

Clarke, M
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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P-2347

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

Re: Expediente No.09-123.789
Solicitud de patente a nombre de INVIRAGEN, INC.

Yo, DILIA MARIA RODRIGUEZ D'ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, de la sociedad INVIRAGEN, INC. domiciliada en Colorado, Estados Unidos de América, solicitante de la patente de la referencia, interpongo recurso de reposición contra la resolución No. 15237 emitida el 5 de abril de 2013 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

En relación con los argumentos presentados por ese despacho en la resolución impugnada No. 15237 emitida el 5 de abril de 2013, es necesario señalar que carecen de un enfoque adecuado de conformidad con las normas, jurisprudencia y reglas técnicas que existen para evaluar la altura inventiva de una invención.

1.1 Violación de los artículos 14, 16 y 18 de la Decisión 486 por una indebida aplicación de la norma basada en un error de interpretación de la misma.

En la resolución impugnada se indica que “La diferencia entre la invención definida en la reivindicación 1 y el kit divulgado e [sic] el documento D1 es el uso de albumina sérica en la composición. El efecto que logra el hecho de incluir albumina consiste en reducir la inactivación el virus vivo atenuado a temperaturas entre 4 y 37°C

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: cómo modificar la composición presente en la forma de kit divulgada en el documento D1 para obtener una composición alternativa de virus vivos atenuados, estable a temperaturas entre 4 y 37°C.

Sin embargo, el documento D2 divulga que polímeros como la albúmina sérica humana estabilizan el material biológicamente activo en contra de la inactivación, previniendo el colapso del material durante la liofilización y permitiendo su almacenamiento en estado sólido (Pág. 34, Párr. 116).

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En consecuencia, la persona del oficio normalmente versada en la materia, utilizaría un albúmina como la que se da a conocer en el documento D2 en la composición del documento D1 para llegar así al kit objeto de la reivindicación 17 de la solicitud. Por lo cual, la materia reclamada se considera obvia.

Puesto que las reivindicaciones dependientes 18 - 23 no mencionan características inventivas adicionales tampoco se pueden considerar inventivas.

La solicitante señala que todos los virus de la solicitud son virus envueltos y que por sus características similares pueden ser protegidos de la degradación por la formulación descrita; sin embargo, se observa que las reivindicaciones independientes no especifican que se trate de virus envueltos y solo se refieren en forma general a virus vivos atenuados, por lo anterior dicho elemento no puede considerarse característico de las composiciones reclamadas.

En referencia al argumento de la solicitante, según el cual las composiciones de los documentos D1 y D2 no comprenden poloxámero 407, es de resaltar que en las reivindicaciones independientes se entiende que al indicar entre "el uno o más copolímeros de bloque" al pluronic, este se encuentra incluido y por lo tanto anticipado por las anterioridades.

La solicitante afirma que la composición de la solicitud se puede administrar por una variedad de modos y no se refiere a formulaciones intranasales como las del documento D1. Al respecto se aclara que la vía de administración no se indicó como una característica técnica de la composición de acuerdo con lo establecido en la reivindicación 1 y según lo afirmado por la solicitante, esa variedad de modos podría incluir la intranasal.

En conclusión, teniendo en cuenta que los argumentos de la solicitante no desvirtúan de manera alguna las objeciones a la patentabilidad ya sustentadas, el Superintendente de Industria y Comercio,"

Sobre este particular, es importante hacer énfasis sobre el hecho que D1 se encuentra dirigido a métodos para proporcionar secado por congelación y por pulverización de formulaciones para formar partículas estables liofilizadas para administración **intranasal** (por favor, ver el resumen de D1). De hecho, esta anterioridad sugiere y reporta una lista interminable de polioles, polímeros y tensioactivos que pueden o no pueden ser empleados en los métodos descritos en el apartado 14 en la página 6 de esta referencia.

Aunado a lo anterior, si una persona medianamente versada en la materia técnica correspondiente, se fija en el Ejemplo 1 que comienza en la página 49 de D1 que describe tres formulaciones que tienen sacarosa, trehalosa, metionina, arginina y Pluronic F68; sacarosa, gelatina, metionina o Pluronic F68, o sacarosa, gelatina y Pluronic F68 de uso para rociar en congelación seca virus influenza, no encontraría ninguna sugerencia para llegar de manera evidente a la presente invención, dado que D1 **falla en reportar o sugerir composiciones para el uso de virus atenuados vivos y estabilizados.**

En este orden de ideas, es importante hacer hincapié sobre el hecho que el virus de la gripe **no es un virus vivo atenuado** de las reivindicaciones actuales y **D1 no da a conocer que las composiciones reivindicadas requieren los tres componentes**, uno o más hidratos de carbono, proteínas y uno o más uno o más copolímeros de bloque EO-PO. Además, D1 no enseña ni sugiere que las formulaciones incluyan poloxámero 407 y uno o más

de trehalosa o de quitosano, que corresponden a los elementos específicos de las reivindicaciones negadas.

Por lo tanto, consideramos que un experto medianamente formado en la técnica, no llegaría de manera evidente a las composiciones reivindicadas y métodos de la presente invención con solo las enseñanzas de esta anterioridad en combinación con D2. En gracia de discusión, dicha persona lo podría llegar a hacer mediante el conocimiento previo de la presente invención, lo cual es un hecho retrospectivo que menoscaba la actividad inventiva de la presente invención.

Otro hecho significativo es que las composiciones reportadas en la anterioridad D1 se encuentran dirigidas a los productos generados por los métodos de D1 (véase el resumen y los párrafos [0012] - [0018]) adecuadas para administración intranasal. Por lo tanto, los componentes de las formulaciones dadas a conocer por este documento se seleccionan para ese propósito.

Nuevamente y de manera respetuosa dirigimos la atención del señor examinador al párrafo [0068] de D1, donde se recita *"En los métodos de la invención, los polioles pueden proporcionar, por ejemplo, un agente incrementador de la viscosidad para reducir los efectos de la tensión de cizalla durante la pulverización. Los polioles pueden proporcionar barreras protectoras y las químicas a las partículas de polvo liofilizado de la invención"*.

Por consiguiente, los polímeros se pueden introducir en las formulaciones de D1 como *"Las hebras lineales o ramificadas de los polímeros puede proporcionar, por ejemplo, el aumento de resistencia estructural a la partícula composiciones de la invención. Los polímeros se pueden aplicar como un protector y / o recubrimiento de liberación tiempo para el exterior de las partículas liofilizadas de la invención "y beneficio" reconstitución de partículas liofilizadas"*. D1 preferiblemente selecciona *"gelatina hidrolizada"* de estas ventajas (véase el párrafo [0069] de D1).

En cuanto al tensioactivo, D1 enseña que *"Un agente tensioactivo puede aumentar la solubilidad de otros componentes de formulación para evitar la agregación o precipitación en concentraciones más altas"* (véase el párrafo [0070] de D1).

Es importante señalar en este punto que las reivindicaciones negadas difieren de lo divulgado en D1, así como también en los componentes incluidos en las formulaciones actualmente reivindicadas en que se seleccionan para estabilizar los virus vivos atenuados. Las composiciones de la presente invención se pueden administrar por una variedad de modos y no se refieren

a formulaciones intranasales como las de D1 (Véase los Ejemplos 1-4, las Figs. 1-4 y 6-7, y las Tablas 1-4 de la presente solicitud presentada originalmente). Por lo tanto, una persona medianamente versada en la materia técnica correspondiente no vería para nada obvio hacer una trasportación de las características técnicas indicadas en D1 a formulaciones reivindicadas para estabilizar los virus vivos atenuados.

En este sentido, es importante señalar que se observaron inesperados efectos de las composiciones reclamadas a partir de experimentos de comparación realizadas en paralelo con otras composiciones (Ver Ejemplo 5, Figs. 4-5 de la presente solicitud) y controles. Por lo tanto, D1 no divulga o sugiere la invención aquí reivindicada.

