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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-039644- -00004-0000

Fecha: 2008-06-20 16:30:35 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 379
Actuación : 538

Referencia : Expediente No. 06.039.644
Asunto : Solicitud de Patente para **UN PROCESO PARA HACER MAMIFEROS TRANSGENICOS QUE PRODUCEN PROTEINAS EXOGENAS EN LECHE Y MAMIFEROS TRANSGENICOS PRODUCIDOS DE ESTA MANERA**
Solicitante : **STERRENBELD BIOTECHNOLOGIE NORTH AMERICA INC.**
Clase : A61K 038/027, A61K 067/027, A61P 005/006
Publicada en : La Gaceta No. **587** Del 18 de enero de 2008
Fecha de Solicitud : 26 de abril de 2006

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo II del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$210.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,

EMILIO FERRERO
T.P.A. No. 31.929

COLO-15292-841-002-5
ASG\AMG\ID-128840\WPC15292
No. M-2008-128840\ASG

NIT 860.041.367-3

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 45,902
FECHA : JUNIO 9 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO	DE BOGOTA 062754387	2678328	09/06/2008	89,445,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
50005-01-01 SOLICITUDES	114 PTC CAP-II EXAMEN DE PATENTIBILID	210,000.00
	TOTAL :	\$ 210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-39644

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **587** DE

FECHA **18 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **16 DE ABRIL DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

- 16 Claims, 4 Drawing Sheets**

METHOD OF PRODUCING A POLYPEPTIDE IN AN UNGULATE

This application is a continuation of U.S. application Ser. No. 09/239,922, Jan. 28, 1999 U.S. Pat. No. 6,011,197 which claims benefit of provisional application 60/073,019, filed January 29, 1998, entitled "Cloning of Biological Organisms from Immortalized Totipotent Cells" (pending); and a CIP of U.S. application Ser. No. 08/812,851, filed Mar. 6, 1997, entitled "Method of Cloning Animals" (pending); and a CIP of application Serial No. PCT/US 98/04345, filed Mar. 5, 1998, entitled "Method of Cloning Animals" (pending); and a CIP of U.S. application Ser. No. 08/812,031, filed Mar. 6, 1997, entitled "Method of Cloning Bovines" (pending), each of which is hereby incorporated by reference in its entirety including any drawings, and from each of which priority is claimed.

FIELD OF THE INVENTION

The invention relates to the cloning of animals.

BACKGROUND OF THE INVENTION

The following discussion of the background of the invention is merely provided to aid the reader in understanding the invention and is not admitted to describe or constitute prior art to the present invention.

Researchers have been developing methods for cloning mammalian animals over the past two decades. These reported methods typically include the steps of (1) isolating a cell, most often an embryonic cell; (2) inserting the cell or nucleus isolated from the cell into an enucleated oocyte (e.g., the oocyte's nucleus was previously extracted), and (3) allowing the embryo to mature in vivo.

The first successful nuclear transfer experiment using mammalian cells was reported in 1983, where the pronuclei isolated from a murine (mouse) zygote were inserted into an enucleated oocyte and resulted in like offspring(s). McGrath & Solter, 1983, *Science* 220:1300-1302. Subsequently, others described the production of chimeric murine embryos (e.g., embryos that contain a subset of cells having significantly different nuclear DNA from other cells in the embryo) using murine primordial germ cells (PGC). These cells are and can give rise to pluripotent cells (e.g., cells that can differentiate into other types of cells but do not differentiate into a grown animal). Matsui et al., 1992, *Cell* 70:841-847 and Resnick et al., 1992, *Nature* 359:550; Kato et al., 1994, *Journal of Reproduction and Fertility Abstract Series*, Society For the Study of Fertility, Annual Conference, Southampton, 13:38.

Some publications related to murine pluripotent cells stress the importance of steel factor for converting precursor cells into pluripotent cells. U.S. Pat. Nos. 5,453,357 and 5,670,372, entitled "Pluripotent Embryonic Stem Cells and Methods of Making Same," issued to Hogan. These same publications indicate that murine pluripotent cells exhibit strong, uniform alkaline phosphatase staining.

Although murine animals were never clearly cloned from nuclear transfer techniques using embryonic cells, some progress was reported in the field of cloning ovine (sheep) animals. One of the first successful nuclear transfer experiments utilizing ovine embryonic cells as nuclear donors was reported in 1986. Willadsen, 1986, *Nature* 320:63-65. A decade later, others reported that additional lambs were cloned from ovine embryonic cells. Campbell et al., 1996, *Nature* 380:64-66 and PCT Publication WO 95/20042. Recently, another lamb was reported to be cloned from ovine

somatic mammary tissue. Wilmut et al., 1997, *Nature* 385:810-813. Some methods for cloning ovine animals focused upon utilizing serum deprived somatic ovine cells and cells isolated from ovine embryonic discs as nuclear donors. PCT Publications WO 96/07732 and WO 97/07669. Other methods for cloning ovine animals involved manipulating the activation state of an in vivo matured oocyte after nuclear transfer. PCT Publication WO 97/07668.

