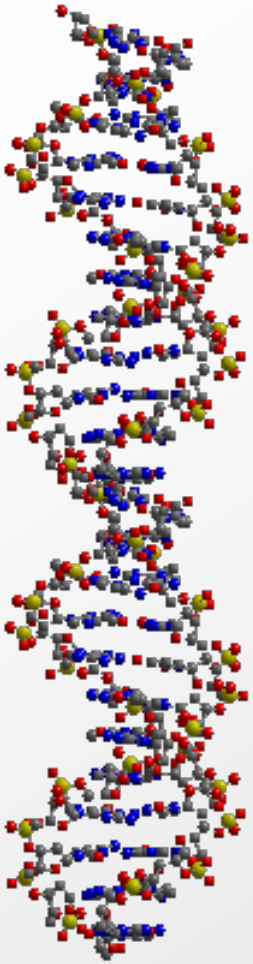
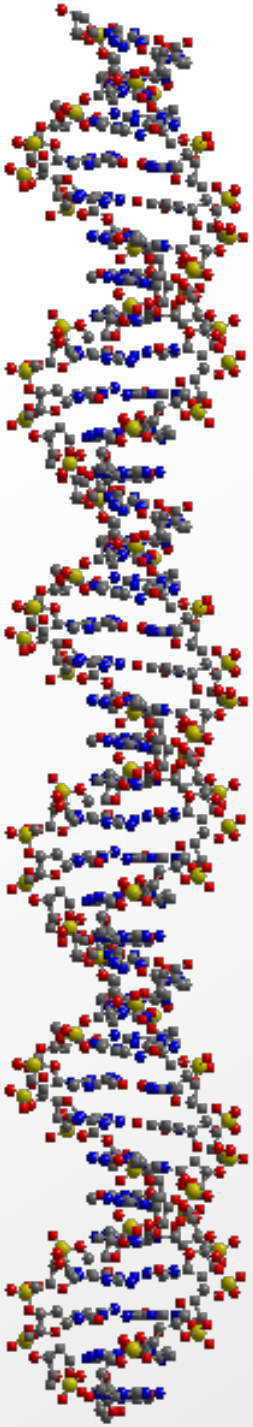
TERAPIA GÊNICA: uma revolução no horizonte (agora com mRNA!!)

Dr. Carlos Frederico Martins Menck
Instituto de Ciências Biomédicas, Universidade de São Paulo



DNA repair lab

ICB-USP



Definição de terapia gênica:

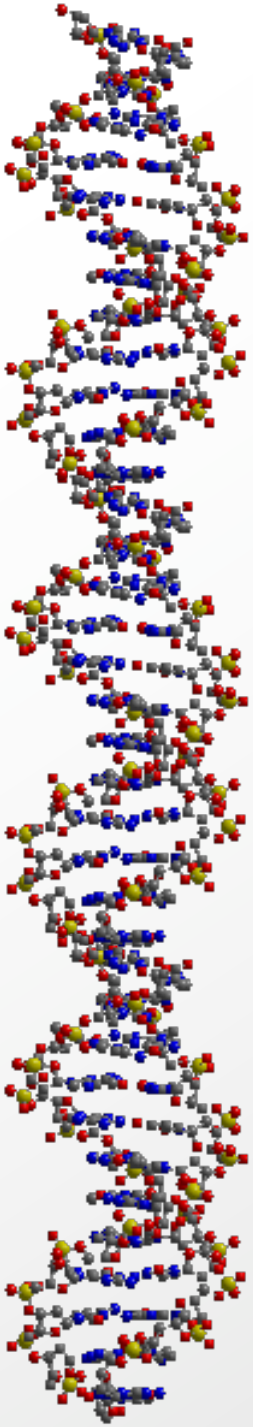
“transferência de material genético novo para células de um indivíduo resultando em benefício terapêutico”

Há mais de trinta anos a Terapia Genética, como capacidade de intervir na saúde humana,

tem sido considerada a

5ª Revolução da Medicina!!!

(Vacinas, esterilização, antibióticos e anestesias)



Alvos da Terapia Gênica:

Doenças genéticas clássicas:

Imunodeficiência (adenosina desaminase)

Fibrose cística (Regulador CF de Cl)

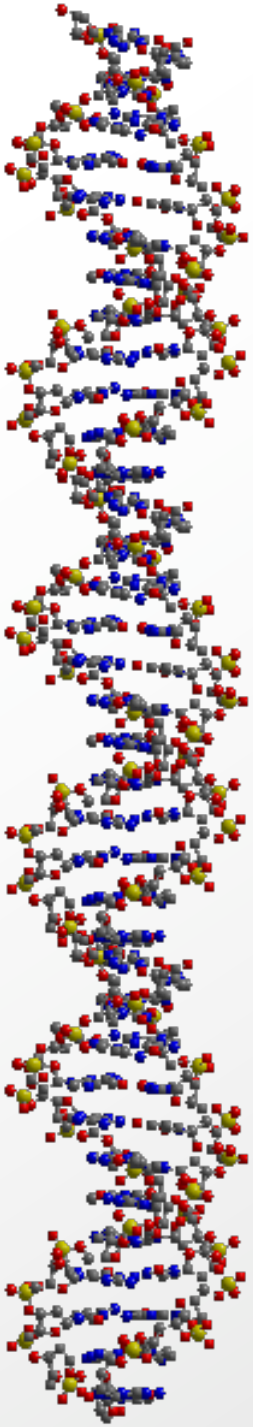
Hemofilias A e B (Fatores VIII e IX)

Doenças genéticas adquiridas:

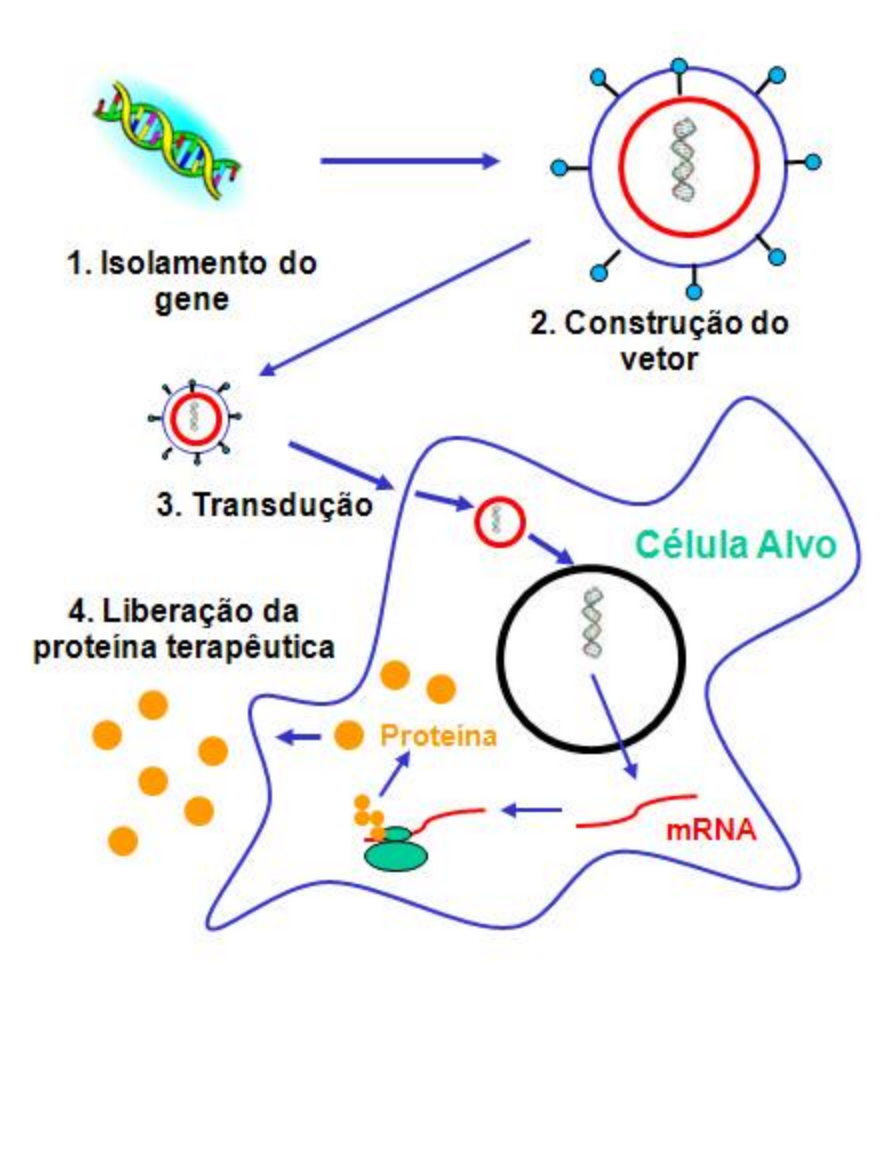
Câncer,

AIDS

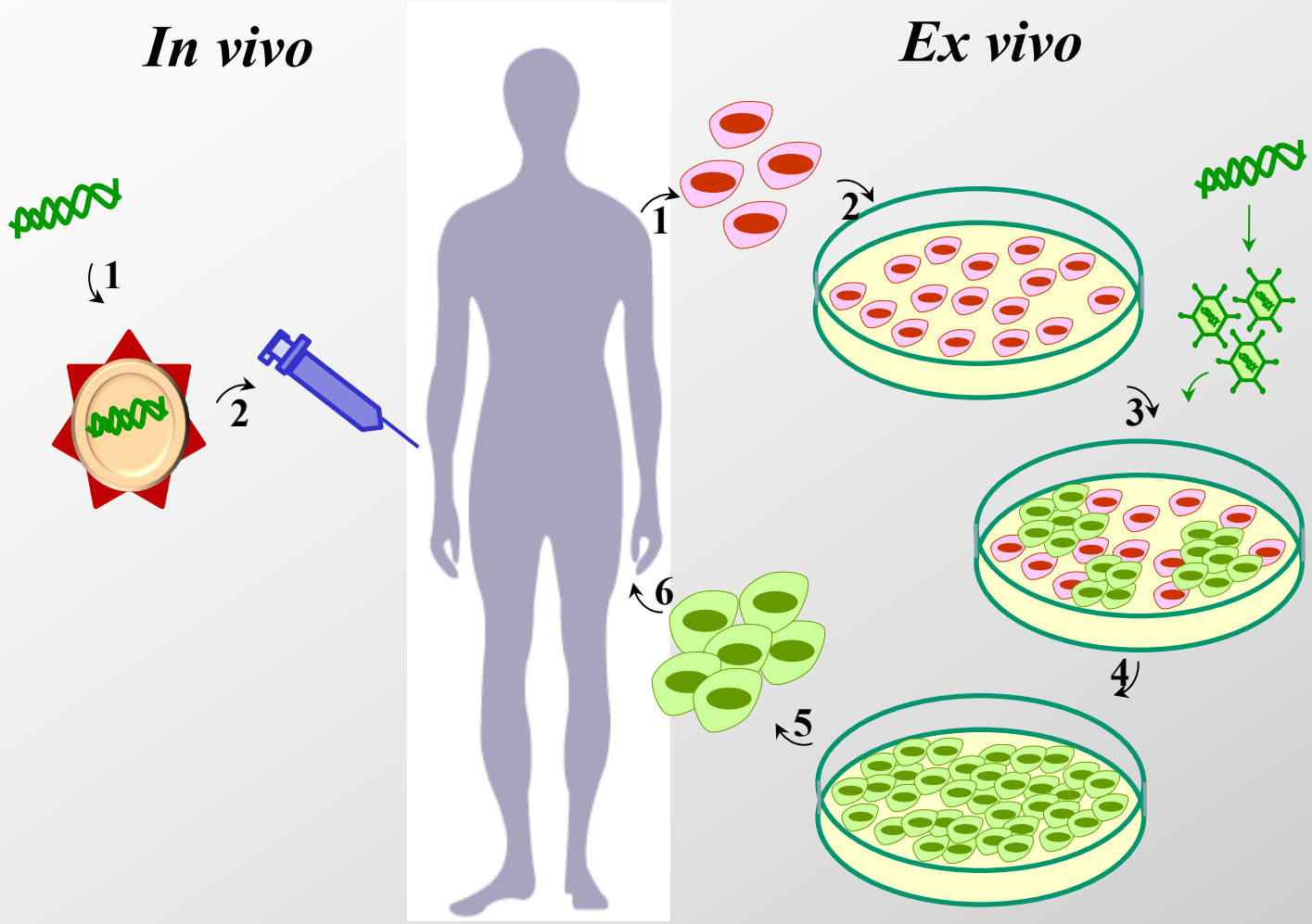
infecções com outros vírus (gripe- H1N1, dengue)



