

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

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Date of mailing
(day/month/year)

02 MAR 2021

Applicant's or agent's file reference
14247-473-228

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 20/55480

International filing date (day/month/year)

14 October 2020 (14.10.2020)

Priority date (day/month/year)

15 October 2019 (15.10.2019)

International Patent Classification (IPC) or both national classification and IPC

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

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

Applicant DRAGONFLY THERAPEUTICS, INC.

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
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Date of completion of this opinion

23 December 2020

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

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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. 5, 6, 22-62

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. 5, 6, 22-62 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 5, 6, 22-62 are multiple claims and are not drafted according to the second and third sentences of PCT 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. 5, 6, 22-62

☐ 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 13ter.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 1-4, 7-21, drawn to an antigen binding site that binds to 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.

The antibody will be searched to the extent that the VH, HCDR1, HCDR2, HCDR3 are the first named full species HCDRs, SEQ ID NOs: 11, 4, and 5, respectively [comprised by VH SEQ ID NO: 37] and the first full species LCDRs, SEQ ID NOs: 6, 7 and 8, respectively [comprised by VL SEQ ID NO: 38]. It is believed that claims 1, 2, 4 (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, 5, 37, 6, 7, 8, 38. Additional HCDRs, VH, LCDRs, VL will be searched upon payment of additional fees. Applicant must specify the claims that encompass any additional elected 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 fully specified: HCDR-1,2,3 SEQ ID NOs: 78, 63, 69 respectively [comprised by VH SEQ ID NO: 76] and LCDR-1,2,3 SEQ ID NOs: 80, 66, 67 [comprised by VL SEQ ID NO: 77] (claims 7, 8, 10, (11,12)(in part)).

The inventions listed as Group I+ 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 CDRs, VH, VL polypeptide sequences of Group I+ and, accordingly, these groups lack unity a priori.

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

-----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.

This shared technical feature was previously disclosed by US 2011/0008355 A1 to Li et al. (hereinafter "Li").

-----continued in Supplemental Box-----

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. Claims 1, 2, 4 (in part) limited to SEQ ID NOs: 11, 4, 5, 37, 6, 7, 8, 38.

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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, 2, 4/(1,2)	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1, 2, 4/(1,2)	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1, 2, 4/(1,2)	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 2, 4/(1,2) meet the criteria set forth in PCT Article 33(2)-33(3) because the prior art does not disclose a

-----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) comprising the amino acid sequences of SEQ ID NOs: 11, 4, and 55, respectively; and

(b) a light chain variable domain (VL) comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 6, 7, and 8, respectively.

As to claim 1, the available art, US 2011/0008355 A1 to Li et al. (hereinafter "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 SYVMH (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 RSSQSLLHSNGNYYLD (SEQ ID NO:6) or RSSQSLLHSNGYNYLD (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 MQSLQTPFT (SEQ ID NO:11)").

Li does not disclose:

-----a heavy chain variable domain (VH) comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 11, 4, and 55, respectively

-----a light chain variable domain (VL) comprising CDR1, CDR2, and CDR3 comprising the amino acid sequences of SEQ ID NOs: 6, 7, and 8, respectively

The available art, US 2016/0264674 A1 to Aduro Biotech Holdings, Europe B.V. (hereinafter "Aduro") discloses a VH CDR1 having 85.7% sequence identity to SEQ ID NO: 11 (SEQ ID NO: 12; 26-GYTFTsY-32 85.7% sequence identity), a VH CDR2 having 83.3% sequence identity to SEQ ID NO: 4 (SEQ ID NO: 12; 52-NPYNDa-57 83.3% sequence identity) and a VH CDR3 having 0.0% sequence identity to SEQ ID NO: 55 (SEQ ID NO: 12; 98-rglgalyy-106 0.0% sequence identity), where the antibody of Aduro is directed to binding the antigen APRIL (para [0011]).

Furthermore, US 2018/0312592 A1 to Cellerant Therapeutics, Inc. (hereinafter "Cellerant") discloses a VL CDR1 having 80.0% sequence identity to SEQ ID NO: 6 (SEQ ID NO: 8; 24-RASESVDsYGnSFmH-38 80.0% sequence identity), a VL CDR2 having 100% sequence identity to SEQ ID NO: 7 (SEQ ID NO: 8; 54-LASNLES-60 100% sequence identity) and a VL CDR3 having 77.7% identity to SEQ ID NO: 8 (SEQ ID NO: 8; 93-QQNNydpWT-101 77.7% sequence identity).

There is nothing of record to lead one of ordinary skill in the art to modify Li, Aduro, and/or Cellerant to arrive at the claimed invention.

Regarding claims 2 and 4/(1,2), the claims ultimately depend from claim 1 and therefore meet the criteria for the same reason.

Claims 1, 2, 4/(1,2) have industrial applicability as defined in PCT Article 33(4) because the subject matter can be made or used by industry.

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Supplemental Box

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

Continuation of:

Box IV-3: Lack of Unity of Invention

As to the shared technical feature 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 RSSQSLHSGNNGNYLD (SEQ ID NO:6) or RSSQSLHSGNGYNYLD (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 MQSLQTPFT (SEQ ID NO:11)").

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

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

Item 4 (cont.): Claims 5, 6, 22-62 are multiple claims and are not drafted according to the second and third sentences of PCT Rule 6.4(a).