

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 14247-474-228		FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 20/55497	International filing date (<i>day/month/year</i>) 14 October 2020 (14.10.2020)	(Earliest) Priority Date (<i>day/month/year</i>) 15 October 2019 (15.10.2019)
Applicant DRAGONFLY THERAPEUTICS, INC.		

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. 21A

- ☒ 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:
 ☒ 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 13ter.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 13ter.1(a)).
 ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
2. ☐ 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.

3. Additional comments:

GenCore ver 6.4.1 SEQ ID NOs: 37, 38 were searched.

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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.: 6-8, 13-15, 24-56, 59-66
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:
-----continued on 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.:
Claims 1-3, 5 (in part), limited to SEQ ID NOS: 11, 4, 55, 5, 37, 6, 7, 8, 38.

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 - C07K 16/28; C07K 16/30; C07K 16/46; A61K 39/395; A61P 35/00 (2020.01)

CPC - C07K 16/2863; C07K 16/2851; C07K 16/2896; C07K 16/468; A61K 39/395; C07K 2317/56; C07K 2317/565; A61P 35/00

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	WO 2019/028027 A1 (DRAGONFLY THERAPEUTICS, INC.) 7 February 2019 (07.02.2019). Especially claims 1, 22	1-3, 5/(2,3)
A	US 2016/0264674 A1 (ADURO BIOTECH HOLDINGS, EUROPE B.V.) 15 September 2016 (15.09.2016). Especially para [0011]; SEQ ID NO: 12	1-3, 5/(2,3)
A	US 2018/0312592 A1 (CELLERANT THERAPEUTICS, INC.) 1 November 2018 (01.11.2018). Especially SEQ ID NO: 8	1-3, 5/(2,3)

☐ 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

23 December 2020

Date of mailing of the international search report

03 MAR 2021

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

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Information on patent family members

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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 1-5, 9-12, 16-23, drawn to a multispecific binding protein that binds NKG2D receptor, FLT3 and CD16.
 Group I+. The multispecific binding protein will be searched to the extent that the second antigen binding site that binds FLT3 comprises the VH, HCDR1, HCDR2, HCDR3 are the first named HCDRs, SEQ ID NOs: 11, 4, and 55, respectively (claim 1(i) [note: SEQ ID NO:55 is a genus and the first named species of it is SEQ ID NO: 5 (claim 3)] [comprised by VH SEQ ID NO: 37] and the first full species LCDRs, SEQ ID NOs: 6, 7 and 8, respectively (claim 1(ii)) [comprised by VL SEQ ID NO: 38].
 It is believed that claims 1-3, 5 (in part) read on this first named invention and thus these claims will be searched without fee to the extent that they encompass SEQ ID NOs: 11, 4, 55, 5, 37, 6, 7, 8, 38. [Note: Claims 57 and 58 have been assigned to Group II+ and are excluded from the first and exemplary election because none of the sequences indicated as first polypeptide, second polypeptide or third polypeptide comprise a full HCDR-1,2,3 and/or LCDR-1,2,3 of the first invention or the exemplary election]. Additional HCDRs, VH, LCDRs, VL will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional elected Additional HCDRs, VH, LCDRs, VL. Applicants must further indicate, if applicable, the claims which read on 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/examined. An exemplary election would be: HCDR1, HCDR2, HCDR3 are SEQ ID NOs: 59, 63, and 64, respectively (claim 1(ii) [note: SEQ ID NO: 59 and 54 are genus and the named species of these are SEQ ID NO: 78 and 79, respectively (claim 10)] [comprised by VH SEQ ID NO: 76] and the LCDRs, SEQ ID NOs: 86, 66, 67, respectively (claim 1(ii)) [note: SEQ ID NO: 86 is genus and the named species of this is SEQ ID NO: 80 (claim 10)] [comprised by VL SEQ ID NO: 77] (claims 1, 9, 10, 12 (in part)).

Group II+: Claims 57, 58 drawn to a protein comprising three polypeptides.
 Group II+ will be searched upon payment of additional fee(s). The composition may be searched, for example, to the extent that the first, second and third polypeptides are SEQ ID NOs: 278, 279, 277, respectively. for an additional fee and election as such. It is believed that claims 57 read on this exemplary invention. Additional bioactive trigger polynucleotide(s) will be searched upon the payment of additional fees. Applicants must indicate, if applicable, which claims read on this 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 named invention to be searched/examined. An exemplary election would be first, second and third polypeptides are SEQ ID NO: 280, 281, 282 respectively (claim 58).

