



UN CAMBIO DE MIRADA EN LA CRÍA ANIMAL APROVECHANDO LA INFORMACIÓN GENÓMICA

Estado Actual, Resultados y Aplicaciones de la Clonación Equina

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Introducción

- Desarrollo de las biotecnologías reproductivas

PRIMERA GENERACIÓN

1908

- Núcleos Pluripotentes

SEGUNDA GENERACIÓN

1970

-Transferencia de embriones.
-Control hormonal del celo.

TERCERA GENERACIÓN

1980

-FIV, sexado de embriones
y espermatozoides.

CUARTA GENERACIÓN

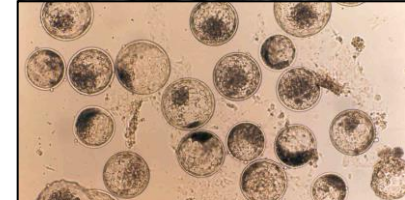
1990

-Clonación de células
somáticas

QUINTA GENERACIÓN

2000

-Transgénesis.
-Células madre.



(Thibier, 2001. Theriogenology)

4ta generación

Práctica reproductiva que tiene como objetivo producir un duplicado genéticamente idéntico de un organismo mediante el reemplazo del núcleo de un ovocito sin fecundar por el de una célula proveniente del organismo original

1932: Hans Spemann

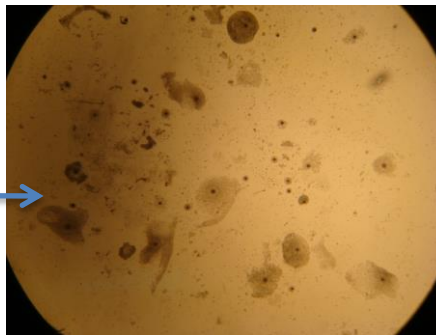
1981: Se anunciaba que: “el desarrollo completo de ratones no es posible por transferencia nuclear” (Illmensee y Hoppe, 1981)

1984: los núcleos de células diferenciadas poseen una reprogramación irreversible y los autores concluyen: “...la clonación de mamíferos por transferencia nuclear es biológicamente imposible...” (McGrath y Solter, 1984)

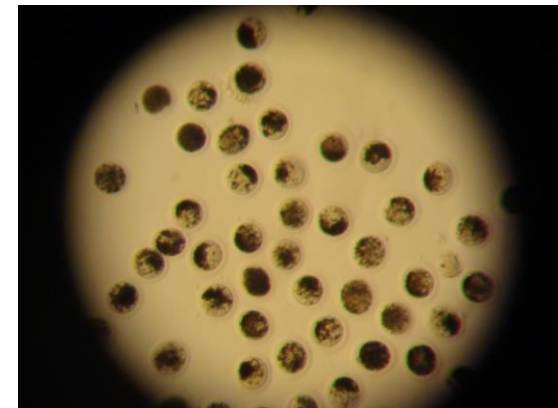
1996:



Metodología



2 ovocitos MII/ovario



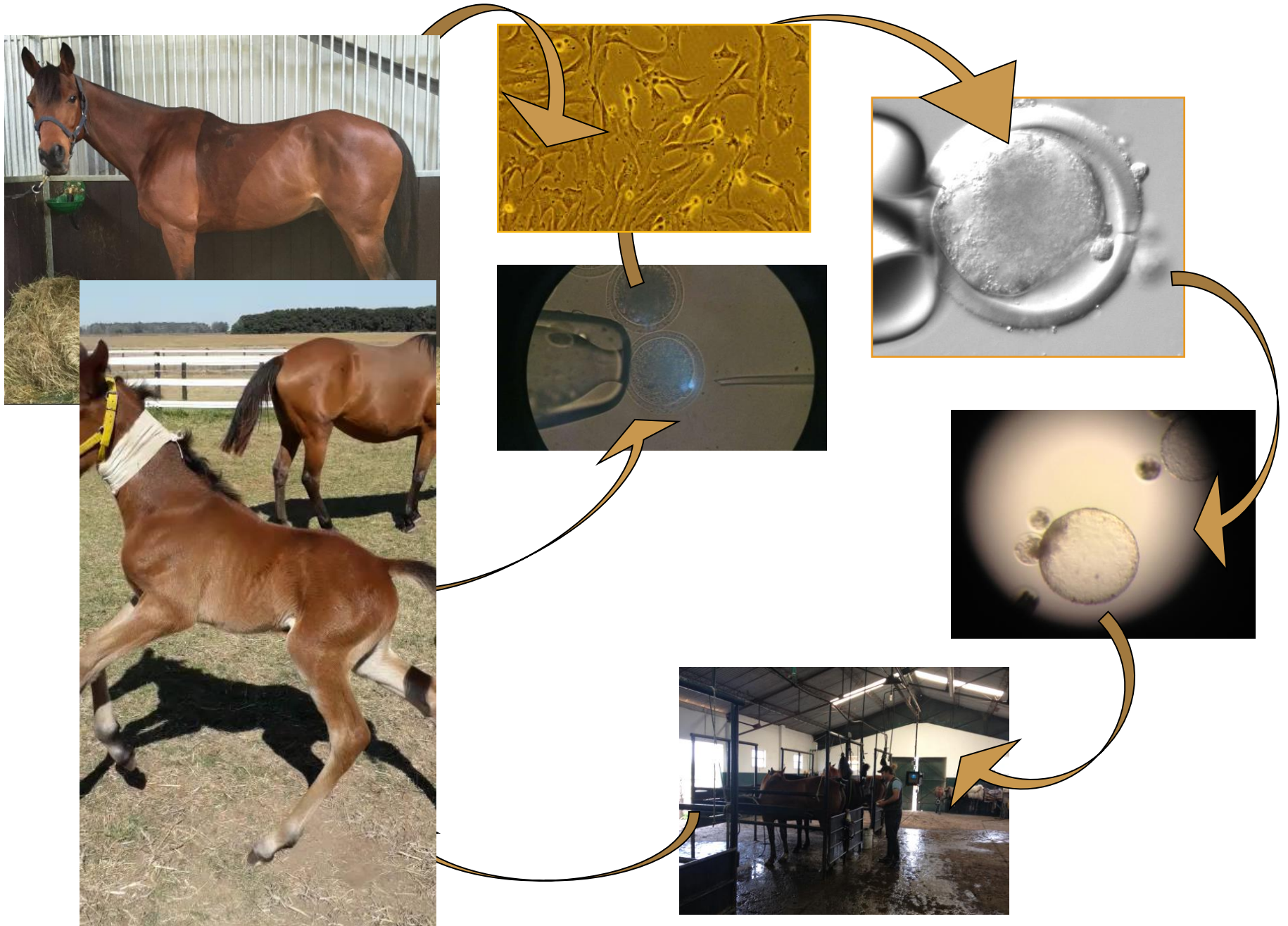
Metodología



Equipamiento principal

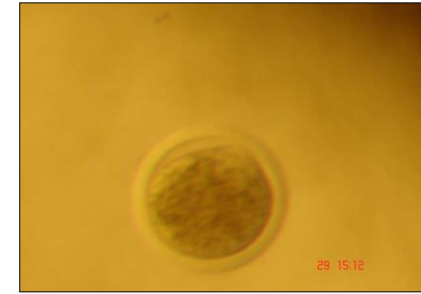
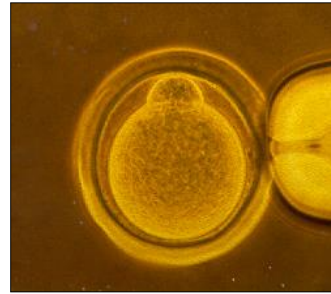
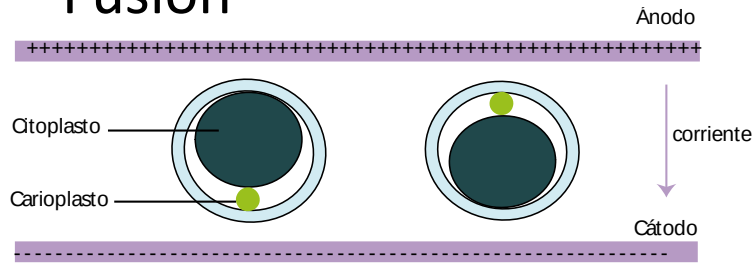


