

PATENT COOPERATION TREATY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
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Applicant's or agent's file reference
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FOR FURTHER ACTION
See paragraph 2 below

International application No.
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Applicant
CELGENE CORPORATION

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
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Madrugá, Jaime

Telephone No. +49 89 2399-0



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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
 - ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
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>13-23, 33, 36, 38-58, 60, 61, 66-70, 72-94</u>
	No: Claims	<u>1-12, 24-32, 34, 35, 37, 59, 62-65, 71, 95, 96</u>
Inventive step (IS)	Yes: Claims	<u>23, 72-81, 94</u>
	No: Claims	<u>1-22, 24-71, 82-93, 95, 96</u>
Industrial applicability (IA)	Yes: Claims	<u>1-96</u>
	No: Claims	

2. Citations and explanations

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

Item V

1 CITATIONS

1.1 The following **documents** are relevant for the present application:

- D1 CN 1 352 301 A (BODE GENE DEV CO LTD SHANGHAI [CN]) 5 June 2002 (2002-06-05)
- D2 CN 110 438 112 A (SUZHOU KENING POLYOL CO LTD) 12 November 2019 (2019-11-12)
- D3 DATABASE GenBank [Online] NCBI; 17 August 2008 (2008-08-17), Shoo, L.P., Rose, R., Doughty, P., Austin, J.J. and Melville, J.: "Recombination activating protein 1, partial [*Amphibolurus uricatus*]", XP002808018, accession no. ACG63874.1;
& SHOO L P ET AL: "Diversification patterns of pebble-mimic dragons are consistent with historical disruption of important habitat corridors in arid Australia", MOLECULAR PHYLOGENETICS AND EVOLUTION, ORLANDO, FL, US, vol. 48, no. 2, 1 August 2008 (2008-08-01), pages 528-542, XP023518614
- D4 DATABASE EBI [Online] EMBL; 17 March 2020 (2020-03-17), Ra Kim S J ET AL: "Solimonas terrae AAA family ATPase", XP055982896, retrieved from EMBL accession no. NGY06094;
& KIM SOO-JIN ET AL: "Solimonas terrae sp. nov., isolated from soil", INTERNATIONAL JOURNAL OF SYSTEMATIC AND EVOLUTIONARY MICROBIOLOGY, vol. 64, no. Pt_4, 1 April 2014 (2014-04-01), pages 1218-1222, XP055982886
- D5 WO 2019/038717 A1 (NOVARTIS AG [CH]; BECKWITH ROHAN ERIC JOHN [US] ET AL.) 28 February 2019 (2019-02-28) cited in the application
- D6 WO 2019/089592 A1 (MASSACHUSETTS GEN HOSPITAL [US]; BRIGHAM & WOMENS HOSPITAL [US] ET AL.) 9 May 2019 (2019-05-09)
- D7 MAX JAN ET AL: "Reversible ON-and OFF-switch chimeric antigen receptors controlled by lenalidomide", SCI. TRANSL. MED, vol. 13, no. 6295, 6 January 2021 (2021-01-06), XP055982210, ; - & JAN MAX ET AL: "Supplementary

Data: Reversible ON- and OFF-switch chimeric antigen receptors controlled by lenalidomide", SCIENCE TRANSLATIONAL MEDICINE, vol. 13, no. 575, 6 January 2021 (2021-01-06), XP055982578

- D8 QUINLAN L. SIEVERS ET AL: "Defining the human C2H2 zinc finger degrome targeted by thalidomide analogs through CRBN", SCIENCE, vol. 362, no. 6414, 1 November 2018 (2018-11-01), page eaat0572, XP055708883
- D9 WO 2019/079569 A1 (NOVARTIS AG [CH]; BRADNER JAMES E [US]) 25 April 2019 (2019-04-25)
- D10 WO 2020/219742 A1 (NOVARTIS AG [CH]; CARBONNEAU SETH [US] ET AL.) 29 October 2020 (2020-10-29)
- D11 JAN MAX ET AL: "Cancer therapies based on targeted protein degradation - lessons learned with lenalidomide", NATURE REVIEWS CLINICAL ONCOLOGY, NATURE, NY, US, vol. 18, no. 7, 2 March 2021 (2021-03-02), pages 401-417, XP037488719

2 THE APPLICATION

- 2.1 The present application concerns engineered polypeptides comprising degradation domains, compounds, compositions, and methods for their preparation and use as for degrading engineered proteins in cells. The degradation domain comprises the sequence FCX₁X₂CGX₃X₄ (SEQ ID NO: 1), preferably FCNQCGAS. The polypeptide is degraded by a degradation agent, which is a small molecule binding the degradation domain and also binding cereblon. The preferred polypeptide of the application is a CAR.

