PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	08 NOV 2017
Applicant's or agent's file reference 74271-018WO0	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US17/49958	01 September 2017 (01.09.2017)	01 September 2016 (01.09.2016)

International Patent Classification (IPC) or both national classification and IPC
IPC - C12N 15/113; A61K 9/00, 31/7125, 31/7088, 45/06, 31/713, 48/005; C12Q 1/68 (2017.01)
CPC - C12N 15/1136, 15/113; A61K 48/005, 9/00, 31/7088, 9/0019, 31/7125, 31/713, 45/06; C12Q 1/68

Applicant AUTOTELIC LLC

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 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 66.1*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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	24 October 2017 (24.10.2017)	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

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(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:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

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**

1. Statement

Novelty (N)	Claims	-***-Please see below-***-	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	-***-Please see below-***-	NO
Industrial applicability (IA)	Claims	-***-Please see below-***-	YES
	Claims	NONE	NO

2. Citations and explanations:

-***-Continued from Box No. V: 1. Statement-***-

Novelty (N): YES: Claims 1-24, 25/23-24, 26/23-24, 27/23-24, 28/23-24, 29/23-24, 30/23-24, 31/23-24, 32/23-24, 33/32/23-24

Inventive step (IS): NO: Claims 1-24, 25/23-24, 26/23-24, 27/23-24, 28/23-24, 29/23-24, 30/23-24, 31/23-24, 32/23-24, 33/32/23-24

Industrial Applicability (IA): YES: Claims 1-24, 25/23-24, 26/23-24, 27/23-24, 28/23-24, 29/23-24, 30/23-24, 31/23-24, 32/23-24, 33/32/23-24

-***-Box No. V: 2. Citations and Explanations-***-

Claims 1-9, 13, and 15-18 lack an inventive step under PCT Article 33(3) as being obvious over the publication entitled "Transforming growth factor-beta 2 gene silencing with trabedersen (AP 12009) in pancreatic cancer" by SCHLINGENSIEPEN, KH et al. (hereinafter "Schlingensiepen") in view of US 2015/0203919 A1 (INSERM (INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE et al.) (hereinafter "Inserm").

As per claim 1, Schlingensiepen discloses Trabedersen therapy (trabedersen is a synthetic 18-mer phosphorothioate antisense oligodeoxynucleotide; page 1193, 2nd column, 2nd paragraph) and administration of therapeutically effective amount of Trabedersen (for further treatment, trabedersen was administered at doses of 16 mg/kg thrice weekly; page 1194, 2nd column, 5th paragraph; Figure 6). Schlingensiepen does not disclose a method for assessing efficacy of drug therapy in a subject in need thereof, comprising, determining the levels of cytokines in a sample obtained from the subject, wherein the subject is undergoing or has undergone treatment comprising and wherein a spike in the level of cytokines relative to reference value indicates that the treatment is efficacious. Inserm does disclose a method for assessing efficacy of drug therapy in a subject in need thereof (methods and kits for predicting the survival time and responsiveness of a patient suffering from a solid cancer; paragraph [0004]), comprising, determining the levels (determining in a tumor sample obtained from the patient the gene expression level; paragraph [0006]) of cytokines (determining the expression level of IL15; paragraph [0031]) in a sample obtained from the subject (in a tumor sample; paragraph [0040]), wherein the subject is undergoing or has undergone treatment (in patients undergoing traditional chemotherapy; paragraph [0132]) comprising and wherein a spike in the level of cytokines relative to reference value indicates that the treatment is efficacious (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher than their predetermined reference values; paragraph [0114]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide a method for assessing efficacy of drug therapy in a subject in need thereof, comprising, determining the levels of cytokines in a sample obtained from the subject, wherein the subject is undergoing or has undergone treatment comprising and wherein a spike in the level of cytokines relative to reference value indicates that the treatment is efficacious, as taught by Inserm, in order to provide diagnostic data for healthcare providers to determine the best treatment plan for a subject.

