Universidad de Chile

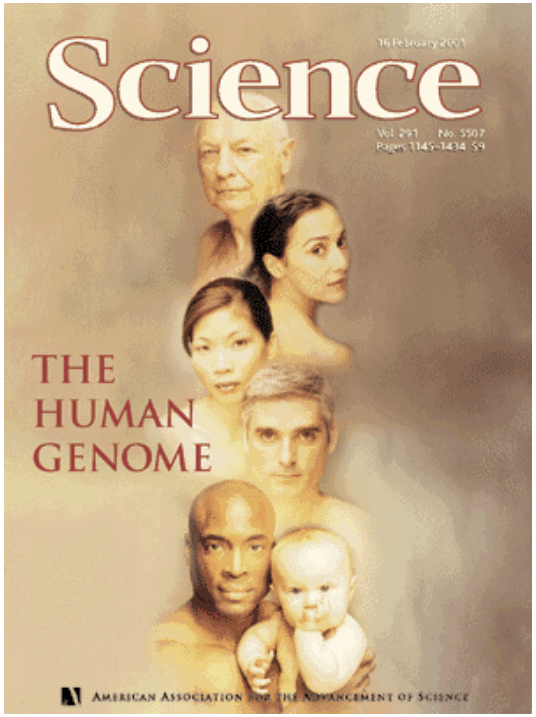
Gero

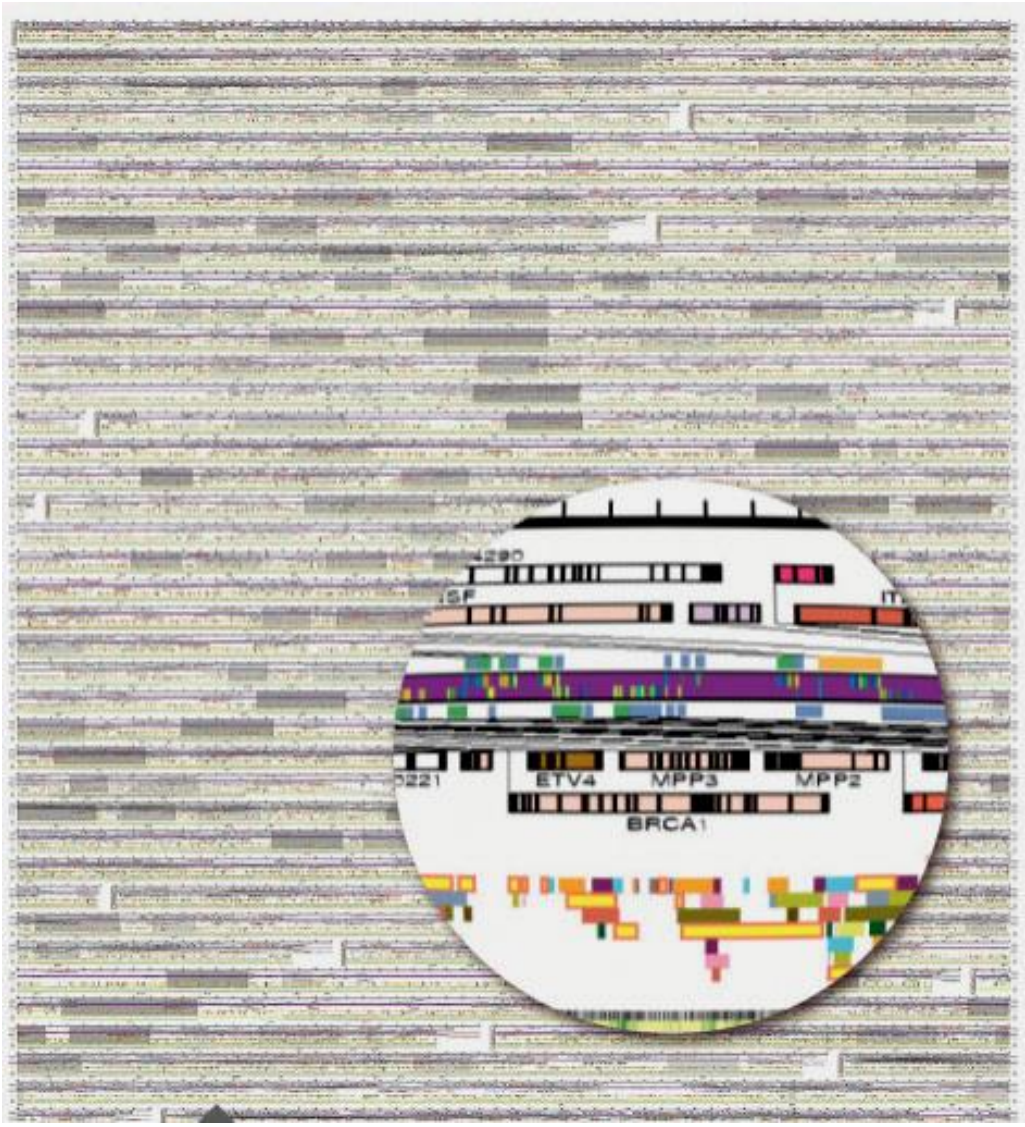
BIOMEDICAL NEUROSCIENCE INSTITUTE CHILE

Terapia génica: ¿Ciencia ficción o una realidad?