3 NOVELTY (Art. 33(2) PCT)

- 3.1 The prior art disclosed polypeptides comprising sequences which fall under independent **claim 1**, namely, comprising sequenced having the consensus SEQ ID NO: 1.
- 3.1.1 Although claim 1 requires an **engineered** polypeptide, "engineered" is not sufficiently clear as to establish a technical difference with the polypeptides of the prior art. For instance, the same sequence can be obtained from a natural source or be engineered, e.g. by modifying other sequences. Also the definition

- of a sub-sequence as a "**degradation domain**" is not sufficient to establish a difference, since this is characterised by the sequence itself, as required by the claims.
- 3.1.2 **D1** (CN1352301) discloses a human enzyme carbamylaspartic dehydrase 9.46, having a sequence comprising comprising the subsequence (FCNYCGGS; Phe-Cys-Asn-tyr-Cys-Gly-Gly-Ser (see SEQ ID NO: 2, aa 19-26 on page 26) which falls under the consensus of SEQ ID NO: 1 of **claim 1** and also the more limited consensus of **claims 2, 7 and 11**. In D1 fusions of these proteins to other sequences are disclosed (see e.g. page 6, lines 18-28), which are seen as engineered polypeptides.
- 3.1.3 **D2** (CN110438112) concerns mutant of D-psicose-3-epimerase and discloses a polypeptide (SEQ ID NO: 2) comprising the sequence (FCQQCGIIQL; Phe-Cys-Gln-Gln-Cys-Gly-Ile-Ile-Gln-Leu; SEQ ID NO: 2, 98-107), which falls under the consensus of SEQ ID NO: 1 (X1-X4 as in the claims) and SEQ ID NO: 2 (X1-X5 as in the claims) of the application. Thus, D2 discloses the subject-matter of **claim 1**. Also the features of dependent **claims 3, 4, 5, 8**.
- 3.1.4 **D3** (GenBank ACG63874) discloses the sequence of a recombination activating protein 1 (*Amphibolurus muricatus* gene RAG-1 fragment; GenBank ACG63874) which comprises the subsequence FCRICGGSF (aa 32-42), which falls under SEQ ID NO: 1 and 2 and also under the scope of present **claims 1-6 and 11**.
- 3.1.5 **D4** (XP055982896; EBI:NGY06094; D4a XP055982886) discloses a sequence of a *Solimonas terrae* AAA family ATPase having the subsequence **FCNQCGASL**, falling under the formula of SEQ ID NO: 1, 2 and also 3 of the application, thus, the subject-matter, of **claims 1-5, 7-11, 12** is disclosed in D4.
- 3.1.6 In summary, the subject-matter of **claims 1-12** lacks novelty over the polypeptides disclosed in D1-D4.
- 3.1.7 In addition, the polypeptides of D1-D4 also comprise the additional features of **claims 32-35, 37, 59**. For instance the polypeptides of D1 are human and active, and present in a cell. D1-D4 also disclose encoding nucleic acids, vectors and cells comprising these. D1 further discloses pharmaceutical compositions comprising the polypeptide referred to above (see claim 17). Thus, the subject-matter of **claims 62-65, 71** also lacks novelty.
- 3.1.8 **Dependent claims 24-31** include functional features, which although not specifically disclosed in D1-D4 are apparently intrinsic to the sequence and thus, are expected to be present in the products of the prior art, since the

application claims that these sequences would behave as degradation domains; According to the teachings application, the proteins of the prior art, having the consensus degradation domain, would be expected to be degraded in the presence of specific degradation agents. Thus, the subject-matter of these claims lacks novelty. In case that the Applicant is of a different opinion, evidence would have to be provided that the polypeptides of the prior art are not degraded, since they comprise sequences which are claimed to behave as degradation domains.