Ahora bien, en cuanto al documento D2, la resolución impugnada indica que *“Sin embargo, el documento D2 divulga que polímeros como la albumina sérica humana estabilizan el material biológicamente activo en contra de la inactivación, previniendo el colapso del material durante la liofilización y el almacenamiento en estado sólido...”*

Sobre este particular, nuevamente nos permitimos insistir sobre el hecho que D2 reporta una composición de virus vivo atenuado que comprende virus vivo atenuado, un poliol, un polímero y un agente tensioactivo en el que el poliol incluye sacarosa, trehalosa, sorbitol y manitol y otros componentes (consulte la página 5, párrafo 16 a través de la página 7, párrafo 20, página 36, ejemplo 1, página 37-página 43, ejemplo 2).

Los solicitantes respetuosamente manifiestan su desacuerdo con esta afirmación. Los inventores respetuosamente indican que D2 en el párrafo 16 en la página 5 hasta el párrafo 20, en la página 7, proporciona una larga lista de posibles polioles, polímeros y tensioactivos, entre los cuales se encuentra la albúmina sérica humana como una de tantas opciones para los polioles.

No obstante, si una persona medianamente versada en la materia técnica se fija en lo reportado en D2, podría corroborar que las formulaciones descritas en D2 principalmente en los Ejemplos 1 y 2 proporcionan gelatina como polímero, F68 como el tensioactivo y sacarosa o rafinosa como los polioles.

En este sentido, es importante dirigir la atención de ese despacho sobre el hecho que D2 no da a conocer la composición reivindicada actualmente de uno o más virus atenuados vivos, uno o más de PO-EO copolímeros de bloque que incluyen poloxámero 407 (Pluronic F127 ®); agentes de una o más proteínas son uno o más albúminas, y uno o más agentes de hidratos

de carbono incluyen trehalosa y/o quitosano en donde la composición es capaz de reducir la inactivación del virus vivo atenuado, elementos de las reivindicaciones independientes 1, 12 y 22. En ninguna parte de D2 existe una composición similar descrita o sugerida. Por lo tanto, una persona llegaría a las composiciones actualmente reivindicadas en la solicitud negada a partir de D2 y D1 únicamente con el conocimiento previo de la presente invención.

Sumado a lo anterior, resulta importante señalar que las reivindicaciones de D2 se encuentran dirigidas a "*métodos y composiciones para preservar materiales bioactivos en una matriz de espuma seca*" (ver el resumen de D2). Además, D2 reporta "*procesos de expansión de una formulación del material bioactivo y un poliol en una espuma seguido por secado de la espuma en una composición seca de la espuma estable*" (véase el resumen de la invención el párrafo [0011] de D2).

Además, esta anterioridad se refiere a una composición de espuma seca para el almacenamiento de una composición de virus en dicha espuma (véanse también los párrafos [0036], [0038], [0061]-[0069], [0074], [0111], los ejemplos y las reivindicaciones). Los polímeros descritos en la D2 se enseñan para proporcionar componentes estructurales en las composiciones de espuma seca (véase el párrafo [0019] de D2).

Con respecto a la membrana lipídica o la matriz vítrea, en D2 se describen los requisitos específicos de temperatura para la preparación de la espuma seca a partir de los lípidos de membranas (véase por ejemplo Resumen de la invención de D2).

Sobre este particular, es importante señalar que en D2 se requiere un sólido que se forma (una espuma). De hecho, las formulaciones de D2 no corresponden a las formulaciones descritas en las reivindicaciones de la solicitud que están dirigidas a la estabilización de composiciones de virus atenuados vivos.

Además, la invención aquí reivindicada no alcanzaría los efectos deseados referenciados por el examinador en cuanto a los ejemplos 1 y 2 de la anterioridad D2, toda vez que de acuerdo con D2, la preparación y uso de formulaciones secas de espuma requieren Pluronic F68, gelatina, sacarosa y una solución amortiguadora de metionina en sus formulaciones (véase, por ejemplo, los párrafos [0122] - [0125]; Ejemplo 1 y 2 de D2).

Así las cosas, la formulación que se especifica en las reivindicaciones independientes 1, 12 o 22 de la presente solicitud no se enseñan o sugieren en el documento D2.

En este sentido, amablemente nos permitimos decir que la presente solicitud describe que "Sin embargo, tal como se demostró en la presente, se observó un inesperado mejoramiento de la estabilidad con la combinación de una albúmina y copolímeros de bloque EO-PO lo cual sugiere interacciones entre los dos componentes y/o entre los componentes y las partículas virales. Además, el aumento de la estabilización de virus en presencia de albúmina no es probable debido a que funciona como proteína portadora en general: otras proteínas tales como gelatina y lactoferrina no mejoran la estabilidad del virus" (véase el párrafo [00054] de la solicitud presentada).

Por lo tanto, el simple uso de albúmina o su mezcla con copolímeros diferentes a EO-PO, no proporciona las ventajas de la invención. De hecho, el aporte de la presente invención es precisamente dicha combinación para lograr la estabilización de los virus atenuados. Además, como bien se indica en la memoria descriptiva, la gelatina de la técnica anterior no es un sustituto en la composición actualmente reivindicada, ya que no funcionó.

Además, también era conocido en la técnica en el momento de presentar la presente invención que "la gelatina pueden causar reacciones alérgicas en niños inmunizados y puede ser causa de eventos adversos relacionados con la vacuna" (véase el párrafo [00045] de la presente solicitud), que podrían comprometer sus usos potenciales en composiciones de vacunas relacionadas de la presente solicitud. Por lo tanto, la gelatina de D1 o D2 se aparta de las presentes formulaciones y por lo tanto, indicar, que el uso de la albúmina sérica humana en lugar de gelatina era evidente, resulta a todas luces una simplificación desacertada del problema técnico abordado por la presente invención.

En conclusión, es claro que D1 y D2 no describen, ni muestran ni sugieren al un experto en la técnica las formulaciones de la presente invención. La combinación de una espuma liofilizada y una congelación de aerosol para administración intranasal no se presenta en las formulaciones actualmente reivindicadas para estabilizar un virus vivo y atenuado.

Además, tanto D1 como D2 se refiere a formulaciones de virus de influenza no formulaciones para los virus vivos atenuados alegadas (ver las reivindicaciones 2, 13, 21 y 28 de las actuales reivindicaciones).

En conclusión, dadas las enseñanzas de D1 y D2, el experto en la técnica no estaría motivado para generar la composición reivindicada actualmente

utilizando albúmina en lugar de gelatina. Además, como se presentó anteriormente, el efecto logrado por las composiciones de la invención en la reducción de la inactivación de un virus vivo y atenuado no se espera por un experto en la técnica en el momento de la presentación de la presente solicitud.

Sobre este particular, nos permitimos recalcar que el análisis de nivel inventivo indicado en la resolución impugnada es claramente el resultado de un análisis del tipo "hindsight" o retrospectivo. De hecho, este tipo de análisis no es permitido para desvirtuar el concepto de altura inventiva.

En este tipo de análisis, el examinador no enfoca su análisis en el momento en el que el solicitante plantea un problema con el fin de solucionar fallas técnicas existentes en los productos convencionales de un campo técnico específico, sino que se enfoca en la solución dada al problema planteado y en la búsqueda de documentos con conceptos análogos. A este respecto dirijo la atención del examinador al "Manual para Examen de Solicitudes de Patentes de Invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina, publicado en la página Web de la Comunidad Andina, donde se establece en la página 74 en cuanto al nivel inventivo "...que la búsqueda de anterioridades se efectúa a posteriori, tomando como punto de partida la misma invención,...el examinador debe realizar el esfuerzo intelectual de colocarse en la situación que ha tenido que afrontar el técnico con conocimientos medios en la materia en un momento en que la invención no era conocida, es decir antes de la invención".(El subrayado es nuestro)

En el presente caso, para el examinador puede resultar "obvio" que el objeto de la presente solicitud se derive de la materia objeto del documento citado sin dar mayor importancia al trabajo desplegado y a la capacidad inventiva del solicitante para lograr llegar a la solución del problema planteado. Es decir, que el examinador no hace su análisis partiendo del problema mismo que existía en la técnica en el momento en que el solicitante dirige todos sus esfuerzos para encontrar una solución, sino que enfoca su estudio en el momento en que el problema ya fue resuelto.