As per claim 2, Schlingensiepen and Inserm, in combination, disclose a method for prognosing cancer in a subject in need thereof, comprising determining efficacy of treatment by the method of claim 1, and Schlingensiepen further discloses wherein determination that the treatment comprising Trabedersen is efficacious is indicative of good prognosis (the clinical relevance of these in vitro observations has already been demonstrated in three phase I/II studies and a randomized, controlled phase IIb study in patients with high-grade glioma showing clear survival benefit of Trabedersen compared with conventional chemotherapy; page 1193, 2nd column, 2nd paragraph).

As per claim 3, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, and Schlingensiepen further discloses wherein the subject has undergone at least one cycle of treatment with Trabedersen or is undergoing treatment comprising Trabedersen (for further treatment, trabedersen was administered at doses of 16 mg/kg thrice weekly; page 1194, 2nd column, 5th paragraph; Figure 6).

As per claim 4, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, and Schlingensiepen further discloses wherein the sample is obtained after administration of Trabedersen (on day 29 after tumor inoculation, the mice were killed; page 1197, 1st column, 2nd paragraph).

-***-Continued Within the Next Supplemental Box-***-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

Box No. VI Certain documents cited

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

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
US 2017/0226518 A1	10 August 2017 (10.08.2017)	09 February 2016 (09.02.2016)	
US 2017/0226517 A1	10 August 2017 (10.08.2017)	09 February 2016 (09.02.2016)	

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

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

Box No. VII Certain defects in the international application

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

Claims 11 and 17 are objected to under PCT Rule 66.2(a)(iii) as containing the following defect in the form or contents thereof: claims 11 and 17 of the instant application depends upon themselves. For the purposes of this examination, an assumption has been made that the claims 11 and 17 will be considered to depend upon claim 1.

Claims 19-21 depend upon 'the method of Claim 11, but Claim 11 does not refer to the reference value in claims 19-21. For purposes of this examination, the assumption has been made that Claims 19-21 should have instead been dependent upon Claim 18 which does refer to the reference value.

Claims 22-23 are objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: in line 2 of both claims 22-23, the term "so a subject" is interpreted as a typographical error and for the purposes of this opinion will be interpreted as the term "to a subject".

Claim 23 is objected to under PCT Rule 66.2(a)(iii) as containing the following defect(s) in the form or contents thereof: Claim 23 is missing a period at the end of the claim.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

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:

Claim 24 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 24 is indefinite for the following reason(s): Claim 24 depends upon 'the method of Claims 23 or 24,' which causes claim 24 to depend upon itself. For purposes of this examination, the assumption has been made that Claim 24 should have instead been dependent upon Claim 23 only.

Claim 30 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 30 is indefinite for the following reason(s): Claim 30 depends upon 'the method of Claim 30,' which causes claim 30 to depend upon itself. For purposes of this examination, the assumption has been made that Claim 30 should have instead been dependent upon Claims 23-24.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

Supplemental Box

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

-***-Continued from Box V: Citations and Explanations-***-

As per claim 5, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, and Schlingensiepen further discloses wherein the subject has undergone one, two, three, four or more cycles of treatment with Trabedersen (for further treatment, trabedersen was administered at doses of 16 mg/kg thrice weekly; page 1194, 2nd column, 5th paragraph; Figure 6).

As per claim 6, Schlingensiepen and Inserm, in combination, disclose the method of claim 5, and Schlingensiepen further discloses comprising Trabedersen indicates that the treatment is efficacious (the clinical relevance of these in vitro observations has already been demonstrated in three phase I/II studies and a randomized, controlled phase IIb study in patients with high-grade glioma showing clear survival benefit of Trabedersen compared with conventional chemotherapy; page 1193, 2nd column, 2nd paragraph). Schlingensiepen does not disclose wherein the spike in the cytokine levels after the first and/or second cycle of treatment. Inserm does disclose wherein the spike in the cytokine levels after the first and/or second cycle of treatment (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher than their predetermined reference values; paragraph [0114]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein the spike in the cytokine levels after the first and/or second cycle of treatment, as taught by Inserm, in order to provide an indication that the treatment is effecting the immune response of the subject.

