PATENT COOPERATION TREATY

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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) 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/EP2019/082810	27.11.2019	29.11.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A61K47/69 A61P35/00

Applicant
MIDATECH LTD

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	Burema, Shiri Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2019/082810

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:

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	4, 5, 9, 11, 13-40, 58-60, 66-68, 70, 71
	No:	Claims	1-3, 6-8, 10, 12, 41-57, 61-65, 69
Inventive step (IS)	Yes:	Claims	14, 16-18, 30-32, 38, 39
	No:	Claims	1-13, 15, 19-29, 33-37, 40-71
Industrial applicability (IA)	Yes:	Claims	1-71
	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

Re Item V

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

1 The patentability of claims 52-69 can be dependent upon their formulation. The EPO, for example, does not recognise as patentable claims 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.

1.1 Patentability, in particular novelty and inventive step, of claims 52-60 and 69 has been assessed according to EPO practice on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/ nanoparticle/conjugate/composition.

2 **Citations**

Reference is made to the following documents:
(Of note: An automated English translation of **D3** is annexed to the present written opinion.)

Reference is made to the following documents:

D1 Hao Meng ET AL: "A Smart Nano-Prodrug Platform with Reactive Drug Loading, Superb Stability, and Fast Responsive Drug Release for Targeted Cancer Therapy",
Macromolecular Bioscience,
vol. 17, no. 10, 2 May 2017 (2017-05-02), page 1600518, XP055667790, DE
ISSN: 1616-5187, DOI: 10.1002/mabi.201600518

D2 Yue Zhang ET AL: "Hyaluronic Acid-Shelled Disulfide-Cross-Linked Nanopolymersomes for Ultrahigh-Efficiency Reactive Encapsulation and CD44-Targeted Delivery of Mertansine Toxin",
ACS applied materials & interfaces,
vol. 10, no. 2, 4 January 2018 (2018-01-04), pages 1597-1604, XP055514488,
US
ISSN: 1944-8244, DOI: 10.1021/acsami.7b17718

D3 CN 107 096 038 A (UNIV SUZHOU) 29 August 2017 (2017-08-29)

D4 WO 2018/141940 A1 (MIDATECH LTD [GB]) 9 August 2018 (2018-08-09)

D5 M. Koufaki ET AL: "Multifunctional Lipoic Acid Conjugates",
Current medicinal chemistry,
vol. 16, no. 35, 1 December 2009 (2009-12-01), pages 4728-4742,
XP055667697,
NL
ISSN: 0929-8673, DOI: 10.2174/092986709789878274

D6 M Stiti ET AL: "Grafting of 4-aminomethylbenzensulfonamide-lipoic acid conjugate on gold nanoparticles",
IOP Conference Series: Materials Science and Engineering,
vol. 28, 7 February 2012 (2012-02-07), page 012032, XP055667853,
DOI: 10.1088/1757-899X/28/1/012032

D7 WO 2017/012591 A1 (GNT BIOTECH & MEDICALS CORP [CN]) 26 January 2017 (2017-01-26)cited in the application

D8 Sarah J. M. Hale ET AL: "DM1 Loaded Ultrasmall Gold Nanoparticles Display Significant Efficacy and Improved Tolerability in Murine Models of Hepatocellular Carcinoma",
Bioconjugate Chemistry,
vol. 30, no. 3, 24 December 2018 (2018-12-24), pages 703-713,
XP055667199,
US
ISSN: 1043-1802, DOI: 10.1021/acs.bioconjchem.8b00873

3 Novelty (Article 33(2) PCT)

3.1 The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 1-3, 6-8, 10, 12, 41-57, 61-65, 69 is not new.

3.2 *Novelty over **D1***

3.2.1 **D1** describes in scheme 1 a compound comprising a maytansinoid (DM1) covalently bonded to a linker, which is covalently bonded to a ligand group having a saturated, unsubstituted cyclic polythiol (i.e. disulfide) moiety being 1,2-dithiolane. There is an cRGD (purple) motif in the linker group, being amino acid derived and containing R^2= H and R^1=H or a naturally occurring amino acid side chain. The linker group is covalently bonded to the ligand group via an

amide bond (purple). cRGD (peptide) is a targeting agent, hence **D1** also discloses a conjugate. **D1** administers said conjugates in PBS (i.e. a pharmaceutical composition) as part of a polymersomal structure ("PS") (i.e. biocompatible polymer which is a bead (scheme 1) to mice by injection for *in vivo* antitumor efficacy measurements (paragraph 4.5). The cancer model used was B16F10, being a melanoma model (i.e. skin cancer).

3.2.2 **D1** therewith describes the subject-matter of claims 1-3, 6-8, 10, 12, 41-42, 46, 48-54, 56-57, 61, 62, 64, 65, 69 which thus lack novelty over **D1**.