Consideramos que el examinador no ha razonado y documentado correctamente la resolución que se impugna, por lo que se ha incumplido con los artículos 14, 16 y 18 de la decisión 486 de la Comunidad Andina de Naciones, por lo que procede la reposición del presente trámite.

Finalmente, es deseo del solicitante informar a ese despacho que la correspondiente solicitud ha sido presentada y concedida en otros países como Nueva Zelanda (Anexo 1), Japón (Anexo 2), Estados Unidos (Anexo 3), Australia (Anexo 4), Israel (Anexo 5). Por lo tanto, resulta sorprendente que

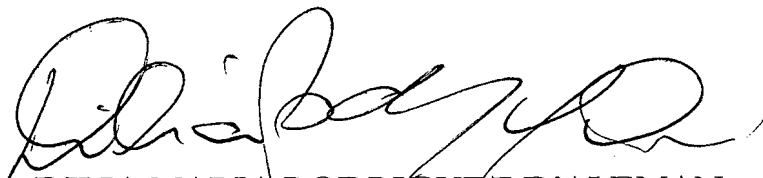
los requisitos de patentabilidad cuya definición es prácticamente la misma a nivel mundial no hayan sido aceptados tan solo en Colombia.

2. 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. 15237** emitida el 5 de abril de 2013 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,



DILIA MARIA RODRIGUEZ D'ALEMAN

CC. 41.654.882

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Clarke, Modet & Cº

COLOMBIA

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ANEXO 1

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ANEXO 1

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11 December 2012

By email and post

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Received

DEC 17 2012

Faegre BD IP Docket

Dear Dr Hanson

GRANT OF PATENT

New Zealand patent 580978

Your ref 78484-384336 Our ref 613069 JBA

We are pleased to report that this patent has been granted in New Zealand. We enclose the Deed of Letters Patent. Here are the details of your patent.

Proprietor	Inviragen, Inc.
Title	METHODS AND COMPOSITIONS FOR LIVE ATTENUATED VIRUSES
Date of grant	5 November 2012
Term	20 year term commences 4 April 2008 Expires 4 April 2028
Renewal fees due	5 March 2013 4 April 2015 4 April 2018 4 April 2021
First renewal (fee estimated)	US\$420

Renewing this patent

This patent has been granted after the first renewal fee would normally have been due. As a result, the first renewal fee is now due within four months from the date of grant.

The previous firm of Faegre & Benson advised we would not be responsible for renewals but we have assumed this instruction is maintained with Faegre Baker Daniels LLP. Please let us know if this is incorrect.

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• innovation protected • integrated processes • intelligent people • increasing potential

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NEW ZEALAND •
AUSTRALIA

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Although you have instructed us that your annuity service will be responsible for paying the renewal fees, we have entered the details of this patent into our records in case you wish us to pay the first renewal fee due. We will not send you any renewal reminders.

Marking products with details of the patent

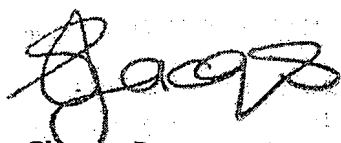
Although marking patented inventions is not compulsory in New Zealand, we recommend using the words 'Patented New Zealand No. 580978' on your patented article. Marking your invention with details of your patent safeguards you against any infringer raising the defence of 'innocent infringement' to a damages claim.

Compulsory licence

In a compulsory licence, the government forces the owner of a patent to grant use of the patent to a third party. A third party may be granted a compulsory licence to use the invention covered by this patent if you do not 'supply the patent on reasonable terms' within three years after grant or four years after filing (whichever period ends later).

Please contact us if you have any questions.

Yours sincerely



Sheryn Jacques
Manager IP renewals

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INTELLECTUAL
PROPERTY
OFFICE

LETTERS PATENT

Number 580978

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

METHODS AND COMPOSITIONS FOR LIVE ATTENUATED VIRUSES

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

AND WHEREAS

INVIRAGEN, INC., 2619 Midpoint Drive, Suite A, Fort Collins, Colorado 80525, 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: AJ PARK, State Insurance Tower, Level 22, 1 Willis Street, Wellington 6011, New Zealand

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 4 April 2008 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 4 April 2008:



Neville Harris

Neville Harris
Commissioner of Patents, Trade Marks and Designs

Intellectual Property Office of New Zealand

P O BOX 9241, Marlon Square, Wellington 6141, New Zealand or DX SX 11129, Wellington

International: +64 3 962 2607 National: 0508 4 IPONZ (0508 447 669)

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What is claimed is:

1. A live attenuated virus composition comprising:
one or more live, attenuated viruses;
one or more poly(ethylene oxide) and poly(propylene oxide) (EO-PO) block copolymers,
the one or more EO-PO block copolymers include Pluronic F127 (poloxamer 407);
one or more proteins agents, the one or more protein agents include one or more
albumins; and
one or more carbohydrate agents, the one or more carbohydrate agents include trehalose,
wherein the composition is capable of reducing inactivation of the live attenuated virus.
2. The composition of claim 1, wherein the live, attenuated viruses are selected from the
group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus,
Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus
families and combinations thereof.
3. The composition of claim 1, wherein the live, attenuated viruses are Flaviviruses.
4. The composition of claim 1, wherein the composition is in aqueous form.
5. The composition of claim 1, wherein the composition is partially or wholly dehydrated.
6. The composition of claim 1, wherein the one or more albumins are selected from the
group consisting of lactalbumins and serum albumins.
7. The composition of claim 1, wherein one of the one or more protein agents is serum
albumin, and one of the one or more carbohydrate agents is trehalose.

8. The composition of claim 1, wherein the EO-PO block copolymer concentration is from 0.1 to 4% (w/v), wherein protein concentration is from 0.001 to 3% (w/v) and the carbohydrate concentration is from 5 to 50% (w/v).

9. A method for decreasing inactivation of a live, attenuated virus composition comprising, combining one or more live attenuated viruses with a composition comprising one or more poly(ethylene oxide) and poly(propylene oxide) (EO-PO) block copolymers, the one or more EO-PO block copolymers include Pluronic F127 (poloxamer 407); one or more proteins agents, the one or more protein agents include one or more albumins; and one or more carbohydrate agents, the one or more carbohydrate agents include trehalose, wherein the composition is capable of reducing inactivation of the live, attenuated virus.

10. The method of claim 9, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.

11. The method of claim 9, further comprising partially or wholly dehydrating the combination.

12. The method of claim 11, further comprising partially or wholly re-hydrating the composition in preparation of a medicament.

13. The method of claim 9, wherein the composition increases the shelf life of a virus composition when the composition is maintained at room temperature or lower compared to a control composition.

14. The method of claim 9, wherein the composition decreases inactivation of an aqueous, live, attenuated virus during one or more freeze and thaw cycles compared to a control composition.

15. The method of claim 9, wherein at least one EO-PO block copolymer is poloxamer 407, at least one of the one or more protein agents is serum albumin, and at least one of the one or more carbohydrate agents is trehalose.

16. The method of claim 9, wherein the virus composition is a medicament for use in a subject to reduce the onset of or prevent a health condition.