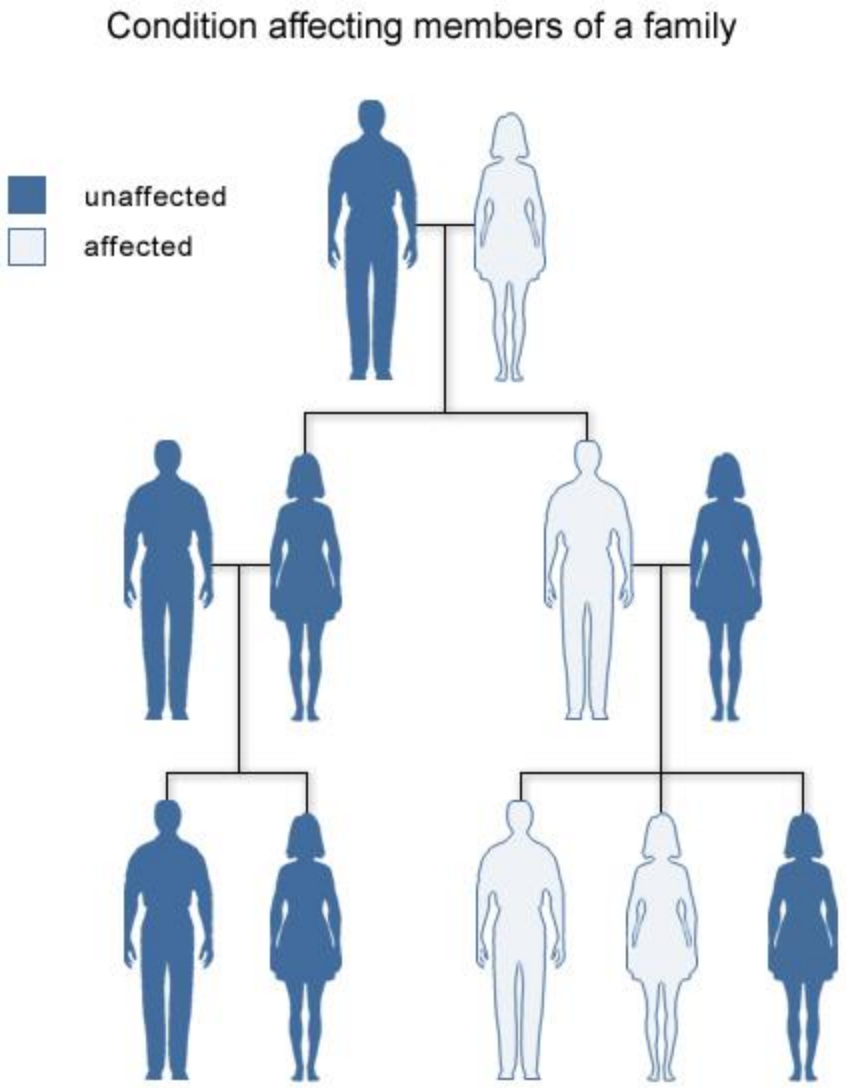
Claudio Hetz

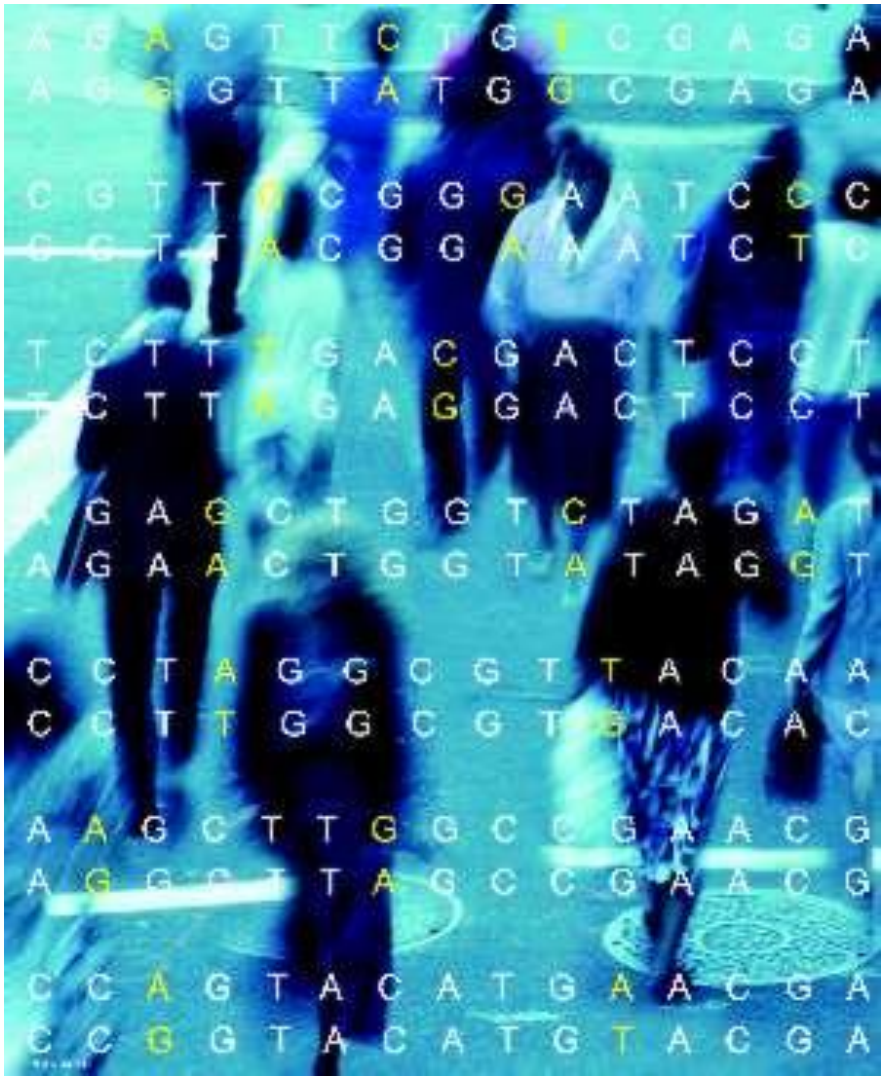
Instituto Milenio de Neurociencia Biomédica (BNI),
Centro FONDAP de Gerociencia, Salud Mental y Metabolismo (GERO)
Universidad de Chile


Science
16 February 2001
Vol. 291 No. 5507
Pages 1145–1434 S9
THE HUMAN GENOME
American Association for the Advancement of Science


ETV4
MPP3
MPP2
BRCA1

Enfermedades hereditarias





U.S. National Library of Medicine

Sociedad, ética, salud

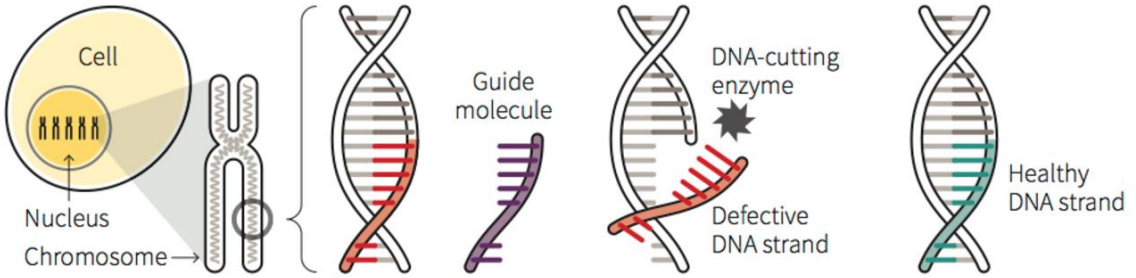
El nuevo mundo de la terapia génica no tiene límites

Curar enfermedades, evitar genes que podrían desarrollarlas o definir, incluso, el color de los ojos son parte de las cosas que la ingeniería genética podrá hacer en un futuro no tan lejano. El problema son sus consecuencias aún desconocidas. LORENA GUZMÁN H.

DNA editing

A DNA editing technique, called CRISPR/Cas9, works like a biological version of a word-processing programme's "find and replace" function.

HOW THE TECHNIQUE WORKS



A cell is transfected with an enzyme complex containing:
- Guide molecule
- Healthy DNA copy
- DNA-cutting enzyme

A specially designed synthetic guide molecule finds the target DNA strand.

An enzyme cuts off the target DNA strand.

The defective DNA strand is replaced with a healthy copy.

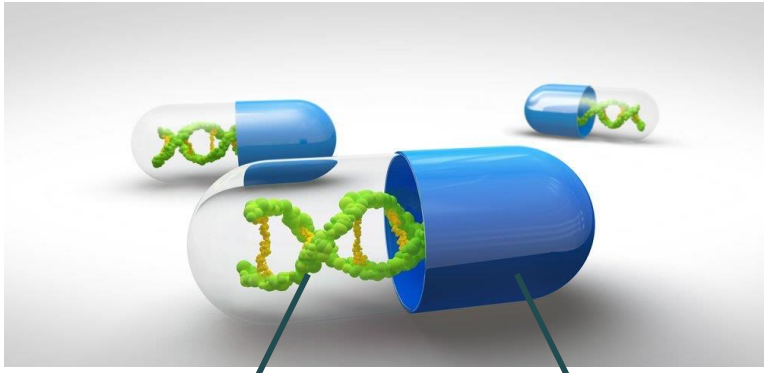
Sources: Reuters; Nature; Massachusetts Institute of Technology

W. Foo, 24/04/2015

REUTERS

¿Qué es la terapia génica?

