

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: A. Patricia Campbell Jones Day 250 Vesey Street New York, NY 10281-1047 United States Of America
--

Date of mailing (day/month/year)	JAN 31 2024
-------------------------------------	--------------------

Applicant's or agent's file reference 14529-138-228		FOR FURTHER ACTION See paragraph 2 below
International application No. PCT/US23/73516	International filing date (day/month/year) 06 September 2023 (06.09.2023)	Priority date (day/month/year) 07 September 2022 (07.09.2022)
International Patent Classification (IPC) or both national classification and IPC IPC - INV. A61K 47/68; A61K 47/54; A61K 47/64; C07K 16/28; C07K 16/36 (2023.01) ADD. A61P 35/00 (2023.01) CPC - INV. A61K 47/6803; A61K 47/54; A61K 47/64; C07K 16/28; C07K 16/36 ADD. A61P 35/00		
Applicant EXELIXIS, 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/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Date of completion of this opinion 18 December 2023 (18.12.2023)	Authorized officer. Shane Thomas PCT Help Desk Telephone No. 571-272-4300
---	---	--

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US23/73516

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(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.

PCT/US23/73516

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. 4-11, 13-32

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. 4-11, 13-32 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 4-11, 13-32 are dependent claims and are 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. 4-11, 13-32

☐ 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 13ter.1(a).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US23/73516

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, 12	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-3, 12	NO
Industrial applicability (IA)	Claims	1-3, 12	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3 and 12 lack an inventive step under PCT Article 33(3) as being obvious over US 2022/0241423 A1 (R.P. Scherer Technologies, LLC.) (hereinafter "Scherer") in view of WO 2019/136309 A1 (ICONIC THERAPEUTICS INC.) (hereinafter "ICONIC").

As per claim 1, Scherer discloses an antibody-drug conjugate ADC (the disclosure provides antibody-drug conjugate; abstract) of formula similar to Formula I (the second conjugate on page 16; paragraph [0219]) comprising: a. an antibody(W is a polypeptide antibody; paragraph [0745]); and b. two or more drugs conjugated to a pyridazine-pyrrolo coupling moiety, each via a linker (two terminal drug moieties are conjugated to the pyridazine-pyrrolo coupling core in the second conjugate on page 16; paragraph [0219]) wherein Z1, Z2, and Z4 are each CR4, R4 are each hydrogen (the hydrogen atoms are linked to the respective carbons in pyridazine-pyrrolo coupling core; paragraph [0219]); Z3 is C-LB -W2 (the carbon atom of the pyridazine-pyrrolo coupling core is linked to the drug moiety through a linker; paragraph [0219]); R1 is hydrogen, R2 and R3 are each alkyl (the hydrogen atom and methyl groups are linked to the pyridazine-pyrrolo coupling core; paragraph [0219]); LA is a first linker -(T1-V1)a-(T2-V2)b-(T3-V3)c-(T4-V4)d-(T5-V5)e-(T6-V6)f- (the -C2H4C(O)NH-C4H8CH(NHC(O)CH2SO3H)C(O)NHCH(iPr)C(O)NHCH(CH3)C(O)NH-Ph*-CH2OC(O)- linker connects the pyridazine-pyrrolo coupling core with the drug; paragraph [0219]), wherein: a is 1, b is 1, c is 1, d is 1, e is and f is 0; provided at least one of a, b, c, d, e, and f are 1; T1 is (C1-C12)alkyl, V1 is -CONR15-, R15 is hydrogen (the C2H4C(O)NH fragment is in the linker; paragraph [0219]); T2 is substituted (C1-C12)alkyl (the substituted C5 alkyl C4H8CH(NHC(O)CH2SO3H) is in the linker; paragraph [0219]) and V2 is -CO- (the C(O) moiety is attached to the C4H8CH(NHC(O)CH2SO3H) fragment; paragraph [0219]); T3 is (AA)p, p is 2 and V3 is a covalent bond (the NHCH(iPr)C(O)NHCH(CH3)C(O) fragment comprising 2 amino acid residues is in the linker; paragraph [0219]); T4 is PABC and V4 is a covalent bond (the para amino -benzyloxycarbonyl moiety NH-Ph*-CH2OC(O) substituted with glycoside, is in the linker, where one hydrogen atom of PABS is replaced with a glycoside, as disclosed in paragraph [00358] of the instant application; paragraph [0219]); T5, T6, V5 and V6 are not chosen, e is and f is (the benzyloxycarbonyl moiety NH-Ph*-CH2OC(O) is linked to the drug moiety, T5, T6, V5 and V6 are not chosen; paragraph [0219]); LB is a second linker