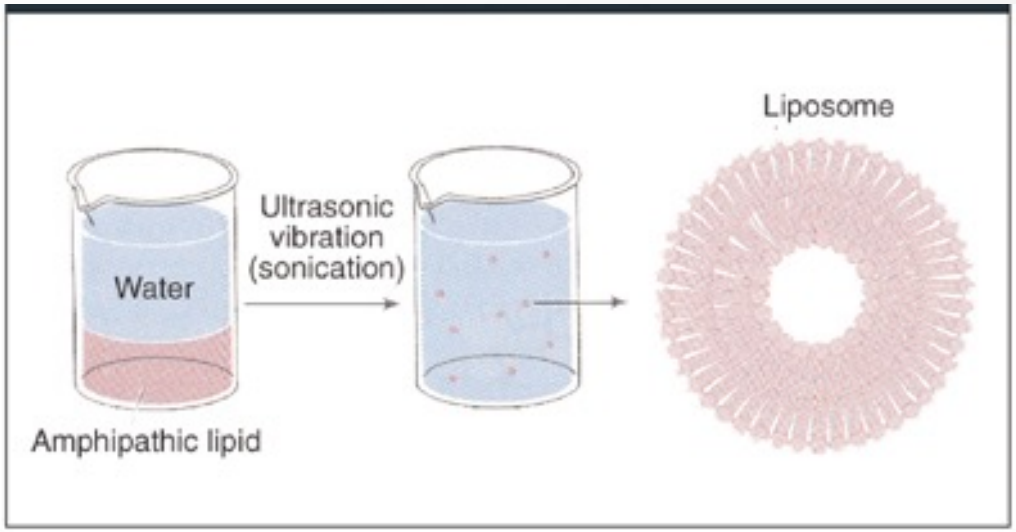
Terapia Gênica... Introduzindo material genético dentro das células:

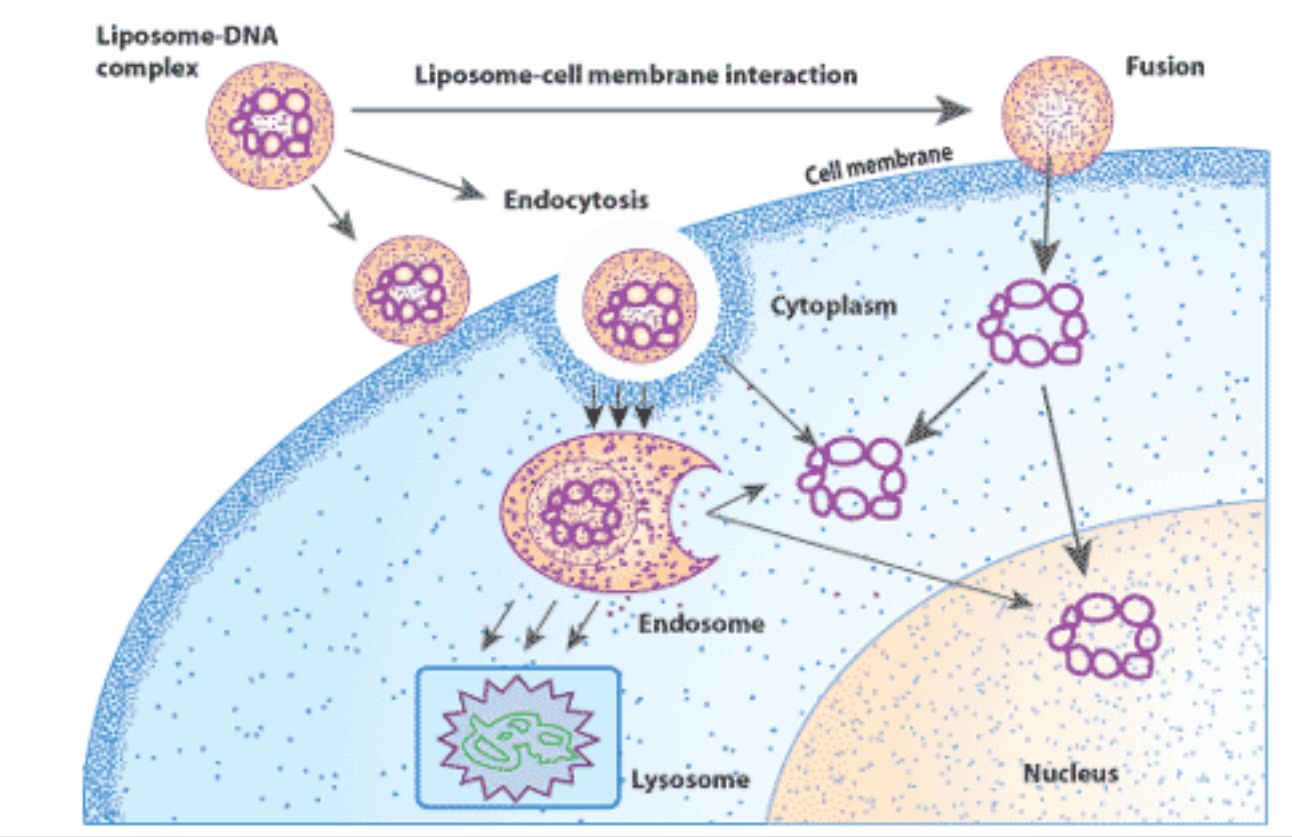


Estratégias de terapia gênica

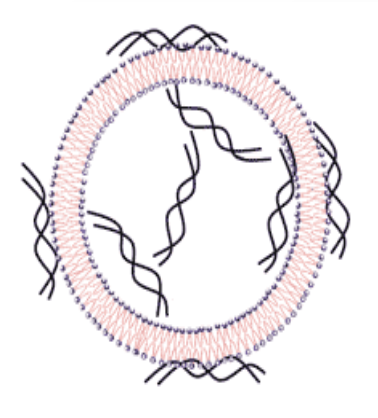


Uso de lipossomos.

