

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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. PCT/US2019/017731	International filing date (day/month/year) 12.02.2019	Priority date (day/month/year) 12.02.2018
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International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/113 A61K31/7088 A61P35/00

Applicant
CODIAK BIOSCIENCES, 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 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 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:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Bucka, Alexander Telephone No. +31 70 340-0 
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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 43bis.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 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:

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. 12, 13, 61, 62(completely); 1-11, 17-38, 41-60(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. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ 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 the whole application or for said claims Nos. 12, 13, 61, 62(completely); 1-11, 17-38, 41-60(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 13ter.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. 14-16, 39, 40, 63-66(completely); 1-11, 17-38, 41-60(partially)

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

1. Statement

Novelty (N)	Yes: Claims	<u>10, 11, 22-27, 59, 60(all partially)</u>
	No: Claims	<u>14-16, 39, 40, 63-66(completely); 1-9, 17-21, 28-38, 41-58(partially)</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>14-16, 39, 40, 63-66(completely); 1-11, 17-38, 41-60(partially)</u>
Industrial applicability (IA)	Yes: Claims	<u>14-16, 39, 40, 63-66(completely); 1-11, 17-38, 41-60(partially)</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

- D1 MEI-JU SU ET AL: "Pancreatic Cancer Cell Exosome-Mediated Macrophage Reprogramming and the Role of MicroRNAs 155 and 125b2 Transfection using Nanoparticle Delivery Systems", SCIENTIFIC REPORTS, vol. 6, no. 1, 22 July 2016, XP55588271
- D2 WO 2016/201323 A1 (UNIV TEXAS [US]) 15 December 2016
- D3 WO 2017/161010 A1 (CODIAK BIOSCIENCES INC [US]) 21 September 2017
- D4 YAQIN ZHANG ET AL: "Adipocyte-derived microvesicles from obese mice induce M1 macrophage phenotype through secreted miR-155", JOURNAL OF MOLECULAR CELL BIOLOGY, vol. 8, no. 6, 25 September 2016, pages 505-517, XP55588319
- D5 WO 2014/082083 A1 (CARIS SCIENCE INC [US]) 30 May 2014
- D6 SAMARESH SAU ET AL: "Multifunctional nanoparticles for cancer immunotherapy: A groundbreaking approach for reprogramming malfunctioned tumor environment", JOURNAL OF CONTROLLED RELEASE, vol. 274, 31 January 2018, pages 24-34, XP55588512
- D7 WO 2017/053722 A1 (IONIS PHARMACEUTICALS INC [US]) 30 March 2017

Re Item III

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

The application lacks unity (cf. item IV *infra*). The ISA issued an invitation pursuant to Article 17(3)(a) PCT and Rule 40.1 PCT to pay additional fees. The Applicant elected not to pay said fees. The search report has been drawn up for the alleged invention first mentioned in the claims (cf. PCT/ISA/210 - claimed invention 1). In accordance with Rule 66.1(e) PCT, applied *mutatis*

mutandis to the Written Opinion of the ISA (cf. Rule 43bis.1(b) PCT), no opinion is given for the subject matter of claimed inventions 2 to 22 (cf. form PCT/ISA 210), for which a search report has not been established.

Re Item IV

Lack of unity of invention

The following separate inventions/groups of inventions have been identified:

1. claims: 14-16, 39, 40, 63-66(completely); 1-11, 17-38, 41-60(partially)
An extracellular vesicle comprising one or more immunomodulating component(s) that, upon contact with a macrophage, selectively repolarizes the macrophage from an M2 to an M1 phenotype, wherein the immunomodulating component inhibits the KRAS gene (such as the oligonucleotide of SEQ ID NO: 6), related methods.
- 2-9. claims: 1-11, 17-38, 41-60(all partially)
An extracellular vesicle comprising one or more immunomodulating component(s) that, upon contact with a macrophage, selectively repolarizes the macrophage from an M2 to an M1 phenotype, wherein the immunomodulating component inhibits in each separate invention one of the genes selected from the group of HRAS, NRAS, HIF1-alpha, HIF1-beta, Spl, P300, LKB1 and AMPK, related methods.
10. claims: 12, 13, 61, 62(completely); 1-11, 17-38, 41-60(partially)
An extracellular vesicle comprising one or more immunomodulating component(s) that, upon contact with a macrophage, selectively repolarizes the macrophage from an M2 to an M1 phenotype, wherein the immunomodulating component inhibits the STAT3 gene, related methods.