- 3.2 In addition, the prior art also disclosed compounds with a similar structure to those of the application, including **Compound D** (third compound of independent **claim 95**).
- 3.2.1 **D5** (WO2019038717), cited in the application [00093], discloses methods for the preparation of 3-(1-oxoisindolin-2-yl)piperidine-2,6-dione compounds and uses thereof, especially uses for the reduction of IKZF2 protein (Helios, Ikaros-2 or IKZF2) protein levels. These are in particular for uses in the treatment of cancer (see claims). One of the compounds disclosed in this patent (I-130) on page 186, is in fact identical to compound D of the present application, the third compound of claims 28, 73, 74, 94 and 95 and is referred to in D5 as 3-(5-(1-benzo[d]thiazol-5-ylmethyl)piperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione, but it is known as 2,6-Piperidinedione, 3-[5-[1-(6-benzothiazolylmethyl)-4-piperidinyl]-1,3-dihydro-1-oxo-2H-isindol-2-yl] or 3-[5-[1-(6-benzothiazolylmethyl)-4-piperidinyl]-1,3-dihydro-1-oxo-2H-isindol-2-yl]-2,6-piperidinedione (Registry Nr. 2291361-02-7, C26 H26 N4 O3 S). The compound was prepared in Example 8 of D5.
- 3.2.2 Thus, the subject-matter of **claims 95-96** lacks novelty over D5.
- 3.2.3 However, the sequence of IKZF2 (also known as Helios or Ikaros-2) does not fall under the formula of SEQ ID NO: 1 or 2 of the application.
- 3.3 In summary, the present application does not satisfy the criterion set forth in Art. 33(2) PCT because the subject-matter of **claims 1-12, 24-35, 37, 59, 62-65, 71, 95-96** is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

4 **INVENTIVE STEP (Art. 33(3) PCT)**

- 4.1 The subject-matter of **claims 1-12, 24-35, 37, 59, 62-65, 71, 95-96** lacks novelty, thus, it does not involve an inventive step (Art. 33(3) PCT).
- 4.2 For the discussion of inventive step, it is important to analyze the technical contribution of the present application to the prior art.
- 4.3 In the application, Ikaros (IKZF1) ZNF2 G-motif was fused to a chimeric antigen receptor (CAR) which retains its function (Ex. 1). Different configurations of IKZF1 ZNF1, ZNF2 and ZNF3 and mutants thereof were tested for degradation with compound A (Ex. 2). The degradation of a IKZF1 ZNF2_3 tagged CAR by compound A inhibits CAR activity (Ex. 3) Mutagenesis of the G-motif was made based on alignments of IKZF1 with other IKZF family members and several compounds were tested as degradation agents; The **IKZF1 ZNF2 Q1F** mutant was heavily ubiquitinated in response to compound B (Ex. 4). Small molecules were screened for potent activity against Q1F degnon and, compounds B, C and D were identified (Ex. 5). IKZF1 ZNF2 Q1F tagged CAR are degraded by the cereblon (CRBN) and Ub proteasome pathway in the presence of compound C (Ex. 6) and, CAR degradation inhibits CAR activity in vitro (Ex. 7) and in cells (Ex. 8). Degradation preserves CAR function after chronic antigen exposure (Ex. 9, 10). Ex. 11 shows that this degnon also works for endogenous proteins (AURA, TOX). Ex 12-15 disclose the synthesis of compounds B, and D. Ex. 16 shows the selectivity of Compounds A, B, C and D on Aiolos, Ikaros , GSTP1 or CK1a; Compounds B, C and D were more selective for the Q1F degnon than Compound A.
- 4.4 In the prior art degnons from Zinc finger domains derived from the IKZF family were known, even as fusion partners to polypeptides, like CAR polypeptides and, wherein degradation of the polypeptide is induced by small molecules, especially immunomodulatory imide drugs (IMiD), like lenalidomide:
- 4.5 **D6** (WO2019089592) discloses CAR fusions with a degradation domain which is a CRBN/Cereblon polypeptide substrate domain capable of binding CRBN in response to drug, thereby promoting ubiquitin pathway-mediated degradation of the drug-responsive CAR. The degradation domain is from proteins including Zn-finger degnons from IKZF1, IKZF3 or other molecules (see claims). The drug is a small molecule like thalidomide, lenalidomide or pomalidomide. Note that lenalidomide has a structure (see first formula on page 58) present in Compounds A,B,C and D of the application. Several sequences of degnons and hybrids thereof, e.g. from IKZF3, as well asand mutations thereof were made (see e.g. p. 2 last para., page 4, para. 2-5; Tables 1-3). Some degnons were

