

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)

Applicant's or agent's file reference 47517-768601		Date of mailing (day/month/year) 14 August 2024 (14.08.2024)
International application No. PCT/US2023/083985		FOR FURTHER ACTION See paragraph 2 below
International filing date (day/month/year) 14 December 2023 (14.12.2023)	Priority date (day/month/year) 05 January 2023 (05.01.2023)	
International Patent Classification (IPC) or both national classification and IPC IPC: See continuation sheet CPC: See continuation sheet		
Applicant HARPOON THERAPEUTICS, INC.		

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will 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/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450	Date of completion of this opinion 23 May 2024 (23.05.2024)	Authorized officer MATOS, Taina
Facsimile No. 571-273-8300		Telephone No. 571-272-4300

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2023/083985

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(b)).
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 13*ter*.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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. See claims listed below

because:

- ☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 4-36, 40-64, 68-84, 87-100, 104-115, 122-127, 131-136, 140-150 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 4-36, 40-64, 68-84, 87-100, 104-115, 122-127, 131-136, and 140-150 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

- ☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

- ☒ no international search report has been established for said claims Nos. 4-36, 38-66, 68-85, 87-100, 104-115, 122-127, 130-136, 138, 140-150

- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a).
 - ☐ See Supplemental Box for further details.

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest and, where applicable, the protest fee.
 - ☐ paid additional fees under protest but the applicable protest fee was not paid.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3, 37-39, 65-67, 85, 86, 101-103, 116-121, 128-130, and 137-139 are drawn to TROP2 binding domains, conditionally active TROP2 binding proteins, multivalent proteins, active drugs, processes for producing a multivalent protein, processes for producing an active drug, methods of increasing a therapeutic index of a TROP2 binding domain, methods of increasing a therapeutic index of a TROP2 binding protein, methods of increasing a therapeutic index of a TROP2 binding protein, and TROP2 targeting conditionally active multispecific proteins.

The first invention of Group I+ is restricted to SEQ ID NO: 1, TROP2 binding domains comprising the same, conditionally active TROP2 binding proteins comprising the same, multivalent proteins comprising the same, active drugs comprising the same, processes for producing a multivalent protein comprising the same, processes for producing an active drug comprising the same, methods of increasing a therapeutic index of a TROP2 binding domain comprising the same, methods of increasing a therapeutic index of a TROP2 binding protein, methods of increasing a therapeutic index of a TROP2 binding protein comprising the same, and TROP2 targeting conditionally active multispecific proteins comprising the same. The first named invention has been selected based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines. Specifically, the first named invention was selected based on the first listed compound species presented in the claims (see claim 3). It is believed that claims 1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, and 139 read on this first named invention and thus these claims will be searched without fee to the extent that they read on.

Applicant is invited to elect additional SEQ ID NOs, TROP2 binding domains comprising the same, conditionally active TROP2 binding proteins comprising the same, multivalent proteins comprising the same, active drugs comprising the same, processes for producing a multivalent protein comprising the same, processes for producing an active drug comprising the same, methods of increasing a therapeutic index of a TROP2 binding domain comprising the same, methods of increasing a therapeutic index of a TROP2 binding protein, methods of increasing a therapeutic index of a TROP2 binding protein comprising the same, and TROP2 targeting conditionally active multispecific proteins comprising the same to be searched in a specific combination by paying an additional fee for each election. An exemplary election would be SEQ ID NO: 2, TROP2 binding domains comprising the same, conditionally active TROP2 binding proteins comprising the same, multivalent proteins comprising the same, active drugs comprising the same, processes for producing a multivalent protein comprising the same, processes for producing an active drug comprising the same, methods of increasing a therapeutic index of a TROP2 binding domain comprising the same, methods of increasing a therapeutic index of a TROP2 binding protein, methods of increasing a therapeutic index of a TROP2 binding protein comprising the same, and TROP2 targeting conditionally active multispecific proteins comprising the same. Additional will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention

Box No. IV Lack of unity of invention

if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the “+” group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulas do not share a significant structural element responsible for TROP2 binding, requiring the selection of alternative amino acid sequences where the TROP2 binding domain “compris[es] an amino acid sequence that is at least about 75% identical to a sequence selected from the group consisting of SEQ ID NOS: 1-57.”

