LCDR3 that comprise SEQ ID NOs: 74-76 (claims 28-30).

Group II+: Claim 27, directed to protein comprising one monovalent human transferrin receptor (TfR) binding domain, wherein the human TfR binding domain binds a human TfR epitope. Group II+ will be searched upon payment of additional fees. The TfR binding domain that binds a human TfR epitope may be searched, for example, to the extent that the epitope encompasses human TfR residues 346-364 FGNMEGDCPSDWKTDSTCR (SEQ ID NO: 119). It is believed that claim 27 limited to said human TfR epitope, read on this exemplary invention. Additional TfR binding domains that bind a human TfR epitope will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected TfR binding domains that bind a human TfR epitope. 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. An exemplary election would be a TfR binding domain that binds a human TfR epitope, wherein the epitope comprises human TfR residues 243-247 FEDLY (SEQ ID NO: 162) and residues 345-364 LFGNMEEGDCPSDWKTDSTCR (SEQ ID NO: 163) (Claim 27).

-----SEE FIRST SUPPLEMENTAL BOX TO CONTINUE-----

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. 1-3, limited to SEQ ID NOs: 1-6 and 27-28

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Box No. V Reasoned statement under Rule 43bis.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	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-3	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-3	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a composition comprising an isolated protein comprising one monovalent human/mouse transferrin receptor (TfR) binding domain (TBD1- see applicant instant specification Tables 1-3) that comprises a heavy chain variable region (VH) and a light chain variable region (VL), the VH comprising complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprising LCDR1, LCDR2, and LCDR3, wherein the VH and VL comprise SEQ ID NOs: 27 and 28, respectively, and:

(1) HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 1 (SYSMN), 21 and 22, wherein, for SEQ ID NO: 21, Xaa1 = R, or SISRSSSYIYYADSVKG (SEQ ID NO: 2), and for SEQ ID NO: 22, Xaa1 = E and Xaa2 = I, or EHGYSNSDAFDI (SEQ ID NO: 3), and: (2) LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 23, 5 (AASSLQS) and 24, wherein, for SEQ ID NO: 23, Xaa1 = N and Xaa2 = A or RASQGISNYLA (SEQ ID NO: 4), and for SEQ ID NO: 24, Xaa1 = R, or LQHNSYPRT (SEQ ID NO: 6), thus, HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 1-3, and LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 4-6.

The relevant prior arts on record are given below.

Regarding claims 1-3, US 2004/0001826 A1 to Gill et al. (hereinafter 'Gill') teaches antibodies that bind TANGO 268, comprising SEQ ID NO: 55, a 5 aa VH CDR1 consisting of SYSMN, identical to the applicant's claimed HCDR1 (SEQ ID NO: 1) (para [0225] "Described ... are antibodies that immunospecifically bind to TANGO 268 (otherwise referred to herein as glycoprotein VI or GPVI).", para [0442] "antibodies that immunospecifically bind to a TANGO 268 polypeptide or fragment thereof comprise a VH CDR1 having the amino acid sequence of SEQ ID NO: 49, 55, 61, 67 or 73 "). Gill does not teach anti-TfR binding domains.

US 2017/0306013 A1 to Kymab Ltd (hereinafter 'Kymab') teaches antibodies that bind to human Nav1.7, comprising SEQ ID NO: 432, a 17 aa CDRH2 (SISRSSSYIYYADSVKG) identical to the applicant's 17 aa HCDR2, SEQ ID NO: 2 (abstract "The invention provides antibodies and fragments thereof which bind to human Nav1.7", see sequence listing for SEQ ID NO: 432). Kymab does not teach anti-TfR binding domains.

