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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-110667-00004-0000

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E S D.

Ref.: Expediente No. 06.110.667
Solicitud de Patente a nombre de
The Trustees of the University of Pennsylvania.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 A No. 94-76, Of. 305, obrando como apoderada de la sociedad The Trustees of the University of Pennsylvania., domiciliada en Philadelphia, Pennsylvania, Estados Unidos de América, solicitante de la patente de la referencia, atentamente me permito presentar:

1. Notificación de la remisión del reporte de búsqueda internacional.
2. Reporte de búsqueda internacional.
3. Copia de la Opinión escrita con su correspondiente traducción al español.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68228

TRATADO DE COOPERACION EN MATERIA DE PATENTES

De AUTORIDAD INTERNACIONAL DE EXAMINACIÓN PRELIMINAR

A See form PCT/ISA/220	PCT OPINION ESCRITA (PCT Regla 43bis.1)	
	Fecha de Envío (día/mes/año) ver formato PCT/ISA/210 (segunda hoja)	
	RESPUESTA VENCE dentro de 2 meses contados desde la fecha de envío	
Referencia del solicitante o agente Ver formato PCT/ISA/220	Fecha de presentación internacional (día/mes/año)	Fecha de pñoridad (día/mes/año)
Solicitud Internacional No PCT/US2005/014485	27/04/2005	28/04/2004
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC C12N 15/86, C12Q1/68		
Solicitante THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA		

1 Este opinión contiene indicaciones relacionadas con los siguientes puntos

I X Base de la opinion
II X Prioridad
III X El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial
IV X Falta de unidad de invención
V X Declaración motivada conforme a la Regla 43bis 1 (a)(i) con relación a la novedad, nivel inventivo o aplicación industrial, citaciones y explicaciones que soportan dicha declaración
VI Ciertos documentos citados
VII Ciertos defectos en la solicitud internacional
VIII Ciertas observaciones en la solicitud internacional

2. SIGUIENTE ACCIÓN

Si una solicitud de examen preliminar internacional es hecha, esta opinión será usualmente considerada como una opinión escrita de la autoridad del examen preliminar internacional Sin embargo, esto no aplica si el solicitante escoge otra autoridad como IPEA y la escogida IPEA ha notificado a la oficina internacional bajo la regla 66 1 bis (b) que opiniones escritas de la autoridad de búsqueda internacional no serán considerados

En está opinión, como se indica arriba, será considerada como una opinión escrita de la IPEA, el solicitante es invitado a presentar a la IPEA una respuesta escrita junto con, si fuera apropiado, modificaciones antes de la expiración de tres meses desde la fecha de envío del formato PCT/ISA/220 o antes de la expiración de 22 meses de la fecha de prioridad, cualquiera que expire con posterioridad

Para opciones adicionales, ver formato PCT/ISA/220

3 Para opciones adicionales ver notas de la formato PCT/ISA/220

Nombre y dirección de la autondad encargada del examen preliminar internacional Oficina de Patentes Europea D-80298 Munich Tel +49 89 2399 - 0 Tx 523656 epmu d Fax +49 89 2399 - 4465	Oficial Autorizado/ Examinador Wimmer, G. Teléfono +49 89 2399-7347
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OPINION ESCRITA

Solicitud internacional No. PCT/US2005/014485

I. BASE DEL INFORME

1 En relación con el idioma, esta opinión ha sido establecida con base en la solicitud internacional como fue presentada, a menos que se indique lo contrario en este ítem

___Esta opinión fue establecida con base en la traducción de la lengua original al siguiente idioma___, que es el idioma de traducción prescrito para los presupuestos de la búsqueda internacional (bajo las reglas 12.3 y 23.1 (b))