The inventions listed as Groups I+ and II+ 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:

Technical Features:

No technical features are shared between the CDR, VH, VL polypeptide sequences of Group I+ or the three polypeptide sequences of Group II+, and accordingly, these groups lack unity a priori.

Additionally, even if Groups I+ and II+ inventions were considered to share the technical features of:

Group I+ inventions share the technical feature of:

1. A protein comprising:
 - (a) a first antigen-binding site that binds NKG2D;
 - (b) a second antigen-binding site that binds FLT3; and
 - (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16,
 wherein the second antigen-binding site that binds FLT3 comprises:
 - (i) a heavy chain variable domain (VH) comprising complementarity-determining region 1 (CDR1), complementarity-determining region 2 (CDR2), and complementarity determining region 3 (CDR3)
 - and a light chain variable domain (VL) comprising CDR1, CDR2, and CDR3

2. Group II+ inventions share the technical feature a protein comprising a first polypeptide, a second polypeptide and a third polypeptide.

However, said shared technical features do not represent a contribution over the prior art and are disclosed by WO 2019/195409 A1 to Dragonfly Therapeutics, Inc. (hereinafter "Dragonfly") [published 10 October 2019], in view of US 2011/0008355 A1 to Li et al. (hereinafter "Li").

-----continued on next sheet-----

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As to shared technical feature #1, Dragonfly discloses a protein comprising:

- (a) a first antigen-binding site that binds NKG2D;
- (b) a second antigen-binding site; and
- (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16 (claim 1; "A protein comprising: (a) a first antigen-binding site that binds NKG2D; (b) a second antigen-binding site that binds Delta like canonical Notch ligand 3 (DLL3); and (c) an antibody fragment crystallizable (Fc) domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16")

wherein the second antigen-binding site comprises:

- (i) a heavy chain variable domain (VH) comprising complementarity-determining region 1 (CDR1), complementarity-determining region 2 (CDR2), and complementarity determining region 3 (CDR3) (claim 3; "The protein according to claim 1 or 2, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including: a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO: 132; a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO: 133; and a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO: 680, 670, 672, 674, 676, 678, or 134").

and a light chain variable domain (VL) comprising CDR1, CDR2, and CDR3 (claim 4; "The protein according to claim 3, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including: a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO: 135; a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO: 136; and a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:137").

Dragonfly does not disclose that the second antigen binding site binds to FLT3 or the heavy and light chain CDRs for the antigen binding molecule that binds FLT3.

However, Li discloses an antigen-binding site that binds FLT3, comprising: (a) a heavy chain variable domain (VH) comprising complementarity-determining region 1 (CDR1), complementarity-determining region 2 (CDR2), and complementarity determining region 3 (CDR3), respectively; and

- (b) a light chain variable domain (VL) comprising CDR1, CDR2, and CDR3 (claim 1; "An antibody that specifically binds human FLT3 (SEQ ID NO: 43) or a FLT3-binding fragment of the antibody, comprising a CDRH1 having the sequence SYMH (SEQ ID NO:2), a CDRH2 having the sequence IINPSGGSTSYAQKFQG (SEQ ID NO:3), a CDRH3 having the sequence GVGAFDAFDI (SEQ ID NO:4) or VVAAAVADY (SEQ ID NO:5), a CDRL1 having the sequence RSSQSLHNSNGNLYD (SEQ ID NO:6) or RSSQSLHNSNGYNYLD (SEQ ID NO:7), a CDRL2 having the sequence LGSNRAS (SEQ ID NO:8), and a CDRL3 having the sequence MQGTHPAIS (SEQ ID NO:9) or MQLSLQTPFT (SEQ ID NO:11)").

It would have been obvious that the antigen binding site of Li that binds to FLT3 could have substituted for the second antigen binding site disclosed by Dragonfly, with the appropriate VH HCDR-1,2,3 and VL LCDR-1,2,3 without undue difficulty and a high probability of success.

As to shared technical feature #2, Dragonfly discloses a protein comprising a first polypeptide, a second polypeptide and a third polypeptide (claim 1).

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

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

Item 4 (cont.): Claims 6-8, 13-15, 24-56, 59-66 are multiple dependent claims and are not drafted according to the second and third sentences of PCT Rule 6.4(a).