17. The method of claim 16, wherein the health condition is selected from the group consisting of West Nile infection, Dengue fever, Japanese encephalitis, Kyasanur Forest disease, Murray Valley encephalitis, St. Louis encephalitis, Tick-borne encephalitis, Yellow fever and Hepatitis C Virus Infection.

18. A kit for decreasing the inactivation of a live, attenuated virus composition comprising:
at least one container; and
a composition comprising one or more proteins agents, the one or more protein agents include one or more albumins; one or more carbohydrate agents, the one or more carbohydrate agents include trehalose; and one or more poly(ethylene oxide) and poly(propylene oxide) (EO-PO) block copolymers, the one or more EO-PO block copolymers include Pluronic F127 (poloxamer 407), wherein the composition decreases inactivation of a live, attenuated virus.

19. The kit of claim 18, wherein the EO-PO block copolymer is poloxamer 407 the protein agent is serum albumin, and the carbohydrate agent is trehalose.

20. The kit of claim 19, wherein the trehalose concentration is from 5 to 50% (w/v).

21. The kit of claim 18, wherein the EO-PO block copolymer, poloxamer 407 concentration is from 0.1 to 4% (w/v).

22. The kit of claim 18, wherein the serum albumin concentration is from 0.001 to 3% (w/v).

23. The kit of claim 18, wherein the composition further comprises one or more live, attenuated viruses.

24. The kit of claim 23, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.

25. A live attenuated virus composition as defined in claim 1 substantially as herein described with reference to any example thereof.

26. A method as defined in claim 9 for decreasing inactivation of a live, attenuated virus composition substantially as herein described with reference to any example thereof.

27. A kit as defined in claim 18 substantially as herein described with reference to any example thereof.

28. The composition of claim 1, wherein the one or more albumins are serum albumins selected from the group consisting of, bovine serum albumin, canine serum albumin human serum albumin, and other serum albumins.

29. The compositions of claim 1, wherein the composition is a more effective cryoprotectant than its individual agents.

30. The composition of claim 18, wherein the composition is in aqueous form and the composition increases shelf life of the live attenuated virus composition.

31. Any invention as described or claimed herein.



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May 15, 2013
 Via e-mail only

Dr. Roberta Jean Hanson
 FAEGRE BAKER DANIELS LLP
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 Denver
 Colorado 80203-4532
 U.S.A.

Re: Y/R: 478484.384332 O/R: PF 09964
 Japanese Patent Application No. 2010-502331
 'METHODS AND COMPOSITIONS FOR LIVE ATTENUATED
 VIRUSES'
 - INVIRAGEN, INC. -

Dear Dr. Hanson:

We are pleased to inform you that the examiner has decided to grant a patent for this application. We are enclosing a copy of a Certified Copy of the Notice of Allowance. In order to have a patent registered and issued from the application, the registration fee (i.e., the 1st to 3rd year annuities) must be paid by **June 13, 2013**. The official fee is 14,100 yen, and the attorney's fee is 17,000 yen. Further, we charge 9,000 yen and miscellaneous expenses for forwarding a Certificate of Patent. If possible, please provide us with your instructions by **June 3, 2013** as to whether we should proceed with paying the registration fee.

A divisional patent application may be filed within 30 days from the date of a Notice of Allowance, i.e., **June 13, 2013**. If a Decision of Appeal Examination has been entered or payment of the registration fee is completed, it will not be possible to file a divisional application for this case. It is possible to file a divisional patent application without paying the registration fee. Accordingly, please also let us know whether or not you would like to file a divisional application by **June 3, 2013**.

After payment of the registration fee, a patent will be issued and later published.

We look forward to receiving your instructions.

Very truly yours,

ONDA TECHNO
 Intl. Patent Attys.

Miki Kuno
 Miki Kuno (Ms.)

MK/co
 Encls.

Gifu Tokyo Osaka Shanghai www.ondatechno.com

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O/R: PF 09964

Forwarding Number: 310005
Forwarding Date: May 14, 2013

CERTIFIED COPY OF THE NOTICE OF ALLOWANCE

Patent Application No. 2010-502331

Date: May 10, 2013

The Examiner of the Patent Office: Yuzo OTA
Reg. No. 3959 4B00

Title of the Invention: METHODS AND COMPOSITIONS FOR LIVE
ATTENUATED VIRUSES

Number of Claims: 12

Applicant for Patent Application:

INVIRAGEN, INC.

Agent: Hironori ONDA (et al.)

As no reason of rejection is found, it is admitted that this application is to be patented.

This is to certify that this certified copy is not different from the record in our file.

Certified Date: May 13, 2013

Secretary of Ministry of
Economy, Trade and Industry

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特許査定

特許出願の番号	特願2010-502331
起案日	平成25年 5月10日
特許庁審査官	太田 雄三 3959 4B00
発明の名称	弱毒生ウイルスのための方法および組成物
請求項の数	12
特許出願人	インビラジェン, インコーポレイテッド
代理人	恩田 博宣 (外 2名)

この出願については、拒絶の理由を発見しないから、特許査定をします。



上記はファイルに記録されている事項と相違ないことを認証する。

認証日 平成25年 5月13日 経済産業事務官 清野 貴明

注意: この書面を受け取った日から30日以内に特許料の納付が必要です。

Clarke, Modet & Cº

COLOMBIA

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ANEXO 2

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Japanese Patent Application No.: 2010-502331

Your Reference: 478484-384332

DRAFT RESPONSE

1. Gist of Response:

Applicant submits that the present application be allowed as a patent for the following reasons.

2. Summary of Official Action:

The Examiner has rejected claims 1-15 under Sec 29(2) and Sec 29(1)(iii) for being obvious and anticipated in light of Cited References 1-2.

3. Regarding amendment:

Please see the attached Draft Claims - September 7 2012 and Draft Amendments to the Specification - September 7 2012.

Support for these claim amendments can be found throughout the specification but at least at paragraphs [00019], [00020], [00021], [00023], [00024], [00052]-[00058], [00061], [00076], [00078], [00080]-[00084] and [0088] and the claims and the examples of the application as originally filed.

In addition, support for regarding F127® now referred to as poloxamer 407, F68® now referred to as poloxamer 188 and P123® now referred to as poloxamer 403, please see Exhibits Ko. Nos 1-3. Amendments to the specification only encompass corrections of obvious typographical errors and the addition of generic names (poloxamers 407, 188 and 403) to trade names that were already present in original specification (F127®, F68® and P123®)

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4. Regarding the Sec. 29(1)(iii) and 29(2) Rejections
[Anticipation and Obviousness]:

(1) The Examiner alleges claims 1-15 are anticipated in light of Cited References 1 and 2.

The Applicants have amended the claims to further clarify the claimed subject matter and more clearly distinguish the pending claims from the prior art. In addition, the Applicants respectfully point out that the claims of Reference 1 are directed to a method of preparing a *stable dry foam composition or a lyophilized dry foam composition* which requires a *lipid membrane* and a *solvent* (see independent claims 1, 41, 59, and 76) or a *dry foam composition* that requires a *lipid membrane* (see independent claims 95 and 129) or a *dry foam composition* that requires a *glass matrix* (see independent claims 136 and 149). Reference 1 fails to disclose a composition of one or more live, attenuated viruses; where the one or more EO-PO block copolymers include poloxamer 407 (Pluronic F127®); the one or more proteins agents, the one or more protein agents are one or more albumins, and one or more carbohydrate agents that include trehalose, wherein the composition is capable of reducing the inactivation of the live attenuated virus, elements of independent claims 1, 11 and 15. Nowhere in Reference 1 is such a composition disclosed or taught.