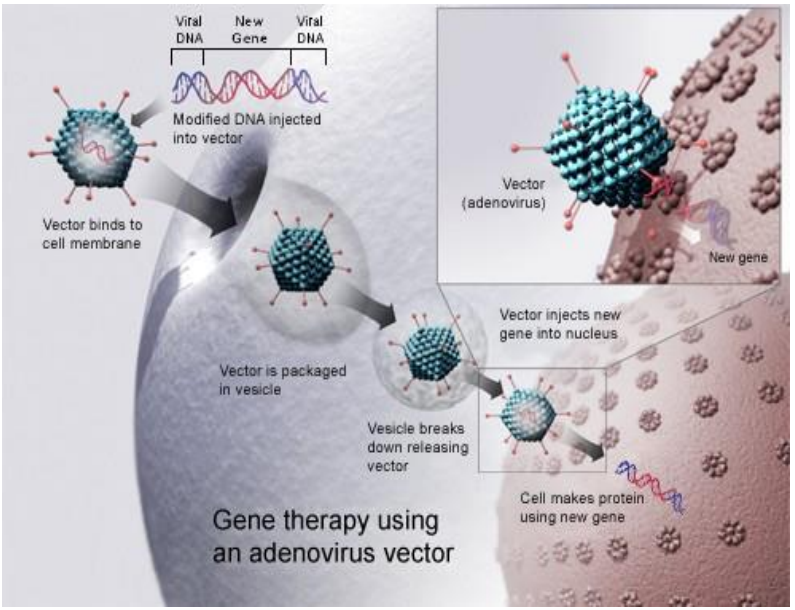
Gen encapsulado



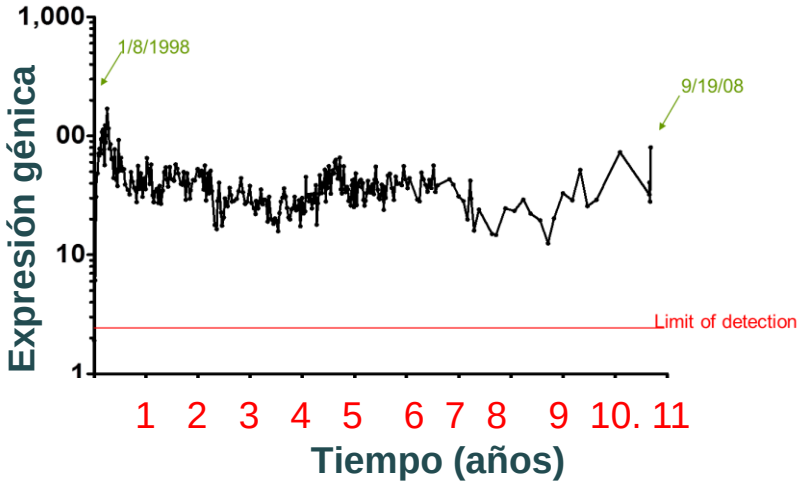
Gen Terapéutico

Cápsula biológica

Vehículo de entrega

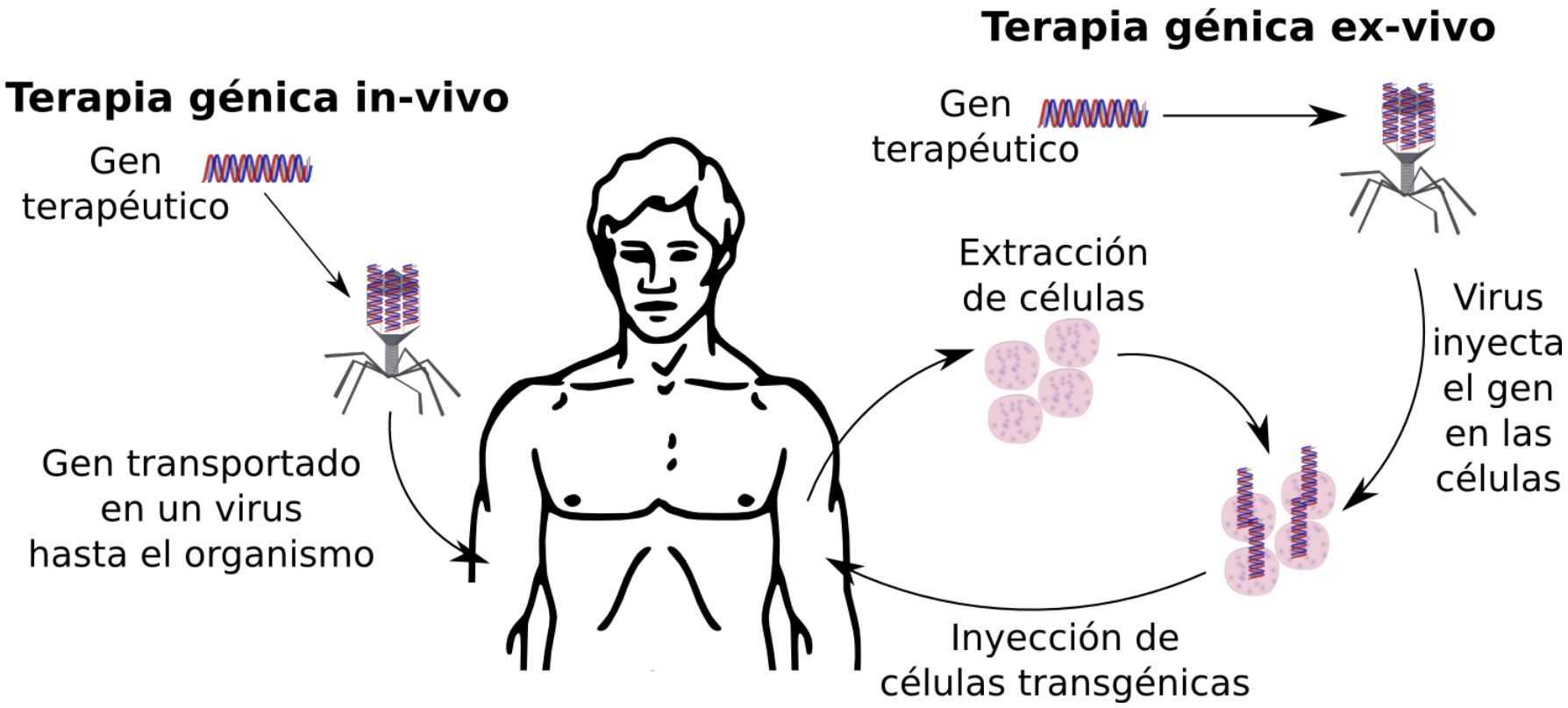


La cápsula:
Virus adeno-asociados (AAV)



- Son muy pequeños (nanometros)
- No se asocian a enfermedades
- No activan el sistema inmune
- No se incorporan al genoma
- Estables por décadas
- Producción GMP

Dos estrategias de tratamiento



Terapia génica (nanotecnolgía)

Tratamiento deficiencia de lipoproteína lipasa

Terapias génica cáncer 2017: CAR-T.

>2,000 pacientes han recibido *AAVs* en más de 140 ensayos clínicos.

- Primera terapia aprobada en Europa 2012, seguida por tres en China.
- Tres terapias aprobadas por la FDA 2017.

NATURE BIOTECHNOLOGY | TRADE SECRETS

$1-million price tag set for Glybera gene therapy

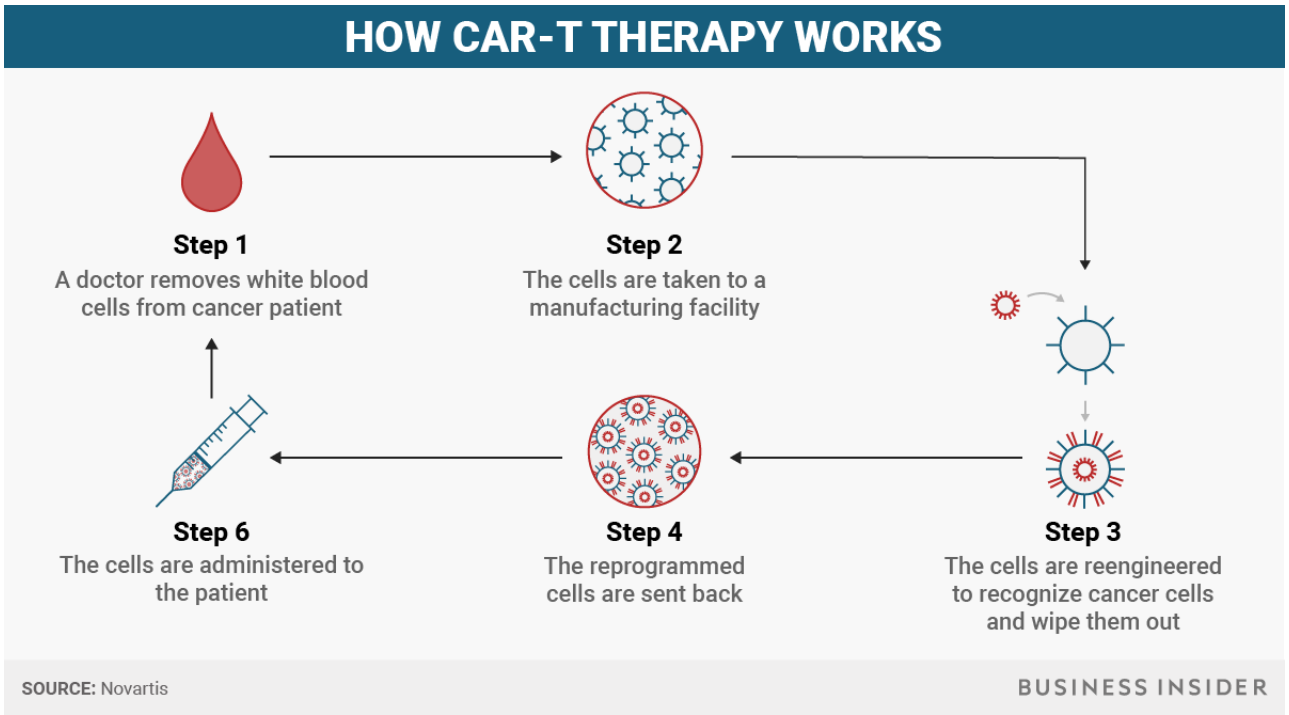
03 Mar 2015 | 00:32 GMT | Posted by Bioentrepreneur | Category: News

The first gene therapy approved in the Western world is set to go on sale in Germany at a cost close to $1 million per treatment. The record-breaking price tag came to light in November 2014, when Amsterdam-based Uniqure and its marketing partner Chiesi, of Parma, Italy, filed a pricing dossier with German authorities to launch Glybera. A few weeks later, the focus on gene therapies sharpened further when Cambridge, Massachusetts–based Bluebird Bio presented striking early clinical data from four beta-thalassemia patients treated with its Lentiglobin BB305 gene therapy, at the American Society of Hematology meeting in San Francisco. Within three months, these patients had begun producing sufficient hemoglobin to reduce or eliminate the need for blood transfusions. Big pharma is taking notice; the most recent gene therapy deal signed in February, between Sanofi's Genzyme unit and Third Rock Ventures' Voyager Therapeutics, both in Cambridge, Massachusetts, is worth up to $845 million. But as gene therapies start to provide solutions for highly penetrant genetic diseases that had been

Gene therapy programs are generating much excitement, but there is little agreement about

Terapia génica: una realidad

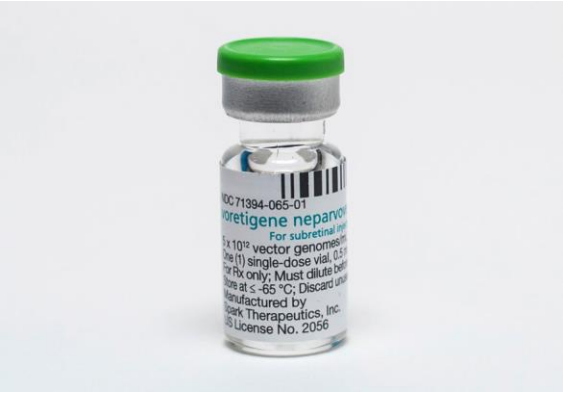
The FDA granted Yescarta Priority Review and Breakthrough Therapy designations. Yescarta also received Orphan Drug designation

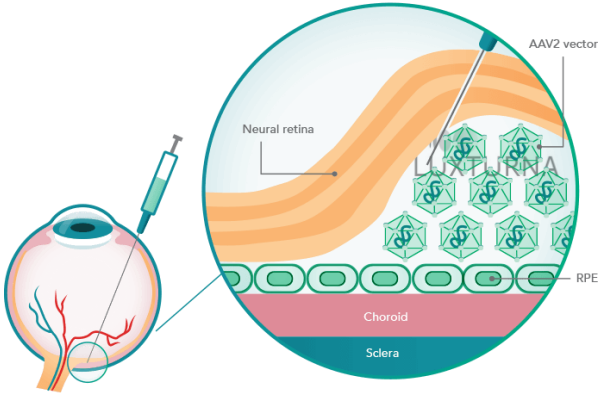


Terapia génica contra la ceguera

Ceguera congénica, enfermedad de Leber

Spark THERAPEUTICS





Terapia génica para SMA (Fase III)

NOVARTIS avexis

AVXS-101 (USD 8.7 billones)

SMA: spinal muscular atrophy

Tipo 0: la enfermedad lleva a la muerte durante el embarazo o después del nacimiento.

