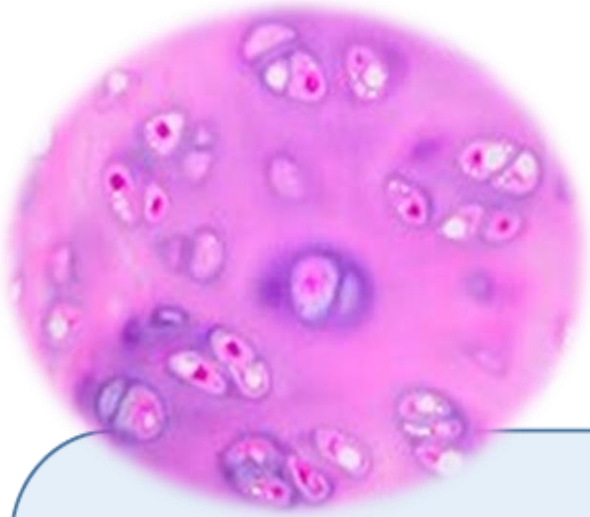
CONGRESO NACIONAL · 67 · 24-26 NOVIEMBRE · BARCELONA 2022

TERAPIAS AVANZADAS EN LA UE

Sol Ruiz, PhD
Jefe División de Biológicos y TA

MINISTERIO DE SANIDAD

agencia española de medicamentos y productos sanitarios



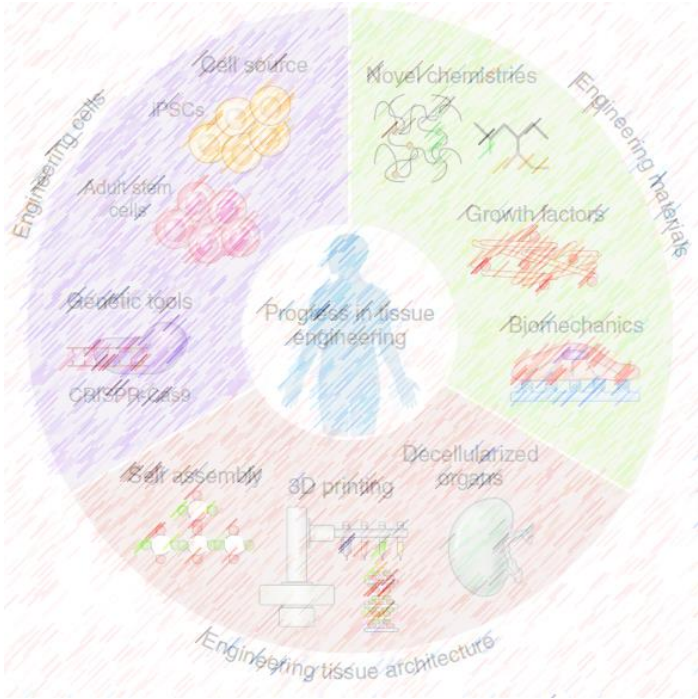
Medicamentos de terapia celular somática

Medicamentos de terapia génica

Medicamentos de terapia avanzada

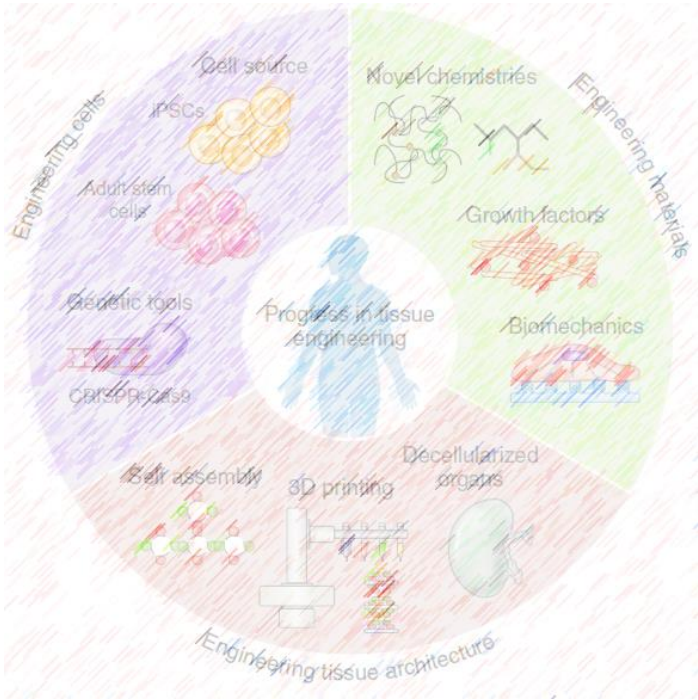
Medicamentos de ingeniería tisular

Medicamentos combinados de terapia avanzada



medicamentos de terapia avanzada

- autorización de comercialización
- investigación clínica
- autorización de uso



medicamentos de terapia avanzada

autorización de comercialización

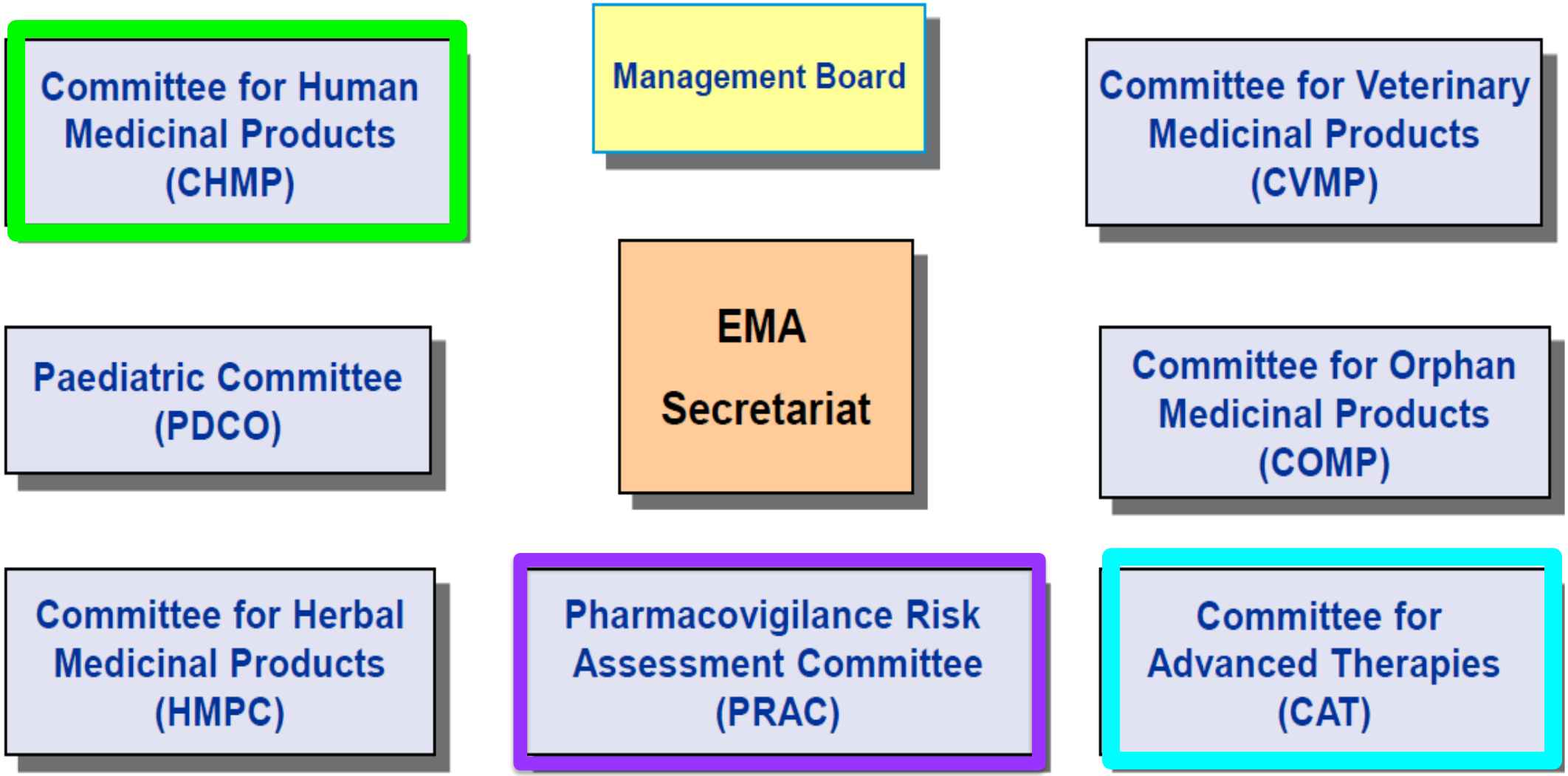
investigación clínica

autorización de uso

procedimiento centralizado

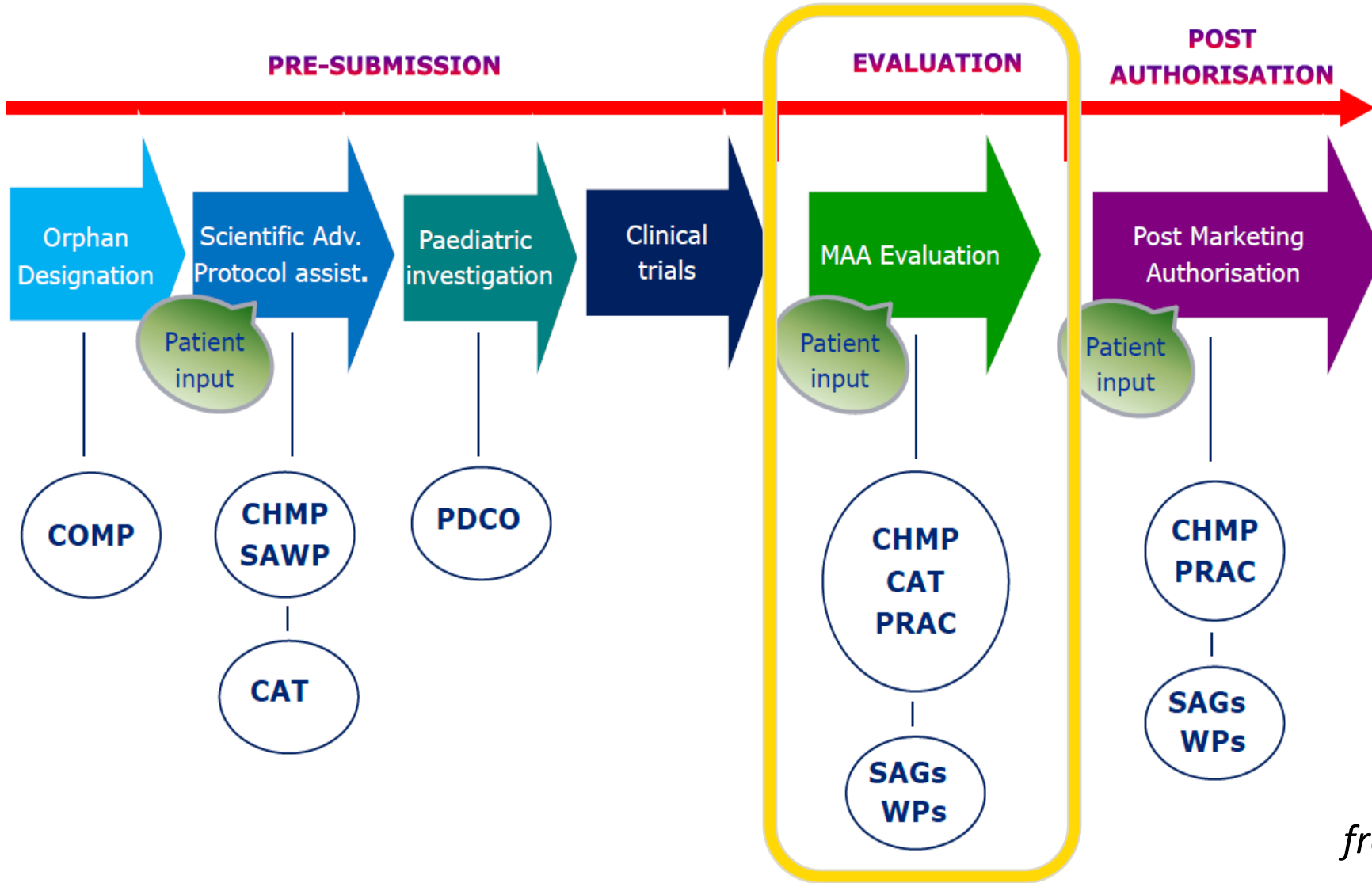
Opinión FINAL sobre medicamentos uso humano

- **27 miembros**
  (1/país)
- **1 NO + 1 ICE**
  (observadores)
- **5 expertos**
  (elegidos por el CHMP)


Committee for Human Medicinal Products (CHMP)
Management Board
Committee for Veterinary Medicinal Products (CVMP)
Paediatric Committee (PDCO)
EMA Secretariat
Committee for Orphan Medicinal Products (COMP)
Committee for Herbal Medicinal Products (HMPC)
Pharmacovigilance Risk Assessment Committee (PRAC)
Committee for Advanced Therapies (CAT)

from EMA

Centralised procedure - product life-cycle



from EMA

www.goal.com/en-bh/news/putellas-wins-uefa-women-champions-league-best-player/blt5a343deb0d17f28f