Further, the recited reference is directed toward a *dry foam composition for storage of a virus composition in a dry foam* (See Abstract, paragraph [0036], [0038], [0061]-[0069], [0074], [0111], the Examples and the Claims). Polymers required by Reference 1 act as *structural constituents* in

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the dry foam compositions (see paragraph [0019] of Reference 1). With respect to the required lipid membrane or the glass matrix of Reference 1, specific temperature requirements for preparing the dry foam from the lipid membranes are disclosed and required (see for example Summary of the Invention of Reference 1). Reference 1 teaches methods for expanding a formulation for storage and the storage formulation is a dry foam which clearly differs from the instantly claimed invention. Reference 1 requires a solid to be formed with formulations that provide such a consistency which clearly differs from the instant claims. Further, merely mentioning some of the components claimed by the instant application fails to disclose or teach the instantly claimed formulation having unexpected results related to preserving a live, attenuated virus formulation. The formulations of Reference 1 could not be readily used in stabilizing live, attenuated virus compositions of the instant claims. In addition, the instantly claimed invention would fail to achieve the desired effects of Reference 1, namely, preparing and using dry foam formulations which for the benefits sought in Reference 1 required gelatin, sucrose and a methione buffer in its formulations (see for example paragraphs [0122]-[0125]; Example 1 of Reference 1). The specified formula in independent claims 1, 11 and 15 of the instant application are not taught or suggested by Reference 1.

(2)The Examiner alleges that claims 1-15 are obvious in light of Cited References 1-2

The Applicants respectfully submit that Reference 2 fails to

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make up for the missing disclosure of Reference 1. Reference 2 teaches methods for intradermal administration of various formulations. Reference 2 discloses laundry lists of possibilities but fails to disclose the specified formulation of independent claims 1, 11 and 15. Further Reference 2 teaches "Methods of Enhancing Immune Response in the Intradermal Compartment..." Reference 2 teaches compositions and methods for increasing immunogenicity of the formulations disclosed. This teaches away from the instantly claimed formulation which is essentially non-immunogenic, inert (see for example paragraph [00083] of the instant application)

In addition, Reference 2 discloses a dermal vaccine formulation for targeted delivery of an immunogenic composition and at least one molecule enhances the presentation and/or availability of the agent to the immune cells (see abstract of Reference 2). Molecules include one or more pre-selected excipients, or one or more gelling agents, or any combination thereof. Of note, Reference 2 teaches that enhanced efficacy of the compositions of the invention is based, in part, on the appreciation and recognition by the inventors that specific combinations of such agents, can act as adjuvants, resulting in enhanced immune response..." The Applicants respectfully submit that the claims of the instant invention are directed to a formulation that enhances stabilization not, an increase in immunogenicity (see for example, Examples 2-6 and 8; and paragraph [00083] of the instant application as filed). Moreover, mouse data represented in Table 5 found between paragraphs [00084] and [00085] of the application as filed demonstrates that compositions of the present invention are

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essentially inert and do not act to enhance immune response.

In addition, the instant claims are not directed to a formulation for targeted delivery as those of Reference 2. In fact, given the teachings of Reference 2, one skilled in the art would not arrive at the instant invention. One skilled in the art reading Reference 2 would arrive at a composition to enhance immunogenicity in an intradermally administered formulation (see for example paragraph [0101] of Reference 2).

Alternatively, the Applicants respectfully submit that Reference 2 does not disclose or teach that a composition requires three or more agents with at least one agent from each of three categories for stabilizing a live attenuated virus composition, elements of independent claims 1, 11 and 15. Reference 2 fails to disclose or suggest that the composition at minimum must have at least three components including an EO-PO block copolymer; one or more proteins agents, and one or more carbohydrate agents that include trehalose, as presented in the pending claims.

Also, the Applicants respectfully submit that compositions of the instant invention are not directed to methods of intradermal administration. Reference 2 merely discloses laundry lists of possible formulations for enhancing intradermal administration (see paragraphs [0112]-[0144] and the figures of Reference 2). Reference 2 is not directed to formulations of the instant application to stabilize live attenuated virus compositions. Reference 2 fails to provide any direction to stabilizing live attenuated virus compositions because it is directed at enhancing intradermal administration and formulations thereof.

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Therefore, for at least the reasons presented above, rejections based on Reference 2 alone or in combination with Reference 1 are improper. Reference 1, generating dry foam formulations and Reference 2 providing methods and compositions for intradermal administration fail to combine to form the instantly claimed formulations. The Applicants respectfully request that the outstanding anticipation and obviousness rejections be withdrawn.

7. Conclusion:

For the reasons described above, the present application complies with the provisions set forth under Sec 29(2) and Sec 29(1)(iii) of the Japanese Patent Law. The Applicant respectfully requests that the present application be granted as a patent.

8. Exhibits:

1. B. Fussnegger BASF ExAct No. 4, April 2000, pages 7-9
2. BASFT Safety data Sheet Pluronic F68 Prill Poloxamer 188

Revision date: 2006/05/25, Version 2.2

3. xxx

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(Translation)

NOTICE OF REASONS FOR REJECTION

Patent Application No. 2010-502331

Examiner: Yuzo OHTA

Date: April 9, 2012

Mailing Date: April 11, 2012

Applicable Sections: Sec. 29(1) and 29(2)

To: Shusaku YAMAMOTO, Patent Attorney (and two others)

The present application is rejected for the following reasons. Any arguments must be submitted within three (3) months from the mailing date of this document.

REASONS

1. The inventions defined by the following claims of the present application are rejected under Sec. 29(1)(iii) of the Japanese Patent Law as being anticipated by the following cited references published or made available to the public through electric telecommunication lines in Japan or in a foreign country prior to the filing of the present application.

2. The inventions defined by the following claims of the present application are rejected under Sec. 29(2) of the Japanese Patent Law as being obvious to those skilled in the art over the following Cited References published or made available to the public through electric telecommunication lines in Japan or in a foreign country prior to the filing of

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Japanese Patent Application No.: 2010-502331

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the present application.

NOTES (See List of Cited References)

- * REASONS: 1 and 2
- * Claims: 1 to 15
- * Cited References: 1 and 2
- * Remarks:

Cited Reference 1 describes a composition for reducing inactivation of various viruses during preservation, comprising virus, serum albumin, saccharides such as trehalose, sucrose, mannitol and the like and surfactant (Claims).

In addition, it is recognized that F-127 and the like were generally used by those skilled in the art prior to the priority date of the present application as a surfactant used for preserving a virus and the like (if needed, refer to Cited Reference 2 and the like). In addition, comprising an attenuated virus in a virus to be preserved (that is, a vaccine) is common technical knowledge for those skilled in the art.

Therefore, the invention defined by the claims of the present application is substantially described in the above-described Cited Reference 1.

Even if it were not so, based on the descriptions of Cited References 1 and 2, using a composition comprising a surfactant, serum albumin, saccharides such as trehalose to produce a composition which can reduce inactivation of attenuated virus and studying an optimal composition which can reduce inactivation would be obvious to those skilled in the art.

In addition, considering the description of the specification, respective components of the composition are not concretely specified. In addition, it is not recognized that the present application invention comprising matter which does not have function for inactivation of virus attains

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significantly remarkable effect which cannot be expected by those skilled in the art over all of the technical scope of the Claims from the descriptions of Cited References 1 and 2.

Accordingly, the inventions defined by the above-described claims could have been easily achieved based on Cited References 1 and 2 and the well-known technology.

List of Cited References

1. Japanese National Phase PCT Laid-Open Publication No. 2005-538939 (corresponding to International Publication No. WO 2003/087327)
 2. International Publication No. WO 2005/074460
-

Record of search for prior art documents

*Classes searched: IPC C12N 7/00

*Database used for search	PubMed
	CA/ MEDLINE/ BIOSIS/ WPIDS (STN)
	JDreamII
	GeNil

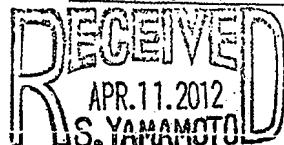
The documents cited in the above record of a search for prior art documents do not form the basis of the reasons for rejection.

