

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)

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Applicant's or agent's file reference
14247-474-228

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 20/55497

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; 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

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
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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 43bis.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 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).

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. 6-8, 13-15, 24-56, 59-66

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. 6-8, 13-15, 24-56, 59-66 are so unclear that no meaningful opinion could be formed (*specify*):

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).

- ☐ 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. 6-8, 13-15, 24-56, 59-66

- ☐ 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 1-5, 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:

-----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 1-3, 5 (in part), limited to SEQ ID NOs: 11, 4, 55, 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	1-3, 5/(2,3)	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-3, 5/(2,3)	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-3, 5/(2,3)	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3, 5/(2,3) meet the requirements set forth in PCT Article 33(2)-33(3) because the prior art does not disclose:

(i) 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
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.

Regarding claim 1, the available art, WO 2019/028027 A1 to Dragonfly Therapeutics, Inc. (hereinafter "Dragonfly") discloses 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 (claim 1; "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) (claim 22; "22. The protein according to any one of claims 1-2 or 20-21, wherein the second antigen-binding site comprises a heavy chain variable domain" [which would comprise a VH CDR1, CDR2, and CDR3]) and a light chain variable domain (VL) comprising CDR1, CDR2, and CDR3 (claim 22; "22. The protein according to any one of claims 1-2 or 20-21, wherein the second antigen-binding site comprises a heavy chain variable domain and a light chain variable domain" [which would comprise a VL CDR1, CDR2, CDR3]).

Dragonfly 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 Dragonfly, Aduro, and/or Cellerant to arrive at the claimed invention.

Regarding claims 2, 3 and 5/(2,3), the claims ultimately depend from claim 1 and therefore meet the criteria for the same reason.

Claims 1-3, 5/(2,3) 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

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").

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 VVAADV (SEQ ID NO:5), a CDRL1 having the sequence RSSQSLHNSNGNYLD (SEQ ID NO:6) or RSSQSLHNSNGNYLD (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)").

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.

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

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Supplemental Box

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

Continuation of:
previous Supplemental Box

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).

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