07/2009	CHONDROCELECT	Autologous chondrocytes
07/2012	GLYBERA	AAV-LPL gene
04/2013	MACI	Matrix-induced autologous chondrocyte implantation
06/2013	PROVENGE	Autologous PBMC activated with PAP-GM-CSF
12/2014	HOLOCLAR	Autologous human corneal epithelial cells
10/2015	IMLYGIC	Oncolytic HSV-1 - GM-CSF
04/2016	STRIMVELIS	Autologous CD34+ - RV hu ADA gene
06/2016	ZALMOXIS	Allogeneic T cells – RV HSV-TK
05/2017	SPHEROX	Spheroids autologous matrix-associated chondrocytes
12/2017	ALOFISEL	Allogeneic expanded adipose stem cells
06/2018	KYMRIAH	Autologous T cells - LV anti-CD19 CAR
06/2018	YESCARTA	Autologous T cells - RV anti-CD19 CD28/CD3 zeta CAR
09/2018	LUXTURNA	AAV2-hu RPE65
05/2019	ZYNTEGLO	Autologous CD34+ - LV βA-T87Q -globin gene
03/2020	ZOLGENSMA	AAV9-SMN1
12/2020	TECARTUS	Autologous T cells - RV anti-CD19 CD28/CD3-zeta CAR
12/2020	LIBMELDY	Autologous CD34+ cell LV human arylsulfatase A gene
07/2021	SKYSONA	Autologous CD34+ cell LV human ABCD1 gene
08/2021	ABECMA	Autologous T cells - LV anti-BCMA

03/2022	**BREYANZI**	Autologous anti-CD19 CD8+/CD4+ T cells
05/2022	**CARVYKTI**	Autologous anti-BCMA T cells
07/2022	**UPSTAZA**	rAAV2-hAADC
08/2022	**ROCTAVIAN**	AAV5-FVIII gene
10/2022	**EBVALLO**	EBV allogeneic T-cells *(pending EC decision)*

CAR-T cells

1	**Kymriah**	tisagenlecleucel	22/08/2018
2	**Yescarta**	axicabtagene ciloleucel	23/08/2018
3	**Tecartus**	Brexucabtagene autoleucel	14/12/2020
4	**Abecma**	idecabtagene vicleucel	18/08/2021
5	**Breyanzi**	lisocabtagene maraleucel	4/04/2022
6	**Carvykti**	ciltacabtagene autoleucel	25/05/2022

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Principio activo:

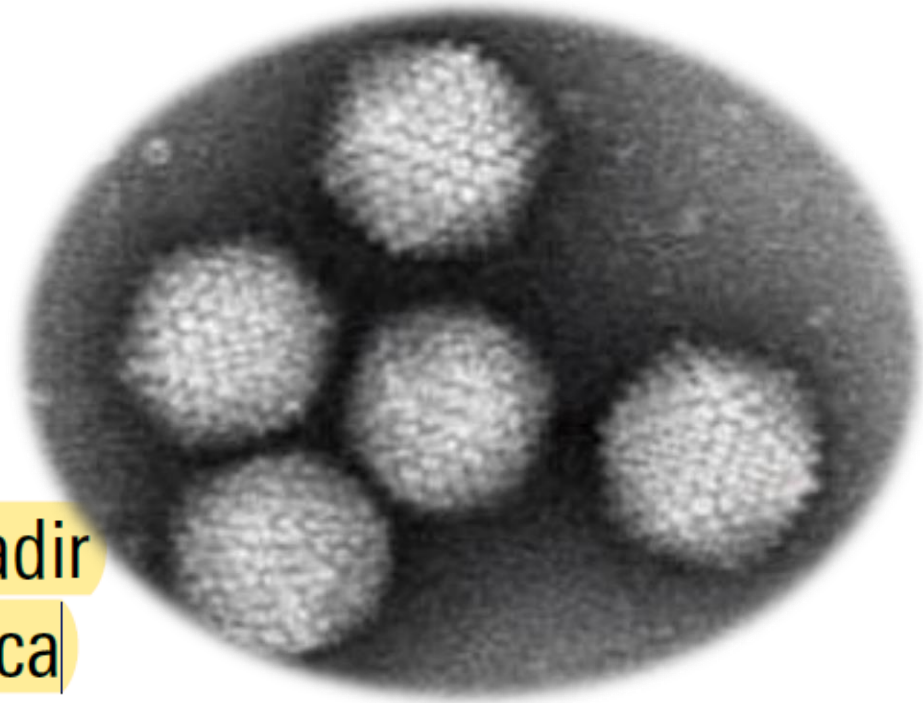
Ácido nucleico recombinante

+ vector viral

- medicamento biológico

Objetivo:

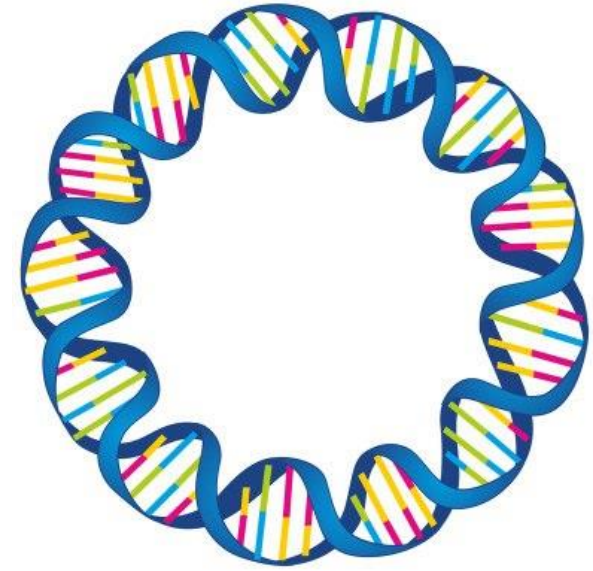
Regular, reparar, sustituir, añadir o eliminar una secuencia génica

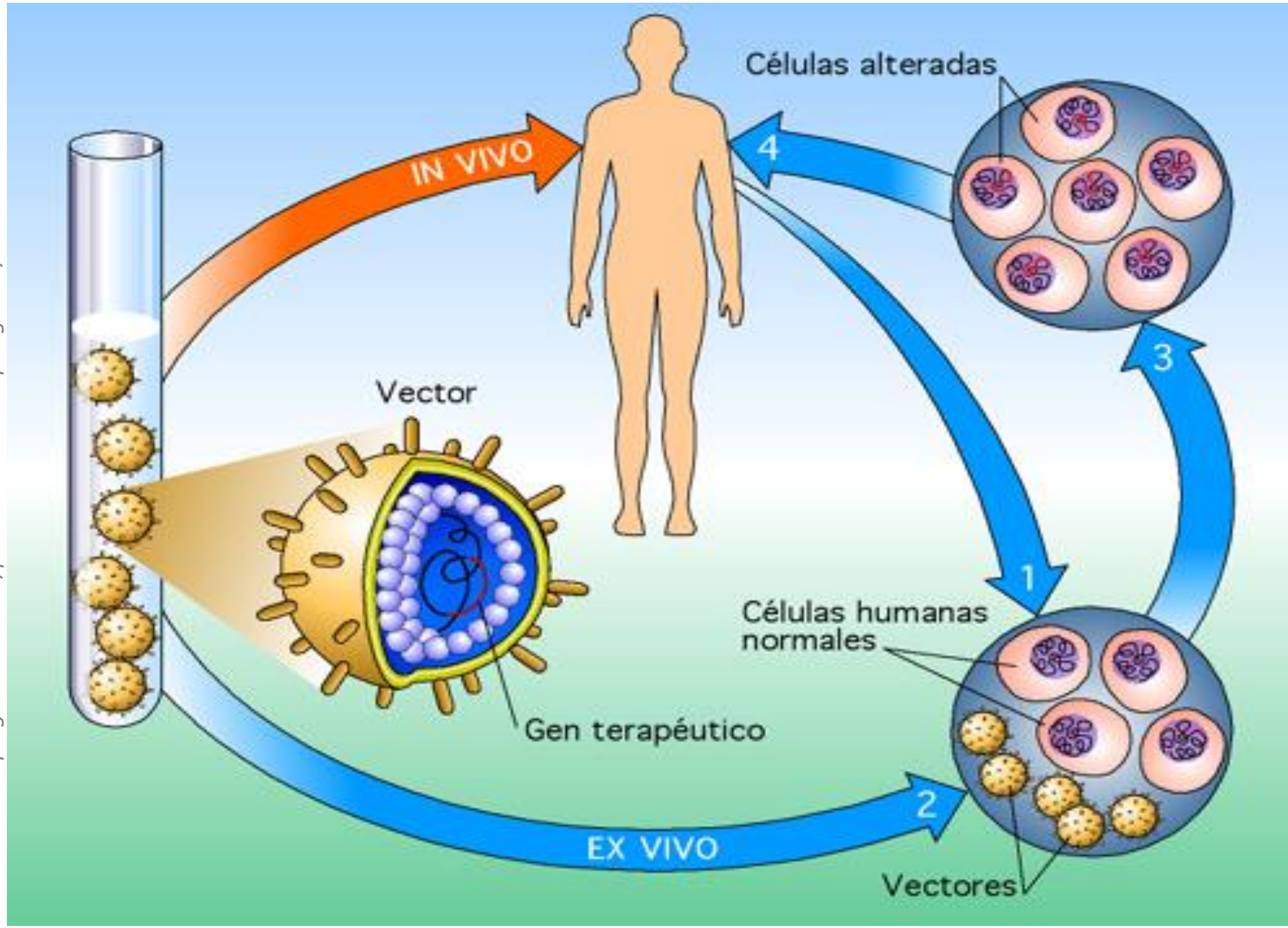


Medicamentos de terapia génica

Vectores Virales

Vectores no Virales





terapiagenica.science/proceso-de-la-terapia-genica/

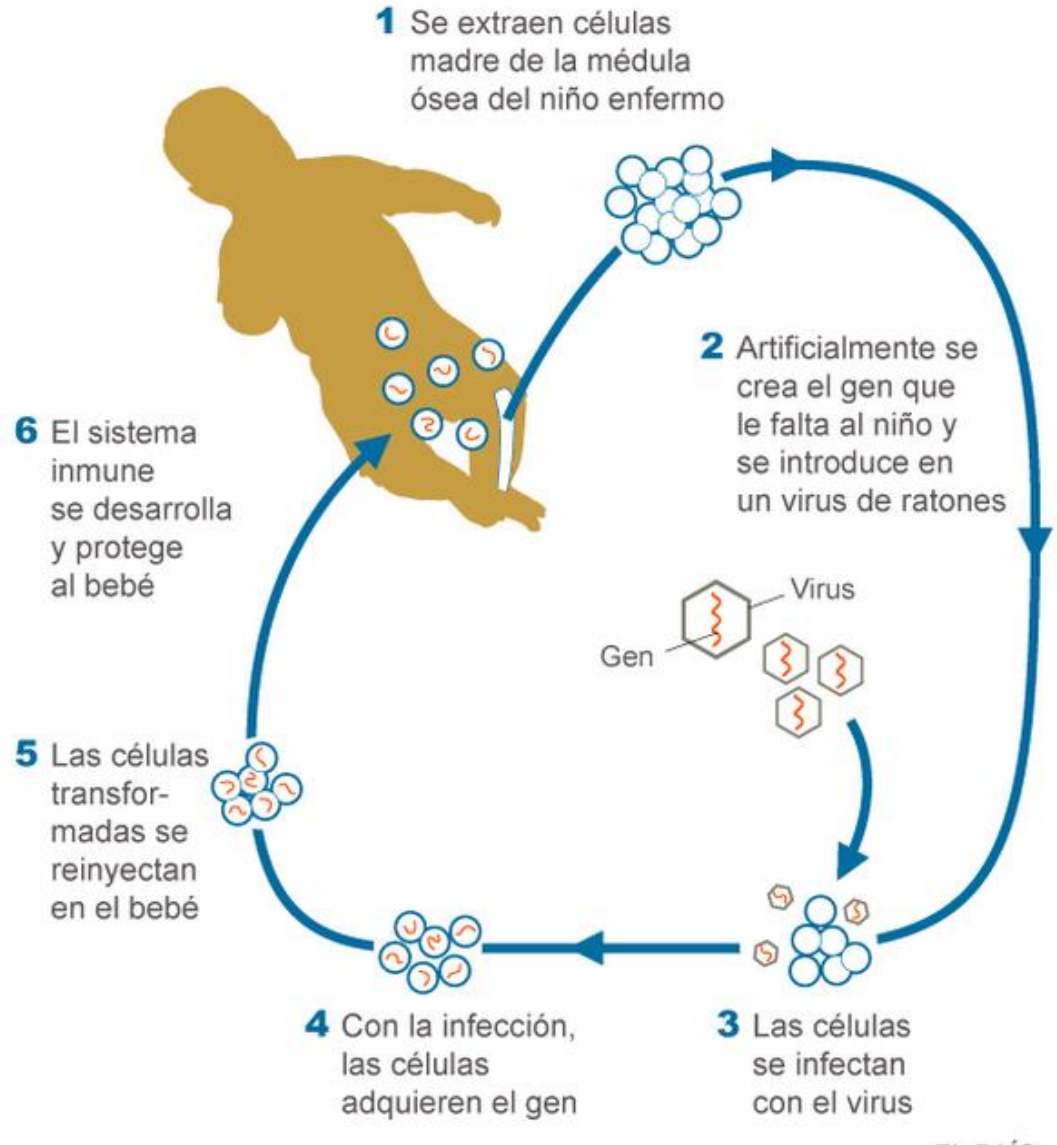
primaryimmune.org/first-gene-therapy-patients-attend-conference

Cynthia and Ashanthi in 1992 with the pioneer physicians of gene therapy: (from left) French Anderson, MD; Michael Blaese, MD; and Kenneth Culver.

elpais.com/elpais/2014/10/15/ciencia/1413372486_108083.html

TERAPIA GÉNICA PARA 'NIÑOS BURBUJA'

La enfermedad se produce porque un gen implicado en la producción de glóbulos blancos (las defensas del organismo) es defectuoso.



