

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 30369		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US 23/71755	International filing date (day/month/year) 07 August 2023 (07.08.2023)	(Earliest) Priority Date (day/month/year) 08 August 2022 (08.08.2022)	
Applicant ELI LILLY AND COMPANY			

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out 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)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,



the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 8A



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c 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.
 - b. ☐ 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.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

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

----- see extra sheet -----

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.: 1-3, limited to SEQ ID NOs: 1-6 and 27-28

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.

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A. CLASSIFICATION OF SUBJECT MATTER

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

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.
A	US 2004/0001826 A1 (GILL et al.) 1 January 2004 (01.01.2004) para [0225], [0442], SEQ ID NO: 55	1-3
A	US 2017/0306013 A1 (KYMAB LTD) 26 October 2017 (26.10.2017) abstract, SEQ ID NO: 432	1-3
A	US 2017/0275362 A1 (MEMORIAL SLOAN-KETTERING CANCER CENTER) 28 September 2017 (28.09.2017), para [0009], [0020], SEQ ID NO: 529	1-3
A	US 2017/0088620 A1 (AMGEN INC.) 30 March 2017 (30.03.2017) claim 18, SEQ ID NO: 32534	1-3
A	WO 2021/207152 A1 (VANDERBILT UNIVERSITY) 14 October 2021 (14.10.2021) abstract, pg 33, ln 12-14, SEQ ID NO: 8576	1-3

☐ 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

27 December 2023

Date of mailing of the international search report

FEB 21 2024

Name and mailing address of the ISA/US

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Continuation of Box No. 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 1-3 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 LFGNMEGDCPSDWKTDSTCR (SEQ ID NO: 163) (Claim 27).

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-s 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 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 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 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 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.

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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.