As per claim 7, Schlingensiepen and Inserm, in combination, disclose the method of claim 5, and Schlingensiepen further discloses wherein the spike in the cytokine levels after the first and/or second cycle of treatment comprising Trabedersen indicates that the prognosis is good (the clinical relevance of these in vitro observations has already been demonstrated in three phase I/II studies and a randomized, controlled phase IIb study in patients with high-grade glioma showing clear survival benefit of Trabedersen compared with conventional chemotherapy; page 1193, 2nd column, 2nd paragraph).

As per claim 8, Schlingensiepen and Inserm, in combination, disclose the method of claim 5, and Schlingensiepen further discloses the first and second cycle of treatment comprising Trabedersen (for further treatment, trabedersen was administered at doses of 16 mg/kg thrice weekly; page 1194, 2nd column, 5th paragraph; Figure 6). Schlingensiepen does not disclose wherein absence of a spike in the cytokine levels after the first and second cycle of treatment indicates that the treatment is not efficacious. Inserm does disclose wherein absence of a spike in the cytokine levels after the first and second cycle of treatment indicates that the treatment is not efficacious (patient with a "Lo" adaptive immune gene signature have a poor survival and do not benefit from chemotherapy treatment; paragraph [0113]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein absence of a spike in the cytokine levels after the first and second cycle of treatment indicates that the treatment is not efficacious, as taught by Inserm, in order to provide diagnostic data for healthcare providers to determine the best treatment plan for a subject.

As per claim 9, Schlingensiepen and Inserm, in combination, disclose the method of claim 6, and Schlingensiepen disclose the first and second cycle of treatment comprising Trabedersen (for further treatment, trabedersen was administered at doses of 16 mg/kg thrice weekly; page 1194, 2nd column, 5th paragraph; Figure 6). Schlingensiepen does not disclose wherein absence of a spike in the cytokine levels after the first and second cycle of treatment is indicative of poor prognosis. Inserm does disclose wherein absence of a spike in the cytokine levels after the first and second cycle of treatment is indicative of poor prognosis (patient with a "Lo" adaptive immune gene signature have a poor survival and do not benefit from chemotherapy treatment; paragraph [0113]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein absence of a spike in the cytokine levels after the first and second cycle of treatment is indicative of poor prognosis, as taught by Inserm, in order to provide diagnostic data for healthcare providers to determine the best treatment plan for a subject.

As per claim 13, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, but Schlingensiepen does not disclose wherein the cytokine is IL-15. However, Inserm does disclose wherein the cytokine is IL-15 (determining the expression level of IL15; paragraph [0031]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein the cytokine is IL-15, as taught by Inserm, in order to provide an indication that the treatment is effecting the immune response of the subject.

As per claim 15, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, but Schlingensiepen does not disclose wherein the cytokine is IL-8, IL-15, IL-6 or a combination thereof. However, Inserm does disclose wherein the cytokine is IL-15 (determining the expression level of IL15; paragraph [0031]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein the cytokine is IL-15, as taught by Inserm, in order to provide an indication that the treatment is effecting the immune response of the subject.

As per claim 16, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, and Schlingensiepen further discloses wherein the subject has cancer (pancreatic cancer; page 1193, 1st column, 1st paragraph).

As per claim 17, Schlingensiepen and Inserm, in combination, disclose the method of claim 1 and Schlingensiepen further discloses wherein the cancer is pancreatic cancer (pancreatic cancer; page 1193, 1st column, 1st paragraph), melanoma or ovarian cancer.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

Supplemental Box

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As per claim 18, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, but Schlingensiepen does not disclose wherein the spike in levels of the cytokine is relative to a reference value. Inserm does disclose wherein the spike in levels of the cytokine is relative to a reference value (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher than their predetermined reference values; paragraph [0114]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein the spike in levels of the cytokine is relative to a reference value, as taught by Inserm, in order to provide diagnostic data for healthcare providers to determine the best treatment plan for a subject.