Tipo 1: Se desarrolla muy rápido, niños mueren a los 2 años.

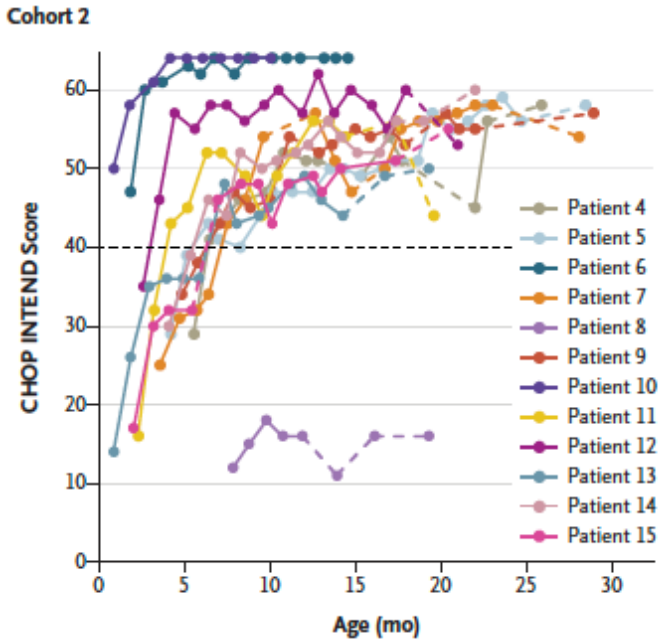
Tipo 2: Lleva a la muestre en la tercera década de vida.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 2, 2017 VOL. 377 NO. 18

Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

J.R. Mendell, S. Al-Zaidy, R. Shell, W.D. Arnold, L.R. Rodino-Klapac, T.W. Prior, L. Lowes, L. Alfano, K. Berry, K. Church, J.T. Kissel, S. Nagendran, J. L'Italien, D.M. Sproule, C. Wells, J.A. Cardenas, M.D. Heitzer, A. Kaspar, S. Corcoran, L. Braun, S. Likhite, C. Miranda, K. Meyer, K.D. Foust, A.H.M. Burghes, and B.K. Kaspar



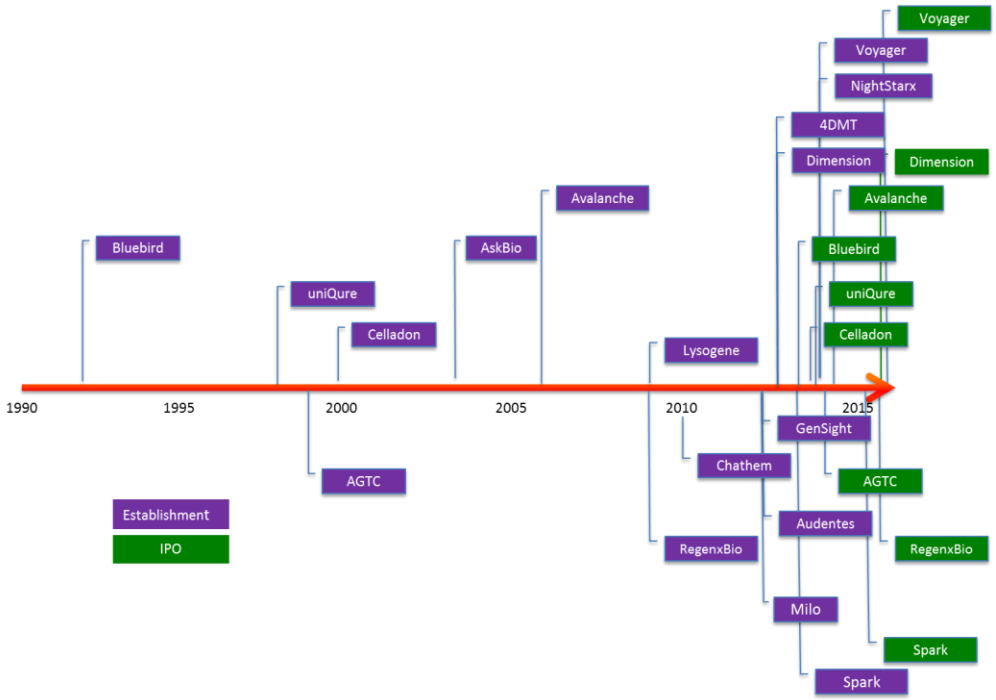
"In our Phase 1 trial, we showed that 92 percent of children are able to sit five seconds or greater, and 75 percent of children are able to sit 30 seconds or greater," Nagendran said, noting that the natural history of SMA type 1 has "zero children" ever being able to sit independently.

Oportunidad de negocios

Inversión, generación de nuevas empresas

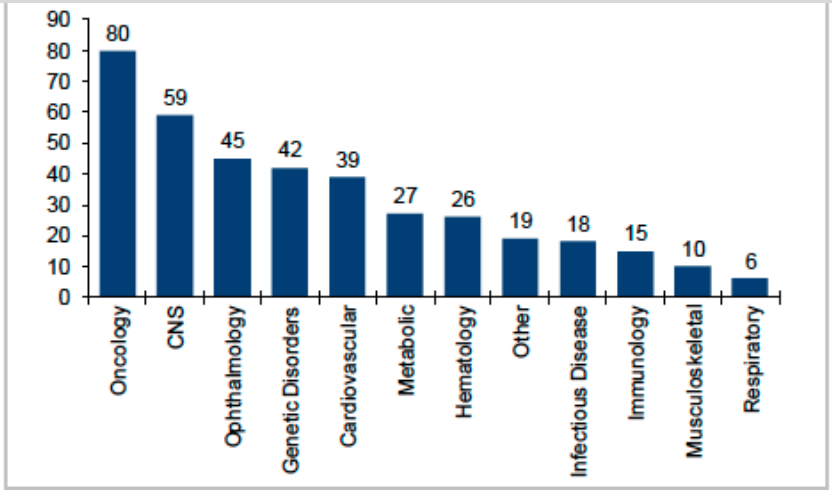
Valoración

Nuevas empresas



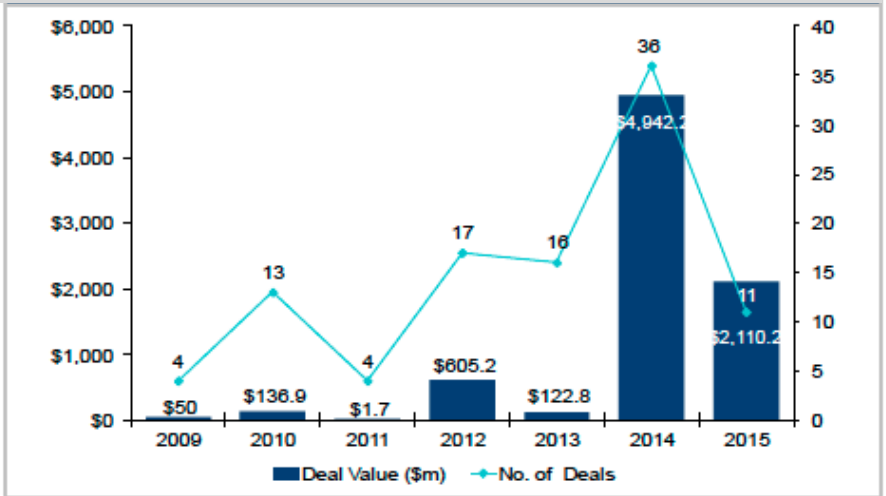
Ensayos clínicos e inversión

Ensayos clínicos 2009-2014



Source: GlobalData Pharma eTrack [Accessed January 28, 2015].