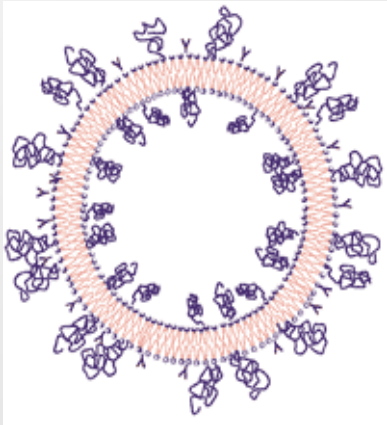


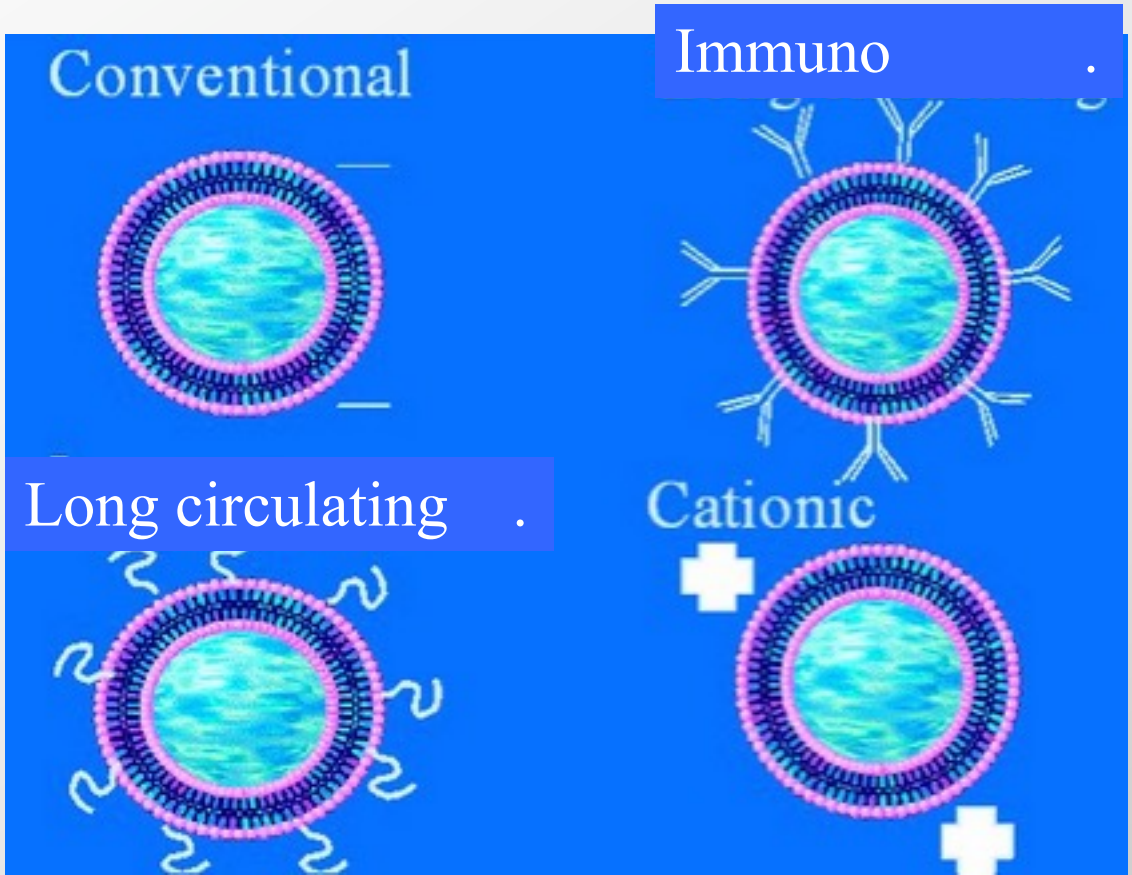


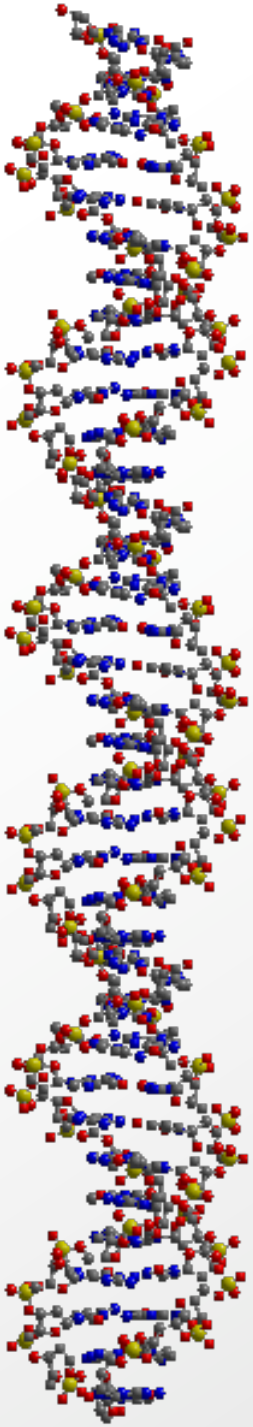
Uso de lipossomos.



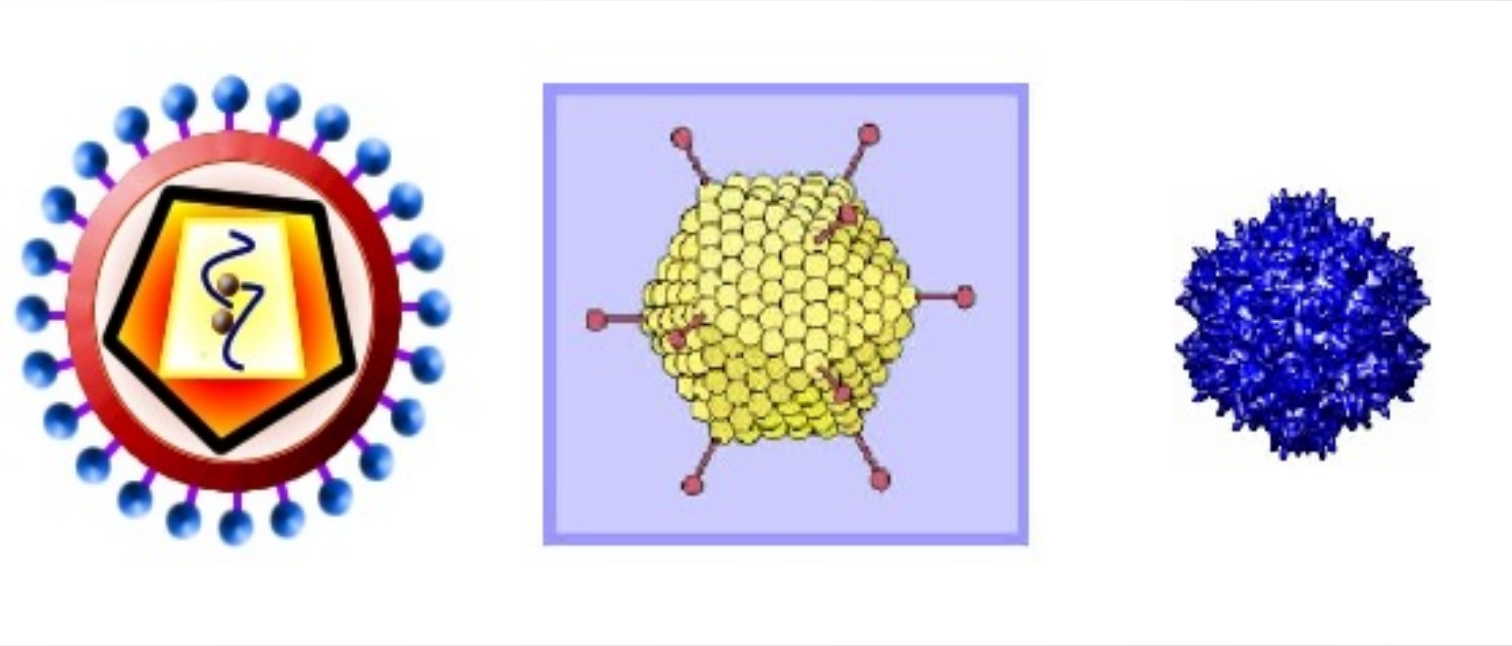
Destinando lipossomos a alvo precisos- uso de anticorpos! Ou outras modificações!!