Metodología

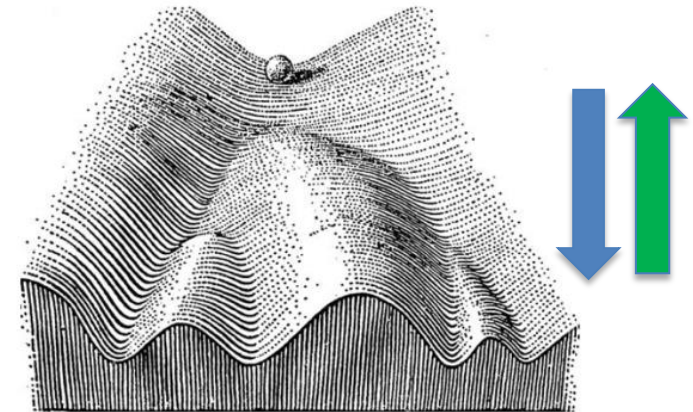
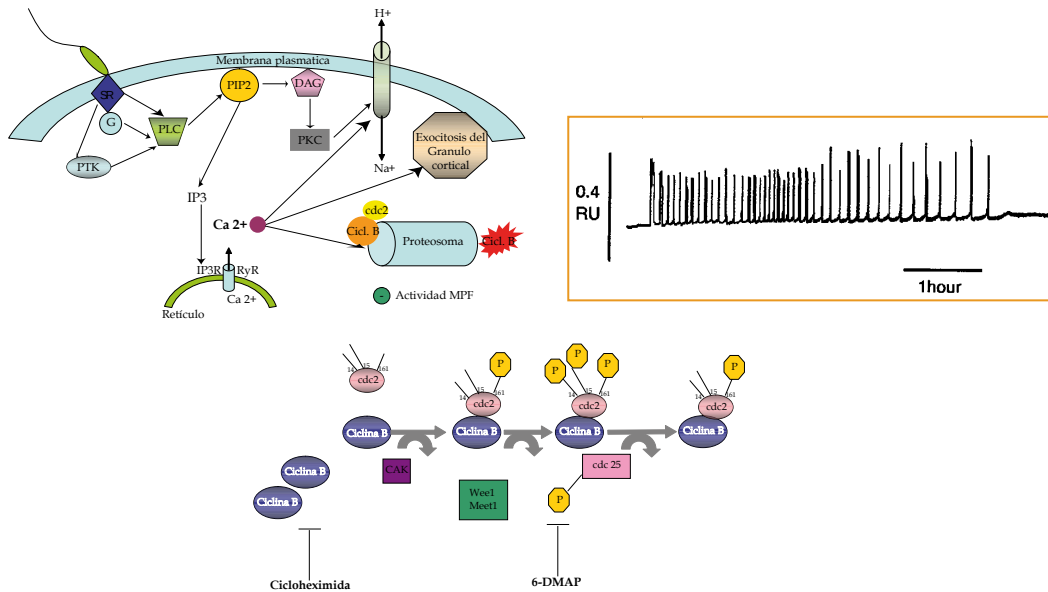


Metodología

Fusión



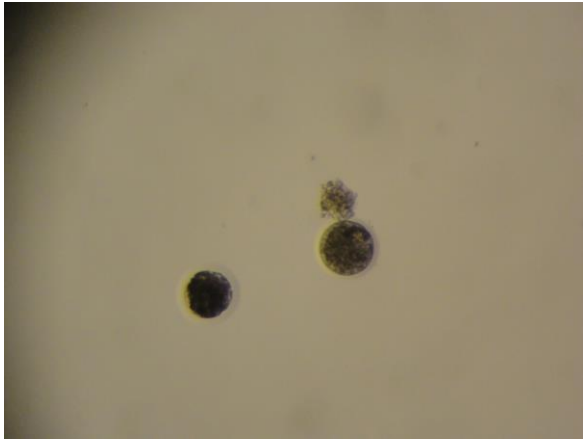
Activación y Reprogramación nuclear



Waddington's Epigenetic Landscape

Eficiencia

Embriones Frescos



→ Día 60: 50% →

1-25%



Embriones Vitificados



→ Día 60: 30% →

1-15%

Cronología de las especies domesticas clonadas

Ovinos (Campbell y col, 1996, Wilmut y col, 1997)