Additionally, even if Groups I+ were considered to share the technical features of a TROP2 binding domain comprising a complementarity determining region 1 (CDR1), a CDR2, and a CDR3; A conditionally active TROP2 binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein at least one of the first target antigen binding domain (T1) and the second target antigen binding domain (T2) comprises a TROP2 binding domain, wherein the TROP2 binding domain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3, wherein the non-CDR loop is capable of binding to the TROP2 binding domain or the second target antigen binding domain, and wherein the binding moiety is capable of masking or masks the binding of the TROP2 binding domain or the second target antigen binding domain to its target; A multivalent protein; An active drug; A process for producing a multivalent protein, said process comprising culturing a host transformed or transfected with a vector comprising one or more nucleic acid sequences encoding the domains of the multivalent protein, under conditions allowing the expression of the multivalent protein and recovering and purifying the produced protein from the culture; A process for producing an active drug, said process comprising culturing a host transformed or transfected with a vector comprising one or more nucleic acid sequences encoding the domains of the active drug, under conditions allowing the expression of the active drug and recovering and purifying the produced drug from the culture; A method of increasing a therapeutic index of a TROP2 binding domain, the method comprising conjugating the TROP2 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the TROP2 binding domain, - wherein the TROP2 binding domain is masked from binding its target by the binding moiety, and - wherein the TROP2 binding domain binds its target upon cleavage of the cleavable linker; A method of increasing a therapeutic index of a TROP2 binding protein comprising a first target antigen binding domain and a second target antigen binding domain, wherein at least one of the first and the second target antigen binding domain comprises a TROP2 binding domain, the method comprising conjugating the first or the second target antigen binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the first or the second target antigen binding domain, - wherein at least one of the first or the second target antigen binding domain is masked from binding its target by the binding moiety, and - wherein the first or the second target antigen binding domain that is masked, binds its target upon cleavage of the cleavable linker; A method of increasing a therapeutic index of a TROP2 binding protein comprising a TROP2 binding domain and a CD3 binding domain, the method comprising conjugating CD3 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, wherein the non-CDR loop comprises a binding site specific for CD3 binding domain; and A TROP2 targeting conditionally active multispecific protein, comprising: a TROP2 binding domain, a CD3 binding domain, an albumin binding domain, wherein the albumin binding domain comprises a non-CDR loops that comprises a binding site specific for the CD3 binding domain and a cleavable linker, wherein the TROP2 binding domain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2021/0292421 A1 to Harpoon Therapeutics Inc. teaches a TROP2 binding domain comprising a complementarity determining region 1 (CDR1), a CDR2, and a CDR3 (the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain

Box No. IV Lack of unity of invention

three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]); A conditionally active TROP2 binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein at least one of the first target antigen binding domain (T1) and the second target antigen binding domain (T2) comprises a TROP2 binding domain, wherein the TROP2 binding domain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3, wherein the non-CDR loop is capable of binding to the TROP2 binding domain or the second target antigen binding domain, and wherein the binding moiety is capable of masking or masks the binding of the TROP2 binding domain or the second target antigen binding domain to its target (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]); A multivalent protein (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), Para. [0007]); An active drug (active drug, Para. [0055]); An active drug (active drug, Para. [0055]); A process for producing a multivalent protein, said process comprising culturing a host transformed or transfected with a vector comprising one or more nucleic acid sequences encoding the domains of the multivalent protein, under conditions allowing the expression of the multivalent protein and recovering and purifying the produced protein from the culture (the binding moieties or the conditionally active binding proteins comprising the binding moieties as described herein, in some embodiments, are produced by introducing vectors encoding the binding moieties or the binding proteins as described above into host cells and culturing said host cells under conditions whereby the binding moieties or the binding proteins, or domains thereof are expressed, Para. [0121]; Trispecific proteins purified from CHO host cells, Para. [0142]); A process for producing an active drug, said process comprising culturing a host transformed or transfected with a vector comprising one or more nucleic acid sequences encoding the domains of the active drug, under conditions allowing the expression of the active drug and recovering and purifying the produced drug from the culture (the binding moieties or the conditionally active binding proteins comprising the binding moieties as described herein, in some embodiments, are produced by introducing vectors encoding the binding moieties or the binding proteins as described above into host cells and culturing said host cells under conditions whereby the binding moieties or the binding proteins, or domains thereof are expressed, Para. [0121]; Trispecific proteins purified from CHO host cells, Para. [0142]); A method of increasing a therapeutic index of a TROP2 binding domain, the method comprising conjugating the TROP2 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the TROP2 binding domain, - wherein the TROP2 binding domain is masked from binding its target by the binding moiety, and - wherein the TROP2 binding domain binds its target upon cleavage of the cleavable linker (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target

Box No. IV Lack of unity of invention

via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]; A method of increasing a therapeutic index of a TROP2 binding protein comprising a first target antigen binding domain and a second target antigen binding domain, wherein at least one of the first and the second target antigen binding domain comprises a TROP2 binding domain, the method comprising conjugating the first or the second target antigen binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the first or the second target antigen binding domain, - wherein at least one of the first or the second target antigen binding domain is masked from binding its target by the binding moiety, and - wherein the first or the second target antigen binding domain that is masked, binds its target upon cleavage of the cleavable linker (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]; A method of increasing a therapeutic index of a TROP2 binding protein comprising a TROP2 binding domain and a CD3 binding domain, the method comprising conjugating CD3 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, wherein the non-CDR loop comprises a binding site specific for CD3 binding domain (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; the first or the second target antigen binding domain binds to CD3, Para. [0008]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]; and A TROP2 targeting conditionally active multispecific protein, comprising: a TROP2 binding domain, a CD3 binding domain, an albumin binding domain, wherein the albumin binding domain comprises a non-CDR loops that comprises a binding site specific for the CD3 binding domain and a cleavable linker, wherein the TROP2 binding domain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3 (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of

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Box No. IV

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masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; the first or the second target antigen binding domain binds to CD3, Para. [0008]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical features.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐

all parts.

☒

the parts relating to claims Nos. 1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, 139

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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

1. Statement

Novelty (N)	Claims	1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, 139	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, 139	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, 139	YES
	Claims	None	NO

2. Citations and explanations:

----- EXPLANATION -----

Claims 1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, and 139 have been analyzed subject to the restriction that the claims read on SEQ ID NO: 1, TROP2 binding domains comprising the same, conditionally active TROP2 binding proteins comprising the same, multivalent proteins comprising the same, active drugs comprising the same, processes for producing a multivalent protein comprising the same, processes for producing an active drug comprising the same, methods of increasing a therapeutic index of a TROP2 binding domain comprising the same, methods of increasing a therapeutic index of a TROP2 binding protein, methods of increasing a therapeutic index of a TROP2 binding protein comprising the same, and TROP2 targeting conditionally active multispecific proteins comprising the same.

Claims 1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, and 139 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest:

Regarding claim 1, the prior art of record, individually or in combination, does not teach or fairly suggest a TROP2 binding domain comprising SEQ ID NO: 1.

The following prior art is made of record to support and further define the reasons claim 1 meets the criteria set out in PCT Article 33(2)-(3):

(i) US 2021/0292421 A1 to Harpoon Therapeutics Inc. (hereinafter, "Harpoon") teaches a TROP2 binding domain (the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]).

(ii) US 2020/0055912 A1 to Orionis Biosciences Nv et al. (hereinafter, "Orionis") teaches an amino acid sequence having 79.8% sequence identity to SEQ ID NO: 1 (The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety, Para. [0003]; The Sequence Listing discloses SEQ ID NO: 482; SEQ ID NO: 482 of Orionis comprises 79.8% sequence identity to instant SEQ ID NO: 1).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 1, as recited above.

