Señor Superintendente
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

T=F=32

Trámite : 011
Evento : 379
Actuación : 412

Referencia : Expediente No. **07.077.615 A**
Asunto : Solicitud de patente para: "**COMPOSICIONES INMUNOGÉNICAS PCV-2**"
Solicitante : **BOEHRINGER INGELHEIM VETMEDICA, INC**
Fecha de solicitud : 30 de julio de 2007

I. RECURSO VÍA GUBERNATIVA

Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad **BOEHRINGER INGELHEIM VETMEDICA, INC** solicitante de la patente de la referencia, por el presente escrito atentamente manifiesto a usted que debidamente notificada de la Resolución No. **35809** del 30 de mayo de 2014, interpongo en su contra el recurso de **REPOSICIÓN**, para que sea revocada y en consecuencia se conceda el privilegio de patente de invención para **"COMPOSICIONES INMUNOGÉNICAS PCV-2"** a favor de **BOEHRINGER INGELHEIM VETMEDICA, INC.**

II. OPORTUNIDAD DE LA IMPUGNACIÓN

La Resolución No. **35809** del 30 de mayo de 2014, con fecha de publicación listado 10 de junio de 2014, fecha de vencimiento 10 de julio de 2014, y fecha del término legal julio 17 de 2014.

III. LA DECISIÓN RECURRIDA

3.1 Mediante la Resolución objeto de la presente impugnación, el Superintendente de Industria y Comercio decidió:

3.1.1 Denegar la patente de invención a la creación titulada: **"COMPOSICIONES INMUNOGÉNICAS PCV-2"**

3.2 En la parte motiva de la providencia, se mencionaron los siguientes fundamentos:

3.2.1 "Que por otra parte el artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina, señala: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*. En cuanto a la reivindicación 5 incluida en el escrito radicado bajo el N° 07-077615-A 00006-0000, no se ajusta a los parámetros establecidos en el artículo 30 anteriormente transcrito, por cuanto no es concisa porque se refiere a portadores, adyuvantes, medio, inactivadores víricos, diluyentes, agentes isotónicos, agentes inmunomoduladores, antibióticos y combinaciones de estos definiendo los ingredientes por su funcionalidad y no por un ingrediente como tal. Por otra parte, es oportuno precisar que el kit de la reivindicación 7 no se ajusta a lo previsto en la guía de examen en la que se ha indicado que la referencia a elementos del método de tratamiento como es el caso del régimen de administración no es admisible en una reivindicación de kit-de-partes. Por lo anterior las reivindicaciones 5 y 7 no pueden considerarse dentro del presente estudio y, en consecuencia, no hay lugar a reconocer para ellas el privilegio de patente solicitado."

3.2.2 "Como se dijo anteriormente, el documento D1 es considerado el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulga una composición inmunogénica que comprende, una proteína ORFs seleccionada del grupo 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 y 13 de circovirus porcino tipo II (Col.30,

reivindicación 12) y un vector vírico baculovirus recombinante. (Col. 7, línea 50 y 51)."

3.2.3 "La diferencia entre la invención, definida en la reivindicación 1 y la composición del documento D1 consiste en que la solicitud se refiere a las secuencias SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO 10 o SEQ ID NO 11; o un polipéptido que se codifica por un ADN que comprende la secuencia ID NO 3 o SEQ ID NO 4."

3.2.4 "El efecto que logra la proteína ORF2 de secuencia SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO 10 o SEQ ID NO 11; o un polipéptido que se codifica por un ADN que comprende la secuencia ID NO 3 o SEQ ID NO 4 es la obtención de una composición inmunogénica contra PCV2 alternativa con potencial inmunogénico."

3.2.5 "Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: "cómo proporcionar una composición inmunogénica alternativa que produzca una respuesta inmunológica contra PCV2."

3.2.6 "Ahora bien, teniendo en cuenta que el documento D2 da a conocer secuencias de aminoácidos de ORF2 de PCV2 (Pág. 2500, Fig. 3), entre ellas la 10489 que es 100% idéntica a la SEQ. ID NO: 5 de la solicitud, y enseña que las secuencias de aminoácidos de ORF2 presentan un porcentaje de identidad del 90 al 100% (Pág. 2495); una persona normalmente versada en la materia, incluiría una proteína del documento D2 y un adyuvante de vacunas PCV2 tal como el carbopol conocido ampliamente en el estado de la técnica3, en la composición que se da a conocer en la anterioridad D1, esperando con certeza, lograr una composición inmunogénica alternativa contra PCV2 tal como la de la reivindicación 1 de la solicitud estudiada."

3.2.7 "Puesto que las reivindicaciones dependientes 2 a 6 no mencionan características adicionales, se considera que tales reivindicaciones tampoco tienen nivel inventivo."

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3.2.8 "El documento D1, considerado el estado de la técnica más cercano a la invención definida en las reivindicaciones 7, divulga un kit que comprende (Col.32, reivindicación 29): un envase que contiene una composición inmunogénica de proteína de ORF2de PCV2 (Col. 32, reivindicación 29) y un antígeno de virus PRRS (Col. 32, reivindicación 26)."

3.2.9 "La diferencia entre la invención, definida en la reivindicación 7 y el kit del documento D1 consiste en que la solicitud se refiere a la composición inmunogénica de cualquiera de las reivindicaciones 1 a 6."

3.2.10 "El efecto que logra el incluir una composición inmunogénica con secuencias de polipéptido alternativas es obtener un kit que contenga composiciones contra PCV2."

3.2.11 "Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: "cómo proporcionar un kit que contenga composiciones inmunogénicas que contengan ORF2 contra PCV2."

3.2.12 "Por su parte, el documento D2 ya divulgaba secuencias de polipéptidos de proteína ORFs contra PCV2 (Pág.2500, Fig. 3)."

3.2.13 "En consecuencia, la persona del oficio normalmente versada en la materia, incluiría secuencias de polipéptidos de proteína ORFs contra PCV2 del documento D2 en la composición inmunogénica del kit divulgado en el documento D1 para llegar así al objeto de la reivindicación 7 de la solicitud. Por lo cual se considera obvia."

3.2.14 "La solicitante argumenta que las enseñanzas de los documentos D1 y/o D2 por si solas o combinadas no derivarían de manera obvia o evidente en la materia objeto de protección y objeta que la vacuna de virus vivo atenuado del documento D1 tiene la desventaja de que puede cambiar o mutar, mientras que la vacuna de subunidad de la presente invención comprende una (o más) proteína (s) que no

es/son capaz de replicar o mutar. La solicitante argumenta además que el documento D2 no enseña la SEQ ID NO: 6 de la solicitud. Es oportuno aclarar que los argumentos presentados no se relacionan con la materia reivindicada y por lo tanto no desvirtúan la afectación de las anterioridades presentadas por el examinador, ya que la solicitud no proporciona evidencia de los posibles cambios o mutaciones producidos por la utilización de un vector de virus atenuado que pueda Demostrar un efecto técnico superior de la composición o kit reclamado, por tanto, el argumento no está relacionado con la solución del problema técnico planteado por la solicitud. Finalmente se aclara a la solicitante, que aunque se demostrara un efecto técnico mejorado, las modificaciones de proteínas están divulgadas en el documento D2, que indica que las secuencias de aminoácidos de ORF2 presentan un porcentaje de identidad del 90 al 100% y divulga una secuencia que es 100% idéntica a la SEQ ID NO: 5 de la solicitud (Pág. 2495)."

IV. OBJETO DEL RECURSO

De acuerdo con los argumentos que expongo a continuación, solicito atentamente a su Despacho lo siguiente:

1. Revocar la Resolución No. **35809** del 30 de mayo de 2014.

2. Conceder el privilegio de patente de invención para **"COMPOSICIONES INMUNOGÉNICAS PCV-2"** a favor de **BOEHRINGER INGELHEIM VETMEDICA, INC.**

V. FUNDAMENTOS DEL RECURSO

Respetuosamente me permito disentir de lo expuesto por ese Despacho en la Resolución objeto del presente recurso, toda vez que la presente solicitud sí cumple con los requerimientos de novedad y nivel inventivo exigidos en la Decisión 486, como se demostrará a continuación:

5.1 Presentación de un nuevo pliego reivindicatorio

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 7 reivindicaciones.

Siguiendo las amables sugerencias del Señor Examinador, se modificaron las reivindicaciones del anterior pliego reivindicatorio en lo que respecta a lo siguiente:

5.1.1 En la reivindicación 1, se reemplazó la oración "*Una composición inmunogénica CARACTERIZADA PORQUE comprende la proteína ORF2 de PCV2 expresada de forma recombinante y un adyuvante,*" por "*Una composición inmunogénica CARACTERIZADA PORQUE comprende la proteína ORF2 recombinante de PCV2* ***expresada por baculovirus*** *y un adyuvante,*"

5.1.2 En la reivindicación 1, se reemplazó la oración "un polipéptido que comprende la secuencia de SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 10 o SEQ ID NO: 11" por "un polipéptido que comprende la secuencia SEQ ID NO: 6"

5.1.3 En la reivindicación 1, se reemplazó la oración "un polipéptido que se codifica por un ADN que comprende la secuencia ID NO: 3 o SEQ ID NO: 4" por "un polipéptido que se codifica por un ADN que comprende SEQ ID NO: 4"

5.1.4 Se modificó la reivindicación 7, donde se eliminaron los siguientes términos que se referencian a continuación:

> *"Un kit que comprende i) un contenedor conteniendo al menos una ~~dosis de la~~ composición inmunogénica de cualquiera de las reivindicaciones 1 a 6, y ii) un contenedor conteniendo una composición inmunogénica comprendiendo el virus vivo PRRS modificado (MLV PRRS) ~~y un manual de instrucción, incluyendo la información para administrar ambas composiciones farmacéuticas.~~"*

5.2 De la claridad del pliego reivindicatorio

En relación con las modificaciones a la reivindicación 1 expresadas en los numerales 5.1.1, 5.1.2 y 5.1.3 de presente memorial, estas se encuentran soportadas en la página 41, línea 21 a página 42, línea 4 de la solicitud internacional original. Adicional a lo anterior, soportes adicionales a esta característica técnica esencial pueden encontrarse en pág. 16 línea 16; pág. 17 líneas 13-5; pág. 21 línea 8; pág. 37 líneas 14-16 de la solicitud internacional original. Adicional a lo anterior, es pertinente aclarar que la modificación 5.1.1 responde a un error tipográfico asociado a la traducción de la solicitud original y a la adición del término "*expresada por baculovirus*" con el fin de definir la invención de manera precisa e inequívoca.

Con respecto a los términos empleados en la reivindicación 5 "*portadores, adyuvantes, medio, inactivadores víricos, diluyentes, agentes isotónicos, agentes inmunomoduladores, antibióticos y combinaciones de estos*" objetados por el Señor Examinador como "*no concisos porque están definiendo los ingredientes por su funcionalidad y no por un ingrediente como tal*" es importante que el Señor Examinador note que dichos términos se encuentran definidos de forma clara y precisa en la descripción de la presente solicitud y por lo tanto, el alcance del pliego reivindicatorio también se encuentra claramente definido. Lo anterior, si se tiene en cuenta que de conformidad con lo señalado en el artículo 51 de la Decisión 486 que afirma que la descripción de una solicitud sirve para interpretar las reivindicaciones: "*El alcance de la protección conferida por la patente estará determinado por el tenor de las reivindicaciones. La descripción y los dibujos, o en su caso, el material biológico depositado, servirán para interpretarlas*". De modo que la objeción formulada a este respecto se debe dar por superada.

En relación con la objeción realizada por el Señor Examinador relacionada con la reivindicación 7, en donde se señala que "*el kit reivindicado no se ajusta a lo previsto en la guía de examen toda vez que el régimen de administración no es admisible en una reivindicación de kit-de-partes*", se procedió a seguir las amables sugerencias del Señor

Examinador y se ha modificado dicha reivindicación eliminando las referencias a un régimen de administración.

Por todo lo expuesto en el presente numeral y lo también argumentado en el numeral 5.1, el pliego reivindicatorio cumple con los requerimientos de claridad, concisión y soporte establecidos en el Artículo 30 de la Decisión 486.

5.3 Con respecto al nivel inventivo

De acuerdo con el Señor Examinador, el documento D1 divulga una composición inmunogénica que comprende, proteína ORFs seleccionada del grupo que comprende 1,2,3,4,5,6,7,8,9,10,11,12 y 13 de circovirus porcina tipo II (col. 13, reivindicación 12) y también divulga que la composición comprende un vector vírico baculovirus recombinante (Col. 7, línea 50 y 51). Sin embargo, luego de revisar el texto íntegro del documento D1 y teniendo en cuenta las modificaciones realizadas al anterior pliego reivindicatorio, mi representada desea poner de presente que, en contraste con lo afirmado por el Señor Examinador, en D1 no existe enseñanza o sugerencia alguna en relación con un vector vírico baculovirus recombinante o un virus PRRS (ver documento D1 anexo al presente memorial). A saber, la Col. 30 citada por el Señor Examinador es parte de un listado de secuencias y la reivindicación 12 apenas se relaciona a "*el método de la reivindicación 11 en donde el adyuvante es un carbómero*". Además, la Col. 7 línea 50 y 51 tiene la oración "*[...] agua, preferiblemente en presencia de cloruro de sodio, la solución obtenida estando en pH ácido. Esta solución [...]*". Por lo tanto, se infiere que el Señor Examinador cita de un documento diferente a US6497883. Después de realizar una búsqueda minuciosa en el texto de D1, los términos "*baculo*", "*baculovirus*", "*baculoviral*" o "*vector bacolvirus*" no fueron encontrados.

En efecto, el documento D1 en la columna 1, líneas 31-54 revela que la invención allí divulgada se refiere a:

> *"La presente invención se refiere a vectores, tales como vectores recombinantes; por ejemplo, los virus recombinantes, tales como virus de la viruela, por ejemplo,*

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virus de la viruela modificado y a métodos para fabricar y usar la misma. En algunas formas de realización, la invención se refiere a los virus de la viruela aviar recombinante, tales como los virus de la viruela del canario, por ejemplo, ALVAC. La invención se refiere además a tales vectores, por ejemplo, poxvirus, que expresan productos génicos, por ejemplo, antígeno (s), ORF (s), y / o epítopo (s) de interés de la misma, de circovirus porcino tipo 2 (PCV2); a composiciones inmunológicas o vacunas. La invención todavía se refiere además a tales vectores, por ejemplo , virus de la viruela, que inducen una respuesta inmune dirigida a o contra productos génicos PCV y / o PCV2; y, a ventajosamente, dichas composiciones que son composiciones inmunológicas, inmunogénicas o de vacuna y / o conferir inmunidad protectora contra la infección por PCV2 . La invención todavía se refiere además a los usos de y métodos para preparar y usar tales vectores y composiciones, así como intermedios de los mismos, y dichos intermedios. Y, la invención se refiere a los productos de los mismos, por ejemplo, a partir de los usos y métodos que implican la recombinante de la invención o virus de la viruela, tales como anticuerpos de expresión".

De tal manera que, D1 se refiere a un campo técnico distinto al de la presente invención, toda vez que en dicho documento no enseña o sugiere sub-unidades de vacunas proteicas. Asimismo, a diferencia de la presente solicitud, en los ejemplos de D1 únicamente se usa y menciona un virus (in vivo) atenuado de viruela recombinante (ALVAC) que contiene el PCV2 ORF2 y ORF1 insertado en el locus C6 de ALVAC, en una orientación de cabeza a cabeza (ver Ejemplos 6, 8 y 9 de D1).

En cuanto al virus ALVAC se describe adicionalmente en el Ejemplo 1 de D1:

"El virus de la viruela del canario parental (cepa Rentschler) es una cepa de vacuna para canarios. La cepa de vacuna se obtuvo a partir un tipo aislado y atenuada a través de más de 200 pases seriados en fibroblastos de embrión de pollo salvaje. Una semilla viral se sometió a cuatro purificaciones en placa sucesivas bajo agar y un clon de placa se amplificó a través de cinco pasajes adicionales, tras lo cual se utilizó el virus de reserva como virus parental en

pruebas de recombinación in vitro. La placa purificada aislada se designa ALVAC. El ALVAC se depositó el 14 de noviembre 1996, en los términos del Tratado de Budapest en la American Type Culture Collection, ATCC número de acceso VR - 2547".

A este respecto, vale la pena resaltar que la diferencia entre las vacunas de vectores de virus recombinantes de D1 y la sùbunidad de vacunas de la presente invención es fundamental en comparación con el uso de virus vivo atenuado, que generalmente tiene la ventaja de una eficacia superior pero la desventaja de que puede cambiar o mutar (y por lo tanto el virus ALVAC utilizado de acuerdo a D1 tendría por lo menos el potencial de volver a una forma virulenta y causar enfermedad en aves), la ventaja de una vacuna de subunidad es que se basa en una (o más) proteína (s) que no es (son) capaz (capaces) de replicar o mutar. Además, debido a que las vacunas de subunidades contienen sólo el antígeno esencial (s) y no todas las otras moléculas que componen el microbio (en particular, que no contiene un viral activo del genoma), las posibilidades de reacciones adversas a la vacuna son menores.

Sin embargo, una desventaja clave de vacunas de subunidades es por lo general que tienen que ser administradas al menos dos veces y que requieren adyuvantes fuertes que a menudo inducen reacciones tisulares. En consecuencia, fue un efecto técnico inesperado de acuerdo con la presente invención que la composición inmunogénica como se reivindica permita la vacunación segura y eficaz con una sola dosis (ver página 41, línea 24 hasta página 42, línea 4 de la solicitud internacional). En contraste, D1 apenas soporta evidencia de vacunación con dos dosis (por favor ver el ejemplo 9 de US6497883, en donde en 9.1 y 9.2 se describe: "*Dos inyecciones de suspensiones virales son aplicadas [...]*" y en 9.3 en "*en el Día 2 los cerdos son vacunados [...] por vía intramuscular en el lado del cuello. En el día 14 se aplica una segunda inyección de vacuna*". Por lo tanto, en contraste con D1 donde se hace una primera vacunación y un refuerzo, la ventaja de la materia de la reivindicación 1 es evidenciada en la administración de una dosis única de la proteína ORF2 recombinante de PCV2 dado que los sorpresivos resultados experimentales obtenidos avalan que la vacunación de cerdos con una única dosis de la proteína ORF2 recombinante de PCV2 es suficiente para

derivar en una protección exitosa en contra de la infección PCV2. En este punto es pertinente que el Señor Examinador note que no se está reclamando el régimen de administración como tal, sino que se está argumentando que la composición reclamada permite, mediante un régimen de administración dado, efectos técnicos ventajosos sobre el arte previo, dichos efectos están avalados por los experimentados realizados por los inventores y debidamente sustentados en la presente solicitud.

D2 (FENAUX M. ET AL, Journal of Clinical Microbiology, Vol.38, No. 7, Págs. 2494-2503) no es un documento válido para afectar el nivel inventivo de la presente invención.

Con respecto al documento D2, y teniendo en cuenta las modificaciones realizadas al pliego reivindicatorio, mi representada desea poner de presente que dicho documento no enseña la secuencia SEQ ID NO: 6. En su lugar, D2 sólo se refiere a la caracterización genética de PCV2, en el que "Para determinar el grado de heterogeneidad genética de PCV-2 aislados, se amplificó el genoma completo de seis PCV-2 aislados de diferentes regiones de América del Norte por PCR y se secuenciaron " y "Análisis filogenéticos y de secuencias confirmaron que existen dos genotipos distintos de PCV: genotipo no patógeno PCV-1 y genotipo PMWS asociado PCV-2 " (ver Resumen de D2).

Adicional a lo anterior, es pertinente que el Señor Examinador note que D2 no menciona en ninguna parte del documento las proteínas expresadas de forma recombinante. A saber, las secuencias de proteína de la Tabla 3 de D2 están apenas basadas en secuenciación de nucleótidos y en un análisis silico del mismo (por favor ver la sección de materiales y métodos, en particular la página 295 columna izquierda, último párrafo de D2). Finalmente, en ninguna parte de D2 se revelan o sugieren las secuencias específicas SEQ ID NO: 4 o SEQ ID NO: 6.

Por lo tanto, a partir de las enseñanzas de los documentos D1 y/o D2 por si solos o combinados, no se derivaría de manera obvia u evidente la materia de invención objeto de protección y recitada en el nuevo pliego reivindicatorio, toda vez que dichos documentos no enseñan ni sugieren como un todo las características técnicas esenciales

de la reivindicación 1. Es decir, dichos documentos no enseñan ni sugieren por si solos o combinados:

> *Una composición inmunogénica que comprende* **la proteína ORF2 recombinante de PCV2 expresada por baculovirus** y un adyuvante,
>
> *en donde dicha proteína ORF2 de PCV2 es:*
>
> *(i) un polipéptido que comprende la secuencia* ***SEQ ID NO: 6; o***
>
> *(ii) un polipéptido que se codifica por un ADN que comprende* ***SEQ ID NO: 4;*** *y*
>
> *en donde el adyuvante seleccionado del grupo que consiste de polímeros de ácido acrílico que se reticulan con éteres de polialquenilo de azúcares o polialcoholes.*

De otro lado, el efecto técnico inesperado que provee el método reivindicado se demuestra con los ejemplos de la descripción y particularmente con el ejemplo 1, tabla 1.

Por consiguiente, el método reivindicado cumple con los requerimientos de patentabilidad del artículo 18 de la Decisión 486.

Como consecuencia de los argumentos previamente presentados, las reivindicaciones independientes 1 y 7 son inventivas sobre el estado del arte. Por lo tanto, las reivindicaciones 2-6 también son inventivas debido a la dependencia de éstas de la reivindicación 1.

Conclusión

Los documentos D1 y D2 no resultan anterioridades válidas capaces de afectar el nivel inventivo de las reivindicaciones 1-7 de la presente solicitud.

Por todo lo anterior, consideramos que la presente solicitud cumple a cabalidad con los requerimientos de patentabilidad exigidos por la legislación actual, por lo que atentamente solicitamos en consideración lo siguiente:

VI. PETICIÓN

Por todo lo anterior, solicito a ese Despacho lo siguiente:

6.1 Que al considerar las razones precedentes se revoque la decisión contenida en la Resolución No. **35809** del 30 de mayo de 2014, en cuanto resuelve negar el privilegio de patente de invención.

6.2 Que se otorgue el privilegio de patente de invención para **"COMPOSICIONES INMUNOGÉNICAS PCV-2"** a favor de **BOEHRINGER INGELHEIM VETMEDICA, INC.**

VII. NOMBRE Y DIRECCIÓN

El nombre y la dirección del solicitante recurrente son los siguientes:

BOEHRINGER INGELHEIM VETMEDICA, INC.
Missouri, St. Joseph
Estados Unidos de América

VIII. NOTIFICACIONES

Atentamente manifiesto a usted que recibiré notificaciones en la Secretaria de su Despacho o en mi oficina de abogada situada en la Carrera 4ª. No. 72-35, piso 4°, de esta ciudad de Bogotá, D.C.

IX. ANEXOS.

1. Nuevo pliego reivindicatorio compuesto por 7 reivindicaciones.
2. Formulario de modificaciones.

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3. Recibo de pago de la tasa por concepto de modificaciones.
4. Listado de secuencias en formato físico y digital.
5. Documento D1: US6497883B1

Señor Superintendente,

LUZ CLEMENCIA DE PÁEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

COLO-15149-0841-017-5
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No. M-2014-268676\DVV

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Industria y Comercio
SUPERINTENDENCIA

Espacio reservado para el adhesivo de radicación

DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES

1. **Identificación del Tramite**

- ☐ **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 ☒

BOEHRINGER INGELHEIM VETMEDICA, 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	Dirección y domicilio del titular	Ciudad
Estados Unidos de América	2621 North Belt Highway, Missouri 64506, St. Joseph, Estados Unidos de América	St. Joseph

Dirección electrónica	No. Fax	Número telefónico
clientes@cavelier.com	2 11 86 50	3 47 36 11

☐ **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:**

Apellidos y Nombre	Documento de identificación	Tarjeta profesional
De Páez Luz Clemencia	C.C. 35.456.344	T.P.A. 23.555

Dirección y domicilio		Ciudad
Carrera 4ª No. 72 –35		Bogotá
Dirección electrónica	**No. Fax**	**Número telefónico**
cavelier@cavelier.com	2 11 86 50	3 47 36 11

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

16

4. Datos del trámite

Corrección:

Expediente No 07077615 A

Aparece

Debe ser

Modificación:

☒ **Modificación al capítulo reivindicatorio.**
Presento nuevo capítulo reivindicatorio compuesto por 7 reivindicaciones y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas.
Respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.

5. Anexos

☒ Comprobante de pago de la tasa para la presentación de la corrección y/o modificación por $128.000.

☐ Poder, si fuere el caso.

☒ Documento que contiene las modificaciones o correcciones.

☐ Copia de la solicitud y sus anexos en formato magnético.

6. Firma	
Nombre y apellidos	Firma
LUZ CLEMENCIA DE PAEZ	Luz Clemencia de Paez
C.C. 35.456.344 de Usaquén	Tarjeta Profesional 23.555

DVV\SDC\WPC15149\ID-268812

REIVINDICACIONES MODIFICADAS

1. Una composición inmunogénica CARACTERIZADA PORQUE comprende la proteína ORF2 recombinante de PCV2 expresada por baculovirus y un adyuvante,

en donde dicha proteína ORF2 de PCV2 es:

(i) un polipéptido que comprende la secuencia SEQ ID NO: 6; o

(ii) un polipéptido que se codifica por un ADN que comprende SEQ ID NO: 4; y

en donde el adyuvante seleccionado del grupo que consiste de polímeros de ácido acrílico que se reticulan con éteres de polialquenilo de azúcares o polialcoholes.

