

AS. 101.954

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-094108-00005-0000

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Act. 325 C/OINFORMACION Folios: 15

Señores

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
DIVISION DE NUEVAS CREACIONES**

E. S. D.

REF: Expediente No. 06 094108 - Solicitud de Patente Entrada en Fase Nacional Corresp. a la Solicitud Internacional  
a favor de **THE PENN STATE RESEARCH FOUNDATION**  
Titulada: MÉTODOS COMBINATORIOS Y COMPOSICIONES PARA EL TRATAMIENTO DE MELANOMA

**JUAN PABLO CADENA SARMIENTO**, vecino de Bogotá, portador de la tarjeta profesional No. 57492, obrando como apoderado de la sociedad **THE PENN STATE RESEARCH FOUNDATION**, según lo acredita el documento de poder presentado en esa División, me permito anexar los siguientes documentos:

1. Copia del Reporte de Búsqueda Internacional y de la Opinión Escrita efectuada por la Oficina Internacional (formas PCT/ISA/220, PCT/ISA/210 y PCT/ISA/237).

De la señora Jefe atentamente,

  
**JUAN PABLO CADENA SARMIENTO**  
C.C. No. 80.410.337 de Usaquén  
Cra. 7 No.71-21, Torre B, Piso 4

# PATENT COOPERATION TREATY

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A

From the INTERNATIONAL SEARCHING AUTHORITY

To:  
JANAE LEHMAN BELL  
MCKEE, VOORHEES & SEASE, PLC  
801 GRAND AVENUE, SUITE 3200  
DES MOINES, IA 50309

## PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT AND  
THE WRITTEN OPINION OF THE INTERNATIONAL  
SEARCHING AUTHORITY, OR THE DECLARATION

*Article 19* (PCT Rule 44.1) *Due 5-21-08*

Date of mailing  
(day/month/year) **21 MAR 2008**

Applicant's or agent's file reference  
P6710 554509

**FOR FURTHER ACTION** See paragraphs 1 and 4 below

International application No.  
PCT/US05/08950

International filing date  
(day/month/year) 18 March 2005 (18.03.2005)

Applicant  
THE PENN STATE RESEARCH FOUNDATION

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

**When?** The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

**Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
1211 Geneva 20, Switzerland. Facsimile No.: (41-22) 338.82.70.

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/ US  
Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P O Box 1450  
Alexandria, Virginia 22313-1450  
Facsimile No. (571) 273-3201

Authorized officer  
/J E Angell/  
Primary Examiner, AU 1635 for: DANA SHIN  
Telephone No. 571-272-1600

# PATENT COÖPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

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|                                                       |                                                                                                                  |                                                                                  |
|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Applicant's or agent's file reference<br>P6710 554509 | <b>FOR FURTHER ACTION</b><br><small>see Form PCT/ISA/220<br/>as well as, where applicable, item 5 below.</small> |                                                                                  |
| International application No.<br>PCT/US05/08950       | International filing date ( <i>day/month/year</i> )<br>18 March 2005 (18.03.2005)                                | (Earliest) Priority Date ( <i>day/month/year</i> )<br>19 March 2004 (19.03.2004) |
| Applicant<br>THE PENN STATE RESEARCH FOUNDATION       |                                                                                                                  |                                                                                  |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the Report**

a. With regard to the language, the international search was carried out 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))

b. ☐ This international search report has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 Rule 43.6 *bis(a)*

c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box No. II)

3. ☒ Unity of invention is lacking (See Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant.  
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant.  
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_

- ☐ as suggested by the applicant.  
☐ as selected by this Authority, because the applicant failed to suggest a figure.  
☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/08950

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 4, 19, 31, 39, 60, and 61  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
No proper sequence listing (e.g., CRF) is submitted for the claimed nucleotide sequences. Furthermore, claim 60 depends from itself and therefore, the metes and bounds for "said agent" (line 1) recited in claim 60 cannot be determined.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims. It is covered by claims Nos. 1-3, 5, 12-18, 20, 27-30, 33-38, and 59

- Remark on Protest**
- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
  - ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
  - ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US05/08950

## A. CLASSIFICATION OF SUBJECT MATTER

IPC: C07H 21/02( 2006.01),21/04( 2006.01);A61K 31/70( 2006.01),A61K 43/04  
C12Q 1/68( 2006.01)