3.3 *Novelty over **D2***

3.3.1 **D2** describes in scheme 1 a compound comprising a maytansinoid (DM1) covalently bonded to a linker, which is covalently bonded to a ligand group having a saturated, unsubstituted cyclic polythiol (i.e. disulfide) moiety being 1,2-dithiolane. Said compound is conjugated to hyaluronic acid (HA) which is a targeting agent to CD44 (page 1598, first sentence), hence **D2** also discloses a conjugate. **D1** administers said conjugates in PBS (i.e. a pharmaceutical composition) as part of a polymersomal structure ("XPS") (i.e. biocompatible polymer which is a bead (scheme 1) to mice by injection for *in vivo* antitumor efficacy measurements (paragraph 2.5). The cancer model used was MDA-MB-231, being a carcinoma model of breast cancer.

3.3.2 **D2** therewith describes the subject-matter of claims 1-3, 6-7, 41, 46, 48-55, 61-63, 69 which thus lack novelty over **D2**.

3.4 *Novelty over **D3***

3.4.1 **D3** describes in paragraphs [0012], [0017] [0018] the same cRGD-PS-DM1 structure as **D1** and in paragraphs [0024]-[0025] the same experiments in B16F10 mice as **D1** (see point 3.2.1). **D3** described in paragraph [0035] the HA-PS-DM1 structure of **D2** (see point 3.3.1). It is used to treat human ovarian cancer in model SKOV-3 (i.e. a carcinoma model). An antibody (i.e. anti-CD19, i.e. selectively binding tumor antigen/ a therapeutic antibody exhibiting ADCC) may also be conjugated to -PS-DM1 instead of cRGD (paragraphs [0010] and [0026], claim 5)

3.4.2 **D3** therewith describes the subject-matter of claims 1-3, 6-8, 10, 12, 41-57, 61-65, 69 which thus lack novelty over **D3**.

4 Inventive step (Article 33(3) PCT)

4.1 Being not new, the subject-matter of claims 1-3, 6-8, 10, 12, 41-57, 61-65, 69 cannot be considered as involving an inventive step (Article 33(3) PCT).

4.2 **D4** may be considered to be the closest prior art and in view thereof, the subject-matter of claims 1-13, 15, 19-29, 33-37, 40-71 does not involve an inventive step (Article 33(3) PCT).

4.2.1 It is however noted that claims 14, 16-18, 30-32, 38 and 39 are considered inventive in view of **D4** and do meet the criteria of Article 33(3) PCT.

4.3 **D4** describes in claims 1,3-5,12-15 a nanoparticle comprising a core comprising a metal (e.g. Au, Ag, Cu, Pt, Pd, Fe, Co, Gd, Zn, preferably Au) and/or a semiconductor; and a plurality of ligands covalently linked to the core, wherein said ligands comprise: at least one (liver-)targeting ligand (which may be a liver tumor targeting ligand, which may be an antibody (page 15, line 36ff), which may be a galactose ligand) covalently linked to the core ("conjugate") via a first linker with a chain length of 2-50 atoms and repeating methylene/ethyleneglycol units, bound to the core via a terminal sulphur atom; at least one payload ligand comprising a bioactive agent (like maytansinoid DM1, claims 8-9); and at least one dilution ligand comprising a polyethyleneglycol (PEG) moiety being e.g. HS-PEG_8-COOH. The diameter of the core is 1-5 nm and the diameter of the ligands is 3-50 nm (claims 16-17). **D4** particularly describes a nanoparticle in claim 18 which is similar to the nanoparticle of claim 37. **D4** describes at page 6, line 18- page 7, line 11 that there may be more than 20 ligands bound to the core, including at least one DM1 (maytansinoid). The maytansinoid (of structure DM1 or DM4 at page 22 and 23) binds directly covalently in a monodentate conjugation via one terminal sulphur to said nanoparticle (claim 18) via its aliphatic saturated unsubstituted monothiol moiety (SH).
D4 discloses in claims 19-22 a pharmaceutical composition thereof with at least one pharmaceutically acceptable carrier or diluent; a sustained release formulation wherein at least a portion of the plurality of nanoparticles are encapsulated in a biocompatible polymer; it being in the form of a microparticle/ microsphere/ bead or film; it being in an injectable form. **D4** further discloses in claims 23, 25-29, the use in medicine, for treating cancer (a proliferative disorder), the cancer being hepatocellular carcinoma (liver cancer), hepatoblastoma, cholangiocarcinoma etc; the administration of a second anti-cancer agent, which may be Sorafenib, Regorafenib and Lenvatinib. Claims

37-38 of **D4** define an article of manufacture comprising the nanoparticle, a container and insert or label, with instructions relating to the use thereof for the mentioned disorders.

4.4 The distinguishing features with claims 1-71 is that maytansinoid is bound to a linker with a cyclic disulfide moiety, e.g. lipoic acid, so that it binds in a bidentate way via two terminal sulphurs to the nanoparticle, where claims 14-18, 29-32, 37-39 further define the stereochemistry.