2. La composición inmunogénica de la reivindicación 1, en donde dicha composición adicional comprende un vector vírico inactivo y sobrenadante de cultivo celular.

3. La composición inmunogénica de la reivindicación 1 o 2, en donde dicha composición comprende etilenimina binaria.

4. La composición inmunogénica de la reivindicación 3, en donde dicha composición comprende tiosulfato de sodio.

5. La composición inmunogénica de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde dicha composición comprende un ingrediente adicional seleccionado del grupo que consiste de portadores, adyuvantes, medio, inactivadores víricos, diluyentes, agentes isotónicos, agentes inmunomoduladores, antibióticos y combinaciones de estos.

6. La composición inmunogénica de la reivindicación 5, en donde dicha composición comprende una sal farmacéuticamente aceptable, preferiblemente solución salina.

7. Un kit que comprende i) un contenedor conteniendo al menos una composición inmunogénica de cualquiera de las reivindicaciones 1 a 6, y ii) un contenedor conteniendo una composición inmunogénica comprendiendo el virus vivo PRRS modificado (MLV PRRS).

DVV\DVV\ID-268813\WPC15149

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

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Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 14 - 0075308

Bogotá D.C., Julio 17 de 2014 - 11:37:24

RECIBIDO DE : CAVELIER ABOGADOS NI 860.041.367 RE

*** Soporte del Pago ***

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*** Conceptos Pagados ***

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				$128.000.00

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

Responsable: _____
-***-

Recibo de Caja Aplicado al Expediente No. _____

Cod: 15149-841-0175

34816-CIP1.ST25
SEQUENCE LISTING

<110> Roof, Mike
Eichmeyer, Mark
Nitzel, Greg
Schaeffer, Merrill
Hayes, Phillip

<120> PCV2 IMMUNOGENIC COMPOSITIONS AND METHODS OF PRODUCING SUCH COMPOSITIONS

<130> 34816-CIP1

<140> UNKNOWN
<141> 2005-01-10

<150> Unknown
<151> 2004-12-30

<160> 11

<170> PatentIn version 3.3

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<213> Artificial

<220>
<223> This is a modified Kozak's sequence.

<400> 1
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<210> 2
<211> 6
<212> DNA
<213> Artificial

<220>
<223> This is a recombinant Eco R1 sequence.

<400> 2
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<210> 3
<211> 713
<212> DNA
<213> Porcine circovirus

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acccatatgt aaactactcc tcccgccata caatccccca acccttctcc taccactccc 480

gttacttcac acccaaacct gttcttgact ccactattga ttacttccaa ccaaataaca 540

aaaggaatca gctttggctg aggctacaaa cctctagaaa tgtggaccac gtaggcctcg 600

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<210> 5
<211> 233
<212> PRT
<213> Porcine circovirus

<400> 5

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Ser His Leu Gly Gln Ile Leu Arg Arg Arg Pro Trp Leu Val His Pro
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Arg His Arg Tyr Arg Trp Arg Arg Lys Asn Gly Ile Phe Asn Thr Arg
35 40 45

Leu Ser Arg Thr Phe Gly Tyr Thr Val Lys Ala Thr Thr Val Thr Thr
50 55 60

Pro Ser Trp Ala Val Asp Met Met Arg Phe Asn Ile Asp Asp Phe Val
65 70 75 80

Pro Pro Gly Gly Gly Thr Asn Lys Ile Ser Ile Pro Phe Glu Tyr Tyr
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Arg Ile Arg Lys Val Lys Val Glu Phe Trp Pro Cys Ser Pro Ile Thr
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Phe Val Thr Lys Ala Thr Ala Leu Thr Tyr Asp Pro Tyr Val Asn Tyr
130 135 140

Ser Ser Arg His Thr Ile Pro Gln Pro Phe Ser Tyr His Ser Arg Tyr
145 150 155 160

Phe Thr Pro Lys Pro Val Leu Asp Ser Thr Ile Asp Tyr Phe Gln Pro
165 170 175

Asn Asn Lys Arg Asn Gln Leu Trp Leu Arg Leu Gln Thr Ser Arg Asn
180 185 190

Val Asp His Val Gly Leu Gly Thr Ala Phe Glu Asn Ser Lys Tyr Asp
195 200 205

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Asn Leu Lys Asp Pro Pro Leu Lys Pro
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<211> 233
<212> PRT
<213> Porcine circovirus

<400> 6

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Arg His Arg Tyr Arg Trp Arg Arg Lys Asn Gly Ile Phe Asn Thr Arg
35 40 45

Leu Ser Arg Thr Phe Gly Tyr Thr Val Lys Ala Thr Thr Val Thr Thr
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Pro Ser Trp Ala Val Asp Met Met Arg Phe Asn Ile Asp Asp Phe Val
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Pro Pro Gly Gly Gly Thr Asn Lys Ile Ser Ile Pro Phe Glu Tyr Tyr
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Arg Ile Arg Lys Val Lys Val Glu Phe Trp Pro Cys Ser Pro Ile Thr
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Gln Gly Asp Arg Gly Val Gly Ser Thr Ala Val Ile Leu Asp Asp Asn
115 120 125

Phe Val Thr Lys Ala Thr Ala Leu Thr Tyr Asp Pro Tyr Val Asn Tyr
130 135 140

Ser Ser Arg His Thr Ile Pro Gln Pro Phe Ser Tyr His Ser Arg Tyr
145 150 155 160

Phe Thr Pro Lys Pro Val Leu Asp Ser Thr Ile Asp Tyr Phe Gln Pro
165 170 175

Asn Asn Lys Arg Asn Gln Leu Trp Leu Arg Leu Gln Thr Ser Arg Asn
180 185 190

Val Asp His Val Gly Leu Gly Thr Ala Phe Glu Asn Ser Lys Tyr Asp
195 200 205

Gln Asp Tyr Asn Ile Arg Val Thr Met Tyr Val Gln Phe Arg Glu Phe
210 215 220

Asn Leu Lys Asp Pro Pro Leu Glu Pro
225 230

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<211> 756
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<223> This sequence is from porcine circovirus type 2, open reading frame 2, together with a portion from the pGEM T-easy vector.

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tttgaatact acagaataag aaaggttaag gttgaattct ggccctgctc ccccatcacc 360

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ccctaagaat tctatcacta gtgaattcgc ggccgc 756

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<211> 10387
<212> DNA
<213> Artificial

<220>
<223> This is the porcine circovirus type 2, ORF2 construct, which includes baculovirus and pGEM T-easy coding sequences.

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ataaaagatt ctaatctgat atgttttaaa acacctttgc ggcccgagtt gtttgcgtac 180

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cacaccctgg gtattgcgcc gcaggaagcc atagatagat tcgaaaaagc cagaggtcac 540

aaaattgaaa gacaaaatta cgttcaagat ttattaattt aattaatatt atttgcattc 600

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cagtgcc 10387

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<212> PRT
<213> Porcine circovirus

<400> 9

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1 5 10 15

His Leu Gly Gln
20

<210> 10
<211> 19
<212> PRT
<213> Porcine circovirus

<400> 10

Pro Arg His His Tyr Arg Pro Arg Arg Lys Asn Gly Ile Phe Asn Thr
1 5 10 15

Thr Leu Ser

<210> 11
<211> 233
<212> PRT
<213> Artificial

<220>
<223> This is an amino acid sequence for porcine circovirus type 2, open reading frame 2.