engineered to enable more robust drug-dependent activation, like the K0 d913 super-degron (see e.g. p. 28, para 2, Fig. 5). The degrons in D6, especially component 2, have always the conserved C and CG of SEQ ID NO: 1 of the application, but none has F (F at position 1 in SEQ ID NO: 1) before the first conserved C. The sequences of most degrons in D6 comprise the sequence QCNQCGAS, which is as SEQ ID NO: 3, but with the wild type Q instead of F at position 1 in SEQ ID NO: 1-3 of the application.

- 4.6 **D7** (XP055982210; Jan et al. 2021; Supplementary material on D7a, XP055982578) discloses the reversible ON-and OFF-switch chimeric antigen receptors (CAR) controlled by lenalidomide (comprising a structure forming part of compounds A, B, C and D of the application). Different degrons (degradation domains) derived from IKZF family members and hybrid zinc fingers are disclosed; the conserved residues in these motifs were analysed (Fig. 3). Some hybrid ZNF show more efficient drug-dependent degradation than the parent zinc finger (e.g. fig. S4A). For instance, the half-maximal degradation concentration (DC50) by lenalidomide or pomalidomide was lower for the six hybrid zinc fingers than for the corresponding parent zinc fingers (fig. S4B)
- 4.7 **D8** (XP055708883; Sievers et al., 2018) discloses a C2H2 ZF library screening for identifying previously unknown degrons and protein targets, especially Zinc finger domain degron motifs from the IKFZ family, like IKZF1. Several motifs were tested and mutant versions made based on the alignments of the motifs from several proteins (see Fig. 3). Their binding and degradation by different compounds, thalidomide, lenalidomide, and pomalidomide was tested. Some motifs had a differential degradation induced by the different drugs. This was tested using fusion proteins comprising the C2H2 zinc-finger domains to GFP (see Fig. 1).
- 4.8 **D9** (WO2019079569) discloses fusion polypeptides comprising (a) a compound of formula (I) / a cereblon/CRBN binding polypeptide (which is a degradation domain) and (b) a heterologous polypeptide (which can be a CAR). Degradation is induced by binding of a compound of formula (I) which can be, among others, lenalidomide, pomalidomide, and thalidomide, having a structure comprised in compounds A, B, C and D of the application (see claims, examples).
- 4.9 **D10** (WO2020219742) discloses fusion polypeptides, comprising a degradation polypeptide and a heterologous polypeptide (e.g. a CAR), wherein: (i) the degradation polypeptide comprises the amino acid sequence of $X_1QCX_2X_3CGX_4X_5X_6X_7$, wherein X_1-X_7 are defined in claim 1 of D8, namely $[F,L]QC[E,N][I,Q]CG[A,F][S,T][F,C][R,T]$. The degradation compound is

preferably lenalidomide, an immunomodulatory imide drug (IMiD) e.g., 3-(4-amino-1-oxoisindolin-2-yl)piperidine-2,6-dione, or a pharmaceutically acceptable salt thereof (claim 1, page 95). Lenalidomide has a structure included in compounds A, B, C and D of the application.

