

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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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/IB2015/056032	International filing date (day/month/year) 07.08.2015	Priority date (day/month/year) 12.08.2014
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International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K39/395 A61P35/00 A61K31/00

Applicant
NOVARTIS AG

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 Bumb, Peter 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. 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>1-61</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>8, 9, 28, 59</u>
	No: Claims	<u>1-7, 10-27, 29-58, 60, 61</u>
Industrial applicability (IA)	Yes: Claims	<u>1-61</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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

V.1 PRIOR ART

D1 (WO2005001092) discloses a pharmaceutical composition comprising an antibody which is conjugated with a toxic moiety, wherein the antibody may be directed against one cancer-antigen selected from the list consisting of ABCC4, C20orf103, CACNA1D, CDH6, CST, ENPP3, FLJ11856, GPR54, HAVCR1, SLC6A3, SLC30A4, TRG@ and TRPM4 (claims 1, 4). This prognosis is based on overexpression of, *inter alia*, CDH6 at mRNA levels in certain cancers (ex. 1).

D2 (Shimazui 1998, NLM9796973) discloses manufacture of mouse anti-human cadherin 6 antibody 2B6-D8 against the extracellular domain (page 2420).

D3 (Paul 2004, XP005532199) discloses mRNA- and immunohistochemistry-level expression of CDH6 in renal cell carcinoma. Patients with abnormal CDH6 expression have a higher risk and poorer prognosis (see Discussion). The authors believe that if cadherin-6 is further validated as prognostic marker it may be possible to target cadherin-6 for further therapies of renal cell cancer.

D4 (Zhao 2011) compares the properties of multiple linkers for delivering DM4-toxin to cancer cells. Sulfo-SPDB-DM4 is reported as having beneficial properties (page 3612, right col.) (page 3615, left col.).

D5 (Sancisi 2013) discloses that cadherin 6 is highly expressed, *inter alia*, in thyroid cancer.

V.2 NOVELTY

The prior art does not disclose on an anti-CDH6 antibody-drug conjugate (ADC). The subject-matter of claims 1-50, 55-56 is novel (A33(2) PCT).

The prior art does not disclose a nucleic acid encoding an anti-huCDH6 antibody. The subject-matter of claims 51-54 is novel (A33(2) PCT).

The prior art does not disclose on an anti-CDH6 antibody comprising structural features as per claims 57-61, the subject-matter of which thus is novel (A33(2) PCT).

V.3 INVENTIVE STEP

V.3.1 ADCs

CLOSEST PRIOR ART - D1 is the closest prior art and discloses that agents that target certain overexpressed cancer cell surface antigens may be used to treat cancer. One mode of targeting such antigens is selecting ADCs as targeting agent. One such explicitly suggested antigen is CDH6.

TECHNICAL DIFFERENCE - Claim 1 then differs from D1 in that the claimed ADC consists of **(a)** a selection of CDH6 from a first list of suggested target-antigens and **(b)** a selection of ADCs from a second list of suggested targeting agents.

TECHNICAL EFFECT - The technical effect resulting from this difference is that, as suggested and implied by D1, CDH6-positive cancers can be treated.

TECHNICAL PROBLEM - The objective technical problem then is "How to provide an alternative cancer medicament ?".

SOLUTION - The applicant proposes to solve the technical problem by the abovementioned double-selection from two lists.

CONCLUSION - D1 explicitly suggests the now claimed combination of features as one of multiple possible options of targeting cancer cells. The skilled person is an immunologist working in the field of cancer-therapy. As such he would know that the suggestions of D1 are based on the paradigm that where a given antigen is overexpressed on cancer cells, it may serve to direct ADCs or immunotoxins to said cells. This is the most direct way of targeting cells, since it does not rely on antagonistic activity against the cell-surface antigen, which in turn would have to rely on a causative role of the cell surface antigen in tumorigenesis. **D3** discloses that CDH6-protein is overexpressed in renal cancer cells. **D5** discloses that CDH6 is overexpressed in other cancers. By applying the teachings of D3/D5 to the list of individualized features as per D1, the skilled person thus would have been motivated and would have expected to be able to treat at least one type of CDH6-overexpressing cancer with an ADC that directs toxins to said cells.