Inversión terapia génica

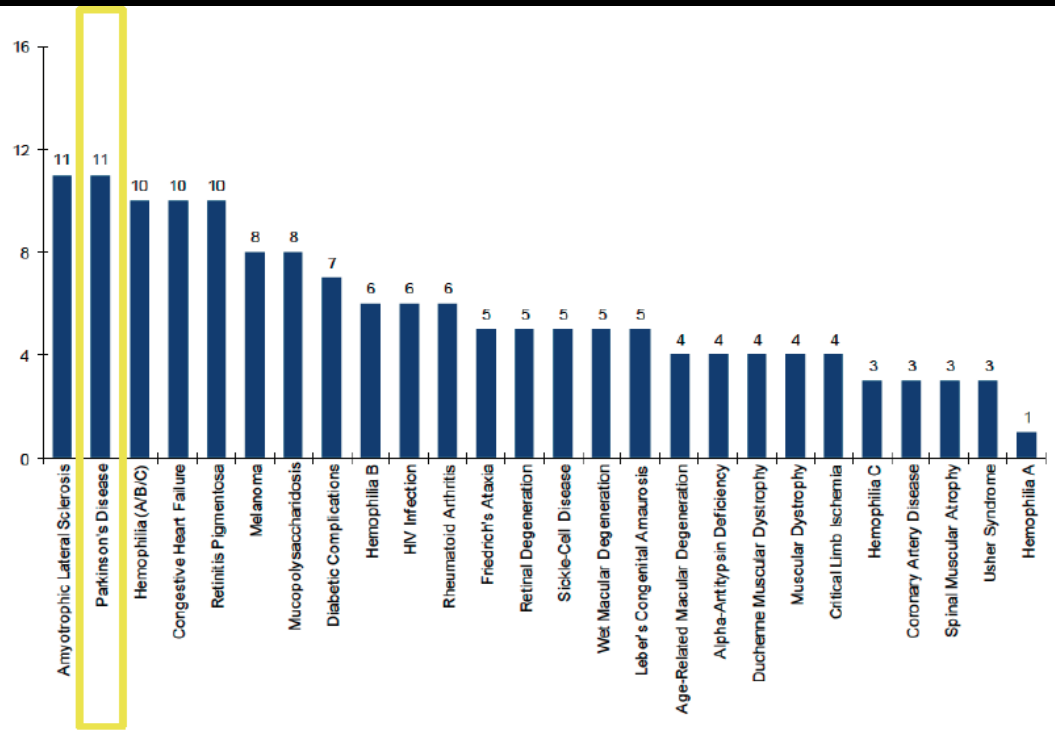


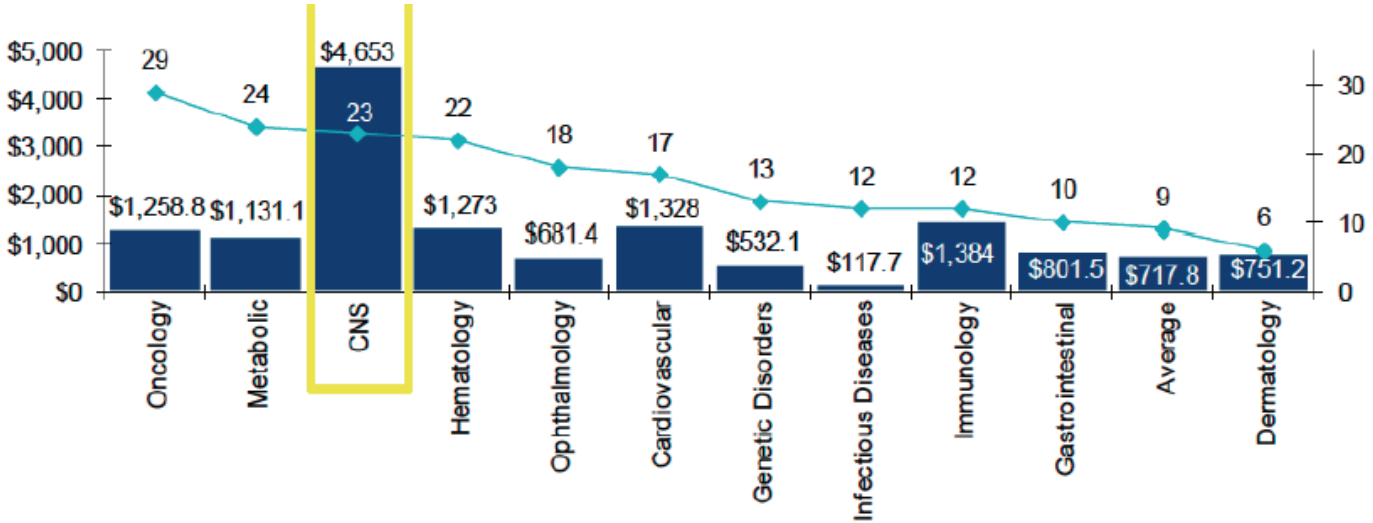
Source: GlobalData, Pharma eTrack [Accessed April 6, 2015].

Valorización actual de nuestras tecnologias (4 patentes):

2-15 millones de dólares. Estudio KimGlobal España.

Ensayos clínicos e inversión



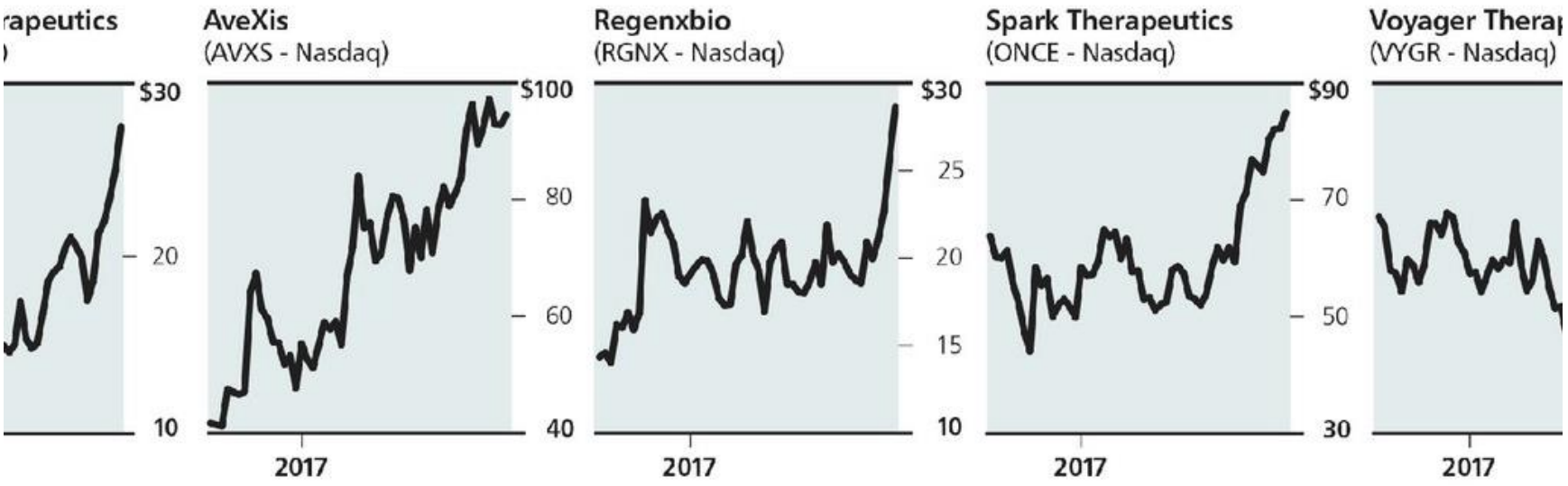


THERAPY PLAYS...

panies are developing replacement gene therapy for different hereditary diseases. The stocks have moved up sharply this y
treatments get approval from the Food and Drug Administration. Any unexpected setbacks, however, could hurt the share

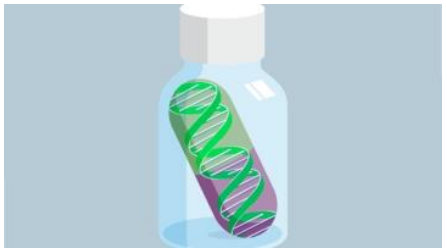
er	Recent Price	YTD Change	Market Value (mil)	2017E EPS	Cash and Equivalents* (mil)	Current or Completed Phase of Clinical Trials	1st Potential Year of Profit	Diseases Targeted
rapeutics / BOLD	$27.41	50%	$762	–$3.51	$145	Phase 1/2	N.A.	X-linked myotubular myopathy, Crigler-Na
	96.14	101	3,069	–6.04	418	Phase 3	2020	Spinal muscular atrophy
GNX	29.40	58	910	–3.08	209	Phase 1/2	2022	Age-related macular degeneration, HoF
eutics / ONCE	87.10	75	3,120	–7.37	239	Phase 3	2019	RPE-65 mediated retinal disease, Hemo
apeutics / VYGR	17.72	39	477	–2.84	141	Phase 1/2	2023	Parkinson's disease