While few lambs were produced, publications that disclose cloned lambs report a cloning efficiency that is, at best, approximately 0.4%. Cloning efficiency, as calculated for the previous estimate, is a ratio equal to the number of cloned lambs divided by the number of nuclear transfers used to produce that number of cloned lambs.

Despite the slower progress endemic to the field of cloning bovine animals, a bovine animal was cloned using embryonic cells derived from 2-64 cell embryos. This bovine animal was cloned by utilizing the nuclear transfer techniques set forth in U.S. Pat. Nos. 4,994,384 and 5,057,420. Others reported that cloned bovine embryos were formed by nuclear transfer techniques utilizing the inner cell mass cells of a blastocyst stage embryo. Sims & First, 1993, *Theriogenology* 39:313 and Keefer et al., 1994, *Mol. Reprod. Dev.* 38:264-268. In addition, another publication reported that cloned bovine embryos were prepared by nuclear transfer techniques that utilized PGCs isolated from fetal tissue. Delhaise et al., 1995, *Reprod. Fert. Develop.* 7:1217-1219; Lavoie 1994, *J. Reprod. Dev.* 37:413-424; and PCT application WO 95/10599 entitled "Embryonic Stem Cell-Like Cells." However, the reports demonstrated that cloned PGC-derived bovine embryos never clearly developed past the first trimester during gestation. Similarly, embryonic stem cell (e.g., cell line derived from embryos which are undifferentiated, pluripotent, and can establish a permanent cell line which exhibits a stable karyotype), ESC, derived bovine embryos never developed past fifty-five days, presumably due to incomplete placental development. Stice et al., 1996, *Biol. Reprod.* 54: 100-110.

Despite the progress of cloning ovine and bovine animals, there remains a great need in the art for methods and materials that increase cloning efficiency. In addition there remains a great need in the art to expand the variety of cells that can be utilized as nuclear donors, especially expanding nuclear donors to non-embryonic cells. Furthermore, there remains a long felt need in the art for karyotypically stable permanent cell lines that can be used for genome manipulation and production of transgenic cloned animals.

SUMMARY

The present invention relates to cloning technologies. The invention relates in part to immortalized, totipotent cells useful for cloning animals, the embryos produced from these cells using nuclear transfer techniques, animals that arise from these cells and embryos, and the methods and processes for creating such cells, embryos, and animals.

The present invention provides multiple advantages over the tools and methods currently utilized in the field of mammalian cloning. Such features and advantages include:

(1) Production of cloned animals from virtually any type of cell. The invention provides materials and methods for reprogramming non-totipotent cells into totipotent cells. These non-totipotent cells may be of non-embryonic origin. This feature of the invention allows for the ability to assess the phenotype of an existing animal and then readily establish a permanent cell line for cloning that animal.

(2) Creation of permanent cell lines from virtually any type of cell. Permanent cell lines provide a nearly unlimited

09/12/2010

Accurate spatial and temporal transgen...

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D2
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Genetics, Gene Regulation, and Expression

Accurate spatial and temporal transgene expression driven by a 3.8-kilobase promoter of the bovine β -casein gene in the lactating mouse mammary gland

Marcelo G. Cerdán¹, Juan I. Young¹, Esilda Zino¹, Tomás L. Falzone¹, Verónica Otero¹, Héctor N. Torres¹, Marcelo Rubinstein^{1,2,*}

Issue



Molecular Reproduction and Development

Volume 49, Issue 3, pages 236–245, March 1998

Article first published online: 7 DEC 1998

DOI: 10.1002/(SICI)1098-

195(199803)49:3<236::AID-

RD3>3.0.CO;2-P

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Additional Information (Show All)

How to Cite Author Information Publication History

References Cited By

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Keywords: casein genes; transgenic mice; gene expression; milk; human growth hormone