- 4.10 The **contribution** of the application is thus seen as, not only to provide variant deignons, but to identify degradation motifs which can be selectively or preferentially modulated by specific compounds. The **actual contribution** was the identification that the degradation motif from IKZF1 ZNF2 Q1F, which comprises sequence FCNQCGAS (SEQ ID NO: 3) in the context of certain Zink finger structures (e.g. SEQ ID NO: 7), can lead to degradation of the fusion protein by compounds B, C or D, more selectively than using compound A.
- 4.11 **D6, D7 or D8** can be considered as the **closest prior art** because they specifically disclose fusions of deignons derived from Zinc finger domains of the IKZF family which can be degraded by induction with IMiD compounds, and especially, they teach variants and mutations in the consensus sequence in order to get differential or preferential degradation by specific IMiD drugs.
- 4.12 **Claims 1-71**
- 4.12.1 The subject-matter of the main **claim 1** differs from the prior art in that the degradation domain comprises SEQ ID NO: 1-3. In fact, the only difference is that the deignons of the application have an F at position 1 in SEQ ID NO: 1-3, while those of the prior art had mainly Q or other amino acids, but apparently not F. However, polypeptides comprising such sequences were known (D1-D4), thus, **claims 1-12, 24-35, 37, 59, 62-65, 71** lack novelty and cannot be considered inventive.
- 4.12.2 It is unclear how the Applicant intends to amend the claims to render a main independent claim which is new over the prior art, since several possibilities are possible from the dependent claims. In view of the high number of dependent claims, it is not meaningful to make a full analysis of each claim and, a summarized opinion is provided for groups of claims.
- 4.12.3 The **differences** are the more defined sequence or structure of the degradation domain (claims 1-23), functional features that the degradation domain binds certain degradation agents or leads to degradation of the polypeptide (claims

- 24-31), the location of the polypeptide (e.g. in vitro, in a cell; claims 30-33, 59-61) or the specific polypeptide fused to the degradation domain (claims 34-58).
- 4.12.4 The **technical effect** of the invention, as discussed above, can be seen in the provision of further degrons based on the zinc finger domains of IKZF family proteins and which can be differentially modulated by different compounds.
- 4.12.5 The **problem** to be solved by the invention, especially **claims 1-61** is summarised as to provide further degradation domains (degrons) suitable for the degradation of polypeptides induced by small molecules as degradation agents. The **solution** would be the features of each of the dependent claims.
- 4.12.6 For **claim 12**, the **solution** is that the degradation domain has the specific sequence FCNQCGAS (SEQ ID NO: 3). However, this sequence was disclosed in the prior art (e.g. D4), thus, the subject-matter of **claim 12** cannot be inventive. The application shows that this domain, especially forming part of certain zinc finger structures, leads to degradation being more specific for certain IMiD compounds, especially Compounds B, C and D of the application. Thus, it appears that the subject-matter of **claim 23**, which comprise SEQ ID NO: 3 as part of zinc finger motives and was shown in the application to be differentially degraded by compounds A, B, C and D, also differently to the same sequence but having the wild type Q instead of F (at position 1 of SEQ ID NO: 1)
- 4.12.7 For dependent **claims 13-23, 36, 38-58, 60-61** (those whose subject-matter is apparently new), there was no suggestion to modify zinc finger degrons of the prior art such as to comprise the consensus sequence FCX₁X₂CGX₃X₄ (SEQ ID NO: 1), with X₁-X₄ defined as in the claims. In the prior art, only the C and CG in SEQ ID NO: 1 were shown to be conserved but there was no disclosure of a degron comprising an **F** at the position corresponding to position 1 in SEQ ID NO: 1. This position is Q in most of the degrons known at the filing date. Thus, the subject-matter of these claims was not structurally obvious over the prior art.
- 4.12.8 However, the main issue is that, although there is a certain flexibility in the specific amino acids at some positions in the consensus degradation domain of zinc finger domains of the IKZF family, as seen e.g. in D6, D7 or D10, not all of the possible sequences falling under SEQ ID NO: 1 or 2 as defined in claims 1-11, can be expected to be regulated as that of SEQ ID NO: 3. There are too many possible amino acids at positions X₁-X₅, e.g. SEQ ID NO: 2 admits 93600 possible combinations. Especially in respect to the preferential degradation by

compounds B, C or D as compared to compound A and as compared to other similar deignons of the prior art, it cannot be reasonably expected that all compounds falling within the consensus degradation domain would behave as SEQ ID NO: 3. The application shows that some such degradation domains work, but it was always done for a few specific sequences and in the context of determined zinc finger structures, namely, those of **claim 23**. The solutions provided in **claims 1-22, 24-61** (even if novelty could be restored) are not considered inventive because not all sequences falling under the structural definition of these claims solve the objective technical problem. Providing alternative degradation domains would be seen as arbitrary solutions in view of those disclosed in the prior art and the high variability of the residues except for the highly conserved "C" and ""CG" residues (See D6, D7, D11).