Bovinos (Cibelli y col, 1998)

Cabras (Bagousi y col, 1999, Keefer y Baldasarre, 2001)

Ratones (Wakayama y col, 1998)

Cerdos (Bethauser y col, 2000, Polejaeva y col, 2000)

Conejo (Chesne y col, 2002)

Gatos (Shin y col, 2002)

Caballo (Galli y col, 2003)

Mula (Woods y col, 2003)

Rata (Zhou y col, 2003)

Bufalo (Shi y col, 2004)

Perros (Lee y col, 2005)

Hurón (Li y col, 2006)

Camellos (Wani y col, 2009)



Usos “geneticos” de la clonacion:

- Investigadores del ambito comercial en el campo medico utilizan la clonacion para crear individuos genéticamente idénticos para utilizar en el testeo de drogas y tratamientos (**eliminando la variabilidad genetica** hace que identificar los efectos del fármaco y el tratamiento entre grupos sea mucho más fácil).
- Mediante el uso de la clonación se puede **aumentar la incidencia de rasgos deseables** como la alta producción de leche o la resistencia a las enfermedades en el ganado, o al menos garantizar que estos rasgos se conserven (mayor incidencia en caracteres de **baja heredabilidad**), disminuyendo el intervalo del **progreso genetico**

Usos “particulares” en el equino

- Obtención de copias de animales específicos con un valor comercial particular (como en el caso de animales de alto rendimiento o reproductores)
- Recuperación de la capacidad de algunos individuos de reproducirse, como por ejemplo los machos castrados o que han sufrido alguna noxa
- Preservación de genética, lo cual incluye la de especies en peligro de extinción o propagación de especies exóticas, como los caballos mongoles (Przewalski's horse)
- Animales de compañía (incluyendo el caballo), con un fin mas emocional que productivo o comercial
- Incrementa la disponibilidad de semen y embriones

¿Para qué?



