



No. 11-050300- -00009-0000

Fecha: 2014-04-01 16:12:57 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 39

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P-2866

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. **11-050.300**
Solicitud de patente a nombre de **TOCAPEN, INC.**

Yo, SILVANA MARIA LOPEZ DIAZ identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, piso 6, obrando como apoderada sustituta de acuerdo con la sustitución adjunta de la sociedad **TOCAPEN, INC.**, solicitante de la patente de la referencia, interpongo recurso de reposición contra la resolución No. **9870** del día 21 de febrero de 2014, expedida por el Superintendente de Industria y Comercio, por medio de la cual se niega el privilegio de patente para la solicitud contenida en el expediente de la referencia

1. FUNDAMENTOS DEL RECURSO

1.1 Actos administrativos previos

En primer lugar, mi mandante se permite manifestar a ese despacho que se reafirma en todos y cada uno de los argumentos que hacen parte integrante de la respuesta al oficio de fondo No. 8587 notificado por fijación en lista el 14 de mayo de 2013, presentada ante ese despacho el 18 de septiembre de 2013.

1.2 Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial nuevo capítulo reivindicatorio el cual consta de ocho () reivindicaciones.

Sobre este particular me permito decir que se presenta tasa por modificación de la solicitud y por 39 reivindicaciones adicionales.

1.3 Nivel inventivo

Ahora bien, el examinador indica en la resolución No. 9870 que las reivindicaciones 1 a 6 de la presente solicitud carecen de nivel inventivo frente a los documentos D1 y D2 citados por su Despacho. La solicitante, de manera respetuosa discrepa totalmente de su opinión.

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En este sentido, en primer lugar, el solicitante presenta un nuevo capítulo de reivindicaciones en el cual queda claro que la presente invención si tiene nivel inventivo como se demostrará también por los siguientes argumentos.

D1 y D2 no enseñan una secuencia de codón humano optimizado con actividad citosina deaminasa (es decir, la SEQ ID NO: 19 desde cerca del nucleótido número 8877 a cerca de 9353). Más aún, la optimización de los codones de citosina deaminasa para la expresión en humanos produjo un efecto técnico inesperado de incrementar dramáticamente la estabilidad del vector. De acuerdo con esto, las reivindicaciones tienen nivel inventivo frente al arte previo citado.

D1 enseña construcciones que contienen la secuencia para la levadura de citosina deaminasa tipo silvestre en donde la secuencia de la levadura ha sido mutada aleatoriamente en sitios seleccionados (por ejemplo, ver D1 en la página 854, 'resumen').

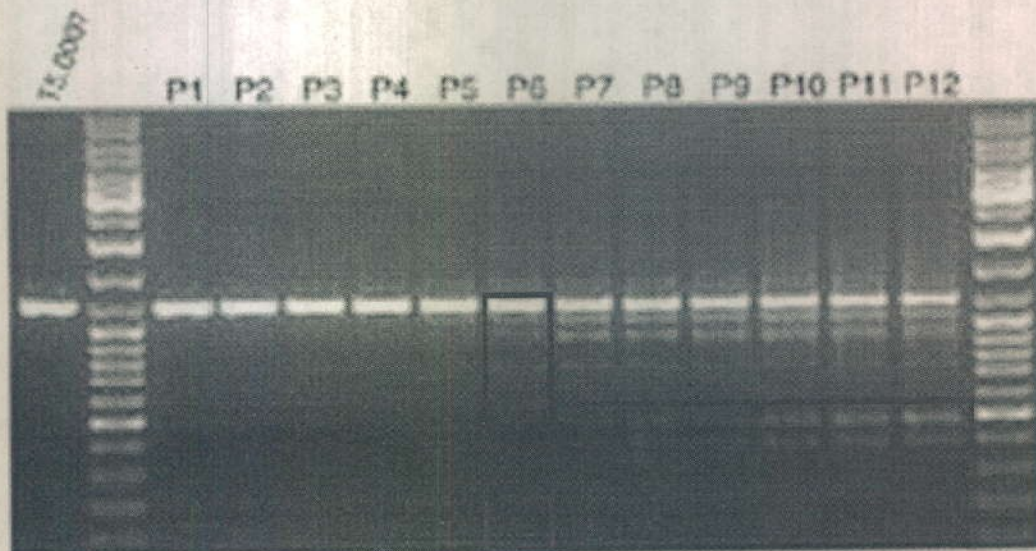
D2 trata sobre el vector de expresión pACE-CD (ver D2 en la página 843, col. 2 # 2 'gen suicida de levadura DC pequeño'; y en la página 850, col. 1, # 2 'pACE-CD') que contiene una secuencia de polinucleótido de levadura de citosina deaminasa tipo silvestre (wt levadura CD) (ver la especificación de la solicitante en el parágrafo [00142] en la 'Tabla: 'construcciones y nombres de vectores' código Tocagen T5.000).

Por lo tanto, D1 y D2 enseñan secuencias de polinucleótidos que son grandemente idénticas a la secuencia de polinucleótido de levadura de citosina deaminasa tipo silvestre.

Las reivindicaciones de la solicitante, sin embargo, **no se** refieren a una secuencia de polinucleótido de levadura de citosina deaminasa tipo silvestre sino que suministran una secuencia de polinucleótido de citosina deaminasa optimizada en codón humano (es decir, una secuencia de polinucleótido de la SEQ ID NO:19 en los sitios 8877 a 9353). La solicitante presenta en **Anexo A**, que suministra una alineación comparativa entre los sitios 8877 a 9353 de la SEQ ID NO:19 (yCD2= codones humanizados de levadura citosina deaminasa y con las tres mutaciones de los codones). Como puede observar claramente su Despacho en el **Anexo A**, las secuencias son estructuralmente distintas, en que existen muchas faltas de coincidencia de los pares base entre las dos secuencias. Más aún, Ssu Despacho debería también reconocer la secuencia de polinucleótido optimizado en codón humano de las reivindicaciones es una secuencia que completamente no ocurra naturalmente o en la naturaleza. Las secuencias descritas en D1 y D2 son básicamente las mismas o idénticas a la secuencia CD de levadura tipo silvestre. Por lo tanto, los argumentos de su Despacho de que D1 y D2 enseñan vectores que comprenden la SEQ ID NO:19 (sitios 8877 a 9353, una secuencia optimizada en codón humano) **no tienen ningún soporte en las divulgaciones**

de D1 y D2. Además, no existe absolutamente ninguna enseñanza en D1 y D2 que pudiera motivar o dirigir a una persona medianamente versada en la materia a producir una secuencia artificial de polinucleótido de citosina deaminasa optimizado en codón humano. Por ejemplo, en ninguna parte en las secciones de discusión de D1 y D2 hay señales o sugerencias de crear una secuencia de citosina deaminasa que contenga codones que han sido optimizados para expresión en humanos.