EL PAÍS

STRIMVELIS

- Tratamiento de pacientes con inmunodeficiencia combinada grave debida a la deficiencia de adenosin deaminasa (ADA)
- Estudio principal en 12 pacientes (6 meses-6 años)
- Los pacientes del estudio no tenían un donante de médula ósea apropiado y el tratamiento alternativo no había funcionado o no estaba disponible.
- Supervivencia del 100% de pacientes 3 años después del tratamiento.
- La tasa de infecciones graves disminuyó después del tratamiento y continuó disminuyendo con un seguimiento a más largo plazo de más de 3 años.

GACETA MÉDICA

gacetamedica.com/investigacion/terapia-genica-curacion-pacientes-hemofilia/

INVESTIGACIÓN

La terapia génica "permitirá la curación de pacientes con hemofilia"

Para los hematólogos, esta enfermedad hereditaria es el prototipo que ha permitido conocer, en general, el código genético de los humanos

Por **Noelia Izquierdo** - 21 abril 2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

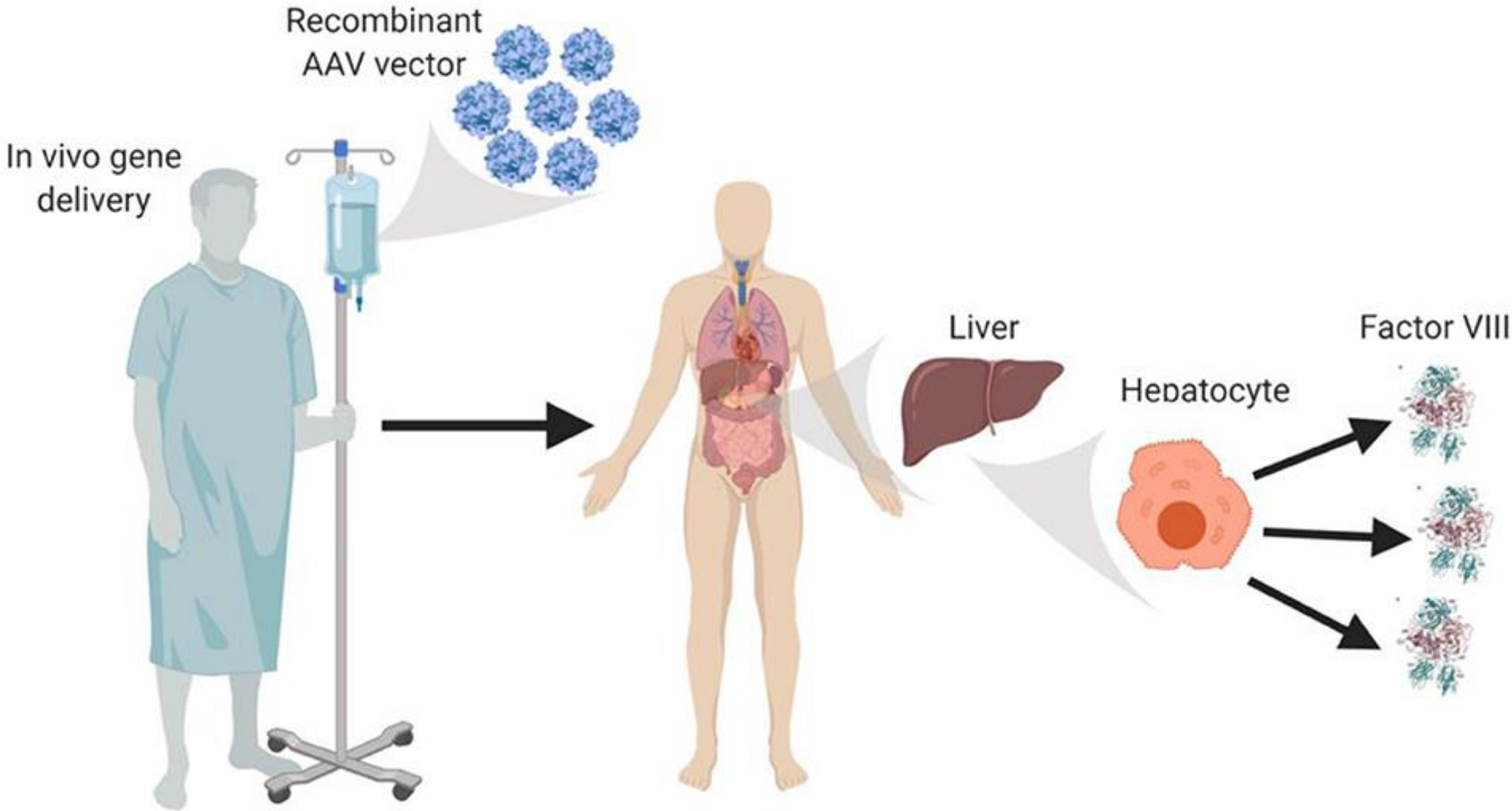
First gene therapy to treat severe haemophilia A

News 24/06/2022

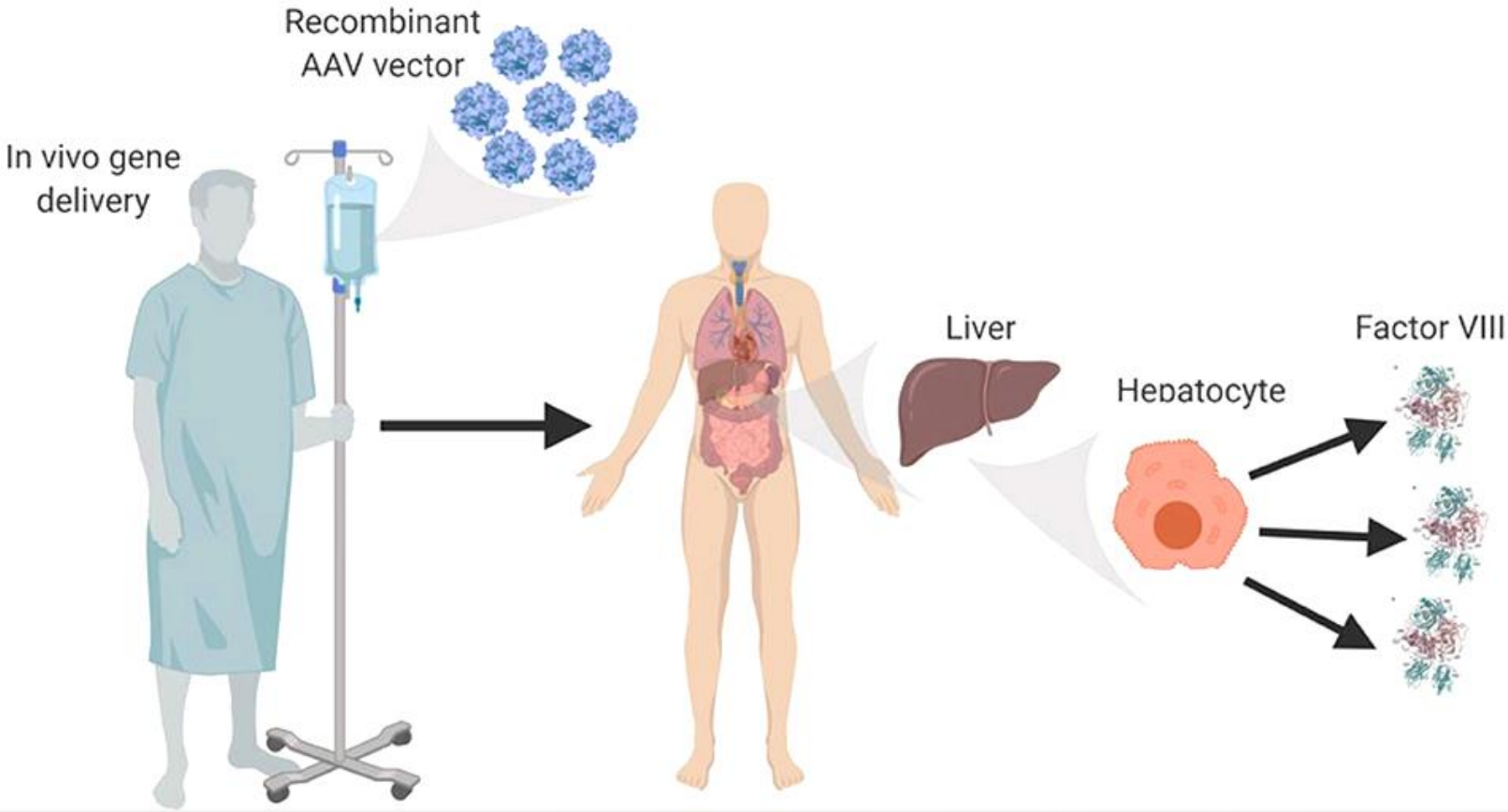
EMA has recommended granting a conditional marketing authorisation in the European Union (EU) for Roctavian (valoctocogene roxaparvovec) for the treatment of severe haemophilia A in adults who do not have factor VIII inhibitors (auto-antibodies produced by the immune system which make factor VIII medicines less effective) and no antibodies to adeno-associated virus serotype 5 (AAV5).

Patients with haemophilia A cannot produce factor VIII (an essential protein required for blood to clot and stop bleeding); they are more prone to bleeding and have prolonged bleeding, e.g. after injury or surgery. Haemophilia A is a rare debilitating disease affecting approximately 0.7 in 10,000 people in the EU. It is life long and may be life threatening when bleeding occurs in the brain, the spinal cord or the gut.

www.frontiersin.org/files/Articles/521124/fimmu-11-00494-HTML/image_m/fimmu-11-00494-g001.jpg



www.frontiersin.org/files/Articles/521124/fimmu-11-00494-HTML/image_m/fimmu-11-00494-g001.jpg



A main study involving 134 adult male patients with severe haemophilia A found that Roctavian was effective at increasing the level of factor VIII activity and that this increase was sustained for at least 2 years. 104 weeks after receiving a single dose of the medicine, 75.4% of the patients had an average factor VIII activity level of at least 5 international units per decilitre (IU/dL), which is a measure of mild haemophilia. In addition, the yearly number of bleeding episodes decreased by 85.5% and the need for additional factor VIII replacement treatment dropped by 97.5%.

Roctavian

(valoctocogén roxaparvovec)

- Aprobación condicional (revisión anual)
- 134 pacientes (18-70 años)
- Seguimiento 66-197 semanas (media: 2,5 años).
- 128 / 134 pacientes (96 %) permanecieron fuera de profilaxis después del tratamiento
- Precio?

www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treat-adults-hemophilia-b

FDA NEWS RELEASE

FDA Approves First Gene Therapy to Treat Adults with Hemophilia B

Share Tweet Linkedin Email Print

More Press Announcements

Immediate Release: November 22, 2022

Today, the U.S. Food and Drug Administration approved Hemgenix (etranacogene dezaparvovec), an adeno-associated virus vector-based gene therapy for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

ents/press-announcements/fda-approves-
at-adults-hemophilia-b

FDA NEWS RELEASE

FDA Approves First Gene Therapy to Treat Adults with Hemophilia B

Share Tweet Linkedin Email Print

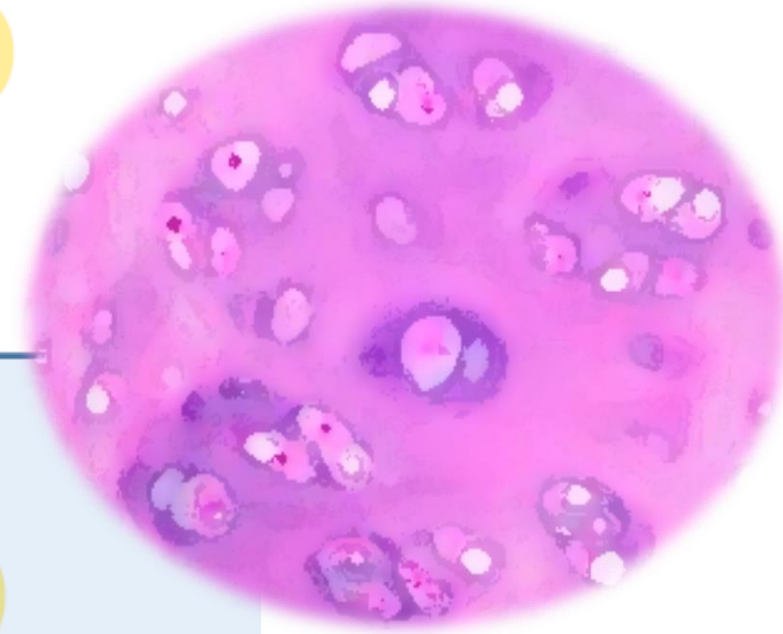
The safety and effectiveness of Hemgenix were evaluated in two studies of 57 adult men 18 to 75 years of age with severe or moderately severe Hemophilia B. Effectiveness was established based on decreases in the men's annualized bleeding rate (ABR). In one study, which had 54 participants, the subjects had increases in Factor IX activity levels, a decreased need for routine Factor IX replacement prophylaxis, and a 54% reduction in ABR compared to baseline.