Claims 2 and 3 depend from claim 1, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 1.

Regarding claim 37, the prior art of record, individually or in combination, does not teach or fairly suggest a conditionally active TROP2 binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (TI), and a second target antigen binding domain (T2), wherein at least one of the first target antigen binding domain (TI) and the second target antigen binding domain (T2) comprises a TROP2 binding domain, wherein the TROP2 binding domain comprises SEQ ID NO: 1, wherein the non-CDR loop is capable of binding to the TROP2 binding domain or the second target antigen binding domain, and wherein the binding moiety is capable of masking

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**

or masks the binding of the TROP2 binding domain or the second target antigen binding domain to its target.

The following prior art is made of record to support and further define the reasons claim 37 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches a conditionally active TROP2 binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein at least one of the first target antigen binding domain (T1) and the second target antigen binding domain (T2) comprises a TROP2 binding domain, wherein the TROP2 binding domain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3, wherein the non-CDR loop is capable of binding to the TROP2 binding domain or the second target antigen binding domain, and wherein the binding moiety is capable of masking or masks the binding of the TROP2 binding domain or the second target antigen binding domain to its target (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]); A multivalent protein (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), Para. [0007]).

(ii) Orionis teaches an amino acid sequence having 79.8% sequence identity to SEQ ID NO: 1 (The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety, Para. [0003]; The Sequence Listing discloses SEQ ID NO: 482; SEQ ID NO: 482 of Orionis comprises 79.8% sequence identity to instant SEQ ID NO: 1).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 1, as recited above.

Regarding claim 67, the prior art of record, individually or in combination, does not teach or fairly suggest an active drug comprising SEQ ID NO: 1.

The following prior art is made of record to support and further define the reasons claim 67 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches an active drug (active drug, Para. [0055]).

(ii) Orionis teaches an amino acid sequence having 79.8% sequence identity to SEQ ID NO: 1 (The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety, Para. [0003]; The Sequence Listing discloses SEQ ID NO: 482; SEQ ID NO: 482 of Orionis comprises 79.8% sequence identity to instant SEQ ID NO: 1).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 1, as recited above.

Claim 86 depends from claim 67, and therefore meets the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 67.

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

Regarding claim 101, the prior art of record, individually or in combination, does not teach or fairly suggest a method of increasing a therapeutic index of a TROP2 binding domain comprising SEQ ID NO: 1, the method comprising conjugating the TROP2 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the TROP2 binding domain, - wherein the TROP2 binding domain is masked from binding its target by the binding moiety, and - wherein the TROP2 binding domain binds its target upon cleavage of the cleavable linker.

The following prior art is made of record to support and further define the reasons claim 101 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches a method of increasing a therapeutic index of a TROP2 binding domain, the method comprising conjugating the TROP2 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the TROP2 binding domain, - wherein the TROP2 binding domain is masked from binding its target by the binding moiety, and - wherein the TROP2 binding domain binds its target upon cleavage of the cleavable linker (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]).

(ii) Orionis teaches an amino acid sequence having 79.8% sequence identity to SEQ ID NO: 1 (The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety, Para. [0003]; The Sequence Listing discloses SEQ ID NO: 482; SEQ ID NO: 482 of Orionis comprises 79.8% sequence identity to instant SEQ ID NO: 1).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 1, as recited above.

Claims 102 and 103 depend from claim 101, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 101.

Regarding claim 116, the prior art of record, individually or in combination, does not teach or fairly suggest a method of increasing a therapeutic index of a TROP2 binding protein comprising a first target antigen binding domain and a second target antigen binding domain, wherein at least one of the first and the second target antigen binding domain comprises a TROP2 binding domain comprising SEQ ID NO: 1, the method comprising conjugating the first or the second target antigen binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the first or the second target antigen binding domain, - wherein at least one of the first or the second target antigen binding domain is masked from binding its target by the binding moiety, and - wherein the first or the second target antigen binding domain that is masked, binds its target upon cleavage of the cleavable linker.

