PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2019/040820	08.07.2019	09.07.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K39/395

Applicant
FIVE PRIME 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 43*bis*.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 usually 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 notifed the International Bureau under Rule 66.1*bis*(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:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Covone-van Hees, M Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2019/040820

Box No. I Basis of the 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(a))

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:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

   see separate sheet

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. 1-31, 38-63(all partially)

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. 1, 61-63(all partially) are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1, 61-63(all partially) are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ no international search report has been established for the whole application or for said claims Nos. 1-31, 38-63(all partially)

☐ 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

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:

   see separate sheet

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

   ☐ all parts.

   ☒ the parts relating to claims Nos. 32-37(completely); 1-31, 38-63(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	32-37(completely); 2, 4-6, 8, 10, 12-14, 17-19, 21-26, 30, 31, 38-59(partially)
	No:	Claims	1, 3, 7, 9, 11, 15, 16, 20, 27-29, 60-63(all partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	32-37(completely); 1-31, 38-63(partially)
Industrial applicability (IA)	Yes:	Claims	32-37(completely); 1-31, 38-63(partially)
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1 Reference is made to the following documents:

WO 2016/144728 A2 (UNIV TEXAS [US]) 15 September 2016 (2016-09-15)

WO 2016/111947 A2 (JOUNCE THERAPEUTICS INC [US]) 14 July 2016 (2016-07-14)

WO 2015/179633 A1 (HUTCHINSON FRED CANCER RES [US]; UNIV TEXAS [US]) 26 November 2015 (2015-11-26)

ANONYMOUS: "Invitrogen Data sheet: CD85d (ILT4) Monoclonal Antibody (42D1),Functional Grade, eBioscience Catalog Number 16-5149-85",

M. Deng ET AL: "A motif in LILRB2 critical for Angptl2 binding and activation",Blood, vol. 124, no. 6, 7 August 2014 (2014-08-07), pages 924-935, XP055204710,ISSN: 0006-4971, DOI: 10.1182/blood-2014-01-549162

WO 2018/013818 A2 (BRISTOL-MYERS SQUIBB COMPANY [US]) 18 January 2018 (2018-01-18)

WO 2015/189638 A2 (UNIV LONDON QUEEN MARY [GB]) 17 December 2015 (2015-12-17)

WO 2008/079246 A2 (MEDAREX INC [US]; PFIZER [US] ET AL.) 3 July 2008 (2008-07-03)

Re Item II

Priority

Should the priority date of the present application turn out not to be valid, then documents WO 2018/187518, WO 2019/126514 and Chen et al. would become relevant in the context of novelty and inventive step.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present claims 1,61-63 relate to antibodies defined only by reference functional features, including unusual parameters e.g. competes for binding, interacts to one or more of a amino acid residues, has binding profile shown in figures etc.

This definition comprises an extremely large number of possible products. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of the products claimed, namely the specific human anti-ILT4 Ab produced in the application.

In addition, the use of functional features and unusual parameters in the present context is considered to lead to a lack of clarity because the claims do not clearly identify the products encompassed by them as not all the parameters can be clearly and reliably determined by indications in the description or by objective procedures which are usual in the art. This makes it impossible to compare the claims to the prior art. As a result, the application does not comply with the requirement of clarity under Article 6 PCT.

The lack of clarity, support and/or disclosure is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of the said claims.

The search of claims 1,61-63 was restricted to the specific exemplified antibodies, as defined in claims 2-14.

Re Item IV

Lack of unity of invention

This Authority considers that the application does not meet the requirements of unity of invention and that there are 8 inventions. The lack of unity objection and identification of the inventions take into account the incomplete search and the lack of clarity, support and disclosure of claim 1 and is based on the antibodies identified by reference to the CDRs as in claims 2 and 3.

1. claims: 1-31, 38-63(all partially)

   Antibody binding to ILT4 designated 9G4, isolated nucleic acid and set of nucleic acid encoding the antibody, composition and cell comprising said nucleic acid, method to prepare the antibody by culturing the said cell, combination with pharmaceutically acceptable carrier, cancer and infectious disease treatment with the said antibody, use of the said antibody of detection

2. claims: 1-31, 38-63(all partially)

   Antibody binding to ILT4 designated 9C8, isolated nucleic acid and set of nucleic acid encoding the antibody, composition and cell comprising said nucleic acid, method to prepare the antibody by culturing the said cell, combination with pharmaceutically acceptable carrier, cancer and infectious disease treatment with the said antibody, use of the said antibody of detection

3. claims: 1-31, 38-63(all partially)