/30/17. Subsequently, Spark raised an additional $380 million. N.A.=Not available. Sources: Ch



Modelo clásico de búsqueda de drogas esta obsoleto

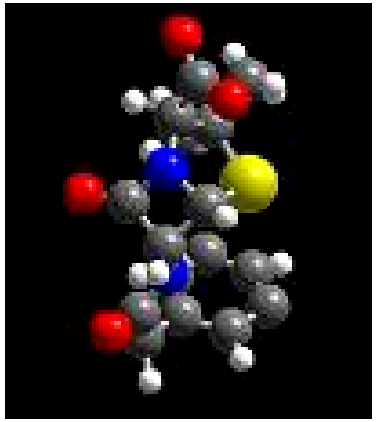
Terapia génica



Desarrollo de drogas (10-12 años)

Función biológica afectada

Identificación de blanco y validación



Hetz·Lab

Laboratory of Cellular Stress and Biomedicine

www.hetzlab.cl

Gero

www.gerochile.cl

BNI

BIOMEDICAL NEUROSCIENCE INSTITUTE

CHILE

www.bni.cl

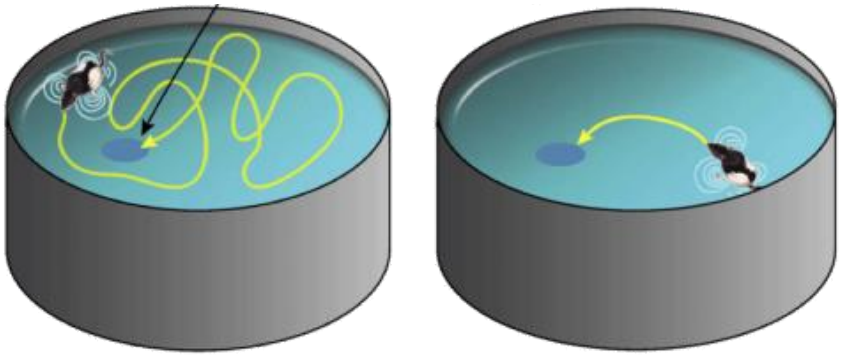
www.loligo.cl

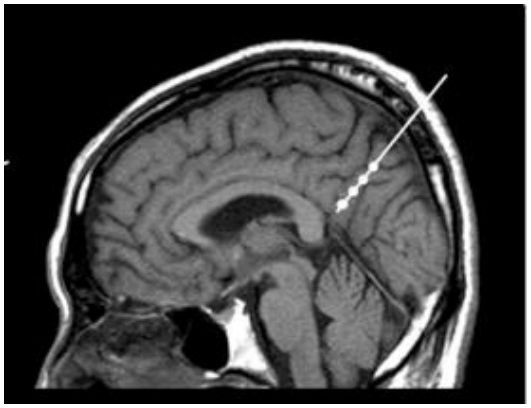
Capacidad de memoria

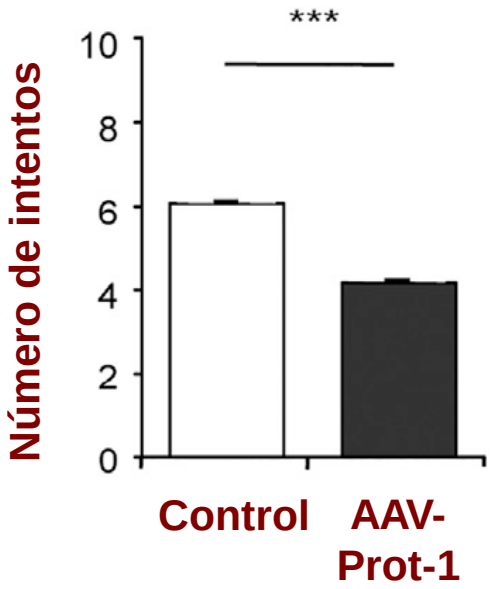
FONDEF
Fondo de Fomento al Desarrollo Científico y Tecnológico

Aprendizaje **Memoria**

Plataforma







Martinez y cols., (2016) *Cell Reports*

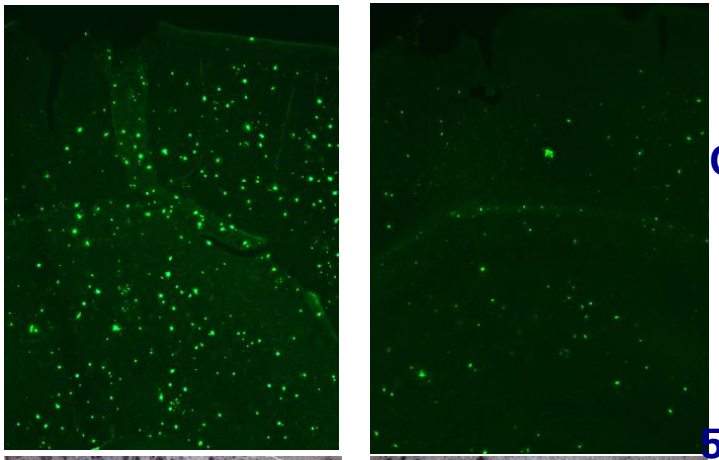
(Solicitud patente 2014)

XBP1s overexpression delayes Alzheimer

Amyloid load

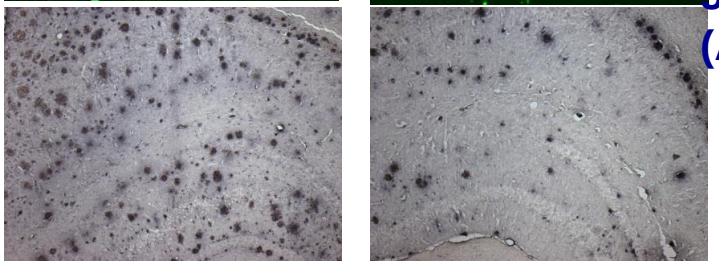
5xFAD | 5xFAD / Tg^{XBP1s}

Thioflavin S



Control

Amyloid b

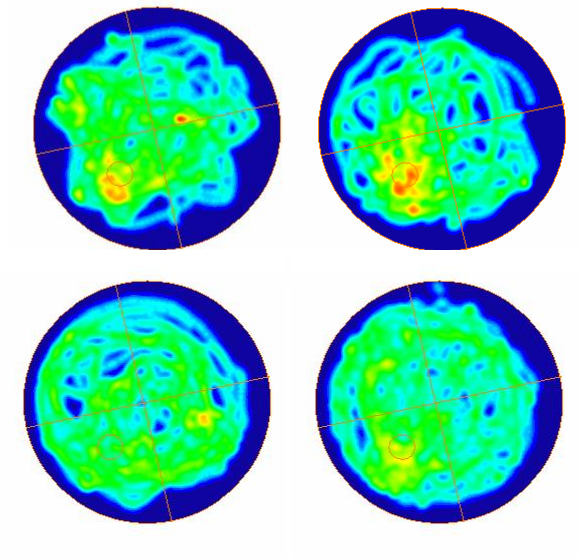


5xFAD (AD model)