Principio activo:

Células o tejidos

Objetivo:

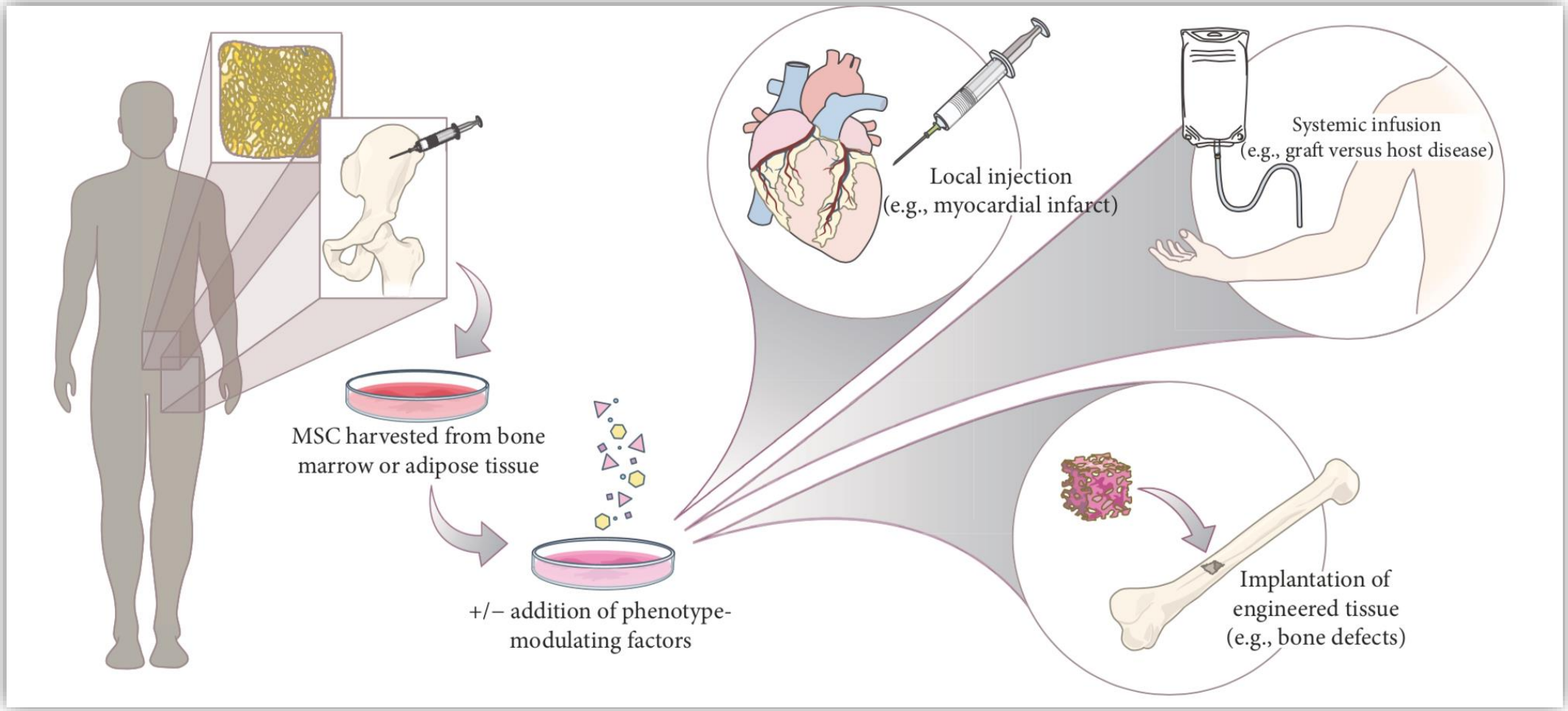
Prevenir, tratar o diagnosticar una enfermedad mediante la acción farmacológica, inmunológica o metabólica de las células o tejidos



Medicamentos de terapia celular somática

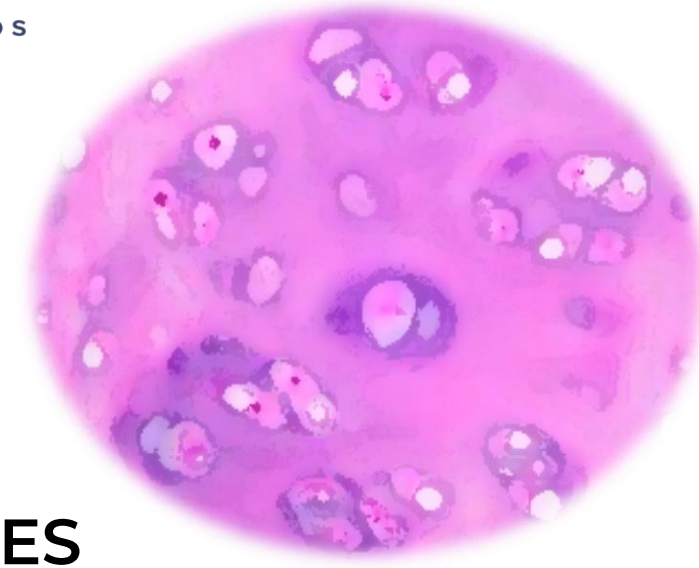
www.hindawi.com/journals/sci/2018/8031718/

células o tejidos



tratamiento, prevención, diagnóstico

Somatic cell therapy medicinal product



- Active substance: CELLS OR TISSUES

  subject to substantial manipulation

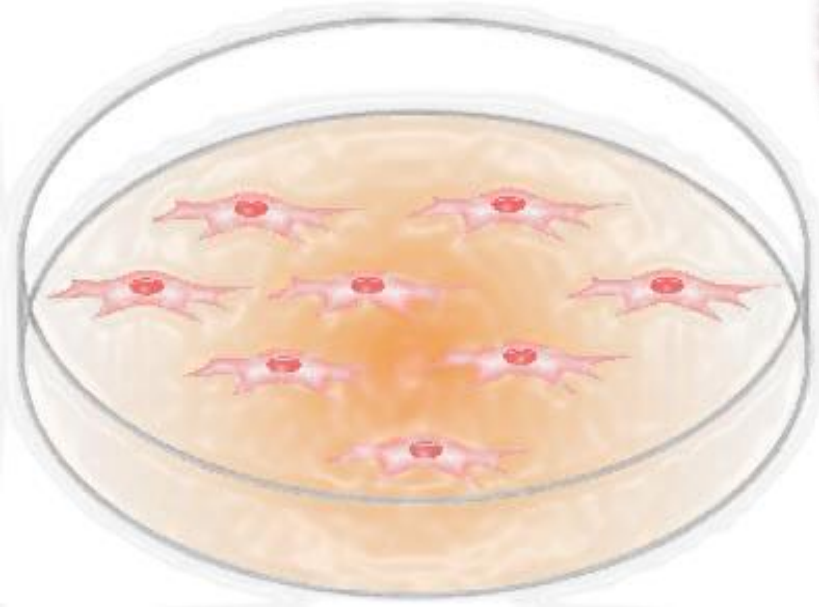
  OR

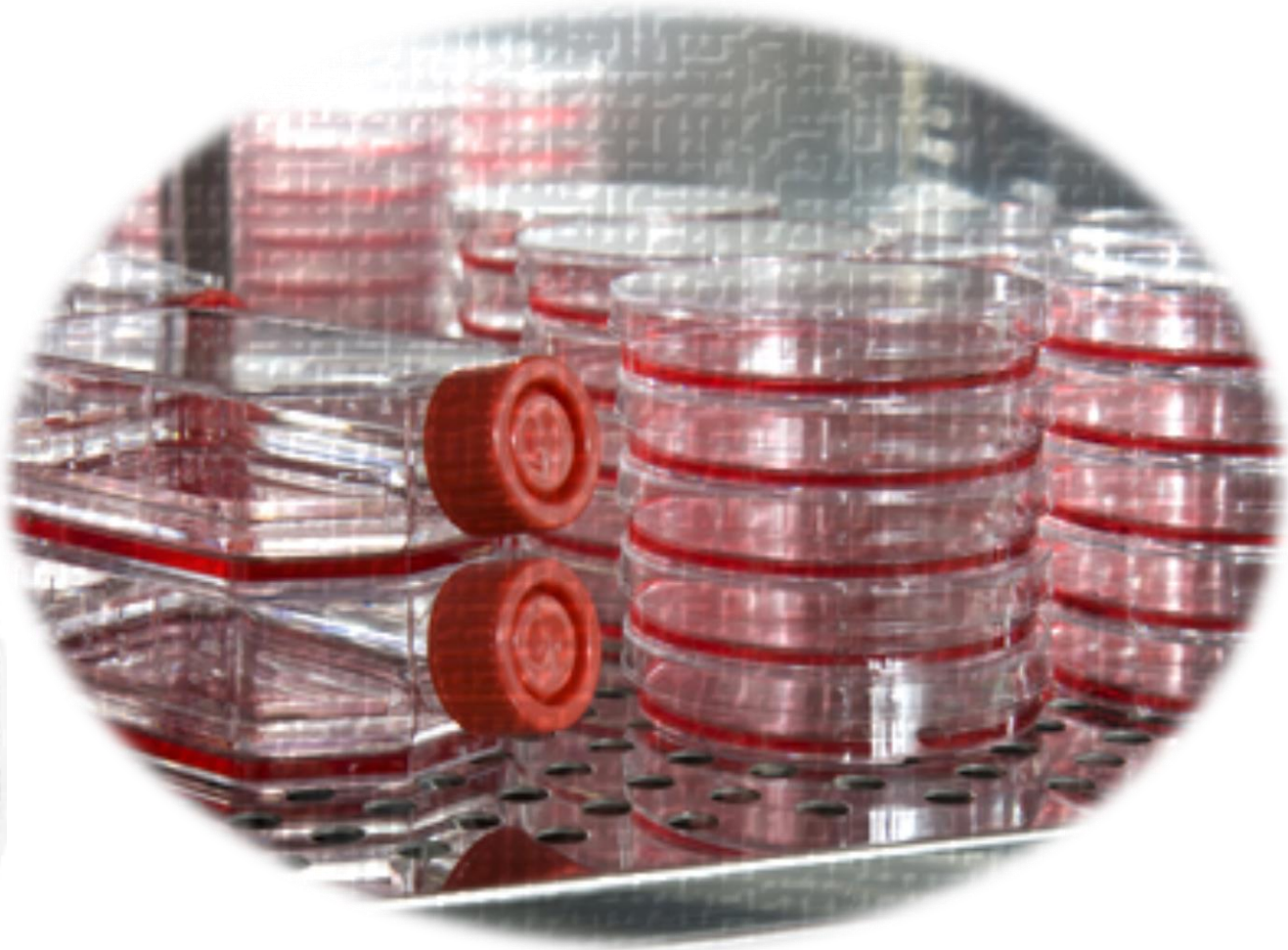
  not intended for the same essential function

- Objective: prevention, treatment, diagnosis of disease through pharmacological, immunological or metabolic action

Directive 2009/120/EC

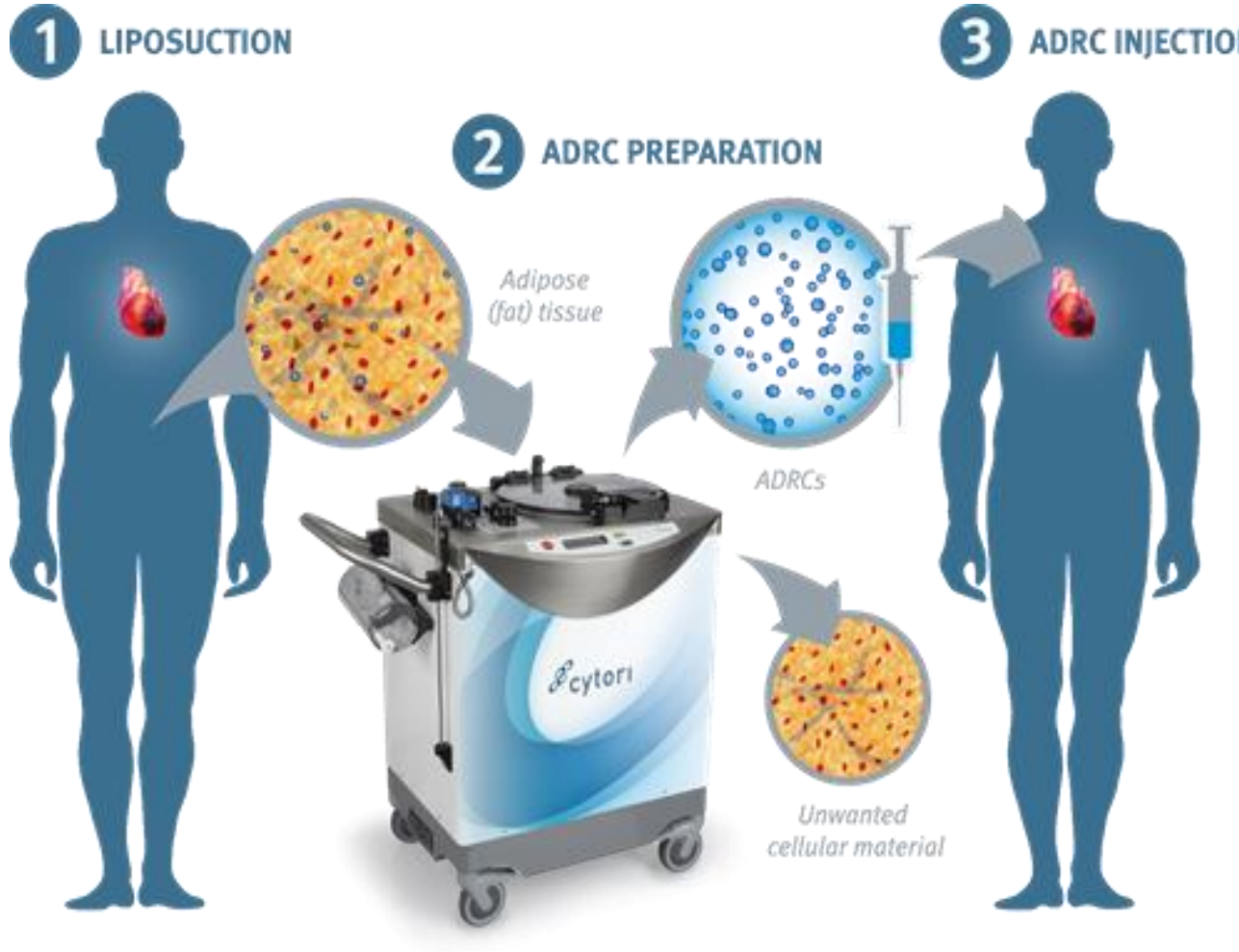
medicamento de terapia celular somática





- manipulación sustancial

medicamento de terapia celular somática



cardiovascularnews.com/cytori-technology-selected-for-nhlbi-funded-trial-in-lvad-patients