2 Respecto a cualquier secuencia nucleótido y/o aminoácido revelado en la solicitud internacional, el examen preliminar internacional fue llevado a cabo con base en la lista de secuencias

a tipo de material

___ lista de secuencias

___ tabla relacionada con la lista de secuencias

b formato del material

___ en formato escrito

___ en formato de computador legible

c tiempo de presentación

___ contenido en la solicitud internacional como fue presentado

___ presentado con la solicitud internacional en computador y legible a computador.

___ allegado subsiguientemente a esta autoridad para los propósitos de la búsqueda

3 ___ En adición, en caso de que haya mas de una copia o versión de la lista de secuencias o/y tabla relacionada presentada, las requeridas opiniones relacionadas con que la información en la subsiguiente o adicionales copias son idénticas de aquellas de la solicitud como fue presentada y que no van mas allá de la solicitud como fue presentada, fueron proporcionadas

4 Comentarios adicionales

OPINION ESCRITA

Solicitud internacional No. PCT/US2005/014485

Casilla No. II Prioridad

- 1 ☒ Este reporte ha sido establecido o como si ninguna prioridad hubiese sido reivindicada dada a una falla en el cumplimiento de tiempo prescrito
☐ una copia de la primera solicitud cuya prioridad ha sido reivindicada (regla 43bis 1 y 66 7 (a))
☐ La traducción de la primera solicitud cuya prioridad ha sido reivindicada (regla 43bis 1 y 66 7 (b))

- 2 ☐ Este reporte ha sido establecido como si ninguna prioridad hubiese sido reivindicada debido a que la reivindicación de prioridad hubiese sido invalida (reglas 43bis 1 y 64 1) Por lo tanto, para el propósito de este reporte, la fecha de presentación internacional indicada arriba es considerada como la fecha relevante

- 3 Observación adicional innecesaria

III. El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial

- 1 Las preguntas de si la invención reivindicada parece ser novedosa, involucrar nivel intensivo (no ser obvia), o ser aplicable industrialmente no se han examinado con respecto a

- ☐ La solicitud internacional completa,
☒ Las reivindicaciones Nos 13-34

En razón a

- ☐ La dicha solicitud internacional, o las dichas reivindicaciones Nos _____ relacionadas con la siguiente materia objeto que no requiere un examen preliminar internacional (especifique)
- ☐ La descripción, reivindicaciones o dibujos (*indique elementos particulares adelante*) o dichas reivindicaciones Nos _____ no son tan claras que no se puede formar un concepto significativo (*especifique*)
- ☐ Las reivindicaciones, o dichas reivindicaciones Nos _____ son de esta forma inadecuadamente soportadas por la descripción que no se puede formar un concepto significativo
- ☒ No se ha establecido reporte de búsqueda internacional para las dichas reivindicaciones Nos 13, 34
- ☐ El listado de secuencias de aminoácido y/o nucleótido no cumplen con el estándar suministrado en el Anexo C de las Instrucciones Administrativas en que

La forma escrita

- ☐ no se ha suministrado
- ☐ no cumple con el estándar

La forma legible por computador

- ☐ no se ha suministrado
- ☐ no cumple con el estándar

- ☐ Las tablas relacionadas con las listas de secuencias de aminoácido y/o nucleótido, si solo en la forma legible por computador, no cumple con los requerimientos técnicos suministrado en el Anexo C-*bis* de las Instrucciones Administrativas
- ☐ Ver hoja separada para detalles adicionales

OPINION ESCRITASolicitud internacional No PCT/US2005/014485

IV. Falta de unidad de invención.

1 En respuesta a la invitación para restringir o pagar tasas adicionales, el solicitante ha

☐ honorarios adicionales pagados

☐ honorarios adicionales de los países bajo protesta

☒ honorarios adicionales no pagados

2 Esta autoridad encontró que el requisito de unidad de invención no es cumplido y escoge de acuerdo con la regla 68 1 no invitar al solicitante a restringir o pagar tasas adicionales