US 2017/0275362 A1 to Memorial Sloan Kettering Cancer Center (hereinafter 'MSKCC') teaches FcRL5 binding domains comprising SEQ ID NO: 529, a 19 aa HCDR3 comprising 74.1% identity (aa 10-19) to the applicant's 12 aa HCDR3, SEQ ID NO: 3 (para [0009] "The presently disclosed subject matter provides CARs ... the CAR comprises an extracellular antigen-binding domain ... where the extracellular antigen-binding domain specifically binds to FcRL5", para [0020] "In certain embodiments, the extracellular antigen-binding domain comprises (a) a heavy chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 311 ... 529"). MSKCC does not teach anti-TfR binding domains.

US 2017/0088620 A1 to Amgen Inc. (hereinafter 'Amgen') teaches Antigen binding proteins that interact with ASGR-1, comprising SEQ ID NO: 32534, a 119 aa VH having 92.7 % identity (aa 1-119) with the applicant's 121 aa VH, SEQ ID NO: 27 (claim 18 "An isolated monoclonal antibody, wherein the isolated monoclonal antibody specifically binds human ASGR-1 and comprises a heavy chain variable domain having at least 90% identity to any of the VH domain amino acid sequences set forth in Table 3-7", see sequence listing for SEQ ID NO: 32534). Amgen does not teach anti-TfR binding domains.

WO 2021/207152 A1 to Vanderbilt University (hereinafter 'Vanderbilt') teaches anti-coronavirus antibodies comprising SEQ ID NO: 8576, a 107 aa VL having 100% identity to the applicant's 107 aa VL, SEQ ID NO: 28. Vanderbilt's SEQ ID NO: 8576 further comprises applicant's LCDR1-3: RASQGISNYLA (SEQ ID NO: 4), AASSLQS (SEQ ID NO: 5 and LQHNSYPRT (SEQ ID NO: 6) (abstract "antibodies and uses thereof for treating, preventing, and detecting coronavirus infection", pg 33, ln 12-14 "In some embodiments, the recombinant antibody or antigen binding fragment thereof of any preceding aspect comprises a VL comprising an amino acid sequence selected from SEQ ID NOs: 8065-10692"). Vanderbilt does not teach anti-TfR binding domains.

-----SEE SECOND SUPPLEMENTAL BOX TO CONTINUE-----

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Supplemental Box

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

Continuation of:

Box No. IV (3) Lack of unity of invention:

Group III+: Claims 42-47, directed to a composition comprising a conjugate of Formula (I): (R-L)_n-P, wherein R is a double stranded RNA (dsRNA) with sense/antisense strands; P is a polypeptide comprising one monovalent human TfR binding domain, L is an optional linker, and n=1 or 2. Group III+ will be searched upon payment of additional fees. The (R-L)_n-P conjugate may be searched, for example, to the extent that n=1, and the conjugate encompasses a TfR binding domain (TBD1) comprising a VH and VL comprise SEQ ID NOs: 27 and 28, respectively, and further comprises VH and VL CDRs:

(1) HCDR1, HCDR2, and HCDR3 that comprise SEQ ID NOs: 1 (SYSMN), 21 and 22, wherein, for SEQ ID NO: 21, Xaa1 = R, or SISRSSSYIYYADSVKG (SEQ ID NO: 2), and for SEQ ID NO: 22, Xaa1 = E and Xaa2 = I, or EHGYSNSDAFDI (SEQ ID NO: 3), and; (2) LCDR1, LCDR2, and LCDR3 that comprise SEQ ID NOs: 23, 5 (AASSLQS) and 24, wherein, for SEQ ID NO: 23, Xaa1 = N and Xaa2 = A or RASQGISNYLA (SEQ ID NO: 4), and for SEQ ID NO: 24, Xaa1 = R, or LQHNSYPRT (SEQ ID NO: 6), thus, HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 1-3, and LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 4-6. It is believed that claims 42-45 and 47, limited to said conjugate, read on this exemplary invention. Additional (R-L)_n-P conjugates will be searched upon the payment of additional fees. Applicants must specify the claims that encompass any additionally elected (R-L)_n-P conjugates. 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. An exemplary election would be a (R-L)_n-P conjugate wherein n=2, and the conjugate encompasses an isolated human TfR binding domain (TBD5) comprising a VH and VL that comprise SEQ ID NOs: 34 and 35, respectively, and: (1) HCDR1, HCDR2, and HCDR3 that comprise SEQ ID NOs: 13 (TYWMH) -15, 25 and 26, wherein, for SEQ ID NO: 25, Xaa1 = G, or RINGDGSRTNYADSVKG (SEQ ID NO: 14), and for SEQ ID NO: 26, Xaa1 = D, or SSYAFDV (SEQ ID NO: 15), and; (2) LCDR1, LCDR2, and LCDR3 that comprise SEQ ID NOs: 16-18, thus, HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 13-15, and LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 16-18 (claims 42-47).