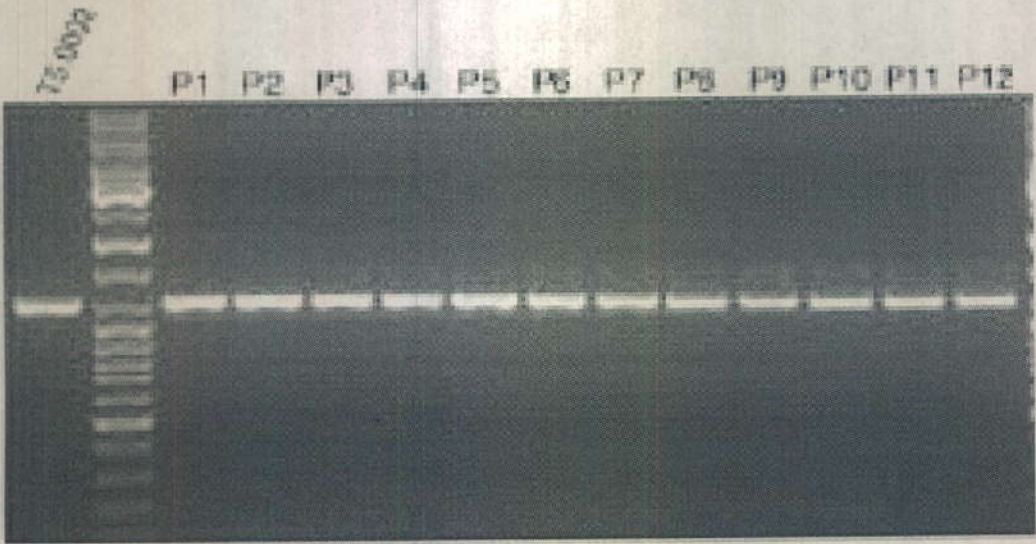
Además, como lo expresó la solicitante en la respuesta al último Oficio de su Despacho, la secuencia reivindicada (es decir, sitios 8877 a 9353 de la SEQ ID NO:19) generó un efecto técnico que no podría esperarse de manera razonable con base en las enseñanzas del estado de la técnica. En particular, no solo se mejoró la expresión de citosina deaminasa en líneas de células humanas, sino que los vectores que comprenden la secuencia humanizada fueron mucho más estables que los mismos vectores que comprenden la levadura wt con base en las secuencias CD (es decir, las secuencias presentadas en D1 y D2). Por ejemplo, las figuras 4, 5 y 6 presentan los datos de estabilidad del CD tipo silvestre comparados con el CD optimizado en codón humano. Como puede verse en la Figura 4, el pACE-yCD (T5.0007), un vector que comprende la secuencia CD de levadura wt, pierde la estabilidad en el paso 6 (empezando la degradación mostrada en el cuadrado rojo):



En contraste, el pACE-yCD (T5.0007), un vector que comprende la secuencia CD optimizada humana, no muestra una pérdida de estabilidad similar y es estable al menos hasta el paso 12:

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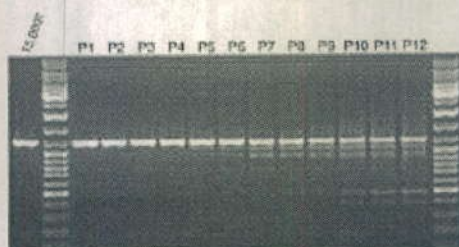
La persona versada en la técnica no hubiera esperado que la “optimización en codón humano” tuviera efectos técnicos en la estabilidad del vector. Además, la persona versada en la materia no hubiera encontrado enseñanzas en D1 y D2 que siquiera le sugirieran tal efecto por la optimización del codón humano. Losx efectos técnicos son claramente inesperados.

La Figura 4 también demostró que la mejora dramática en la estabilidad del vector resulta de la optimización del codón humano y no depende de las mutaciones estabilizadas por calor (por ejemplo, las mutaciones enseñadas en D1):

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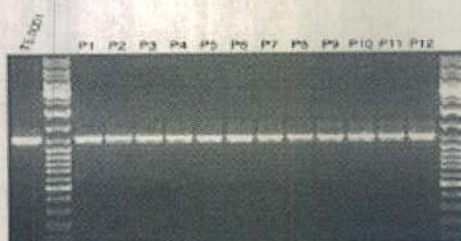
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pAC3-yCD (T5.0007)



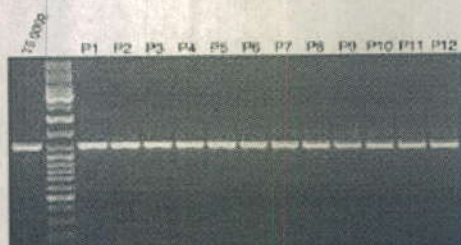
pAC3 backbone
wild-type yeast CD

pAC3-yCD1 (T5.0001)



pAC3 backbone
human codon
optimized CD

pAC3-yCD2 (T5.0002)



pAC3 backbone
human codon
optimized heat
stabilized CD

Adicionalmente, los vectores que comprenden la secuencia CD con codón humano optimizado suministran los siguientes efectos técnicos adicionales:

- (1) Un incremento significativo en la producción de 5FU/min.mg de proteína en una línea celular de glioblastoma primario humano (ver la solicitud de la solicitante en los párrafos [00163]-[00164] y la Figura 6); y
- (2) Fueron muchísimo más efectivos en la supresión de tumores in un modelo ratón/xenoinjerto humano subcutáneo in vivo que los vectores con secuencias CD que no fueron optimizadas en codón humano (ver la presente solicitud en los párrafos [00165]-[00166]).