<400> 11

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1 5 10 15

Ser His Leu Gly Gln Ile Leu Arg Arg Arg Pro Trp Leu Val His Pro
20 25 30

Arg His Arg Tyr Arg Trp Arg Arg Lys Asn Gly Ile Phe Asn Thr Arg
35 40 45

Leu Ser Arg Thr Phe Gly Tyr Thr Val Lys Ala Thr Thr Val Arg Thr

```
50                  55                  60

Pro Ser Trp Ala Val Asp Met Met Arg Phe Asn Ile Asp Asp Phe Val
65                  70                  75                  80

Pro Pro Gly Gly Gly Thr Asn Lys Ile Ser Ile Pro Phe Glu Tyr Tyr
                85                  90                  95

Arg Ile Lys Lys Val Lys Val Glu Phe Trp Pro Cys Ser Pro Ile Thr
            100                 105                 110

Gln Gly Asp Arg Gly Val Gly Ser Thr Ala Val Ile Leu Asp Asp Asn
        115                 120                 125

Phe Val Thr Lys Ala Thr Ala Leu Thr Tyr Asp Pro Tyr Val Asn Tyr
    130                 135                 140

Ser Ser Arg His Thr Ile Pro Gln Pro Phe Ser Tyr His Ser Arg Tyr
145                 150                 155                 160

Phe Thr Pro Lys Pro Val Leu Asp Ser Thr Ile Asp Tyr Phe Gln Pro
                165                 170                 175

Asn Asn Lys Arg Asn Gln Leu Trp Leu Arg Leu Gln Thr Ser Arg Asn
            180                 185                 190

Val Asp His Val Gly Leu Gly Thr Ala Phe Glu Asn Ser Ile Tyr Asp
        195                 200                 205

Gln Asp Tyr Asn Ile Arg Val Thr Met Tyr Val Gln Phe Arg Glu Phe
    210                 215                 220

Asn Leu Lys Asp Pro Pro Leu Lys Pro
225                 230
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Industria y Comercio
SUPERINTENDENCIA

PLANILLA DE RADICACIÓN - DIGITALIZACIÓN DIARIA
RELACIÓN DE ANEXOS

Dependencia: 2020	Fecha: 14 / 7 / 17 (AAAA MM DD)	Recorrido: 3

Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐

Radicador: | Planilla:

ID	No. Radicación	Consecutivo	Item
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2			
3			
4			
5			
6			
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8			
9			
10			
11			
12			
13			
14			
15			
16			
17			

Item	Unidad de Conservación
1	Bolsa
2	Caja
3	Libro
4	Sobre
5	Tomo
6	Otro
Item	*Soporte Documental*
7	CD X
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones:
El CD Anexo contiene un total de Archivos:
(1) Archivo en formato PDF, los cuales fueron procesados en el folio (32) correctamente

Paola G

US006497883B1

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

(10) **Patent No.: US 6,497,883 B1**
(45) **Date of Patent: Dec. 24, 2002**

(54) **PORCINE CIRCOVIRUS RECOMBINANT POXVIRUS VACCINE**

(75) Inventors: **Michel Bublot**, Delmar, NY (US); **Jennifer M. Perez**, East Nassau, NY (US); **Catherine E. Charreyre**, St.-Laurent De Mure (FR)

(73) Assignee: **Merial**, Lyons (FR)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/583,545**

(22) Filed: **Jun. 1, 2000**

Related U.S. Application Data

(60) Provisional application No. 60/138,478, filed on Jun. 10, 1999.

(51) **Int. Cl.**[7] **A61K 39/12**; C12N 15/00

(52) **U.S. Cl.** **424/204.1**; 424/199.1; 424/209.1; 424/218.1; 435/320.1; 435/235.1; 536/23.72

(58) **Field of Search** 424/199.1, 204.1, 424/209.1, 218.1; 536/23.72; 435/320.1, 235.1

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* cited by examiner

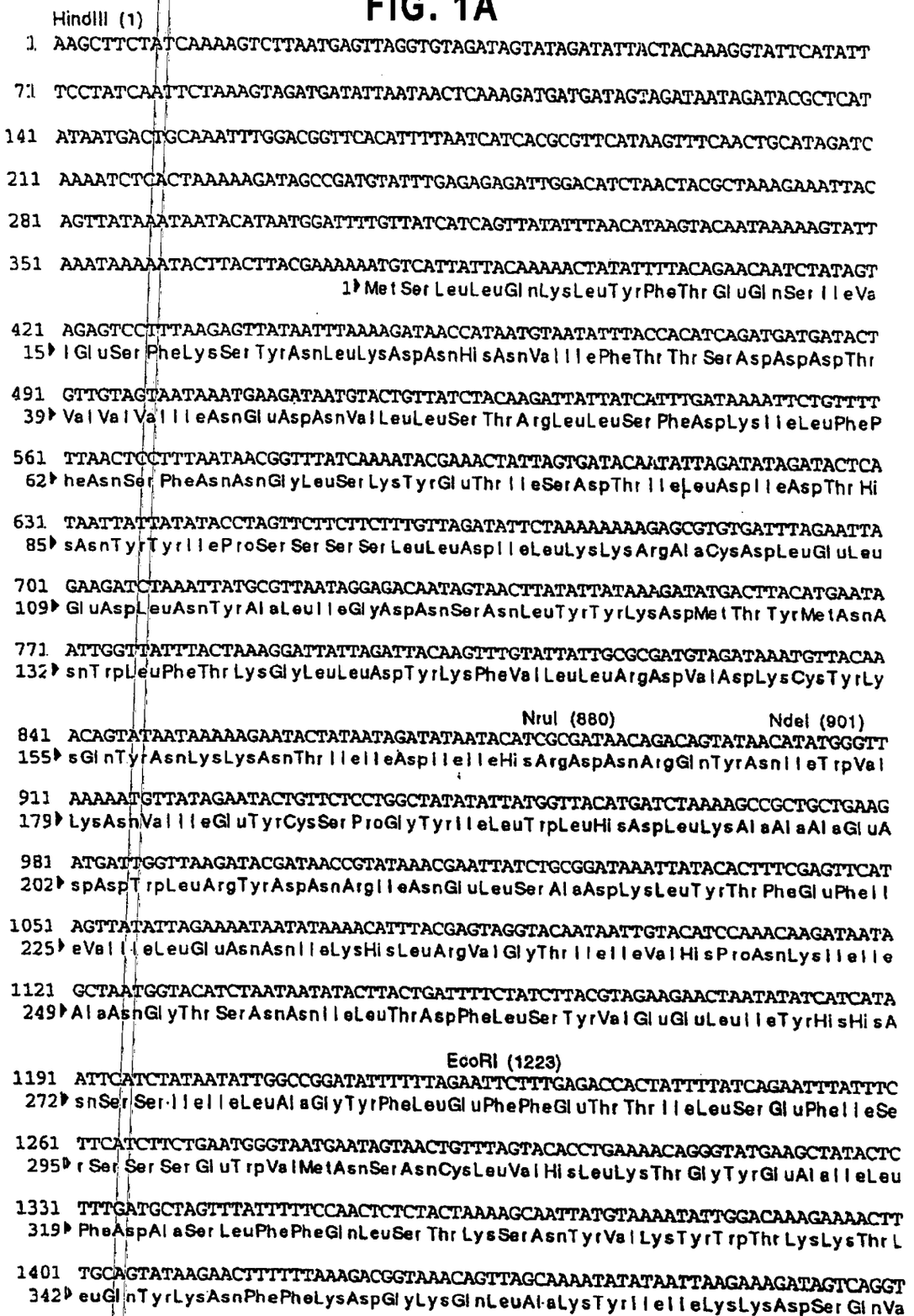
Primary Examiner—Ali R. Salimi
(74) *Attorney, Agent, or Firm*—Frommer Lawrence & Haug, LLP; William S. Frommer; Thomas J. Kowalski

(57) **ABSTRACT**

What is described is a recombinant poxvirus, such as avipox virus, containing foreign DNA from porcine circovirus 2. What are also described are immunological compositions containing the recombinant poxvirus for inducing an immunological response in a host animal to which the immunological composition is administered. Also described are methods of treating or preventing disease caused by porcine circovirus 2 by administering the immunological compositions of the invention to an animal in need of treatment or susceptible to infection by porcine circovirus 2.

26 Claims, 11 Drawing Sheets

FIG. 1A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141 ATAATGACTGCAAATTTGGACGGTTCACATTTTAATCATCACGCGTTCATAAGTTTCAACTGCATAGATC
211 AAAATCTCACTAAAAAGATAGCCGATGTATTTGAGAGAGATTGGACATCTAACTACGCTAAAGAAATTAC
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351 AAATAAAAATACTTACTTACGAAAAAATGTCATTATTACAAAAACTATATTTTACAGAACAATCTATAGT
1 Met Ser LeuLeuGlnLysLeuTyrPheThr GluGlnSer IleVa
421 AGAGTCCTTTAAGAGTTATAATTTAAAAGATAACCATAATGTAATATTTACCACATCAGATGATGATACT
15 IGluSer PheLysSer TyrAsnLeuLysAspAsnHisAsnVal IlePheThr Thr SerAspAspAspThr
491 GTTGTAGTAATAAATGAAGATAATGTACTGTTATCTACAAGATTATTATCATTTGATAAAATTCTGTTTT
39 Val Val Val IleAsnGluAspAsnVal LeuLeuSer Thr ArgLeuLeuSer PheAspLys IleLeuPheP
561 TTAACTCCTTTAATAACGGTTTATCAAAATACGAAACTATTAGTGATACAATATTAGATATAGATACTCA
62 heAsnSer PheAsnAsnGlyLeuSer LysTyrGluThr IleSerAspThr IleLeuAsp IleAspThr Hi
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85 sAsnTyrTyr IleProSer Ser Ser Ser LeuLeuAsp IleLeuLysLysArgAlaCysAspLeuGluLeu
701 GAAGATCTAAATTATGCGTTAATAGGAGACAATAGTAACTTATATTATAAAGATATGACTTACATGAATA
109 GluAspLeuAsnTyrAlaLeu IleGlyAspAsnSerAsnLeuTyrTyrLysAspMet Thr TyrMetAsnA
771 ATTGGTTATTTACTAAAGGATTATTAGATTACAAGTTTGTATTATTGCGCGATGTAGATAAATGTTACAA
132 snTrpLeuPheThr LysGlyLeuLeuAspTyrLysPheVal LeuLeuArgAspVal AspLysCysTyrLy
NruI (880) NdeI (901)
841 ACAGTATAATAAAAAGAATACTATAATAGATATAATACATCGCGATAACAGACAGTATAACATATGGGTT
155 sGlnTyrAsnLysLysAsnThr IleIleAsp IleIleHisArgAspAsnArgGlnTyrAsn IleTrpVal
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179 LysAsnVal IleGluTyrCysSer ProGlyTyr IleLeuTrpLeuHisAspLeuLysAlaAlaAlaGluA
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202 spAspTrpLeuArgTyrAspAsnArg IleAsnGluLeuSer AlaAspLysLeuTyrThr PheGluPhe I
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225 eVal IleLeuGluAsnAsn IleLysHisLeuArgVal GlyThr IleIleVal HisProAsnLys IleIle
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249 AlaAsnGlyThr SerAsnAsn IleLeuThrAspPheLeuSer TyrVal GluGluLeu IleTyrHisHisA
EcoRI (1223)
1191 ATTCATCTATAATATTGGCCGGATATTTTTTAGAATTCTTTGAGACCACTATTTTATCAGAATTTATTTC
272 snSer Ser·IleIleLeuAlaGlyTyrPheLeuGluPhePheGluThr Thr IleLeuSer GluPhe IleSe
1261 TTCATCTTCTGAATGGGTAATGAATAGTAACTGTTTAGTACACCTGAAAACAGGGTATGAAGCTATACTC
295 r Ser Ser Ser GluTrpVal MetAsnSer AsnCysLeuVal HisLeuLysThr GlyTyrGluAla IleLeu
1331 TTTGATGCTAGTTTATTTTTCCAACTCTCTACTAAAAGCAATTATGTAAAATATTGGACAAAGAAAACTT
319 PheAspAlaSer LeuPhePheGlnLeuSer Thr LysSer AsnTyrVal LysTyrTrpThr LysLysThr L
1401 TGCAGTATAAGAACTTTTTTAAAGACGGTAAACAGTTAGCAAAATATATAATTAAGAAAGATAGTCAGGT
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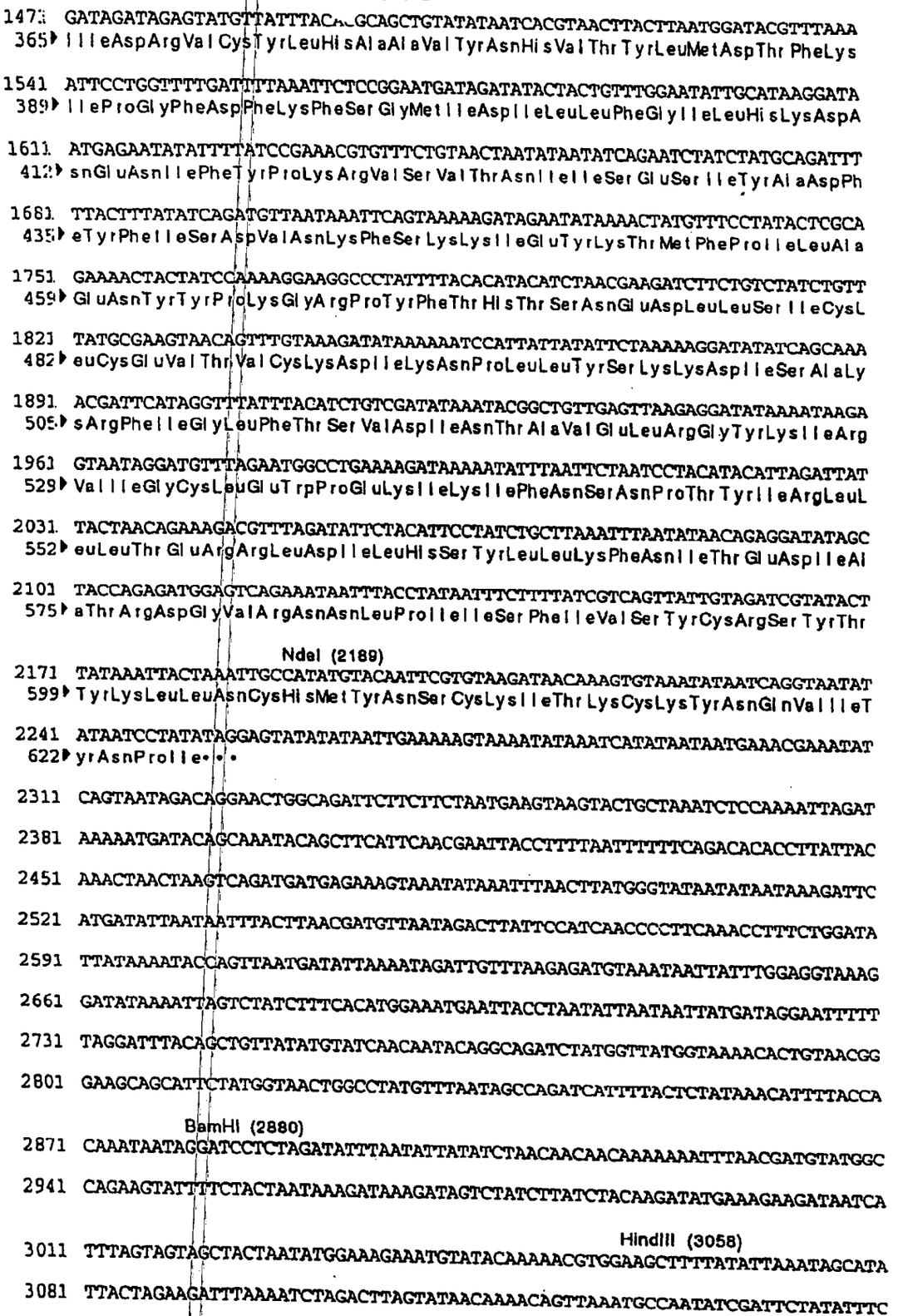
FIG. 1B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1541 ATTCCTGGTTTTGATTTTAAATTCTCCGGAATGATAGATATACTACTGTTTGGAATATTGCATAAGGATA
389 IleProGlyPheAspPheLysPheSerGlyMetIleAspIleLeuLeuPheGlyIleLeuHisLysAspA
1611 ATGAGAATATATTTTATCCGAAACGTGTTTCTGTAACTAATATAATATCAGAATCTATCTATGCAGATTT
412 snGluAsnIlePheTyrProLysArgValSerValThrAsnIleIleSerGluSerIleTyrAlaAspPh
1681 TTACTTTATATCAGATGTTAATAAATTCAGTAAAAAGATAGAATATAAAACTATGTTTCCTATACTCGCA
435 eTyrPheIleSerAspValAsnLysPheSerLysLysIleGluTyrLysThrMetPheProIleLeuAla
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482 euCysGluValThrValCysLysAspIleLysAsnProLeuLeuTyrSerLysLysAspIleSerAlaLy
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505 sArgPheIleGlyLeuPheThrSerValAspIleAsnThrAlaValGluLeuArgGlyTyrLysIleArg
1961 GTAATAGGATGTTTAGAATGGCCTGAAAAGATAAAAATATTTAATTCTAATCCTACATACATTAGATTAT
529 ValIleGlyCysLeuGluTrpProGluLysIleLysIlePheAsnSerAsnProThrTyrIleArgLeuL
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622 yrAsnProIle•••
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2801 GAAGCAGCATTCTATGGTAACTGGCCTATGTTTAATAGCCAGATCATTTTACTCTATAAACATTTTACCA
BamHI (2880)
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3081 TTACTAGAAGATTTAAAATCTAGACTTAGTATAACAAAACAGTTAAATGCCAATATCGATTCTATATTTC

FIG. 1C

3151 ATCATAACAGTAGTACATTAATCAGTGATATACTGAAACGATCTACAGACTCAACTATGCAAGGAATAAG

3221 CAATATGCCAATTATGTCTAATATTTTAACTTTAGAACTAAAACGTTCTACCAATACTAAAAATAGGATA

3291 CGTGATAGGCTGTTAAAAGCTGCAATAAATAGTAAGGATGTAGAAGAAATACTTTGTTCTATACCTTCGG

3361 AGGAAAGAACTTTAGAACAACTTAAGTTTAATCAAACTTGTATTTATGAACACTATAAAAAAATTATGGA

3431 AGATACAAGTAAAAGAATGGATGTTGAATGTCGTAGTTTAGAACATAACTATACGGCTAACTTATATAAA

3501 GTGTACGGACAAAACGAATATATGATTACTTATATACTAGCTCTCATAAGTAGGATTAATAATATTATAG

3571 AAACTTTAAAATATAATCTGGTGGGGCTAGACGAATCTACAATACGTAATATAAATTATATAATTTCACA

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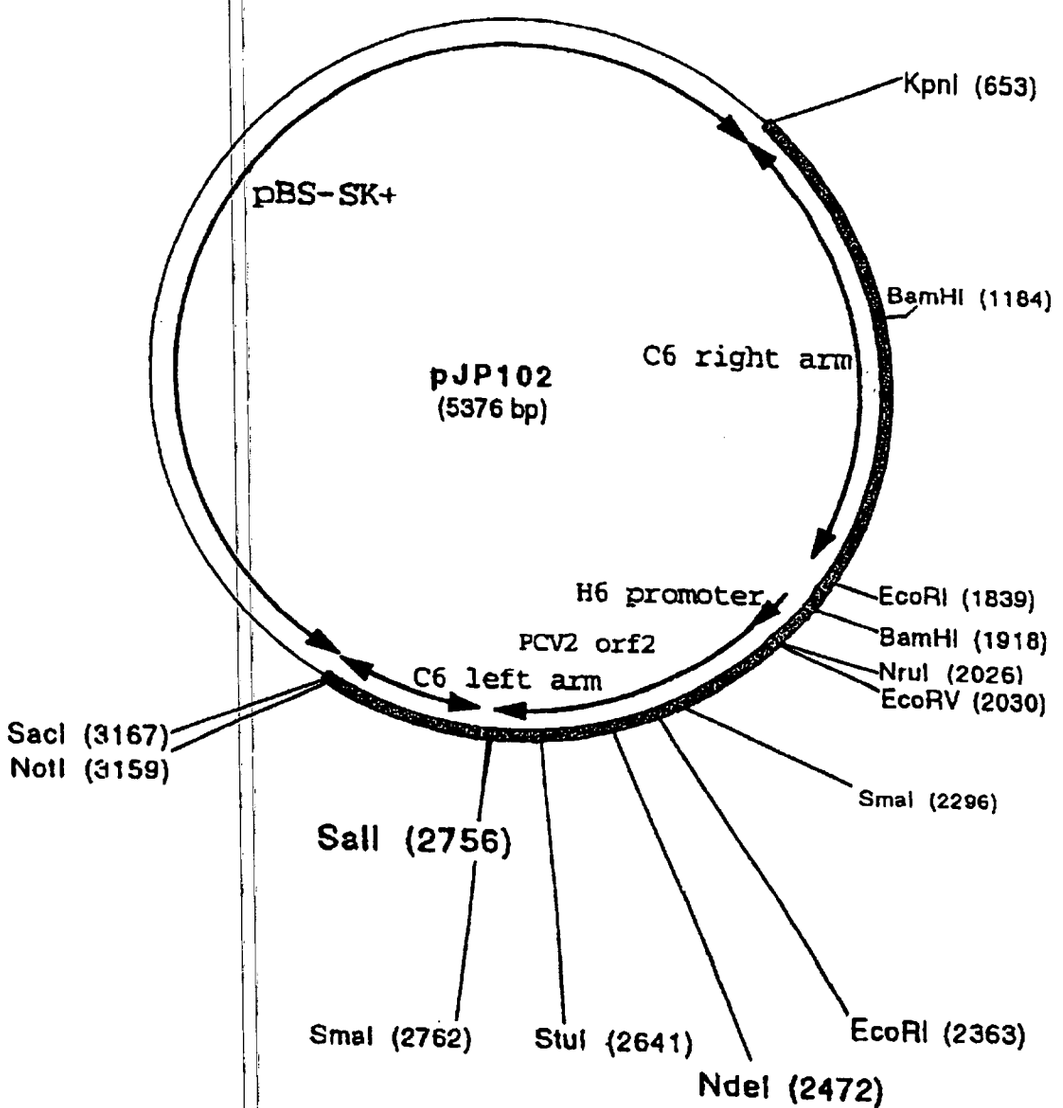
FIG. 2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pBS-SK+
BamHI (1184)
C6 right arm
pJP102
(5376 bp)
H6 promoter
EcoRI (1839)
PCV2 orf2
BamHI (1918)
NruI (2026)
C6 left arm
EcoRV (2030)
SacI (3167)
NotI (3159)
SmaI (2296)
SalI (2756)
SmaI (2762)
StuI (2641)
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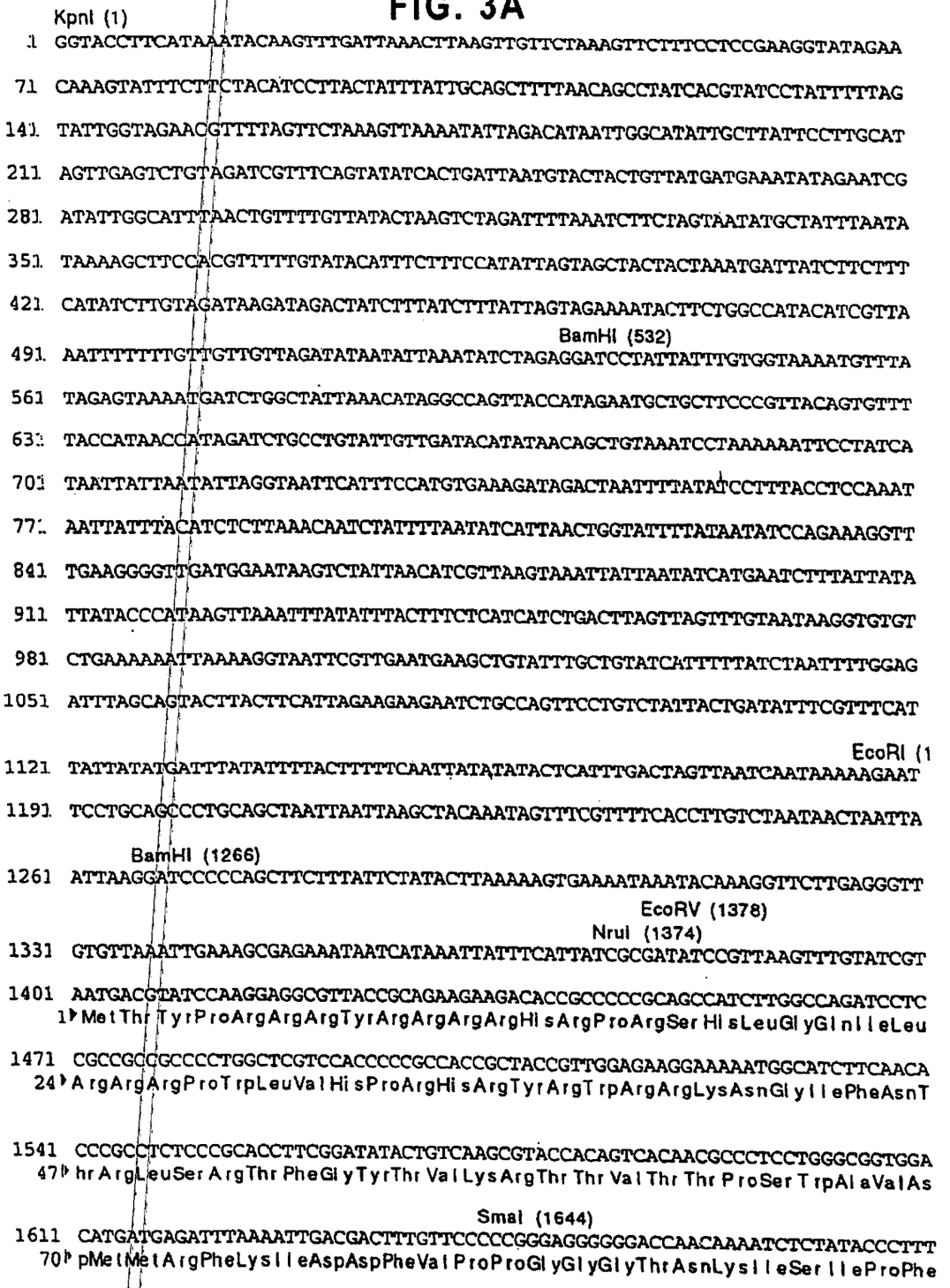
NdeI (2472)

3B

FIG. 3A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1 GGTACCTTCATAAATACAAGTTTGATTAAACTTAAGTTGTTCTAAAGTTCTTTCCTCCGAAGGTATAGAA
71 CAAAGTATTTCTTCTACATCCTTACTATTTATTGCAGCTTTTAACAGCCTATCACGTATCCTATTTTTAG
141 TATTGGTAGAACGTTTTAGTTCTAAAGTTAAAATATTAGACATAATTGGCATATTGCTTATTCCTTGCAT
211 AGTTGAGTCTGTAGATCGTTTCAGTATATCACTGATTAATGTACTACTGTTATGATGAAATATAGAATCG
281 ATATTGGCATTTAACTGTTTTGTTATACTAAGTCTAGATTTTAAATCTTCTAGTAATATGCTATTTAATA
351 TAAAAGCTTCCACGTTTTTGTATACATTTCTTTCCATATTAGTAGCTACTACTAAATGATTATCTTCTTT
421 CATATCTTGTAGATAAGATAGACTATCTTTATCTTTATTAGTAGAAAATACTTCTGGCCATACATCGTTA
BamHI (532)
491 AATTTTTTTGTTGTTGTTAGATATAATATTAAATATCTAGAGGATCCTATTATTTGTGGTAAAATGTTTA
561 TAGAGTAAAATGATCTGGCTATTAAACATAGGCCAGTTACCATAGAATGCTGCTTCCCGTTACAGTGTTT
631 TACCATAACCATAGATCTGCCTGTATTGTTGATACATATAACAGCTGTAAATCCTAAAAAATTCCTATCA
701 TAATTATTAATATTAGGTAATTCATTTCCATGTGAAAGATAGACTAATTTTATATCCTTTACCTCCAAAT
771 AATTATTTACATCTCTTAAACAATCTATTTTAATATCATTAACTGGTATTTTATAATATCCAGAAAGGTT
841 TGAAGGGGTTGATGGAATAAGTCTATTAACATCGTTAAGTAAATTATTAATATCATGAATCTTTATTATA
911 TTATACCCATAAGTTAAATTTATATTTACTTTCTCATCATCTGACTTAGTTAGTTTGTAATAAGGTGTGT
981 CTGAAAAAATTAAAAGGTAATTCGTTGAATGAAGCTGTATTTGCTGTATCATTTTTATCTAATTTTGGAG
1051 ATTTAGCAGTACTTACTTCATTAGAAGAAGAATCTGCCAGTTCCTGTCTATTACTGATATTTCGTTTCAT
EcoRI (1
1121 TATTATATGATTTATATTTTACTTTTTCAATTATATATACTCATTTGACTAGTTAATCAATAAAAAGAAT
1191 TCCTGCAGCCCTGCAGCTAATTAATTAAGCTACAAATAGTTTCGTTTTCACCTTGTCTAATAACTAATTA
BamHI (1266)
1261 ATTAAGGATCCCCCAGCTTCTTTATTCTATACTTAAAAAGTGAAAATAAATACAAAGGTTCTTGAGGGTT
EcoRV (1378)
NruI (1374)
1331 GTGTTAAATTGAAAGCGAGAAATAATCATAAATTATTTCATTATCGCGATATCCGTTAAGTTTGTATCGT
1401 AATGACGTATCCAAGGAGGCGTTACCGCAGAAGAAGACACCGCCCCCGCAGCCATCTTGGCCAGATCCTC
1 MetThrTyrProArgArgArgTyrArgArgArgArgHisArgProArgSerHisLeuGlyGlnIleLeu
1471 CGCCGCCGCCCCTGGCTCGTCCACCCCCGCCACCGCTACCGTTGGAGAAGGAAAAATGGCATCTTCAACA
24 ArgArgArgProTrpLeuValHisProArgHisArgTyrArgTrpArgArgLysAsnGlyIlePheAsnT
1541 CCCGCCTCTCCCGCACCTTCGGATATACTGTCAAGCGTACCACAGTCACAACGCCCTCCTGGGCGGTGGA
47 hrArgLeuSerArgThrPheGlyTyrThrValLysArgThrThrValThrThrProSerTrpAlaValAs
SmaI (1644)
1611 CATGATGAGATTTAAAATTGACGACTTTGTTCCCCCGGGAGGGGGGACCAACAAAATCTCTATACCCTTT
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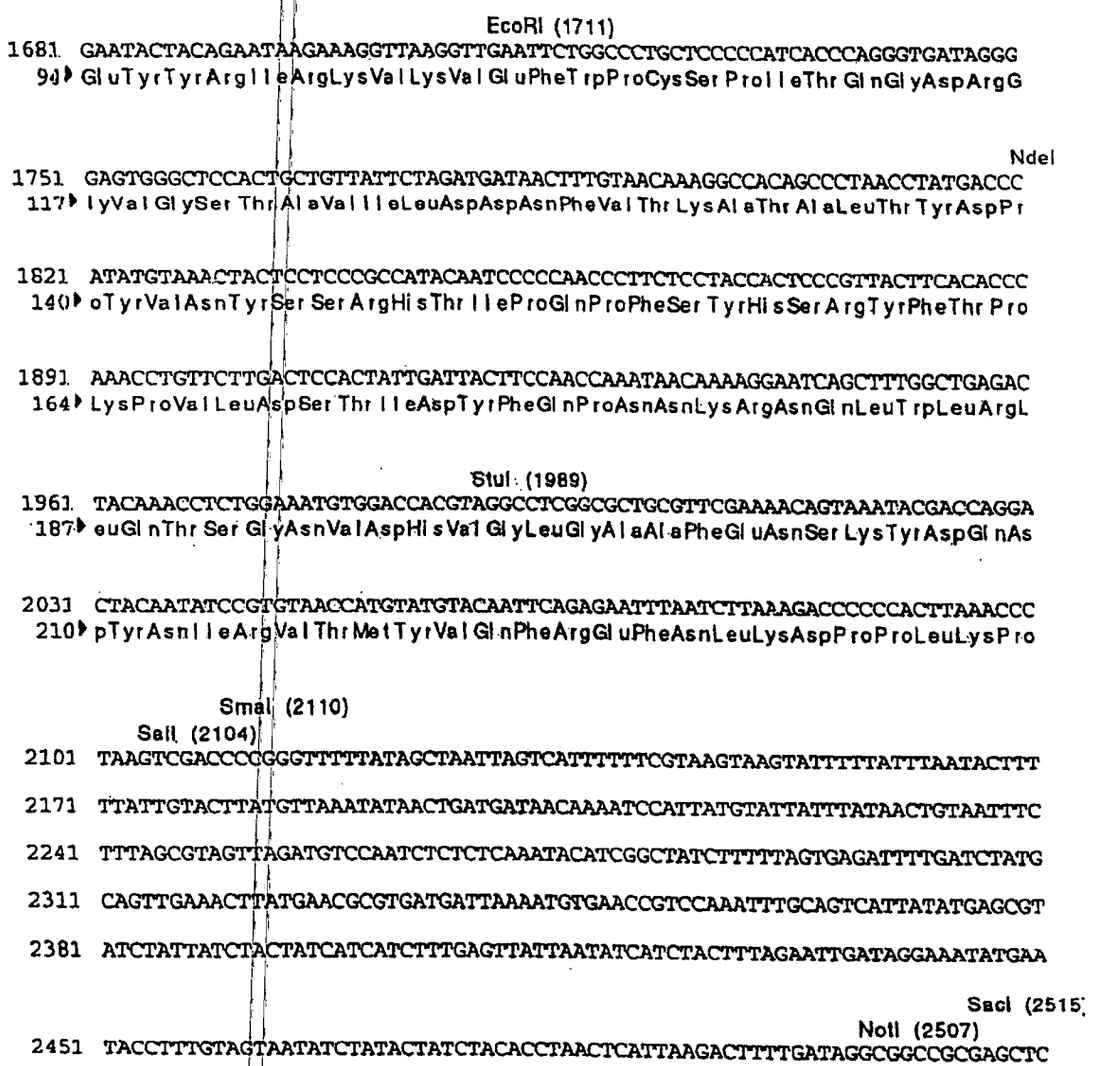
FIG. 3B


EcoRI (1711)
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94 GluTyrTyrArgIleArgLysValLysValGluPheTrpProCysSerProIleThrGlnGlyAspArgG
NdeI
1751 GAGTGGGCTCCACTGCTGTTATTCTAGATGATAACTTTGTAACAAAGGCCACAGCCCTAACCTATGACCC
117 lyValGlySerThrAlaValIleLeuAspAspAsnPheValThrLysAlaThrAlaLeuThrTyrAspPr
1821 ATATGTAAACTACTCCTCCCGCCATACAATCCCCCAACCCTTCTCCTACCACTCCCGTTACTTCACACCC
140 oTyrValAsnTyrSerSerArgHisThrIleProGlnProPheSerTyrHisSerArgTyrPheThrPro
1891 AAACCTGTTCTTGACTCCACTATTGATTACTTCCAACCAAATAACAAAAGGAATCAGCTTTGGCTGAGAC
164 LysProValLeuAspSerThrIleAspTyrPheGlnProAsnAsnLysArgAsnGlnLeuTrpLeuArgL
StuI (1989)
1961 TACAAACCTCTGGAAATGTGGACCACGTAGGCCTCGGCGCTGCGTTCGAAAACAGTAAATACGACCAGGA
187 euGlnThrSerGlyAsnValAspHisValGlyLeuGlyAlaAlaPheGluAsnSerLysTyrAspGlnAs
2031 CTACAATATCCGTGTAACCATGTATGTACAATTCAGAGAATTTAATCTTAAAGACCCCCCACTTAAACCC
210 pTyrAsnIleArgValThrMetTyrValGlnPheArgGluPheAsnLeuLysAspProProLeuLysPro
SmaI (2110)
SalI (2104)
2101 TAAGTCGACCCCGGGTTTTTATAGCTAATTAGTCATTTTTTCGTAAGTAAGTATTTTTATTTAATACTTT
2171 TTATTGTACTTATGTTAAATATAACTGATGATAACAAAATCCATTATGTATTATTTATAACTGTAATTTC
2241 TTTAGCGTAGTTAGATGTCCAATCTCTCTCAAATACATCGGCTATCTTTTTAGTGAGATTTTGATCTATG
2311 CAGTTGAAACTTATGAACGCGTGATGATTAAAATGTGAACCGTCCAAATTTGCAGTCATTATATGAGCGT
2381 ATCTATTATCTACTATCATCATCTTTGAGTTATTAATATCATCTACTTTAGAATTGATAGGAAATATGAA
SacI (2515)
NotI (2507)
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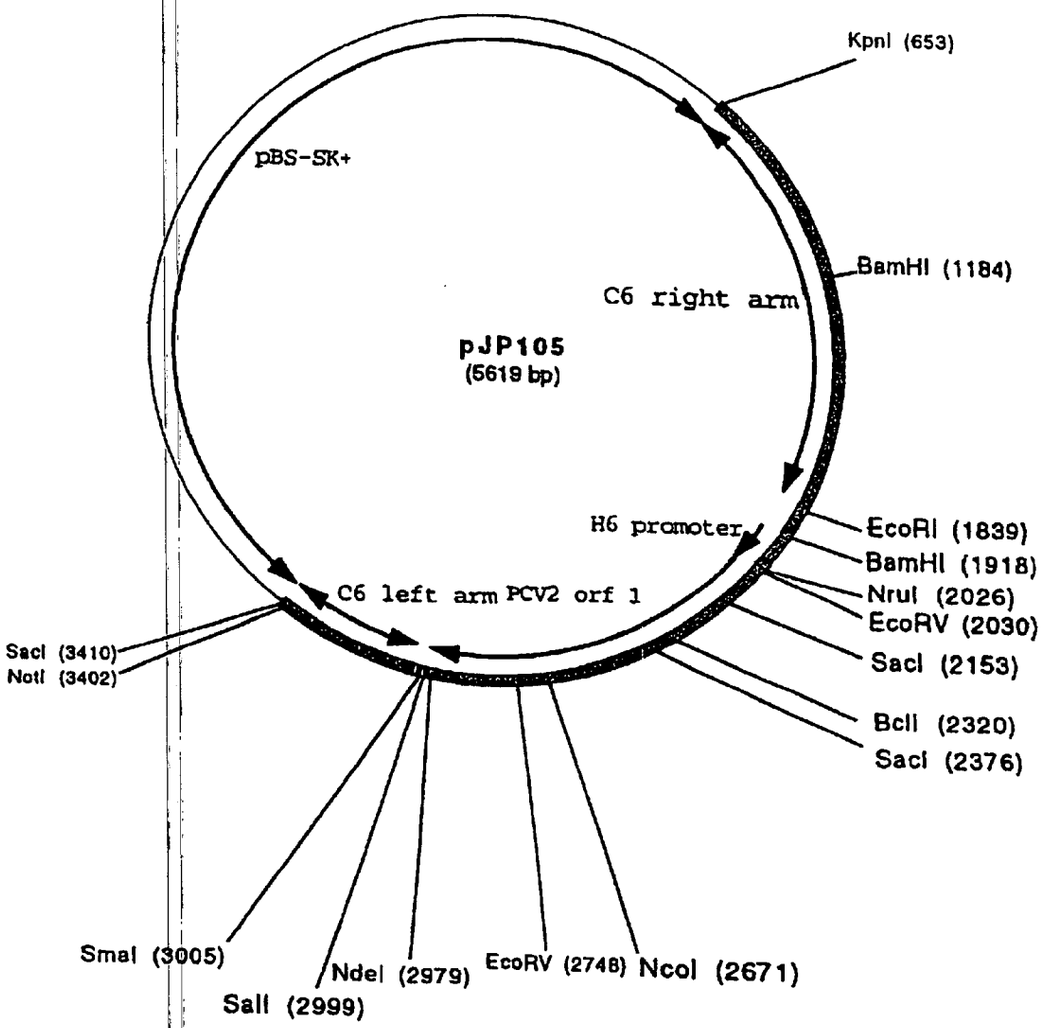
FIG. 4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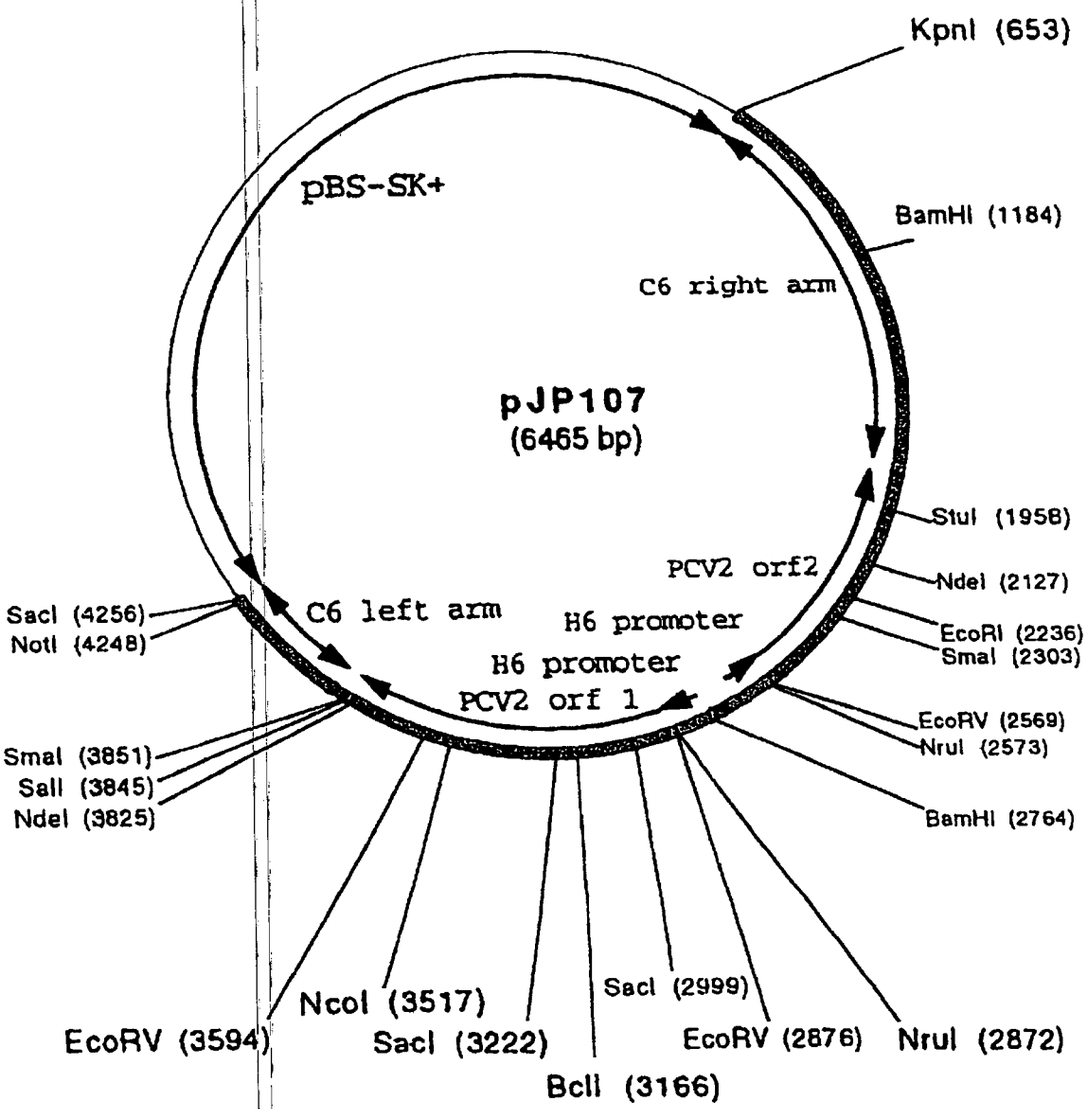
pBS-SK+
BamHI (1184)
C6 right arm
pJP105
(5619 bp)
H6 promoter
EcoRI (1839)
BamHI (1918)
NruI (2026)
EcoRV (2030)
SacI (2153)
BclI (2320)
SacI (2376)
C6 left arm PCV2 orf 1
SacI (3410)
NotI (3402)
SmaI (3005)
SalI (2999)
NdeI (2979)
EcoRV (2748)
NcoI (2671)

FIG. 5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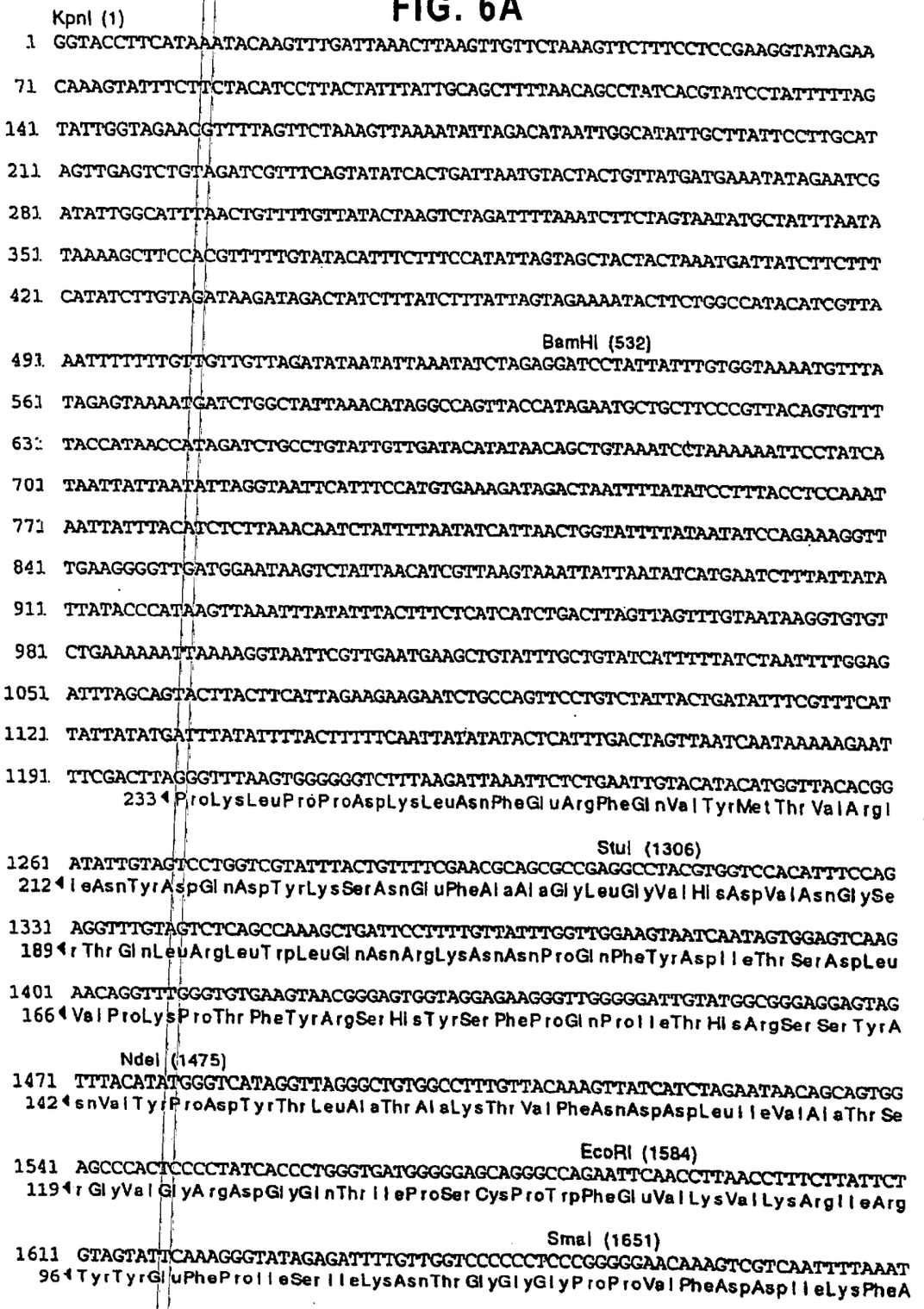
BamHI (1184)
C6 right arm
pJP107
(6465 bp)
StuI (1958)
PCV2 orf2
NdeI (2127)
SacI (4256)
NotI (4248)
C6 left arm
H6 promoter
EcoRI (2236)
SmaI (2303)
H6 promoter
PCV2 orf 1
EcoRV (2569)
NruI (2573)
SmaI (3851)
SalI (3845)
NdeI (3825)
BamHI (2764)
SacI (2999)
NcoI (3517)
EcoRV (3594)
SacI (3222)
EcoRV (2876)
NruI (2872)
BclI (3166)

FIG. 6A


KpnI (1)
1 GGTACCTTCATAAATACAAGTTTGATTAAACTTAAGTTGTTCTAAAGTTCTTTCCTCCGAAGGTATAGAA
71 CAAAGTATTTCTTCTACATCCTTACTATTTATTGCAGCTTTTAACAGCCTATCACGTATCCTATTTTTAG
141 TATTGGTAGAACGTTTTAGTTCTAAAGTTAAAATATTAGACATAATTGGCATATTGCTTATTCCTTGCAT
211 AGTTGAGTCTGTAGATCGTTTCAGTATATCACTGATTAATGTACTACTGTTATGATGAAATATAGAATCG
281 ATATTGGCATTTAACTGTTTTGTTATACTAAGTCTAGATTTTAAATCTTCTAGTAATATGCTATTTAATA
351 TAAAAGCTTCCACGTTTTTGTATACATTTCTTTCCATATTAGTAGCTACTACTAAATGATTATCTTCTTT
421 CATATCTTGTAGATAAGATAGACTATCTTTATCTTTATTAGTAGAAAATACTTCTGGCCATACATCGTTA
BamHI (532)
491 AATTTTTTTGTTGTTGTTAGATATAATATTAAATATCTAGAGGATCCTATTATTTGTGGTAAAATGTTTA
561 TAGAGTAAAATGATCTGGCTATTAAACATAGGCCAGTTACCATAGAATGCTGCTTCCCGTTACAGTGTTT
631 TACCATAACCATAGATCTGCCTGTATTGTTGATACATATAACAGCTGTAAATCCTAAAAAAATTCCTATCA
701 TAATTATTAATATTAGGTAATTCATTTCCATGTGAAAGATAGACTAATTTTATATCCTTTACCTCCAAAT
771 AATTATTTACATCTCTTAAACAATCTATTTTAATATCATTAACTGGTATTTTATAATATCCAGAAAGGTT
841 TGAAGGGGTTGATGGAATAAGTCTATTAACATCGTTAAGTAAATTATTAATATCATGAATCTTTATTATA
911 TTATACCCATAAGTTAAATTTATATTTACTTTCTCATCATCTGACTTAGTTAGTTTGTAATAAGGTGTGT
981 CTGAAAAAATTAAAAGGTAATTCGTTGAATGAAGCTGTATTTGCTGTATCATTTTTATCTAATTTTGGAG
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1191 TTCGACTTAGGGTTTAAGTGGGGGGTCTTTAAGATTAAATTCTCTGAATTGTACATACATGGTTACACGG
233 ProLysLeuProProAspLysLeuAsnPheGluArgPheGlnValTyrMetThrValArgI
StuI (1306)
1261 ATATTGTAGTCCTGGTCGTATTTACTGTTTTCGAACGCAGCGCCGAGGCCTACGTGGTCCACATTTCCAG
212 IleAsnTyrAspGlnAspTyrLysSerAsnGluPheAlaAlaGlyLeuGlyValHisAspValAsnGlySe
1331 AGGTTTGTAGTCTCAGCCAAAGCTGATTCCTTTTGTTATTTGGTTGGAAGTAATCAATAGTGGAGTCAAG
189 rThrGlnLeuArgLeuTrpLeuGlnAsnArgLysAsnAsnProGlnPheTyrAspIleThrSerAspLeu
1401 AACAGGTTTGGGTGTGAAGTAACGGGAGTGGTAGGAGAAGGGTTGGGGGATTGTATGGCGGGAGGAGTAG
166 ValProLysProThrPheTyrArgSerHisTyrSerPheProGlnProIleThrHisArgSerSerTyrA
NdeI (1475)
1471 TTTACATATGGGTCATAGGTTAGGGCTGTGGCCTTTGTTACAAAGTTATCATCTAGAATAACAGCAGTGG
142 snValTyrProAspTyrThrLeuAlaThrAlaLysThrValPheAsnAspAspLeuIleValAlaThrSe
EcoRI (1584)
1541 AGCCCACTCCCCTATCACCCTGGGTGATGGGGGAGCAGGGCCAGAATTCAACCTTAACCTTTCTTATTCT
119 rGlyValGlyArgAspGlyGlnThrIleProSerCysProTrpPheGluValLysValLysArgIleArg
SmaI (1651)
1611 GTAGTATTCAAAGGGTATAGAGATTTTGTTGGTCCCCCCTCCCGGGGGAACAAAGTCGTCAATTTTAAAT
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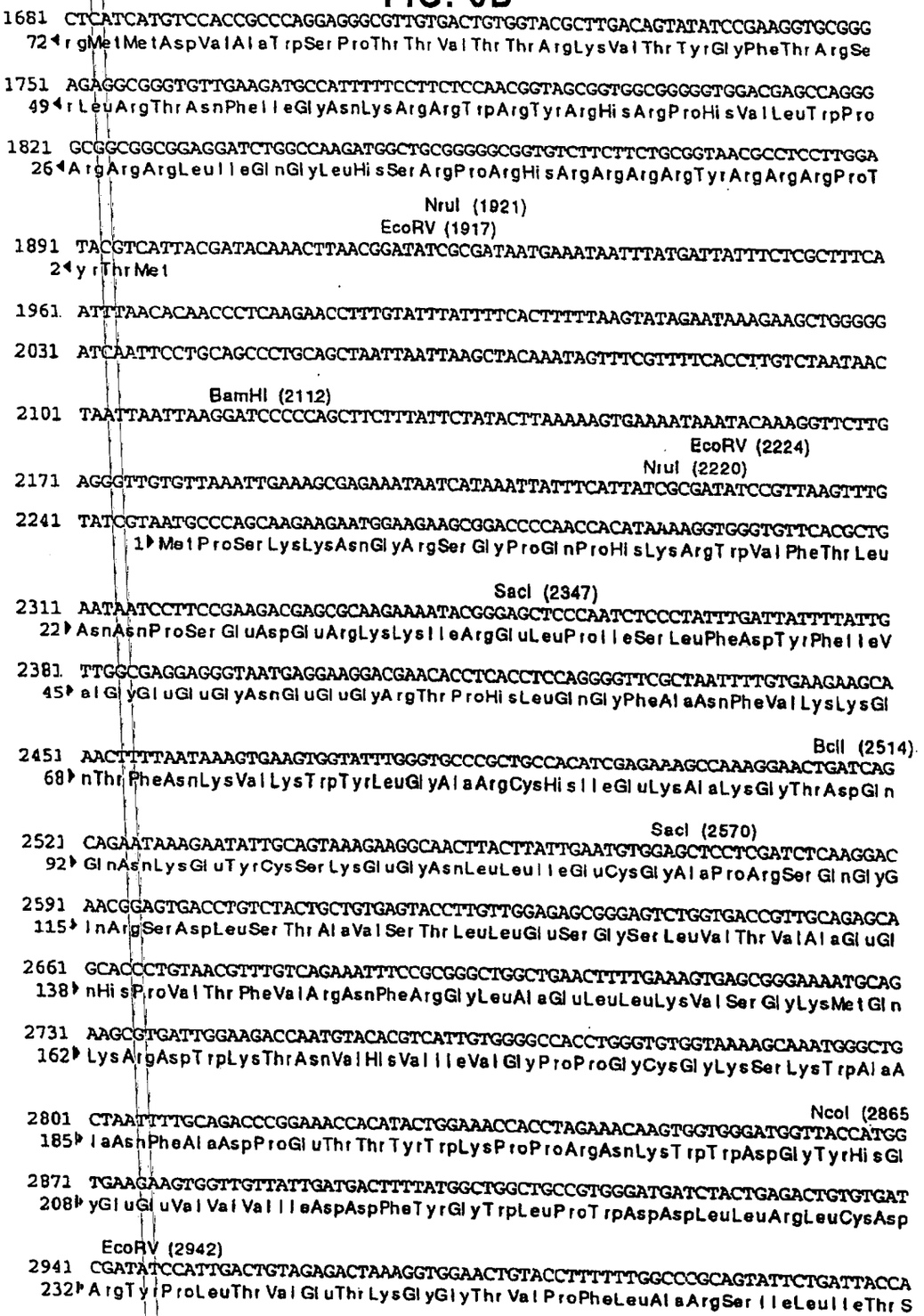
FIG. 6B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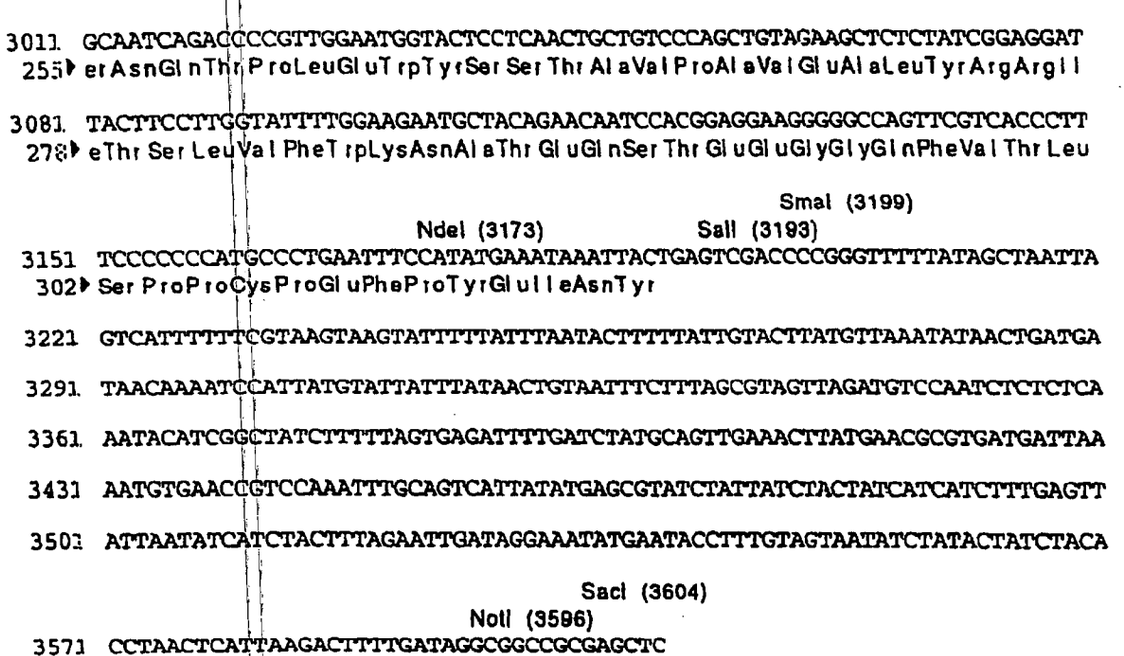
72 rgMetMetAspValAlaTrpSerProThrThrValThrThrArgLysValThrTyrGlyPheThrArgSe
1751 AGAGGCGGGTGTTGAAGATGCCATTTTTCCTTCTCCAACGGTAGCGGTGGCGGGGGTGGACGAGCCAGGG
49 rLeuArgThrAsnPheIleGlyAsnLysArgArgTrpArgTyrArgHisArgProHisValLeuTrpPro
1821 GCGGCGGCGGAGGATCTGGCCAAGATGGCTGCGGGGGCGGTGTCTTCTTCTGCGGTAACGCCTCCTTGGA
26 ArgArgArgLeuIleGlnGlyLeuHisSerArgProArgHisArgArgArgArgTyrArgArgArgProT
NruI (1921)
EcoRV (1917)
1891 TACGTCATTACGATACAAACTTAACGGATATCGCGATAATGAAATAATTTATGATTATTTCTCGCTTTCA
2 yrThrMet
1961 ATTTAACACAACCCTCAAGAACCTTTGTATTTATTTTCACTTTTTAAGTATAGAATAAAGAAGCTGGGGG
2031 ATCAATTCCTGCAGCCCTGCAGCTAATTAATTAAGCTACAAATAGTTTCGTTTTCACCTTGTCTAATAAC
BamHI (2112)
2101 TAATTAATTAAGGATCCCCCAGCTTCTTTATTCTATACTTAAAAAGTGAAAATAAATACAAAGGTTCTTG
EcoRV (2224)
NruI (2220)
2171 AGGGTTGTGTTAAATTGAAAGCGAGAAATAATCATAAATTATTTCATTATCGCGATATCCGTTAAGTTTG
2241 TATCGTAATGCCCAGCAAGAAGAATGGAAGAAGCGGACCCCAACCACATAAAAGGTGGGTGTTCACGCTG
1 MetProSerLysLysAsnGlyArgSerGlyProGlnProHisLysArgTrpValPheThrLeu
SacI (2347)
2311 AATAATCCTTCCGAAGACGAGCGCAAGAAAATACGGGAGCTCCCAATCTCCCTATTTGATTATTTTATTG
22 AsnAsnProSerGluAspGluArgLysLysIleArgGluLeuProIleSerLeuPheAspTyrPheIleV
2381 TTGGCGAGGAGGGTAATGAGGAAGGACGAACACCTCACCTCCAGGGGTTCGCTAATTTTGTGAAGAAGCA
45 alGlyGluGluGlyAsnGluGluGlyArgThrProHisLeuGlnGlyPheAlaAsnPheValLysLysGl
BclI (2514)
2451 AACTTTTAATAAAGTGAAGTGGTATTTGGGTGCCCGCTGCCACATCGAGAAAGCCAAAGGAACTGATCAG
68 nThrPheAsnLysValLysTrpTyrLeuGlyAlaArgCysHisIleGluLysAlaLysGlyThrAspGln
SacI (2570)
2521 CAGAATAAAGAATATTGCAGTAAAGAAGGCAACTTACTTATTGAATGTGGAGCTCCTCGATCTCAAGGAC
92 GlnAsnLysGluTyrCysSerLysGluGlyAsnLeuLeuIleGluCysGlyAlaProArgSerGlnGlyG
2591 AACGGAGTGACCTGTCTACTGCTGTGAGTACCTTGTTGGAGAGCGGGAGTCTGGTGACCGTTGCAGAGCA
115 InArgSerAspLeuSerThrAlaValSerThrLeuLeuGluSerGlySerLeuValThrValAlaGluGl
2661 GCACCCTGTAACGTTTGTCAGAAATTTCCGCGGGCTGGCTGAACTTTTGAAAGTGAGCGGGAAAATGCAG
138 nHisProValThrPheValArgAsnPheArgGlyLeuAlaGluLeuLeuLysValSerGlyLysMetGln
2731 AAGCGTGATTGGAAGACCAATGTACACGTCATTGTGGGGCCACCTGGGTGTGGTAAAAGCAAATGGGCTG
162 LysArgAspTrpLysThrAsnValHisValIleValGlyProProGlyCysGlyLysSerLysTrpAlaA
NcoI (2865
2801 CTAATTTTGCAGACCCGGAAACCACATACTGGAAACCACCTAGAAACAAGTGGTGGGATGGTTACCATGG
185 laAsnPheAlaAspProGluThrThrTyrTrpLysProProArgAsnLysTrpTrpAspGlyTyrHisGl
2871 TGAAGAAGTGGTTGTTATTGATGACTTTTATGGCTGGCTGCCGTGGGATGATCTACTGAGACTGTGTGAT
208 yGluGluValValValIleAspAspPheTyrGlyTrpLeuProTrpAspAspLeuLeuArgLeuCysAsp
EcoRV (2942)
2941 CGATATCCATTGACTGTAGAGACTAAAGGTGGAACTGTACCTTTTTTGGCCCGCAGTATTCTGATTACCA
232 ArgTyrProLeuThrValGluThrLysGlyGlyThrValProPheLeuAlaArgSerIleLeuIleThrS

FIG. 6C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255 erAsnGlnThrProLeuGluTrpTyrSerSerThrAlaValProAlaValGluAlaLeuTyrArgArgIl
3081 TACTTCCTTGGTATTTTGGAAGAATGCTACAGAACAATCCACGGAGGAAGGGGGCCAGTTCGTCACCCTT
278 eThrSerLeuValPheTrpLysAsnAlaThrGluGlnSerThrGluGluGlyGlyGlnPheValThrLeu
SmaI (3199)
NdeI (3173)
SalI (3193)
3151 TCCCCCCCATGCCCTGAATTTCCATATGAAATAAATTACTGAGTCGACCCCGGGTTTTTATAGCTAATTA
302 SerProProCysProGluPheProTyrGluIleAsnTyr
3221 GTCATTTTTTCGTAAGTAAGTATTTTTATTTAATACTTTTTATTGTACTTATGTTAAATATAACTGATGA
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3501 ATTAATATCATCTACTTTAGAATTGATAGGAAATATGAATACCTTTGTAGTAATATCTATACTATCTACA
SacI (3604)
NotI (3596)
3571 CCTAACTCATTAAGACTTTTGATAGGCGGCCGCGAGCTC

PORCINE CIRCOVIRUS RECOMBINANT POXVIRUS VACCINE

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority from U.S. application Ser. No. 60/138,478, filed Jun. 10, 1999. Reference is made to WO-A-99 18214, 1998, French applications Nos. 97/12382, 98/00873, 98/03707, filed Oct. 3, 1997, Jan. 22, 1998, and Mar. 20, 1998, and WO99/29717. Each of the aforementioned U.S., PCT and French applications, and each document cited in the text and the record or prosecution of each of the aforementioned U.S., PCT and French applications ("application cited documents") and each document referenced or cited in each of the application cited documents, is hereby incorporated herein by reference; and, technology in each of the aforementioned U.S., PCT and French applications, and each document cited in the text and the record or prosecution of each of the aforementioned U.S., PCT and French applications can be used in the practice of this invention.