The presently claimed ADCs are described as possessing advantageous properties compared with the compounds specifically referred to in the prior art, but these properties are ones which the person skilled in the art would expect such compounds to possess, so that he is likely to be led to make this double selection from D1. In other words, the skilled person would have had a reasonable expectation of success that anti-CDH6 ADCs as suggested in D1 would kill CDH6-overexpressing cancer cells, which is the mode of action already suggested/implied by D1 itself. The subject-matter of claim 1 does not involve an inventive step (A33(3) PCT).

Claims 2-4, 7 (see Item VIII), 10 (see Item VIII), 11-21, 37-38, 39-50, 55-56 do not introduce any features over claim 1 which go beyond the application of routine design-features and obvious medical uses. The subject-matter of claims 2-4, 7 (see Item VIII), 10 (see Item VIII), 11-21, 37-38, 39-50, 55-56 does not involve an inventive step (A33(3) PCT).

Moreover, sulfo-SPDB-DM4 is a well known linker-drug design option for ADCs known to have beneficial properties (**see D4**). The subject-matter of claims 22-24, 27 (see Item VIII), 29 (see Item VIII), 30-36 does not involve an inventive step (A33(3) PCT).

V.3.2 nucleic acids

CLOSEST PRIOR ART - D2 is the closest prior art and discloses an antibody having the functional property of binding to an epitope of human CDH6 (same as in present claim 1).

TECHNICAL DIFFERENCE & EFFECT - Claim 51 differs from D2 in that such functionally defined antibody is now encoded by a nucleic acid, which allows recombinant expression.

CONCLUSION - The provision of monoclonal antibodies that merely bind a known antigen of interest, and the provision of corresponding recombinant nucleic acid, vectors, host cells and methods of production is deemed trivial. The subject-matter of claims 51-54 does not involve an inventive step (A33(3) PCT).

V.3.3 antibodies *per se* - six CDRs

CLOSEST PRIOR ART - D2 is the closest prior art and discloses an antibody having the functional property of binds to an epitope of human CDH6 (same as in present claim 1).

TECHNICAL DIFFERENCE & EFFECT - Claim 57 differs from D2 in that the claimed antibody comprises six CDRs from one of mAbs (i) NOV0712, (ii) NOV0710, (iii) NOV0719, (iv) NOV1127, (v) NOV0670, (vi) NOV0672, (vii) NOV0674, (viii) NOV0682, (ix) NOV0685, (x) NOV0689, (xi) NOV0690, (xii) NOV0691, (xiii) NOV0692, (xiv) NOV0693, (xv) NOV0695, (xvi) NOV0699, (xvii) NOV0705, (xviii) NOV0709, (xix) NOV0713, (xx) NOV0718, (xxi) NOV0720, (xxii) NOV1126, (xxiii) NOV1132 (see present Tables 5-6).

The objective technical effect resulting from these six CDRs (i)-(xxiii) is binding to the respective parent antibodies' epitopes. The majority of these clones have only been characterized in terms of binding to the extracellular domain of huCDH6 (see e.g. Table 7) but no intrinsic biological activity is apparent.

Since the frameworks are completely undefined it is not credible to predict that all variants covered by the claims are less immunogenic than the mouse mAbs of D2.

TECHNICAL PROBLEM - The objective technical problem that is solved by the distinguishing features thus is "How to provide alternative antibodies that bind the extracellular domain of huCDH6 ?".

CONCLUSION - The provision of monoclonal antibodies that merely bind a known antigen of interest, particularly the same extracellular domain as in the prior art, is routinely done in the art. The skilled person would routinely provide *de novo* antibodies having equivalent functional properties. Doing so it is virtually impossible, not to arrive at previously unknown amino acid sequences.. Providing new antibody-sequences *per se* thus does not go beyond the normal progress of technology. Unless a particular technical effect is associated with the choice of certain antibody-sequences from all possible antibody sequences, the choice of such sequences is deemed arbitrary. The subject-matter of claim 57 does not involve an inventive step (A33(3) PCT).

Claim 58 further allows for non-sense, non-conservative amino acid substitutions between structurally unrelated, individually obtained antibodies and does not introduce any inventive feature over claim 57 *per se*. The subject-matter of claim 58 does not involve an inventive step (A33(3) PCT).