11-22. claims: 1-11, 17-38, 41-60(all partially)

An extracellular vesicle comprising one or more immunomodulating component(s) that, upon contact with a macrophage, selectively repolarizes the macrophage from an M2 to an M1 phenotype,

wherein the immunomodulating component inhibits in each separate invention one of the genes selected from the group of STAT6, n-MYC, c-MYC, HCAR1, A2AB, IDO, TDO, Arginase, Glutaminase, CEBP/beta, Pi3K-gamma, and PKM2,

related methods.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the reasons outlined below.

Claim 1 is directed to an extracellular vesicle comprising immunomodulating components that, upon contact with a macrophage, selectively repolarizes the macrophage from an M2 to an M1 phenotype. Claim 1 is directed to a product as such and not to any particular use. The vesicle merely has to suitably repolarize macrophages. Claim 1 defines neither the structure of the immunomodulating components nor any precise effect of these components.

The "immunomodulating components" are defined in the dependent claims as nucleic acids (miRNA, siRNA, antisense) inhibiting 22 different genes such as KRAS, n-MYC, c-MYC, etc. (cf. claims 4, 6, 8).

Extracellular vesicles comprising immunomodulating components such as micro-RNAs, siRNAs or antisense oligonucleotides have been repeatedly described in the state of the art.

By way of example, D1 teaches exosomes (cf. claim 3) that comprise miR-155 and miR-125, i. e. immunomodulating components (cf. D1, pages 2, 9, 10; figures 6, 7). These exosomes comprising immunomodulating components repolarize macrophages from the M2 to the M1 phenotype (cf. D1, figures 6, 7). D2 teaches exosomes comprising siRNAs targeting KRAS, i. e. one of the genes explicitly mentioned in claim 8 (cf. D2, example 1, claims 1, 2, 10, 18-20, 34-40). Thus, these vesicles will have the same effect, when brought into contact with macrophages, i. e. they are capable to repolarize macrophages from an M2 to an M1 phenotype. D3 likewise teaches exosomes comprising nucleic acids inhibiting KRAS, c-MYC or n-MYC, three of the target genes recited in claim 8 (cf. D3, example 12, claims

1, 5, 9, 10, 19-24). While neither D3 nor the present application exemplify any effect of the inhibition of c-MYC or n-MYC on macrophages, it is to be expected that, based on their identical structural composition, the exosomes described in D3 will have the same capability to repolarize macrophages as the presently claimed exosomes inhibiting c-MYC or n-MYC. D4 teaches further exosomes comprising miR-155, i. e. immunomodulating components (cf. D4, pages 506-509, figures 4, 5, 6). MiR-155 inhibits its target genes such as SOCS1, which is involved in immune responses, and ultimately STAT6, which is one of the target genes recited in claim 8 (cf. D4, page 2; figure 6 for STAT6 inhibition). These exosomes comprising immunomodulating components repolarize macrophages from the M2 to the M1 phenotype (cf. D4, figures 4, 5).

In the light of these prior art documents D1 to D4, the problem underlying the present application is to provide alternative, further extracellular vesicles comprising immunomodulating components that, upon contact with a macrophage, are capable to selectively repolarize macrophages from an M2 to an M1 phenotype.

The present application offers 22 groups of solutions to this problem, as outlined in more detail above.

There is no single general inventive concept covering all the separate inventions claimed in the application at issue. The application at issue states that the provided vesicles are, upon contact with macrophages, suitable to repolarize the macrophages towards an M1 phenotype (cf. paragraph 0003). However, as is evident from the cited prior art, such vesicles or exosomes suitable to modify the phenotype of macrophages towards the M1 phenotype are known (cf. D1, pages 2, 9, 10; figures 6, 7; D4, pages 506-509, figures 4, 5, 6). D2 and D3 teach exosomes comprising siRNAs targeting KRAS, i. e. one of the genes explicitly mentioned in claim 8 (cf. D2, example 1, claims 1, 2, 10, 18-20, 34-40; D3, example 12, claims 1, 5, 9, 10, 19-24) that inevitably, due to their identical structural composition, will have the same effect as the presently claimed vesicles.