USPC: 536/23.1,24.5;514/44;435/6,375

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 24.5; 514/44; 435/6,375

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                         | Relevant to claim No.               |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| A          | COLLISSON et al., Treatment of metastatic melanoma with an orally available inhibitor of the Ras-Raf-MAPK cascade.<br>Cancer Research, 15 September 2003, Vol 63, pages 5669-5673.         |                                     |
| X          | HINGORANI et al., Suppression of BRAF(V599E) in human melanoma abrogates transformation.                                                                                                   | 15, 17, 29-30, 33                   |
| Y          | Cancer Research, 1 September 2003, Vol 63, pages 5198-5202.                                                                                                                                | 35, 59                              |
| Y          | NICHOLSON et al., The protein kinase B/Akt signalling pathway in human malignancy.<br>Cellular Signalling, 2002, Vol 14, pages 381-395.                                                    | 1-3, 5, 12-18, 20, 27-30, 33-38, 59 |
| A          | ZINDA et al., AKT-1, -2, and -3 are expressed in both normal and tumor tissues of the lung, breast, prostate, and colon.<br>Clinical Cancer Research, August 2001, Vol 7, pages 2475-2479. |                                     |



Further documents are listed in the continuation of Box C.



See patent family annex.

| Special categories of cited documents:                                                                                                                                  |                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| "A" document defining the general state of the art which is not considered to be of particular relevance                                                                | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                                              |
| "E" earlier application or patent published on or after the international filing date                                                                                   | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone                                                                     |
| "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" document referring to an oral disclosure, use, exhibition or other means                                                                                            | "&" document member of the same patent family                                                                                                                                                                                                    |
| "P" document published prior to the international filing date but later than the priority date claimed                                                                  |                                                                                                                                                                                                                                                  |

Date of the actual completion of the international search

06 March 2008 (06.03.2008)

Date of mailing of the international search report

21 MAR 2008

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

Commissioner for Patents

P.O. Box 1450

Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Authorized officer

/J E Angell/

Primary Examiner AU 1635 for: DANA SHIN

Telephone No. 571-272-1600

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US05/08950

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                 | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------------|-----------------------|
| A          | US 2004/0082534 A1 (GLEAVE et al) 29 April 2004 (29.04.2004)                                                       |                       |
| Y          | US 2003/0035790 A1 (CHEN et al) 20 February 2003 (20.02.2003), paragraphs 0005, 0081, 0137, 0164, 0180, 0207, 0250 | 12-14, 27-28          |
| Y          | US 2003/0125359 A1 (LYONS et al) 3 July 2003 (03.07.2003), paragraphs 0043, 0045; Figure 2: claims 1, 5, 7-8.      | 34                    |

INTERNATIONAL SEARCH REPORT

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International application No.  
PCT/US05/08950  
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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

The inventions listed as Groups 1-16 (see Form PCT/ISA/206 mailed 13 June 2007) do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions were found to have no special technical features that define a contribution over the prior art of Nicholson et al.

Continuation of B. FIELDS SEARCHED Item 3:

Medline, Biosis, Embase, Scisearch, CA, EAST

search terms: ATK3, melanoma, siRNA, RNAi, tumor, B-raf, apoptosis, skin tumor, decarbazine, irradiation, BAY 43-9006.

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:  
JANAE LEHMAN BELL  
MCKEE, VOORHEES & SEASE, PLC  
801 GRAND AVENUE, SUITE 3200  
DES MOINES, IA 50309

## PCT

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

*Response due:* **21 MAR 2008**

*6-21-08 P*

Applicant's or agent's file reference

P6710 554509

**FOR FURTHER ACTION**

See paragraph 2 below

International application No.

PCT/US05/08950

International filing date (day/month/year)

18 March 2005 (18.03.2005)

Priority date (day/month/year)

19 March 2004 (19.03.2004)

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

IPC: C07H 21/02( 2006.01);21/04( 2006.01);A61K 31/70( 2006.01);A61K 43/04 C12Q 1/68( 2006.01)

USPC: 536/23.1,24.5;514/44

Applicant

THE PENN STATE RESEARCH FOUNDATION

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 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 66.1bis(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.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US

Mail Stop PCT, Attn: ISA/US  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Date of completion of this opinion

06 March 2008 (06.03.2008)

Authorized officer

/J E Angell/

Primary Examiner, AU 1635 for: DANA SHIN

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US05/08950

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Box No. 1 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 43bis.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. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished 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 and/or table(s) relating thereto 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/US ~~05/08950~~ 05/08950

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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. 4-11, 19-26, 31-32, 39, 58 and 60-62

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 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. 4-11, 19-26, 31-32, 39, 58 and 60-62
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper 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 a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form 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 a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

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International application No.

