PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	06 DEC 2018
Applicant's or agent's file reference 47460-1102	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 18/48879	30 August 2018 (30.08.2018)	31 August 2017 (31.08.2017)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 45/00, A61K 31/00, C07K 14/16 (2018.01)
CPC - A61K 31/513, G01N 2333/16, G01N 2333/155, C07D 495/12

Applicant THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

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 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
- ☐ 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 66.1*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/US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	8 November 2018	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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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 (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:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☒ furnished subsequent to the international filing date for the purposes of international search only:

      ☒ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

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 forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

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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. 5-10, 15-20, 25-28, 33-38, 43-46

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. 5-10,15-20, 25-28, 33-38,43-46 are so unclear that no meaningful opinion could be formed *(specify)*:

because they 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. 5-10, 15-20, 25-28, 33-38, 43-46

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

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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	1-4, 11-14, 21-24, 29-32 and 39-42	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-4, 11-14, 21-24, 29-32 and 39-42	NO
Industrial applicability (IA)	Claims	1-4, 11-14, 21-24, 29-32 and 39-42	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-4, 11-14, 21-24, 29-32 and 39-42 lack an inventive step under PCT Article 33(3) as being obvious over US 2010/0168004 A1 to Williams et al. (hereinafter 'Williams') in view of the journal article entitled "Intracellular Crotonyl-CoA Stimulates Transcription through p300-Catalyzed Histone Crotonylation" by Sabari et al. (hereinafter 'Sabari').

Regarding claim 1, Williams teaches a method of reactivating a latent human immunodeficiency virus (HIV) in one or more cells of a patient infected with HIV (Abstract "The present invention provides methods and compositions useful for the elimination of latent HIV reservoirs that persist despite HAART. The methods and compositions overcome this latent barrier by inducing the replication of HIV in latently infected T cells while preventing the spread of the newly produced virions to uninfected cells by providing HAART simultaneously. Compositions of the invention comprise an activator of latent HIV expression, such as prostratin, and an inhibitor of histone deacetylase, such as TSA."). Although Williams thus teaches combinations of agents to reactivate HIV, Williams does not teach administering a crotonylation-inducing agent to the patient to reactivate the latent HIV in the one or more cells of the patient.

However, Sabari teaches that increasing crotonyl-CoA leads to activation of gene expression (Abstract- "Levels of histone crotonylation are regulated by the cellular concentration of crotonylCoA, which can be altered through genetic and environmental perturbations. In a cell -based model of transcriptional activation, increasing or decreasing the cellular concentration of crotonyl-CoA leads to enhanced or diminished gene expression, respectively, which correlates with the levels of histone crotonylation flanking the regulatory elements of activated genes.", pg 213, col 2, para 1 "we establish a role for histone crotonylation in ... cell-based models of transcriptional activation. We demonstrate that by experimentally altering the cellular concentration of crotonyl-CoA, the histones that flank specific regulatory elements exhibit an increased level of H3K18Cr and that the expression of that gene is positively effected."). In light of the fact that Williams teaches administering an agent that activates HIV gene expression as part of a combination treatment to treat latent HIV (Abstract- "Compositions of the invention comprise an activator of latent HIV expression, such as prostratin, and an inhibitor of histone deacetylase, such as TSA. A surprising finding of this invention is that the inhibitor of the histone deacetylase synergizes the effect of prostratin thus, allowing administering to a patient a lower, non-toxic dose of prostratin"), it would have been obvious to an artisan of ordinary skill in the art to experiment with administering crotonyl-CoA as part of the HIV treatment taught by Williams to reactivate HIV transcrition in a patient with latent HIV.

Regarding claim 11, Williams teaches a method of treating human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) in a patient (Abstract- "The present invention provides methods and compositions useful for the elimination of latent HIV reservoirs that persist despite HAART"; para [0003] -"Human Immunodeficiency Virus (HIV) is the etiologic agent that is responsible for AIDS, a syndrome characterized by depletion of CD4+ T-lymphocytes and collapse of the immune system"), however Williams fails to teach the method comprising administering a crotonylation-inducing agent to the patient to reactivate a latent human immunodeficiency virus (HIV) in the patient.