Abstract

The spatial, temporal, and hormonal pattern of expression of the β -casein gene is highly regulated and confined to the epithelial cells of the lactating mammary gland. Previous studies have shown that 1.7 kb of the bovine β -casein promoter were able to drive cell-specific and hormone-dependent expression to a mouse mammary cell line but failed to in accurate expression to the mammary gland of transgenic mice. We investigated here the ability of 3.8 kb of the bovine β -casein gene promoter to drive the expression of the human growth hormone (hGH) gene in transgenic mice. A Northern blot analysis using total RNA obtained from different tissues of lactating and nonlactating females revealed the presence of hGH mRNA only in the mammary gland of lactating females. hGH mRNA was not detectable in the mammary gland of virgin females or males. A developmental analysis showed hGH mRNA only peaked on parturition, resembling more closely the bovine β -casein temporal expression pattern rather than the murine. In situ hybridization studies performed on mammary gland sections showed that the cellular pattern of hGH expression was homogeneous in all lobules from heterozygous and homozygous transgenic mice. Silver grain count on the tissue sections highly correlated with the hGH contents in the milk determined by radioimmunoassay ($r = 0.996$). Thus 3.8 kb of the bovine β -casein promoter directed a high expression of a reporter gene to the lactating mammary gland of transgenic mice in a tissue-specific and developmentally regulated manner. *Mol. Reprod. Dev.* 49:236–245, 1998 Wiley-Liss, Inc.

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All Authors

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

Abogado
Emilio Ferrero

ASUNTO

Radicación 06-39644
Trámite 011
Evento 001
Actuación 430
Oficio
Folios 006

NO 06 45

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☐
No. Sol. Internacional PCT/US2004/032019
Publicación Internacional WO 2005/033281

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 65 a 123 como se radicó inicialmente.
Reivindicaciones: Folios: 124 a 136 como se radicó inicialmente.
Figuras: Folios: 137 a 141 como se radicó inicialmente.
Prioridad: 30/09/2003, Estado Unidos, US 60/506,735
30/09/2003, Estado Unidos, US 60/506,736
25/03/2004, Estados Unidos, US 60/556,027
25/03/2004, Estados Unidos, US 60/556,026

2. Objeto de la invención

Título de la solicitud: "Un proceso para hacer mamíferos transgénicos que producen proteínas exógenas en leche y mamíferos transgénicos producidos de esta manera".

El objeto de la presente solicitud de patente de invención consiste en suministrar un método para producir mamíferos transgénicos a través de la caracterización y refinamiento de la técnica de transferencia nuclear de la célula somática existente.

5. Excepción a la patentabilidad (artículo 20 D486 literal a)-d))

Adicionalmente, los métodos propuestos para hacer un mamífero transgénico implican una etapa que requiere la intervención quirúrgica dentro del organismo animal, específicamente la etapa f) que se refiere a “implantar dicho embrión en el útero de un mamífero receptivo; y una etapa que se refiere a un método de tratamiento, como es la etapa g) que se refiere a “monitorear la gestación a través del nacimiento del mamífero transgénico. Estas etapas hacen parte de la materia que se considera excepción a la patentabilidad

De esta manera y de acuerdo a lo establecido en el artículo 20 de la Decisión 486 el contenido de las citadas reivindicaciones deberá excluirse.

6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:
Fecha de presentación de la solicitud prioritaria 30/09/2003 y 25/03/2004.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación
D1	US 6.395.958	Method of producing a polypeptide in an ungulate	28/05/2002
D2	Cerdán <i>et al.</i> ,	Accurate spatial and temporal transgenes expresión driven by a 3.8 kilobase promoter of teh bovine beta-casein gene in the lactating Mouse mammary gland	04/1998

Resumen de los documentos citados:

D1: Divulga tecnologías de clonación, en parte en células inmortalizadas y células totipotentes útiles para clonación de animales, los embriones producidos de esas células usando técnicas de transferencia nuclear, animales desarrollados de estas células y embriones.

D2: Se investiga la habilidad del segmento de 3.8 kb del gen de la β -caseína bovina para promover la expresión dirigida del gen de la hormona humana del crecimiento (hGH) en ratones transgénicos.

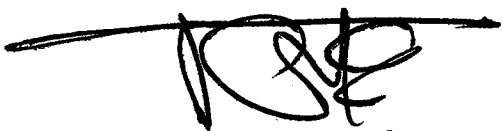
7. Análisis de patentabilidad (artículo 14 D486)

7.1. Novedad (artículo 16 D486)

La solicitud reclama un plásmido que comprende un gen que codifica una proteína de interés operablemente ligada a un promotor de beta caseína y a un gen β lactamasa.

Tal como lo manifestó la autoridad de búsqueda internacional, el documento de Cerdán (D2) enseña un plásmido comprendiendo una secuencia de DNA que codifica para la hormona del crecimiento humano, operablemente unida a un promotor β -caseína, donde el plásmido también contiene un gen para resistencia a ampicilina, β -lactamasa (pág 237). Por otra parte, a partir de esta divulgación se

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.



JOSE LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha

14 ENE. 2011

CONCEPTO TÉCNICO No. 4196	EXAMINADOR TÉCNICO Código No.202052
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