Several publications are referenced in this application. Full citation to these documents is found at the end of the specification preceding the claims, and/or where the document is cited. These documents pertain to the field of this invention; and, each of the documents cited or referenced in this application ("herein cited documents") and each document cited or referenced in herein cited documents are hereby incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to vectors, such as recombinant vectors; for instance, recombinant viruses, such as poxviruses, e.g., modified poxviruses and to methods of making and using the same. In some embodiments, the invention relates to recombinant avipox viruses, such as canarypox viruses, e.g., ALVAC. The invention further relates to such vectors, e.g., poxviruses, that express gene products, e.g., antigen(s), ORF(s), and/or epitope(s) of interest therefrom, of porcine circovirus 2 (PCV2); to immunological compositions or vaccines. The invention yet further relates to such vectors, e.g., poxviruses, that induce an immune response directed to or against PCV2 gene products and/or PCV2; and, to advantageously, such compositions that are immunological, immunogenic or vaccine compositions and/or confer protective immunity against infection by PCV2. The invention yet further relates to the uses of and methods for making and using such vectors and compositions, as well as intermediates thereof, and said intermediates. And, the invention relates to the products therefrom, e.g., from the uses and methods involving the inventive recombinant or poxvirus, such as antibodies from expression.

BACKGROUND OF THE INVENTION

Postweaning multisystemic wasting syndrome (PMWS) is a recently recognized disease of young pigs. PMWS is characterized clinically by progressive weight loss and other symptoms such as tachypnea, dyspnea and jaundice. Pathologically, lymphocytic and granulomatous infiltrates, lymphadenopathy, and, more rarely, lymphocytic and granulomatous hepatitis and nephritis have been observed (Clark, 1997; Harding, 1997).

This disease has been described in different European countries as well as in North America. Treatment and prevention of this disease are not currently available.

Several lines of evidence point to porcine circovirus as the etiologic agent of PMWS (Ellis et al., 1998). Circoviruses have been recovered from pigs with PMWS, and antibodies to porcine circovirus have been demonstrated in pigs with the disease.

Circoviruses are single stranded circular DNA viruses found in a range of animal and plant species. Porcine circovirus was originally isolated as a contaminant from a continuous pig kidney cell line. The cell culture isolate has been designated PK-15 (Meehan et al., 1997). More recently, porcine circovirus obtained from pigs with PMWS has been compared to PK-15. Such viruses differ substantially from PK-15 at the nucleotide and protein sequence level, and have been designated PCV2 (Meehan et al., 1998; Hamel et al., 1998).

As many as thirteen open reading frames (ORFs) have been identified in the PCV2 genome (COL1 to COL13 in the French patent application 98 03707). Four of these ORFs share substantial homology with analogous ORFs within the genome of PK-15. ORF1 (Meehan et al., 1998; corresponding to COL4 in the French patent application 98 03707), comprising nt 398-1342 (GenBank accession number AF055392), has the potential to encode a protein with a predicted molecular weight of 37.7 kD. ORF2 (Meehan et al., 1998; corresponding to COL13 in the French patent application 98 03707), comprising nt 1381-1768 joined to 1-314 (GenBank accession number AF055392), may encode a protein with a predicted molecular weight of 27.8 kD. ORF3 (Meehan et al., 1998; corresponding to COL7 in the French patent application 98 03707), comprising nt 1018-704 (GenBank accession number AF055392), may encode a protein with a predicted molecular weight of 11.9 kD. ORF4 (Meehan et al., 1998; corresponding to COL10 in the French patent application 98 03707), comprising nt 912-733 (GenBank accession number AF055392), may encode a protein with a predicted molecular weight of 6.5 kD.

ORF1 of PCV2 is highly homologous (86% identity) to the ORF1 of the PK-15 isolate (Meehan et al., 1998). The ORF1 protein of PK-15 has been partially characterized (Meehan et al., 1997; Mankertz et al., 1998a). It is known to be essential for virus replication, and is probably involved in the viral DNA replication.

Protein sequence identity between the respective ORF2s was lower (66% identity) than that of the ORF1s but each of the ORF2s shared a highly conserved basic N-terminal region, similar to that observed in the N-terminal region of the major structural protein of the avian circovirus chicken anemia virus (CAV) (Meehan et al., 1998). Recently, Mankertz et al. (1998b) has suggested that the ORF2 of the PK-15 isolate (designated ORF 1 in Mankertz et al., 1998b) codes for a capsid protein.

Greater differences were observed between the respective ORF3s and ORF4s of the PK-15 isolate and PCV2. In each case, there was a deletion of the C-terminal region of PCV2 ORF4 and ORF3 compared to the corresponding ORFs present in the genome of the PK-15 isolate. The highest protein sequence homology was observed at the N-terminal regions of both ORF3 and ORF4 (Meehan et al., 1998).

The transcription analysis of the genome of PCV2 has not been published yet. Recent data obtained with the PK-15 isolate indicated that the ORF2 transcript is spliced (Mankertz et al., 1998b).

Vaccinia virus has been used successfully to immunize against smallpox, culminating in the worldwide eradication of smallpox in 1980. With the eradication of smallpox, a new role for poxviruses became important, that of a genetically

engineered vector for the expression of foreign genes (Panicali and Paoletti, 1982; Paoletti et al., 1984). Genes encoding heterologous antigens have been expressed in vaccinia, often resulting in protective immunity against challenge by the corresponding pathogen (reviewed in Tartaglia et al., 1990). A highly attenuated strain of vaccines, designated MVA, has also been used as a vector for poxvirus-based vaccines. Use of MVA is described in U.S. Pat. No. 5,185,146.

Two additional vaccine vector systems involve the use of naturally host-restricted poxviruses, avipox viruses. Both fowlpoxvirus (FPV; Taylor et al. 1988a, b) and canarypoxvirus (CPV; Taylor et al., 1991 & 1992) have been engineered to express foreign gene products. Fowlpox virus (FPV) is the prototypic virus of the Avipox genus of the Poxvirus family. The virus causes an economically important disease of poultry which has been well controlled since the 1920's by the use of live attenuated vaccines. Replication of the avipox viruses is limited to avian species (Matthews, 1982) and there are no reports in the literature of avipoxvirus causing a productive infection in any non-avian species including man. This host restriction provides an inherent safety barrier to transmission of the virus to other species and makes use of avipoxvirus based vaccine vectors in veterinary and human applications an attractive proposition.

FPV has been used advantageously as a vector expressing antigens from poultry pathogens. The hemagglutinin protein of a virulent avian influenza virus was expressed in an FPV recombinant (Taylor et al., 1988c). After inoculation of the recombinant into chickens and turkeys, an immune response was induced which was protective against either a homologous or a heterologous virulent influenza virus challenge (Taylor et al., 1988c). FPV recombinants expressing the surface glycoproteins of Newcastle Disease Virus have also been developed (Taylor et al., 1990; Edbauer et al., 1990).

Other attenuated poxvirus vectors have been prepared by genetic modifications of wild type strains of virus. The NYVAC vector, derived by deletion of specific virulence and host-range genes from the Copenhagen strain of vaccinia (Tartaglia et al., 1992) has proven useful as a recombinant vector in eliciting a protective immune response against an expressed foreign antigen.

Another engineered poxvirus vector is ALVAC, derived from canarypox virus (ALVAC was deposited with American Type Culture Collection, P.O. Box 1549, Manassas, Va. 20108, USA, under the terms of the Budapest Treaty on Nov. 14, 1996, and is designated as Accession Number VR-2547). ALVAC does not productively replicate in non-avian hosts, a characteristic thought to improve its safety profile (Taylor et al., 1991 & 1992). Both ALVAC and NYVAC are BSL-1 vectors.

One approach to the development of a subunit PCV2 vaccine is the use of live viral vectors to express relevant PCV2 ORFs. Recombinant poxviruses can be constructed in two steps known in the art and analogous to the methods for creating synthetic recombinants of poxviruses such as the vaccinia virus and avipox virus described in U.S. Pat. Nos. 4,769,330; 4,722,848; 4,603,112; 5,110,587; 5,174,993; 5,494,807; and 5,505,941, the disclosures of which are incorporated herein by reference. It can thus be appreciated that provision of a PCV2 recombinant poxvirus, and of compositions and products therefrom particularly ALVAC based PCV2 recombinants and compositions and products therefrom, especially such recombinants containing ORFs 1 and/or 2 of PCV2, and compositions and products therefrom would be a highly desirable advance over the current state of technology.

OBJECTS AND SUMMARY OF THE INVENTION

It is therefore an object of this invention to provide compositions and methods for treatment and prophylaxis of infection with PCV2. It is also an object to provide a means to treat or prevent PMWS.

In one aspect, the present invention relates to an antigenic, immunological, immunogenic, or vaccine composition or a therapeutic composition for inducing an antigenic, immunogenic or immunological response in a host animal inoculated with the composition. The composition advantageously includes a carrier or diluent and a recombinant virus, such as a recombinant poxvirus. The recombinant virus or poxvirus contains and expresses an exogenous nucleic acid molecule encoding an ORF, antigen, immunogen, or epitope of interest from PCV2, or a protein that elicits an immunological response against PCV2 or conditions caused by PCV2, such as PMWS. For instance, the recombinant virus can be a modified recombinant virus or poxvirus; for example, such a virus or poxvirus that has inactivated therein virus-encoded genetic functions, e.g., nonessential virus-encoded genetic functions, so that the recombinant virus has attenuated virulence and enhanced safety. And, the invention further provides the viruses used in the composition, as well as methods for making and uses of the composition and virus.

The virus used in the composition according to the present invention is advantageously a poxvirus, particularly a vaccinia virus or an avipox virus, such as fowlpox virus or canarypox virus and more advantageously, ALVAC. The modified recombinant virus can include, e.g., within a non-essential region of the virus genome, a heterologous DNA sequence which encodes an antigenic protein, e.g., derived from PCV2 ORFs, e.g., PCV2 ORF 1 and/or 2.

In yet another aspect, the present invention relates to an immunogenic composition containing a modified recombinant virus having inactivated nonessential virus-encoded genetic functions so that the recombinant virus has attenuated virulence and enhanced safety. The modified recombinant virus includes, e.g., within a non-essential region of the virus genome, a heterologous DNA sequence which encodes an antigenic protein (e.g., derived from PCV2 ORFs, especially ORFS 1 and/or 2) wherein the composition, when administered to a host, is capable of inducing an immunological response specific to the antigen.

In a still further aspect, the present invention relates to a modified recombinant virus having nonessential virus-encoded genetic functions inactivated therein so that the virus has attenuated virulence, and wherein the modified recombinant virus further contains DNA from a heterologous source, e.g., in a nonessential region of the virus genome. The DNA can code for PCV2 genes such as any or all of PCV2 ORF1, ORF2, ORF3, or ORF4 (Meehan et al., 1998), or epitope(s) of interest therefrom. The genetic functions can be inactivated by deleting an open reading frame encoding a virulence factor or by utilizing naturally host-restricted viruses. The virus used according to the present invention is advantageously a poxvirus, e.g., a vaccinia virus or an avipox virus, such as fowlpox virus or canarypox virus.

Advantageously, the open reading frame that is deleted from the poxvirus or virus geneome is selected from the group consisting of J2R, B13R+B14R, A26L, A56R, C7L–K1L, and I4L (by the terminology reported in Goebel et al., 1990); and, the combination thereof. In this respect, the open reading frame comprises a thymidine kinase gene, a hemorrhagic region, an A type inclusion body region, a hemag-

glutinin gene, a host range gene region or a large subunit, ribonucleotide reductase; or, the combination thereof.

A suitable modified Copenhagen strain of vaccinia virus is identified as NYVAC (Tartaglia et al., 1992), or a vaccinia virus from which has been deleted J2R, B13R+B14R, A26L, A56R, C7L–K11 and 14L or a thymidine kinase gene, a hemorrhagic region, an A type inclusion body region, a hemagglutinin gene, a host range region, and a large subunit, ribonucleotide reductase (See also U.S. Pat. Nos. 5,364,773, 5,494,807, and 5,762,938, with respect to NYVAC and vectors having additional deletions or inactivations from those of NYVAC that are also useful in the practice of this invention).

Preferably, the poxvirus vector is an ALVAC or, a canarypox virus which was attenuated, for instance, through more than 200 serial passages on chick embryo fibroblasts (Rentschler vaccine strain), a master seed therefrom was subjected to four successive plague purifications under agar from which a plague clone was amplified through five additional passages. (See also U.S. Pat. Nos. 5,756,103 and 5,766,599 with respect to ALVAC and TROVAC (an attenuated fowlpox virus useful in the practice of this invention); and U.S. Pat. Nos. 6,004,777, 5,990,091, 5,770,212, 6,033,904, 5,869,312, 5,382,425, and WO 95/30018, with respect to vectors that also can be used in the practice of this invention, such as vectors having enhanced expression, vectors having functions deleted therefrom and vectors useful with respect to porcine hosts (for instance, vectors useful with porcine hosts can include a poxvirus, including a vaccinia virus, an avipox virus, a canarypox virus, and a swinepox virus), as well as with respect to terms used and teachings herein such as "immunogenic composition", "immunological composition", "vaccine", and "epitope of interest", and dosages, routes of administration, formulations, adjuvants, and uses for recombinant viruses and expression products therefrom).

The invention in yet a further aspect relates to the product of expression of the inventive recombinant poxvirus and uses therefor, such as to form antigenic, immunological or vaccine compositions for treatment, prevention, diagnosis or testing; and, to DNA from the recombinant poxvirus which is useful in constructing DNA probes and PCR primers.

These and other embodiments are disclosed or are obvious from and encompassed by the following detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

A better understanding of the present invention will be had by referring to the accompanying drawings, incorporated herein by reference, in which:

FIG. **1** (SEQ ID NOS:1 and 2) shows the nucleotide sequence of a 3.7 kilobase pair fragment of ALVAC DNA containing the C6 open reading frame.

FIG. **2** shows the map of pJP102 donor plasmid.

FIG. **3** (SEQ ID NOS:8 9 and 10) shows the nucleotide sequence of the 2.5 kilobase pair fragment from pJP 102 donor plasmid from the KpnI (position 653) to the SacI (position 3166) restriction sites.

FIG. **4** shows the map of pJP105 donor plasmid.

FIG. **5** shows the map of pJP107 donor plasmid.

FIG. **6** (SEQ ID NOs: 14 and 15) shows the nucleotide sequence of the 3.6 kilobase pair fragment from pJP107 donor plasmid from the KpnI (position 653) to the SacI (position 4255) restriction sites.

DETAILED DESCRIPTION

In one aspect, the present invention relates to a recombinant virus, such as a recombinant poxvirus, containing therein a DNA sequence from PCV2, e.g., in a non-essential region of the poxvirus genome. The poxvirus is advantageously an avipox virus, such as fowlpox virus, especially an attenuated fowlpox virus, or a canarypox virus, especially an attenuated canarypox virus, such as ALVAC.

According to the present invention, the recombinant poxvirus expresses gene products of the foreign PCV2 gene. Specific ORFs of PCV2 are inserted into the poxvirus vector, and the resulting recombinant poxvirus is used to infect an animal. Expression in the animal of PCV2 gene products results in an immune response in the animal to PCV2. Thus, the recombinant poxvirus of the present invention may be used in an immunological composition or vaccine to provide a means to induce an immune response which may, but need not be, protective.

The administration procedure for recombinant poxvirus-PCV2 or expression product thereof, compositions of the invention such as immunological, antigenic or vaccine compositions or therapeutic compositions, can be via a parenteral route (intradermal, intramuscular or subcutaneous). Such an administration enables a systemic immune response, or humoral or cell-mediated responses.

More generally, the inventive poxvirus-PCV2 recombinants, antigenic, immunological or vaccine poxvirus-PCV2 compositions or therapeutic compositions can be prepared in accordance with standard techniques well known to those skilled in the pharmaceutical or veterinary art. Such compositions can be administered in dosages and by techniques well known to those skilled in the medical or veterinary arts taking into consideration such factors as the age, sex, weight, species and condition of the particular patient, and the route of administration. The compositions can be administered alone, or can be co-administered or sequentially administered with compositions, e.g., with "other" immunological, antigenic or vaccine or therapeutic compositions thereby providing multivalent or "cocktail" or combination compositions of the invention and methods employing them. Again, the ingredients and manner (sequential or co-administration) of administration, as well as dosages can be determined taking into consideration such factors as the age, sex, weight, species and condition of the particular patient, and, the route of administration. In this regard, reference is made to U.S. Pat. No. 5,843,456, incorporated herein by reference, and directed to rabies compositions and combination compositions and uses thereof.

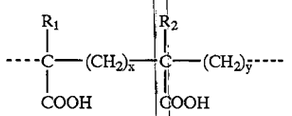
Examples of compositions of the invention include liquid preparations for orifice, e.g., oral, nasal, anal, vaginal, peroral, intragastric, etc., administration such as suspensions, syrups or elixirs; and, preparations for parenteral, subcutaneous, intradermal, intramuscular or intravenous administration (e.g., injectable administration) such as sterile suspensions or emulsions. In such compositions the recombinant poxvirus or antigens may be in admixture with a suitable carrier, diluent, or excipient such as sterile water, physiological saline, glucose or the like. The compositions can also be lyophilized. The compositions can contain auxiliary substances such as wetting or emulsifying agents, pH buffering agents, adjuvants, gelling or viscosity enhancing additives, preservatives, flavoring agents, colors, and the like, depending upon the route of administration and the preparation desired. Standard texts, such as "REMINGTON'S PHARMACEUTICAL SCIENCE", 17th edition, 1985, incorporated herein by reference, may be consulted to prepare suitable preparations, without undue experimentation. Suitable dosages can also be based upon the Examples below.