- Cambio de función celular esencial

MINISTERIO DE SANIDAD Y POLÍTICA SOCIAL

agencia española de medicamentos y productos sanitarios

Nota informativa

Advertencia sobre la oferta de tratamientos no autorizados basados en el uso de células madre

16 de abril de 2010

La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) tiene conocimiento de la oferta directa a ciudadanos y pacientes de diferentes tratamientos basados en la manipulación de células madre y postulados para un amplio espectro de enfermedades, en general enfermedades graves y crónicas. Todas las agencias nacionales europeas comparten la preocupación por este hecho y ello ha llevado a que la Agencia Europea del Medicamento (EMA) haga pública una nota *(Concerns over unregulated medicinal products containing stem cells*, EMA/763463/2009) en la que se alerta de la oferta a pacientes de medicamentos con células madre no regulados.

La AEMPS quiere trasladar e
siguientes consideraciones pa
tales prácticas:

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

agencia española de medicamentos y productos sanitarios

Nota informativa

Agencia Española de Medicamentos y Productos Sanitarios
AEMPS

LA AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS ADVIERTE SOBRE LA POSIBLE CONFUSIÓN EN LA OFERTA DE TRATAMIENTOS CON CÉLULAS MADRE

Fecha de publicación: 22 de octubre de 2012

Categoría: AEMPS, MEDICAMENTOS DE USO HUMANO, MEDICAMENTOS ILEGALES, COSMÉTICOS.
Referencia: AEMPS, 10/2012

La Agencia Española de Medicamentos y Productos Sanitarios quiere advertir sobre la posible confusión en la que se pueda caer ante la utilización profusa de términos relacionados con las terapias basadas en células madre para situaciones tan dispares como el tratamiento de enfermedades o el uso de cosméticos.

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

Nota informativa

Agencia Española de Medicamentos y Productos Sanitarios
AEMPS

CONSIDERACIONES SOBRE LOS PRODUCTOS SANITARIOS UTILIZADOS PARA LA OBTENCIÓN DE CÉLULAS AUTÓLOGAS Y LA CLASIFICACIÓN DEL PRODUCTO RESULTANTE COMO MEDICAMENTO DE TERAPIA AVANZADA

Fecha de publicación: 12 de julio de 2018

Categoría: MEDICAMENTOS DE USO HUMANO, PRODUCTOS SANITARIOS
Referencia: MUH, 4 /2018

La Agencia Española de Medicamentos y Productos Sanitarios informa sobre la consideración que tienen los productos sanitarios que se ofrecen para obtener células autólogas, así como el producto final obtenido.

www.aemps.gob.es/medicamentos-de-uso-humano/terapias-avanzadas/

La Paz desarrolla el primer medicamento europeo basado en células madre de la grasa

Los hospitales europeos podrán usarlo en 2011 para tratar fístulas en enfermedad de Crohn y otras patologías que requieren cicatrización

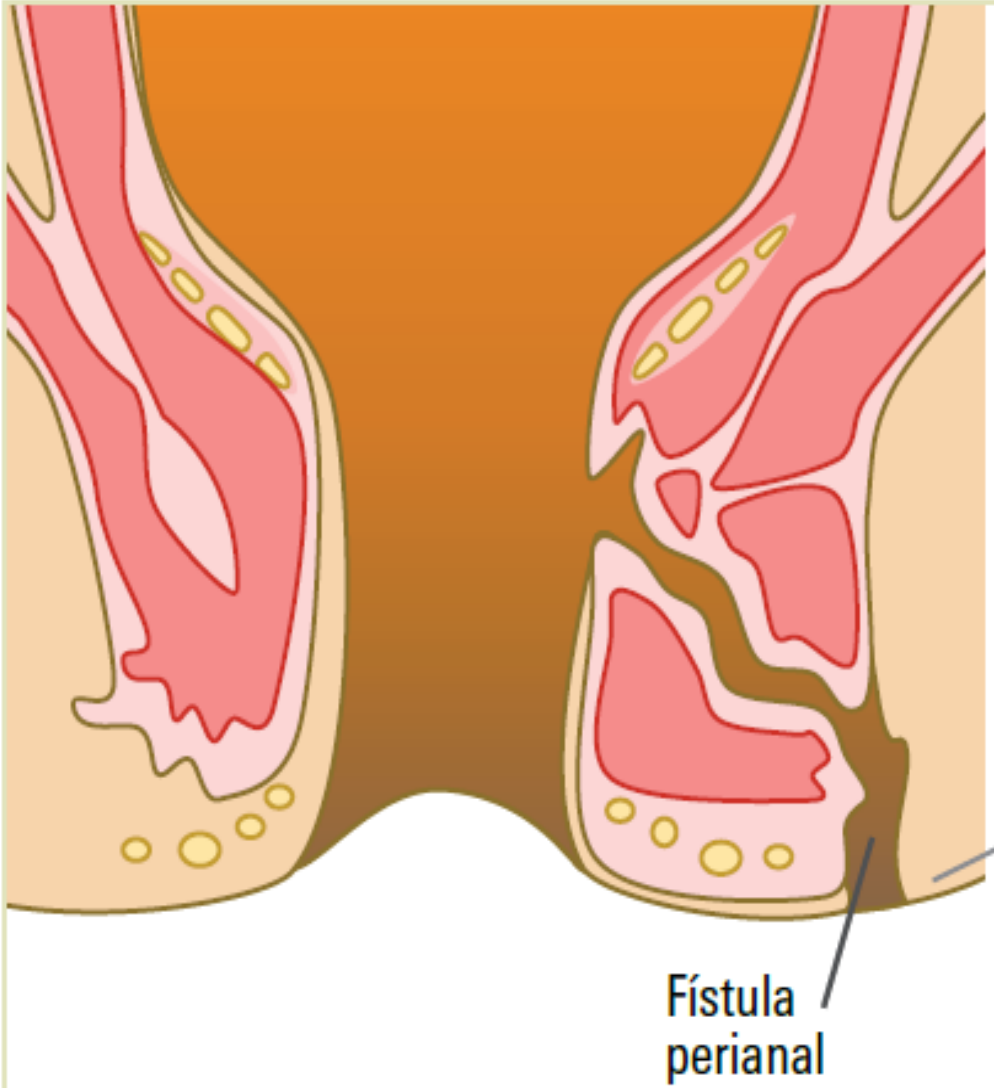
Madrid - 03 JUL 2009 - 14:24 CEST

Siete años de trabajo están a punto de dar sus frutos en forma de medicamento pionero. De momento, lo que ya han conseguido los investigadores del hospital de La Paz (Madrid) es comprobar el éxito del uso de las células madre de la grasa para tratar fístulas. Un ensayo clínico de fase II ha demostrado que las fístulas cicatrizan gracias a la inyección de células madre del propio paciente ya cultivadas. En 2011, cuando concluya la fase III del ensayo, ya estará listo el primer medicamento basado en células madre de la Unión Europea. Y se habrá desarrollado en un hospital español, que ahora coordina el estudio con 49 hospitales de nueve países europeos.

elpais.com/sociedad/2009/07/03/actualidad/1246572011_850215.html

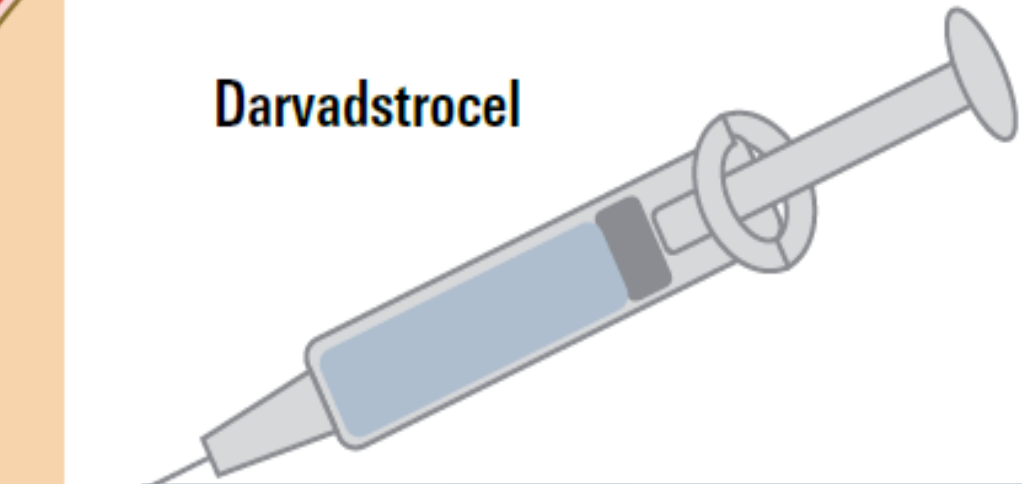
ALOFISEL

- Autorización de comercialización: 23/03/2018
- Medicamento huérfano
- Células madre alogénicas (de donante sano) obtenidas de tejido adiposo
- Tratamiento de fístulas perianales complejas en pacientes con enfermedad de Crohn



120 millones de células/dosis (4 viales; 30 millones de células/vial 6 mL)

Darvadstrocel



tratamiento de las fístulas perianales complejas en pacientes adultos con enfermedad de Crohn luminal inactiva o leve.

S Ruiz (2018). *Terapias avanzadas en patologías musculares, articulares e inmunológicas* en *Trastornos osteoarticulares, musculares e inmunológicos*. Consejo General de Colegios Oficiales de Farmacéuticos (ed.)