3 Esta autoridad considera que el requisito de unidad de invención de acuerdo con la regla 13 1, 13 2 y 13 3 es

☐ cumplida

☒ no cumplida por las siguientes razones

ver hoja separada

4. En consecuencia, las siguientes partes de la solicitud internacional fueron materia del examen preliminar internacional y se estableció un reporte de

☐ todas las partes

☒ las partes relacionadas con las reivindicaciones Nos 1-12

V. Declaración motivada conforme a la Regla 43bis.1 (a)(i) con relación a la novedad, nivel inventivo o aplicación Industrial; citas y explicaciones que sustentan dicha declaración

1. Declaración

Novedad (N)	SI	Reivindicaciones	11
	NO	Reivindicaciones	1-10, 12
Nivel inventivo (IS)	SI	Reivindicaciones	
	NO	Reivindicaciones	1-12
Aplicación Industrial (IA)	SI	Reivindicaciones	1-12
	NO	Reivindicaciones	

2. Citas y explicaciones

Ver hoja separada

**OPINIÓN ESCRITA DE LA AUTORIDAD
DE BÚSQUEDA INTERNACIONAL
(HOJA SEPARADA)**

**Solicitud Internacional No.
PCT/US2005/014485**

Re Ítem IV

Las Invenciones separadas / Grupos de Invenciones son

I) Reivindicaciones 1-12

Un vector que comprende un primer casete de expresión que codifica una primera proteína reportera que esta flanqueado por un primer conjunto de sitios de restricción, y un segundo casete de expresión que codifica una segunda proteína reportera y que esta flanqueado por un segundo conjunto de sitios de restricción, y métodos que emplean tales vectores

II) Reivindicaciones 13-29

Un método para generar un vector de transferencia que comprende las etapas de.

- a) Mezclar, en presencia de un primer grupo de enzimas, un plásmido de acuerdo con el grupo 1 antes definido con un primer casete de expresión heteróloga flanqueado por el primer conjunto de enzimas de restricción
- b) Seleccionar para la ausencia del primer reportero
- c) Mezclar, en presencia de un segundo grupo de enzimas, el plásmido con un segundo casete de expresión heteróloga flanqueado por el segundo conjunto de enzimas de restricción
- d) Seleccionar para la ausencia del segundo reportero

III) Reivindicaciones 30-34

Una composición que contiene un vector viral, el vector comprende un primero y un segundo casetes de expresión heteróloga, en donde los casetes de expresión heteróloga se expresan independientemente

Ellos no están unidos de tal manera que formen un único concepto inventivo general (Regla 13.1 PCT) por las siguientes razones

El concepto común en todos los grupos definidos antes es un vector que comprende dos casetes independientes de expresión heteróloga, el concepto común en los grupos 1 y 2 es un vector que comprende dos genes reporteros independientes, flanqueados por sitios de restricción Sin embargo, en el arte previo se ha descrito una plétora de tales constructos, ver e.g., Contreras et al (2003) o WO0155371 Por lo tanto es carente de un nivel inventivo común

Se debe señalar que debido a la carencia de novedad para el concepto común del grupo 1, las reivindicaciones dependientes se pueden considerar como invenciones separadas, sin embargo éste informe de búsqueda podría ser establecido para la materia objeto de todas las reivindicaciones 1-12

Re ítem V

1 Se hace referencia los siguientes documentos

D1	CONTRERAS JUAN L ET AL "Double genetic Modification of adenovirus fiber with RGD polylysine motifs significantly enhances gene transfer to isolated human pancreatic islets "TRANSPLATATION (HAGERSTOWN) vol 76, no 1, 15 July 2003 (2003-07-15), páginas 252-261, XP0002347132 ISSN 0041-1337
D2	WO 01/55371 A (THE SCRIPPS RESEARCH INSTITUTE, MAURO, VINCENT,P, EDELMAN, GERALD, M) 2 August 2001 (2001-08-02)
D3	KAPTURCZAK MATTHIAS H ET AL "Tritansduction of human and munne pancreatic islet cells using a bioisronic recombinant adeno-associated viral (aAAV) vector" DIABETES, vol 50, no Supplement 2, June 2001(2001-06) página A86, XP002347274 & 61ST SCIENTIFIC SESSIONS OF THE AMERICAN DIABETES ASSOCIATION, PHILADELPHIA, PENNSYLVANIA, USA, JUNE 22-26, 2001 ISSN 0012-1797