The compositions can contain at least one adjuvant compound chosen from the polymers of acrylic or methacrylic acid and the copolymers of maleic anhydride and alkenyl derivative.

The preferred adjuvant compounds are the polymers of acrylic or methacrylic acid which are cross-linked, especially with polyalkenyl ethers of sugars or polyalcohols. These compounds are known by the term carbomer (Phameuropa Vol. 8, No. 2, June 1996). Persons skilled in the art can also refer to U.S. Pat. No. 2,909,462 (incorporated herein by reference) which describes such acrylic polymers cross-linked with a polyhydroxylated compound having at least 3 hydroxyl groups, preferably not more than 8, the hydrogen atoms of at least three hydroxyls being replaced by unsaturated aliphatic radicals having at least 2 carbon atoms. The preferred radicals are those containing from 2 to 4 carbon atoms, e.g. vinyls, allyls and other ethylenically unsaturated groups. The unsaturated radicals may themselves contain other substituents, such as methyl. The products sold under the name Carbopol® (BF Goodrich, Ohio, USA) are particularly appropriate. They are cross-linked with an allyl sucrose or with allyl pentaerythritol. Among then, there may be mentioned Carbopol® 974P, 934P and 971P.

Among the copolymers of maleic anhydride and alkenyl derivative, the copolymers EMA® (Monsanto) which are copolymers of maleic anhydride and ethylene, linear or cross-linked, for example cross-linked with divinyl ether, are preferred. Reference may be made to J. Fields et al., Nature, 186: 778–780, 4 June 1960, incorporated herein by reference.

From the point of view of their structure, the polymers of acrylic or methacrylic acid and the copolymers EMA® are preferably formed of basic units of the following formula:



in which:

R_1 and R_2, which are identical or different, represent H or CH_3

x=0or 1, preferably x=1

y=1 or 2, with x+y=2

For the copolymers EMA®, x=0 and y=2. For the carbomers, x=y=1.

The dissolution of these polymers in water leads to an acid solution which will be neutralized, preferably to physiological pH, in order to give the adjuvant solution into which the vaccine itself will be incorporated. The carboxyl groups of the polymer are then partly in COO^- form.

Preferably, a solution of adjuvant according to the invention, especially of carbomer, is prepared in distilled water, preferably in the presence of sodium chloride, the solution obtained being at acidic pH. This stock solution is diluted by adding it to the desired quantity (for obtaining the desired final concentration), or a substantial part thereof, of water charged with NaCl, preferably physiological saline (NaCL 9 g/l) all at once in several portions with concomitant or subsequent neutralization (pH 7.3 to 7.4), preferably with NaOH. This solution at physiological pH will be used as it is for mixing with the vaccine, which may be especially stored in freeze-dried, liquid or frozen form.

The polymer concentration in the final vaccine composition will be 0.01% to 2% w/v, more particularly 0.06 to 1% w/v, preferably 0.1 to 0.6% w/v. The immunological compositions according to the invention may be associated to at least one live attenuated, inactivated, or sub-unit vaccine, or recombinant vaccine (e.g. poxvirus as vector or DNA plasmid) expressing at least one immunogen from another pig pathogen.

The invention encompasses vectors encoding and expressing equivalent nucleotide sequences, that is to say the sequences which change neither the functionality or the strain specificity (say strain of type 1 and strain of type 2) of the gene considered or those of the polypeptides encoded by this gene. The sequences differing through the degeneracy of the code are, of course, included.

The PCV-2 sequences used in the examples are derived from Meehan et al. (Strain Imp.1010; ORF1 nucleotides 398–1342; ORF2 nucleotides 1381–314; and correspond respectively to ORF4 and ORF13 in U.S. application Ser. No. 09/161,092 of Sep. 25 1998 and to COL4 and COL13 in WO-A-9918214). Other PCV-2 strains and their sequences have been published in WO-A-9918214 and are called Imp1008, Imp999, Imp1011-48285 and Imp1011-48121, as well as in A.L. Hamel et al. J. Virol. June 1998, vol 72, 6: 5262–5267 (GenBank AF027217) and in I. Morozov et al. J. Clinical Microb. September 1998 vol. 36, 9: 2535–2541, as well as GenBank AF086834, AF086835 and AF086836, and give access to equivalent ORF sequences. These sequences, or ORFs therefrom, or regions thereof encoding an antigen or epitope of interest can also be used in the practice of this invention.

The invention also encompasses the equivalent sequences to those used herein and in documents cited herein; for instance, sequences that are capable of hybridizing to the nucleotide sequence under high stringency conditions (see, e.g., Sambrook et al. (1989). Among the equivalent sequences, there may also be mentioned the gene fragments conserving the immunogenicity of the complete sequence, e.g., an epitope of interest.

The homology of the whole genome between PCV types 1 and 2 is about 75%. For ORF1, it is about 86%, and for ORF2, about 66%. On the contrary, homologies between genomes and between ORFs within type 2 are generally above 95%.

Also, equivalent sequences useful in the practice of this present invention, for ORF1, are those sequences having an homology equal or greater than 88%, advantageously 90% or greater, preferably 92% or 95% or greater with ORF1 of strain Imp1010, and for ORF2, are those sequences having an homology equal or greater than 80%, advantageously 85% or greater, preferably 90% or 95% or greater with ORF2 of strain Imp1010.

ORF1 and ORF2 according to Meehan 1998 has the potential to encode proteins with predicted molecular weights of 37.7 kD and 27.8 kD respectively. ORF3 and ORF4 (according to Meehan et al. 1998, correspond to ORF7 and ORF10 respectively in WO-A-9918214) has the potential to encode proteins with predicted molecular weights of 11.9 and 6.5 kD respectively. The sequence of these ORFs is also available in Genbank AF 055392. They can also be incorporated in plasmids and be used in accordance with the invention alone or in combination, e.g. with ORF1 and/or ORF2.

The other ORFs 1–3 and 5, 6, 8–9, 11–12 disclosed in U.S. application Ser. No. 09/161,092 of Sep. 25 1998 (COLs 1–3 and 5, 6, 8–9, 11–12 in WO-A-9918214), or region(s) thereof encoding an antigen or epitope of interest, may be used in the practice of this invention, e.g., alone or in combination or otherwise with each other or with the ORFs 1 and 2 or region(s) thereof encoding antigen(s) or epitope (s).

This invention also encompasses the use of equivalent sequences; for instance, from ORFs of various PCV-2 strains cited herein. For homology, one can determine that there are equivalent sequences which come from a PCV strain having

an ORF2 and/or an ORF1 which have an homology as defined above with the corresponding ORF of strain 1010.

For ORF3 according to Meehan, an equivalent sequence has homology thereto that is advantageously, for instance, equal or greater than 80%, for example 85% or greater, preferably 90% or 95% or greater with ORF3 of strain Impl010. For ORF4 according to Meehan 1998, advantageously an equivalent sequence has homology that is equal or greater than 86%, advantageously 90% or greater, prefcrably than 95% or greater with ORF4 of strain Imp1010.

From the genomic nucleotide sequence, e.g. those disclosed in WO-A-99 18214, it is routine art to determine the ORFs using a standard software, such as MacVector®. Also, alignment of genomes with that of strain 1010 and comparison with strain 1010 ORFs allows the one skilled in the art to readily determine the ORFs of the genome of another strain (e.g. other strains disclosed in WO-A-99 18214 or in other herein cited documents).

Using software or making sequence alignment is not undue experimentation and provides direct access to equivalent ORFs or nucleic acid molecules.

Nucleotide sequence homology can be determined using the "Align" program of Myers and Miller, ("Optimal Alignments in Linear Space", CABIOS 4, 11–17, 1988, incorporated herein by reference) and available at NCBI. Alternatively or additionally, the term "homology" or "identity", for instance, with respect to a nucleotide or amino acid sequence, can indicate a quantitative measure of homology between two sequences. The percent sequence homology can be calculated as $(N_{ref}-N_{dif})^* 100N_{ref}$, wherein N_{dif} is the total number of non-identical residues in the two sequences when aligned and wherein N_{ref} is the number of residues in one of the sequences. Hence, the DNA sequence AGTCAGTC will have a sequence similarity of 75% with the sequence AATCAATC (N_{ref}=8; N_{dif}=2).

Alternatively or additionally, "homology" or "identity" with respect to sequences can refer to the number of positions with identical nucleotides or amino acids divided by the number of nucleotides or amino acids in the shorter of the two sequences wherein alignment of the two sequences can be determined in accordance with the Wilbur and Lipman algorithm (Wilbur and Lipman, 1983 PNAS USA 80:726, incorporated herein by reference), for instance, using a window size of 20 nucleotides, a word length of 4 nucleotides, and a gap penalty of 4, and computer-assisted analysis and interpretation of the sequence data including alignment can be conveniently performed using commercially available programs (e.g., Intelligenetics™Suite, Intelligenetics Inc. CA).. When RNA sequences are said to be similar, or have a degree of sequence identity or homology with DNA sequences, thymidine (T) in the DNA sequence is considered equal to uracil (U) in the RNA sequence.

RNA sequences within the scope of the invention can be derived from DNA sequences, by thymidine (T) in the DNA sequence being considered equal to uracil (U) in RNA sequences.

Additionally or alternatively, amino acid sequence similarity or identity or homology can be determined using the BlastP program (Altschul et al., Nucl. Acids Res. 25, 3389–3402, incorporated herein by reference) and available at NCBI. The following references (each incorporated herein by reference) provide algorithms for comparing the relative identity or homology of amino acid residues of two proteins, and additionally or alternatively with respect to the foregoing, the teachings in these references can be used for determining percent homology or identity: Needleman S B and Wunsch C D, "A general method applicable to the search for similarities in the amino acid sequences of two proteins," *J. Mol. Biol.* 48:444–453 (1970); Smith T F and Waterman M S, "Comparison of Bio-sequences," *Advances in Applied Mathematics* 2:482–489 (1981); Smith T F, Waterman M S and Sadler J R, "Statistical characterization of nucleic acid sequence functional domains," *Nucleic Acids Res.,* 11:2205–2220 (1983); Feng D F and Dolittle R F, "Progressive sequence alignment as a prerequisite to correct phylogenetic trees," *J. of Molec. Evol.,* 25:351–360 (1987); Higgins D G and Sharp P M, "Fast and sensitive multiple sequence alignment on a microcomputer," *CABIOS,* 5: 151–153 (1989); Thompson J D, Higgins D G and Gibson T J, "ClusterW: improving the sensitivity of progressive multiple sequence alignment through sequence weighing, positions-specific gap penalties and weight matrix choice, *Nucleic Acid Res.,* 22:4673–480 (1994); and, Devereux J, Haeberlie P and Smithies O, "A comprehensive set of sequence analysis program for the VAX," *Nucl. Acids Res.,* 12: 387–395 (1984).

This invention not only allows for administration to adult pigs, but also to the young and to gestating females; in the latter case, this makes it possible, in particular, to confer passive immunity onto the newborns (maternal antibodies). Preferably, female pigs are inoculated prior to breeding; and/or prior to serving, and/or during gestation. Advantageously, at least one inoculation is done before serving and it is preferably followed by an inoculation to be performed during gestation, e.g., at about mid-gestation (at about 6–8 weeks of gestation) and/or at the end of gestation (at about 11–13 weeks of gestation). Thus, an advantageous regimen is an inoculation before mating and/o serving and a booster inoculation during gestation. Thereafter, there can be reinoculation before each serving and/or during gestation at about mid-gestation and/or at the end of gestation. Preferably, reinoculations are during gestation. Male pigs also can be inoculated, e.g., prior to mating.

Piglets, such as piglets from vaccinated females (e.g., inoculated as herein discussed), are inoculated within the first weeks of life, e.g., inoculation at one and/or two and/or three and/or four and/or five weeks of life. Preferably, piglets are first inoculated within the first week of life or within the third week of life (e.g., at the time of weaning). Advantageously, such piglets are then boosted two to four weeks later.

The present invention is additionally described by the following illustrative, non-limiting Examples.

EXAMPLES

The invention in a preferred embodiment is directed to recombinant poxviruses containing therein a DNA sequence from PCV2 in a nonessential region of the poxvirus genome. The recombinant poxviruses express gene products of the foreign PCV2 gene. In particular, ORF2 and ORF1 genes encoding PCV2 proteins were isolated, characterized and inserted into ALVAC (canarypox vector) recombinants. The molecular biology techniques used are the ones described by Sambrook et al. (1989).

Cell Lines and Virus Strains. The strain of PCV2 designated Imp.1010-Stoon has been previously described (Meehan et al., 1998). It was isolated from mesenteric lymph node tissues from a diseased pig originating from Canada. Cloning of the PCV2 genome was described by Meehan et al. (1998). Plasmid pGem7Z-Imp1010-Stoon-EcoRI No. 14 contains the PCV2 genome as an EcoRI fragment inserted into the EcoRI site of plasmid pGem-7Z (Promega, Madison, Wis.). The complete nucleotide sequence of the Imp.1010-Stoon PCV2 strain has been determined by Mee-

han et al. (1998) and is available under the GenBank accession number AF055392.

The parental canarypox virus (Rentschler strain) is a vaccinal strain for canaries. The vaccine strain was obtained from a wild type isolate and attenuated through more than 200 serial passages on chick embryo fibroblasts. A master viral seed was subjected to four successive plaque purifications under agar and one plaque clone was amplified through five additional passages after which the stock virus was used as the parental virus in in vitro recombination tests. The plaque purified canarypox isolate is designated ALVAC. ALVAC was deposited Nov. 14, 1996 under the terms of the Budapest Treaty at the American Type Culture Collection, ATCC accession number VR-2547.

The generation of poxvirus recombinants involves different steps: (1) construction of an insertion plasmid containing sequences ("arms") flanking the insertion locus within the poxvirus genome, and multiple cloning site (MCS) localized between the two flanking arms (e.g., see Example 1); (2) construction of donor plasmids consisting of an insertion plasmid into the MCS of which a foreign gene expression cassette has been inserted (e.g. see Examples 2 to 5); (3) in vitro recombination in cell culture between the arms of the donor plasmid and the genome of the parental poxvirus allowing the insertion of the foreign gene expression cassette into the appropriate locus of the poxvirus genome, and plaque purification of the recombinant virus (e.g. see Example 6).

PCV2 recombinant immunogens may be used in association with PCV1 immunogens, for immunization of animals against PMWS. In a least preferred approach, PCV1 immunogens may be used without PCV2 immunogens.

Example 1

Construction of Canarypox Insertion Plasmid at C6 Locus

FIG. 1 (SEQ ID NO:1) is the sequence of a 3.7 kb segment of canarypox DNA. Analysis of the sequence revealed an ORF designated C6L initiated at position 377 and terminated at position 2254. The following describes a C6 insertion plasmid constructed by deleting the C6 ORF and replacing it with a multiple cloning site (MCS) flanked by transcriptional and translational termination signals. A 380 bp PCR fragment was amplified from genomic canarypox DNA using oligonucleotide primers C6A1 (SEQ ID NO:2) and C6B1 (SEQ ID NO:3). A 1155 bp PCR fragment was amplified from genomic canarypox DNA using oligonucleotide primers C6C1 (SEQ ID NO:4) and C6D1 (SEQ ID NO:5). The 380 bp and 1155 bp fragments were fused together by adding them together as template and amplifying a 1613 bp PCR fragment using oligonucleotide primers C6A1 (SEQ ID NO:2) and C6D1 (SEQ ID NO:5). This fragment was digested with SacI and KpnI, and ligated into pBluescript SK+ (Stratagene, La Jolla, Calif., USA) digested with SacI/KpnI. The resulting plasmid, pC6L was confirmed by DNA sequence analysis. It consists of 370 bp of canarypox DNA upstream of C6 ("C6 left arm"), vaccinia early termination signal, translation stop codons in six reading frames, an MCS containing SmaI, PstI, XhoI and EcoRI sites, vaccinia early termination signal, translation stop codons in six reading frames and 1156 bp of downstream canary pox sequence ("C6 right arm").

Plasmid pJP099 was derived from pC6L by ligating a cassette containing the vaccinia H6 promoter (described in Taylor et al. (1988c), Guo et al. (1989), and Perkus et al. (1989)) coupled to a foreign gene into the SmaI/EcoRI sites of pC6L. This plasmid pJP099 contains a unique EcoRV site and a unique NruI site located at the 3' end of the H6 promoter, and a unique SalI site located between the STOP codon of the foreign gene and the C6 left arm. The ~4.5 kb EcoRV/SalI or NruI/SalI fragment from pJP099 contains therefore the plasmid sequence (pBluescript SK+; Stratagene, La Jolla, Calif., USA), the 2 C6 arms and the 5' end of the H6 promoter until the EcoRV or NruI site.

Sequences of the Primers

Primer C6A1 (SEQ ID NO:3)

ATCATCGAGCTCGCGGCCGCCTATCAAAAGTCTT-AATGAGTT

Primer C6B1 (SEQ ID NO:4)

GAATTCCTCGAGCTGCAGCCCGGGTTTTTATAG-CTAATTAGTCATTTTTTCGTAAGTA AGTATTTT-TATTTAA

Primer C6C1 (SEQ ID NO:5)

CCCGGGCTGCAGCTCGAGGAATTCTTTT-TATTGATTAACTAGTCAAATGAGTATATA TAAT-TGAAAAAGTAA

Primer C6D1 (SEQ ID NO:6)

GATGATGGTACCTTCATAAATACAAGTTTGATTAAA-CTTAAGTTG

Example 2

Construction of ALVACC Donor Plasmid for PCV2 0RF2

Plasmid pGem7Z-Imp1010-Stoon-EcoRI No. 14, containing the PCV2 genome as an EcoRI fragment in plasmid pGem-7Z, was digested with EcoRI, and a 1768 bp fragment was isolated and ligated.

In order to insert PCV2 ORF 2 into an appropriate ALVAC insertion vector: Primers JP760 (SEQ ID NO:6) and JP773 (SEQ ID NO:7) were used to amplify PCV2 ORF 2 from the 1768 bp ligated EcoRI fragment (see above) resulting in PCR J1304. Primer JP760 (SEQ ID NO:7) contains the 3' end of the H6 promoter from EcoRV and the 5' end of PCV2 ORF 2. Primer JP773 (SEQ ID NO:8) contains the 3' end of PCV2 ORF 2 followed by a SalI site. The product of PCR J1304 was then digested with EcoRV/SalI and cloned as a ~750 bp fragment into a ~4.5 kb EcoRVISalI fragment from pJP099 (see above in Example 1). The resulting plasmid was confirmed by sequence analysis and designated pJP102 (see the map of pJP102 in FIG. **2** and the sequence (SEQ ID NO:9) in FIG. **3**). The sequence of ORF 2 matches sequence available in GenBank, Accession Number AF055392. The donor plasmid pJP102 (linearized with NotI) was used in an in vitro recombination (IVR) test to generate ALVAC recombinant vCP1614 (see Example 6).