Clonación en Argentina: resultados Crest View Genetics- ViaGen

DONANTE	PADRILLO	SEX	F.Parto	Observaciones
B02 CUARTETERA	OPEN CHIMENTO	F	2013-03-11	Nacido
B02 CUARTETERA	THE LEOPARD	M	2013-01-30	Nacido
C01 LAPA	DOLFINA ACIDO	F	2013-01-01	Nacido
C02 LAPA	DOLFINA MILLONARIO	M	2012-10-25	Nacido
C03 LAPA	DOLFINA MILLONARIO	M	2012-10-22	Nacido
C03 LAPA	DOLFINA MILLONARIO	F	2013-03-06	Nacido
C03 LAPA	DOLFINA MILLONARIO	M	2012-11-07	Nacido
A02 RAPTOR	DOLFINA EL MESSI	F	06/09/2013	Nacido
A02 RAPTOR	DOLFINA EL MESSI	M	17/11/13	
A02 RAPTOR	DURAZNO	M	21/08/2013	Nacido
A02 RAPTOR	OPEN BALLET	M		
A02 RAPTOR	OPEN BALLET	M	20/09/2013	
A02 RAPTOR	OPEN CHIMENTO	M	baja 23-5-13	
A03 RAPTOR	DOLFINA ACIDO	F		
A03 RAPTOR	DOLFINA OBELISCO	F		
A03 RAPTOR	DURAZNO	F	31/10/13	
A03 RAPTOR	OPEN CHIMENTO	M	15/09/2013	
A03 RAPTOR	OPEN CHIMENTO	F	14/08/2013	Nacido
A03 RAPTOR	OPEN CHIMENTO	M	16/10/13	
B01 CUARTETERA	DOLFINA ENTALLADO	F		
B01 CUARTETERA	MR. SHINER	M	20/10/13	
B01 CUARTETERA	OPEN CHIMENTO	F	18/08/2013	Nacido
B02 CUARTETERA	DOLFINA EL VENTURA	F	29/11/13	
B02 CUARTETERA	DOLFINA MILLONARIO	F	30/08/2013	Nacido
B02 CUARTETERA	MACHITOS CHELO	M	30/10/13	
B03 CUARTETERA	CLASSIFY	F	30/08/2013	Nacido
B03 CUARTETERA	DOLFINA EL VENTURA	M	20/11/13	
B03 CUARTETERA	MR. SHINER	M	07/11/13	
B03 CUARTETERA	MR. SHINER	M	07/11/13	
B04 CUARTETERA	CLASSIFY	M	30/08/2013	Nacido
B04 CUARTETERA	DOLFINA EL VENTURA	M	12/11/13	
B04 CUARTETERA	DOLFINA ENTALLADO	F		
B04 CUARTETERA	GRAND REWARD	F		
B05 CUARTETERA	DOLFINA PADRE NUESTRO	I	baja 23-5-13	
B05 CUARTETERA	DOLFINA PADRE NUESTRO	F		
B05 CUARTETERA	GRAND REWARD	M		
B05 CUARTETERA	OPEN CHIMENTO	F	15/08/2013	Nacido
C01 LAPA	DOLFINA MILLONARIO	M	26/07/2013	Nacido
C01 LAPA	DOLFINA MILLONARIO	M	16/08/2013	Nacido
C01 LAPA	DOLFINA MILLONARIO	F	30/08/2013	Nacido
C01 LAPA	DOLFINA PADRE NUESTRO	M		
C01 LAPA	OPEN BALLET	M		
C02 LAPA	DOLFINA EL MESSI	F	17/11/2013	
C02 LAPA	DOLFINA MILLONARIO	M	13/09/2013	
C02 LAPA	OPEN BALLET	M	05/08/2013	Nacido
C03 LAPA	DOLFINA EL MESSI	M	17/09/2013	
C03 LAPA	DOLFINA MILLONARIO	F	16/08/2013	Nacido
C03 LAPA	DOLFINA PADRE NUESTRO	M		

Clonación equina



Prometea-2003
Galli *et al*



Clonación equina



≈180 equinos clonados (70% polo) 2007-2012



Some of your animals have more income potential than others. Our services help you identify, preserve, and reproduce the genetics of those animals.

Clonación equina

Argentina:

Polo, 2008, FVet-Halitus



Criollo, 2011, FAUBA



A Primer on Cloning and Its Use in Livestock Operations



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Animal Cloning

The responses to the questions provided in this document represent the FDA's view in light of the conclusions and recommendations outlined in the Animal Cloning Risk Assessment, Risk Management Plan, and Guidance for Industry #179.

Content current as of:
08/29/2018

Is it Safe to Eat Food from Clones?

Yes. Food from cattle, swine, and goat clones is as safe to eat as food from any other cattle, swine, or goat. But it's important to remember that the primary purpose of clones is for breeding, not eating. Dairy, beef, or pork clones make up only a tiny fraction of the total number of food producing animals in the United States. Instead, their offspring would be the animals actually producing meat or milk for the food supply.

Dairy clones will produce milk after they give birth, and the dairy farmers will want to be able to drink that milk or put it in the food supply. Once clones used for breeding meat-producing animals can no longer reproduce, their breeders may also want to be able to put them into the food supply.

In order to determine whether there would be any risk involved in eating meat or milk from clones or their offspring, in 1999 the FDA asked the National Academy of Sciences (NAS) to identify science-based concerns associated with animal biotechnology, including cloning. The NAS gathered an independent group of top, peer-selected scientists from across the country to conduct this study. The scientists delivered their report in the fall of 2002. That report stated that theoretically there were no concerns for the safety of meat or milk from clones. On the other hand, the report expressed a low level of concern due to a lack of information on the clones at that time, and not for any specific scientific reasons. The report also stated that the meat and milk from the offspring of clones posed no unique food safety concerns.

After reviewing all this information, FDA found that it could not distinguish a healthy clone from a healthy conventionally bred animal. All of the blood values, overall health records, and behaviors were in the same range for clones and conventional animals of the same breed raised on the same farms. FDA also observed that milk from dairy clones does not differ significantly in composition from milk from conventionally bred animals.