De acuerdo a lo anterior, si D1 es visto como el estado de la técnica más cercano a la presente invención, entonces el problema técnico sería suministrar una secuencia de polinucleótidos mejorada que codifica para citosina deaminasa. LA solicitante ha resuelto este problema mediante suministrar una secuencia optimizada en codón humano que codifica para citosina deaminasa. D1 no sugiere que la optimización del codón humano de la secuencia de polinucleótidos que codifican para citosina deaminasa produce el efecto técnico de la presente invención. La persona versada en la técnica no se hubiera ido por modificar o adaptar las enseñanzas de D1 de esta manera. Por lo tanto las reivindicaciones

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tienen nivel inventivo frente al estado de la técnica.

De otro lado, que también demuestra que la presente invención tiene nivel inventivo son las patentes otorgadas en otros países para la misma invención contenida en el expediente No. 11-050-300:

- Una patente otorgada en Nueva Zelanda (Patente No. 592070).
- Una nota de aceptación ha sido emitida para la solicitud de patente Estadounidense No. 13/072.705. La patente será otorgada tan pronto se paguen las tasas correspondientes.
- La última acción oficial emitida para la solicitud Europea No. 09820986.9 indicó que las reivindicaciones son nuevas y tienen nivel inventivo frente al estado de la técnica. Los únicos problemas pendientes en esta solicitud tienen que ver con claridad. Por favor note: La Oficina de Patentes Europea suministró una discusión extensa en cuanto a porque las reivindicaciones son nuevas y no obvias frente al arte previo.

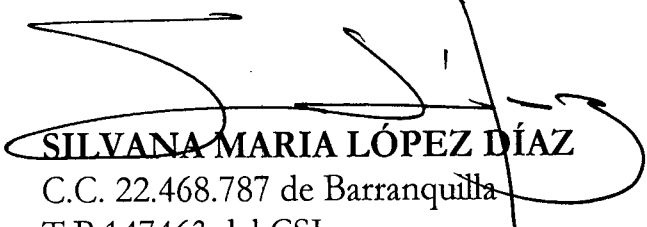
En resumen, me permito establecer nuevamente que debido a los argumentos expuestos anteriormente y los radicados ante esa Superintendencia el 18 de septiembre de 2013, la presente solicitud cumple cabalmente con los requisitos de patentabilidad de la invención en las nuevas reivindicaciones que presento.

Teniendo en cuenta lo dicho anteriormente, solicito a usted lo siguiente:

a) Que de conformidad con lo previsto por los artículos 3 (inciso 3); 35 (inciso 2) y 59 (inciso 2) del Código Contencioso Administrativo se consideren y se resuelvan TODOS los argumentos y TODAS las cuestiones planteadas así como las que aparezcan con motivo de este recurso.

b) Que se revoque la resolución No. 9870 del día 21 de febrero de 2014 expedida por el Superintendente de Industria y Comercio, y se proceda a conceder el privilegio de patente de invención a la solicitud de mi mandante

Señor Superintendente,



SILVANA MARIA LÓPEZ DÍAZ

C.C. 22.468.787 de Barranquilla

T.P 147463 del CSJ

notificaciones@clarkemodet.com.co

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ANEXOS

Nuevas reivindicaciones

Anexo A

Copias de la patente de Nueva Zelandia, la nota de aceptación
Estadounidense y la última acción oficial Europea.

DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES

1. Identificación del Trámite
- ☐ Error material ☒ Modificación a una Solicitud en trámite
- ☒ Patente de Invención
☐ Patente de Modelo de Utilidad
☐ Registro de Diseño Industrial
☐ Esquema de Trazado de Circuitos Integrados

2. Datos del solicitante

Persona Natural ☐

Persona Jurídica ☒

TOCAPEN INC.

Nombre o denominación / Nombre o razón social completa
Nombre representante legal

Tipo de empresa

Micro ☐

Pequeña ☐

Mediana ☐

Otra ☐

Documento de identificación:

☐ C.C.

☐ C.E.

☐ NIT

☐ Otro

Número

Nacionalidad/País de constitución Estados Unidos de América	Dirección y domicilio del titular 3030 Bunker Hill Street, Suite 230, San Diego, California 92109,	Ciudad San Diego, California
Dirección electrónica	No. Fax	Número telefónico

☐

Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:

SILVANA MARIA LÓPEZ DÍAZ

C.C. 22.468.787

147463 CSJ

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección y domicilio	Ciudad	
Carrera 11 No. 86-53, Piso 6, Bogotá D.C., Colombia	Bogotá D.C.	
Dirección electrónica	No. Fax	Número telefónico
notificaciones@clarkemodet.com.co	6350824	6181088

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general

4. Datos del trámite

Corrección:

Expediente No. 11-050.300

Aparece _____

Debe ser _____

Modificación:

Presentación Solicitud Divisional.

Modificación al capítulo descriptivo.

☐

Modificación al capítulo Reivindicatorio

Presento junto con este Recurso nuevo capítulo reivindicatorio el cual consta de 8 reivindicaciones. Se presenta tasa por modificación de la solicitud y por 39 reivindicaciones adicionales.

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Modificación al resumen.

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Modificación a los dibujos.

Modificación al solicitante

5. Anexos

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Comprobante de pago de la tasa para la presentación de la corrección y/o modificación

☐

Poder, si fuere el caso.

☒

Documento que contiene las modificaciones o correcciones.

☐

Copia de la solicitud y sus anexos en formato magnético.