Sequence of the Primers

JP760 (SEQ ID NO:7)

CAT-CAT-CAT-GAT-ATC-CGT-TAA-GTT-TGT-ATC-GTA-ATG-ACG-TAT-CCA-AGG-AGG-CG

JP773 (SEQ ID NO:8)

TAC-TAC-TAC-GTC-GAC-TTA-GGG-TTT-AAG-TGG-GGG-GTC

Example 3

Construction of an ALVACC Donor Plasmid for PCV2 0RF2 and ORF1

PCV2 ORF1 was amplified by PCR using primers JP774 (SEQ ID NO:9) and JP775 (SEQ ID NO:10) on plasmid pGem7Z-Imp1010-Stoon-EcoRI No. 14 resulting in PCR J1311. Primer JP774 (SEQ ID NO:10) contains the 3' end of the H6 promoter from NruI and the 5' end of PCV2 ORF1. Primer JP775 (SEQ ID NO:11) contains the 3' end of PCV2 ORF1 followed by a SalI site. The product of PCR J1311 (~1 Kb) was cloned into pCR2.1 (Invitrogen, Carlsbad, Calif.). The resulting plasmid was confirmed by sequence analysis and designated pJP104. The sequence of ORF1 matches

sequence available in GenBank, Accession Number AF055392. A ~970 bp NruISalI fragment was isolated from pJP104 and cloned into a ~4.5 kb NruI/SalI fragment from pJP099 (see Example 1), resulting in a plasmid which was confirmed by restriction analysis and designated pJP105 (see FIG. **4**). The donor plasmid pJP105 could be used in an in vitro recombination test (described in Example 6) to generate ALVAC recombinant expressing the PCV2 ORF1.

A ~838 bp BamHI/SalI from pJP102 (see Example 2) was blunted using the Klenow fragment of DNA polymerase, and was cloned into the Klenow-blunted EcoRI site of pJP105. Clones were checked for orientation of insert by restriction analysis and a head-to-head orientation was chosen. This plasmid was confirmed by sequence analysis and designated pJP107 (see the map of pJP107 in FIG. **5** and the sequence (SEQ ID NO:11) in FIG. **6**). The donor plasmid pJP107 (linearized with NotI) was used in an in vitro recombination 5 (IVR) test to generate the ALVAC recombinant vCP1615 (see Example 6).

Sequence of the Primers

JP774 (SEQ ID NO:7)

CAT-CAT-CAT-TCG-CGA-TAT-CCG-TTA-AGT-TTG-TAT-CGT-AAT-GCC-CAG-CAA-GAA-GAA-TGG

JP775 (SEQ ID NO:12)

TAC-TAC-TAC-GTC-GAC-TCA-GTA-ATT-TAT-TTC-ATA-TGG

Example 4

Construction of ALVACC Donor Plasmid for PCV1 RF2

Plasmid pPCV1 (B. Meehan et al. J. Gen. Virol. 1997. 78. 221–227), containing the PCV1 genome as a PstI fragment in plasmid pGem-7Z, was used as a template to amplify the PCV1 ORF2.

In order to insert PCV2 ORF 2 into an appropriate ALVAC insertion vector: Primers JP787 (SEQ ID NO:16) and JP788 (SEQ ID NO:17) were used to amplify PCV1 ORF 2 from plasmid pPCV1 (see above) resulting in PCR J1315. Primer JP787 (SEQ ID NO:16) contains the 3' end of the H6 promoter from EcoRV and ORF 2 followed by a SalI site. The product of PCR J1315 was then digested with EcoRV/SalI and cloned as a ~750 bp fragment into a ~4.5 kb EcoRV/SalI fragment from pJP099 (see above in Example 1). The resulting plasmid was confirmed by sequence analysis and designated pJP113. The sequence of ORF 2 matches sequence available in GenBank, Accession Number U49186. The donor plasmid pJP113 (linearized with NotI) was used in an in vitro recombination (IVR) test to generate ALVAC recombinant vCP1621 (see Example 7).

Sequence of the Primers

JP787 (SEQ ID NO:17)

CAT-CAT-CAT-GAT-ATC-CGT-TAA-GTT-TGT-ATC-GTA-ATG-ACG-TGG-CCA-AGG-AGG-CG

JP788 (SEQ ID NO:13)

TAC-TAC-TAC-GTC-GAC-TTA-TTT-ATT-TAG-AGG-GTC-TTT-TAG-G

Example 5

Construction of an ALVACC Donor Plasmid for PCV1 RF2 and ORF1

Plasmid pPCV1 (see Example 4 above), containing the PCV1 genome as a PstI fragment in plasmid pGem-7Z, was digested with PstI, and a 1759 bp fragment was isolated and ligated.

Primers JP789 (SEQ ID NO:14) and JP790 (SEQ ID NO:15) were used to amplify PCV1 ORF1 from the 1759 bp ligated PstI fragment (see above), resulting in PCR J1316. Primer JP789 (SEQ ID NO:14) contains the 3' end of the H6 promoter from NruI and the 5' end of PCV1 ORF1. Primer JP790 (SEQ ID NO:15) contains the 3' end of PCV1 ORF1 followed by a SalI site. The product of PCR J1316 (~1 Kb) was cloned into pCR2.1 (Invitrogen, Carlsbad, Calif.). The resulting plasmid was confirmed by sequence analysis and designated pJP114. The sequence of ORF1 matches sequence available in GenBank, Accession Number U49186. A ~970 bp NruI/SalI fragment was isolated from pJP114 and cloned into a ~4.5 kb NruI/SalI fragment from pJP099 (see Example 1), resulting in a plasmid which was confirmed by restriction analysis and designated pJP115. The donor plasmid pJP115 could be used in an in vitro recombination test (described in Example 7) to generate ALVAC recombinant expressing the PCV1 ORF1.

A ~838 bp BamHI/SalI from pJP113 (see Example 4) was blunted using the Klenow fragment of DNA polymerase, and was cloned into the Klenow-blunted EcoRI site of pJP115. Clones were checked for orientation of insert by restriction analysis and a head-to-head orientation was chosen. This plasmid was confirmed by sequence analysis and designated pJP117. The donor plasmid pJP117 (linearized with NotI) was used in an in vitro recombination (IVR) test to generate the ALVAC recombinant vCP1622 (see Example 7).

Sequence of the Primers

JP789 (SEQ ID NO:18)

CAT-CAT-CAT-TCG-CGA-TAT-CCG-TTA-AGT-TTG-TAT-CGT-AAT-GCC-AAG-CAA-GAA-AAG-CGG

JP790 (SEQ ID NO:19)

TAC-TAC-TAC-GTC-GAC-TCA-GTA-ATT-TAT-TTT-ATA-TGG

Example 6

Generation of ALVAC-PCV2 RECOMBINANTS

Plasmids pJP102 (see Example 2 and FIG. **2**) and pJP107 (see Example 3 and FIG. **5**) were linearized with NotI and transfected into ALVAC infected primary CEF cells by using the calcium phosphate precipitation method previously described (Panicali and Paoletti, 1982; Piccini et al., 1987). Positive plaques were selected on the basis of hybridization to specific PCV2 radiolabeled probes and subjected to four sequential rounds of plaque purification until a pure population was achieved. One representative plaque from each IVR was then amplified and the resulting ALVAC recombinants were designated vCP1614 and vCP1615. The vCP1614 virus is the result of recombination events between ALVAC and the donor plasmid pJP102, and it contains the PCV2 ORF2 inserted into the ALVAC C6 locus. The vCP1615 virus is the result of recombination events between ALVAC and the donor plasmid pJP107, and it contains the PCV2 ORF2 and ORF1 inserted into the ALVAC C6 locus in a head-to-head orientation.

In a similar fashion, a recombinant ALVAC expressing only PCV2 ORF1 can be generated using the donor plasmid pJP105 described in Example 3.

Immunofluorescence. In order to determine if the PCV2 proteins were expressed in ALVAC recombinant infected Vero cells, immunofluorescence (IF) analysis was performed. Infected Vero cells were washed with PBS 24 hrs after infection (m.o.i. of approx. 10) and fixed with 95% cold aceton for 3 minutes at room temperature. Five monoclonal antibody (MAb) preparations (hybridoma supernatant) specific for PCV2 ORF1 (PCV2 199 1D3GA & PCV2 210 7G5GD) or ORF2 (PCV2 190 4C7CF, PCV2 190 2B1BC & PCV2 190 3A8BC) were used as the first antibody. These specific monoclonal antibodies were obtained from Merial-Lyon. Monoclonal antibodies can also be obtained following the teachings of documents cited herein, e.g. WO-A-99 18214, 1998, French applications Nos. 97/12382, 98/00873,

98/03707, filed Oct. 3, 1997, Jan. 22, 1998, and Mar. 20, 1998, and WO99/29717, incorporated herein by reference. The IF reaction was performed as described by Taylor et al. (1990).

PCV2 specific immunofluorescence with the three ORF2-specific antibodies could be detected in cells infected with vCP1614 and cells infected with vCP1615. PCV2 specific immunofluorescence with the two ORF1 -specific antibodies could be detected in cells infected with vCP1615 only. These results indicated that, as expected, vCP1614 expresses only ORF2, whereas vCP1615 expresses both ORF1 and ORF2. No fluorescence was detected in parental ALVAC infected Vero cells, nor in uninfected Vero cells.

Example 7

Generation of ALVAC-PCV1 Recombinants

Plasmids pJP113 (see Example 4) and pJP117 (see Example 5) were linearized with NotI and transfected into ALVAC infected primary CEF cells by using the calcium phosphate precipitation method previously described (Panicali and Paoletti, 1982; Piccini et al., 1987). Positive plaques were selected on the basis of hybridization to specific PCV1 radiolabeled probes and subjected to four sequential rounds of plaque purification until a pure population was achieved. One representative plaque from each IVR was then amplified and the resulting ALVAC recombinants were designated vCP1621 and vCP1622. The vCP1621 virus is the result of recombination events between ALVAC and the donor plasmid pJP113, and it contains the PCV1 ORF2 inserted into the ALVAC C6 locus. The vCP1622 virus is the result of recombination events between ALVAC and the donor plasmid pJP117, and it contains the PCV1 ORF2 and ORF1 inserted into the ALVAC C6 locus in a head-to-head orientation.

In a similar fashion, a recombinant ALVAC expressing only PCV1 ORF1 can be generated using the donor plasmid pJP115 described in Example 5.

Immunofluorescence. In order to determine if the PCV1 proteins were expressed in ALVAC recombinant infected Vero cells, immunofluorescence (IF) analysis was performed. Infected Vero cells were washed with PBS 24 hrs after infection (m.o.i. of approx 10) and fixed with 95% cold aceton efor 3 minutes at room temperature. A specific anti-PCV1 pig polyclonal serum (Allan G. et al. Vet. Microbiol. 1999. 66: 115–123) was used as the first antibody. The IF reaction was performed as described by Taylor et al. (1990).

PCV1 specific immunofluorescence could be detected in cells infected with vCP1621 and cells infected with vCP1622. These results indicated that, as expected, vCP1621 and vCP1622 express PCV1-specific products. No fluorescence was detected with a PCV2-specific pig polyclonal serum in cells infected with vCP1621 and in cells infected with vCP1622. No fluorescence was detected in parental ALVAC infected Vero cells, nor in uninfected Vero cells.

Example 8

Formulation of Recombinant Canarypox Viruses with Carbopol™ 974P

For the preparation of vaccines, recombinant canarypox viruses vCP1614 and vCP1615 (Example 6) can be mixed with solutions of carbomer. In the same fashion, recombinant canarypox viruses vCP1621 and vCP1622 (Example 7) can be mixed with solutions of carbomer. The carbomer component used for vaccination of pigs according to the present invention is the Carbopol™ 974P manufactured by the company BF Goodrich (molecular weight of # 3,000,000). A 1.5 % Carbopol™ 974P stock solution is first prepared in distilled water containing 1 g/l of sodium chloride. This stock solution is then used for manufacturing a 4 mg/ml Carbopol™ 974P solution in physiological water. The stock solution is mixed with the required volume of physiological water, either in one step or in several successive steps, adjusting the pH value at each step with a 1N (or more concentrated) sodium hydroxide solution to get a final pH value of 7.3–7.4. This final Carbopol™ 974P solution is a ready-to-use solution for reconstituting a lyophilized recombinant virus or for diluting a concentrated recombinant virus stock. For example, to get a final viral suspension containing 10^8 pfu per dose of 2 ml, one can dilute 0,1 ml of a 10^9 pfU/ml stock solution into 1,9 ml of the above Carbopol™ 974P 4 mg/ml ready-to-use solution. In the same fashion, Carbopol™ 974P 2 mg/ml ready-to-use solutions can also be prepared.

Example 9

Immunization of Pigs and Subsequent Challenge

9.1. Immunization of 1 Day-Old Piglets

Groups of piglets, caesarian-derived at Day 0, are placed into isolators. The piglets are vaccinated by intramuscular route at Day 2 with various vaccine solutions. Vaccine viral suspensions are prepared by dilution of recombinant viruses stocks in sterile physiological water (NaCl 0.9 %). Suitable ranges for viral suspensions can be determined empiracally, but will generally range from 10^6 to 10^{10}, and preferably about 10^{10}, pfu/dose. Vaccine solutions can also be prepared by mixing the recombinant virus suspension with a solution of Carbopol™ 974P, as described in Example 8.

Piglets are vaccinated either with:

Recombinant virus vCP1614 (Example 2);

Recombinant virus vCP1615 (Example 3);

Recombinant virus vCP1614 mixed with Carbopol (4 mg/ml solution); or

Recombinant virus vCP1615 mixed with Carbopol (4 mg/ml solution).

The viral suspensions contain 10^8 plaque forming units (pfu) per dose. Each viral suspension is injected by intramuscular route under a volume of 1 ml. The intramuscular injection is administered into the muscles of the neck.

Two injections of viral suspensions are administered at Day 2 and Day 14 of the experiment. A challenge is done on Day 21 by an oronasal administration of a viral suspension prepared from a culture of PCV-2 virulent strain. After challenge, piglets are monitored during 3 weeks for clinical signs specific of the post-weaning multisystemic syndrome. The following signs are scored:

Rectal temperature: daily monitoring for 2 weeks post-challenge, then 2 measures of rectal temperature during the third week.

Weight: piglets are weighed right before the challenge, and then weekly during the first 3 weeks post-challenge.

Blood samples are taken at Day 2, day 14, Day 21, Day 28, Day 35 and Day 42 of the experiment in order to monitor viremia levels and anti-PCV-2 specific antibody titers.

Necropsies: at Day 42, all surviving piglets are humanely euthanized and necropsied to look for specific PWMS macroscopic lesions. Tissue samples are prepared from liver, lymph nodes, spleen, kidneys and thymus in order to look for specific histological lesions.

9.2. Immunization OF 5–7 Week-Old Piglets

5–7 week-old piglets, free of anti-PCV-2 specific maternal antibodies, are vaccinated by intramuscular route with various vaccine solutions. Vaccine viral suspensions are prepared by dilution of recombinant viruses stocks in sterile physiological water (NaCl 0.9%). Vaccine solutions can also

be prepared by mixing the recombinant virus suspension with a solution of Carbopol™ 974P, as described in Example 8.

Piglets are vaccinated either with:

Recombinant virus vCP1614 (Example 2);

Recombinant virus vCP1615 (Example 3);

Recombinant virus vCP1614 mixed with Carbopol (4 mg/ml solution); or

Recombinant virus vCP1615 mixed with Carbopol (4 mg/ml solution).

The viral suspensions contain 10^8 plaque forming units (pfu) per dose. Each viral suspension is injected by intramuscular route under a volume of 2 ml. The intramuscular injection is administered into the muscles of the neck. Two injections of the viral suspensions are administered at Day 0 and Day 21 of the experiment. A challenge is done at Day 35 by an oronasal administration of a viral suspension prepared from a culture of PCV-2 virulent strain. After challenge, piglets are monitored during 8 weeks for clinical signs specific of the post-weaning multisystemic syndrome. The clinical monitoring is identical to the one described in Example 9.1. except that total duration of monitoring is 8 weeks instead of 3 weeks.

Necropsies are done throughout the experiment for piglets dying from the challenge and at the end of the experiment (Day 97) for all surviving piglets. Tissue samples are the same as described in Example 9.1.

9.3. Immunization of Newborn Piglets

Groups of 3 or 4 piglets, caesarian-delivered day O are placed into isolators. Day 2 the piglets are vaccinated with 10^8 pfu of vCP1614, vCP1615 or parental ALVAC vector in 1 ml of PBS by intramuscular route on the side of the neck. A second injection of vaccine or placebo is administered at day 14. Vaccination with ALVAC recombinant is well tolerated by piglets and no evidence of adverse reaction to vaccination is noted. The piglets are challenged day 21 by oronasal administration of a PCV-2 viral suspension, 1 ml in each nostril. Day 45 necropsies are performed and samples of tissues are collected for virus isolation. Necropsy results: PMWS is characterized generally by lymphadenopathy and more rarely by hepatitis or nephritis. So the gross findings in lymph nodes are scored for each piglet in the following manner: 0=no visible enlargement of lymph nodes; 1=mild lymph nodes enlargement, restricted to bronchial lymph nodes; 2=moderate lymph nodes enlargement, restricted to bronchial lymph nodes; 3=severe lymph nodes enlargement, extended to bronchial, submandibullar prescapular and inguinal lymph nodes.

Groups	Scores
vCP 1614	0.5
	0.0
	0.0
	1.0
mean	0.38
standard deviation	0.48
vCP 1615	0.0
	0.5
	0.5
	1.0
mean	0.5
standard deviation	0.41
Controls	2.0
	2.5
	2.5
	2.5
mean	2.38
standard deviation	0.25

Bronchial lymphadenopathy for PCV-2 is a prominent gross finding. A significant reduction of the lymph nodes lesion in relation to control group is observed after immunization with vCP 1614 and vCP1615 ($p \leqq 0.05$).

Having thus described in detail preferred embodiments of the present invention, it is to be understood that the invention defined by the appended claims is not to be limited to particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit or scope of the present invention.

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SEQUENCE LISTING

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ata ctc ttt gat gct agt tta ttt ttc caa ctc tct act aaa agc aat     1372
Ile Leu Phe Asp Ala Ser Leu Phe Phe Gln Leu Ser Thr Lys Ser Asn
            320                 325                 330

tat gta aaa tat tgg aca aag aaa act ttg cag tat aag aac ttt ttt     1420
Tyr Val Lys Tyr Trp Thr Lys Lys Thr Leu Gln Tyr Lys Asn Phe Phe
        335                 340                 345

aaa gac ggt aaa cag tta gca aaa tat ata att aag aaa gat agt cag     1468
Lys Asp Gly Lys Gln Leu Ala Lys Tyr Ile Ile Lys Lys Asp Ser Gln
    350                 355                 360

gtg ata gat aga gta tgt tat tta cac gca gct gta tat aat cac gta     1516
Val Ile Asp Arg Val Cys Tyr Leu His Ala Ala Val Tyr Asn His Val
365                 370                 375                 380

act tac tta atg gat acg ttt aaa att cct ggt ttt gat ttt aaa ttc     1564
Thr Tyr Leu Met Asp Thr Phe Lys Ile Pro Gly Phe Asp Phe Lys Phe
                385                 390                 395

tcc gga atg ata gat ata cta ctg ttt gga ata ttg cat aag gat aat     1612
Ser Gly Met Ile Asp Ile Leu Leu Phe Gly Ile Leu His Lys Asp Asn
            400                 405                 410

gag aat ata ttt tat ccg aaa cgt gtt tct gta act aat ata ata tca     1660
Glu Asn Ile Phe Tyr Pro Lys Arg Val Ser Val Thr Asn Ile Ile Ser
        415                 420                 425

gaa tct atc tat gca gat ttt tac ttt ata tca gat gtt aat aaa ttc     1708
Glu Ser Ile Tyr Ala Asp Phe Tyr Phe Ile Ser Asp Val Asn Lys Phe
    430                 435                 440

agt aaa aag ata gaa tat aaa act atg ttt cct ata ctc gca gaa aac     1756
Ser Lys Lys Ile Glu Tyr Lys Thr Met Phe Pro Ile Leu Ala Glu Asn
445                 450                 455                 460

tac tat cca aaa gga agg ccc tat ttt aca cat aca tct aac gaa gat     1804
Tyr Tyr Pro Lys Gly Arg Pro Tyr Phe Thr His Thr Ser Asn Glu Asp
                465                 470                 475

ctt ctg tct atc tgt tta tgc gaa gta aca gtt tgt aaa gat ata aaa     1852
Leu Leu Ser Ile Cys Leu Cys Glu Val Thr Val Cys Lys Asp Ile Lys
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            480                 485                 490

aat cca tta tta tat tct aaa aag gat ata tca gca aaa cga ttc ata     1900
Asn Pro Leu Leu Tyr Ser Lys Lys Asp Ile Ser Ala Lys Arg Phe Ile
        495                 500                 505