In the Risk Assessment, FDA concluded that meat and milk from cattle, swine, and goat clones is as safe as food we eat from those species now. Although we don't have any particular concerns about sheep clones, we did not have enough information to make a decision on the safety of food from sheep clones.

For another study similar to the one conducted on cow clones, the agency also evaluated the health of offspring sexually derived from swine clones, as well as the composition of their meat. After reviewing this very large data set, the agency concluded that all of the blood values, overall health records, and meat composition profiles of the progeny of clones were in the same range as for very closely genetically related conventionally bred swine. Based on these results, other studies from scientific journals, and our understanding of the biological processes involved in cloning, the agency agreed with NAS that food from the sexually reproduced offspring of clones is as safe as food that we eat every day. We reiterate, however, that the sexually reproduced offspring of clones would produce almost all of the food from the overall cloning/breeding process.

<https://www.fda.gov/animal-veterinary/animal-cloning/primer-cloning-and-its-use-livestock-operations>

London 2012 - Los Juegos abren la puerta a los caballos clonados



La FEI y el Comité Olímpico Internacional (COI) han aceptado finalmente incorporar animales clonados en las distintas disciplinas de equitación

ONE-TRICK GENES? A LOOK AT THE LEGALITY OF BANNING ANIMAL CLONES FROM COMMERCIAL PROVING GROUNDS, 2014,
Laura E. Peet, Journal of Law, Technology and Policy, Vol 14 (565-589)

Clonación equina

Brasil: In Vitro Brasil, Turbante (septiembre 2012)



O garanhão teve seu **material genético** guardado por 15 anos. Ele está inscrito no livro “**Guinness**” como o **cavalo** que produziu o maior número de filhos do mundo (1.678). O cavalo chegou a ser avaliado em mais de US\$ 1 milhão, mas José Osvaldo Junqueira, seu proprietário, nunca quis vendê-lo.

Clonación equina

8 de Agosto de 2013



AQHA Cloning Lawsuit Resources

**Abraham & Veneklasen Joint Venture
Vs American Quarter Horse Association**

**Judge orders quarter horse association to register
clones**

ABIERTO DE HURLINGHAM

Miércoles 16 de octubre de 2013 | 11:00

La era del clon ya es una realidad en el polo argentino

Debutó Show Me, la primera yegua de este tipo que juega en nuestro país; para Adolfo Cambiaso, es un gran paso