6. Firma

SILVANA MARIA LÓPEZ DÍAZ

Nombre y apellidos

Firma



C.C. 22.468.787

Tarjeta Profesional T.P. 147463 CSJ

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0016946

Bogotá D.C., Febrero 12 de 2014 - 17:03:19

RECIBIDO DE : CLARKE MODET

NI 830.008.643

***** Soporte del Pago *****

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	617584870	11/02/2014	71.020.500.00

***** Conceptos Pagados *****

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACIONES	EN N.CREACION CORRECCION A SOLICITUD EN TRAMITE / MODIFICA	128.000.00	128.000.00
				\$128.000.00

SON: **CIENTO VEINTIOCHO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-050300- -00009-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 412 REPOSPRESRECU Folios: 39

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Febrero 12 de 2014 - 17:03:43

P-2886 9

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

-/-

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0035201

Bogotá D.C., Abril 01 de 2014 - 13:23:34

RECIBIDO DE : CLARKE MODET

NI 83.008.643

RE

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR PAGO
RECIBO DE CA	999999999	25570	06/03/2014		546.000.00
RECIBO DE CA	999999999	25607	06/03/2014		330.000.00
RECIBO DE CA	999999999	25608	06/03/2014		330.000.00
RECIBO DE CA	999999999	25611	06/03/2014		21.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO
39 50005-01-01 SOLICITUDESCONCEPTO
1607 REIVINDICACION PATENTE UNITARIA
ADICIONAL A LAS 10 INIC

Vr.UNDITARIO	Vr.CONCEPTO
31.000.00	1.209.000.00
	<u>\$1.209.000.00</u>

SON: **UN MILL&OACUTE;N DOSCIENTOS NUEVE MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-050300- -00009-0000

Fecha: 2014-04-01 16:12:57 Dep. 2020 DIR.NUEVASCR
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Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: Info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

, Abril 1 de 2014 - 13:23:35

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REIVINDICACIONES

1. Un polinucleótido modificado que comprende:

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un polinucleótido optimizado de codón humano que comprende la SEQ ID NO:19 de pares base 8877 a 9353 que codifican un polipéptido de SEQ ID NO: 4, en donde el polipéptido comprende actividad desaminasa citosina (CD).

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2. El polinucleótido modificado de la reivindicación 1, en donde el polinucleótido 1-50 mutaciones inactivas.

- 15 3. El polinucleótido modificado de la reivindicación 1, que comprende adicionalmente un polinucleótido UPRT OPRT que codifica un polipéptido que tiene actividad UPRT o OPRT ligada operablemente al polipéptido que tiene actividad CD, en donde el polinucleótido comprende la secuencia tal como se da en la SEQ ID NO: 11 o 15.

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4. El polinucleótido modificado de la reivindicación 3, en donde el polinucleótido UPRT OPRT se separa del polinucleótido que codifica el polipéptido que tiene actividad CD mediante un ligador, en donde el polinucleótido comprende la secuencia tal como se da en la SEQ ID NO: 13 o 17.

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5. El polinucleótido modificado de la reivindicación 3, en donde el polinucleótido codifica un polipéptido que comprende una secuencia como se establece en la SEQ ID
5 NO:12 o 16.
6. El polinucleótido modificado de la reivindicación 4, en donde el polinucleótido codifica un polipéptido que comprende una secuencia como se establece en la SEQ ID
10 NO:14 o 18.
7. Un vector que comprende un polinucleótido de la reivindicación 1, 2, 4 o 5.
- 15 8. El vector de la reivindicación 7, en donde el vector es un plásmido.
9. El vector de la reivindicación 7, en donde el vector es un vector de expresión.
20
10. El vector de la reivindicación 7, en donde el vector comprende un vector vírico.
11. El vector de la reivindicación 10, en donde el vector
25 vírico comprende un retrovirus de replicación competente.

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12. Una célula anfitriona que contiene el vector de la reivindicación 8, 9, 10, u 11.
13. Una célula anfitriona que comprende un polinucleótido de la reivindicación 1, 2, 3 o 4.
14. La célula anfitriona de la reivindicación 13, en donde la célula anfitriona comprende una célula humana.
15. La célula anfitriona de la reivindicación 14, en donde la célula anfitriona comprende una célula que comprende un trastorno proliferativo de la célula.
16. La célula anfitriona de la reivindicación 13, en donde la célula anfitriona comprende una célula humana establemente transformada.
17. La célula anfitriona de la reivindicación 16, en donde la célula anfitriona comprende un trastorno proliferativo de la célula.
18. La célula anfitriona de la reivindicación 15 o 17, en donde la célula anfitriona comprende glioblastoma multiforme.
19. La célula anfitriona de la reivindicación 13, en donde la célula anfitriona se transforma *in vivo*.

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20. Un retrovirus competente de replicación recombinante (RCR) que comprende:

5 una proteína GAG retrovímica;

una proteína POL retrovímica;

una envoltura retrovímica;

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un polinucleótido retrovímico que comprende Secuencias (LTR) de Repetición de Terminal Largo en el extremo 3' de la secuencia de polinucleótido retrovímico, una secuencia promotora en el extremo 5' de el polinucleótido retrovímico, dicho promotor es adecuado para la expresión en una célula de mamífero, un dominio de ácido nucleico gag, un dominio de ácido nucleico pol y un dominio de ácido nucleico env;

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un casete que comprende un sitio interno de entrada al ribosoma (IRES) ligado operablemente a un ácido nucleico heterólogo que comprende un polinucleótido de la reivindicación 1, en donde el casete se posiciona 5' en el 3' LTR y 3' en el dominio de ácido nucleico env que codifica la envoltura retrovímica; y

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las secuencias que actúan cis necesarias para transcripción inversa, empaque e integración en una célula objetivo.

- 5 21. El retrovirus de la reivindicación 20, en donde la secuencia de polinucleótido retroviral se deriva de virus de leucemia de murino (MLV), Virus de leucemia de murino de Moloney (MoMLV), Virus de leucemia felina o Virus de leucemia de mono Gibbon (GALV).
- 10 22. El retrovirus de la reivindicación 20 o 21, en donde el MLV es un MLV anfitriónico.
- 15 23. El retrovirus de la reivindicación 20, en donde el retrovirus es un retrovirus gama.
24. El retrovirus de la reivindicación 20, en donde la célula objetivo es una célula neoplásica.
- 20 25. El retrovirus de la reivindicación 20, en donde la secuencia promotora se asocia con un gen regulador del crecimiento.
- 25 26. El retrovirus de acuerdo con la reivindicación 20, en donde la secuencia promotora comprende una secuencia promotora específica de tejido.

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27. El retrovirus de acuerdo con la reivindicación 26, en donde la secuencia promotora específica de tejido comprende por lo menos un elemento de respuesta a andrógeno (ARE).