If you have any inquiries concerning this Notice of Reasons for Rejection, or wish to have an interview with the Examiner, please contact us.

整理番号:

発送番号:247006 発送日:平成24年 4月11日

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拒絶理由通知書

Official Action

Due Date

7/11(Wed)

特許出願の番号

特願2010-502331

起案日

平成24年 4月 9日

特許庁審査官

太田 雄三

3959 4B00

特許出願人代理人

山本 秀策 (外 2名) 様

適用条文

第29条第1項、第29条第2項

この出願は、次の理由によって拒絶をすべきものです。これについて意見がありましたら、この通知書の発送の日から3か月以内に意見書を提出してください。

理 由

1. この出願の下記の請求項に係る発明は、その出願前に日本国内又は外国において、頒布された下記 of 刊行物に記載された発明又は電気通信回線を通じて公衆に利用可能となった発明であるから、特許法第29条第1項第3号に該当し、特許を受けることができない。

2. この出願の下記の請求項に係る発明は、その出願前に日本国内又は外国において、頒布された下記 of 刊行物に記載された発明又は電気通信回線を通じて公衆に利用可能となった発明に基いて、その出願前にその発明の属する技術の分野における通常の知識を有する者が容易に発明をすることができたものであるから、特許法第29条第2項の規定により特許を受けることができない。

記 (引用文献等については引用文献等一覧参照)

- ・理由: 1, 2
- ・請求項: 1-15
- ・引用文献等: 1, 2
- ・備考:

引例1には、様々なウイルスの保存中の不活性化を低減できる組成物として、ウイルス、血清アルブミン、トレハロース、スクロース、マンニトール等の糖類及び界面活性剤を含むものが記載されている(【特許請求の範囲】)。

また、ウイルス等を保存する際に用いる界面活性剤としてF-127等は、本願優先日前当業者には一般的に使用されていたものと認められる(必要であれば文献2等参照)、及び保存するウイルスの中に弱毒ウイルスを含むこと(つまり

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ワクチン) は当業者には技術常識である。

したがって、本願請求項に係る発明は上記引例1に実質的に記載されたものである。

例えそうでないとしても、引例1, 2の記載に基づいて、F-127等を含む界面活性剤、血清アルブミン、トレハロース等の糖類を含む組成物を用いて、弱毒生ウイルスの不活性化を低減できる組成物を作製すること及び不活性化を低減できる最適な組成を検討することは、当業者が容易に想到し得るものである。

そして、明細書の記載を参酌しても、組成物の個々の成分が具体的特定されておらず、またウイルスの不活性化に対して機能を有さないものを含む本願発明が、引例1, 2の記載から請求項の技術的範囲全てにわたって、当業者が予測し得ないような格別顕著な効果を奏するものとは認められない。

よって、上記請求項に係る発明は引例1, 2及び周知技術に基づいて容易に発明できたものである。

引用文献等一覧

1. 特表2005-538939号公報
2. 国際公開第2005/074460号

先行技術文献調査結果の記録

- ・調査した分野 IPC C12N 7/00
- ・使用した電子データベース PubMed
CA/MEDLINE/BIOSIS/WPIDS (STN)
JDreamII
GeNii

この先行技術文献調査結果の記録は拒絶理由を構成するものではありません。

この拒絶理由通知の内容に関するお問い合わせ、または面接のご希望がございましたら下記までご連絡下さい。

特許審査第三部生命工学 太田 雄三
TEL. 03(3581)1101 内線3448
FAX. 03(3501)0491

Allowed Claims of JP 2010-502331

1. A live attenuated virus composition comprising:
one or more live, attenuated viruses;
one or more polyoxyethylene-polyoxypropylene (EO-PO) block copolymer(s), the one or more EO-PO block copolymers include poloxamer 407 (Pluronic F127®);
one or more proteins agents, the one or more protein agents are one or more albumins,
and
one or more carbohydrate agents, the one or more carbohydrate agents include trehalose,
wherein the composition is capable of reducing the inactivation of the live attenuated virus.
2. The composition of claim 1, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.
3. The composition of any of the preceding claims, wherein the live, attenuated viruses are Flaviviruses.
4. The composition of any of the preceding claims, wherein the composition is partially or wholly dehydrated.
5. The composition of any of the preceding claims, wherein the protein agent(s) is one or more albumins, wherein the one or more albumins are selected from the group consisting of serum albumins derived from a vertebrate species and ovalbumin.
6. The composition of any of the preceding claims, wherein at least one surfactant agent is an EO-PO block copolymer, at least one protein agent is serum albumin, and at least one carbohydrate agent is trehalose.
7. The composition of any of the preceding claims, wherein the EO-PO block copolymer concentration is from 0.1 to 4% (w/v), wherein the one or more albumins concentration is from 0.001 to 3% (w/v) and the one or more carbohydrate agents concentration is from 5 to 50% (w/v).
8. An *in vitro* method for decreasing inactivation of a live, attenuated virus composition comprising, combining one or more live attenuated viruses with a composition of any of the preceding claims, wherein the composition is capable of reducing inactivation of the live, attenuated virus.
9. The method of claim 8, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.

10. The method of claim 8, wherein the composition increases the shelf life of a virus composition and wherein the composition is maintained at room temperature or lower compared to a control composition.

11. The method of claim 8, wherein the composition decreases inactivation of an aqueous live, attenuated virus during one or more freeze and thaw cycles.

12. A kit for decreasing the inactivation of a live, attenuated virus composition comprising:
at least one container; and
a composition of any one of claims 1-7, wherein the composition decreases inactivation of a live, attenuated virus.

Clarke, Modet & C^o

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ANEXO 3

000034



US008084039B2

(12) **United States Patent**
Stinchcomb et al.

(10) **Patent No.:** **US 8,084,039 B2**
(45) **Date of Patent:** **Dec. 27, 2011**

(54) **METHODS AND COMPOSITIONS FOR LIVE ATTENUATED VIRUSES**

(75) Inventors: **Dan T. Stinchcomb**, Fort Collins, CO (US); **Jorge E. Osorio**, Mount Horeb, WI (US); **O'Neil Wiggan**, Fort Collins, CO (US)

(73) Assignee: **Invtrogen, Inc.**, Fort Collins, CO (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 625 days.

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(51) Int. Cl. **A61K 39/12** (2006.01)
C12N 1/04 (2006.01)

(52) U.S. Cl. **424/204.1; 435/235.1; 435/243**

(58) Field of Classification Search **None**
See application file for complete search history.

(56) **References Cited**

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Primary Examiner — Stacy B. Chen

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(57) **ABSTRACT**

Embodiments herein relate to compositions of and methods for live viruses. In certain embodiments, a live, attenuated virus composition includes, but is not limited to, one or more live, attenuated viruses and compositions to reduce inactivation and/or degradation of the live, attenuated virus. In other embodiments, the live, attenuated virus composition may be a vaccine composition. In yet other compositions, a live, attenuated virus composition may include at least one carbohydrate, at least one protein and at least one high molecular weight surfactants for reducing inactivation and/or degradation of the live, attenuated virus.

30 Claims, 9 Drawing Sheets

In another exemplary method, stabilizing effects of compositions were demonstrated including trehalose, rHSA and a pluronic co-polymer with dehydrated DEN-2 PDK 53 vaccines. 1×10^4 pfu of DEN-2 PDK 53 vaccine virus formulated in accordance with procedures disclosed herein. Formulated vaccines were placed in serum vials and subjected to conventional lyophilization procedures. Dried vaccines were stoppered under vacuum, stored at either 37° C. or 4° C. for 14 days followed by reconstitution of the vaccine to its original liquid volume by addition of sterile water. Viral activity of the reconstituted vaccine was assessed as outlined earlier. At 37° C., in the presence of compositions containing trehalose, rHSA and a pluronic co-polymer formulated in phosphate buffered saline, an average viral titer loss of 1 log was observed (FIG. 9). No loss in viral activity was observed for formulated dehydrated DEN-2 PDK 53 viral vaccines stored at 4° C. for 14 days. These results demonstrate effective preservation of a dehydrated viral vaccine utilizing compositions disclosed herein.

