PATENT COOPERATION TREATY

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* 06/12/2011
Applicant's or agent's file reference PCT 1104/MRrk	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2011/052475	7 June 2011	8 June 2010

International Patent Classification (IPC) or both national classification and IPC
Int. Cl.

C12N 15/30 (2006.01) ***C07K 14/44*** (2006.01)
A61K 31/395 (2006.01) ***G01N 31/00*** (2006.01)

Applicant
INDIAN INSTITUTE OF SCIENCE et al

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

[X]	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
[X]	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
[ ]	Box No. VI	Certain documents cited
[X]	Box No. VII	Certain defects in the international application
[X]	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 66.1*bis*(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	Date of completion of this opinion	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	1 December 2011	**ALAN BROWNLEE** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6283 2943

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/IB2011/052475

Box No. I Basis of this opinion

1. With regard to the **language,** this opinion has been established on the basis of:

   [X] 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*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      [ ] on paper

      [X] in electronic form

   b. (time)

      [ ] in the international application as filed

      [ ] together with the international application in electronic form

      [ ] subsequently to this Authority for the purposes of search

4. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/IB2011/052475

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **1, 2, 5 – 15, 17 and 18**	**YES**
	Claims **3, 4, 16 and 19**	**NO**
Inventive step (IS)	Claims **1, 2, 8 - 15**	**YES**
	Claims **3 – 7, 16 – 18 and 19**	**NO**
Industrial applicability (IA)	Claims **1 – 19**	**YES**
	Claims **NONE**	**NO**

2. Citations and explanations:

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: US 2007/0207992 A1
D2: BOSHOFF A *et al.* SA Journal of Science vol. 100: p665 – 677 (2004)

The present application relates to a polynucleotide sequence encoding HeatShock Protein 90 (HSP90) of *Trypanosoma evansi*, processes for inhibiting and identifying inhibition of HSP90 of Plasmodium and Trypanosoma by Geldanamycin and its derivative 17-AAG and a method of treating disease based on this process.

NOVELTY (N)

Citation D1 discloses that geldanamycin inhibits HSP90 of Plasmodium and has antimalarial activity ([0009], [0056]) and that *P. falciparum* and *Trypanosoma cruzi* among other parasites are lethally susceptible to geldanamycin via interaction with HSP90 ([0057], [0059]). D1 further discloses 17-AAG as an effective geldanamycin derivative ([0063]) and the synthesis of 17-AAG and testing of it and other geldanamycin derivatives against *P. falciparum* ([0068]). D1 yet further discloses the therapeutic use of geldanamycin and derivatives against human parasitic infections ([0069], [0070]) and the processing of these actives with pharmaceutical carriers or excipients such as granulating agents, binding agents etc. ([0070], [0071]).

In view of D1, claims 3, 4, 16 and 19 are not novel and do not meet the requirements of Article 33(2) of the PCT with regard to novelty.

Claims 1, 2, 5 – 15, 17 and 18 are novel in light of document D1. D1 is silent on a polynucleotide sequence as set forth in SEQ ID NO:1; HSP90 in samples taken from infected species; a process for inhibiting HSP90 from *T. evansi* or *P. berghei* by administering 17-AAG or a method of treating Surra by administering geldanamycin or 17-AAG to a mammal. D1 is also silent on an amplicon of TeHSP90 or PbHSP90. Therefore claims 1, 2, 5 – 15, 17 and 18 are novel and meet the requirements of Article 33(2) of the PCT with regard to novelty.

.../Continued in Supplemental Box I

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/IB2011/052475

Box No. VII Certain defects in the international application

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

Some of the figures of the application are poorly legible or indistinct. In particular see Figs 1, 3(A and B), 4 and 6.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/IB2011/052475

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 7 lacks clarity. Claim 7 relates to the process of claim 4 "... wherein the Geldanamycin is at a concentration ranging from about 20 µl/mg to about 50 µl/mg of lysate of the protein". There is no meaningful antecedent for "lysate of the protein". In addition, a unit of "µl/mg" cannot constitute a meaningful concentration in the absence of any information about the form of the Geldanamycin.