Learning & memory

Water maze

AAV-GFP | AAV-XBP1s



Duran C., Espinoza S. et al – Unpublished

Mouse models to study human disease

Identification
Mutation in human genes

↓

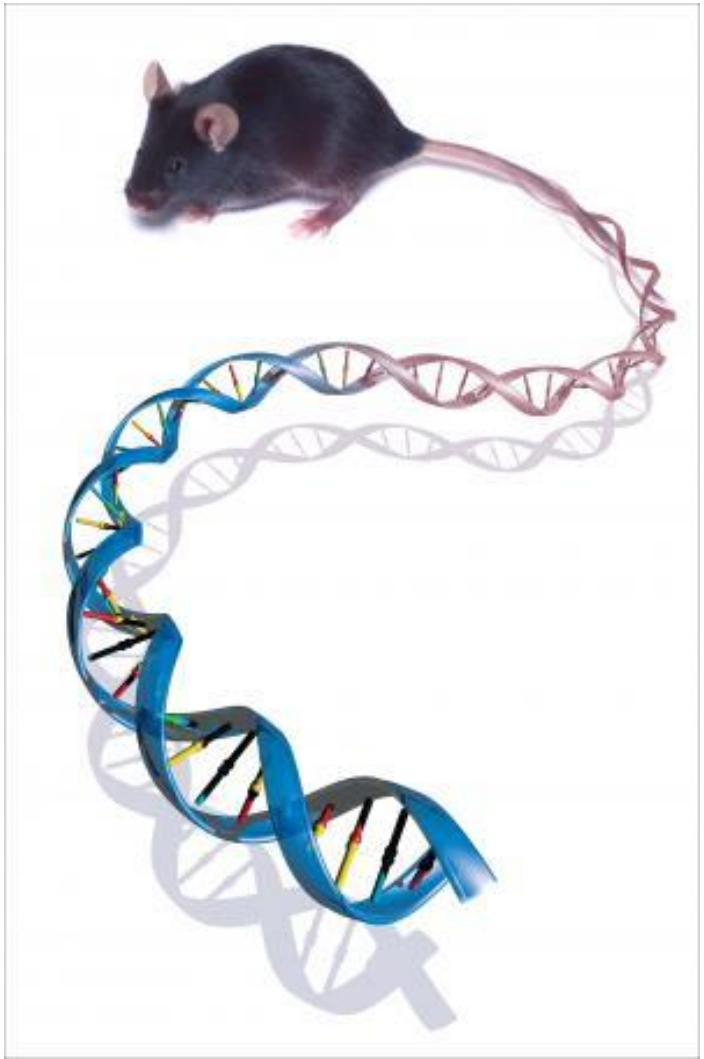
Transgenic mice

↓

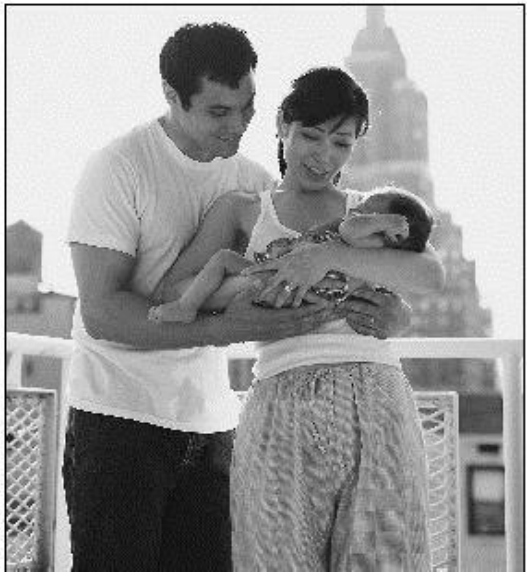
Monitoring disease features

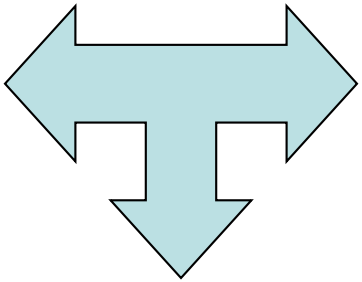
↓

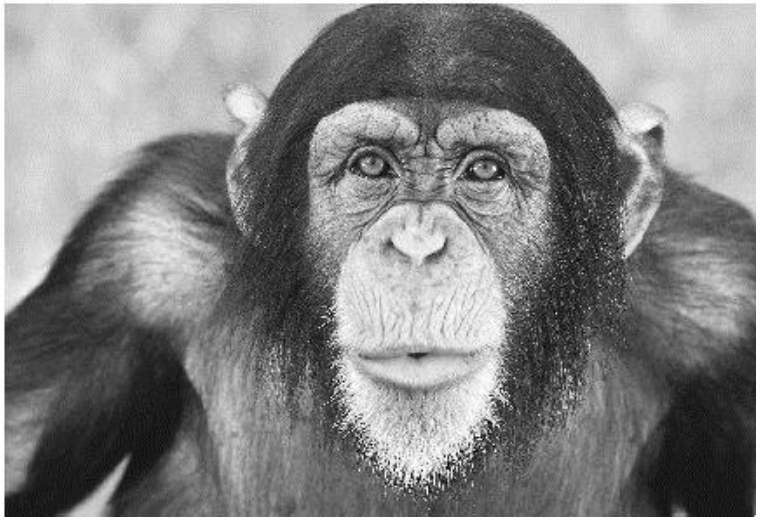
Disease mechanisms
Targets & intervention

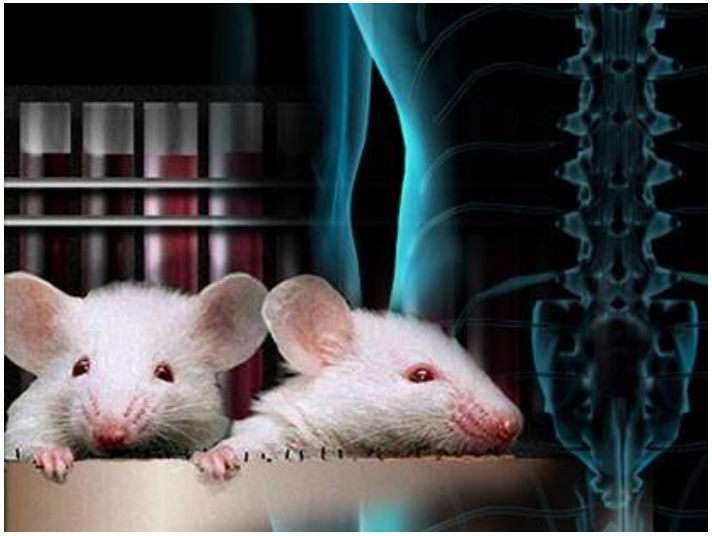


Donde estudiar el origen de una enfermedad?