4.12.9 Thus, the ISA is of the preliminary opinion that **claims 1-22, 24-61**, lack an inventive step. The same opinion of a lack of inventive step also applies to **claims 62-71** since the formula of SEQ ID NO: 1 and 2 is very broad to make it credible that the problem was solved over the whole scope.

4.12.10 In **claim 28** specific compounds are listed, namely, compounds referred to as Compounds B, C and D. However, as discussed above, this claim also lacks novelty it is assumed that the broad formula of SEQ ID NO: 1 and 2 is sufficient for degradation. If the Applicant could provide convincing arguments that this is not the case, then, more defined sequences (e.g. SEQ ID NO: 3) would have to be considered as essential features of the invention and should be features of all the independent claims.

4.13 **Claims 72-81**

4.13.1 These claims are directed to methods of reducing the level of an engineered polypeptide of previous claims (comprising a degradation domain of SEQ ID NO: 1) contacting the polypeptide with specific degradation agents compounds B, C or D, or tautomers and salts thereof. Since these are method claims, the degradation is a functional feature, thus, the subject-matter is limited to those polypeptides with degradation domains falling within SEQ ID NO: 1 but which do lead to a degradation induced by these specific compounds.

4.13.2 Compounds B and C were apparently not disclosed in the prior art, but compound C was known and disclosed for degrading IKZF family members (see D5). However, there was no suggestion or expectation that compounds B, C or D would degrade polypeptides comprising a degradation domain having the sequence of SEQ ID NO: 1.

4.13.3 Thus, for **claims 72-81**, it can be accepted that the subject-matter is inventive over the prior art.

4.14 **Claims 82-94**

4.14.1 The same opinion of a lack of inventive step raised above for claims 1-11, 13-22, 24-71 also applies to **82-93** since the formula of SEQ ID NO: 1 and 2 is too broad to make it credible that the problem was solved over the whole scope.

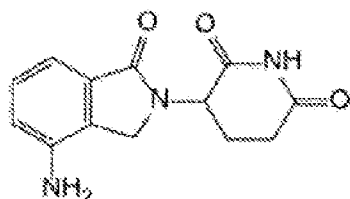
4.14.2 For **claim 94**, where specific compounds are used, in D5, compound D was disclosed (I-130, page 186) and meant for uses to reduce Helios (Ikaros-2 or IKZF2) protein levels and to treat cancer. However, in D5, there was no disclosure of any polypeptide having the degradation domain of SEQ ID NO: 1. Thus, for the same reasons as discussed for claims 72-81, the ISA is of the opinion that the subject-matter of **claim 94** can be considered inventive.

4.15 **Claims 95-96**

4.15.1 These claims lack novelty in view of the disclosure of compound D in D5 (I-130, page 186) and pharmaceutical compositions with it. Thus, for these claims, no inventive step can be acknowledged.

4.15.2 It appears however that Compounds B and C had not been disclosed. Based on the capacity of these compounds to differentially induce degradation of proteins comprising a degradation domain, in particular preferential degradation of polypeptides comprising the degradation domain of SEQ ID NO: 3 (FCNQCGAS), as seen in the examples of the application, it appears that these compounds could also be considered inventive. The reasons are as follows:

4.15.3 For these claims, D6 or D7 could be seen as closest prior art. In these documents, lenalidomide was used as the degradation agent. **Lenalidomide** has the following structure (see e.g. D6, p. 58):