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28. El retrovirus de acuerdo con la reivindicación 27, en donde el elemento de respuesta a andrógeno se deriva del promotor probasina.

10 29. El retrovirus de acuerdo con la reivindicación 26, en donde la secuencia promotora específica de tejido comprende un promotor probasina.

15 30. El retrovirus de acuerdo con la reivindicación 20, en donde el promotor comprende un promotor CMV que tiene una secuencia como se establece en la SEQ ID NO: 19, 20, o 22 a partir del nucleótido 1 a cerca del nucleótido 582 y que es capaz de dirigir e iniciar la transcripción.

20 31. El retrovirus de la reivindicación 20, en donde el promotor comprende una secuencia como se establece en la SEQ ID NO: 19 o 20 a partir del nucleótido 1 a cerca del nucleótido 582.

25 32. El retrovirus de la reivindicación 20, en donde el promotor comprende un polinucleótido de dominio CMV-R-U5.

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33. El retrovirus de la reivindicación 32, en donde el dominio CMV-R-U5 comprende el promotor inmediatamente temprano del citomegalovirus humano ligado a una región MLV R-U5.
34. El retrovirus de la reivindicación 33, en donde el polinucleótido de dominio CMV-R-U5 comprende una secuencia como se establece en la SEQ ID NO: 19, 20, o 22 desde cerca del nucleótido 1 a cerca del nucleótido 1202 en donde el polinucleótido promueve la transcripción de una molécula de ácido nucleico ligada operablemente a esta.
35. El retrovirus de la reivindicación 20, en donde el gag del polinucleótido se deriva de un retrovirus gama.
36. El retrovirus de la reivindicación 35, en donde el dominio de ácido nucleico gag comprende una secuencia desde cerca del nucleótido número 1203 a cerca del nucleótido 2819 de la SEQ ID NO: 19.
37. El retrovirus de la reivindicación 20, en donde el dominio pol del polinucleótido se deriva de un retrovirus gama.

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38. El retrovirus de la reivindicación 37, en donde el dominio pol comprende una secuencia desde cerca del nucleótido número 2820 a cerca del nucleótido 6358 de la SEQ ID NO: 19.

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39. El retrovirus de la reivindicación 20, en donde el dominio env comprende una secuencia desde cerca del nucleótido número 6359 a cerca del nucleótido 8323 de la SEQ ID NO:19.

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40. El retrovirus de la reivindicación 20, en donde el IRES se deriva de un virus de encefalomiocarditis.

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41. El retrovirus de la reivindicación 40, en donde el IRES comprende una secuencia desde cerca del nucleótido número 8327 a cerca del nucleótido 8876 de la SEQ ID NO:19.

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42. El retrovirus de la reivindicación 20, en donde el ácido nucleico heterólogo comprende un polinucleótido que tiene una secuencia como se establece en la SEQ ID NO:3, 5, 11, 13, 15 o 17.

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43. El retrovirus de la reivindicación 20, en donde el ácido nucleico heterólogo codifica un polipéptido que comprende una secuencia como se establece en la SEQ ID NO:4.

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Rvs modificadas
Marzo 31, 2014

44. El retrovirus de la reivindicación 20, en donde el ácido nucleico heterólogo es codón humano optimizado y codifica un polipéptido como se establece en la SEQ ID NO: 4.
45. El retrovirus de la reivindicación 20, en donde el ácido nucleico heterólogo comprende una secuencia como se establece en la SEQ ID NO: 19 desde cerca del nucleótido número 8877 a cerca de 9353.
46. El retrovirus de la reivindicación 45, en donde el LTR 3' se deriva de un retrovirus gama.
47. El retrovirus de la reivindicación 46, en donde el LTR 3' comprende un dominio U3-R-U5.
48. El retrovirus de la reivindicación 46, en donde el LTR 3' comprende una secuencia como se establece en la SEQ ID NO: 19 desde cerca del nucleótido 9405 a cerca de 9998.
49. El retrovirus de la reivindicación 20, en donde el polinucleótido retrovítico comprende una secuencia como se establece en la SEQ ID NO: 19, 20, o 22.

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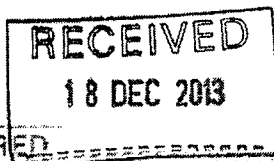


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DEADLINES ENTERED	
1.	11 / 14 / 14
2.	___ / ___ / ___
3.	___ / ___ / ___

Application No. 09 820 986.9 - 1405	Ref. 327250EP/CMH	Date 11.12.2013
Applicant Tocagen Inc.		

Communication pursuant to Article 94(3) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(2) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 126(2) and 131(2) and (4) EPC. One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (R. 50(1) EPC).

If filing amendments, you must identify them and indicate the basis for them in the application as filed. Failure to meet either requirement may lead to a communication from the Examining Division requesting that you correct this deficiency (R. 137(4) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Art. 94(4) EPC).

The notification of this communication starts the 24-month period according to Rule 36(1)(a) EPC for filing a voluntary divisional application divided from this application or from any sequential application. For further information see Guidelines for Examination, A-IV, 1.1.1.2 and 1.1.1.4.

Important note

As from **01.04.2014** the 24-month time period under Rule 36(1)(a) EPC for filing a voluntary divisional application shall cease to apply. Thus, a divisional application may be filed while the earlier European patent application is still **pending**.

For further details, see the information published on the EPO website under www.epo.org.

Registered letter

EPO Form 2001 12.10GSX

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Schulz, Regine
Primary Examiner
For the Examining Division

Enclosure(s): 4 page/s reasons (Form 2906)

The examination is being carried out on the **following application documents**

Description, Pages

2-11, 13, 15-33, as published
35-48, 50-54,
56-69

1, 12, 14, 34, 49, filed in electronic form on
55

24-05-2012

Sequence listings, SEQ ID NO

1-22 filed with entry into the regional phase before the EPO

Claims, Numbers

1-15 filed in electronic form on

24-05-2012

Drawings, Sheets

1/29-29/29 as published

1 AMENDMENTS (Art. 123(2) EPC)

1.1 The amendments filed upon entry into the regional phase before the EPO do not introduce any subject-matter which extends beyond the content of the application. A basis can be found in the description and / or the previous set of claims as indicated in the letter L1. Therefore, the requirements of Art. 123(2) EPC are considered as having been met.