FIG. 9. represents stability of lyophilized DEN-2 PDK 53 at different temperatures. Log titer loss of formulated lyophilized DEN-2 PDK 53 vaccine virus following incubation at 37° C. or 4° C. for 2 weeks as indicated. Formulations F1 (15% trehalose, 2% copolymer poloxamer 407, Pluonic F127®, 1% rHSA) and F2 (15% trehalose, 2% copolymer poloxamer 407, Pluonic F127®, 0.01% rHSA) were formulated in phosphate buffered saline. Formulation F3 (15% trehalose, 2% copolymer poloxamer 407, Pluonic F127®, 0.01% rHSA) was formulated in 10 mM Tris base.

All of the COMPOSITIONS and METHODS disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods have been described in terms of preferred embodiments, it is apparent to those of skill in the art that variations maybe applied to the COMPOSITIONS and METHODS and in the steps or in the sequence of steps of the methods described herein without departing from the concept, spirit and scope herein. More specifically, certain agents that are both chemically and physiologically related may be substituted for the agents described herein while the same or similar results would be achieved. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept as defined by the appended claims.

All documents, or portions of documents, cited in this application, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety.

What is claimed is:

1. A live attenuated virus composition comprising:
 - one or more live, attenuated viruses;
 - one or more poly(ethylene oxide) and poly(propylene oxide) (EO-PO) block copolymers, the one or more EO-PO block copolymers include poloxamer 407,
 - one or more proteins agents, the one or more protein agents include one or more albumins selected from the group consisting of lactalbumins and serum albumins, and
 - one or more carbohydrate agents, the one or more carbohydrate agents include trehalose, wherein the composition is capable of reducing the inactivation of the live attenuated virus.
2. The virus composition of claim 1, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus,

Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.

3. The virus composition of claim 1, wherein the live, attenuated viruses are Flaviviruses.

4. The virus composition of claim 1, wherein the composition is in aqueous form.

5. The virus composition of claim 1, wherein the composition is partially or wholly dehydrated.

6. The virus composition of claim 1, wherein the one or more albumins include serum albumins derived from a vertebrate species.

7. The virus composition of claim 1, wherein the one or more co-polymers is poloxamer 407, the one or more protein agents is serum albumin, and the one or more carbohydrate agent is trehalose.

8. The virus composition of claim 7, wherein the one or more copolymers concentration is 0.1 to 4% (w/v), wherein the one or more albumins concentration is from 0.001 to 3% (w/v) and the one or more carbohydrates concentration is from 5 to 50% (w/v).

9. A method for decreasing inactivation of a live, attenuated virus composition comprising, combining one or more live attenuated viruses with a composition comprising one or more EO-PO block copolymers, the EO-PO block copolymers include poloxamer 407, one or more proteins agents, the one or more protein agents include one or more albumins selected from the group consisting of lactalbumins and serum albumins; and

one or more carbohydrate agents, the one or more carbohydrate agents include trehalose, wherein the composition is capable of reducing inactivation of the live, attenuated virus.

10. The method of claim 9, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.

11. The method of claim 9, further comprising partially or wholly dehydrating the combination.

12. The method of claim 11, further comprising partially or wholly re-hydrating the composition prior to administration.

13. The method of claim 9, wherein the composition increases the shelf life of an aqueous virus composition.

14. The method of claim 9, wherein the composition decreases inactivation of an aqueous live, attenuated virus for 24 hours or greater.

15. The method of claim 9, wherein the composition decreases inactivation of an aqueous live, attenuated virus during one or more freeze and thaw cycles.

16. The method of claim 9, wherein the one or more copolymers is poloxamer 407, the one or more protein agents is serum albumin, and the one or more carbohydrate agent is trehalose.

17. The method of claim 9, wherein the virus composition is administered to a subject to reduce the onset of or prevent a health condition.

18. The method of claim 17, wherein the virus is selected from the group consisting of West Nile, Dengue, Japanese encephalitis, St. Louis encephalitis, Tick-borne encephalitis, and Yellow fever.

19. A kit for decreasing the inactivation of a live, attenuated virus composition comprising:

at least one container; and
a composition comprising one or more albumins, the one or more albumins selected from the group consisting of

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lactalbumins and serum albumins, one or more carbohydrate agents, the one or more carbohydrate agents include trehalose, and one or more EO-PO block copolymers, the EO-PO block copolymers include poloxamer 407.

20. The kit of claim 19, wherein at least one albumin is serum albumin.

21. The kit of claim 19, wherein the trehalose concentration is from 5 to 50% (w/v).

22. The kit of claim 19, wherein the poloxamer 407 concentration is from 0.1 to 4% (w/v).

23. The kit of claim 20, wherein the serum albumin concentration is from 0.001 to 3% (w/v).

24. The kit of claim 19, wherein the composition further comprises one or more live, attenuated viruses.

25. The kit of claim 24, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.

26. A live attenuated virus composition comprising:
one or more live, attenuated viruses;
one or more EO-PO block co-polymers including poloxamer 407; having a concentration of 0.1 to 4% (w/v);

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one or more albumins, the one or more albumins selected from the group consisting of lactalbumins and serum albumins; having a concentration from 0.001 to 3% (w/v) and

5 one or more carbohydrate agents, the one or more carbohydrate agent include trehalose, wherein the composition is capable of reducing the inactivation of the live attenuated virus and wherein the composition is in aqueous form.

10 27. The composition of claim 26, wherein the one or more albumins are serum albumins selected from the group consisting of, bovine serum albumin, canine serum albumin, human serum albumin, and other serum albumins.

15 28. The composition of claim 27, wherein stabilization effects of the agents together are synergistic compared to individual agents.

29. The compositions of claim 27, wherein the composition is a more effective cryoprotectant than its individual agents.

20 30. The composition of claim 26, wherein the composition is in aqueous form and the composition increases shelf life of the live attenuated virus composition.

* * * * *

Clarke, Modet & C^o

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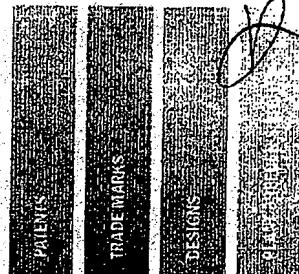
ANEXO 4

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ANEXO 4



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Date of issue: 22 February 2013

Patent Examination Report No. 2

Application Details

Patent Application No.: 2008279576
Applicant/s: Inviragen, Inc.
Your reference: 40134972/NPA/AYC/SZP
Earliest Priority Date: 06 April 2007
Examination Request Date: 13 March 2012

Your application has been examined under Section 45 of the *Patents Act 1990*.

Actions you can take

While the application is otherwise in order for acceptance, it cannot be accepted because there is a current postponement of acceptance in place.

You must respond to this report in order to gain acceptance. The Commissioner will only proceed to accept the application if you file a clear and unambiguous statement requesting the postponement be withdrawn.

Please note that IP Australia will not monitor when the date for postponement has expired, and will not review whether the application can be accepted in the absence of a response to this report. If no response is filed by the final date for acceptance the application will lapse.

Please note also that a response requesting postponement be withdrawn filed more than 12 months after the first report will attract the usual response fees.

You have until 18 October 2014 to overcome all my objection(s) otherwise your application will lapse.



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You will need to pay a monthly fee for any response you file after 12 months from the date of the first report.

You will also need to pay any annual continuation fees that apply. Information about fees may be obtained by phoning 1300 651 010 or by visiting www.ipaustralia.gov.au.