Claims 1, 18, and 20 lack an inventive step under PCT Article 33(3) as being obvious over Inserm in view of Schlingensiepen.

As per claim 1, Inserm discloses a method for assessing efficacy of drug therapy in a subject in need thereof (methods and kits for predicting the survival time and responsiveness of a patient suffering from a solid cancer; paragraph [0004]), comprising, determining the levels (determining in a tumor sample obtained from the patient the gene expression level; paragraph [0006]) of cytokines (determining the expression level of IL15; paragraph [0031]) in a sample obtained from the subject (in a tumor sample; paragraph [0040]), wherein the subject is undergoing or has undergone treatment (in patients undergoing traditional chemotherapy; paragraph [0132]) comprising and wherein a spike in the level of cytokines relative to reference value indicates that the treatment is efficacious (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher than their predetermined reference values; paragraph [0114]). Inserm does not disclose Trabedersen therapy and administration of therapeutically effective amount of Trabedersen. Schlingensiepen does disclose Trabedersen therapy (trabedersen is a synthetic 18-mer phosphorothioate antisense oligodeoxynucleotide; page 1193, 2nd column, 2nd paragraph) and administration of therapeutically effective amount of Trabedersen (for further treatment, trabedersen was administered at doses of 16 mg/kg thrice weekly; page 1194, 2nd column, 5th paragraph; Figure 6). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Inserm invention to provide Trabedersen therapy and, administration of therapeutically effective amount of Trabedersen as taught by Schlingensiepen, in order to provide a treatment that inhibits cell proliferation and blocks cancer cell migration.

As per claim 18, Inserm and Schlingensiepen, in combination, disclose the method of claim 1, and Inserm further discloses wherein the spike in levels of the cytokine is relative to a reference value (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher than their predetermined reference values; paragraph [0114]).

As per claim 20, Inserm and Schlingensiepen, in combination, disclose the method of claim 18, and Inserm discloses wherein the reference value is the level of the cytokine in a sample obtained from a subject that has cancer (determining in a tumor sample obtained from the patient the gene expression level and comparing every expression level determined at step i) with their predetermined reference value; paragraph [0006]). Inserm does not disclose and has not been treated with Trabedersen. However, Schlingensiepen does disclose and has not been treated with Trabedersen (receiving either vehicle controls or trabedersen; page 1194; 2nd column, 5th paragraph). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Inserm invention to provide and has not been treated with Trabedersen, as taught by Schlingensiepen, in order to provide a baseline reference.

Claims 22-24, 26/23-24, 28/23-24, 29/23-24, 30, 31/23-24, 32/23-24, and 33/32/23-24 lack an inventive step under PCT Article 33(3) as being obvious over the publication entitled "Treatment with trabedersen, an anti-TGF-beta 2 antisense, primed tumors to subsequent chemotherapies" by HWANG, L et al. (hereinafter "Hwang") in view of Inserm.

As per claim 22, Hwang discloses a method, comprising: administering a therapeutically effective amount of Trabedersen to a subject diagnosed with cancer (trabedersen cycle; page 1, 2nd paragraph), so as to sensitize a tumor in the subject to one or more chemotherapeutic agents (trabedersen primed the tumors to subsequent chemotherapy; page 1, 1st paragraph); subsequently administering a therapeutically effective amount of one or more chemotherapeutic agents to the subject (chemotherapy on 2nd line followed with subsequent Trabedersen 4/10 regimen as third line was ineffective with OS; page 1, 3rd paragraph). Hwang does not disclose determining the levels of cytokines in a sample obtained from the subject, wherein a spike in the level of cytokines indicates that the treatment is efficacious. Inserm does disclose determining the levels of cytokines in a sample obtained from the subject (determining the expression level of IL15; paragraph [0031]), wherein a spike in the level of cytokines indicates that the treatment is efficacious (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher than their predetermined reference values; paragraph [0114]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide determining the levels of cytokines in a sample obtained from the subject, wherein a spike in the level of cytokines indicates that the treatment is efficacious, as taught by Inserm, in order to provide diagnostic data for healthcare providers to determine the best treatment plan for a subject.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