2 CLARITY (Art. 84 EPC)

2.1 The present set of claims *a whole* lacks clarity (cf. Guidelines F-IV, 4.1) because of the various 'and/or' combinations used to define the subject-matter of claims 1, 2, 4 and 7 that do not allow for immediate and unambiguous understanding of the scope of any of these claims, i.e. which subject-matter is encompassed and which is not. This applies particularly to claim 7 comprising 15 of such and/or combinations. Furthermore, the Applicant's attention is drawn to the fact that expressions like *preferably* used in claim 1 'have no limiting effect on the scope of the claim', i.e. they are regarded 'as **entirely optional**' (Guidelines, C-IV, 4.9). The subject-matter of claim 1 therefore is considered as directed to *a vector* - as well as claims 2 - 4 referring back to it.

In line with the above, the present set of claims does not meet the requirements of Art. 84 EPC with regard to conciseness either.

Moreover, there is no technical evidence that might be considered *fair* support that the retrovirus of claim 7 comprising the nucleic acid sequence of SEQ ID NO: 19 from base pairs 8877 - 9353 'and / or' (a) further heterologous nucleic acid sequence(s) such as SEQ ID NO: 3, 5, 11, 13, 15, 17 would result in the same technical effect as pAC3-CD2 (T5.0002) (cf. Example 6, [00164], p.68, l. 2 - 4, Fig. 6; Example 7, [00166], p.69, l. 5 - 10). The subject-matter of claims 12 and 13 in as far as they refer back to these embodiments do not meet the requirements with regard to clarity and support either.

The Applicant is reminded of the fact that the expression '*...for treating a subject*' does not further define the polynucleotide of claim 10 since it is construed as '*suitable for*' according to the Guidelines F-IV, 4.13. However, it leaves the reader in doubt whether the underlying idea was to claim the medical use of the respective compound. In that case, the wording needs to be amended and the proper format employed. The same objections apply to the present wording of claims 12 and 13.

SEQ ID NO: 19 and 20 appear to be identical - however, back references in claim 7 suggest that they comprised sequence variations with regard to e.g. the promoters encompassed therein. Moreover, reference to claim 20 has been deleted in claims 9, 11 and 18, and thereby indicating that it could be omitted.

In order to improve clarity of claim 1, its wording should be amended so that it reads

'A vector comprising... polynucleotide comprising base pairs 8877 - 9353 of SEQ ID NO: 19...'

3 **NON UNITY** (Art. 82 EPC)

- 3.1 The objections raised in the previous communication (ESOP) have been overcome by the amendments and therefore, are no longer maintained.

4 **NOVELTY** (Art. 54 EPC)

- 4.1 1YSB_B (161 aa) disclosed in D1 comprises the polypeptide of SEQ ID NO: 4 (158 aa), i.e. is identical for 158 amino acids (aa), and has an N-terminal extension of 3 aa.

- 4.2 As the nucleotide sequence encoding 1YSB_B (cf. D1) was *not* publically available, the examiner assumes that the '*... polynucleotide comprising base pairs 8877 - 9353 of SEQ ID NO: 19*' referred to in claim 1 was novel

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over the nucleic acid sequence encoding 1YSB_B. Therefore, the subject-matter of claims 1 and any claims referring back to it or being dependent thereof is novel in the sense of Art. 54 EPC.

5 INVENTIVE STEP (Art. 56 EPC)

- 5.1 D2 is considered as closest prior art to the subject-matter of claim 5 and discloses a (mammalian expression) vector comprising a polynucleotide encoding a protein which has cytosine deaminase activity (p. 866, left-hand side column, second paragraph).
- 5.2 The subject-matter of claim 1 differs from this known vector with regard to the nucleic acid sequence of the polynucleotide encoding such a polypeptide.
- 5.3 The technical effect associated with this difference appears to be the increase in specific activity of cytosine deaminase in tissue culture cells (cf. Example 6, [00164], p.68, l. 2 - 4, Fig. 6) and increased antitumor efficiency (cf. Example 7, [00166], p.69, l. 5 - 10).
- 5.4 The problem to be solved is considered as the provision of a further vector for the expression of another polynucleotide encoding a protein with improved functional properties.
- 5.5 As neither D2, nor any of the other documents cited provided an incentive or suggested the modifications introduced into the nucleotide sequence encoding cytosine deaminase (CD), the solution proposed in claim 1 is considered as non-obvious. Fig. 1 of D2 already depicts A23L, V108L and I140L which were modified in order to increase thermal stability (cf. p. 55, [00140] of the description) but different constructs were used for the *in vivo* experiments described in D2 (cf. Fig. 2). In view of the state of the art, it appears unlikely that the skilled person would have arrived at the solution of claim 1 and therefore, an inventive step could be acknowledged provided that the wording of said claim were limited to a scope that can be considered as meeting the requirements of Art. 84 EPC with regard to clarity / support and further more as commensurate with the application's contribution to the state of the art: as a technical effect was only observed for pAC3-CD2 (T5.0002) and not for any of the other embodiments referred to or encompassed by the various and/or combinations of e.g. claims 7, the present set of claims needs to be amended as suggested above.

6 COMMENT

- 6.1 The Applicant is requested to file new claims which take account of the above comments.

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- 6.2 In order to facilitate the examination of the conformity of the amended application with the requirements of Art. 123(2) EPC, the Applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.
- If the Applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.
- 6.3 When filing amended claims the Applicant should at the same time bring the description into conformity with the amended claims. Any reference to subject-matter excluded from patentability (Art. 53(c) EPC) should be deleted or indicated as background art or information useful for understanding the disclosure. Care should be taken during revision, especially of the introductory portion and any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Art. 123(2) EPC).
- 6.4 To meet the requirements of Rule 42(1)(b) EPC, the documents D1 - D3 should be identified in the description and their relevant content should be indicated. The Applicant should ensure that it is clear from the description which features of the subject-matter of independent claims 1, 18 and 20 are known from these documents.