	Grupo de Alofisel (Alofisel + tratamiento	Grupo de control (placebo + tratamiento	Valor de P
	estándar*) N = 103	estándar*) N = 102	
Remisión combinada en la semana 24 (% pacientes)	52	35	0,019
Remisión combinada en la semana 52 (% pacientes)	56	38	0,009

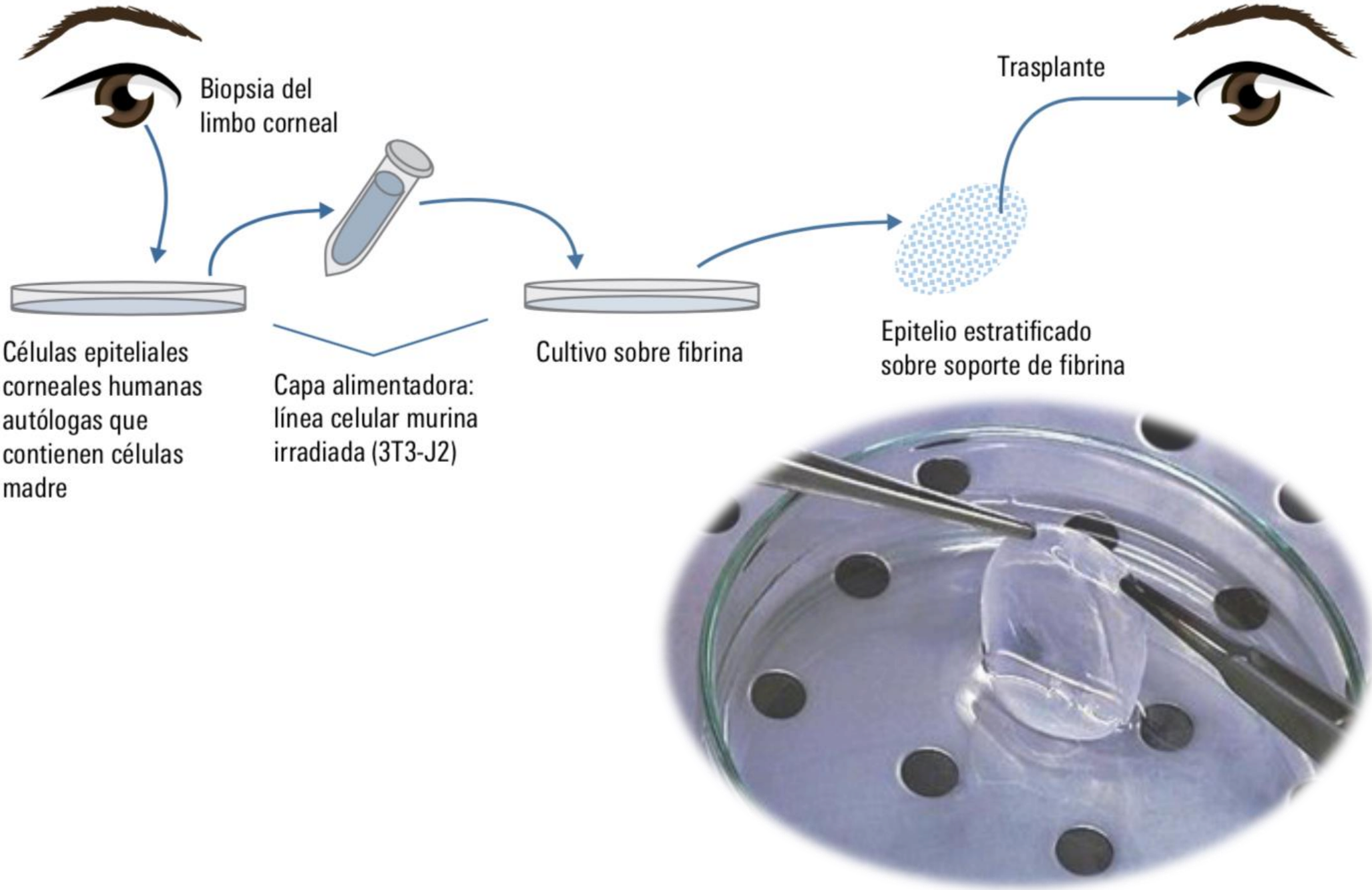
*Incluyendo el drenaje del absceso, la colocación/retirada del setón, el curetaje, la sutura de los orificios internos y el tratamiento farmacológico.

Video correcta administración de Alofisel: www.youtube.com/watch?v=L1Fnz67qT-c

HOLOCLAR

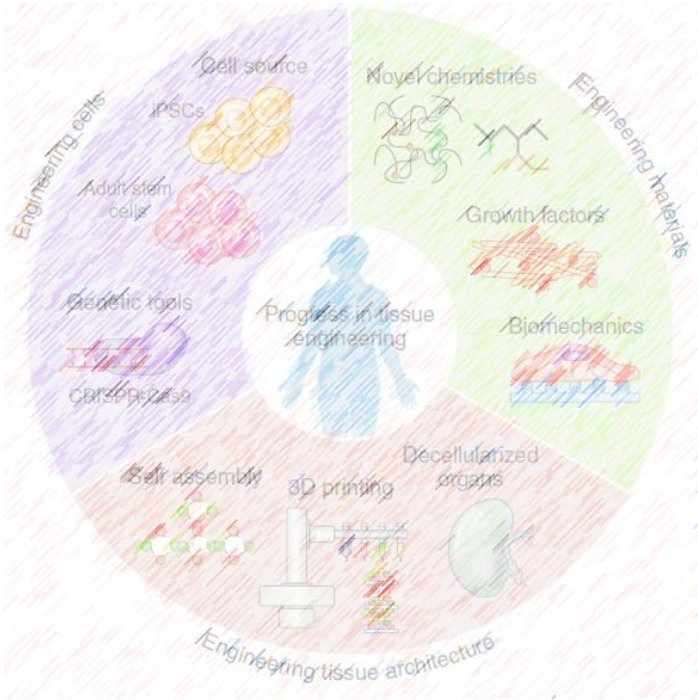
Holoclar® ha sido el primer medicamento basado en **células madre** que ha obtenido autorización de comercialización en la UE. Es además un medicamento huérfano (es decir, que se usa para tratar afecciones potencialmente mortales o crónicamente debilitantes que afectan a no más de 5 de cada 10.000 personas en la UE) que obtuvo la autorización de comercialización en la UE en febrero de 2015. Consiste en una lámina circular transparente de 300.000 a 1.200.000 células epiteliales corneo-

Holoclar® se utiliza para el tratamiento de pacientes adultos con deficiencia de células madre limbares (LSCD, *limbal stem cell deficiency*) de moderada a grave debido a quemaduras oculares por agentes físicos o químicos. Está destinado a ser trasplantado en el ojo afectado de estos pacientes después de la eliminación del epitelio corneal alterado. La dosis re-


Biopsia del
limbo corneal
Trasplante
Células epiteliales
corneales humanas
autólogas que
contienen células
madre
Capa alimentadora:
línea celular murina
irradiada (3T3-J2)
Cultivo sobre fibrina
Epitelio estratificado
sobre soporte de fibrina

¿Qué beneficios ha demostrado tener Holoclar en los estudios realizados?

En un estudio retrospectivo de series de casos de pacientes, Holoclar ha demostrado ser eficaz para restaurar de forma estable el epitelio corneal en pacientes con deficiencia de células madre limbares moderada o grave causada por quemaduras. Un año después de la implantación de Holoclar, se consideró que los implantes habían tenido éxito en 75 de los 104 pacientes estudiados (72 %), basándose en la presencia de un epitelio corneal estable, sin lesiones superficiales y con poca o ninguna neovascularización (una característica frecuente de la deficiencia de células madre limbares). Hubo también reducciones de los síntomas de los pacientes, tales como el dolor y la inflamación, y mejoras de la visión.



medicamentos de terapia avanzada

autorización de comercialización

investigación clínica

autorización de uso

Reglamento (CE) No 1394/2007

(6) El presente Reglamento constituye una *lex specialis* que introduce disposiciones adicionales a las establecidas en la Directiva 2001/83/CE. El ámbito de aplicación del mismo debe ser la reglamentación de los medicamentos de terapia avanzada que estén destinados a ser comercializados en los Estados miembros y estén preparados industrialmente o en cuya fabricación intervenga un proceso industrial, de conformidad con el ámbito de aplicación general de la legislación farmacéutica comunitaria que se establece en el título II de la Directiva 2001/83/CE. Deben excluirse del ámbito del presente Reglamento los medicamentos de terapia avanzada preparados ocasionalmente, de acuerdo con normas de calidad específicas, y empleados en un mismo Estado miembro, en un hospital y bajo la responsabilidad profesional exclusiva de un médico colegiado, con el fin de cumplir una prescripción facultativa individual de un producto hecho a medida destinado a un solo paciente, asegurando, al mismo tiempo, que no se menoscaban las normas comunitarias relativas a la calidad y la seguridad.

Cláusula de exclusión hospitalaria

BOLETÍN OFICIAL DEL ESTADO
Núm. 144 Sábado 14 de junio de 2014 Sec. I. Pág. 45068

I. DISPOSICIONES GENERALES

MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

6277 *Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial.*

El Reglamento (CE) n.º 1394/2007 del Parlamento Europeo y del Consejo, de 13 de noviembre de 2007, sobre medicamentos de terapia avanzada y por el que se modifican la Directiva 2001/83/CE y el Reglamento (CE) n.º 726/2004, define como «medicamento de terapia avanzada» a los medicamentos de terapia génica, los medicamentos de terapia celular somática, los productos de ingeniería tisular y los medicamentos combinados de terapia avanzada.

autorizaciones de uso de medicamentos de terapia avanzada en España

NOMBRE	TITULAR DE LA AUTORIZACIÓN DE USO	FECHA AUTORIZACIÓN DE USO	FICHA TÉCNICA
NC1- SUSPENSIÓN CELULAR EN PLASMA AUTÓLOGO 100-300×106 CELULAS-HOSPITAL UNIVERSITARIO PUERTA DE HIERRO MAJADAHONDA, 1 jeringa precargada **NC1**	HOSPITAL UNIVERSITARIO PUERTA DE HIERRO MAJADAHONDA	29-01-2019	FT Ficha técnica pdf
ARI-0001 DISPERSION PARA PERFUSION QUE CONTIENE 0,1-1×10^6 CELULAS/KG – HOSPITAL CLINIC DE BARCELONA **ARI-0001**	HOSPITAL CLINIC BARCELONA C/Villaroel, 170 Barcelona	01-02-2021	FT Ficha técnica pdf

www.aemps.gob.es/medicamentos-de-uso-humano/terapias-avanzadas/autorizaciones-de-uso-de-medicamentos-de-terapia-avanzada/?lang=en

1. NOMBRE DEL MEDICAMENTO

NC1 Suspensión celular en plasma autólogo, 100-300x10^6 células – Hospital Universitario Puerta de Hierro Majadahonda

Células mesenquimales troncales autólogas de médula ósea.

2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA

La sustancia activa de este medicamento son las células mesenquimales troncales adultas autólogas de médula ósea expandidas, a una concentración de 100.000 células/µl.

Excipientes: Plasma sanguíneo autólogo

3. FORMA FARMACÉUTICA

Suspensión para inyección.

Restringido exclusivamente para uso hospitalario.

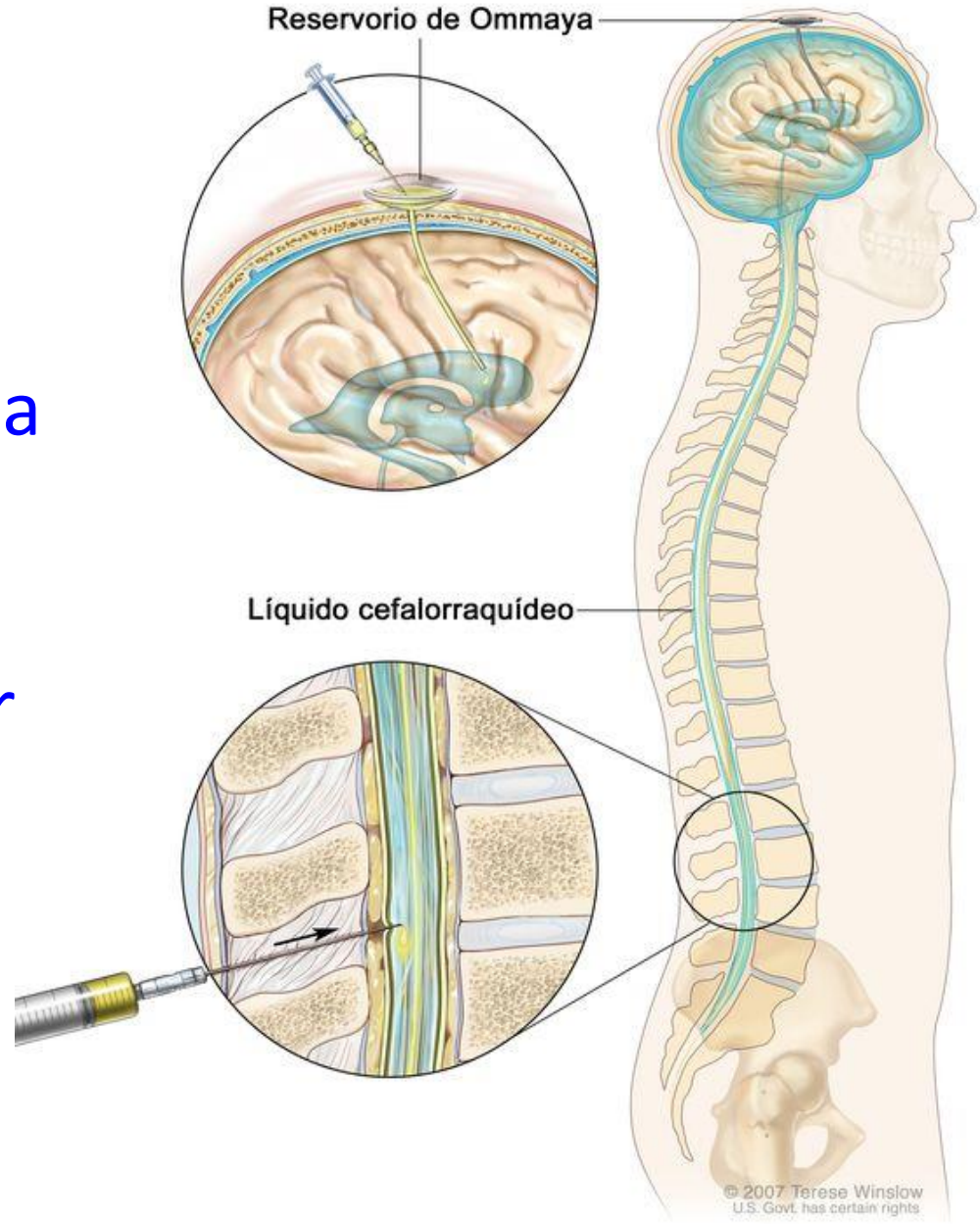
4.1 Indicaciones terapéuticas

NC1 está indicado en el tratamiento de pacientes adultos (≤65 años) con secuelas de lesión medular traumática crónica, que presenten lesiones medulares incompletas a nivel dorsal o lumbar.