Claim 19 lacks clarity. Claim 19 defines a combination of different processes and methods which cannot be given a meaningful construction. Consequently, I have construed the claim to relate to a choice of any one of the independent claims 3, 4, 8, 9, 16 or 17.

Present claims 8 and 9 and their dependent claims 10 – 15 and 19 relate to a process for identifying inhibition of HSP 90 of designated parasite species:

8. *A process for identifying inhibition of (HSP90) of Trypanosoma species by compounds selected from a group comprising GA and 17-AAG optionally along with at least one pharmaceutically acceptable excipient, said process comprising acts of :*
    a) *isolating and amplifying sequence coding for the T. evansi HSP90 (TeHSP90) to obtain an amplicon;*
    b) *cloning the amplicon into a vector to obtain recombinant TeHSP90 sequence ; and*
    c) *infecting subject with the recombinant TeHSP90 sequence followed by administering GA or 17-AAG to identify said Trypanosoma HSP90 inhibition.*
9. *A process for identifying inhibition of (HSP90) of Plasmodium species by 17-AAG, optionally along with at least one pharmaceutically acceptable excipient, said process comprising acts of :*
    a) *isolating and amplifying sequence coding for the Plasmodium berghei HSP90 (PbHSP90) to obtain an amplicon;*
    b) *cloning the amplicon into a vector to obtain recombinant PbHSP90 sequence ; and*
    c) *infecting subject with the recombinant PbHSP90 sequence followed by administering 17-AAG to identify said Plasmodium HSP90 inhibition.*

Background

The only sequence information and method of cloning for a parasite HSP90 disclosed in the specification is for the *T. evansi* HSP90 (TeHSP90), along with methods for production of the recombinant TeHSP90 protein. There is no disclosure of any method for the act (c) of "infecting subject with the recombinant ... sequence (sic.)" followed by administering the stated inhibitor and identifying HSP90 inhibition. There is no disclosure of any information in the specification that would allow the skilled person to isolate DNA sequence coding for *P. berghei* HSP90.

Objection under Article 5

PCT Article 5 requires that the description shall disclose the invention in a manner sufficiently clear and complete for the invention 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.

.../Continued in Supplemental Box III

Supplemental Box I

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

Continuation of: **BOX V**

INVENTIVE STEP (IS)

Claims 3, 4, 16 and 19 are not novel and therefore also lack an inventive step.

Claims 5, 6, 7, 17 and 18 lack an inventive step in light of the disclosures of document D1:

Citation D1 teaches that geldanamycin inhibits HSP90 of Plasmodium and has antimalarial activity ([0009], [0056]) and that *P. falciparum* and *Trypanosoma cruzi* among other parasites are lethally susceptible to geldanamycin via interaction with HSP90 ([0057], [0059]). D1 further discloses 17-AAG as an effective geldanamycin derivative ([0063]) and the synthesis of 17-AAG and testing of it and other geldanamycin derivatives against *P. falciparum* ([0068]). D1 yet further discloses the therapeutic use of geldanamycin and derivatives against human parasitic infections ([0069], [0070]) and the processing of these actives with pharmaceutical carriers or excipients such as granulating agents, binding agents etc. ([0070], [0071]).

The difference between claims 5 – 7 and D1 is the sampling of HSP90 from organisms taken from infected blood, serum etc. and selection of certain concentrations of geldanamycin or 17-AAG. These steps are not considered to be inventive. It would be routine for the person skilled in the art to identify appropriate biological samples and to arrive at effective concentrations of 17-AAG or geldanamycin to inhibit HSP90 in such samples. Regarding claims 17 and 18, it would also be obvious for the skilled person, in light of the teaching of D1 that geldanamycin and 17-AAG are effective agents to treat malaria and disease caused by *T. cruzi*, to try these agents in mammals to treat Surra disease caused by the related organism *T. evansi*.

Claims 3 – 7, and 16 - 19 lack an inventive step in light of the disclosures of document D2:

Document D2 teaches that geldanamycin (GA) and its less toxic derivative 17-AAG are effective inhibitors of HSP90 (page 670, last para.). D2 further teaches that heat shock proteins play a vital role in parasite pathogenesis, particularly in Plasmodium and Trypanosoma infections (page 671) and that Plasmodium grown in human erythrocytes was suppressed by GA (*ibid*, col. 2, para. 2). The HSP90 protein of Plasmodium is suggested as a possible target for specific inhibitors, and HSP90 of *T. cruzi* and *T. brucei* is discussed (*ibid* and para. 3).