This takes away the linking concept possibly unifying the groups of inventions claimed in the present application. The different target genes to be inhibited that are recited in claim 8 are structurally and functionally different. In addition, exosomes comprising immunomodulating components that inhibit

some of the same target genes have been described in the state of the art (cf. D3 for exosomes inhibiting KRAS and c-MYC; D4 for exosomes inhibiting STAT6).

Subjects 1 to 22 are not linked by a single general inventive concept required to be present by Article 3(4)(iii) and Rule 13.1 PCT, since the technical problem identified above and alternative solutions to this problem have been known in the prior art. When considering the whole set of claims in the light of the description, no further technical features could be identified, which could serve as same or corresponding technical features in the sense of Rule 13.2 PCT to restore unity of invention.

As prescribed in Article 17(3)(a) PCT, the invention first mentioned in the claims (subject 1, claims 14-16, 39, 40, 63-66, completely; 1-11, 17-38, 41-60, partially) has been the subject of the search.

The subjects 2 to 22 are not mutually linked by a further general inventive concept and searching each subject requires a major search effort.

Re Item V

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

Re Invention 1 (relating to nucleic acids inhibiting KRAS such as SEQ ID NO: 6)

- 1 **Claim 1**, as far as it relates to invention 1, is directed to an extracellular vesicle comprising nucleic acids inhibiting KRAS that, upon contact with a macrophage, selectively repolarizes the macrophage from an M2 to an M1 phenotype. Claim 1 is directed to a product as such and not to any particular use. The vesicle merely has to be suitable to repolarize macrophages.

The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of **claims 1 to 9, 14 to 21, 28 to 58 and 63 to 66** is not new in the sense of Article 33(2) PCT in view of the disclosure of D2, which describes exosomes comprising siRNAs targeting the KRAS gene (cf. D2, example 1, claims 1, 2, 10, 18-20, 34-40). These vesicles have the capability to repolarize macrophages from an M2 to an M1 phenotype. The

vesicles contain further therapeutic compounds such as antibodies (cf. D2, paragraphs 103-105) and are suitable to treat cancers such as pancreatic cancer (cf. D2, paragraphs 87, 88).

- 2 The subject matter of **claims 1 to 9, 14 to 21 and 28 to 43** is not new in the sense of Article 33(2) PCT in view of the disclosure of D3, which describes exosomes comprising siRNAs targeting the KRAS gene (cf. D3, claims 1, 5, 9, 10, 19-24). These vesicles have the capability to repolarize macrophages from an M2 to an M1 phenotype.
- 3 Dependent **claims 10, 11, 22 to 27, 59 and 60** 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 in respect of an inventive step (Article 33(3) PCT). Claims 11, 12, 59 and 60 refer to the use of antisense oligonucleotide having a specific sequence. However, the prior art teaches antisense nucleotides targeting the very same region of the KRAS transcript (cf. D7, SEQ ID NO: 392, which is identical to SEQ ID NO: 6 over the central 16 nucleotides). Merely selecting a structurally highly similar antisense molecule for inhibiting KRAS does not require any inventive skill and does not seem to be associated with any unexpected effect. Claims 22 to 25 refer to the inclusion of specific antibodies into the exosomes. D2, the closest prior art, teaches the inclusion of antibodies into the extracellular vesicles. The skilled person would have seriously contemplated the inclusion of further, alternative antibodies that are frequently used in cancer therapy (cf. D6, passage bridging pages 25 and 26; for a review). Claims 26 and 27 refer to exosomes comprising PTGFRN. PTGFRN is known to be present on extracellular vesicles (cf. D5, claims 1, 14-16) and its inclusion in exosomes/vesicles would have been obvious to the skilled person. The presence of PTGFRN in the exosomes does not seem to be associated with any discernible effect.
- 4 The subject matter of **claims 1 to 11, 14 to 60 and 63 to 66** is industrially applicable in the sense of Article 33(4) PCT.

- 5 The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to methods of treatment (cf. **claims 35 to 60 and 63 to 66**) or to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

- 6 The attention of the Applicant is drawn to the fact that the application may not be amended in such a way that it contains subject matter which extends beyond the content of the application as filed (Article 34(2)(b) PCT).