4.4.1 The further distinguishing features with claim 43-45 is that a conjugate is provided with a tumor antigen binding, therapeutic antibody.

4.5 From Figure 2 it seems as though the conjugation of DM1 via an -(*S)*-Ala-lipoic acid- linker has the technical effect of yielding lower IC_{50} values. However, this is not the case, i.e. higher IC_{50} values are shown in Figure 2, for the -(*R)*-Ala-lipoic acid- linker. With the exception of claims 14, 16-18, 30-32, 38 and 39, all other claims (insofar not dependent on claims 14, 16-18, 30-32, 38 and 39) are not limited to a linker motif with the stereochemistry of -(*S)*-Ala-.

4.6 Therefore, the technical effect is not achieved over the full scope of claims 1-13, 15, 19-29, 33-37, 40-71 and an inventive step cannot be acknowledged for these claims.

4.6.1 Absent a technical effect, the problem to be solved starting from **D4** becomes *how to provide an alternative DM1-gold-nanoparticle conjugate?*

4.6.2 Lipoic acid-like linkers are conventionally used in the art to bind anti-cancer drugs to gold nanoparticles in a bidentate way via two terminal sulfur atoms (**D5-D7**). Absent a technical effect it would be obvious for the skilled person to implement a lipoic acid linker as in **D5-D7** to conjugate the maytansinoid anti-cancer drug of **D4** to the gold nanoparticle in order to solve the problem of providing an alternative. The skilled person would therefore arrive at the subject-matter of claims 1-13, 15, 19-29, 33-37, 40-71 which is therefore considered to lack an inventive step in view of **D4** and any of **D5-D7**.

4.7 However, for claims 14, 16-18, 30-32, 38 and 39 an inventive step can be acknowledged as these are limited to an -(*S)*-Ala-lipoic acid- linker for which an effect has been shown.

4.7.1 The problem to be solved starting from **D4** becomes *how to provide a DM1-gold-nanoparticle conjugate with lower* IC_{50} *values?*

4.7.2 The solution of using an -(*S)*-Ala-lipoic acid- linker would not be obvious for the skilled person since there is no pointer in the prior art towards the influence of this particular linker and stereochemistry on the DM1-gold-nanoparticle conjugates' IC_{50} values. The skilled person would therefore not arrive at the subject-matter of claims 14, 16-18, 30-32, 38 and 39 which is therefore considered inventive in view of **D4**.

Re Item VI

Certain documents cited

5 The examination has been carried out assuming that the priority of the application is valid, as the period under Rule 17.1 PCT for furnishing a copy of the priority document has not yet expired at the time of the search and the validity of the priority claim could not have been assessed.

5.1 However, attention is drawn to the fact that **D8** which have been cited in the search report as "P" documents may become relevant to the patentability of the claims during further prosecution/ in the national/regional examination phase(s).

Re Item VII

Certain defects in the international application

6 Rule 5.1(a)(ii) PCT requires that the relevant background art disclosed in **D1-D7** be mentioned in the description and that these documents be identified therein.

Re Item VIII

Certain observations on the international application

7 The application does not meet the requirements of Articles 5 and 6 PCT, because the claims are not sufficiently disclosed (Article 5 PCT) and unclear (Article 6 PCT) for the following reasons:

7.1 The present claims relate to a maytansinoid compound with *any* linker group with *any* cyclic polythiol moiety; a nanoparticle with *any* metal and/or semiconductor core, *any* dilution ligand and a conjugate with *any* targeting agent. Support within the meaning of Article 6 PCT is to be found, however, only for a very small proportion of these compounds, nanoparticles and conjugates claimed. In the present case, the claims lack support and the application lacks

disclosure. It does not seem plausible that all compounds, nanoparticles and conjugates falling within the definition of the claims would yield working embodiments and would be undue burden for the skilled person to test them all.

7.2 Claims 41-47 are insufficiently disclosed (Article 5 PCT) and lack support / clarity (Article 6 PCT) since there are no examples in the patent application demonstrating the conjugation of the maytansinoid-lipoic acid compound to an antibody and it is not clear from claims 41-47 how this construct would structurally look like (e.g. which antibodies are suitable, whether the antibody would conjugate to the linker of the maytansinoid-compound, or via its cyclic polythiol moiety; whether the linker defined in claims 46-47 is an additional linker or the same as in the maytansinoid compound, where it would be cleavable etc).

7.3 The claims encompasses an undetermined number of compounds or moieties which are defined only by reference to a desired functional activity (e.g. "a linker group", "ligand group", "targeting ligand", "dilution ligand" etc). These functional terms do not give a specific technical guidance for the ascertainment of the scope of the claim as to which compounds or moieties are having the desired function *and are at the same time compatible in the context of the invention, yielding working embodiments* without imposing an unreasonable burden, and thus can be seen as a mere invitation to the skilled person to perform a research program in order to find the suitable variants in contravention of Article 6 PCT.