The following prior art is made of record to support and further define the reasons claim 116 meets the criteria set out in PCT Article 33(2)-(3):

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**

(i) Harpoon teaches a method of increasing a therapeutic index of a TROP2 binding protein comprising a first target antigen binding domain and a second target antigen binding domain, wherein at least one of the first and the second target antigen binding domain comprises a TROP2 binding domain, the method comprising conjugating the first or the second target antigen binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the first or the second target antigen binding domain, - wherein at least one of the first or the second target antigen binding domain is masked from binding its target by the binding moiety, and - wherein the first or the second target antigen binding domain that is masked, binds its target upon cleavage of the cleavable linker (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]).

(ii) Orionis teaches an amino acid sequence having 79.8% sequence identity to SEQ ID NO: 1 (The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety, Para. [0003]; The Sequence Listing discloses SEQ ID NO: 482; SEQ ID NO: 482 of Orionis comprises 79.8% sequence identity to instant SEQ ID NO: 1).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 1, as recited above.

Claims 117-121 depend from claim 116, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 116.

Regarding claim 128, the prior art of record, individually or in combination, does not teach or fairly suggest a method of increasing a therapeutic index of a TROP2 binding protein comprising a TROP2 binding domain comprising SEQ ID NO: 1 and a CD3 binding domain, the method comprising conjugating CD3 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, wherein the non-CDR loop comprises a binding site specific for CD3 binding domain.

The following prior art is made of record to support and further define the reasons claim 128 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches a method of increasing a therapeutic index of a TROP2 binding protein comprising a TROP2 binding domain and a CD3 binding domain, the method comprising conjugating CD3 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, wherein the non-CDR loop comprises a binding site specific for CD3 binding domain (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the

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Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; the first or the second target antigen binding domain binds to CD3, Para. [0008]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]).

(ii) Orionis teaches an amino acid sequence having 79.8% sequence identity to SEQ ID NO: 1 (The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety, Para. [0003]; The Sequence Listing discloses SEQ ID NO: 482; SEQ ID NO: 482 of Orionis comprises 79.8% sequence identity to instant SEQ ID NO: 1).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 1, as recited above.

Claim 129 depends from claim 128, and therefore meets the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 128.

Regarding claim 137, the prior art of record, individually or in combination, does not teach or fairly suggest a TROP2 targeting conditionally active multispecific protein, comprising: a TROP2 binding domain, a CD3 binding domain, an albumin binding domain, wherein the albumin binding domain comprises a non-CDR loops that comprises a binding site specific for the CD3 binding domain and a cleavable linker, wherein the TROP2 binding domain comprises SEQ ID NO: 1.

The following prior art is made of record to support and further define the reasons claim 137 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches a TROP2 targeting conditionally active multispecific protein, comprising: a TROP2 binding domain, a CD3 binding domain, an albumin binding domain, wherein the albumin binding domain comprises a non-CDR loops that comprises a binding site specific for the CD3 binding domain and a cleavable linker, wherein the TROP2 binding domain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3 (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; the first or the second target antigen binding domain binds to CD3, Para. [0008]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]).

(ii) Orionis teaches an amino acid sequence having 79.8% sequence identity to SEQ ID NO: 1 (The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety, Para. [0003]; The Sequence Listing discloses SEQ ID NO: 482; SEQ ID NO: 482 of Orionis comprises 79.8% sequence identity to instant SEQ ID NO: 1).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 1, as recited above.