2 En la reivindicación 1 y sus reivindicaciones dependientes, no son claras una vanedad de expresiones

El término "polivalente", por ejemplo, puede tener una vanedad de significados, en el presente caso, se asumió que su significado se refiere a un plásmido que lleva múltiples casetes de expresión

Asimismo, parece que una "espina dorsal plásmida" no sería diferente físicamente de un "plásmido", sino que más bien se refiere a un uso prefendo (como un vector genénco de clonación)

Tampoco es claro "casete movable", puesto que cualquier secuencia de ácido nucleico es "movible", i e , puede ser extirpada, utilizando los medios apropiados Además, a partir de la expresión "localizado en un pnmer locus de un genoma viral" no es claro si el plásmido contiene un genoma viral completo, o solo una parte de éste, en el último caso, se puede interpretar que el plásmido comprende e g , solamente un único nucleótido de un genoma viral

"Un gen reportero detectable" es bien, redundante o no claro, el examinador al menos desconoce cualquier "gen reportero no detectable"

Lo más importante, el término "enzima rara de restricción", no es claro, puesto que uno no conocería cuales enzimas se consideran "raras"

Además, no es claro cuál es el significado para la expresión "que comprende tres o más loci" (reivindicación 2) puesto que se puede considerar que cualquier ácido nucleico tiene tantos loci como nucleótidos (sin embargo se puede especular, que el significado para el solicitante se refiere a sitios de restrcción que se pueden utilizar para insertar genes reporteros)

De la misma manera, el término "una región del gen" (reivindicaciones 3-5), se puede referir e g , a un gen único, o a una región grande que comprende o esta adyacente a un gen

A la luz de esto, la reivindicación 1 se interpreto para referirse a

Un plásmido que comprende un primero y un segundo casetes de expresión localizados en un genoma viral, estando flanqueados cada uno de los casetes de expresión por un conjunto de sitios de restricción y que codifican un gen reportero, en donde difieren el conjunto de sitios de restricción que flanquean el primero y segundo casetes de expresión

- 3 El arte previo describe una vanedad de tales plásmidos; por ejemplo, D1 describe constructos adenovirales que llevan dos genes reporteros (GFP y luciferasa) D2 describe constructos retrovirales que expresan uno o, en incorporaciones, dos genes reporteros (ver e g reivindicación 98); D3 describe un vector viral adeno-asociado que comprende dos casetes independientes de expresión de reporteros fluorescentes Aunque en éstos documentos no se establece explícitamente, es claro que los casetes de genes reporteros están o pueden estar flanqueados por diferentes sitios de restricción, tal que una persona versada usaría rutinariamente diferentes sitios de restricción en la construcción de un plásmido multi-componente

Más aún, puesto que cualquier gen puede utilizarse como gen reportero, aún constructos virales tipo nativo comprometen la novedad de la reivindicación, puesto que ellos codifican dos o más genes, que están flanqueados naturalmente por vanos sitios de restricción (por lo menos dentro de una distancia indefinida)

Por lo tanto a la luz del arte previo al menos las reivindicaciones 1-10 y 12 carecen de novedad