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NOTICE OF ALLOWANCE AND FEE(S) DUE

26138 7590 02/18/2014
Joseph R. Baker, APC
Gavrilovich, Dodd & Lindsey LLP
4660 La Jolla Village Drive, Suite 750
San Diego, CA 92122

EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 02/18/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/072,705	03/26/2011	Harry E. Gruber	00014-007US1	6574

TITLE OF INVENTION: GENE THERAPY VECTORS AND CYTOSINE DEAMINASES

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	05/19/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or **Fax** (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26138 7590 02/18/2014
Joseph R. Baker, APC
Gavrilovich, Dodd & Lindsey LLP
4660 La Jolla Village Drive, Suite 750
San Diego, CA 92122

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/072,705	03/26/2011	Harry E. Gruber	00014-007US1	6574

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nonprovisional	SMALL	\$480	\$0	\$0	\$480	05/19/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
MARVICH, MARIA	1633	435-320100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. Use of a **Customer Number is required.**

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
- (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1	_____
2	_____
3	_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/072,705	03/26/2011	Harry E. Gruber	00014-007US1	6574
26138 7590 02/18/2014				
Joseph R. Baker, APC Gavrilovich, Dodd & Lindsey LLP 4660 La Jolla Village Drive, Suite 750 San Diego, CA 92122				
EXAMINER MARVICH, MARIA				
ART UNIT PAPER NUMBER				
1633				

DATE MAILED: 02/18/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 205 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 205 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Notice of Allowability	Application No. 13/072,705	Applicant(s) GRUBER ET AL.	
	Examiner MARIA MARVICH	Art Unit 1633	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to an after final 1/22/14.
☐ A declaration(s)/affidavit(s) under 37 CFR 1.130(b) was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are 1,3-5,7-9,11-21,23-26 and 29-52. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)	5. ☒ Examiner's Amendment/Comment
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____	6. ☐ Examiner's Statement of Reasons for Allowance
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material	7. ☐ Other _____
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____	

/MARIA MARVICH/ Primary Examiner, Art Unit 1633	
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DETAILED ACTION

The present application is being examined under the pre-AIA first to invent provisions. This action is in response to an after final amendment filed 1/22/14. Claims 1, 3-5, 7-9, 11-21, 23-26 and 29-52 are pending in this application.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in an interview with Joseph Baker on 2/13/14.

The application has been amended as follows:

IN THE CLAIMS:

Cancel claims 6, 10, 22, 27, 28 and 53-58

Claim 4. (Currently Amended) The isolated polynucleotide of claim 1, further comprising a UPRT or OPRT polynucleotide encoding a polypeptide having UPRT or OPRT activity operably linked to the polypeptide having CD activity wherein the UPRT or OPRT polynucleotide is separated from the polynucleotide encoding the polypeptide having CD activity by a linker.

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Claim 7. (Currently Amended) An isolated polynucleotide comprising: a first coding sequence comprising SEQ ID NO:3 ~~the polynucleotide of claim 1~~ encoding a polypeptide having cytosine deaminase ~~activity~~; and a second coding sequence encoding [[a]] an UPRT or an OPRT polypeptide ~~having UPRT or OPRT activity~~ wherein the first coding sequence is operably linked to the second coding sequence.

Claim 8. (Currently Amended) The isolated polynucleotide of claim 7, wherein the first and the second coding sequences are separated by a nucleic acid sequence encoding a peptide linker.

Claim 11. (Currently Amended) A vector comprising [[a]] the polynucleotide of claim 1.

Claim 14. (Currently Amended) The vector of claim 11, wherein the vector ~~comprises~~ is a viral vector.

Claim 15. (Currently Amended) The vector of claim 14, wherein the viral vector ~~comprises~~ is a replication competent retrovirus.

Claim 16. (Currently Amended) An ~~in-vitro~~ in vitro host cell containing the vector of claim 12.

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Claim 17. (Currently Amended) An ~~in-vitro~~ in vitro host cell comprising a polynucleotide of claim 1

Claim 18. (Currently Amended) The ~~in-vitro~~ in vitro host cell of claim 17, wherein the host cell is a human cell.

Claim 19. (Currently Amended) The ~~in-vitro~~ in vitro host cell of claim 18, wherein the host cell ~~comprises~~ is a cell comprising a cell proliferative disorder.

Claim 20. (Currently Amended) The ~~in-vitro~~ in vitro host cell of claim 17, wherein the host cell ~~comprises~~ is a stably transformed human cell.

Claim 21. (Currently Amended) The ~~in-vitro~~ in vitro host cell of claim 19, wherein the host cell ~~comprises~~ is obtained from a glioblastoma multiforme.

Claim 23. (Original) A recombinant replication competent retrovirus (RCR) comprising:

a retroviral GAG protein;

a retroviral POL protein;

a retroviral envelope;

a retroviral polynucleotide comprising Long-Terminal Repeat (LTR) sequences at the 3' end of the retroviral polynucleotide sequence, a promoter sequence at the 5' end of the retroviral polynucleotide, said promoter being suitable for expression in a mammalian cell and operably

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linked to[[.]] a gag nucleic acid that encodes the GAG protein domain, a pol nucleic acid that encodes the POL protein domain and an env nucleic acid that encodes the retroviral envelope domain;

a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid comprising a polynucleotide of claim 1, wherein the cassette is positioned 5' to the 3' LTR and 3' to the ~~env~~ env nucleic acid ~~domain~~ encoding the retroviral envelope; and

cis-cis-acting sequences necessary for reverse transcription, packaging and integration in a target cell.

Claim 31. (Currently Amended) The retrovirus according to claim 23, wherein the promoter comprises a CMV promoter ~~having a sequence as set forth in SEQ ID NO:19, 20, or 22 from nucleotide 1 to about nucleotide 582 and may include modification to one or more nucleic acid bases and which is capable of directing and initiating transcription.~~

Claim 35. (Currently Amended) The retrovirus of claim 34, wherein the CMV-R-U5 domain polynucleotide comprises a sequence as set forth in SEQ ID NO:19, 20, or 22 from ~~about~~ nucleotide 1 to ~~about~~ nucleotide 1202 or sequences that are at least 95% identical to a sequence as set forth in SEQ ID NO:19, 20, or 22, wherein the polynucleotide promotes transcription of a nucleic acid molecule operably linked thereto

Claim 37. (Currently Amended) The retrovirus of claim 36, wherein the *gag* nucleic acid ~~domain~~ comprises [[a]] the sequence from ~~about~~ nucleotide number 1203 to ~~about~~ nucleotide 2819 of SEQ ID NO: 19 or a sequence having at least 95%, 98%, 99% or 99.8% identity thereto.