The same reasoning then also applies, *mutatis mutandis*, to ADCs and detection-means comprising such non-inventive antibodies. The subject-matter of claims 5-6, 25-26, 60-61 does not involve an inventive step (A33(3) PCT).

V.3.4 antibodies *per se* - VH+VL, HC+LC

CLOSEST PRIOR ART - D2 is the closest prior art and discloses an antibody having the functional property of binds to an epitope of human CDH6 (same as in present claim 1).

TECHNICAL DIFFERENCE & EFFECT - Claim 8 differs from D2 in that the claimed antibody comprises the Fv-domain from one of mAbs (i) NOV0712, (ii) NOV0710, (iii) NOV0719, (iv) NOV1127, (v) NOV0670, (vi) NOV0672, (vii) NOV0674, (viii) NOV0682, (ix) NOV0685, (x) NOV0689, (xi) NOV0690, (xii) NOV0691, (xiii) NOV0692, (xiv)

NOV0693, (xv) NOV0695, (xvi) NOV0699, (xvii) NOV0705, (xviii) NOV0709, (xix) NOV0713, (xx) NOV0718, (xxi) NOV0720, (xxii) NOV1126, (xxiii) NOV1132 (see present Tables 5-6).

The objective technical effect resulting from these six CDRs (i)-(xxiii) is binding to the respective parent antibodies' epitopes, with the respective antibodies' affinities. Concretely, this means an affinity of ca.3.023 pM to 9.329 nM against huCDH6 (Table 8) for embodiments (i)-(xxi). The affinity for embodiments (xxii-xxiii) is not known.

At the same time the HuCal-derived Fv-domains (now comprising defined framework-regions) will be less immunogenic when administered to a human patient.

TECHNICAL PROBLEM - The prior art does not report any affinity-values for a monoclonal anti-huCDH6 antibody. The objective technical problem that is solved by the distinguishing features thus is "How to provide *improved* antibodies that bind the extracellular domain of huCDH6 ?".

CONCLUSION - The provision of particular antibodies and antibody-sequences having particular, unexpected properties is indicative of inventive step. The subject-matter of claim 8 meets the requirements of A33(3) PCT.

The same reasoning then also applies to claims 9 and 28 and 59 (A33(3) PCT).

V.4 PATENTABILITY

Claims 39-50 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. 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.

Re Item VII

Certain defects in the international application

VII.1 Claims shall not, except where absolutely necessary, rely, in respect of the technical features of the invention, on references to the description or drawings. In particular, they shall not rely on such references as: "as described in part ... of the description," or "as illustrated in figure ... of the drawings."

Claims 6, 19, 26, 34, 48, 58 contravene R6.2(a) PCT.

Re Item VIII

Certain observations on the international application

LACK OF CLARITY

VIII.1 The scope of claims 6, 26, 58 is unclear (A6 PCT). It is formulated as a dependent claim (e.g. dependent on claim 6) but then introduce changes with respect to the backreferenced claim. Thus, these claims do not comprise all technical features of the backreferenced claims and are not a bona fide dependent claims. This then also raises doubts as to whether *other* features of the preceding claims (e.g. the function of CDH-6 binding) may also be missing.

The same objection also applies, mutatis mutandis, to claims 7, 27 (A6 PCT)

The same objection also applies, mutatis mutandis, to claims 10, 29 (A6 PCT). This is exacerbated by the fact that these claims refer to sequence-identity but fail to define with respect to which reference-sequence the identity is determined. These sequences may be identical to themselves. These claims are thus technically meaningless.

VIII.2 The scope of claims 18-21, 33-36, 49-50 is unclear (A6 PCT). These claims are product-claims, which normally refer to a single product comprising certain technical features or components. The term "in combination" does not make it clear in what technical relation the different components are, i.e. whether they are present within the same composition, the same kit, used in the same method, or present in spatially separate containers.

VIII.3 The scope of claims 46-50 is unclear (A6 PCT). These claims refer back to a purpose-limited product (medical use) claim 45. Claims 46-50 then only refer back to the antibody drug conjugate recited in claim 45, but not the purpose-limitation. It is thus unclear whether claims 46-50 fall within the product-claim-category or the medical-use-claim-category.