Claim 139 depends from claim 137, and therefore meets the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 137.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2023/083985

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

Claims 1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, and 139 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

2nd Invention

Novelty (N) Claims 1-3, 37, 67, 86, 101-103, 116-120, 128, 129, 137, 139 YES

Claims None NO

Inventive step (IS) Claims 1-3, 37, 67, 86, 101-103, 116-120, 128, 129, 137, 139 YES

Claims None NO

Industrial applicability (IA) Claims 1-3, 37, 67, 86, 101-103, 116-120, 128, 129, 137, 139 YES

Claims None NO

Claims 1-3, 37, 67, 86, 101-103, 116-120, 128, 129, 137, and 139 have been analyzed subject to the restriction (2nd invention) that the claims read on SEQ ID NO: 55, TROP2 binding domains comprising the same, conditionally active TROP2 binding proteins comprising the same, multivalent proteins comprising the same, active drugs comprising the same, processes for producing a multivalent protein comprising the same, processes for producing an active drug comprising the same, methods of increasing a therapeutic index of a TROP2 binding domain comprising the same, methods of increasing a therapeutic index of a TROP2 binding protein, methods of increasing a therapeutic index of a TROP2 binding protein comprising the same, and TROP2 targeting conditionally active multispecific proteins comprising the same.

Claims 1-3, 37, 67, 86, 101-103, 116-120, 128, 129, 137, and 139 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest:

The following prior art is made of record to support and further define the reasons claim 1 meets the criteria set out in PCT Article 33(2)-(3):

(i) US 2021/0292421 A1 to Harpoon Therapeutics Inc. (hereinafter, "Harpoon") teaches a TROP2 binding domain (the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]).

(ii) US 2017/0174762 A1 to Boehringer Ingelheim International GmbH (hereinafter, "Boehringer") teaches an amino acid sequence having 81.5% sequence identity to SEQ ID NO: 55 (Preferred embodiments are polypeptides comprising... a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22, Paras. [0153]-[0154] SEQ ID NO:22 of Boehringer comprises 81.5% sequence identity to instant SEQ ID NO: 55).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 55, as recited above.

Claims 2 and 3 depend from claim 1, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 1.

Regarding claim 37, the prior art of record, individually or in combination, does not teach or fairly suggest a conditionally active TROP2 binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein at least one of the first target antigen binding domain (T1) and the second target antigen binding domain (T2) comprises a TROP2 binding domain, wherein the TROP2 binding domain comprises SEQ ID NO: 1, wherein the non-CDR loop is capable of binding to the TROP2 binding domain or the second target antigen binding domain, and wherein the binding moiety is capable of masking or masks the binding of the TROP2 binding domain or the second target antigen binding domain to its target.

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**Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement**

The following prior art is made of record to support and further define the reasons claim 37 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches a conditionally active TROP2 binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein at least one of the first target antigen binding domain (T1) and the second target antigen binding domain (T2) comprises a TROP2 binding domain, wherein the TROP2 binding domain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3, wherein the non-CDR loop is capable of binding to the TROP2 binding domain or the second target antigen binding domain, and wherein the binding moiety is capable of masking or masks the binding of the TROP2 binding domain or the second target antigen binding domain to its target (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]; A multivalent protein (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), Para. [0007]).

(ii) Boehringer teaches an amino acid sequence having 81.5% sequence identity to SEQ ID NO: 55 (Preferred embodiments are polypeptides comprising... a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22, Paras. [0153]-[0154] SEQ ID NO:22 of Boehringer comprises 81.5% sequence identity to instant SEQ ID NO: 55).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 55, as recited above.

Regarding claim 67, the prior art of record, individually or in combination, does not teach or fairly suggest an active drug comprising SEQ ID NO: 1.

The following prior art is made of record to support and further define the reasons claim 67 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches an active drug (active drug, Para. [0055]).

(ii) Boehringer teaches an amino acid sequence having 81.5% sequence identity to SEQ ID NO: 55 (Preferred embodiments are polypeptides comprising... a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22, Paras. [0153]-[0154] SEQ ID NO:22 of Boehringer comprises 81.5% sequence identity to instant SEQ ID NO: 55).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 55, as recited above.

Claim 86 depends from claim 67, and therefore meets the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 67.