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
  - ☐ paid additional fees under protest and, where applicable, the protest fee
  - ☐ paid additional fees under protest but the applicable protest fee was not paid
  - ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

☐ complied with

☒ not complied with for the following reasons:

See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:

☐ all parts.

☒ the parts relating to claims Nos. 1-3, 5, 12-18, 20, 27-30, 33-38, and 59

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.  
PCT/US05/08950

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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 <u>NONE</u>                               | YES |
|                               | Claims <u>1-3,5,12-18,20,27-30,33-38, and 59</u> | NO  |
| Inventive step (IS)           | Claims <u>NONE</u>                               | YES |
|                               | Claims <u>1-3,5,12-18,20,27-30,33-38, and 59</u> | NO  |
| Industrial applicability (IA) | Claims <u>1-3,5,12-18,20,27-30,33-38, and 59</u> | YES |
|                               | Claims <u>NONE</u>                               | NO  |

2. Citations and explanations:

Claims 1-3, 5, 12-18, 20, 27-30, 33-38, and 59 lack an inventive step under PCT Article 33(3) as being obvious over Nicholson et al. (*Cellular Signalling*, 2002, 14:381-395) in view of Hingorani et al. (*Cancer Research*, 2003, 63:5198-5202), Lyons et al. (US 2003/0125359 A1), and Chen et al. (US 2003/0035790 A1).

The claims are drawn to pharmaceutical composition for treating a melanoma tumor comprising an agent that reduces Akt3 and B-raf activity, wherein the Akt3 and B-raf inhibitor agents are siRNA molecules or the B-raf inhibitor is BAY 43-9006, and the methods of inhibiting/ treating a melanoma tumor by administering said pharmaceutical composition, wherein the methods further comprise administering decarbazine or irradiation.

Nicholson et al. teach that the activation of the Akt signaling pathway comprising Akt 3 is associated with tumorigenesis, tumor proliferation and cancer progression. They also teach that B-Raf is a PKB/Akt substrate. See Table 1. They teach that different PKB/Akt substrates play roles in different cell types. They teach that PKB/Akt signaling activation is insufficient to initiate tumor and therefore interaction with other substrates or other signaling pathways is necessary for tumor initiation and progression. They teach that inhibition of PKB/Akt has an anticancer potential and can reduce the threshold doses of anticancer drugs. See page 392. Nicholson et al. do not expressly teach a combination therapy for treating a melanoma tumor by combining Akt3 and B-Raf inhibitors, nor do they teach that such inhibitors are siRNA molecules.

Hingorani et al. teach that B-Raf-V599E is overexpressed human melanoma cells. They teach that an siRNA molecule targeted against B-Raf-V599E inhibits growth arrest of melanoma cells, promotes apoptosis of said cells, and abrogates transformed phenotype. They teach that B-Raf-V599E is therefore a highly desirable therapeutic target for melanoma cancers.

Lyons et al. teach that BAY 43-9006 is a RAF kinase inhibitor that can be used to treat a cancer.

Chen et al. teach a combination therapy for treating cancer such as melanoma comprising administering antimetabolites (e.g., decarbazine), alkylating agents, irradiation, and other drugs that induce apoptosis of tumor cells.

It would have been obvious to one of ordinary skill in the art to make and use the combined therapy of Akt3 inhibitor, B-Raf-V599E inhibitor, and other forms of known chemotherapeutic agents in order to treat a melanoma. Since interaction between Akt signaling and its substrates was known to not only initiate but metastasize a tumor and such interaction depends on the specific cell type in which the substrate is active, and since B-raf was a known Akt substrate, and since B-Raf-V599E was a known therapeutic target for melanoma cancers, one of ordinary skill in the art would have been motivated to combine inhibitors for the two molecules known to interact with each other for initiation and progression of melanoma tumor cells. Furthermore, since additional anticancer treatments such as irradiation, decarbazine, alkylating agents were known to be co-administered with other forms of anticancer drugs as taught by Chen et al., one of ordinary skill in the art would have been motivated to further add other anticancer therapeutic agents to achieve enhanced anti-melanoma effects. In view of the foregoing, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US05/08950

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**Box No. VIII Certain observations on the international application**

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

Claim 60 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 60 is indefinite for the following reason(s): Claim 60 recites, "The pharmaceutical composition of claim 60 wherein said agent is" in line 1. Since there is no antecedent basis for the claimed "said agent", one of ordinary skill in the art would not be able to ascertain what the "said agent" is referring to.

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## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

#### What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

**When ?** Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

**How ?** Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is not English or French, the letter must be in English: if the language of the international

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## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers, claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1bis(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion 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 (Rule 43bis.1(c)).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.