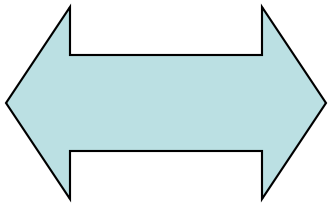


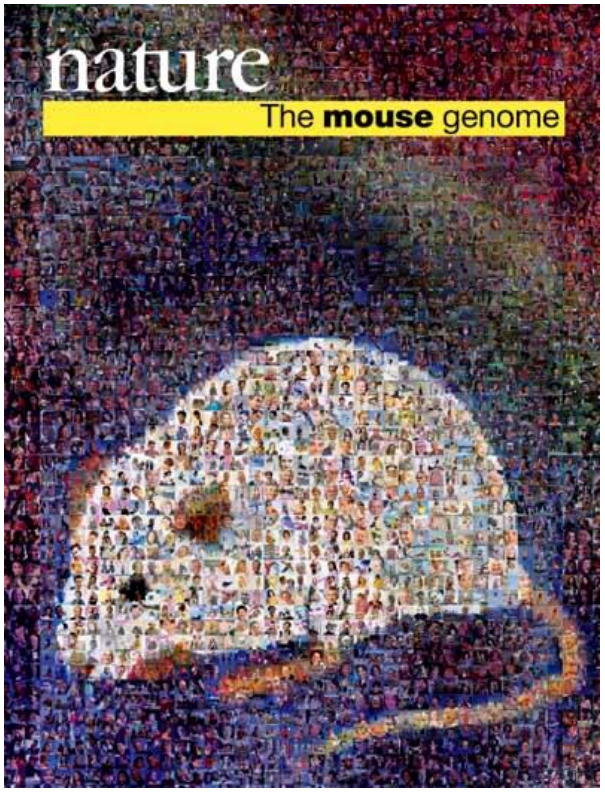






Genoma de ratón:
Una herramienta para entender el genoma humano

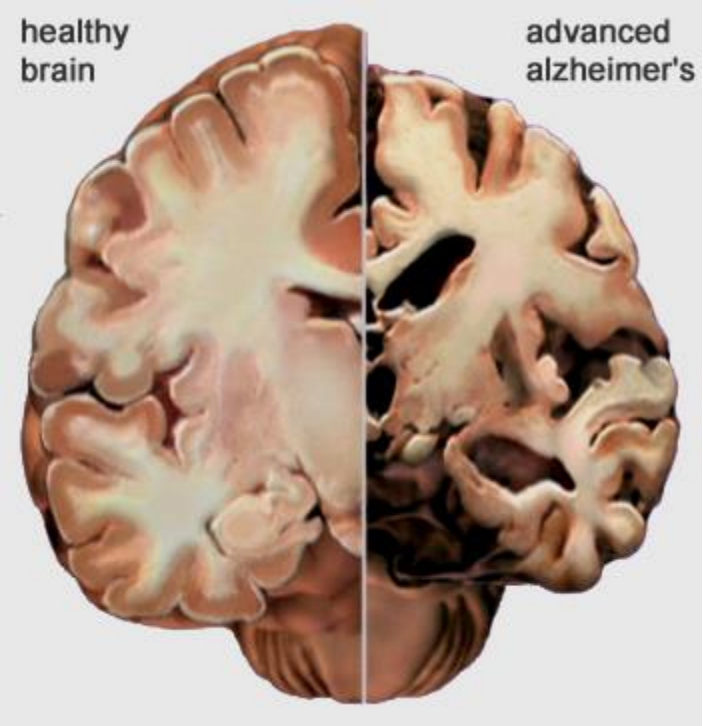


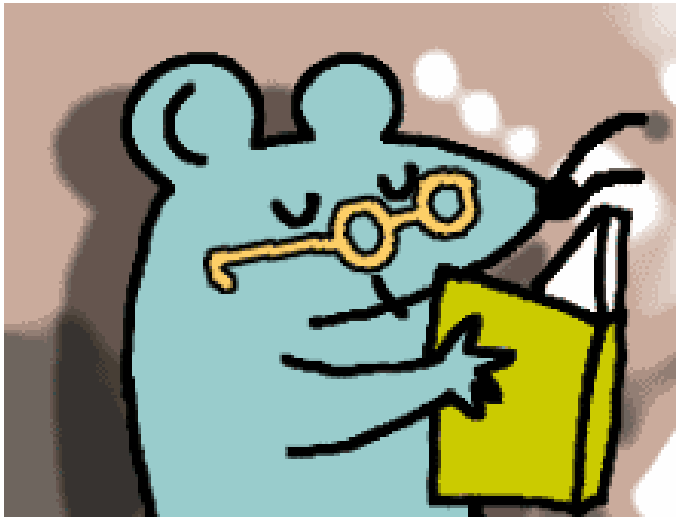


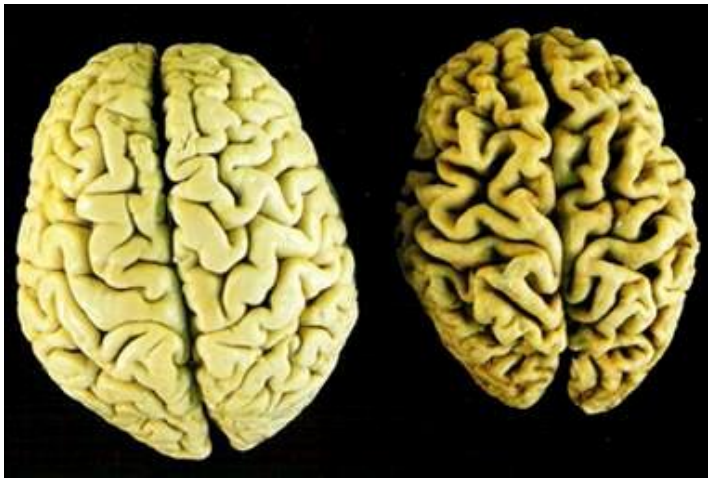
Animales transgénicos recapitulan enfermedades humanas

Gen
obesidad o
diabetes

Animales transgénicos recapitulan enfermedades humanas

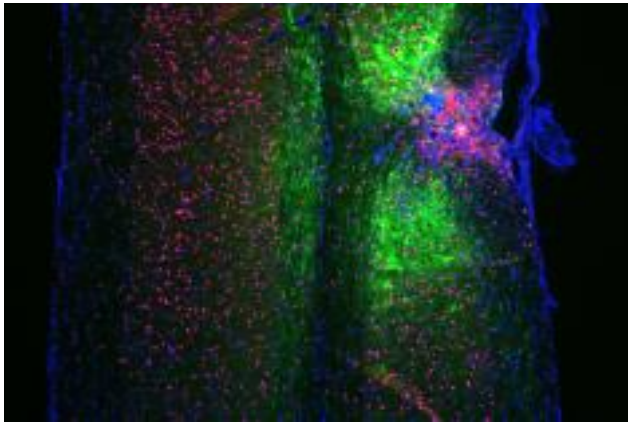


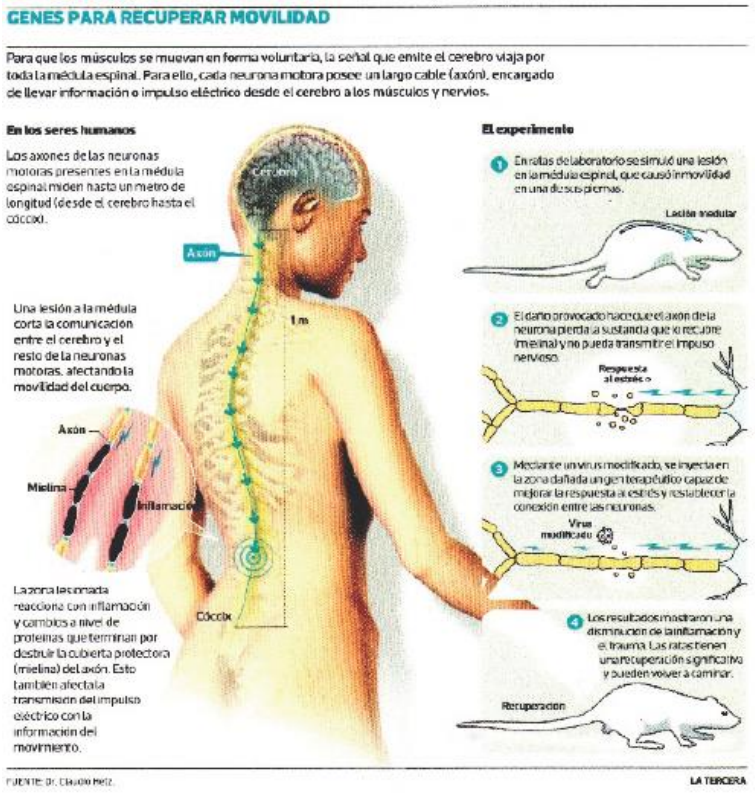




Mejora motora

- Uno de los cuatro proyectos premiado por la North America Spine Society (NASS) 2012.
- Premiado por la Christopher Reeve and Dana Foundation 2012.
- Escogido como mejor trabajo del año por el congreso anual de la NASS 2013.
- Mejor tesis de magister de Chile 2012 – Premio Federico Leyton Sociedad de Biología de Chile.





Reportaje laboratorio - La Tercera

Vectores: elementos clave en la terapia génica

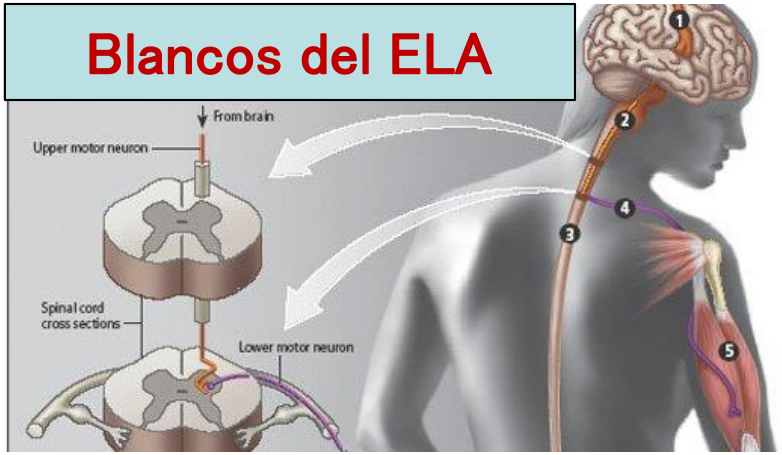
Table 2: Main Groups of Viral Vectors and Their Characteristics

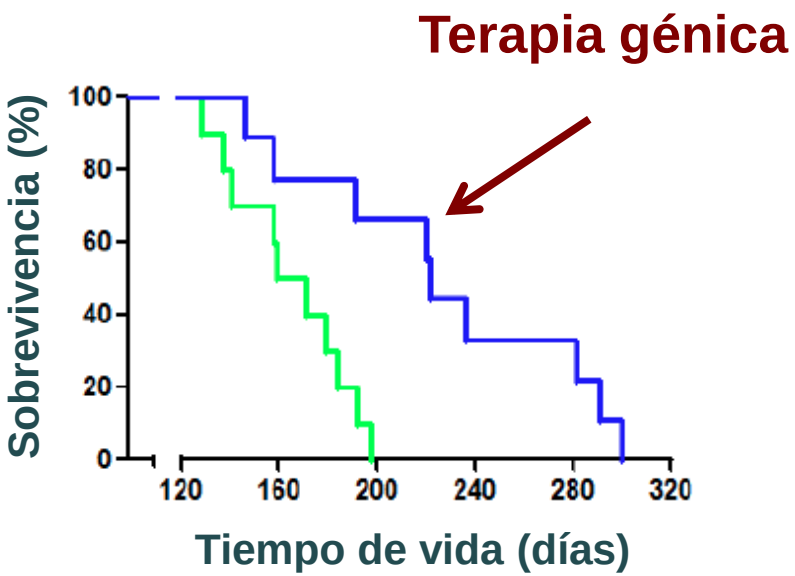
Vector	Genetic Material	Tropism	Inflammatory Potential	Main Limitations	Main Advantages
Enveloped					
Retrovirus	RNA	Dividing cells only	Low	Only transduces dividing cells; integration might induce oncogenesis	Persistent gene transfer in dividing cells
Lentivirus	RNA	Broad	Low	Integration might induce oncogenesis	Persistent gene transfer in most tissues
HSV-1	dsDNA	Strong for neurons	High	Inflammatory; transient expression in cells other than neurons	Large packaging capacity; strong tropism for neurons
Non-Enveloped					
AAV	ssDNA	Broad, with possible exception of hematopoietic cells	Low	Small packaging capacity compared with other vectors	Non-inflammatory; non-pathogenic
Adenovirus	dsDNA	Broad	High	Capsid mediates a potent inflammatory response	Extremely efficient transduction of most tissues

Source: Thomas et al., 2003.

Notes: dsDNA = double-stranded DNA; HSV-1 = herpes simplex virus type 1; ssDNA = single-stranded DNA.

Terapia génica en ELA experimental





(Solicitud patente 2015)