Las lesiones medulares dorsales o lumbares completas están excluidas, con la excepción de lesiones completas localizadas quísticas, con cavidad centro-medular que no se extienda más de 1-3 segmentos medulares.

NC1

Administración intratecal de una dosis global de 300 millones de células divididas en dos administraciones separadas por 90 días



1. NOMBRE DEL MEDICAMENTO

ARI-0001 dispersión para perfusión, que contiene 0,1 - 1 x 10^6 células/kg – Hospital Clínic de Barcelona

2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA

2.1. Descripción General

ARI-0001 (también llamada linfocitos T transducidos con CAR ANTI-CD19 (A3B1)4-1BB/CD3ζ) es un producto clasificado como terapia avanzada – terapia génica debido a que la sustancia activa son linfocitos T diferenciados autólogos de sangre periférica expandidos y transducidos con un lentivirus para expresar un receptor antigénico quimérico con especificidad anti-CD19 (A3B1) conjugado con las regiones coestimuladoras 4-1BB y CD3z.

4.1. Indicaciones Terapéuticas

ARI-0001 está indicado en el tratamiento de la leucemia linfoblástica aguda (LLA) de células B CD19+ en recaída o refractaria tras un mínimo de dos líneas de tratamiento o en recaída post-trasplante en pacientes adultos mayores de 25 años.

EMA pilot offers enhanced support to academic and non-profit developers of advanced therapy medicinal products

Share

News 29/09/2022

www.ema.europa.eu/en/news/ema-pilot-offers-enhanced-support-academic-non-profit-developers-advanced-therapy-medicinal-products

EMA is launching a pilot to support the translation of basic research developments into medicines that could make a difference in patients' lives in the European Economic Area (EEA). The pilot is open to academic sponsors and non-profit organisations who are developing advanced therapy medicinal products (ATMPs). These medicines for human use are based on genes, tissues or cells and might offer ground-breaking treatment options to patients.

The pilot will focus on the needs of non-profit academic developers. They are a major contributor to the development of ATMPs and diagnostic and delivery devices, but experience has shown that navigating regulatory requirements can be challenging.

During the pilot, EMA will provide enhanced regulatory support for up to five selected ATMPs that address unmet clinical needs and are solely developed by academic and non-profit developers in Europe. EMA will guide the participants through the regulatory process with the aim to optimise the development of the ATMPs, starting from best practice principles for manufacturing to planning clinical development that meets regulatory standards.

The pilot's first participant has already been selected. This ATMP is ARI-0001, a chimeric antigen receptor (CAR) product based on patients' own T-cells, that is developed by the Hospital Clínic Barcelona. In December 2021, the product was granted eligibility to PRIME, EMA's scheme to support the development of medicines that target an unmet medical need.

Importantly, no new regulatory tool will be introduced as part of this pilot. However, the aim is to assess what further support or regulatory tool may be provided to enhance the number of ATMPs reaching patients in the EEA. In the process, EMA is keen to learn how to better interact with and support academic developers.

The pilot participants will benefit from all the available regulatory flexibilities and development support measures, such as fee reductions and waivers. The progress will be closely monitored, and initial results of the pilot are expected to be available in 3-4 years. Upon completion, a report will be published and a workshop with relevant stakeholders may be organised to discuss the learnings.

www.ema.europa.eu/en/news/ema-pilot-offers-enhanced-support-academic-non-profit-developers-advanced-therapy-medicinal-products

PIONEERING STEM-CELL TRIALS IN JAPAN REPORT PROMISING RESULTS

Research on using induced pluripotent stem cells to treat disease has received significant investment.

By Smriti Mallapaty

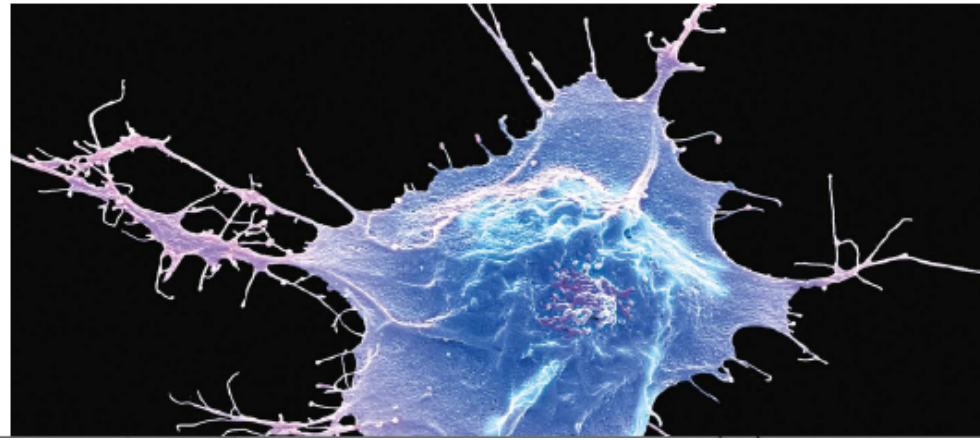
Some of the first trials to test whether reprogrammed stem cells can repair diseased organs have begun to report positive results. Research teams involved in the studies, all based in Japan, say the data provide early hints that the hotly anticipated technology works. But many researchers outside the country are cautious about overstating the significance of the trials, saying they were small and the results have yet to be peer reviewed.

Induced pluripotent stem (iPS) cells are those that have been reprogrammed from mature cells — often taken from the skin — into an embryonic-cell-like state. From there, they can turn into any cell type and can be used to repair damaged organs.

In January, researchers reported in a preprint that the first person in Japan to receive heart-muscle cells made from reprogrammed stem cells had improved heart function after the procedure (S. Miyagawa *et al*. Preprint at medRxiv https://doi.org/h94g; 2022). In April, another group announced that several people's vision had improved after their diseased corneas were transplanted with corneal cells made from reprogrammed stem cells — a world first.

Ongoing trials are "delivering encouraging first insights into the evolution of iPS-cell-based therapies, from lab to patient", says Wolfram-Hubertus Zimmermann, a pharmacologist at the University Medical Centre Göttingen in Germany.

The biggest impact of the trials in Japan so far is that they "give people confidence all over the world that it is doable", says Kapil Bharti,



each of four participants. At a press conference on 4 April, Nishida reported that three participants had markedly improved vision a year after their operations — a fourth participant's sight remained mostly the same because they had cataracts. He says the initial disease has not returned in any of the participants, some of whom had surgery more than two years ago; this suggests the cells survived the transplant. He is preparing a manuscript for publication and peer review, and he plans to start a larger trial, with more than ten participants.

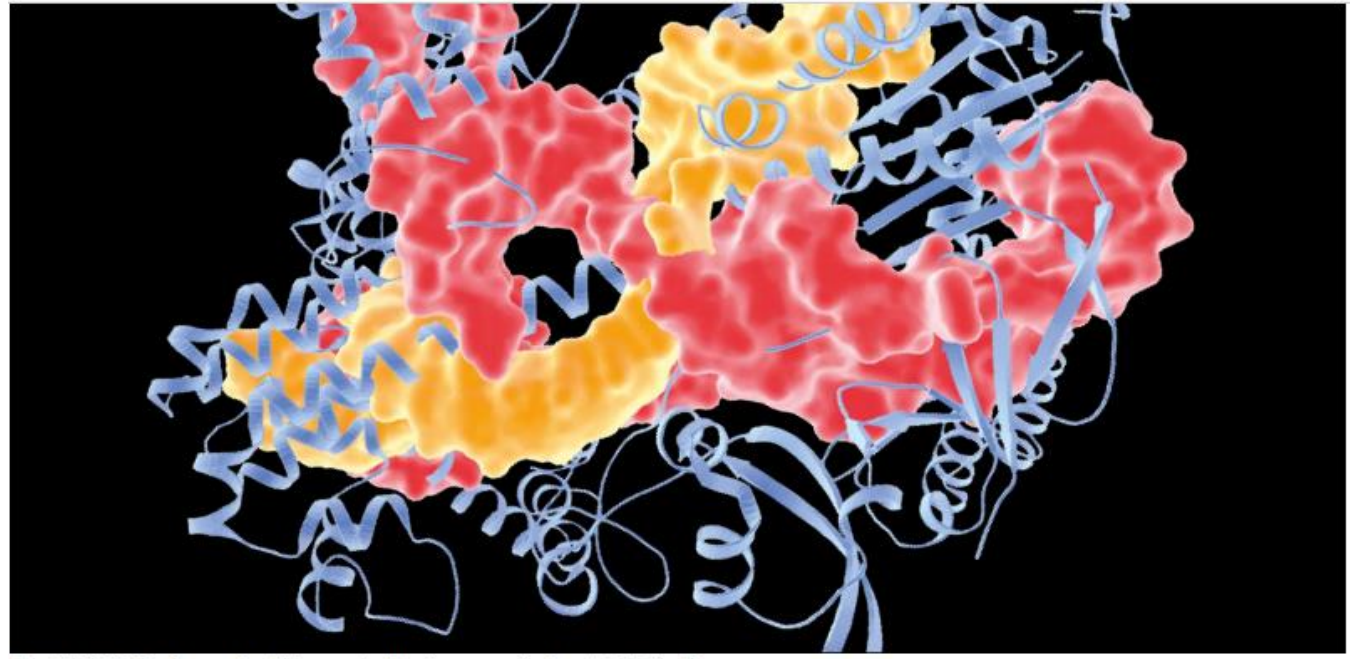
Researchers outside Japan say the cornea trial is too small to establish the treatment's effectiveness, but they are encouraged by the results. "I'm sure the patients are seeing better and that is a good sign," says Bharti, who is leading a trial of a treatment for macular degeneration using reprogrammed stem cells. But, he says, "we should be careful to not call these efficacious trials".

In Japan, the observed beneficial effect of the cells has boosted scientists' morale. "I'm very happy that the cornea could show that now," says Masayo Takahashi, an ophthalmologist and president of cell-therapy company Vision Care in Kobe. The results are very important for regenerative medicine in Japan, she says.

There are also promising signs from the ongoing trial in which donor cells are reprogrammed into heart-muscle cells, says study leader Yoshiki Sawa, a cardiac surgeon at Osaka University. In his preprint posted in January, he reported results on the first of three people to receive the treatment. Sawa now says that all three — whose ages range between the fifties and seventies — have recovered and are working. He aims to recruit another five participants by the end of this year.

The report is important and it is good to see that the participant did not develop tumours or an irregular heartbeat, says Zimmermann, who is also running a trial using iPS-cell-derived heart-muscle cells. But it is not clear whether any improvements in symptoms were a result of the transplanted cells or due to other aspects of the surgery. The participant

Nature 609
8 September 2022



The CRISPR–Cas9 complex (blue and yellow) can precisely cut DNA (red).

CRISPR CANCER TRIAL SUCCESS PAVES WAY FOR PERSONALIZED TREATMENTS

'Most complicated therapy ever' tailors bespoke, genome-edited immune cells to attack tumours.

By Heidi Ledford

A small clinical trial has shown that researchers can use CRISPR gene editing to alter immune cells so that they will recognize mutated proteins specific to a person's tumours. Those cells can then be safely set loose in the body to find and destroy their target.

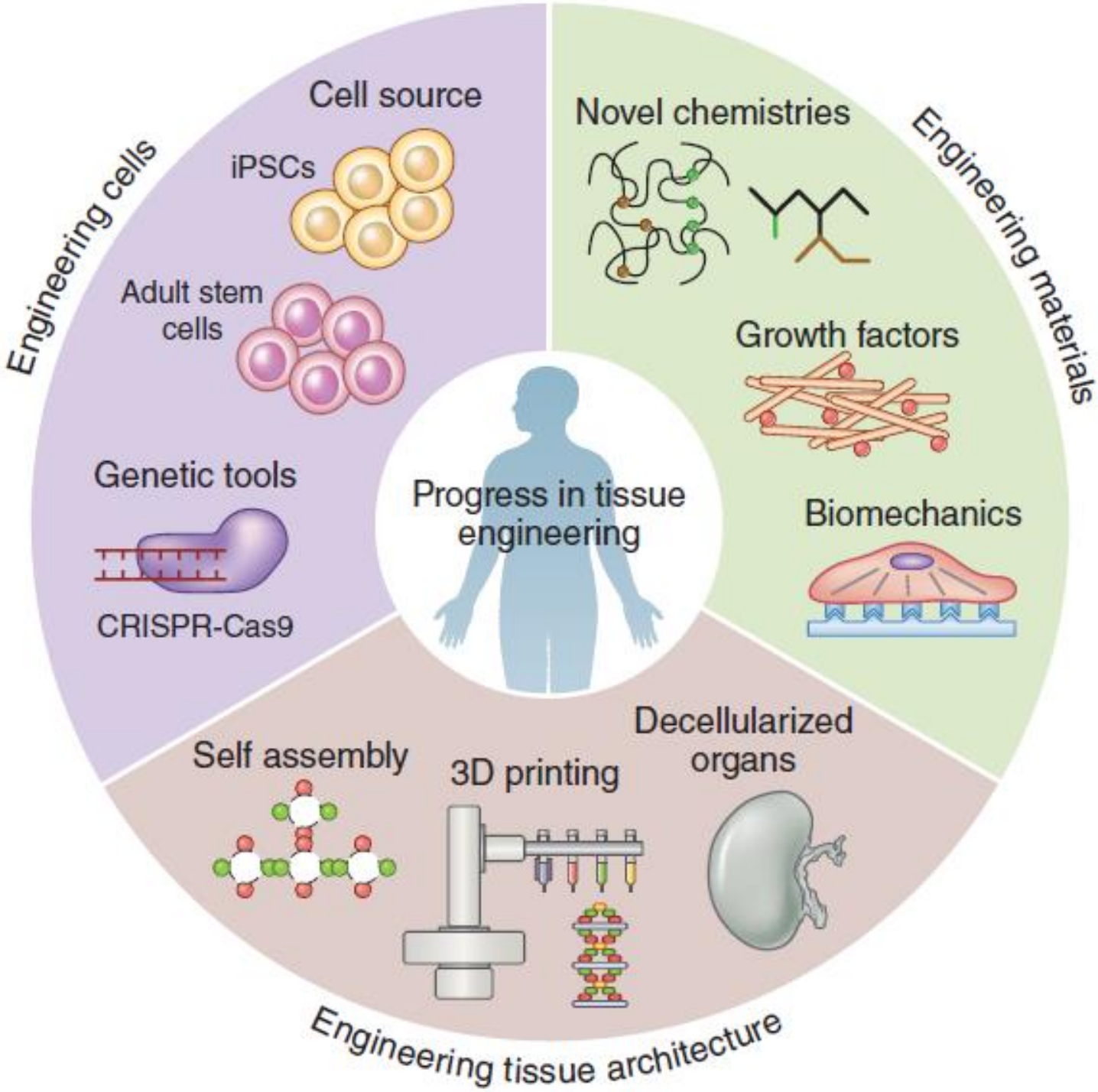
It is the first attempt to combine two hot areas in cancer research: gene editing to create personalized treatments, and engineering immune cells called T cells so as to better target tumours. The approach was tested in 16 people with solid tumours, including in the breast and colon.