However, Sabari teaches that increasing crotonyl-CoA leads to activation of gene expression (Abstract- "Levels of histone crotonylation are regulated by the cellular concentration of crotonylCoA, which can be altered through genetic and environmental perturbations. In a cell -based model of transcriptional activation, increasing or decreasing the cellular concentration of crotonyl-CoA leads to enhanced or diminished gene expression, respectively, which correlates with the levels of histone crotonylation flanking the regulatory elements of activated genes.", pg 213, col 2, para 1 "we establish a role for histone crotonylation in ... cell-based models of transcriptional activation. We demonstrate that by experimentally altering the cellular concentration of crotonyl-CoA, the histones that flank specific regulatory elements exhibit an increased level of H3K18Cr and that the expression of that gene is positively effected."). In light of the fact that Williams teaches administering an agent that activates HIV gene expression as part of a combination treatment to treat latent HIV (Abstract- "Compositions of the invention comprise an activator of latent HIV expression, such as prostratin, and an inhibitor of histone deacetylase, such as TSA. A surprising finding of this invention is that the inhibitor of the histone deacetylase synergizes the effect of prostratin thus, allowing administering to a patient a lower, non-toxic dose of prostratin"), it would have been obvious to an artisan of ordinary skill in the art to experiment with administering crotonyl-CoA as part of the HIV treatment taught by Williams to reactivate HIV transcrition in a patient with latent HIV.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V(2) Citations and Explanations:

Regarding claim 21, Williams teaches a pharmaceutical composition for treating a patient infected with a human immunodeficiency virus (HIV) (para [0168] -"In one aspect the present invention provides a pharmaceutical composition or a medicament comprising at least an activator of latent HIV expression and an inhibitor of HDAC of the present invention and optionally a pharmaceutically acceptable carrier. A pharmaceutical composition or medicament can be administered to a subject for the treatment of, for example, a condition or disease as described herein"), however fails to teach the pharmaceutical composition comprising a crotonylation-inducing agent.

However, Sabari teaches that increasing crotonyl-CoA leads to activation of gene expression (Abstract- "Levels of histone crotonylation are regulated by the cellular concentration of crotonylCoA, which can be altered through genetic and environmental perturbations. In a cell-based model of transcriptional activation, increasing or decreasing the cellular concentration of crotonyl-CoA leads to enhanced or diminished gene expression, respectively, which correlates with the levels of histone crotonylation flanking the regulatory elements of activated genes.", pg 213, col 2, para 1 "we establish a role for histone crotonylation in ... cell-based models of transcriptional activation. We demonstrate that by experimentally altering the cellular concentration of crotonyl-CoA, the histones that flank specific regulatory elements exhibit an increased level of H3K18Cr and that the expression of that gene is positively effected."). In light of the fact that Williams teaches administering an agent that activates HIV gene expression as part of a combination treatment to treat latent HIV (Abstract- "Compositions of the invention comprise an activator of latent HIV expression, such as prostratin, and an inhibitor of histone deacetylase, such as TSA. A surprising finding of this invention is that the inhibitor of the histone deacetylase synergizes the effect of prostratin thus, allowing administering to a patient a lower, non-toxic dose of prostratin"), it would have been obvious to an artisan of ordinary skill in the art to experiment with including crotonyl-CoA as part of the HIV composition taught by Williams to reactivate HIV transcrition in a patient with latent HIV.

Regarding claim 29, Williams teaches a method of reactivating a latent virus in one or more cells of a patient infected with the virus (Abstract- "Compositions of the invention comprise an activator of latent HIV expression, such as prostratin, and an inhibitor of histone deacetylase, such as TSA"), however fails to teach the method comprising administering a crotonylation-inducing agent to the patient to reactivate the latent virus in the one or more cells of the patient.