Regarding claim 101, the prior art of record, individually or in combination, does not teach or fairly suggest a method of increasing a therapeutic index of a TROP2 binding domain comprising SEQ ID NO: 1, the method comprising conjugating the TROP2 binding domain to a binding moiety comprising a

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Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the TROP2 binding domain, - wherein the TROP2 binding domain is masked from binding its target by the binding moiety, and - wherein the TROP2 binding domain binds its target upon cleavage of the cleavable linker.

The following prior art is made of record to support and further define the reasons claim 101 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches a method of increasing a therapeutic index of a TROP2 binding domain, the method comprising conjugating the TROP2 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the TROP2 binding domain, - wherein the TROP2 binding domain is masked from binding its target by the binding moiety, and - wherein the TROP2 binding domain binds its target upon cleavage of the cleavable linker (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]).

(ii) Boehringer teaches an amino acid sequence having 81.5% sequence identity to SEQ ID NO: 55 (Preferred embodiments are polypeptides comprising... a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22, Paras. [0153]-[0154] SEQ ID NO:22 of Boehringer comprises 81.5% sequence identity to instant SEQ ID NO: 55).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 55, as recited above.

Claims 102 and 103 depend from claim 101, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 101.

Regarding claim 116, the prior art of record, individually or in combination, does not teach or fairly suggest a method of increasing a therapeutic index of a TROP2 binding protein comprising a first target antigen binding domain and a second target antigen binding domain, wherein at least one of the first and the second target antigen binding domain comprises a TROP2 binding domain comprising SEQ ID NO: 1, the method comprising conjugating the first or the second target antigen binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the first or the second target antigen binding domain, - wherein at least one of the first or the second target antigen binding domain is masked from binding its target by the binding moiety, and - wherein the first or the second target antigen binding domain that is masked, binds its target upon cleavage of the cleavable linker.

The following prior art is made of record to support and further define the reasons claim 116 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches a method of increasing a therapeutic index of a TROP2 binding protein comprising a first target antigen binding domain and a second target antigen binding domain, wherein at least one of the first and the second target antigen binding domain comprises a TROP2 binding domain, the method comprising conjugating the first or the second target antigen binding domain to a binding moiety

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**Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement**

comprising a cleavable linker and a non-CDR loop, - wherein the non-CDR loop comprises a binding site specific for the first or the second target antigen binding domain, - wherein at least one of the first or the second target antigen binding domain is masked from binding its target by the binding moiety, and - wherein the first or the second target antigen binding domain that is masked, binds its target upon cleavage of the cleavable linker (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]).

(ii) Boehringer teaches an amino acid sequence having 81.5% sequence identity to SEQ ID NO: 55 (Preferred embodiments are polypeptides comprising... a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22, Paras. [0153]-[0154] SEQ ID NO:22 of Boehringer comprises 81.5% sequence identity to instant SEQ ID NO: 55).

None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 55, as recited above.

Claims 117-120 depend from claim 116, and therefore meet the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 116.

Regarding claim 128, the prior art of record, individually or in combination, does not teach or fairly suggest a method of increasing a therapeutic index of a TROP2 binding protein comprising a TROP2 binding domain comprising SEQ ID NO: 1 and a CD3 binding domain, the method comprising conjugating CD3 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, wherein the non-CDR loop comprises a binding site specific for CD3 binding domain.

The following prior art is made of record to support and further define the reasons claim 128 meets the criteria set out in PCT Article 33(2)-(3):

(i) Harpoon teaches a method of increasing a therapeutic index of a TROP2 binding protein comprising a TROP2 binding domain and a CD3 binding domain, the method comprising conjugating CD3 binding domain to a binding moiety comprising a cleavable linker and a non-CDR loop, wherein the non-CDR loop comprises a binding site specific for CD3 binding domain (The conditionally active binding proteins described in the present disclosure exhibit improved the binding affinities towards the target, for example a tumor antigen expressed on a cell surface, Para. [0111]; a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; the first or the second target antigen binding domain binds to CD3, Para. [0008]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions

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
	(CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]). (ii) Boehringer teaches an amino acid sequence having 81.5% sequence identity to SEQ ID NO: 55 (Preferred embodiments are polypeptides comprising... a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22, Paras. [0153]-[0154] SEQ ID NO:22 of Boehringer comprises 81.5% sequence identity to instant SEQ ID NO: 55). None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 55, as recited above. Claim 129 depends from claim 128, and therefore meets the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 128. Regarding claim 137, the prior art of record, individually or in combination, does not teach or fairly suggest a TROP2 targeting conditionally active multispecific protein, comprising: a TROP2 binding domain, a CD3 binding domain, an albumin binding domain, wherein the albumin binding domain comprises a non-CDR loops that comprises a binding site specific for the CD3 binding domain and a cleavable linker, wherein the TROP2 binding domain comprises SEQ ID NO: 1. The following prior art is made of record to support and further define the reasons claim 137 meets the criteria set out in PCT Article 33(2)-(3): (i) Harpoon teaches a TROP2 targeting conditionally active multispecific protein, comprising: a TROP2 binding domain, a CD3 binding domain, an albumin binding domain, wherein the albumin binding domain comprises a non-CDR loops that comprises a binding site specific for the CD3 binding domain and a cleavable linker, wherein the TROP2 binding domain comprises a complementarity determining region 1 (CDR1), a CDR2, and a CDR3 (a conditionally active binding protein comprising a binding moiety (M) which comprises a non-CDR loop, a cleavable linker (L), a first target antigen binding domain (T1), and a second target antigen binding domain (T2), wherein the first target antigen binding domain (T1) comprises an immunoglobulin molecule, wherein the non-CDR loop is capable of binding to the first target antigen binding domain, and wherein the binding moiety is capable of masking the binding of the first target antigen binding domain to its target, Para. [0007]; the binding moiety is capable of masking the binding of the target antigen binding domain (such as an immunoglobulin molecule) or a non-immunoglobulin binding molecule to its target via specific intermolecular interactions between the binding moiety and the target antigen binding domain, Para. [0005]; the target antigen domain binds to a tumor antigen. In some embodiments, the tumor antigen comprises... Trop2, Para. [0006]; the first or the second target antigen binding domain binds to CD3, Para. [0008]; The variable domains of both light and heavy immunoglobulin chains contain three hypervariable loops, or complementarity-determining regions (CDRs). The three CDRs of a V domain (CDR1, CDR2, CDR3) cluster at one end of the beta barrel, Para. [0080]). (ii) Boehringer teaches an amino acid sequence having 81.5% sequence identity to SEQ ID NO: 55 (Preferred embodiments are polypeptides comprising... a second immunoglobulin single variable domain having the amino acid sequence as shown in SEQ ID NO:22, Paras. [0153]-[0154] SEQ ID NO:22 of Boehringer comprises 81.5% sequence identity to instant SEQ ID NO: 55). None of the prior art taken alone or in combination fairly teach or suggest an amino acid sequence having 100% sequence identity to SEQ ID NO: 55, as recited above. Claim 139 depends from claim 137, and therefore meets the criteria set out in PCT Article 33(2)-(3) for at least the same reasons as claim 137. Claims 1-3, 37, 67, 86, 101-103, 116-120, 128, 129, 137, and 139 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2023/083985

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**

Claims 1-3, 37, 67, 86, 101-103, 116-121, 128, 129, 137, and 139 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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Supplemental Box

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

Continuation of IPC: *C07K 16/28* (2024.01); *C07K 16/30* (2024.01); *C07K 19/00* (2024.01); *A61K 39/395* (2024.01); *A61P 35/00* (2024.01)

Continuation of CPC: *C07K 16/2863*; *A61K 39/3955*; *C07K 16/2809*; *C07K 16/30*; *C07K 19/00*; *A61K 2039/505*; *A61P 35/00*; *C07K 2317/31*; *C07K 2319/50*