- 4 En relación con la matena objeto de la reivindicación 11, esta no se puede evaluar para todos los virus denvados de constructos del arte previo, si los casetes de expresión en ella están flanqueados por sitios de restricción según se listan en la reivindicación,
- Sin embargo, el arte previo describe numerosos constructos virales con dos o más genes heterólogos (y en particular genes reporteros estándar tales como GFP, Luciferasa, LacZ etc) Es de allí obvio para una persona versada que tales genes heterólogos pueden ser insertados (y por lo tanto flanqueados) por sitios de restricción, en particular sitios únicos de restricción, la selección de los sitios de restricción listados a ese respecto en la reivindicación 11 representa una selección arbitraria y no conduce a un efecto sorprendente, y por lo tanto carece de actividad inventiva (Art 56 EPC)

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

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

To
HOWSON AND HOWSON
Attn. Kodroff, Cathy
Spring House Corporate Center
P.O. Box 457
Spring House, PA 19477
UNITED STATES OF AMERICA

DOCKET
DUE DATE 6/5/06

(PCT Rule 44.1)

Date of mailing
(day/month/year) 05/04/2006

Applicant's or agent's file reference

UPN-Q3402PCT

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No

PCT/US2005/014485

International filing date

(day/month/year) 27/04/2005

Applicant

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

- 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 18 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 International Searching Authority



European Patent Office, P B 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 851 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Stefanie Buchler

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*, 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 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 18 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 (Administrative Instructions, 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 English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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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 on any of the 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.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference UPN-Q3402PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below	
International application No PCT/US2005/014485	International filing date (day/month/year) 27/04/2005	(Earliest) Priority Date (day/month/year) 28/04/2004
Applicant THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA		

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 6 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 ☐ 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

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Box 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..
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

- 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 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

see additional 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 an additional fee, this Authority did not invite payment of any additional fee.

- 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

1-12

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-12

A vector comprising a first expression cassette encoding a first reporter protein and being flanked by a first set of restriction sites, and a second expression cassette encoding a second reporter protein and being flanked by a second set of restriction sites.

2. claims: 13-29

A method for generating a transfer vector comprising the steps of
a) mixing, in the presence of a first set of enzymes, a plasmid according to above defined group 1 with a first heterologous expression cassette flanked by the first set of restriction enzymes
b) selecting for the absence of the first reporter
c) mixing, in the presence of a second set of enzymes, the plasmid with a second heterologous expression cassette flanked by the second set of restriction enzymes
d) selecting for the absence of the second reporter.

3. claims: 30-34

a composition containing a viral vector, the vector comprising a first and a second heterologous expression cassette, wherein the expression cassettes are independently expressed.

A CLASSIFICATION OF SUBJECT MATTER C12N15/86 C12Q1/68		
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) C12N C12Q		
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 practical, search terms used) EPO-Internal, BIOSIS, WPI Data		
C DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	CONTRERAS JUAN L ET AL: "Double genetic modification of adenovirus fiber with RGD polylysine motifs significantly enhances gene transfer to isolated human pancreatic islets." TRANSPLANTATION (HAGERSTOWN), vol. 76, no. 1, 15 July 2003 (2003-07-15), pages 252-261, XP002347132 ISSN: 0041-1337 the whole document	1-12
X	WO 01/55371 A (THE SCRIPPS RESEARCH INSTITUTE; MAURO, VINCENT, P; EDELMAN, GERALD, M;) 2 August 2001 (2001-08-02) claim 98 ----- -/-	1-8, 10-12
☒ 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		
"E" earlier document but published on or after the international filing date		
"L" 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)		
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		
"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		
"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		
"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		
"B" document member of the same patent family		
Date of the actual completion of the international search 8 December 2005		Date of mailing of the international search report 05.04.2006
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+31-70) 340-3016		Authorized officer Wimmer, G

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	KAPTURCZAK MATTHIAS H ET AL: "Transduction of human and murine pancreatic islet cells using a bicistronic recombinant adeno-associated viral (rAAV) vector" MOLECULAR THERAPY, vol. 5, no. 2, February 2002 (2002-02), pages 154-160, XP002347274 ISSN: 1525-0016 the whole document	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/014485