However, Sabari teaches that increasing crotonyl-CoA leads to activation of gene expression (Abstract- "Levels of histone crotonylation are regulated by the cellular concentration of crotonylCoA, which can be altered through genetic and environmental perturbations. In a cell-based model of transcriptional activation, increasing or decreasing the cellular concentration of crotonyl-CoA leads to enhanced or diminished gene expression, respectively, which correlates with the levels of histone crotonylation flanking the regulatory elements of activated genes.", pg 213, col 2, para 1 "we establish a role for histone crotonylation in ... cell-based models of transcriptional activation. We demonstrate that by experimentally altering the cellular concentration of crotonyl-CoA, the histones that flank specific regulatory elements exhibit an increased level of H3K18Cr and that the expression of that gene is positively effected."). In light of the fact that Williams teaches administering an agent that activates HIV gene expression as part of a combination treatment to treat latent HIV (Abstract- "Compositions of the invention comprise an activator of latent HIV expression, such as prostratin, and an inhibitor of histone deacetylase, such as TSA. A surprising finding of this invention is that the inhibitor of the histone deacetylase synergizes the effect of prostratin thus, allowing administering to a patient a lower, non-toxic dose of prostratin"), it would have been obvious to an artisan of ordinary skill in the art to experiment with administering crotonyl-CoA as part of the HIV treatment taught by Williams to reactivate HIV transcrition in a patient with latent HIV.

Regarding claim 39, Williams teaches a pharmaceutical composition for treating a patient infected with a virus (HIV) (para [0168] -"In one aspect the present invention provides a pharmaceutical composition or a medicament comprising at least an activator of latent HIV expression and an inhibitor of HDAC of the present invention and optionally a pharmaceutically acceptable carrier. A pharmaceutical composition or medicament can be administered to a subject for the treatment of, for example, a condition or disease as described herein."), however fails to teach the pharmaceutical composition comprising a crotonylation-inducing agent.

However, Sabari teaches that increasing crotonyl-CoA leads to activation of gene expression (Abstract- "Levels of histone crotonylation are regulated by the cellular concentration of crotonylCoA, which can be altered through genetic and environmental perturbations. In a cell-based model of transcriptional activation, increasing or decreasing the cellular concentration of crotonyl-CoA leads to enhanced or diminished gene expression, respectively, which correlates with the levels of histone crotonylation flanking the regulatory elements of activated genes.", pg 213, col 2, para 1 "we establish a role for histone crotonylation in ... cell-based models of transcriptional activation. We demonstrate that by experimentally altering the cellular concentration of crotonyl-CoA, the histones that flank specific regulatory elements exhibit an increased level of H3K18Cr and that the expression of that gene is positively effected."). In light of the fact that Williams teaches administering an agent that activates HIV gene expression as part of a combination treatment to treat latent HIV (Abstract- "Compositions of the invention comprise an activator of latent HIV expression, such as prostratin, and an inhibitor of histone deacetylase, such as TSA. A surprising finding of this invention is that the inhibitor of the histone deacetylase synergizes the effect of prostratin thus, allowing administering to a patient a lower, non-toxic dose of prostratin"), it would have been obvious to an artisan of ordinary skill in the art to experiment with including crotonyl-CoA as part of the HIV composition taught by Williams to reactivate HIV transcrition in a patient with latent HIV.

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Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Previous Page:

Regarding claims 2, 12, 22, 30 and 40 the combination of Williams and Sabari makes obvious the method of claims 1, 11, 29 and compositions of claims 21, and 39. Sabari further teaches wherein the crotonylation-inducing agent is crotonyl-coenzyme A (Abstract- "Levels of histone crotonylation are regulated by the cellular concentration of crotonylCoA, which can be altered through genetic and environmental perturbations. In a cell-based model of transcriptional activation, increasing or decreasing the cellular concentration of crotonyl-CoA leads to enhanced or diminished gene expression, respectively, which correlates with the levels of histone crotonylation flanking the regulatory elements of activated genes.").

Regarding claims 3, 13, 23, 31 and 41 the combination of Williams and Sabari makes obvious the method of claims 1, 11, 29 and compositions of claims 21, and 39. Williams further teaches the method further comprising administering a histone deacetylase (HDAC) inhibitor to the patient (Abstract- "Compositions of the invention comprise an activator of latent HIV expression, such as prostratin, and an inhibitor of histone deacetylase, such as TSA").

Regarding claims 4, 14, 24, 32 and 42, the combination of Williams and Sabari makes obvious the method of claims 1, 11, 29 and compositions of claims 21, and 39. Williams further teaches wherein the HDAC inhibitor is trichostatin A (TSA) (para [0021]- "The present invention is based, in part, on the Applicants' discovery that HDAC inhibitors, such as trichostatin A and valproic acid, synergize with a small molecule activator of latent HIV expression, such as prostratin, to activate a latent HIV reservoir").

Claims 1-4, 11-14, 21-24, 29-32 and 39-42 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.