ggt tta ttt aca tct gtc gat ata aat acg gct gtt gag tta aga gga     1948
Gly Leu Phe Thr Ser Val Asp Ile Asn Thr Ala Val Glu Leu Arg Gly
    510                 515                 520

tat aaa ata aga gta ata gga tgt tta gaa tgg cct gaa aag ata aaa     1996
Tyr Lys Ile Arg Val Ile Gly Cys Leu Glu Trp Pro Glu Lys Ile Lys
525                 530                 535                 540

ata ttt aat tct aat cct aca tac att aga tta tta cta aca gaa aga     2044
Ile Phe Asn Ser Asn Pro Thr Tyr Ile Arg Leu Leu Leu Thr Glu Arg
                545                 550                 555

cgt tta gat att cta cat tcc tat ctg ctt aaa ttt aat ata aca gag     2092
Arg Leu Asp Ile Leu His Ser Tyr Leu Leu Lys Phe Asn Ile Thr Glu
            560                 565                 570

gat ata gct acc aga gat gga gtc aga aat aat tta cct ata att tct     2140
Asp Ile Ala Thr Arg Asp Gly Val Arg Asn Asn Leu Pro Ile Ile Ser
        575                 580                 585

ttt atc gtc agt tat tgt aga tcg tat act tat aaa tta cta aat tgc     2188
Phe Ile Val Ser Tyr Cys Arg Ser Tyr Thr Tyr Lys Leu Leu Asn Cys
    590                 595                 600

cat atg tac aat tcg tgt aag ata aca aag tgt aaa tat aat cag gta     2236
His Met Tyr Asn Ser Cys Lys Ile Thr Lys Cys Lys Tyr Asn Gln Val
605                 610                 615                 620

ata tat aat cct ata taggagtata tataattgaa aaagtaaaat ataaatcata     2291
Ile Tyr Asn Pro Ile
                625

taataatgaa acgaaatatc agtaatagac aggaactggc agattcttct tctaatgaag   2351

taagtactgc taaatctcca aaattagata aaaatgatac agcaaataca gcttcattca   2411

acgaattacc ttttaatttt ttcagacaca ccttattaca aactaactaa gtcagatgat   2471

gagaaagtaa atataaattt aacttatggg tataatataa taaagattca tgatattaat   2531

aatttactta acgatgttaa tagacttatt ccatcaaccc cttcaaacct ttctggatat   2591

tataaaatac cagttaatga tattaaaata gattgtttaa gagatgtaaa taattatttg   2651

gaggtaaagg atataaaatt agtctatctt tcacatggaa atgaattacc taatattaat   2711

aattatgata ggaatttttt aggatttaca gctgttatat gtatcaacaa tacaggcaga   2771

tctatggtta tggtaaaaca ctgtaacggg aagcagcatt ctatggtaac tggcctatgt   2831

ttaatagcca gatcatttta ctctataaac attttaccac aaataatagg atcctctaga   2891

tatttaatat tatatctaac aacaacaaaa aaatttaacg atgtatggcc agaagtattt   2951

tctactaata aagataaaga tagtctatct tatctacaag atatgaaaga agataatcat   3011

ttagtagtag ctactaatat ggaaagaaat gtatacaaaa acgtggaagc ttttatatta   3071

aatagcatat tactagaaga tttaaaatct agacttagta taacaaaaca gttaaatgcc   3131

aatatcgatt ctatatttca tcataacagt agtacattaa tcagtgatat actgaaacga   3191

tctacagact caactatgca aggaataagc aatatgccaa ttatgtctaa tattttaact   3251

ttagaactaa aacgttctac caatactaaa aataggatac gtgataggct gttaaaagct   3311

gcaataaata gtaaggatgt agaagaaata ctttgttcta taccttcgga ggaaagaact   3371

ttagaacaac ttaagtttaa tcaaacttgt atttatgaac actataaaaa aattatggaa   3431

gatacaagta aaagaatgga tgttgaatgt cgtagtttag aacataacta tacggctaac   3491

ttatataaag tgtacggaca aaacgaatat atgattactt atatactagc tctcataagt   3551
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aggattaata atattataga aactttaaaa tataatctgg tggggctaga cgaatctaca 3611

atacgtaata taaattatat aatttcacaa agaacaaaaa aaaatcaagt ttctaatacc 3671

ttatagataa actatatttt ttaccactga 3701

<210> SEQ ID NO 2
<211> LENGTH: 625
<212> TYPE: PRT
<213> ORGANISM: Canarypox virus

<400> SEQUENCE: 2

Met Ser Leu Leu Gln Lys Leu Tyr Phe Thr Glu Gln Ser Ile Val Glu
1 5 10 15

Ser Phe Lys Ser Tyr Asn Leu Lys Asp Asn His Asn Val Ile Phe Thr
20 25 30

Thr Ser Asp Asp Asp Thr Val Val Val Ile Asn Glu Asp Asn Val Leu
35 40 45

Leu Ser Thr Arg Leu Leu Ser Phe Asp Lys Ile Leu Phe Phe Asn Ser
50 55 60

Phe Asn Asn Gly Leu Ser Lys Tyr Glu Thr Ile Ser Asp Thr Ile Leu
65 70 75 80

Asp Ile Asp Thr His Asn Tyr Tyr Ile Pro Ser Ser Ser Ser Leu Leu
85 90 95

Asp Ile Leu Lys Lys Arg Ala Cys Asp Leu Glu Leu Glu Asp Leu Asn
100 105 110

Tyr Ala Leu Ile Gly Asp Asn Ser Asn Leu Tyr Tyr Lys Asp Met Thr
115 120 125

Tyr Met Asn Asn Trp Leu Phe Thr Lys Gly Leu Leu Asp Tyr Lys Phe
130 135 140

Val Leu Leu Arg Asp Val Asp Lys Cys Tyr Lys Gln Tyr Asn Lys Lys
145 150 155 160

Asn Thr Ile Ile Asp Ile Ile His Arg Asp Asn Arg Gln Tyr Asn Ile
165 170 175

Trp Val Lys Asn Val Ile Glu Tyr Cys Ser Pro Gly Tyr Ile Leu Trp
180 185 190

Leu His Asp Leu Lys Ala Ala Ala Glu Asp Asp Trp Leu Arg Tyr Asp
195 200 205

Asn Arg Ile Asn Glu Leu Ser Ala Asp Lys Leu Tyr Thr Phe Glu Phe
210 215 220

Ile Val Ile Leu Glu Asn Asn Ile Lys His Leu Arg Val Gly Thr Ile
225 230 235 240

Ile Val His Pro Asn Lys Ile Ile Ala Asn Gly Thr Ser Asn Asn Ile
245 250 255

Leu Thr Asp Phe Leu Ser Tyr Val Glu Glu Leu Ile Tyr His His Asn
260 265 270

Ser Ser Ile Ile Leu Ala Gly Tyr Phe Leu Glu Phe Phe Glu Thr Thr
275 280 285

Ile Leu Ser Glu Phe Ile Ser Ser Ser Ser Glu Trp Val Met Asn Ser
290 295 300

Asn Cys Leu Val His Leu Lys Thr Gly Tyr Glu Ala Ile Leu Phe Asp
305 310 315 320

Ala Ser Leu Phe Phe Gln Leu Ser Thr Lys Ser Asn Tyr Val Lys Tyr
325 330 335

Trp Thr Lys Lys Thr Leu Gln Tyr Lys Asn Phe Phe Lys Asp Gly Lys

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            340                 345                 350

Gln Leu Ala Lys Tyr Ile Ile Lys Lys Asp Ser Gln Val Ile Asp Arg
        355                 360                 365

Val Cys Tyr Leu His Ala Ala Val Tyr Asn His Val Thr Tyr Leu Met
    370                 375                 380

Asp Thr Phe Lys Ile Pro Gly Phe Asp Phe Lys Phe Ser Gly Met Ile
385                 390                 395                 400

Asp Ile Leu Leu Phe Gly Ile Leu His Lys Asp Asn Glu Asn Ile Phe
                405                 410                 415

Tyr Pro Lys Arg Val Ser Val Thr Asn Ile Ile Ser Glu Ser Ile Tyr
            420                 425                 430

Ala Asp Phe Tyr Phe Ile Ser Asp Val Asn Lys Phe Ser Lys Lys Ile
        435                 440                 445

Glu Tyr Lys Thr Met Phe Pro Ile Leu Ala Glu Asn Tyr Tyr Pro Lys
    450                 455                 460

Gly Arg Pro Tyr Phe Thr His Thr Ser Asn Glu Asp Leu Leu Ser Ile
465                 470                 475                 480

Cys Leu Cys Glu Val Thr Val Cys Lys Asp Ile Lys Asn Pro Leu Leu
                485                 490                 495

Tyr Ser Lys Lys Asp Ile Ser Ala Lys Arg Phe Ile Gly Leu Phe Thr
            500                 505                 510

Ser Val Asp Ile Asn Thr Ala Val Glu Leu Arg Gly Tyr Lys Ile Arg
        515                 520                 525

Val Ile Gly Cys Leu Glu Trp Pro Glu Lys Ile Lys Ile Phe Asn Ser
    530                 535                 540

Asn Pro Thr Tyr Ile Arg Leu Leu Leu Thr Glu Arg Arg Leu Asp Ile
545                 550                 555                 560

Leu His Ser Tyr Leu Leu Lys Phe Asn Ile Thr Glu Asp Ile Ala Thr
                565                 570                 575

Arg Asp Gly Val Arg Asn Asn Leu Pro Ile Ile Ser Phe Ile Val Ser
            580                 585                 590

Tyr Cys Arg Ser Tyr Thr Tyr Lys Leu Leu Asn Cys His Met Tyr Asn
        595                 600                 605

Ser Cys Lys Ile Thr Lys Cys Lys Tyr Asn Gln Val Ile Tyr Asn Pro
    610                 615                 620

Ile
625


<210> SEQ ID NO 3
<211> LENGTH: 42
<212> TYPE: DNA
<213> ORGANISM: Canarypox virus

<400> SEQUENCE: 3

atcatcgagc tcgcggccgc ctatcaaaag tcttaatgag tt                          42


<210> SEQ ID NO 4
<211> LENGTH: 73
<212> TYPE: DNA
<213> ORGANISM: Canarypox virus

<400> SEQUENCE: 4

gaattcctcg agctgcagcc cgggttttta tagctaatta gtcatttttt cgtaagtaag       60

tatttttatt taa                                                          73
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<210> SEQ ID NO 5
<211> LENGTH: 72
<212> TYPE: DNA
<213> ORGANISM: Canarypox virus

<400> SEQUENCE: 5

cccgggctgc agctcgagga attcttttta ttgattaact agtcaaatga gtatatataa 60

ttgaaaaagt aa 72

<210> SEQ ID NO 6
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Canarypox virus

<400> SEQUENCE: 6

gatgatggta ccttcataaa tacaagtttg attaaactta agttg 45

<210> SEQ ID NO 7
<211> LENGTH: 53
<212> TYPE: DNA
<213> ORGANISM: Canarypox virus

<400> SEQUENCE: 7

catcatcatg atatccgtta agtttgtatc gtaatgacgt atccaaggag gcg 53

<210> SEQ ID NO 8
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: ALVAC

<400> SEQUENCE: 8

tactactacg tcgacttagg gtttaagtgg ggggtc 36

<210> SEQ ID NO 9
<211> LENGTH: 2520
<212> TYPE: DNA
<213> ORGANISM: ALVAC
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (1402)..(2100)

<400> SEQUENCE: 9

ggtaccttca taaatacaag tttgattaaa cttaagttgt tctaaagttc tttcctccga 60

aggtatagaa caaagtattt cttctacatc cttactattt attgcagctt ttaacagcct 120

atcacgtatc ctatttttag tattggtaga acgttttagt tctaaagtta aaatattaga 180

cataattggc atattgctta ttccttgcat agttgagtct gtagatcgtt tcagtatatc 240

actgattaat gtactactgt tatgatgaaa tatagaatcg atattggcat ttaactgttt 300

tgttatacta agtctagatt ttaaatcttc tagtaatatg ctatttaata taaaagcttc 360

cacgtttttg tatacatttc tttccatatt agtagctact actaaatgat tatcttcttt 420

catatcttgt agataagata gactatcttt atctttatta gtagaaaata cttctggcca 480

tacatcgtta aatttttttg ttgttgttag atataatatt aaatatctag aggatcctat 540

tatttgtggt aaaatgttta tagagtaaaa tgatctggct attaaacata ggccagttac 600

catagaatgc tgcttcccgt tacagtgttt taccataacc atagatctgc ctgtattgtt 660

gatacatata acagctgtaa atcctaaaaa attcctatca taattattaa tattaggtaa 720

ttcatttcca tgtgaaagat agactaattt tatatccttt acctccaaat aattatttac 780

atctcttaaa caatctattt taatatcatt aactggtatt ttataatatc cagaaaggtt 840

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tgaaggggtt gatggaataa gtctattaac atcgttaagt aaattattaa tatcatgaat    900

ctttattata ttatacccat aagttaaatt tatatttact ttctcatcat ctgacttagt    960

tagtttgtaa taaggtgtgt ctgaaaaaat taaaaggtaa ttcgttgaat gaagctgtat   1020

ttgctgtatc atttttatct aattttggag atttagcagt acttacttca ttagaagaag   1080

aatctgccag ttcctgtcta ttactgatat ttcgtttcat tattatatga tttatatttt   1140

acttttcaa ttatatatac tcatttgact agttaatcaa taaaaagaat tcctgcagcc   1200

ctgcagctaa ttaattaagc tacaaatagt ttcgttttca ccttgtctaa taactaatta   1260

attaaggatc ccccagcttc tttattctat acttaaaaag tgaaaataaa tacaaaggtt   1320

cttgagggtt gtgttaaatt gaaagcgaga aataatcata aattatttca ttatcgcgat   1380

atccgttaag tttgtatcgt a atg acg tat cca agg agg cgt tac cgc aga      1431
                       Met Thr Tyr Pro Arg Arg Arg Tyr Arg Arg
                         1               5                  10

aga aga cac cgc ccc cgc agc cat ctt ggc cag atc ctc cgc cgc cgc      1479
Arg Arg His Arg Pro Arg Ser His Leu Gly Gln Ile Leu Arg Arg Arg
                15                  20                  25

ccc tgg ctc gtc cac ccc cgc cac cgc tac cgt tgg aga agg aaa aat      1527
Pro Trp Leu Val His Pro Arg His Arg Tyr Arg Trp Arg Arg Lys Asn
            30                  35                  40

ggc atc ttc aac acc cgc ctc tcc cgc acc ttc gga tat act gtc aag      1575
Gly Ile Phe Asn Thr Arg Leu Ser Arg Thr Phe Gly Tyr Thr Val Lys
        45                  50                  55

cgt acc aca gtc aca acg ccc tcc tgg gcg gtg gac atg atg aga ttt      1623
Arg Thr Thr Val Thr Thr Pro Ser Trp Ala Val Asp Met Met Arg Phe
    60                  65                  70

aaa att gac gac ttt gtt ccc ccg gga ggg ggg acc aac aaa atc tct      1671
Lys Ile Asp Asp Phe Val Pro Pro Gly Gly Gly Thr Asn Lys Ile Ser
75                  80                  85                  90

ata ccc ttt gaa tac tac aga ata aga aag gtt aag gtt gaa ttc tgg      1719
Ile Pro Phe Glu Tyr Tyr Arg Ile Arg Lys Val Lys Val Glu Phe Trp
                95                 100                 105

ccc tgc tcc ccc atc acc cag ggt gat agg gga gtg ggc tcc act gct      1767
Pro Cys Ser Pro Ile Thr Gln Gly Asp Arg Gly Val Gly Ser Thr Ala
            110                 115                 120

gtt att cta gat gat aac ttt gta aca aag gcc aca gcc cta acc tat      1815
Val Ile Leu Asp Asp Asn Phe Val Thr Lys Ala Thr Ala Leu Thr Tyr
        125                 130                 135

gac cca tat gta aac tac tcc tcc cgc cat aca atc ccc caa ccc ttc      1863
Asp Pro Tyr Val Asn Tyr Ser Ser Arg His Thr Ile Pro Gln Pro Phe
    140                 145                 150

tcc tac cac tcc cgt tac ttc aca ccc aaa cct gtt ctt gac tcc act      1911
Ser Tyr His Ser Arg Tyr Phe Thr Pro Lys Pro Val Leu Asp Ser Thr
155                 160                 165                 170

att gat tac ttc caa cca aat aac aaa agg aat cag ctt tgg ctg aga      1959
Ile Asp Tyr Phe Gln Pro Asn Asn Lys Arg Asn Gln Leu Trp Leu Arg
                175                 180                 185

cta caa acc tct gga aat gtg gac cac gta ggc ctc ggc gct gcg ttc      2007
Leu Gln Thr Ser Gly Asn Val Asp His Val Gly Leu Gly Ala Ala Phe
            190                 195                 200

gaa aac agt aaa tac gac cag gac tac aat atc cgt gta acc atg tat      2055
Glu Asn Ser Lys Tyr Asp Gln Asp Tyr Asn Ile Arg Val Thr Met Tyr
        205                 210                 215

gta caa ttc aga gaa ttt aat ctt aaa gac ccc cca ctt aaa ccc          2100
Val Gln Phe Arg Glu Phe Asn Leu Lys Asp Pro Pro Leu Lys Pro
    220                 225                 230
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taagtcgacc ccgggttttt atagctaatt agtcattttt tcgtaagtaa gtatttttat 2160

ttaatacttt ttattgtact tatgttaaat ataactgatg ataacaaaat ccattatgta 2220

ttatttataa ctgtaatttc tttagcgtag ttagatgtcc aatctctctc aaatacatcg 2280

gctatctttt tagtgagatt ttgatctatg cagttgaaac ttatgaacgc gtgatgatta 2340

aaatgtgaac cgtccaaatt tgcagtcatt atatgagcgt atctattatc tactatcatc 2400

atctttgagt tattaatatc atctacttta gaattgatag gaaatatgaa tacctttgta 2460

gtaatatcta tactatctac acctaactca ttaagacttt tgataggcgg ccgcgagctc 2520

<210> SEQ ID NO 10
<211> LENGTH: 233
<212> TYPE: PRT
<213> ORGANISM: ALVAC

<400> SEQUENCE: 10

Met Thr Tyr Pro Arg Arg Arg Tyr Arg Arg Arg Arg His Arg Pro Arg
1 5 10 15

Ser His Leu Gly Gln Ile Leu Arg Arg Arg Pro Trp Leu Val His Pro
20 25 30

Arg His Arg Tyr Arg Trp Arg Arg Lys Asn Gly Ile Phe Asn Thr Arg
35 40 45

Leu Ser Arg Thr Phe Gly Tyr Thr Val Lys Arg Thr Thr Val Thr Thr
50 55 60

Pro Ser Trp Ala Val Asp Met Met Arg Phe Lys Ile Asp Asp Phe Val
65 70 75 80

Pro Pro Gly Gly Gly Thr Asn Lys Ile Ser Ile Pro Phe Glu Tyr Tyr
85 90 95

Arg Ile Arg Lys Val Lys Val Glu Phe Trp Pro Cys Ser Pro Ile Thr
100 105 110

Gln Gly Asp Arg Gly Val Gly Ser Thr Ala Val Ile Leu Asp Asp Asn
115 120 125

Phe Val Thr Lys Ala Thr Ala Leu Thr Tyr Asp Pro Tyr Val Asn Tyr
130 135 140

Ser Ser Arg His Thr Ile Pro Gln Pro Phe Ser Tyr His Ser Arg Tyr
145 150 155 160

Phe Thr Pro Lys Pro Val Leu Asp Ser Thr Ile Asp Tyr Phe Gln Pro
165 170 175

Asn Asn Lys Arg Asn Gln Leu Trp Leu Arg Leu Gln Thr Ser Gly Asn
180 185 190

Val Asp His Val Gly Leu Gly Ala Ala Phe Glu Asn Ser Lys Tyr Asp
195 200 205

Gln Asp Tyr Asn Ile Arg Val Thr Met Tyr Val Gln Phe Arg Glu Phe
210 215 220

Asn Leu Lys Asp Pro Pro Leu Lys Pro
225 230

<210> SEQ ID NO 11
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: ALVAC

<400> SEQUENCE: 11

catcatcatt cgcgatatcc gttaagtttg tatcgtaatg cccagcaaga agaatgg 57

<210> SEQ ID NO 12

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<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: ALVAC

<400> SEQUENCE: 12

tactactacg tcgactcagt aatttatttc atatgg 36

<210> SEQ ID NO 13
<211> LENGTH: 3609
<212> TYPE: DNA
<213> ORGANISM: ALVAC

<400> SEQUENCE: 13

ggtaccttca taaatacaag tttgattaaa cttaagttgt tctaaagttc tttcctccga 60

aggtatagaa caaagtattt cttctacatc cttactattt attgcagctt ttaacagcct 120

atcacgtatc ctatttttag tattggtaga acgttttagt tctaaagtta aaatattaga 180

cataattggc atattgctta ttccttgcat agttgagtct gtagatcgtt tcagtatatc 240

actgattaat gtactactgt tatgatgaaa tatagaatcg atattggcat ttaactgttt 300

tgttatacta agtctagatt ttaaatcttc tagtaatatg ctatttaata taaaagcttc 360

cacgtttttg tatacatttc tttccatatt agtagctact actaaatgat tatcttcttt 420

catatcttgt agataagata gactatcttt atctttatta gtagaaaata cttctggcca 480

tacatcgtta aatttttttg ttgttgttag atataatatt aaatatctag aggatcctat 540

tatttgtggt aaaatgttta tagagtaaaa tgatctggct attaaacata ggccagttac 600

catagaatgc tgcttcccgt tacagtgttt taccataacc atagatctgc ctgtattgtt 660

gatacatata acagctgtaa atcctaaaaa attcctatca taattattaa tattaggtaa 720

ttcatttcca tgtgaaagat agactaattt tatatccttt acctccaaat aattatttac 780

atctcttaaa caatctattt taatatcatt aactggtatt ttataatatc cagaaaggtt 840

tgaaggggtt gatggaataa gtctattaac atcgttaagt aaattattaa tatcatgaat 900

ctttattata ttatacccat aagttaaatt tatatttact ttctcatcat ctgacttagt 960

tagtttgtaa taaggtgtgt ctgaaaaaat taaaaggtaa ttcgttgaat gaagctgtat 1020

ttgctgtatc atttttatct aattttggag atttagcagt acttacttca ttagaagaag 1080

aatctgccag ttcctgtcta ttactgatat ttcgtttcat tattatatga tttatatttt 1140

acttttttcaa ttatatatac tcatttgact agttaatcaa taaaaagaat ttcgacttag 1200

ggtttaagtg gggggtcttt aagattaaat tctctgaatt gtacatacat ggttacacgg 1260

atattgtagt cctggtcgta tttactgttt tcgaacgcag cgccgaggcc tacgtggtcc 1320

acatttccag aggtttgtag tctcagccaa agctgattcc ttttgttatt tggttggaag 1380

taatcaatag tggagtcaag aacaggtttg ggtgtgaagt aacgggagtg gtaggagaag 1440

ggttgggggga ttgtatggcg ggaggagtag tttacatatg ggtcataggt tagggctgtg 1500

gcctttgtta caaagttatc atctagaata acagcagtgg agcccactcc cctatcaccc 1560

tgggtgatgg gggagcaggg ccagaattca accttaacct ttcttattct gtagtattca 1620

aagggtatag agattttgtt ggtcccccct cccgggggaa caaagtcgtc aattttaaat 1680

ctcatcatgt ccaccgccca ggagggcgtt gtgactgtgg tacgcttgac agtatatccg 1740

aaggtgcggg agaggcgggt gttgaagatg ccatttttcc ttctccaacg gtagcggtgg 1800

cgggggtgga cgagccaggg gcggcggcgg aggatctggc caagatggct gcgggggcgg 1860

tgtcttcttc tgcggtaacg cctccttgga tacgtcatta cgatacaaac ttaacggata 1920

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tcgcgataat gaaataattt atgattattt ctcgctttca atttaacaca accctcaaga   1980

acctttgtat ttattttcac tttttaagta tagaataaag aagctggggg atcaattcct   2040

gcagccctgc agctaattaa ttaagctaca aatagtttcg ttttcacctt gtctaataac   2100

taattaatta aggatccccc agcttcttta ttctatactt aaaaagtgaa aataaataca   2160

aaggttcttg agggttgtgt taaattgaaa gcgagaaata atcataaatt atttcattat   2220

cgcgatatcc gttaagtttg tatcgtaatg cccagcaaga agaatggaag aagcggaccc   2280

caaccacata aaaggtgggt gttcacgctg aataatcctt ccgaagacga gcgcaagaaa   2340

atacgggagc tcccaatctc cctatttgat tattttattg ttggcgagga gggtaatgag   2400

gaaggacgaa cacctcacct ccaggggttc gctaattttg tgaagaagca aacttttaat   2460

aaagtgaagt ggtatttggg tgcccgctgc cacatcgaga aagccaaagg aactgatcag   2520

cagaataaag aatattgcag taaagaaggc aacttactta ttgaatgtgg agctcctcga   2580

tctcaaggac aacggagtga cctgtctact gctgtgagta ccttgttgga gagcgggagt   2640

ctggtgaccg ttgcagagca gcaccctgta acgtttgtca gaaatttccg cgggctggct   2700

gaacttttga aagtgagcgg gaaaatgcag aagcgtgatt ggaagaccaa tgtacacgtc   2760

attgtggggc cacctgggtg tggtaaaagc aaatgggctg ctaattttgc agacccggaa   2820

accacatact ggaaaccacc tagaaacaag tggtgggatg gttaccatgg tgaagaagtg   2880

gttgttattg atgactttta tggctggctg ccgtgggatg atctactgag actgtgtgat   2940

cgatatccat tgactgtaga gactaaaggt ggaactgtac ctttttggc ccgcagtatt   3000

ctgattacca gcaatcagac cccgttggaa tggtactcct caactgctgt cccagctgta   3060

gaagctctct atcggaggat tacttccttg gtattttgga agaatgctac agaacaatcc   3120

acggaggaag ggggccagtt cgtcaccctt tccccccat gccctgaatt tccatatgaa   3180

ataaattact gagtcgaccc cgggttttta tagctaatta gtcatttttt cgtaagtaag   3240

tatttttatt taatactttt tattgtactt atgttaaata taactgatga taacaaaatc   3300

cattatgtat tatttataac tgtaatttct ttagcgtagt tagatgtcca atctctctca   3360

aatacatcgg ctatcttttt agtgagattt tgatctatgc agttgaaact tatgaacgcg   3420

tgatgattaa aatgtgaacc gtccaaattt gcagtcatta tatgagcgta tctattatct   3480

actatcatca tctttgagtt attaatatca tctactttag aattgatagg aaatatgaat   3540

acctttgtag taatatctat actatctaca cctaactcat taagactttt gataggcggc   3600

cgcgagctc                                                          3609
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<210> SEQ ID NO 14
<211> LENGTH: 236
<212> TYPE: PRT
<213> ORGANISM: ALVAC

<400> SEQUENCE: 14