-(T7-V7)g-(T8-V8)h-(T9-V9)i-(T10-V10)j-(T11-V11)k-(T12-V12)l-(T13-V13)m-

(the second -NHC(O)C2H4C(O)NHC4H8CH(NHC(O)CH2SO3H) C(O)NHCH(iPr)C(O)NHCH(CH3)C(O)NH-Ph*-CH2OC(O)- linker connects the pyridazine-pyrrolo coupling core with the drug; paragraph [0219]), g is 1, h is 1, i is 1, k is 1, l is and m is 0; provided at least one of g, h, i, j, k, 1, and m is 1; T7 is a covalent bond, V7 is -NR15CO-, R15 is hydrogen (the NHC(O) fragment is in the linker; paragraph [0219]); T8 is substituted (C1-C12)alkyl (the substituted C5 alkyl C4H8CH(NHC(O)CH2SO3H) is in the linker; paragraph [0219]) and V8 is -CO- (the C(O) moiety is attached to the C4H8CH(NHC(O)CH2SO3H) fragment; paragraph [0219]); T9 is (AA)p, p is 2 and V9 is a covalent bond (the NHCH(iPr)C(O)NHCH(CH3)C(O) fragment comprising 2 amino acid residues is in the linker; paragraph [0219]); T10 is PABC and V10 is a covalent bond (the para amino -benzyloxycarbonyl moiety NH-Ph*-CH2OC(O) substituted with glycoside, is in the linker, where one hydrogen atom of PABS is replaced with a glycoside, as disclosed in paragraph [00358] of the instant application; paragraph [0219]); T11, T12, T13, V11, V12, V13 are a covalent bond (the benzyloxycarbonyl moiety NH-Ph*-CH2OC(O) is linked to the second drug moiety, T11, T12, T13, V11, V12, V13 are a covalent bond; paragraph [0219]); W1 is a first drug; and W2 is a second drug (two terminal drug moieties are attached to the linkers in the antibody-drug conjugate; paragraph [0219]). Scherer does not disclose wherein Ab represents the antibody that binds to tissue factor TF. However, ICONIC discloses wherein Ab represents the antibody that binds to tissue factor TF (antibodies that specifically bind to human tissue factor were used in anti-TF antibody-drug conjugates for treatment of breast cancer; abstract; claim 260). It would have been obvious to a person of ordinary skill in the art, before the relevant date, to have modified the ADC, as previously disclosed by Scherer, in order to have provided for wherein Ab represents the antibody that binds to tissue factor TF, as previously disclosed by ICONIC (ICONIC; abstract; claim 260), to provide the antibody that is effective in delivery of the therapeutic drug to a desired site of action where the cancer cells are present (Scherer; abstract; paragraph [1063]) to improve the effectiveness of the antibody-drug conjugate in treatment of breast cancer (Scherer; figures 71, 103; paragraph [1338]) (ICONIC; abstract; claim 260). Further, provided that Scherer and ICONIC both disclose the use of the antibody-drug conjugate for treatment of breast cancer (Scherer; figures 71, 103; paragraph [1338]) (ICONIC; abstract; claim 260), the modification to Scherer's ADC, of providing for wherein Ab represents the antibody that binds to tissue factor TF, would provide the benefit of providing the antibody that is effective in delivery of the therapeutic drug to a desired site of action where the cancer cells are present (Scherer; abstract; paragraph [1063]) to improve the effectiveness of the antibody-drug conjugate in treatment of breast cancer (Scherer; figures 71, 103; paragraph [1338]) (ICONIC; abstract; claim 260).

-Continued in Supplemental Box-

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US23/73516

Box No. VI Certain documents cited

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

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 2023/220620 A2	16 November 2023 (16.11.2023)	10 May 2023 (10.05.2023)	13 May 2022 (13.05.2022)

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

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

Supplemental Box

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

Continuation of:

-Continued From Box V. 2: Citations and Explanations-

As per claim 2, Scherer and ICONIC, in combination, disclose the ADC of claim 1, and Scherer further discloses wherein T1 is (C1-C12)alkyl, V1 is -CONR15-, R15 is hydrogen (the C2H4C(O)NH fragment is in the linker; paragraph [0219]); T2 is substituted (C1-C12)alkyl (the substituted C5 alkyl C4H8CH(NHC(O)CH2SO3H) is in the linker; paragraph [0219]) and V2 is -CO- (the C(O) moiety is attached to the C4H8CH(NHC(O)CH2SO3H) fragment; paragraph [0219]); T3 is (AA)p, p is 2 and V3 is a covalent bond (the NHCH(iPr)C(O)NHCH(CH3)C(O) fragment comprising 2 amino acid residues is in the linker; paragraph [0219]); T4 is PABC and V4 is a covalent bond (the para amino -benzyloxycarbonyl moiety NH-Ph*-CH2OC(O) substituted with glycoside, is in the linker, where one hydrogen atom of PABS is replaced with a glycoside, as disclosed in paragraph [00358] of the instant application; paragraph [0219]); T5, T6, V5 and V6 each are a covalent bond, e is and f is (the benzyloxycarbonyl moiety NH-Ph*-CH2OC(O) is linked to the drug moiety, T5, T6, V5 and V6 are each a covalent bond; paragraph [0219]).