Al menos 370 clones equinos nacidos en todo el Mundo

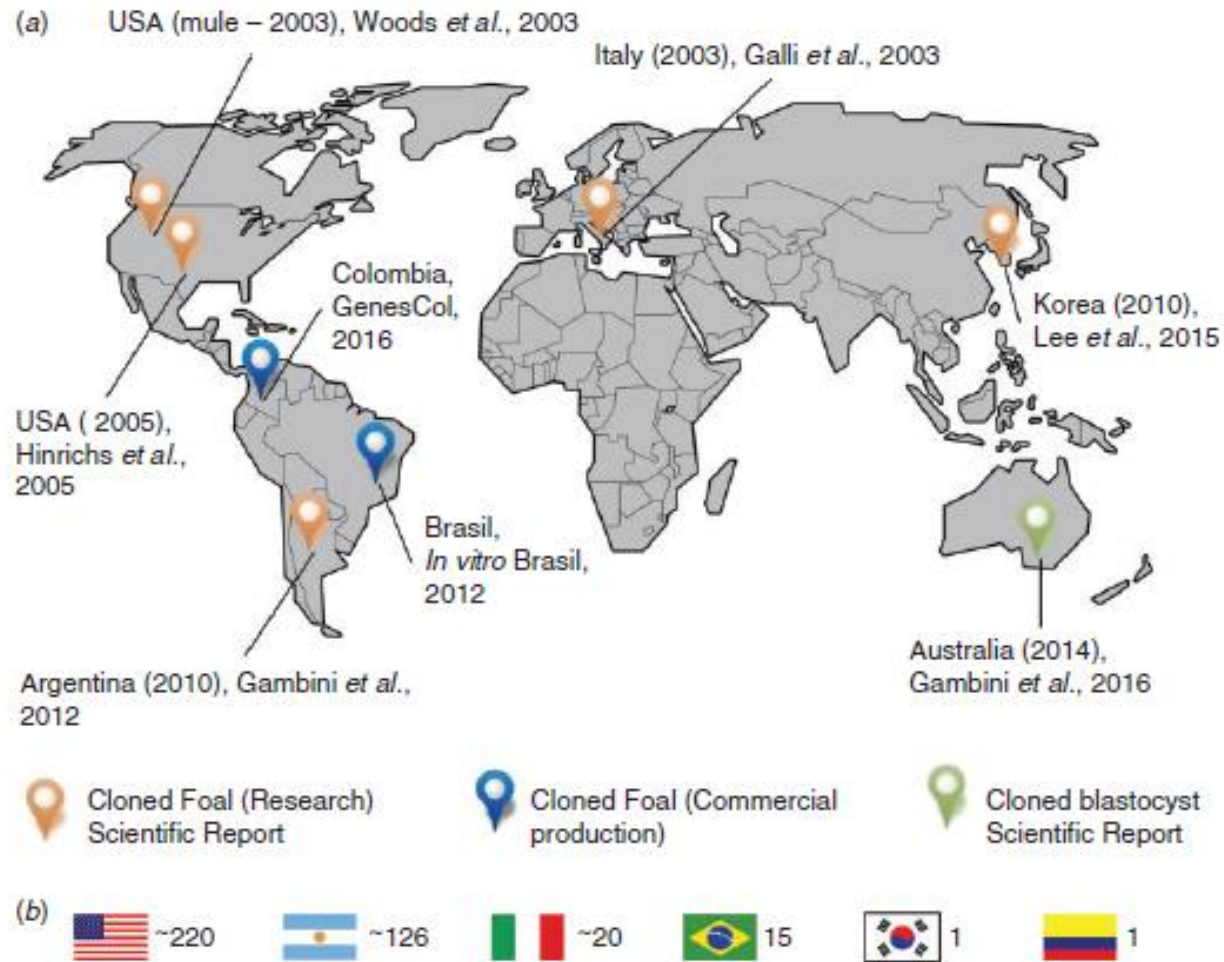


Fig. 3. (a) Worldwide distribution of reports of the first equine clones in different countries. (World map image from <https://commons.wikimedia.org/wiki/File:BlankMap-World-1985.png>, accessed 8 October 2017; licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license, modified.) (b) Estimated number of cloned horses produced in different countries by 2016.

Table 1. Some of the main breeds of horses cloned reported until 2016

Breed	Reference
Criollo Argentino	Gambini <i>et al.</i> (2012)
Polo pony	Gambini <i>et al.</i> (2014), Olivera <i>et al.</i> (2016), Kheiron ^A , Crestview Genetics ^A
Haflinger	Galli <i>et al.</i> (2003), Lagutina <i>et al.</i> (2005)
Warmblood	Lee <i>et al.</i> (2015)
Arabian horse	Lagutina <i>et al.</i> (2005), Crestview Genetics ^A
Thoroughbred	Kheiron ^A
Jumping horse	Gambini <i>et al.</i> (2014), ViaGen ^B , Kheiron ^A
Paso colombiano	GenesCol ^A
Paso fino	ViaGen ^B
Cutting horse	ViaGen ^B
Mangalarga marchador	<i>In vitro</i> Brasil Clonagem ^A
Campolina	<i>In vitro</i> Brasil Clonagem ^A
Bucking horse	ViaGen ^B
Barrel racing horse	ViaGen ^B
Quarter horse	ViaGen ^B

^APersonal communication, June 2017.

^BSee ‘Our Equine Client Stories’ at <http://www.viagen.com>, accessed 8 October 2017.

Empresas privadas de clonación equina en Argentina han producido mas de 120 individuos clonados:

- Kheiron
- Clonarg
- Crest View- ViaGen



Clonación en Argentina: resultados

Cuartetera: 10 clones



Colibrí: 3 clones



Lapa: 6 clones



Aiken Cura: 3 clones



¿Por que es tan costoso clonar equinos?