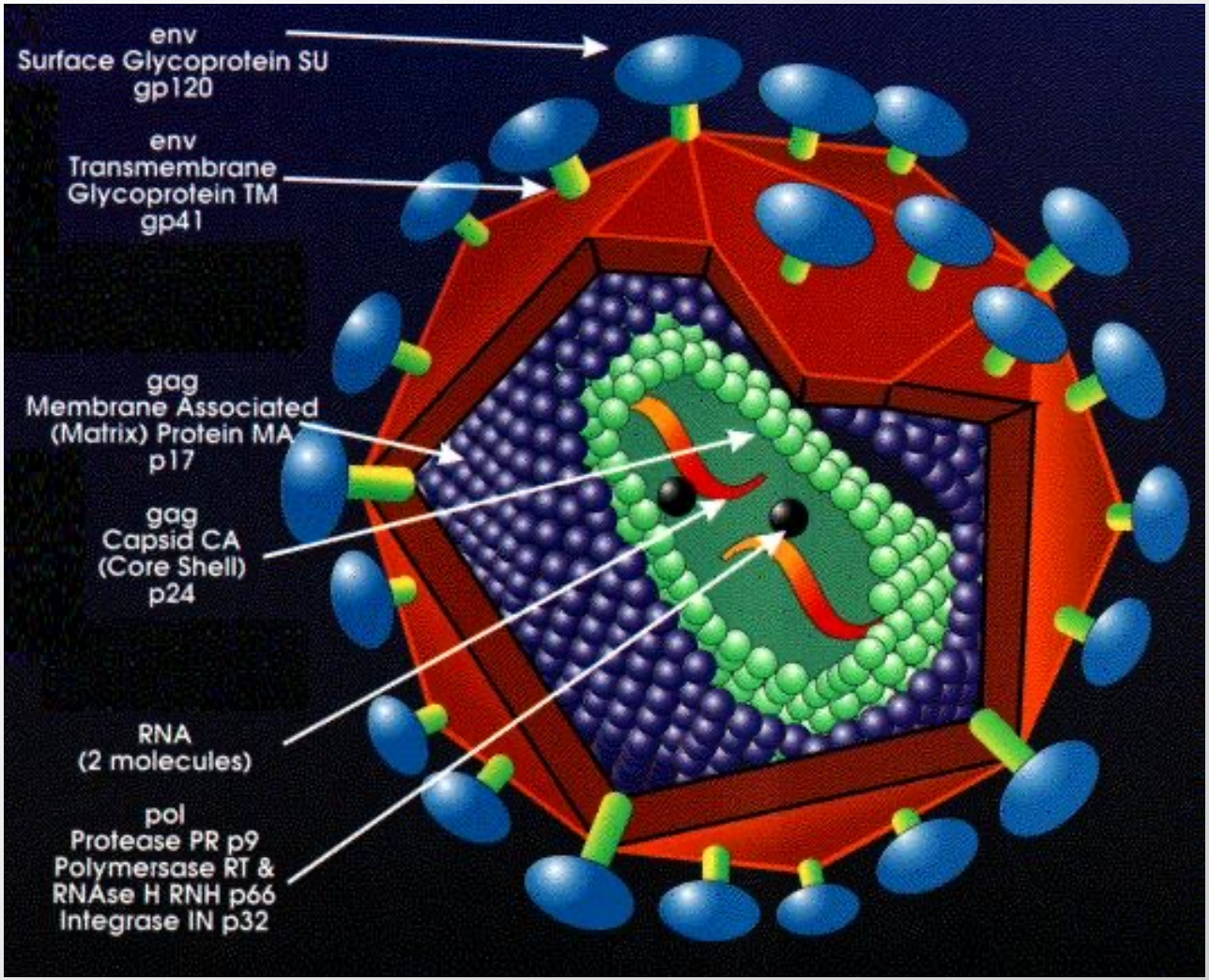


3) Vetores virais.