Supplemental Box

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As per claim 23, Hwang discloses a method, comprising: administering a therapeutically effective amount of Trabedersen to a subject diagnosed with cancer (trabedersen cycle; page 1, 2nd paragraph), so as to sensitize a tumor in the subject to one or more chemotherapeutic agents (trabedersen primed the tumors to subsequent chemotherapy; page 1, 1st paragraph). Hwang does not disclose determining the levels of cytokines in a sample obtained from the subject, wherein a spike in the level of cytokines indicates that the treatment is efficacious. Inserm does disclose determining the levels of cytokines in a sample obtained from the subject (determining the expression level of IL15; paragraph [0031]), wherein a spike in the level of cytokines indicates that the treatment is efficacious (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher than their predetermined reference values; paragraph [0114]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide determining the levels of cytokines in a sample obtained from the subject, wherein a spike in the level of cytokines indicates that the treatment is efficacious, as taught by Inserm, in order to provide diagnostic data for healthcare providers to determine the best treatment plan for a subject.

As per claim 24, Hwang and Inserm, in combination, disclose the method of claim 23, and Hwang further discloses treatment comprising Trabedersen (trabedersen cycle; page 1, 2nd paragraph). Hwang does not disclose wherein determination that the treatment is efficacious is indicative of good prognosis. However, Inserm does disclose wherein determination that the treatment is efficacious is indicative of good prognosis (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher or lower than their predetermined reference values; paragraph [0114]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide wherein determination that the treatment is efficacious is indicative of good prognosis, as taught by Inserm, in order to provide an indication that the treatment is effecting the immune response of the subject.

As per claims 26/23-24, Hwang and Inserm, in combination, disclose the method of claims 23-24, but Hwang does not disclose wherein the cytokine is IL-15 (determining the expression level of IL15; paragraph [0031]). However, Inserm does disclose wherein the cytokine is IL-15 (determining the expression level of IL15; paragraph [0031]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide wherein the cytokine is IL-15, as taught by Inserm, in order to provide an indication that the treatment is effecting the immune response.

As per claims 28/23-24, Hwang and Inserm, in combination, disclose the method of claims 23-24, but Hwang does not disclose wherein the cytokine IS IL-8, IL-15 (determining the expression level of IL15; paragraph [0031]), IL6 or a combination thereof. However, Inserm does disclose wherein the cytokine is IL-15 (determining the expression level of IL15; paragraph [0031]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide wherein the cytokine is IL-15, as taught by Inserm, in order to provide an indication that the treatment is effecting the immune response of the subject.

As per claims 29/23-24, Hwang and Inserm, in combination, disclose the method of claims 23-24, and Hwang further discloses wherein the subject has cancer (patients with advanced pancreatic cancer; page 1, 2nd paragraph).

As per claims 30/23-24, Hwang and Inserm, in combination, disclose the method of claims 23-24, and Hwang further discloses wherein the cancer is pancreatic cancer (patients with advanced pancreatic cancer; page 1, 2nd paragraph), melanoma or ovarian cancer.

As per claims 31/23-24, Hwang and Inserm, in combination, disclose the method of claims 23-24, and Hwang further discloses wherein the sample is obtained after administration of Trabedersen (blood samples from 18 patients were taken at the screening/baseline visit, after completion of the first 2 treatment cycles at Day 29; page 1, 2nd paragraph).