- Alto costo de los ovarios



- Baja eficiencia de la técnica por baja eficiencia en el laboratorio, pero principalmente por perdidas luego de la transferencia embrionaria, en general por problemas en la reprogramacion



- Bajo numero de grupos de trabajo dedicados a mejorar la técnica en equinos, como consecuencia de los dos puntos anteriores, a lo que se suman los intereses comerciales de las empresas

- Estacionalidad de la especie

RESEARCH ARTICLE

In Vitro and *In Vivo* Development of Horse Cloned Embryos Generated with iPSCs, Mesenchymal Stromal Cells and Fetal or Adult Fibroblasts as Nuclear Donors

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Futuro de la clonación equina: aumentar la eficiencia

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Just Accepted

This article has been peer reviewed and accepted for publication. It is in production and has not been edited, so may differ from the final published form.

Targeting epigenetic nuclear reprogramming in aggregated cloned equine embryos

Thiago Damasceno, Gabriela, Richard Fry, Angus McKinnon, Kerri Fry, Jennifer Kelly, Paul Verma, Chelsie Burden, Daniel Salamone, Andrés Gambini

Abstract

Epigenetic perturbations during the reprogramming process have been described as the primary cause of the low efficiency of Somatic Cell Nuclear Transfer (SCNT). In this study, we tested three strategies targeting nuclear reprogramming to investigate the impact on equine SCNT. Firstly, we evaluated the effect of treating somatic cells with chetomin, a fungal secondary metabolite reported to inhibit the trimethylation on histone 3 lysine 9 (H3K9me3). Secondly, caffeine was added to the culture media during the enucleation of oocytes and prior to activation of reconstructed embryos as a protein phosphatase inhibitor to improve nuclear reprogramming. Thirdly, we tested the effect of the histone deacetylase inhibitor Trichostatin A (TSA) added during both activation and early embryo culture. Although, none of these treatments significantly improved the developmental rates of the in vitro aggregated cloned equine embryos, the first equine cloned foal born in Australia was produced with somatic cells treated with chetomin. The present study describes the use of chetomin, caffeine and TSA for the first time in horses serving as a starting point for the establishment of future protocols to target epigenetic reprogramming for improving the efficiency of equine cloning.

RD19239 Accepted 10 August 2019

QUINTA GENERACIÓN

2000

-Transgénesis.
-Células madre.

+

EDICION GENICA

infobae

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CIENCIA

Avance científico mundial: investigadores argentinos lograron generar clones equinos con genomas mejorados

Utilizando la técnica CRISPR-Cas9 o llamada "tijera genética", lograron alterar el ADN de un caballo de polo para mejorar su potencial y destreza

- Miostatina ?
- MC1R Melanocortin 1 receptor

Table 1. Current status of assisted reproductive technologies in livestock, a personal opinion.

	progress	practical use	research activity
	last 30 years	present	present
AI	+	++++	+
MOET	+	+++	-
Oocyte	++	+++	+
IVF	+	+++	+
embryo culture	++++	+++	+++
cryopreservation	+	+++	+
embryonic stem cells	-	-	+
SCNT	+++	+	++
recipient animals	++	+++	+
unknowns	+++	+++	++
	++++ intense + minimal	+++ moderate - absent	++ low



Proceedings of the 33rd Annual Scientific Meeting of the European Embryo Transfer Association (AETE); Bath, United Kingdom, September 8th and 9th, 2017.

Achievements and unmet promises of assisted reproduction technologies in large animals: a personal perspective

Cesare Galli¹

Avantea and Fondazione, Avantea, Cremona, Italy.

Conclusiones

Es una técnica sumamente *ineficiente y por ello cara!!*

Requiere de personal altamente capacitado

No duplica ciertas características fenotípicas, todo el genotipo

Es una herramienta biotecnológica importante para obtener animales de alto valor que por alguna razón no se encuentran en el circuito reproductivo (castrados, problemas reproductivos)

NO es una herramienta *per se* de mejoramiento genético, sólo es una fotocopiadora biológica!!



MUCHAS GRACIAS!!!