Claims 3 – 7 and 16 – 19 differ from D2 in the description of a process for inhibiting parasite HSP90 by 17-AAG or trypanosome HSP90 by GA, the source of biological samples, the effective concentrations of inhibitors used, selection of a pharmaceutically effective excipient, or a method of treating malaria or Surra by administering GA or 17-AAG. In the light of the teaching of D2 the person skilled in the art would be naturally led to examine the efficacy of these inhibitors in a method of treating disease in mammals. It would be obvious to try 17-AAG or GA as an inhibitor of Trypanosoma HSP90 by contacting the compound and the protein. It would be mere routine to derive appropriate samples and drug concentrations and it would be obvious to the skilled person to extend this information to establish a method to treat Surra disease caused by the closely related organism *T. evansi* and to include a commonly known excipient in such a method of treatment.

Therefore claims 3 – 7 and 16 - 19 do not involve an inventive step and do not comply with the requirements of Article 33(3) of the PCT.

.../Continued in Supplemental Box II

Supplemental Box III

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

Continuation of: **BOX VIII**

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 across the entire scope of the claim without undue experimentation.

Claim 8 is directed to a process that includes the step (c) of "infecting subject with the recombinant TeHSP90 sequence " followed by administering GA or 17-AAG and identifying HSP90 inhibition. I construe this to mean "injecting" with the recombinant protein, or some similar technique. It is not disclosed how the activity of the "injected" protein would be assessed (presumably against a background of homologous host proteins), nor how inhibition would be determined. Hence it is considered that the specification does not disclose the invention of claim 8 in a manner sufficiently clear and complete for the invention to be carried out by the skilled addressee and that the description therefore does not meet the requirements of Article 5 of the PCT.

Claim 9 is directed to a process comprising steps of "a) isolating and amplifying sequence coding for the *P. berghei* HSP90 ... to obtain an amplicon; b) cloning the amplicon into a vector to obtain recombinant PbHSP90 sequence; and c) "infecting subject with the recombinant PbHSP90 sequence" followed by administering 17-AAG to identify HSP90 inhibition. It is considered that, in the absence of any confirmatory sequence information for *P. berghei* HSP90, it would require undue experimentation on the part of the skilled person to isolate and clone the PbHSP90 sequence and produce recombinant protein. As for the objection above to Claim 8, I have construed step "c)" to mean injecting the recombinant PbHSP90 protein into a subject, and, as for that preceding objection, the specification does not disclose any information that would enable the skilled addressee to assess the activity of the injected protein nor its inhibition. Hence it is considered that the specification does not disclose the invention of claim 9 in a manner sufficiently clear and complete for the invention to be carried out by the skilled addressee and that the description therefore does not meet the requirements of Article 5 of the PCT.

It follows that the invention defined in claims 10 – 15 and claim 19 cannot be carried out by the skilled person in the absence of adequate and clear description for the claims to which they append.

In addition it is noted that claim 11 is unclear because there is no meaningful antecedent for the "lysate of the HSP90" in claim 8.

In light of the present construction of the claims, claims 12 and 13 lack clarity. It is not apparent why "injecting" recombinant TeHSP90 sequence or recombinant PbHSP90 sequence would necessarily have any effect on the survival of the subjects. Hence there is no antecedent for the survival rate of the subject being diminished according to claims 8 or 9. Therefore claims 12 and 13 are unclear.

Supplemental Box II

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

Continuation of: **Supplemental Box I**

None of the prior art documents discloses a polynucleotide sequence as set forth in SEQ ID NO: 1 encoding T. evansi HSP90 defined in claims 1 and 2, nor suggests a process for identifying inhibition of HSP90 of *T. evansi* or *P. berghei* using recombinant protein sequence from these organisms as defined in claims 8 – 15. Therefore the subject matter of claims 1, 2 and 8 – 15 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 claims 1 – 19 is considered to meet the requirements of Industrial Applicability under article 33(4) of the PCT because it can be made, or used in, industry.