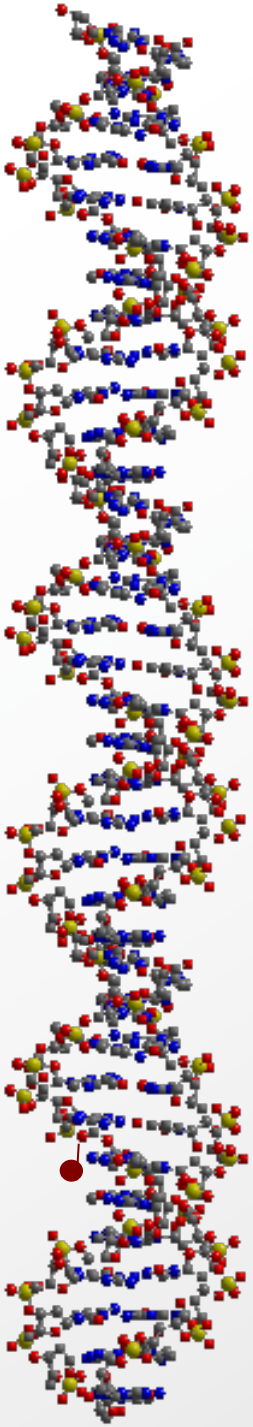


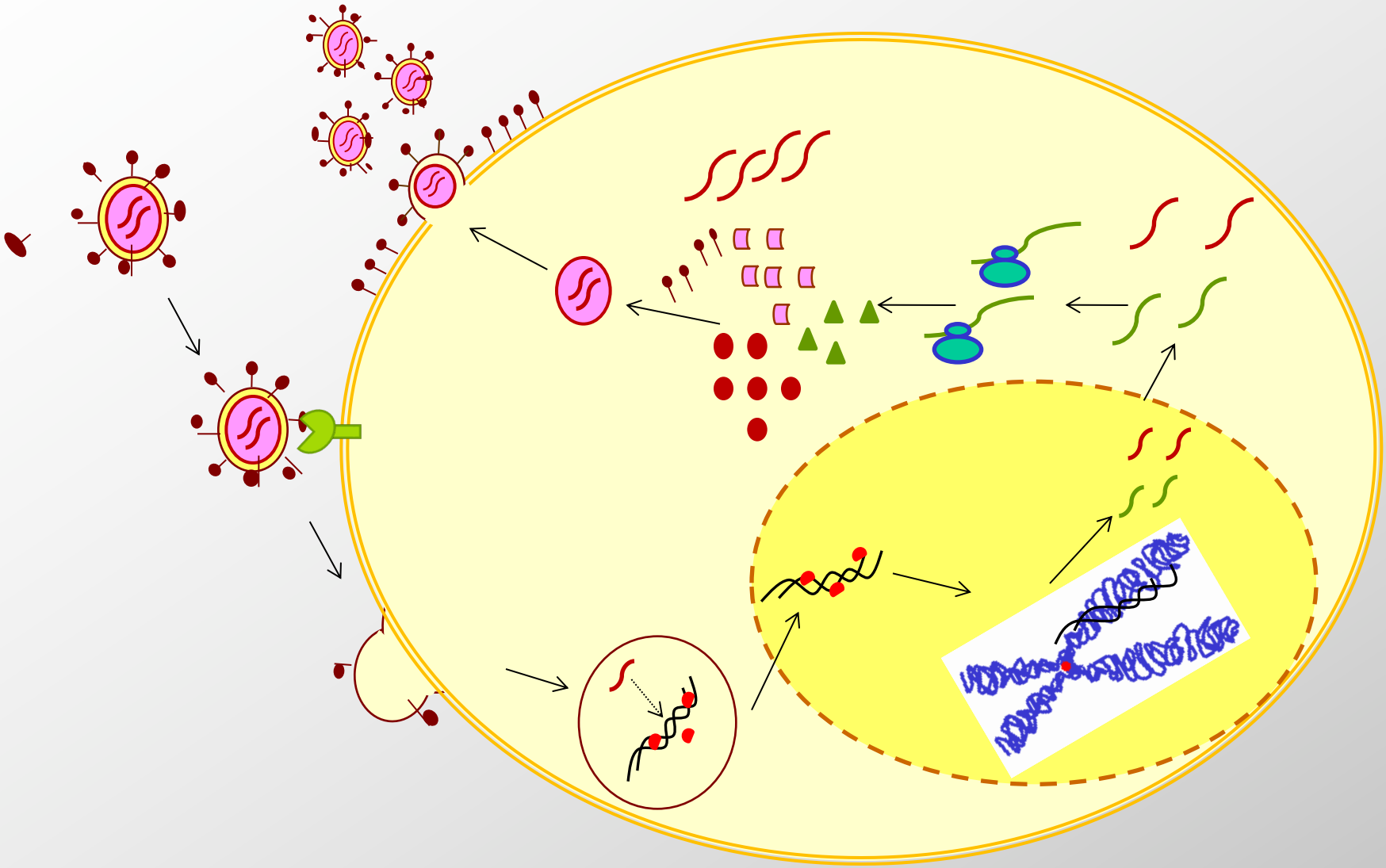
Retrovírus **Adenovírus** **Vírus Adeno-associado.**

Vetores derivados de retrovírus.



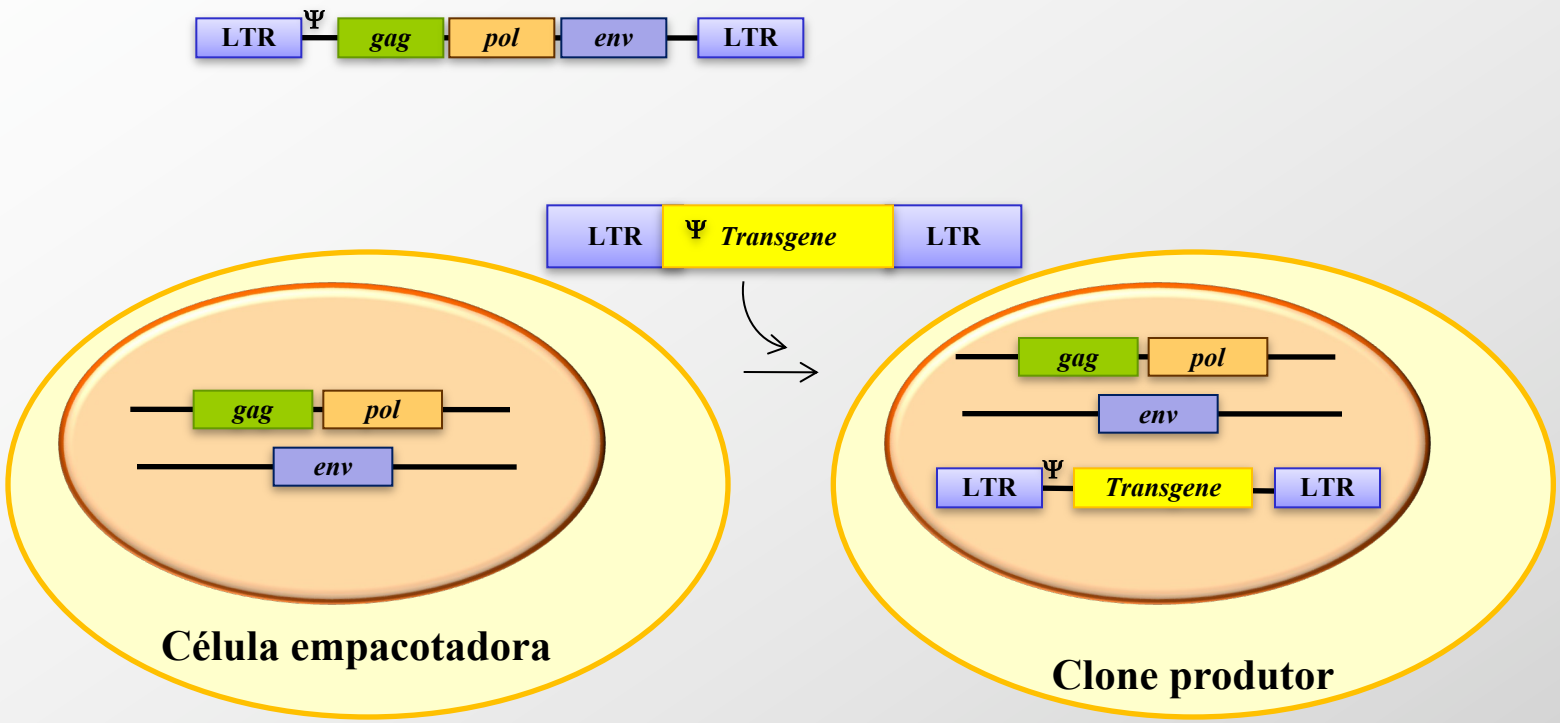
Ciclo de replicação do retrovírus.

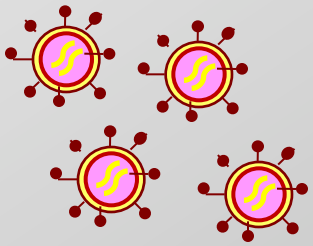




Construção de um vetor retroviral.

