

PATENT COOPERATION TREATY

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing (day/month/year)
09 August 2024

Applicant's or agent's file reference 59541-740601	FOR FURTHER ACTION See paragraph 2 below
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International application No. PCT/US2024/027301	International filing date (day/month/year) 1 May 2024	Priority date (day/month/year) 2 May 2023
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International Patent Classification (IPC) or both national classification and IPC

C07D 417/14 (2006.01) A61K 51/04 (2006.01) A61P 35/00 (2006.01) C07D 403/14 (2006.01) C07D 413/14 (2006.01)
C07D 513/04 (2006.01) C07D 519/00 (2006.01)

Applicant

RAYZEBIO, 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 AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustalia.gov.au	Date of completion of this opinion 9 August 2024	Authorised Officer Kate Bryce AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6222 3682
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**WRITTEN OPINION OF THE
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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 (under 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 <i>bis</i> .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 13ter.1(a)). ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4.	☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5.	Additional comments:

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Box No. II Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The claimed priority date is found to be valid.

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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: **126 & 133**

because:

☐ the said international application, or the said claim Nos.

relate to the following subject matter which does not require an international search (*specify*):

the subject matter listed in Rule 67 on which, under Article 34(4)(a)(i), an international preliminary examination [or a written opinion, via the application of Rule 43bis.1(b)], is not required to be carried out, including

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos.
are so unclear that no meaningful opinion could be formed (*specify*):

☐ 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. **126 & 133**

☐ 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/US2024/027301									
Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement										
1. Statement <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; vertical-align: top;">Novelty (N)</td> <td style="width: 50%; vertical-align: top;"> Claims 1-125, 127-132 & 134-139 Claims NONE </td> <td style="width: 20%; text-align: center; vertical-align: top;"> YES NO </td> </tr> <tr> <td style="vertical-align: top;">Inventive step (IS)</td> <td style="vertical-align: top;"> Claims 2, 4, 5, 16, 19, 20, 24, 27, 28, 40-42, 56, 57, 59-61, 65, 66, 75, 76, 79, 80, 83-85, 101, 104, 105, 116, 117 & 120 Claims 1, 3, 6-15, 17, 18, 21-23, 25, 26, 29-39, 43-55, 58, 62-64, 67-74, 77, 78, 81, 82, 86-100, 102, 103, 106-115, 118, 119, 121-125, 127-132 & 134-139 </td> <td style="text-align: center; vertical-align: top;"> YES NO </td> </tr> <tr> <td style="vertical-align: top;">Industrial applicability (IA)</td> <td style="vertical-align: top;"> Claims 1-125, 127-132 & 134-139 Claims NONE </td> <td style="text-align: center; vertical-align: top;"> YES NO </td> </tr> </table>			Novelty (N)	Claims 1-125, 127-132 & 134-139 Claims NONE	YES NO	Inventive step (IS)	Claims 2, 4, 5, 16, 19, 20, 24, 27, 28, 40-42, 56, 57, 59-61, 65, 66, 75, 76, 79, 80, 83-85, 101, 104, 105, 116, 117 & 120 Claims 1, 3, 6-15, 17, 18, 21-23, 25, 26, 29-39, 43-55, 58, 62-64, 67-74, 77, 78, 81, 82, 86-100, 102, 103, 106-115, 118, 119, 121-125, 127-132 & 134-139	YES NO	Industrial applicability (IA)	Claims 1-125, 127-132 & 134-139 Claims NONE	YES NO