```
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  1               5                  10                  15

Met Thr Val Arg Ile Asn Tyr Asp Gln Asp Tyr Lys Ser Asn Glu Phe
             20                  25                  30

Ala Ala Tyr Leu Tyr Val His Asp Val His Asp Val Asn Tyr Ser Thr
         35                  40                  45

Gln Leu Arg Leu Trp Leu Gln Asn Arg Lys Asn Asn Pro Gln Phe Tyr
     50                  55                  60
```

-continued

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Asp Ile Thr Ser Asp Leu Val Pro Lys Pro Thr Phe Tyr Arg Ser His
 65                  70                  75                  80

Tyr Ser Phe Pro Gln Pro Ile Thr His Arg Ser Ser Tyr Gln Val Tyr
                85                  90                  95

Pro Asp Tyr Thr Leu Ala Thr Ala Lys Thr Val Phe Gln Asp Asp Leu
            100                 105                 110

Ile Val Ala Thr Ser Gly Val Gly Arg Asp Gly Gln Thr Ile Pro Ser
        115                 120                 125

Cys Pro Trp Phe Glu Val Lys Val Lys Arg Ile Arg Tyr Tyr Glu Phe
    130                 135                 140

Pro Ile Ser Ile Lys Gln Thr Gly Gly Gly Pro Pro Val Phe Asp Asp
145                 150                 155                 160

Ile Lys Phe Arg Met Met Asp Val Ala Trp Ser Pro Thr Thr Val Thr
                165                 170                 175

Thr Arg Lys Val Thr Tyr Gly Phe Thr Arg Ser Leu Arg Thr Asn Phe
            180                 185                 190

Ile Gly Asn Lys Arg Arg Trp Arg Tyr Arg His Arg Pro His Val Leu
        195                 200                 205

Trp Pro Arg Arg Arg Leu Ile Gln Gly Leu His Ser Arg Pro Arg His
    210                 215                 220

Arg Arg Arg Arg Tyr Arg Arg Arg Pro Tyr Thr Met
225                 230                 235


<210> SEQ ID NO 15
<211> LENGTH: 314
<212> TYPE: PRT
<213> ORGANISM: ALVAC

<400> SEQUENCE: 15

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Trp Val Phe Thr Leu Asn Asn Pro Ser Glu Asp Glu Arg Lys Lys Ile
             20                  25                  30

Arg Glu Leu Pro Ile Ser Leu Phe Asp Tyr Phe Ile Val Gly Glu Glu
         35                  40                  45

Gly Asn Glu Glu Gly Arg Thr Pro His Leu Gln Gly Phe Ala Asn Phe
     50                  55                  60

Val Lys Lys Gln Thr Phe Asn Lys Val Lys Arg Tyr Leu Gly Ala Arg
 65                  70                  75                  80

Cys His Ile Glu Lys Ala Lys Gly Thr Asp Gln Gln Asn Lys Glu Tyr
                85                  90                  95

Cys Ser Lys Glu Gly Asn Leu Leu Ile Glu Cys Gly Ala Pro Arg Ser
            100                 105                 110

Gln Gly Gln Arg Ser Asp Leu Ser Thr Ala Val Ser Thr Leu Leu Glu
        115                 120                 125

Ser Gly Ser Leu Val Thr Val Ala Glu Gln His Pro Val Thr Phe Val
    130                 135                 140

Arg Asn Phe Arg Gly Leu Ala Glu Leu Leu Lys Val Ser Gly Lys Met
145                 150                 155                 160

Gln Lys Arg Asp Trp Lys Thr Asn Val His Val Ile Val Gly Pro Pro
                165                 170                 175

Gly Cys Gly Lys Ser Lys Trp Ala Ala Asn Phe Ala Asp Pro Glu Thr
            180                 185                 190

Thr Tyr Trp Lys Pro Pro Arg Asn Lys Trp Trp Asp Gly Tyr His Gly
        195                 200                 205
```

-continued

```
Glu Glu Val Val Val Ile Asp Asp Phe Tyr Gly Trp Leu Pro Trp Asn
    210                 215                 220

Asp Leu Leu Arg Leu Cys Asp Arg Tyr Pro Leu Thr Val Glu Thr Lys
225                 230                 235                 240

Gly Gly Thr Val Pro Phe Leu Ala Arg Ser Ile Leu Ile Thr Ser Asn
                245                 250                 255

Gln Thr Pro Leu Glu Trp Tyr Ser Ser Thr Ala Val Pro Ala Val Glu
            260                 265                 270

Ala Leu Tyr Arg Arg Ile Thr Ser Leu Val Phe Trp Lys Asn Ala Thr
        275                 280                 285

Glu Gln Ser Thr Glu Glu Gly Gly Gln Phe Val Thr Leu Ser Pro Pro
    290                 295                 300

Cys Pro Glu Phe Pro Tyr Glu Ile Asn Tyr
305                 310


<210> SEQ ID NO 16
<211> LENGTH: 53
<212> TYPE: DNA
<213> ORGANISM: ALVAC

<400> SEQUENCE: 16

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<210> SEQ ID NO 17
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: ALVAC

<400> SEQUENCE: 17

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<210> SEQ ID NO 18
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: ALVAC

<400> SEQUENCE: 18

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<210> SEQ ID NO 19
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: ALVAC

<400> SEQUENCE: 19

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```

What is claimed is:

1. A recombinant poxvirus comprising an isolated DNA molecule selected from the group consisting of ORFs 1 to 13 of porcine circovirus type II, wherein the poxvirus is:

ALVA C, or

a poxvirus having all the identifying characteristics of ALVAC.

2. The recombinant poxvirus of claim **1** wherein the recombinant poxvirus is a recombinant ALVAC canarypox virus.

3. The recombinant poxvirus of claim **2** wherein the isolated DNA molecule is in the C6 locus of the ALVAC canarypox virus genome.

4. The recombinant poxvirus of claim **1** wherein the isolated DNA molecule comprises PCV2 ORF1, PCV2 ORF2, or PCV2 ORF1 and PCV2 ORF2.

5. The recombinant poxvirus of claim **4** wherein the isolated DNA molecule is in the C6 locus of the ALVAC canarypox virus genome.

6. An immunological composition comprising the recombinant poxvirus of any one of claims **1** to **3**, **4** or **5**, and a carrier.

7. The immunological composition of claim **6**, which contains an adjuvant.

8. The immunological composition of claim **7**, wherein the adjuvant is a carbomer.

9. A method of expressing a porcine circovirus ORF in a cell cultured in vitro comprising introducing into the cell the recombinant poxvirus as claimed in any one of claims **1** to **3**, **4** or **5** under conditions which allow expression of the isolated DNA molecule by the recombinant poxvirus.

10. A method for inducing an immunological response against porcine circovirus in a host capable of an immunological response against porcine circovirus comprising administering to the host the recombinant poxvirus of any one of claims **1** to **3**, **4** or **5**.

11. The method of claim **10** wherein the recombinant poxvirus is administered with an adjuvant.

12. The method of claim **11** wherein the adjuvant is a carbomer.

13. An immunological composition comprising a recombinant avipox virus comprising an isolated DNA molecule selected from the group consisting of ORFs 1 to 13 of porcine circovirus type II, and a carbomer adjuvant.

14. The immunological composition of claim **13** wherein the isolated DNA molecule encodes PCV2 ORF1, PCV2 ORF2, or PCV2 ORF1 and PCV2 ORF2.

15. The immunological composition of any one of claim **13** or **14** wherein the avipox virus is a canarypox virus.

16. A recombinant avipox virus comprising an isolated DNA molecule comprising porcine circovirus type II (PCV2) open reading frames 1 and 2 (ORFs 1 and 2).

17. The recombinant avipox virus of claim **16** which is a recombinant canarypox virus.

18. An immunological composition comprising the recombinant avipox virus of any one of claim **16** or **17** and a carrier.

19. A method of expressing a gene product in a cell cultured in vitro comprising introducing into the cell the recombinant avipox virus as claimed in any one of claim **16** or **17** under conditions which allow expression of the isolated DNA molecule by the recombinant avipox virus.

20. A method for inducing an immunological response against porcine circovirus in a host capable of an immunological response against porcine circovirus comprising administering to the host the recombinant avipox virus of any of claim **16** or **17**.

21. A method for inducing an immunological response against porcine circovirus in a host capable of an immunological response against porcine circovirus comprising administering to the host the composition of any one of claim **13** or **14**.

22. A method for inducing an immunological response against porcine circovirus in a host capable of an immunological response against porcine circovirus comprising administering to the host the composition of claim **15**.

23. The method of claim **10** wherein the host is a porcine.

24. The method of claim **20** wherein the host is a porcine.

25. The method of claim **21** wherein the host is a porcine.

26. The method of claim **22** wherein the host is a porcine.

* * * * *

34816-CIP1.ST25
SEQUENCE LISTING

<110> Roof, Mike
Eichmeyer, Mark
Nitzel, Greg
Schaeffer, Merrill
Hayes, Phillip

<120> PCV2 IMMUNOGENIC COMPOSITIONS AND METHODS OF PRODUCING SUCH COMPOSITIONS

<130> 34816-CIP1

<140> UNKNOWN
<141> 2005-01-10

<150> Unknown
<151> 2004-12-30

<160> 11

<170> PatentIn version 3.3

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<211> 8
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<213> Artificial

<220>
<223> This is a modified Kozak's sequence.

<400> 1
ccgccatg 8

<210> 2
<211> 6
<212> DNA
<213> Artificial

<220>
<223> This is a recombinant Eco R1 sequence.

<400> 2
gaattc 6

<210> 3
<211> 713
<212> DNA
<213> Porcine circovirus

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ttggccagat cctccgccgc cgcccctggc tcgtccaccc ccgccaccgc taccgttgga 120

gaaggaaaaa tggcatcttc aacacccgcc tctcccgcac cttcggatat actgtggaga 180

aggaaaaatg gcatcttcaa cacccgcctc tcccgcacct tcggatatac tgtgacgact 240

ttgttccccc gggaggggag accaacaaaa tctctatacc ctttgaatac tacagaataa 300

gaaaggttaa ggttgaattc tggccctgct cccccatcac ccagggtgat aggggagtgg 360

gctccactgc tgttattcta gatgataact ttgtaacaaa ggccacagcc ctaacctatg 420

acccatatgt aaactactcc tcccgccata caatccccca acccttctcc taccactccc 480

gttacttcac acccaaacct gttcttgact ccactattga ttacttccaa ccaaataaca 540

aaaggaatca gctttggctg aggctacaaa cctctagaaa tgtggaccac gtaggcctcg 600

gcactgcgtt cgaaaacagt aaatacgacc aggactacaa tatccgtgta accatgtatg 660

tacaattcag agaatttaat cttaaagacc ccccacttaa accctaaatg aat 713

<210> 4
<211> 713
<212> DNA
<213> Porcine circovirus

<400> 4
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ttggccagat cctccgccgc cgcccctggc tcgtccaccc ccgccaccgc taccgttgga 120

gaaggaaaaa tggcatcttc aacacccgcc tctcccgcac cttcggatat actgtcaagg 180

ctaccacagt cacaacgccc tcctgggcgg tggacatgat gagatttaat attgacgact 240

ttgttccccc gggaggggggg accaacaaaa tctctatacc ctttgaatac tacagaataa 300

gaaaggttaa ggttgaattc tggccctgct cccccatcac ccagggtgat aggggagtgg 360

gctccactgc tgttattcta gatgataact ttgtaacaaa ggccacagcc ctaacctatg 420

acccatatgt aaactactcc tcccgccata caatccccca acccttctcc taccactccc 480

gttacttcac acccaaacct gttcttgact ccactattga ttacttccaa ccaaataaca 540

aaaggaatca gctttggctg aggctacaaa cctctagaaa tgtggaccac gtaggcctcg 600

gcactgcgtt cgaaaacagt aaatacgacc aggactacaa tatccgtgta accatgtatg 660

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<210> 5
<211> 233
<212> PRT
<213> Porcine circovirus

<400> 5

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1 5 10 15

Ser His Leu Gly Gln Ile Leu Arg Arg Arg Pro Trp Leu Val His Pro
20 25 30

Arg His Arg Tyr Arg Trp Arg Arg Lys Asn Gly Ile Phe Asn Thr Arg
35 40 45

Leu Ser Arg Thr Phe Gly Tyr Thr Val Lys Ala Thr Thr Val Thr Thr
50 55 60

Pro Ser Trp Ala Val Asp Met Met Arg Phe Asn Ile Asp Asp Phe Val
65 70 75 80

Pro Pro Gly Gly Gly Thr Asn Lys Ile Ser Ile Pro Phe Glu Tyr Tyr
85 90 95

Arg Ile Arg Lys Val Lys Val Glu Phe Trp Pro Cys Ser Pro Ile Thr
100 105 110

Gln Gly Asp Arg Gly Val Gly Ser Thr Ala Val Ile Leu Asp Asp Asn
115 120 125

Phe Val Thr Lys Ala Thr Ala Leu Thr Tyr Asp Pro Tyr Val Asn Tyr
130 135 140

Ser Ser Arg His Thr Ile Pro Gln Pro Phe Ser Tyr His Ser Arg Tyr
145 150 155 160

Phe Thr Pro Lys Pro Val Leu Asp Ser Thr Ile Asp Tyr Phe Gln Pro
165 170 175

Asn Asn Lys Arg Asn Gln Leu Trp Leu Arg Leu Gln Thr Ser Arg Asn
180 185 190

Val Asp His Val Gly Leu Gly Thr Ala Phe Glu Asn Ser Lys Tyr Asp
195 200 205

Gln Asp Tyr Asn Ile Arg Val Thr Met Tyr Val Gln Phe Arg Glu Phe
210 215 220

Asn Leu Lys Asp Pro Pro Leu Lys Pro
225 230

<210> 6
<211> 233
<212> PRT
<213> Porcine circovirus

<400> 6

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1 5 10 15

Ser His Leu Gly Gln Ile Leu Arg Arg Arg Pro Trp Leu Val His Pro
20 25 30

Arg His Arg Tyr Arg Trp Arg Arg Lys Asn Gly Ile Phe Asn Thr Arg
35 40 45

Leu Ser Arg Thr Phe Gly Tyr Thr Val Lys Ala Thr Thr Val Thr Thr
50 55 60

Pro Ser Trp Ala Val Asp Met Met Arg Phe Asn Ile Asp Asp Phe Val
65 70 75 80

Pro Pro Gly Gly Gly Thr Asn Lys Ile Ser Ile Pro Phe Glu Tyr Tyr
85 90 95

Arg Ile Arg Lys Val Lys Val Glu Phe Trp Pro Cys Ser Pro Ile Thr
100 105 110

Gln Gly Asp Arg Gly Val Gly Ser Thr Ala Val Ile Leu Asp Asp Asn
115 120 125

Phe Val Thr Lys Ala Thr Ala Leu Thr Tyr Asp Pro Tyr Val Asn Tyr
130 135 140

Ser Ser Arg His Thr Ile Pro Gln Pro Phe Ser Tyr His Ser Arg Tyr
145 150 155 160

Phe Thr Pro Lys Pro Val Leu Asp Ser Thr Ile Asp Tyr Phe Gln Pro
165 170 175

Asn Asn Lys Arg Asn Gln Leu Trp Leu Arg Leu Gln Thr Ser Arg Asn
180 185 190

Val Asp His Val Gly Leu Gly Thr Ala Phe Glu Asn Ser Lys Tyr Asp
195 200 205

Gln Asp Tyr Asn Ile Arg Val Thr Met Tyr Val Gln Phe Arg Glu Phe
210 215 220

Asn Leu Lys Asp Pro Pro Leu Glu Pro
225 230

<210> 7
<211> 756
<212> DNA
<213> Artificial

<220>
<223> This sequence is from porcine circovirus type 2, open reading frame 2, together with a portion from the pGEM T-easy vector.

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caccgccccc gcagccatct tggccagatc ctccgccgcc gcccctggct cgtccacccc 120

cgccaccgct accgttggag aaggaaaaat ggcatcttca acacccgcct ctcccgcacc 180

ttcggatata ctgtcaaggc taccacagtc acaacgccct cctgggcggt ggacatgatg 240

agatttaata ttgacgactt tgttcccccg ggaggggga ccaacaaaat ctctataccc 300

tttgaatact acagaataag aaaggttaag gttgaattct ggccctgctc ccccatcacc 360

cagggtgata ggggagtggg ctccactgct gttattctag atgataactt tgtaacaaag 420

gccacagccc taacctatga cccatatgta aactactcct cccgccatac aatcccccaa 480

cccttctcct accactcccg ttacttcaca cccaaacctg ttcttgactc cactattgat 540

tacttccaac caaataacaa aaggaatcag ctttggctga ggctacaaac ctctagaaat 600

gtggaccacg taggcctcgg cactgcgttc gaaaacagta aatacgacca ggactacaat 660

atccgtgtaa ccatgtatgt acaattcaga gaatttaatc ttaaagaccc cccacttgaa 720

ccctaagaat tctatcacta gtgaattcgc ggccgc 756

<210> 8
<211> 10387
<212> DNA
<213> Artificial

<220>
<223> This is the porcine circovirus type 2, ORF2 construct, which includes baculovirus and pGEM T-easy coding sequences.

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ataaaagatt ctaatctgat atgttttaaa acacctttgc ggcccgagtt gtttgcgtac 180

gtgactagcg aagaagatgt gtggaccgca gaacagatag taaaacaaaa ccctagtatt 240

ggagcaataa tcgatttaac caacacgtct aaatattatg atggtgtgca ttttttgcgg 300

gcgggcctgt tatacaaaaa aattcaagta cctggccaga ctttgccgcc tgaaagcata 360

gttcaagaat ttattgacac ggtaaaagaa tttacagaaa agtgtcccgg catgttggtg 420

ggcgtgcact gcacacacgg tattaatcgc accggttaca tggtgtgcag atatttaatg 480

cacaccctgg gtattgcgcc gcaggaagcc atagatagat tcgaaaaagc cagaggtcac 540

aaaattgaaa gacaaaatta cgttcaagat ttattaattt aattaatatt atttgcattc 600

tttaacaaat actttatcct attttcaaat tgttgcgctt cttccagcga accaaaacta 660

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gattaggccg gatattctcc accacaatgt tggcaacgtt gatgttacgt ttatgctttt 780

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atcaaatccc aagatgtgta taaaccacca aactgccaaa aaatgaaaac tgtcgacaag 3240

ctctgtccgt ttgctggcaa ctgcaagggt ctcaatccta tttgtaatta ttgaataata 3300

aaacaattat aaatgctaaa tttgtttttt attaacgata caaaccaaac gcaacaagaa 3360

catttgtagt attatctata attgaaaacg cgtagttata atcgctgagg taatatttaa 3420

aatcattttc aaatgattca cagttaattt gcgacaatat aattttattt tcacataaac 3480

tagacgcctt gtcgtcttct tcttcgtatt ccttctcttt ttcatttttc tcctcataaa 3540

aattaacata gttattatcg tatccatata tgtatctatc gtatagagta aatttttgt 3600

tgtcataaat atatatgtct tttttaatgg ggtgtatagt accgctgcgc atagtttttc 3660

tgtaatttac aacagtgcta ttttctggta gttcttcgga gtgtgttgct ttaattatta 3720

aatttatata atcaatgaat ttgggatcgt cggttttgta caatatgttg ccggcatagt 3780

acgcagcttc ttctagttca attacaccat tttttagcag caccggatta acataacttt 3840

ccaaaatgtt gtacgaaccg ttaaacaaaa acagttcacc tccctttttct atactattgt 3900

ctgcgagcag ttgtttgttg ttaaaaataa cagccattgt aatgagacgc acaaactaat 3960

atcacaaact ggaaatgtct atcaatatat agttgctgat atcatggaga taattaaaat 4020

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His Leu Gly Gln
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Thr Leu Ser

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<212> PRT
<213> Artificial

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<223> This is an amino acid sequence for porcine circovirus type 2, open reading frame 2.

<400> 11

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Ser His Leu Gly Gln Ile Leu Arg Arg Arg Pro Trp Leu Val His Pro
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Arg His Arg Tyr Arg Trp Arg Arg Lys Asn Gly Ile Phe Asn Thr Arg
35 40 45

Leu Ser Arg Thr Phe Gly Tyr Thr Val Lys Ala Thr Thr Val Arg Thr

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                85                  90                  95

Arg Ile Lys Lys Val Lys Val Glu Phe Trp Pro Cys Ser Pro Ile Thr
            100                 105                 110

Gln Gly Asp Arg Gly Val Gly Ser Thr Ala Val Ile Leu Asp Asp Asn
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Phe Val Thr Lys Ala Thr Ala Leu Thr Tyr Asp Pro Tyr Val Asn Tyr
    130                 135                 140

Ser Ser Arg His Thr Ile Pro Gln Pro Phe Ser Tyr His Ser Arg Tyr
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Phe Thr Pro Lys Pro Val Leu Asp Ser Thr Ile Asp Tyr Phe Gln Pro
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Asn Asn Lys Arg Asn Gln Leu Trp Leu Arg Leu Gln Thr Ser Arg Asn
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Val Asp His Val Gly Leu Gly Thr Ala Phe Glu Asn Ser Ile Tyr Asp
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Gln Asp Tyr Asn Ile Arg Val Thr Met Tyr Val Gln Phe Arg Glu Phe
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Asn Leu Lys Asp Pro Pro Leu Lys Pro
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