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0155371	A	02-08-2001	
		AU 3117101 A	07-08-2001
		AU 3120601 A	07-08-2001
		BR 0107930 A	15-06-2004
		BR 0107943 A	28-01-2003
		CA 2398541 A1	02-08-2001
		CA 2398790 A1	02-08-2001
		EP 1274838 A1	15-01-2003
		EP 1259602 A1	27-11-2002
		WO 0155369 A1	02-08-2001

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No PCT/US2005/014485	International filing date (day/month/year) 27 04 2005	Priority date (day/month/year) 28 04 2004
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International Patent Classification (IPC) or both national classification and IPC
C12N15/86, C12Q1/68

Applicant
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA

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 usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, 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 three 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  European Patent Office D-80288 Munich Tel +49 89 2399 - 0 Tx 523656 epmu d Fax +49 89 2399 - 4465	Authorized Officer Wimmer, G Telephone No +49 89 2399-7347 
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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. I Basis of the 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, unless otherwise indicated under this item
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23 1(b))
- 2 With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, 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
☐ in written format
☐ in computer readable form
 - c time of filing/furnishing
☐ contained in the international application as filed
☐ filed together with the international application in computer readable form
☐ furnished subsequently to this Authority for the purposes of search
- 3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table 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.
- 4 Additional comments

Box No. II Priority

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

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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 13-34

because:

- ☐ the said international application, or the said claims Nos relate to the following subject matter which does not require an international preliminary examination (*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
- ☒ no international search report has been established for the whole application or for said claims Nos 13-34
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions
- ☐ See separate sheet for further details

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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:
- ☐ paid additional fees
 - ☐ paid additional fees under protest.
 - ☒ 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 separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application
- ☐ all parts.
 - ☒ the parts relating to claims Nos 1-12

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)	Yes. Claims	11
	No: Claims	1-10, 12
Inventive step (IS)	Yes. Claims	
	No: Claims	1-12
Industrial applicability (IA)	Yes. Claims	1-12
	No: Claims	

2 Citations and explanations

see separate sheet

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166 24

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

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Re Item IV.

The separate inventions/groups of inventions are:

I) Claims 1-12

A vector comprising a first expression cassette encoding a first reporter protein and being flanked by a first set of restriction sites, and a second expression cassette encoding a second reporter protein and being flanked by a second set of restriction sites, and methods employing such vectors.

II) Claims 13-29

A method for generating a transfer vector comprising the steps of

- a) mixing, in the presence of a first set of enzymes, a plasmid according to above defined group 1 with a first heterologous expression cassette flanked by the first set of restriction enzymes
- b) selecting for the absence of the first reporter
- c) mixing, in the presence of a second set of enzymes, the plasmid with a second heterologous expression cassette flanked by the second set of restriction enzymes
- d) selecting for the absence of the second reporter.

III) Claims 30-34

a composition containing a viral vector, the vector comprising a first and a second heterologous expression cassette, wherein the expression cassettes are independently expressed

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The concept common to all of the above defined groups is a vector comprising two independent heterologous expression cassettes, the concept common to groups 1 and 2 is a vector comprising two independent reporter genes, flanked by restriction sites. However, a plethora of such constructs has been described in the prior art; see e.g. Contreras et al. (2003) or WO0155371. A common inventive concept is therefore lacking.

It should be noted that due to the lack of novelty for the common concept of group 1, dependent claims may be regarded as separate inventions; this search report however

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AUTHORITY (SEPARATE SHEET)**

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could be established for subject-matter of all of claims 1-12.

Re Item V.