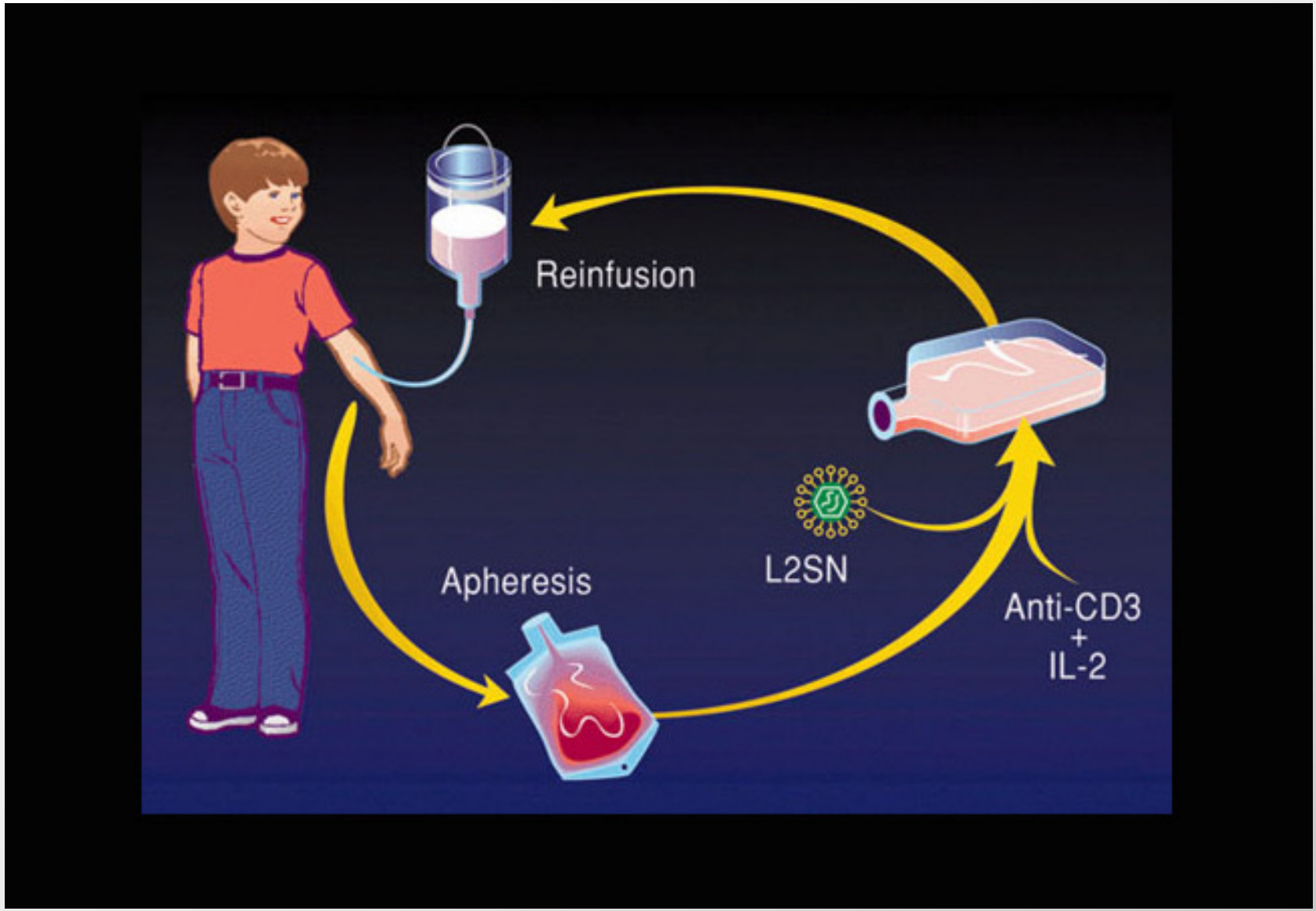
B

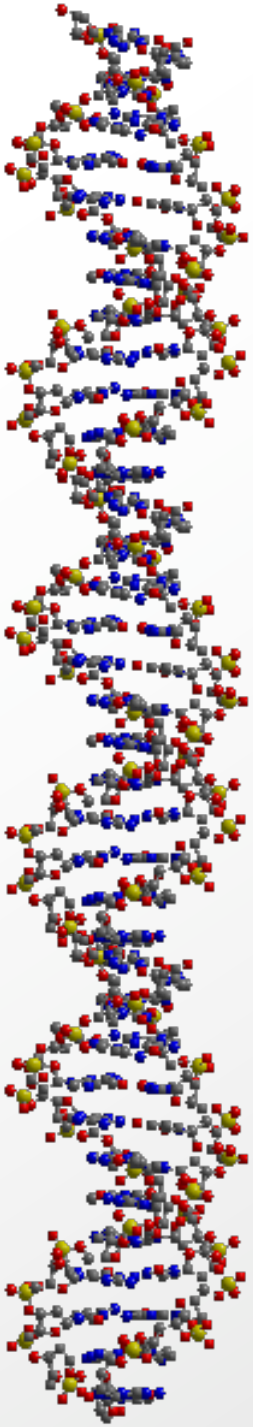




Retrovírus recombinante

Terapia ex-vivo com retrovírus.





Terapia gênica de problemas com o gene ADA.

Desoxiadenosina

↓

Acúmulo é tóxico para algumas células

→ ~~ADA~~ → Desoxiinosina

Via de salvação das purinas

→ Depleção de linfócitos T

↓

Deficiência imunológica!

Terapia gênica da deficiência em adenosina deaminase

1990 equipe liderada pelo Dr. French Anderson-

Terapia *ex vivo* - linfócitos de duas crianças

Resultados:

As crianças começam a recuperar o sistema imunológico

Ashanti de Silva

Projeto similar foi feito para 10 crianças X-linked SCID, com recuperação do sistema imunológico!

Ashanti e Cindy, as duas primeiras pessoas a receber Terapia Gênica Em 2013!

R. Michael Blaese, MD with Ashanthi DeSilva (left) and Cindy Kisik at the IDF 2013 National Conference, June 29.

X-linked SCID- bubble boys

No more 'bubble boy': Gene therapy gives kids normal lives

A decade later, children born with no immune systems ride horses, play games, get dirty

By JoNel Aleccia
Health writer

Children's health on NBCNEWS.com

The New England Journal of Medicine

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VOLUME 346 APRIL 18, 2002 NUMBER 16

SUSTAINED CORRECTION OF X-LINKED SEVERE COMBINED IMMUNODEFICIENCY BY EX VIVO GENE THERAPY

SALIMA HACEIN-BEY-ABINA, PH.D., FRANÇOISE LE DEIST, M.D., PH.D., FRÉDÉRIQUE CARLIER, B.S., CÉCILE BOUNEAUD, PH.D., CHRISTOPHE HUE, B.S., JEAN-PIERRE DE VILLARTAY, PH.D., ADRIAN J. THRASHER, M.D., PH.D., NICOLAS WULFFRAAT, M.D., RICARDO SORENSEN, M.D., SOPHIE DUPUIS-GIROD, M.D., ALAIN FISCHER, M.D., PH.D., AND MARINA CAVAZZANA-CALVO, M.D., PH.D.