As per claims 32/23-24, Hwang and Inserm, in combination, disclose the method of claims 23-24, but Hwang does not disclose wherein the spike in levels of the cytokine is relative to a reference value. Inserm does disclose wherein the spike in levels of the cytokine is relative to a reference value (every expression level determined at step i) with their predetermined reference value and iii) concluding that the patient will significantly respond to the treatment when all expression levels determined at step i) are higher or lower than their predetermined reference values; paragraph [0114]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide wherein the spike in levels of the cytokine is relative to a reference value, as taught by Inserm, in order to provide an indication that the treatment is effecting the immune response of the subject.

As per claims 33/32/23-24, Hwang and Inserm, in combination, disclose the method of claims 32/23-24, and Hwang further discloses treatment with Trabedersen (trabedersen cycle; page 1, 2nd paragraph). Hwang does not disclose wherein the reference value is the level of the cytokine in the sample obtained from the same subject prior to treatment. Inserm does disclose wherein the reference value is the level of the cytokine in the sample obtained from the same subject prior to treatment (allows the comparison of the expression level in one sample, e.g., a patient sample, to another sample, or between samples from different sources; paragraph [0097]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide wherein the reference value is the level of the cytokine in the sample obtained from the same subject prior to treatment, as taught by Inserm, in order to provide an indication that the treatment is effecting the immune response of the subject.

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

Supplemental Box

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-***-Continued from Previous Supplemental Box-***-

Claim 10 lacks an inventive step under PCT Article 33(3) as being obvious over Schlingensiepen in view of Inserm, and in further view of Hwang.

As per claim 10, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, but Schlingensiepen does not disclose wherein treatment comprising Trabedersen comprises administering Trabedersen to the subject for at least one cycle to sensitize the tumor to chemotherapeutic agent and subsequently administering the chemotherapeutic agent. However, Hwang does disclose wherein treatment comprising Trabedersen comprises administering Trabedersen to the subject for at least one cycle to sensitize the tumor to chemotherapeutic agent and subsequently administering the chemotherapeutic agent (trabedersen primed the tumors to subsequent chemotherapy; page1, 1st paragraph). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein treatment comprising Trabedersen comprises administering Trabedersen to the subject for at least one cycle to sensitize the tumor to chemotherapeutic agent and subsequently administering the chemotherapeutic agent, as taught by Hwang, in order to provide a more effective cancer treatment.

Claim 11 lacks an inventive step under PCT Article 33(3) as being obvious over Schlingensiepen in view of Inserm, and in further view of the publication entitled "Efficacy of Combined Treatment with Trabedersen and Dacarbazine in a Xenograft Mouse Model of Malignant Melanoma" by SAGAN, D et al. (hereinafter "Sagan").

As per claim 11, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, but Schlingensiepen does not disclose wherein the chemotherapeutic agents are paclitaxel, dacarbazine, alkylating agents or checkpoint inhibitors. However, Sagan does disclose wherein the chemotherapeutic agent is dacarbazine (synergistical and/or additive therapeutic effect of trabedersen and dacarbazine; Poster 51). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein the chemotherapeutic agent is dacarbazine, as taught by Sagan, in order to provide a more effective cancer treatment.

Claims 12 and 14 lack an inventive step under PCT Article 33(3) as being obvious over Schlingensiepen in view of Inserm, and in further view of the publication entitled "The relationships between serum cytokine levels and tumor infiltrating immune cells and their clinical significance in colorectal cancer" by VAYRYNEN, JP et al. (hereinafter "Vayrynen").

As per claim 12, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, but Schlingensiepen does not disclose wherein the cytokine is IL-8. However, Vayrynen does disclose wherein the cytokine is IL-8 (increased serum IL-6, IL-7 and IL-8 levels; page 113, 1st column, 2nd paragraph). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein the cytokine is IL-8, as taught by Vayrynen, in order to provide an indication that the treatment is effecting the immune response of the subject.