Basis of the report

Last amendment item no. 1 .

In examining your application I have taken into account:

- the PCT pamphlet as originally filed
- the proposed amendments under S104 filed on 13 February 2013

Statement of Novelty, Inventive Step and Patentable Subject Matter

Novelty/Inventive Step	Claim No. 1-34	Yes
	Claim No. NONE	No
Patentable Subject Matter	Claim No. 1-34	Yes
	Claim No. NONE	No

Documents Cited or Considered Relevant

D1 : US 2005/0255121 A1 (CAMPBELL et al.) 17 November 2005 #
Category: A Claims: 1-34

D2 : WO 2003/086443 A1 (MEDIMMUNE VACCINES, INC.) 23 October 2003 ^
Category: A Claims: 1-34

D3 : WO 2003/087327 A2 (MEDIMMUNE VACCINES, INC.) 23 October 2003 ^
Category: A Claims: 1-34

Cited in the International Search Report and the IPRPI/IPRP II

^ Identified in the EP search report for application no. EP 08826570 dated 22 September 2011

Special categories of cited documents (based on PCT standard):

A: Document defining the general state of the art which is not considered to be of particular relevance.

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Clarke, Modet & C^o

COLOMBIA

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ANEXO 5

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DR. SHLOMO COHEN & Co.

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May 29, 2013
 10065/0113.000

BY E-MAIL

Re: Israel Patent Application No. 201429 (PCT/US2008/059472)
 -- METHODS AND COMPOSITIONS FOR LIVE ATTENUATED
 VIRUSES
 In the name of Inviragen, Inc.
 Your Ref: 78484 – 384331
 Our Ref: 10065/0113.000

ACTION REQUIRED

Deadline for acceptance fees payment: August 21, 2013

Dear Dr. Hanson,

We are pleased to inform you that the Patent Office has concluded the examination of the present application.

The application will be accepted and published in the Official Gazette for possible oppositions by **August 21, 2013**.

Divisional applications claiming subject matter not claimed in the present application may be filed prior to the publication of the application and only if the parent application is still pending. Accordingly, once publication is effected, the option of filing divisional applications for the present application will no

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longer be available. Therefore, please advise us as soon as possible, whether you would like us to file one or more divisional applications in the present case.

Finally, we take this opportunity to remind you of the duty to report to the Patent Office any additional material cited against the parallel foreign applications and patents, including material cited in pre- or post-grant oppositions and revocation proceedings, up until acceptance of the Israeli application (i.e., before the publication). Please keep us updated in this regard.

The total costs involved in the publication of a patent application in Israel are **US\$ 380.00**, as follows: our fees -- US\$ 100; plus disbursements (e.g., photocopies, couriers, etc.) -- US\$ 41; Patent Office fees \$ 239. The total sum includes reporting the Patent Office Notice of Acceptance, reviewing the copy of the application provided by the Patent Office, reporting to the Patent Office re publication, reporting to yourselves and monitoring the publication in the Patent Office Gazette.

We do not charge for reviewing the Certificate of Registration, returning it to the Patent Office if erroneous, and forwarding it to yourselves with a report concerning renewal dates and options.

The Israel Patent Office will publish the application on **August 21, 2013**, unless we request re-opening of the prosecution. In the absence of your instructions, we will advise the Patent Office to proceed with the publication of the application.

Yours sincerely,

Dr. Shlomo Cohen & Co.

What is claimed is:

1. A live attenuated virus composition comprising:
one or more live, attenuated viruses;
one or more poly(ethylene oxide) and poly(propylene oxide) (EO-PO) block copolymers;
the one or more EO-PO block copolymers include poloxamer 407,
one or more proteins agents, the one or more protein agents are
one or more albumins selected from the group consisting of lactalbumin and serum
albumins, and
one or more carbohydrate agents, the one or more carbohydrate agents include trehalose,
wherein the composition is capable of reducing inactivation of the live attenuated virus.
2. The composition of claim 1, wherein the live, attenuated viruses are selected from the
group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus,
Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus
families and combinations thereof.
3. The composition of claim 1, wherein the live, attenuated viruses are Flaviviruses.
4. The composition of claim 1, wherein the composition is in aqueous form.
5. The composition of claim 1, wherein the composition is partially or wholly dehydrated.
6. The composition of claim 1, wherein one of the one or more protein agents is serum
albumin derived from a vertebrate species.
7. The composition of claim 1, wherein the one or more copolymers concentration is 0.1 to
4% (w/v), wherein one or more albumins concentration is from 0.001 to 3% (w/v) and the one or
more carbohydrates concentration is from 5 to 50% (w/v).

8. A method for decreasing inactivation of a live, attenuated virus composition comprising, combining one or more live attenuated viruses with a composition comprising one or more poly(ethylene oxide) and poly(propylene oxide) (EO-PO) block copolymers, the one or more EO-PO block copolymers include poloxamer 407, one or more protein agents, the one or more protein agents are one or more albumins selected from the group consisting of lactalbumin and serum albumins; and one or more carbohydrate agents, the one or more carbohydrate agents include trehalose, wherein the composition is capable of reducing inactivation of the live, attenuated virus.
9. The method of claim 8, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.
10. The method of claim 8, further comprising partially or wholly dehydrating the combination.
11. The method of claim 10, further comprising partially or wholly re-hydrating the composition prior to administration
12. The method of claim 8, wherein the composition increases the shelf life of a virus composition when the composition is maintained at room temperature or lower compared to a control composition.
13. The method of claim 8, wherein the composition decreases inactivation of an aqueous live, attenuated virus during one or more freeze and thaw cycles compared to a control composition.
14. The method of claim 8, wherein the one or more copolymers is poloxamer 407, the one or more protein agents is serum albumin, and the one or more carbohydrate agents is trehalose.

15. The method of claim 8, wherein the virus composition is a medicament for use in a subject to reduce the onset of, or prevent a health condition.
16. The method of claim 15, wherein the health condition is selected from the group consisting of West Nile infection, Dengue fever, Japanese encephalitis, St. Louis encephalitis, Tick-borne encephalitis, and Yellow fever.
17. A kit for decreasing the inactivation of a live, attenuated virus composition comprising:
at least one container; and
a composition according to any one of claims 1-7.
18. The kit of claim 17, wherein at least one albumin is serum albumin.
19. The kit according to any one of claims 17 or 18, wherein the trehalose concentration is from 5 to 50% (w/v).
20. The according to any one of claims 17-19, wherein the poloxamer 407 concentration is from 0.1 to 4% (w/v).
21. The kit according to any one of claims 17-20, wherein the serum albumin concentration is from 0.001 to 3% (w/v).
22. The kit of claim 17, wherein the composition further comprises one or more live, attenuated viruses.
23. The kit of claim 22, wherein the live, attenuated viruses are selected from the group consisting of Flavivirus, Togavirus, Coronavirus, Rhabdovirus, Filovirus, Paramyxovirus, Orthomyxovirus, Bunyavirus, Arenavirus, Retrovirus, Hepadnavirus, Herpesvirus, Poxvirus families and combinations thereof.

24. A live attenuated virus composition comprising:
one or more live, attenuated viruses;
one or more EO-PO block co-polymers including poloxamer 407; having a concentration of 0.1 to 4% (w/v);
one or more albumins, the one or more albumins selected from the group consisting of lactalbumin and serum albumins; having a concentration from 0.001 to 3% (w/v) and
one or more carbohydrate agents, the one or more carbohydrate agents include trehalose,
wherein the composition is capable of reducing the inactivation of the live attenuated virus and
wherein the composition is in aqueous form.
25. The composition of claim 24, wherein the one or more albumins are serum albumins selected from the group consisting of bovine serum albumin, canine serum albumin, human serum albumin, and other serum albumins.

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