The inventions listed as Groups I+, II+ and 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

No technical features are shared between the amino acid sequences of the TfR binding domain of Groups I+ and Group II+, and the TfR epitope amino acid sequences of Group II+, accordingly, these groups lack unity a priori.

Additionally, even if the inventions listed as Group I+ were considered to share technical features, these shared technical features are previously disclosed by the prior art, as further discussed below.

Group I+ requires an isolated monovalent human/mouse TfR binding domain polypeptide, not required by group II+ and III+.

Group II+ requires a TfR binding domain polypeptide that binds to a specific (amino acid) epitope of human TfR, not required by groups I+ and III+.

Group III+ requires a conjugate comprising a double stranded RNA (dsRNA) with sense/antisense strands linked to a TfR binding domain, not required by groups I+ and II+.

Common Technical Features

The inventions of Groups I+, II+ and III+ share the technical feature of a human TfR binding domain, e.g., comprising a VH, a VL, HCDR1-3 and LCDR1-3.

However, this shared technical feature does not represent a contribution over prior art, because the shared technical feature is taught by US 2015/0110791 A1 to Genentech Inc. (hereinafter 'Genentech').

Genentech teaches human TfR binding domains (abstract "The present invention relates to anti-transferrin receptor antibodies and methods of their use.", para [0019] "the invention provides an isolated antibody that binds to human transferrin receptor (TfR) ... In one aspect ... the antibody is a human antibody."), comprising VH, VL (para [0028] "the antibody comprises a VH or VL sequence"), and HCDR1-3 and LCDR1-3 (see TABLE 4: Light and Heavy Chain CDRs").

Groups I+, II+ and III+ therefore lack unity under PCT Rule 13 because they do not share the same or corresponding special technical feature.

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Supplemental Box

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

Continuation of:

Box No. V citations and explanations:

There is no prior art on record that discloses the claimed subject matter, specifically, a composition comprising an isolated protein comprising one monovalent human/mouse transferrin receptor (TfR) binding domain (TBD1- see applicant instant specification Tables 1-3) that comprises a heavy chain variable region (VH) and a light chain variable region (VL), the VH comprising complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprising LCDR1, LCDR2, and LCDR3, wherein the VH and VL comprise SEQ ID NOs: 27 and 28, respectively, and:

(1) HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 1 (SYSMN), 21 and 22, wherein, for SEQ ID NO: 21, Xaa1 = R, or SISRSSSYIYYADSVKG (SEQ ID NO: 2), and for SEQ ID NO: 22, Xaa1 = E and Xaa2 = I, or EHGYSNSDAFDI (SEQ ID NO: 3), and: (2) LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 23, 5 (AASSLQS) and 24, wherein, for SEQ ID NO: 23, Xaa1 = N and Xaa2 = A or RASQGISNYLA (SEQ ID NO: 4), and for SEQ ID NO: 24, Xaa1 = R, or LQHNSYPRT (SEQ ID NO: 6), thus, HCDR1, HCDR2, and HCDR3 comprise SEQ ID NOs: 1-3, and LCDR1, LCDR2, and LCDR3 comprise SEQ ID NOs: 4-6.

Thus, claims 1-3 meet the criteria set out in PCT Article 33(2)-(3).

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