As per claim 3, Scherer and ICONIC, in combination, disclose the ADC of claims 1-2, and Scherer further discloses wherein T1 is (C1-C12)alkyl, V1 is -CONH- (the C2H4C(O)NH fragment is in the linker; paragraph [0219]); T2 is substituted (C1-C12)alkyl (the substituted C5 alkyl C4H8CH(NHC(O)CH2SO3H) is in the linker; paragraph [0219]) and V2 is -CO- (the C(O) moiety is attached to the C4H8CH(NHC(O)CH2SO3H) fragment; paragraph [0219]); T3 is (AA)p, p is 2 and V3 is absent (the NHCH(iPr)C(O)NHCH(CH3)C(O) fragment comprising 2 amino acid residues is in the linker; paragraph [0219]); T4 is PABC and V4 is absent (the para amino -benzyloxycarbonyl moiety NH-Ph*-CH2OC(O) substituted with glycoside, is in the linker, where one hydrogen atom of PABS is replaced with a glycoside, as disclosed in paragraph [00358] of the instant application; paragraph [0219]); a, b, c, and d are each 1; and e and f are each (the -C2H4C(O)NH-C4H8CH(NHC(O)CH2SO3H)C(O)NHCH(iPr)C(O)NHCH(CH3)C(O)NH-Ph*-CH2OC(O)- linker connects the pyridazine-pyrrolo coupling core with the drug; paragraph [0219]).

As per claim 12, Scherer discloses an ADC (the disclosure provides antibody-drug conjugate; abstract) represented by a formula similar to Formula II (second conjugate on page 16; paragraph [0219]), wherein: Ab represents an antibody (W is a polypeptide antibody; paragraph [0745]); and s is 1 (one antibody moiety W is in the conjugate; paragraph [0219]), and in a separate embodiment Scherer further discloses the compound comprising CH3(OCH2CH2)8-C(O)NH- side moieties (the CH3(OCH2CH2)8-C(O)NH- side moieties are attached to the main chain of the second compound on page 37; paragraph [0444]). It would have been obvious to a person of ordinary skill in the art, before the relevant date, to have modified the ADC, as previously disclosed by Scherer, in order to have provided for the compound comprising CH3(OCH2CH2)8-C(O)NH- side moieties, as previously disclosed by Scherer in a separate embodiment (paragraph [0444]), to replace the acidic hydrophilic HOSO2CH2C(O)NH- side moieties with the neutral hydrophilic CH3(OCH2CH2)8-C(O)NH- side moieties, to improve the effectiveness of the conjugate in delivery of the therapeutic drug to a desired site of action where the cancer cells are present (paragraph [1063]). Further, provided that in both embodiments Scherer discloses the compound comprising linking moieties of similar structures having hydrophilic side chains (paragraphs [0219], [0444]), and where the linking moieties are designed for used in antibody-drug conjugate for delivery of the therapeutic drug to a desired site of action where the cancer cells are present (abstract; paragraph [1063]), the modification to Scherer's ADC, of providing for the compound comprising CH3(OCH2CH2)8-C(O)NH- side moieties, would provide the benefit of replacing the acidic hydrophilic HOSO2CH2C(O)NH- side moieties with the neutral hydrophilic CH3(OCH2CH2)8-C(O)NH- side moieties, to improve the effectiveness of the conjugate in delivery of the therapeutic drug to a desired site of action where the cancer cells are present (paragraph [1063]). Scherer does not disclose wherein Ab represents the antibody that binds to tissue factor TF. However, ICONIC discloses wherein Ab represents the antibody that binds to tissue factor TF (antibodies that specifically bind to human tissue factor were used in anti-TF antibody-drug conjugates for treatment of breast cancer; abstract; claim 260). It would have been obvious to a person of ordinary skill in the art, before the relevant date, to have modified the ADC, as previously disclosed by Scherer, in order to have provided for wherein Ab represents the antibody that binds to tissue factor TF, as previously disclosed by ICONIC (ICONIC; abstract; claim 260), to provide the antibody that is effective in delivery of the therapeutic drug to a desired site of action where the cancer cells are present (Scherer; abstract; paragraph [1063]) to improve the effectiveness of the antibody-drug conjugate in treatment of breast cancer (Scherer; figures 71, 103; paragraph [1338]) (ICONIC; abstract; claim 260). Further, provided that Scherer and ICONIC both disclose the use of the antibody-drug conjugate for treatment of breast cancer (Scherer; figures 71, 103; paragraph [1338]) (ICONIC; abstract; claim 260), the modification to Scherer's ADC, of providing for wherein Ab represents the antibody that binds to tissue factor TF, would provide the benefit of providing the antibody that is effective in delivery of the therapeutic drug to a desired site of action where the cancer cells are present (Scherer; abstract; paragraph [1063]) to improve the effectiveness of the antibody-drug conjugate in treatment of breast cancer (Scherer; figures 71, 103; paragraph [1338]) (ICONIC; abstract; claim 260).

Claims 1-3 and 12 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.