Novelty (N)	Claims 1-125, 127-132 & 134-139 Claims NONE	YES NO									
Inventive step (IS)	Claims 2, 4, 5, 16, 19, 20, 24, 27, 28, 40-42, 56, 57, 59-61, 65, 66, 75, 76, 79, 80, 83-85, 101, 104, 105, 116, 117 & 120 Claims 1, 3, 6-15, 17, 18, 21-23, 25, 26, 29-39, 43-55, 58, 62-64, 67-74, 77, 78, 81, 82, 86-100, 102, 103, 106-115, 118, 119, 121-125, 127-132 & 134-139	YES NO									
Industrial applicability (IA)	Claims 1-125, 127-132 & 134-139 Claims NONE	YES NO									
2. CITATIONS AND EXPLANATIONS: <u>CITATIONS</u> D1: CHEN, K.-T. & SEIMBILLE, Y. 'New Developments in Carbonic Anhydrase IX-Targeted Fluorescence and Nuclear Imaging Agents', Int. J. Mol. Sci. 2022, Vol. 23, 6125. D2: WO 2016/196628 A1 (THE JOHNS HOPKINS UNIVERSITY) 08 December 2016 D3: WO 2017/161170 A1 (PURDUE RESEARCH FOUNDATION) 21 September 2017 <u>NOVELTY (N)</u> D1 reviews developments in the fluorescence and nuclear-imaging of carbonic anhydrase IX (CAIX). The document discloses several multivalent imaging probes comprising either several of the same CAIX inhibitor or dual-motifs (See pages 13-18, sections 4.5 & 4.6). The probes [^{99m}Tc]Tc-L2-PEG36-EC20 and XYISMR comprise metal chelating agents conjugated to multiple CAIX inhibitors by a forked linker (See page 14, compound 22 & page 17, compounds 33 and 34). None of the disclosed conjugates fall within the scope of the present claims and as a result the invention is novel in light of this document. D2 discloses bivalent CAIX targeted radioligands comprising CAIX inhibitors linked to a DOTA or NOTA metal chelator via a forked ligand similar to those defined in the present claims (See pages 3-4). The disclosed conjugates comprise bis(4-hydroxyphenyl)- and 1,3,4-thiadiazolyl CAIX inhibitor groups (See XYISMR-01, -04 & -06, pages 13-14). The conjugates and pharmaceutical compositions comprising them find use in the imaging and treatment of tumours expressing CAIX including clear cell renal cell carcinoma (ccRCC) (See page 30; page 55, lines 18-24; Examples 3 & 4, pages 71-78; & claim 13). The document also exemplifies a complex with ¹⁷⁷Lu and suggests that the radiometal ²²⁵Ac may be used (See page 26 & claim 7). The disclosed conjugates do not fall within the scope of independent claims 1, 2, 53 or 69 as, for example, the triazole ring of the disclosed compounds, corresponding to B¹ of present claim 53, lacks the required substituent when B¹ is heteroaryl. The present claims are novel in light of this document. D3 discloses CAIX targeting SPECT (single-photon emission computed tomography) imaging agents (See abstract). Some of the disclosed agents comprise two CAIX inhibitors conjugated, via a forked linker, to a ^{99m}Tc chelating moiety (See page 7, 2nd and 3rd compounds). The probes may be used to image cancers expressing CAIX (See e.g. claims 92-102). However, none of the disclosed compounds fall within the scope of the present claims. None of the prior art documents disclose conjugates as defined by claims 1, 2, 53 and 69. Therefore the subject matter of claims 1-125, 127-132 and 134-139 is new and meets the requirements of Article 33(2) of the PCT with regard to novelty. <u>INVENTIVE STEP (IS)</u> The problem solved by the present application is to provide further multivalent CAIX imaging agents with selectivity for CAIX over other carbonic anhydrases (See for eg. para [0008]).											