Claim 38. (Currently Amended) The retrovirus of claim 23, wherein the *pol* ~~domain~~ of the polynucleotide is obtained from a gammaretrovirus.

Claim 39. (Currently Amended) The retrovirus of claim 38, wherein the *pol* ~~pol domain~~ nucleic acid comprises [[a]] the sequence from ~~about~~ nucleotide number 2820 to ~~about~~ nucleotide 6358 of SEQ ID NO:19 or a sequence having at least 95%, 98%, 99% or 99.9% identity thereto.

Claim 40. (Currently Amended) The retrovirus of claim 23, wherein the *env* ~~domain~~ nucleic acid comprises [[a]] the sequence from ~~about~~ nucleotide number 6359 to ~~about~~ nucleotide 8323 of SEQ ID NO:19 or a sequence having at least 95%, 98%, 99% or 99.8% identity thereto.

Claim 42. (Currently Amended) The retrovirus of claim 41, wherein the IRES comprises [[a]] the sequence from ~~about~~ nucleotide number 8327 to ~~about~~ nucleotide 8876 of SEQ ID NO:19 or a sequence having at least 95%, 98%, or 99% identity thereto.

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Claim 46. (Currently Amended) The retrovirus of claim 23, wherein the heterologous nucleic acid comprises nucleotides 8877-9353 ~~a sequence as set forth in~~ of SEQ ID NO: 19 ~~from about nucleotide number 8877 to about 9353.~~

Claim 49. (Currently Amended) The retrovirus of claim 48, wherein the 3' LTR comprises nucleotides 9405-9353 ~~a sequence as set forth in~~ SEQ ID NO:19 ~~from about nucleotide 9405 to about 9998~~ or a sequence that is at least 95%, 98% or 99.5% identical thereto.

Claim 50. (Currently Amended) The retrovirus of claim 23, wherein the retroviral polynucleotide comprises the sequence as set forth in SEQ ID NO:19, 20, or 22.

Conclusion

The claims have been renumbered in the following order: 1, 3, 4, 5, 7, 8, 9, 11, 12, 16, 13, 14, 15, 17, 18, 19, 21, 20, 23, 24, 25, 26, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 46, 47, 48, 49, 50, 51, 52.

Claim 4 is amended to incorporate the limitations of claim 6 as claim 4 is actually a duplicate of claim 7 while claim 6 is not. Claim 7 has been amended so that all dependent claims have proper antecedent basis. The amendment has led to confusion as to which is "the polynucleotide" i.e. recited in the dependent claims. As well, UPRT is misspelled. Claims 8 and 11 are amended to add the article "the" to provide clearer antecedent basis.

Claims 18-21 are amended for reasons set forth in the office actions mailed 3/29/13 and 10/22/13. Additional amendment to these claims to italicize words has been made.

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Claim 22 is drawn to an *in vitro* host cell. But, the host cell is described as “transformed *in vivo*”. This is contradictory and unclear. The cell cannot be *in vitro* and *in vivo*.

Claim 23 was amended to clarify antecedent basis and as well to delete reference to “domain” which suggests only part of the sequence.

Claim 27 and 28 are cancelled as it does not further limit the structure of claim 23. In other words, the fact that the cell is of a particular type does not alter the retroviral structure.

Claim 31 was simplified to encompass a CMV promoter as a CMV promoter with one or more modifications does not have an upper limit of modifications. To this end, a CMV promoter is well known in the art. For similar reasons, claims 35, 36, 37, 38, 39, 40, 42, 46, 49 and 50 are amended to delete too broad references such as “about” or “as set forth in”.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/MARIA MARVICH/
Primary Examiner, Art Unit 1633

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INTELLECTUAL
PROPERTY
OFFICE

LETTERS PATENT

Number **592070**

ELIZABETH THE SECOND, by the Grace of God Queen of New Zealand and Her Other Realms and Territories, Head of the Commonwealth, Defender of the Faith; To all to whom these presents shall come, Greeting:

WHEREAS pursuant to the Patents Act 1953 an application has been made for a patent of an invention for

GENE THERAPY VECTORS AND CYTOSINE DEAMINASES

(more particularly described in the complete specification relating to the application)

AND WHEREAS

Tocagen Inc., 3030 Bunker Hill Street, Suite 230, San Diego, CA 92109, United States of America

(hereinafter together with his or their successors and assigns or any of them called "the patentee") is entitled to be registered as the proprietor of the patent hereinafter granted:

Address for service: CULLEN & CO, Level 32, 239 George Street, Brisbane, QLD 4001, Australia

NOW, THEREFORE, We by these letters patent give and grant to the patentee our special licence, full power, sole privilege, and authority, that the patentee by himself, his agents, or licensees and no others, may subject to the provisions of any statute or regulation for the time being in force make, use, exercise and vend the said invention within New Zealand and its dependencies during a term of twenty years from 26 September 2009 and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the said term:

AND WE strictly command all our subjects whomsoever within New Zealand and its dependencies that they do not at any time during said term either directly or indirectly make use of or put into practice the said invention, nor in any way imitate the said invention without the consent, licence, or agreement of the patentee in writing under his hand, on pain of incurring such penalties as are prescribed by law and of being answerable to the patentee according to law for his damages thereby occasioned:

PROVIDED ALWAYS:

- (1) That these letters patent shall determine and become void if the patentee does not from time to time pay the renewal fees prescribed by law in respect of the patent:
- (2) That these letters patent are revocable on any of the grounds prescribed by the Patents Act 1953 as grounds for revoking letters patent:
- (3) That nothing in these letters patent shall prevent the granting of licences in the manner in which and for the considerations on which they may by law be granted:
- (4) That these letters patent shall be construed in the most beneficial sense for the advantage of the patentee.

IN WITNESS whereof We have caused these letters patent to be signed and sealed on 5 November 2012 with effect from 26 September 2009.



Neville Harris

Neville Harris
Commissioner of Patents, Trade Marks and Designs

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