Antibody binding to ILT4 designated 2H2, isolated nucleic acid and set of nucleic acid encoding the antibody, composition and cell comprising said nucleic acid, method to prepare the antibody by culturing the said cell, combination with pharmaceutically acceptable carrier, cancer and infectious disease treatment with the said antibody, use of the said antibody of detection

4. claims: 1-31, 38-63(all partially)

Antibody binding to ILT4 designated 2E5, isolated nucleic acid and set of nucleic acid encoding the antibody, composition and cell comprising said nucleic acid, method to prepare the antibody by culturing the said cell, combination with pharmaceutically acceptable carrier, cancer and infectious disease treatment with the said antibody, use of the said antibody of detection

5. claims: 1-31, 38-63(all partially)

Antibody binding to ILT4 designated 24E5, isolated nucleic acid and set of nucleic acid encoding the antibody, composition and cell comprising said nucleic acid, method to prepare the antibody by culturing the said cell, combination with pharmaceutically acceptable carrier, cancer and infectious disease treatment with the said antibody, use of the said antibody of detection

6. claims: 32-37(completely); 1-31, 38-63(partially)

Antibody binding to ILT4 designated 21D9 including the mutants in the framework mutations, isolated nucleic acid and set of nucleic acid encoding the antibody, composition and cell comprising said nucleic acid, method to prepare the antibody by culturing the said cell, combination with pharmaceutically acceptable carrier, cancer and infectious disease treatment with the said antibody, use of the said antibody of detection

7. claims: 1-31, 38-63(all partially)

Antibody binding to ILT4 designated 21A5 including the mutants in the framework mutations, isolated nucleic acid and set of nucleic acid encoding the antibody, composition and cell comprising said nucleic acid, method to prepare the antibody by culturing the said cell, combination with pharmaceutically acceptable carrier, cancer and infectious disease treatment with the said antibody, use of the said antibody of detection

8. claims: 1-31, 38-63(all partially)

Antibody binding to ILT4 designated 10F10 including the mutants on the framework mutations, isolated nucleic acid and set of nucleic acid encoding the antibody, composition and cell comprising said nucleic acid, method to prepare the antibody by culturing the said cell, combination with pharmaceutically acceptable carrier, cancer and infectious disease treatment with the said antibody, use of the said antibody of detection

The reasons, for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

Present set of claims relates to human antibodies binding to ILT4 and interrelated products, methods and medical use claims.

A priori, the common matter linking together all the alternatives within the claims is the provision of human antibodies binding to ILT4.

However, at the priority date of the present application, antibodies binding to ILT4 are known in the art from WO 2016/111947 (D1: pg.106 l.19) Deng et al. (D2. pg.925 col.1 para. 3) WO 2016/144728 (D3: pg.68 l.24 - pg.69 l.6; fig.6), WO 2015/179633 (D4: pg. 53 para 144). The antibodies are murine and not human, however, this different feature is trivial.

The common matter does therefore not comprise a novel and inventive common linking technical feature.

The objective remaining problem of the application is the provision of alternative antibodies binding to ILT4.

Judging from the examples, the antibodies bind to different epitopes and have different (pharmaco)kinetic properties, that is, they do not share any common property beyond the binding to ILT4.

Therefore they represent different technical solutions to the problem of providing alternative anti-ILT4 antibodies.

As no other technical feature can be distinguished which, in the light of the prior art, could be regarded as special technical feature on which an unifying concept for the present inventions could be based, there is no single inventive concept underlying the claimed inventions of the present application.

Hence, the claims comprise neither the same, nor corresponding special technical features, so the technical relationship between the subject matter of the claims required

by Rule 13.2 PCT is lacking and the claims are not so linked as to form a single general inventive concept as required by Rule 13.1 PCT.

Consequently the application does not meet the requirement for unity of invention.

The Applicant paid one additional search fee for invention 6 i.e. claims 32-37 (completely) and claims 1-31,38-63 (partially).

The search report and search opinion covers therefore Invention 1 and 6.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Invention 1

2 **Novelty and Inventive Step** (Art.33(2) PCT and (Art.33(3) PCT)

2.1 WO 2016/144728 (**D3**) is directed to the production of monoclonal antibodies binding to LILRB (=ILT) including LILRB2 (=ILT4). The antibodies show anti-cancer properties. Some are specific for LILRB2 (=ILT4) (see fig.6,19).

2.2 WO 2016/111947 (**D1**) studies the effect of anti-LILRB2(=ILT4) mAb 42D1 on macrophage and dendritic cell activity (see pg.106 ex.8) and claims the medical use to treat cancer (see claims).