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D2 discloses bivalent CAIX targeted radioligands comprising bis(4-hydroxyphenyl)- and 1,3,4-thiadiazolyl- CAIX inhibitor groups linked to a DOTA or NOTA metal chelator via a forked linker similar to those defined in the present claims (See D2 pages 3-4; XYISMR-01, -04 & -06, pages 13-14 & e.g. pres app. compound 100.2, pages 93). Complexes of the conjugates with radio metals such as ¹⁷⁷Lu, ²²⁵Ac or ⁶⁴Cu are used in the imaging and treatment of tumours expressing CAIX including clear cell renal cell carcinoma (ccRCC) (See page 30; page 55, lines 18-24; page 56; Examples 3 & 4, pages 71-78; & claim 13).

The prior art conjugates do not fall within the scope of the present claims as the linker conjugating the metal chelator to the CAIX inhibitory moieties differs.

The difference between the conjugates of the present claims and the prior art lies in the requirement for the claimed probes to possess an additional ring in the linker, either at the fork as defined in claims 1 and 2; or within one of the arms of the linker; or for the variable B¹ as defined in claim 53 to be substituted when heteroaryl (See claims 1 & 2, ring A; claim 53, B¹; & claim 69, A²).

In light of the teaching of D2, it is considered that a person skilled in the art seeking to prepare additional CAIX imaging agents would prepare further conjugates comprising the metal chelators and CAIX targeting moieties as disclosed in D2, but would perform conservative substitutions in the linker portion, with the expectation that the new probes would likely retain their activity. The skilled worker would be aware, for example, that the replacement of an alkylene with a saturated cycloalkyl group would maintain the hydrophobic character of the linker and the activity of the conjugate would likely be retained. Similarly, the replacement of portions of the hydrophilic heteroalkyl stretch of TL₂ with heterocyclic rings, or the introduction of a ring at the junction of the two arms, are modifications which a skilled person in the art would consider obvious to explore given the linker portion would be expected to easily tolerate conservative variations (See e.g. pres. app. compounds 101.2, 103, 104 cf. XYISMR-01). The specification does not describe a surprising result arising from the modification of the linker or any particular problem to be overcome which acted as a barrier. It is considered that the difference between D2 and the present claims resides only in an arrangement which is a mere technical equivalent. It would be clearly obvious to a person skilled in the art that the linker taught in D2 could be altered without changing the way the invention works. Consequently, the subject matter of claims 1, 3, 6-15, 17, 18, 21-23, 25, 26, 29-39, 43-55, 58, 62-64, 67-74, 77, 78, 81, 82, 86-100, 102, 103, 106-115, 118, 119, 121-125, 127-132 and 134-139 cannot be considered inventive when compared with the disclosure of D2 and common general knowledge and these claims do not meet the requirements of Article 33(3) of the PCT with regards to inventive step.

It is considered that it would not be obvious to a person skilled in the art to modify the conjugates of D2 to comprise four targeting moieties in the specific arrangement defined in claim 2 and as a result the claim is considered inventive. Similarly, the subject matter of claims 4, 5, 16, 19, 20, 24, 27, 28, 40-42, 56, 57, 59-61, 65, 66, 75, 76, 79, 80, 83-85, 101, 104, 105, 116, 117 and 120 is considered inventive as it would not be obvious to a person skilled in the art in light of the teaching of D2, alone or in combination with common general knowledge in the art, to prepare the conjugates defined by these claims. Therefore the subject matter of these claims is not obvious and meets the requirements of Article 33(3) of the PCT with regard to inventive step.

INDUSTRIAL APPLICABILITY (IA)

The invention defined in the claims is considered to meet the requirements of Industrial Applicability under Article 33(4) of the PCT because it can be made by, or used in, industry.

E Category Document/s listed in Box VI:

There is a document(s) listed as an E category document in Box VI because it:

- discloses subject matter that is of particular relevance to this application and
- is an earlier application or patent but published on or after the international filing date of this application

Under the PCT, only documents published before the priority date of the instant application can deprive the claims of that application of novelty.

However, the relevance of a document published after the priority date of the application under consideration is dependent on national law in individual countries.

E category document/s may become significant in the National Phase.

International Application No.

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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)

E : WO 2024/094827 A1

10 May 2024

02 November 2023

02 November 2022

See Supplemental Box for Details

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)

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International Application No.

Box No. VII Certain defects in the international application

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The following defects in the form or contents of the international application have been noted:

Claims 126 and 133 do not comply with Rule 6.2(a) because they rely on references to the description and/or drawings.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY Box No. VIII Certain observations on the international application	International Application No. PCT/US2024/027301
The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: • The description does not comply with PCT Article 5 because it does not disclose the invention in a manner sufficiently clear and complete to be carried out by a person skilled in the art. The PCT Guidelines state that the disclosure of the claimed invention is considered sufficiently clear and complete if it provides information which is sufficient to allow the invention to be carried out by a person skilled in the art as of the international filing date, without undue experimentation. Although a reasonable amount of trial and error is permissible, a person skilled in the art must, on the basis of the disclosure of the claimed invention and the general knowledge, be able to carry out the invention without undue experimentation. The invention defined in claims 53, 69 and relevant dependent claims encompasses a broad range of conjugates, particularly with regard to the TL₁ and TL₂ moieties. The specification only provides details of the production of conjugates of formulae (B) and (C) as found in the present examples. While these examples provide teaching as to how a person skilled in the art might prepare a range of the moieties encompassed by TL₁ and TL₂ as defined in claims 53 and 69, the specification does not contain any schemes, examples or general teaching to indicate how the synthetic methods disclosed may be extended to the full scope of these groups and all of the combinations and permutations encompassed. For example, there are no schemes or examples to provide direction as to how to prepare compounds wherein all of the variables W¹, A¹, T¹, B¹, S¹ and Y¹ or W², X², Y², A², S², T² and B² are present or all absent and it is considered that the person skilled in the art would be unable to extend the teaching of the description to the whole of the field claimed by using routine methods of experimentation or analysis. Consequently, the description only provides information as to how to prepare the narrow range of the conjugates exemplified and variations and extrapolations thereof which a person skilled in the art could make without undue experimentation, which represents a small fraction of the conjugates claimed. Accordingly, the description does not provide sufficient information to enable the skilled person to perform the invention over the whole width of the claims, without undue burden or the need for further invention. • Furthermore, claims 53, 69 and relevant dependent claims do not meet the requirements of Article 6 of the PCT because they are not supported by the matter disclosed in the specification. The scope of the claims must not be broader than is justified by the description and they must be enabled by the description across their entire scope. The conjugates exemplified in the specification comprise targeting moieties which bind to carbonic anhydrase IX linked to a metal chelating agent and it is the CAIX binding moieties which provide the selectivity for cells overexpressing CAIX. Claims 1 and 2 place a functional limitation on TL₁ and TL₂ specifying that these groups bind to carbonic anhydrase IX. Claims 53 and 69 in contrast, do not and instead list structural limitations for these groups. However, given the breadth and variability of the variables which make up the TL₁ and TL₂ groups in claims 53 and 69 these moieties lack any significant structural element which might be expected to provide the required CAIX binding activity. As an example, the vast majority of known CAIX inhibitors and also indeed the majority of the present examples, comprise a sulfonamide functionality, as it has been identified that this group coordinates with zinc ions in the active site enabling inhibition (See D1, Fig. 3,4 & 8 & page 7, lines 1-2). The present claims do not specify the presence of such a group and instead one of the relevant variables (R¹²) may represent one or more of 30+ options including -S(=O)₂NR^cR^d or may be absent. As a result with no functional limitation or significant structural element which might confer CAIX binding activity, the scopes of claims 53 and 69 (and relevant dependent claims) extend beyond the disclosure and therefore are not fully supported under Article 6. • Claims 135-137 do not meet the requirements of Article 6 of the PCT because they are not supported by the matter disclosed in the specification. The scope of the claims must not be broader than is justified by the description and they must be enabled by the description across their entire scope. Claim 135 is directed to diagnosing or imaging any disease or disorder using the claimed radiopharmaceutical conjugates. Such broad categories of diseases result from equally broad biochemical aetiologies. The specification indicates that the conjugates of the instant claims are specific for CAIX and can be used to label and image cells expressing the CAIX receptor. These probes therefore find use in the imaging of cancer cells overexpressing this receptor. As such, there is no basis for the use of the conjugates in the imaging of any disease or disorder, similarly all cancers as defined in claim 137. In the same way there is no basis for the treatment of all diseases, disorders or cancers using the radiopharmaceuticals of the invention as defined in claim 136. Consequently, the claims are considered to not meet the requirements of Article 6.	

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International Application No.

Box No. VIII Certain observations on the international application

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- Claims 1, 2, 53, 69 and relevant dependent claims do not meet the requirements of Article 5 of the PCT because the invention is not disclosed in a manner sufficiently clear and complete for the invention to be carried out by a person skilled in the art. Said claims are directed to compounds of Formulae (A), (A'), (B) or (C) comprising variables which are “optionally substituted” with substituents that are not limited by the claims or by a dictionary definition to defined options (See para [0025]-[0048] of the specification). The term as defined places no limitation on what the substituents may be. The provision of exemplary substituents does not limit the scope of the claims. Other possibilities include substituents that may have their own pharmacological activities. Such a substitution would be expected by a person skilled in the art to change the way in which the current compounds exert their biological effects. Consequently, the person skilled in the art would not expect that all substituents would behave in the same way and that changing of optional substituents on the compounds of the invention would not lead to predictable results, and therefore an undue burden would be placed on said skilled person for further invention to determine compounds in the scope of the claims that would show the desired biological activity.

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International Application No.

Supplemental Box

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Continuation of: **Box VI**

WO 2024/094827 (D4) discloses highly selective CAIX imaging agents comprising multiple CAIX binding moieties conjugated to a radiometal chelator via a forked linker comprising a pyrrolidiny1 group at the junction of the arms (See abstract). The agents comprise either two or four binding moieties, wherein such groups include 5-chloro-2-sulfamoylthiophen-3-yl and 5-sulfamoyl-1,3,4-thiodiazol-2-yl (See Table 4, page 56 & e.g compounds 58-70, 99, & 113, pages 26-38). The document teaches metal chelators such as DOTA and NOTA and radiometals including ^{99m}Tc , ^{64}Cu , ^{225}Ac and ^{177}Lu may be used and that the agents may be used in the imaging or treatment of hypoxia-related cancers (See page 62, lines 20-27). As a result, this document is relevant to claims 1-3, 6-8, 12, 17, 21-23, 25, 27, 30-33, 49, 121-123, 125, 127-132 and 134-139 for the purposes of novelty.