1. Reference is made to the following documents:

- D1: CONTRERAS JUAN L ET AL: "Double genetic modification of adenovirus fiber with RGD polylysine motifs significantly enhances gene transfer to isolated human pancreatic islets." TRANSPLANTATION (HAGERSTOWN), vol. 76, no. 1, 15 July 2003 (2003-07-15), pages 252-261, XP002347132 ISSN: 0041-1337
- D2: WO 01/55371 A (THE SCRIPPS RESEARCH INSTITUTE, MAURO, VINCENT, P; EDELMAN, GERALD, M;) 2 August 2001 (2001-08-02)
- D3: KAPTURCZAK MATTHIAS H ET AL: "Transduction of human and murine pancreatic islet cells using a bicistronic recombinant adeno-associated viral (rAAV) vector" DIABETES, vol. 50, no. Supplement 2, June 2001 (2001-06), page A86, XP002347274 & 61ST SCIENTIFIC SESSIONS OF THE AMERICAN DIABETES ASSOCIATION; PHILADELPHIA, PENNSYLVANIA, USA; JUNE 22-26, 2001 ISSN: 0012-1797

2. A variety of expressions in claim 1 and its dependent claims are unclear.

The term "polyvalent", for instance, may have a variety of meanings; in the present case, it was assumed that it was meant to refer to a plasmid carrying multiple expression cassettes

Likewise, it appears that a "plasmid backbone" would be not physically different from a "plasmid", but rather refers to a preferred use (as a generic cloning vector).

A "movable cassette" is also unclear, since *any* nucleic acid sequence is "movable", i.e. can be excised, using the proper means. Further, from the expression "located within a first locus of a viral genome" it is not clear whether the plasmid contains an entire viral genome, or just a part of it; in the latter case, the plasmid may be interpreted to comprise e.g. only a single nucleotide of a viral genome.

A "detectable reporter gene" is either redundant or unclear, the examiner is at least unaware of any "undetectable reporter gene".

Most importantly, the term "rare restriction enzyme" is unclear, since one would not know which enzymes are considered "rare"

Furthermore, it is not clear what is meant by the term "comprising three or more loci" (claim 2), since any nucleic acid can be considered to have as many "loci" as nucleotides (it may however be speculated, that the applicant meant to refer to restriction sites which may be used to insert reporter genes). Likewise, the term "a gene region" (claims 3-5) may e.g. refer to a single gene, or a large region comprising or adjacent to one gene

In the light of this, claim 1 was interpreted to refer to
A plasmid comprising a first and a second expression cassette located within a viral genome, each of the expression cassettes being flanked by a set of restriction sites and encoding a reporter gene, wherein the set of restriction sites flanking the first and the second expression cassettes differ.

3. . The prior art describes a variety of such plasmids; for instance, D1 describes adenoviral constructs carrying two reporter genes (GFP and Luciferase), D2 describes retroviral constructs expressing one or, in embodiments, two reporter genes (see e.g. claim 98); D3 describes an Adeno-associated viral vector comprising two independent fluorescent reporter expression cassettes. Although not explicitly stated in these documents, it is clear that the reporter gene cassettes are or may be flanked by different restriction sites, since the skilled person would routinely use different restriction sites in constructing a multi-component plasmid.

Moreover, since *any* gene may be used as a reporter gene, even wild-type viral constructs compromise novelty of the claim, since they encode two or more genes, which are naturally flanked by various restriction sites (at least within an undefined distance).

At least claims 1-10 and 12 therefore lack novelty in the light of the prior art.

4. Concerning subject-matter of claim 11, it cannot be assessed for all virus derived constructs of the prior art, whether expression cassettes therein are flanked by restriction sites as listed in the claim;
however, the prior art describes numerous viral constructs with two or more heterologous genes (and in particular "standard" reporter genes such as GFP,

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AUTHORITY (SEPARATE SHEET)**

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Luciferase, lacZ etc). It is therein obvious to the skilled person that such heterologous genes may be inserted (and thereby flanked) by *any* restriction sites, in particular unique restriction sites; the choice of the sites listed in claim 11 therein represents an arbitrary choice and does not lead to a surprising effect, and therefore lacks inventive activity (Art. 56 EPC)