As per claim 14, Schlingensiepen and Inserm, in combination, disclose the method of claim 1, but Schlingensiepen does not disclose wherein the cytokine is IL-6. However, Vayrynen does disclose wherein the cytokine is IL-6 (increased serum IL-6, IL-7 and IL-8 levels; page 113, 1st column, 2nd paragraph). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Schlingensiepen invention to provide wherein the cytokine is IL-6, as taught by Vayrynen, in order to provide an indication that the treatment is effecting the immune response of the subject.

Claims 19 and 21 lack an inventive step under PCT Article 33(3) as being obvious over Inserm in view of Schlingensiepen, and in further view of US 2012/0301887 A1 (BANKAITIS-DAVIS, DM et al.) (hereinafter "Bankaitis").

As per claim 19, Inserm and Schlingensiepen, in combination, disclose the method of claim 18, but Inserm does not disclose treatment with Trabedersen (trabedersen is a synthetic 18-mer phosphorothioate antisense oligodeoxynucleotide; page 1193, 2nd column, 2nd paragraph). Schlingensiepen does disclose treatment with Trabedersen (trabedersen is a synthetic 18-mer phosphorothioate antisense oligodeoxynucleotide; page 1193, 2nd column, 2nd paragraph). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Inserm invention to provide treatment with Trabedersen, as taught by Schlingensiepen, in order to provide a treatment that inhibits cell proliferation and blocks cancer cell migration. Inserm does not disclose wherein the reference value is the level of the cytokine in the sample obtained from the same subject prior to treatment. However, Bankaitis does disclose wherein the reference value is the level of the cytokine in the sample obtained from the same subject prior to treatment (sample is taken prior to the subject receiving treatment; paragraph [0012]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Inserm invention to provide wherein the reference value is the level of the cytokine in the sample obtained from the same subject prior to treatment, as taught by Bankaitis, in order to provide a baseline for evaluation of post-treatment cytokine levels.

As per claim 21, Inserm and Schlingensiepen, in combination, disclose the method of claim 18, but Inserm does not disclose wherein the reference value is the level of the cytokine in a sample obtained from a subject whose cancer is in remission. However, Bankaitis does disclose wherein the reference value is the level of the cytokine in a sample obtained from a subject whose cancer is in remission (from cancer remission; paragraph [0179]). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Inserm invention to provide wherein the reference value is the level of the cytokine in a sample obtained from a subject whose cancer is in remission, as taught by Bankaitis, in order to provide monitoring of the subject's cancer status.

-***-Continued Within the Next Supplemental Box-***-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US17/49958

Supplemental Box

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

-***-Continued from Previous Supplemental Box-***-

Claims 25/23-24 and 27/23-24 lack an inventive step under PCT Article 33(3) as being obvious over Hwang in view of Inserm, and in further view of Vayrynen.

As per claims 25/23-24, Hwang and Inserm, in combination, disclose the method of claims 23-24, but Hwang does not disclose wherein the cytokine is IL-8. However, Vayrynen does disclose wherein the cytokine is IL-8 (increased serum IL-6, IL-7 and IL-8 levels; page 113, 1st column, 2nd paragraph). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide wherein the cytokine is IL-8, as taught by Vayrynen, in order to provide an indication that the treatment is effecting the immune response of the subject.

As per claims 27/23-24, Hwang and Inserm, in combination, disclose the method of claims 23-24, but Hwang does not disclose wherein the cytokine is IL-6. However, Vayrynen does disclose wherein the cytokine is IL-6 (increased serum IL-6, IL-7 and IL-8 levels; page 113, 1st column, 2nd paragraph). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the Hwang invention to provide wherein the cytokine is IL-6, as taught by Vayrynen, in order to provide an indication that the treatment is effecting the immune response of the subject.

Claims 1-24, 25/23-24, 26/23-24, 27/23-24, 28/23-24, 29/23-24, 30, 31/23-24, 32/23-24, and 33/32/23-24 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.