"It is probably the most complicated therapy ever attempted in the clinic," says study co-author Antoni Ribas, a cancer researcher and physician at the University of California, Los Angeles. "We're trying to make an army out of a patient's own T cells."

The results were published in *Nature* (S. P. Foy *et al. Nature* https://doi.org/jk4f; 2022) and presented at the Society for Immunotherapy of Cancer meeting in Boston, Massachusetts, on 10 November.

Ribas and his colleagues began by sequencing DNA from blood samples and tumour biopsies, to look for mutations that are found in the tumour but not in the blood. This had to be done for each person in the trial. "The mutations are different in every cancer," says Ribas. "And although there are some shared mutations, they are the minority."

The researchers then used algorithms to predict which of the mutations were likely to be capable of provoking a response from T cells, a type of white blood cell that patrols the body looking for errant cells. "If [T cells] see something that looks not normal, they kill it," says Stephanie Mandl, chief scientific


Engineering cells
Cell source
iPSCs
Adult stem cells
Genetic tools
CRISPR-Cas9
Engineering materials
Novel chemistries
Growth factors
Biomechanics
Progress in tissue engineering
Engineering tissue architecture
Self assembly
3D printing
Decellularized organs

MUCHAS GRACIAS!

sruiz@aemps.es

AGENCIA ESPAÑOLA DE

MINISTERIO DE SANIDAD

agencia española de medicamentos y productos sanitarios

BACK UP

medicamento de terapia avanzada

DEBE CUMPLIR LA LEGISLACIÓN DE MEDICAMENTOS

- **autorización:** comercialización, investigación clínica, uso compasivo…
- garantías de **calidad, seguridad, eficacia**
- son aplicables **GMP** (producción y control), **GLP** (estudios no clínicos) y **GCP** (ensayos clínicos)

aemps

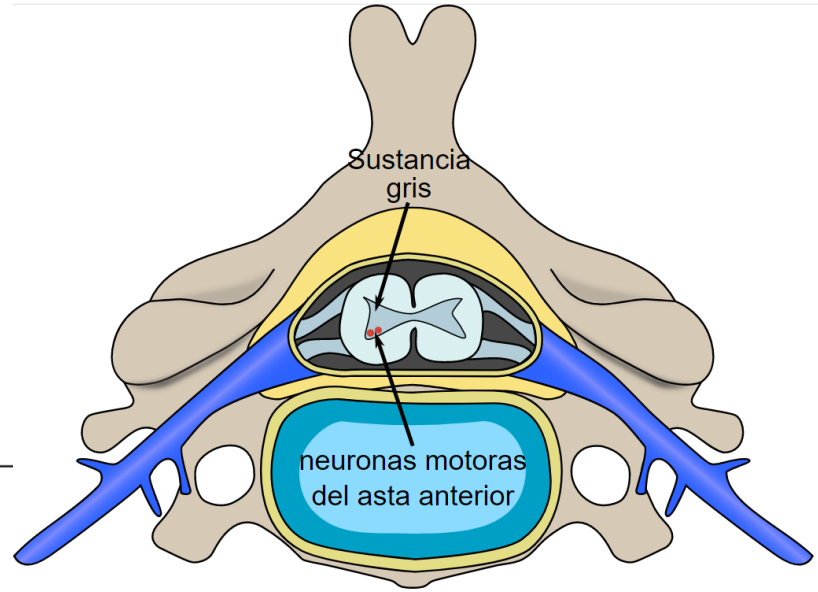
- investigación clínica, uso compasivo
- autorización de uso (*cláusula de exclusión*)

ema

autorización de comercialización en la UE

De Cervical vertebra blank.svg: Fred the OysterPolio spinal diagram.PNG: DO11.10Polio spinal diagram es.png: RøgeDerived: Angelito7 - Cervical vertebra blank.svgPolio spinal diagram.PNGPolio spinal diagram es.png, CC BY-SA 4.0, commons.wikimedia.org/w/index.php?curid=59609002

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



27 March 2020
EMA/163207/2020
Media and Public Relations

Press release

New gene therapy to treat spinal muscular atrophy

EMA has recommended granting a conditional marketing authorisation in the European Union for the gene therapy Zolgensma (onasemnogene abeparvovec) to treat babies and young children with spinal muscular atrophy (SMA), a rare and often fatal genetic disease that causes muscle weakness and progressive loss of movement.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medicine name	Therapeutic area	International non-proprietary name (INN) / common name	Authorisation status	Conditional approval	Exceptional circumstances	Accelerated assessment	Orphan medicine	Marketing authorisation date
Glybera	Hyperlipoproteinemia Type I	alipogene tiparvovec	Withdrawn	no	yes	no	no	25/10/2012
Imlygic	Melanoma	talimogene laherparepvec	Authorised	no	no	no	no	16/12/2015
Zalmoxis	Hematopoietic Stem Cell Transplant	allogeneic T cells genetically	Withdrawn	yes	no	no	no	18/08/2016
Yescarta	Lymphoma, Follicular; Lymphoma,	axicabtagene ciloleucel	Authorised	no	no	no	yes	23/08/2018
Luxturna	Leber Congenital Amaurosis; Retin	voretigene neparvovec	Authorised	no	no	no	yes	22/11/2018
Zynteglo	beta-Thalassemia	betibeglogene autotemcel	Withdrawn	yes	no	yes	yes	29/05/2019
Zolgensma	Muscular Atrophy, Spinal	onasemnogene abeparvovec	Authorised	yes	no	no	yes	18/05/2020
Tecartus	Lymphoma, Mantle-Cell	Brexucabtagene autoleucel	Authorised	yes	no	no	yes	14/12/2020
Libmeldy	Leukodystrophy, Metachromatic	Autologous CD34+ cells enc	Authorised	no	no	no	yes	17/12/2020
Skysona	Adrenoleukodystrophy	elivaldogene autotemcel	Withdrawn	no	no	no	no	16/07/2021
Abecma	Multiple Myeloma; Neoplasms; Car	idecabtagene vicleucel	Authorised	yes	no	no	yes	18/08/2021
Breyanzi	Lymphoma, Large B-Cell, Diffuse; L	lisocabtagene maraleucel	Authorised	no	no	no	no	4/04/2022
Carvykti	Multiple Myeloma	ciltacabtagene autoleucel	Authorised	yes	no	no	yes	25/05/2022
Upstaza	Amino Acid Metabolism, Inborn Erro	eladocagene exuparvovec	Authorised	no	yes	no	yes	18/07/2022
Roctavian		Valoctocogene roxaparvovec	Authorised	yes	no	no	yes	24/08/2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Yescarta	Lymphoma, Follicular; Lymphoma,	axicabtagene ciloleucel	Authorised	no	no	no	yes	23/08/2018
Luxturna	Leber Congenital Amaurosis; Retin	voretigene neparvovec	Authorised	no	no	no	yes	22/11/2018
Zynteglo	beta-Thalassemia	betibeglogene autotemcel	Withdrawn	yes	no	yes	yes	29/05/2019
Zolgensma	Muscular Atrophy, Spinal	onasemnogene abeparvovec	Authorised	yes	no	no	yes	18/05/2020
Tecartus	Lymphoma, Mantle-Cell	Brexucabtagene autoleucel	Authorised	yes	no	no	yes	14/12/2020
Libmeldy	Leukodystrophy, Metachromatic	Autologous CD34+ cells enc	Authorised	no	no	no	yes	17/12/2020
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Breyanzi	Lymphoma, Large B-Cell, Diffuse; L	lisocabtagene maraleucel	Authorised	no	no	no	no	4/04/2022
Carvykti	Multiple Myeloma	ciltacabtagene autoleucel	Authorised	yes	no	no	yes	25/05/2022
Upstaza	Amino Acid Metabolism, Inborn Erro	eladocagene exuparvovec	Authorised	no	yes	no	yes	18/07/2022
Roctavian		Valoctocogene roxaparvovec	Authorised	yes	no	no	yes	24/08/2022

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Medicine name	Therapeutic area	International non-proprietary name (INN) / common name	Authorisation status	Conditional approval	Accelerated assessment	Orphan medicine	Marketing authorisation date
Kymriah	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	tisagenlecleucel	Authorised	no	no	yes	22/08/2018
Tecartus	Lymphoma, Mantle-Cell	Brexucabtagene autolel	Authorised	yes	no	yes	14/12/2020
Yescarta	Lymphoma, Follicular; Lymphoma, Large B-Cell, Diffus	axicabtagene ciloleucel	Authorised	no	no	yes	23/08/2018
Zynteglo	beta-Thalassemia	betibeglogene autotem	**Withdrawn**	yes	yes	yes	29/05/2019
Carvykti	Multiple Myeloma	ciltacabtagene autoleuc	Authorised	yes	no	yes	25/05/2022
Breyanzi	Lymphoma, Large B-Cell, Diffuse; Lymphoma, Follicul	lisocabtagene maraleuc	Authorised	no	no	no	4/04/2022
Abecma	Multiple Myeloma; Neoplasms; Cancer; Neoplasms, I	idecabtagene vicleucel	Authorised	yes	no	yes	18/08/2021
Skysona	Adrenoleukodystrophy	elivaldogene autotemce	**Withdrawn**	no	no	no	16/07/2021
Alofisel	Rectal Fistula	darvadstrocel	Authorised	no	no	yes	23/03/2018

5. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

Uncertainty in the knowledge about the beneficial effects

Risks

Unfavourable effects

Uncertainty in the knowledge about the unfavourable effects

Balance

Importance of favourable and unfavourable effects

Benefit-risk balance

Discussion on the benefit-risk assessment

5.1. Conclusions

The overall B/R of <name of product> <is> <positive> provided <general statement on conditions>; is <negative>.


Risk
RISK MANAGEMENT PLAN
Benefit

COVID-19 pandemic

All info here >

QUICK LINKS

- Latest updates >
- Vaccines >
- Treatments >
- Guidance for developers and companies >

MEDICINES | COMMITTEES

CHMP highlights: November 2022

COVID-19 | VACCINES

VidPrevtyn Beta recommended for approval in the EU

CHMP statistics: November 2022

Positive opinions on new medicines	4 Total	84 Total 2022
New [non-orphan] medicines	1	
Orphan medicines	0	
Biosimilars	1	
Generic / hybrids / informed consent	2	
Negative opinions on new medicines	0 Total	2 Total 2022
Positive opinions on extensions of therapeutic indications	13* Total	78 Total 2022
Withdrawn applications for new medicines	2 Total	15 Total 2022

www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-7-10-november-2022

Medicines for human use under evaluation

Share

Each month, the European Medicines Agency's (EMA) publishes an updated list of medicines for human use currently under evaluation by EMA's Committee for Medicinal Products for Human Use (CHMP) to obtain a marketing authorisation in the European Union (EU).

For information on **treatments and vaccines for COVID-19,** including those under evaluation by the CHMP:

- Treatments and vaccines for COVID-19

The CHMP meets once per month. Its evaluations of **marketing authorisation applications** submitted through the **centralised procedure** provide the basis for authorisation of medicines in Europe.

Monthly lists of medicines under evaluation by the CHMP are available dating back to 2012. They contain the **international non-proprietary names (INN)** and **therapeutic areas** of innovative medicines. The INN contains only the active moiety for generic medicines and biosimilar medicines, with

terapia avanzada

Medicamentos de ingeniería tisular

Principio activo:
Células o tejidos

Objetivo:
Reemplazo, sustitución o reparación estructural del tejido

Medicamentos combinados de terapia avanzada

Principio activo:
Células o tejidos
+ producto sanitario

Objetivo:
Reemplazo, sustitución o reparación estructural del tejido