- 4.15.4 This structure, except for the -NH₂ radical, is included in the structure of compounds A, B, C and D of the application. It was known that this structure was important for binding to CRBN (Cereblon; see Box 3 of D11)
- 4.15.5 The **difference** is the rest of the molecules. The **technical effect** is that Compounds B, C and D induce better degradation than compound A, preferentially for degradation domains comprising SEQ ID NO: 3 (FCNQCGAS).
- 4.15.6 The **problem** would be to provide further compounds for inducing selective degradation of polypeptides with a degradation domain, especially of SEQ ID NO: 3 (or even SEQ ID NO: 1 and 2). The **solution** is to provide compounds B and C.
- 4.15.7 This solution was not disclosed and their effect was not obvious or predictable, especially for the degradation domain of SEQ ID NO: 3.
- 4.15.8 Thus, for compounds B and C, and pharmaceutical compositions comprising these, an inventive step might be acknowledged. For compound D, it is not possible since it was known from D5. However, specific uses of these compounds, especially to degrade polypeptides comprising a degradation domain comprising SEQ ID NO: 3, might be the basis of possible patentable subject-matter.
- 4.15.9 In summary, the subject-matter of **claims 95-96** is not inventive (Art. 33(3) PCT)
- 4.16 As a conclusion, the ISA is of the opinion that the present application does therefore not satisfy the criterion set forth in Art. 33(3) PCT because the subject-matter of **claims 1-22, 24-71, 82-93, 95-96** does not involve an inventive step (Rule 65(1)(2) PCT).

5 PATENTABILITY

- 5.1 For the assessment of present **claims 72-94** on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The

EPO, for example, does not recognise as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for use in a medical treatment.

- 5.2 **Claims 72-81** are directed methods to reduce the level of a polypeptide defined in previous claims, however, it covers methods *in vitro*, in a cell and, *in vivo*, thus, the category of these claims is unclear because it also covers methods of treatment.

Item VIII

6 **CLARITY, SUPPORT and DISCLOSURE (Art. 6, 5 PCT)**

- 6.1 The application does not meet the requirements of Art. 6 PCT because claims are not clear for the following reasons:
- 6.2 As discussed above under novelty, claim 1 requires an **engineered** polypeptide, but "engineered" is not clear as to establish a technical difference with the polypeptides of the prior art. The same sequence can be obtained from a natural source or be engineered, e.g. by modifying other sequences.
- 6.3 The definition of a sequence as a "**degradation domain**" is not sufficient to establish a difference, since this is characterised by the sequence itself.
- 6.4 **Claims 24-31** require that "the engineered polypeptide is ubiquitinated and/or degraded in a cell in the presence of the degradation agent", however, these are rather steps of a process, but cannot further define the claimed polypeptide. Moreover, it is unclear whether the ubiquitinated polypeptide or even the degraded polypeptide is part of the claimed subject-matter. Thus, these claims lack clarity (Art. 6 PCT).
- 6.5 It appears from the description as a whole and in particular from the examples that some degradation domains, especially comprising SEQ ID NO: 3, have specific properties of differentially being degraded by compounds B, C or D, as compared to compound A or as compared to degradation domains from e.g. IKZF1 G domain. As discussed above, although there is a certain flexibility in the amino acids at some positions in the consensus degradation domain (see D6, D7 or D10), not all of the possible sequences falling under SEQ ID NO: 1 or 2 as defined in claims 1-11, can be expected to be regulated as that of SEQ ID NO: 3. There are too many possible amino acids at positions X₁-X₅, e.g. SEQ ID NO: 2 admits 93600 possible combinations. Especially in respect to the preferential degradation by compounds B, C or D as compared to compound A

and as compared to other similar degrons of the prior art, it cannot be reasonably expected that all compounds falling within the consensus degradation domain would behave as SEQ ID NO: 3. The application shows that some such degradation domains work, but it was always done for a few specific sequences and in the context of determined zinc finger structures. Thus, at present, it seems that specific sequences are essential technical features of the present invention. This essential technical feature is however not present in **claims 1-11, 13-22, 24-94**. For these reasons these claims are considered to lack clarity according to Art. 6 PCT taken in combination with Rule 6.3 (b) PCT (see PCT Preliminary Examination Guidelines III.4.3).

- 6.6 The present set of claims does not comply with the requirements of Art. 6 PCT because it lacks conciseness. There is a **multiplicity of independent and dependent claims**, which is not justified and does not comply with the requirements of PCT (see Appendix to Chapter 5 of the ISPE Guidelines, GL/ISPE A5.16[2], A5.42[1],[2]).