PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	27.04.2018
Applicant's or agent's file reference: PP-B2004	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/KR2018/000395	09.01.2018	09.01.2017

International Patent Classification (IPC) or both national classification and IPC

C12Q1/68(2006.01)i, G01N33/574(2006.01)i, G01N33/68(2006.01)i, A61K31/11(2006.01)i, A61K31/167(2006.01)i, A61K48/00(2006.01)i

Applicant

INDUSTRY-ACADEMIC COOPERATION FOUNDATION, YONSEI UNIVERSITY

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 or 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/KR	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/KR2018/000395

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:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/KR2018/000395

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

Novelty (N)	Claims	1-9	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-9	NO
Industrial applicability (IA)	Claims	1-9	YES
	Claims	None	NO

2. Citations and explanations:

Reference is made to the following documents:

D1: RYU, Mi Hyeon et al., "The Immunohistochemical Expression of Snail and E-cadherin in Oral Squamous Cell Carcinoma", Kor. J. Oral. Maxillofac. Pathol., 2009, vol. 33, no. 1, pp. 37-46

D2: YOOK, J. I. et al., "A Wnt-Axin2-GSK3 Cascade Regulates Snail1 Activity in Breast Cancer Cells", Nature Cell Biology, December 2006, vol. 8, no. 12, pp. 1398-1406

D3: AHN, S.-G. et al., "The Anticancer Mechanism of 2'-hydroxycinnamaldehyde in Human Head and Neck Cancer Cells", International Journal of Oncology, 2015, vol. 47, pp. 1793-1800

1. Novelty and Inventive Step

1.1 Claims 1-8

[Technical Comparison 1: comparison to document D1 with

respect to Snail gene]

Independent Claims: Claims 1, 4, 6, and 8

Document D1, which is considered to be the closest prior art to the invention as set forth in claims 1, 4, 6, and 8, discloses the detection of the positivity of Snail in oral squamous cell carcinoma (see the abstract, and the right column on page 39-page 40).

Claims 1, 4, 6, and 8 differ from document D1 in that the latter does not mention a method for providing information, a kit, and a pharmaceutical composition, which all relate to the prediction or diagnosis of oral precancer or oral cancer. However, the invention as in the claims could be obviously derived by a person skilled in the art from the disclosure of document D1.

Therefore, claims 1, 4, 6, and 8 are novel, but lack an inventive step in view of document D1 (PCT Article 33(2) and (3)].

Dependent Claims: Claims 2, 3, 5, and 7

The kinds of sample and the measurement of gene expression that are limited by claims 2, 3, 5, and 7 are matters that a person skilled in the art could easily derive in light of analysis assays typically used in the art, such as the immunohistochemical staining disclosed in document D1 (see the right column on page 39).

Therefore, claims 2, 3, 5, and 7 are also novel, but lack an inventive step in view of document D1 (PCT Article 33(2) and (3)).

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**

[Technical Comparison 2: comparison to a combination of documents D1 and D2 with respect to Axin2 gene]

Independent Claims: Claims 1, 4, 6, and 8

Document D1, which is considered to be the closest prior art to the invention as set forth in claims 1, 4, 6, and 8, discloses the detection of the positivity of Snail in oral squamous cell carcinoma (see the abstract, and the right column on page 39-page 40).

Claims 1, 4, 6, and 8 differ from document D1 in that the invention as in the former targets the Axin2 gene. Document D2, which has a Snail gene-related technique in common with document D1, discloses that the activity of Snail in breast cancer cells is regulated by a Wnt-Axin2-GSK3β signaling pathway (see the abstract and figures 1-2). When considering that a typical intracellular signaling pathway is similar in cancer cells, a person skilled in the art could easily postulate that Snail in oral cancer is also regulated by a Wnt-Axin2-GSK3β signaling pathway. In this context, the identification of Axin2 in oral cancer would be an obvious matter to a person skilled in the art. Thus, it would be obvious to a person skilled in the art to derive the invention as in the claims by combining documents D1 and D2.

Therefore, claims 1, 4, 6, and 8 are novel, but lack an inventive step in view of a combination of documents D1 and D2 (PCT Article 33(2) and (3)).

Dependent Claims: Claims 2, 3, 5, and 7

The kinds of sample and the measurement of gene expression that are limited by claims 2, 3, 5, and 7 are matters that a person skilled in the art could easily derive in light of analysis assays typically used in the art, such as the immunohistochemical staining disclosed in document D1 (see the right column on page 39).

Therefore, claims 2, 3, 5, and 7 are also novel, but lack an inventive step in view of a combination of documents D1 and D2 (PCT Article 33(2) and (3)).

1.2 Claim 9

(※ The international search report and the written opinion have been established on the basis of the assumption that claim 9 is an independent claim pertaining to a medicinal use of the specific compound although drafted in the form of a dependent claim which is dependent on claim 9.)

Claim 9 specifically delimits gene expression-regulating compounds (2′-Hydroxycinnamaldehyde, HCA, or 2′-benzoyloxycinnamaldehyde, BCA). Substantially, the delimitation is considered a medicinal use itself of the specific compounds in delaying or regulating the progression of oral precancerous legions or recurring oral cancer, irrespective of the gene expression regulating mechanism.

Document D3, which is the closest prior art to the

invention as set forth in claim 9, shows that HCA and BCA have an anticancer mechanism in an oral cancer cell line (see the abstract, the left column on page 1794, page 1795, and figures 2-4). It would be an obvious matter to a person skilled in the art to postulate a medicinal use of the present application from the anticancer mechanism of HCA and BCA. A pharmaceutical composition of the compound could also be obviously configured by a person skilled in the art.

Consequently, claim 9 is novel, but lacks an inventive step in view of document D3 (PCT Article 33(2) and (3)).

2. Industrial Applicability

The invention as set forth in claims 1-9 is industrially applicable (PCT Article 33(4)).