2.3 None of the available prior art documents discloses the anti-ILT4 mAb 9G4 (CDRs seq.125-130), the subject-matter of claims 1-31,38-63 is therefore novel (Art.33(2) PCT).

2.4 However, claims 1, 15, 16, 20, 60-63 are not limited by sequences and are therefore anticipated by D1 and D3.

2.5 Equally D1 or D3 may be considered as the closest prior art, from which the subject-matter of claim 1 (mAb 9G4) differs in that it is human antibody. No other differences could be prima facie identified.

2.6 The effect of the difference is a less immunogenic antibody.

2.7 The problem to be solved by the present invention may therefore be regarded as the provision of less immunogenic anti-ILT4 mAb.

2.8 The solution proposed in claim 1 (mAb 9G4) of the present application cannot be considered to involve an inventive step (Article 33(3) PCT). The production of antibodies from different origins is a straightforward possibility for the person skilled in the art, who would produce e.g. human or mouse Ab according to the needs and without the exercise of any inventive skills and solves merely a

standard problem, i.e. the improved applicability of said antibodies when used in the corresponding organisms.

2.9 Remaining claims do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step: they are mainly standard alternatives in this technical field, which fall within the routine skills of those in the art, and which do not appear to lead to any surprising effects or advantages.

Invention 6

1 **Novelty and Inventive Step** (Art.33(2) PCT and (Art.33(3) PCT)

1.1 WO 2016/144728 (**D3**) is directed to the production of monoclonal antibodies binding to LILRB (=ILT) including LILRB2 (=ILT4). The antibodies show anti-cancer properties. Some are specific for LILRB2 (=ILT4) (see fig.6,19).

1.2 WO 2016/111947 (**D1**) studies the effect of anti-LILRB2(=ILT4) mAb 42D1 on macrophage and dendritic cell activity (see pg.106 ex.8) and claims the medical use to treat cancer (see claims).

1.3 Claims 1, 15, 16, 20, 60-63 are not limited by sequences and are therefore anticipated by D1 and D3.

1.4 WO 2008/079246 (**D4**), WO 2018/013818 (**D5**), WO 2015/189638 (**D6**) show respectively 100% sequence identity with seq.11 (VL of 21D9) (D4 seq.85, D5 seq.30) and 100% sequence identity with 3LCDRs i.e. seq.155-157 (D6 seq. 1008). The antibodies of the prior art are combined with a different VH and bind to a different target (CD44, TIM-3 and histones respectively).

1.5 At least claims 1,3,7,9,11,20,27-29 which refer to only the VL or the 3 LCRDs are anticipated by D4-D6.

1.6 In the application the properties of the antibody 21D9 is compared with a commercial anti-ILT4 Ab. This is however not the only antibody binding to ILT4 known in the art. D1 and D3 also disclose anti-ILT4 Ab. The Applicant is therefore kindly requested to bring non-obvious/unexpected properties of the claimed antibody over the known anti-ILT4 Ab.

1.7 D1 and D3 discloses anti-ILT4 Ab. Equally D1 or D3 may be considered as the closest prior art, from which the subject-matter of claim 1 (mAb 21D9) differs in that it is human antibody. No other differences could be prima facie identified.

1.8 The effect of the difference is a less immunogenic antibody.

1.9 The problem to be solved by the present invention may therefore be regarded as the provision of less immunogenic anti-ILT4 mAb.

1.10 The solution proposed in claim 1 (mAb 21D9) of the present application cannot be considered to involve an inventive step (Article 33(3) PCT). The production of antibodies from different origins is a straightforward possibility for the person skilled in the art, who would produce e.g. human or mouse Ab according to the needs and without the exercise of any inventive skills and solves merely a standard problem, i.e. the improved applicability of said antibodies when used in the corresponding organisms.

1.11 Remaining claims do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step: they are mainly standard alternatives in this technical field, which fall within the routine skills of those in the art, and which do not appear to lead to any surprising effects or advantages.

Re Item VI

Certain documents cited

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2018/187518	11/10/2028	05/04/2018	07/04/07
WO 2019/126514	27/06/2019	20/12/2018	22/12/2017
Chen et al	22/10/2018 (online)		

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in D1 or D3 is not mentioned in the description, nor are these documents identified therein

Re Item VIII

Certain observations on the international application

Claim 45 refers to an isolated nucleic acid which encodes heavy and/**or** light chain. The distinguishing features and effect are linked to both heavy and light chains, since one variable chain is usually not functional. Claim 45 should accordingly be amended to refer to both chains.