Gene therapy of X-linked severe combined immunodeficiency by use of a pseudotyped gammaretroviral vector

H Bobby Gaspar, Kathryn L Parsley, Steven Howe, Doug King, Kimberly C Gilmour, Joanna Sinclair, Gaby Brouns, Manfred Schmidt, Christof Von Kalle, Torben Barington, Marianne A Jakobsen, Hans O Christensen, Abdulaziz Al Ghonaium, Harry N White, John L Smith, Roland J Levinsky, Robin R Ali, Christine Kinnon, Adrian J Thrasher

Lancet 2004; 364: 2181–87

See Comment page 2155

Molecular Immunology Unit, Institute of Child Health,

Mas realmente funcionou?????

o tratamento tradicional?

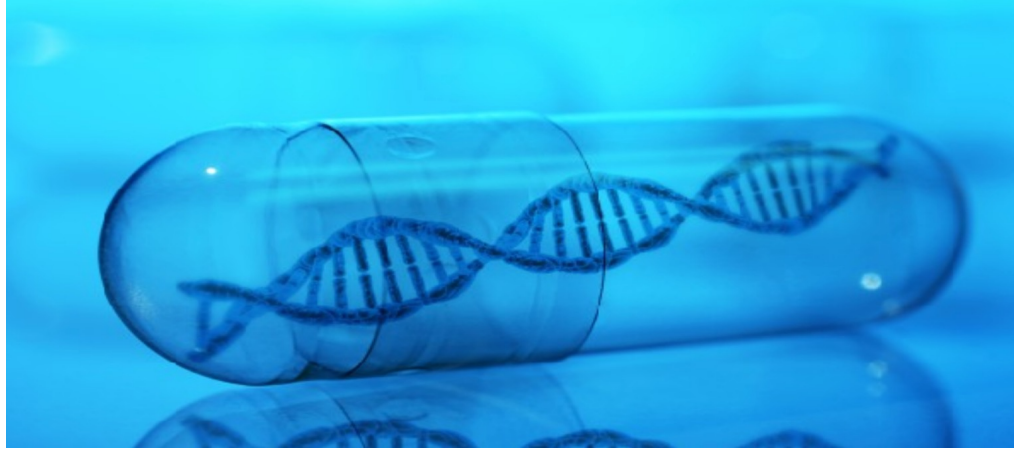
(transplante de medula óssea)

Science
AAAS

***LMO2*-Associated Clonal T Cell Proliferation in Two Patients after Gene Therapy for SCID-X1**
S. Hacein-Bey-Abina *et al.*
Science **302**, 415 (2003);
DOI: 10.1126/science.1088547

De 19 pacientes (só crianças), 5 tiveram leucemia (4 no gene LMO2!),

Outros também tiveram tumores! Por que?



Hum Gene Ther. 2017 Nov;28(11):972-981. doi: 10.1089/hum.2017.175.

Twenty-Five Years of Gene Therapy for ADA-SCID: From Bubble Babies to an Approved Drug.

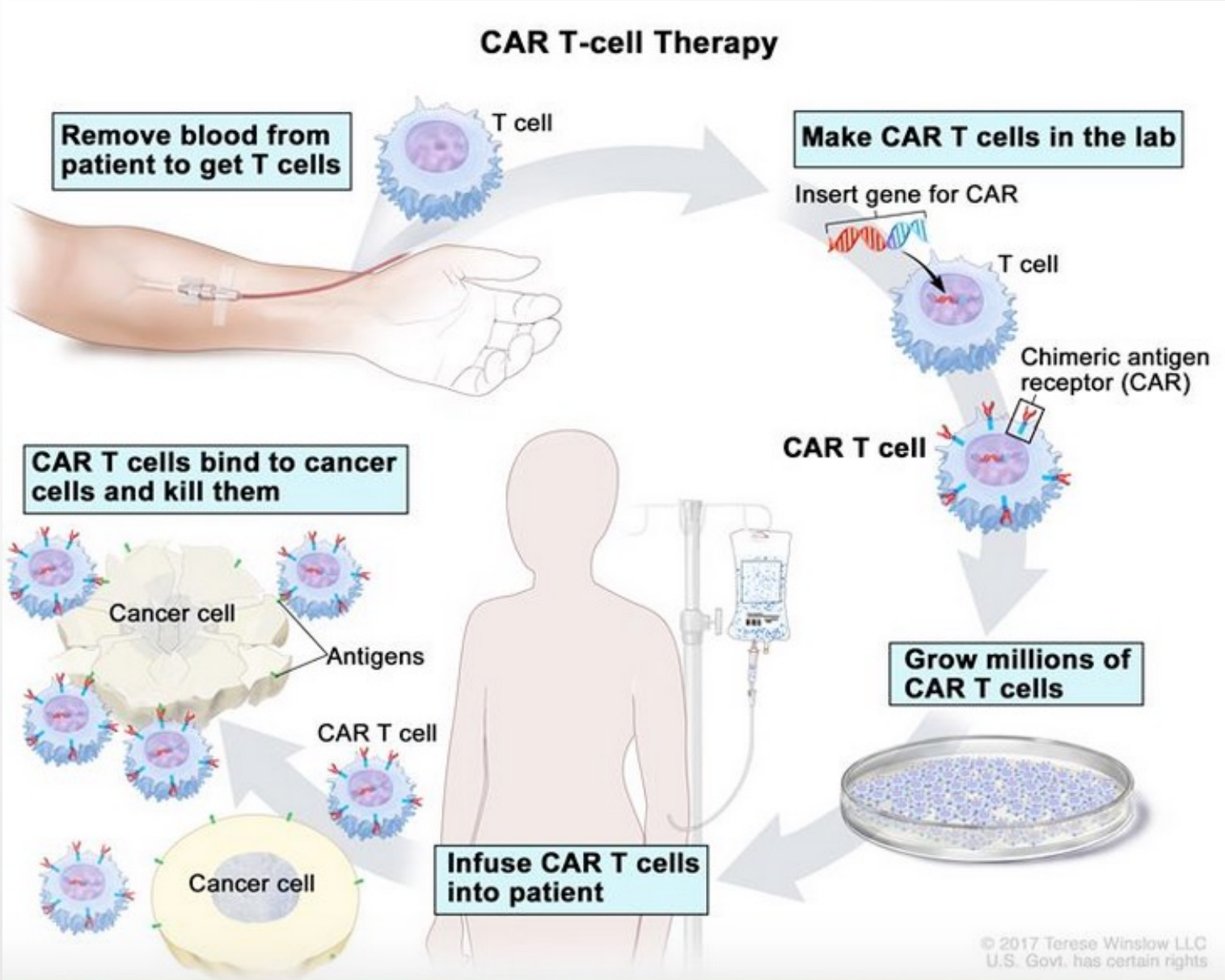
Ferrua F[1,2], Aiuti A[1,2].

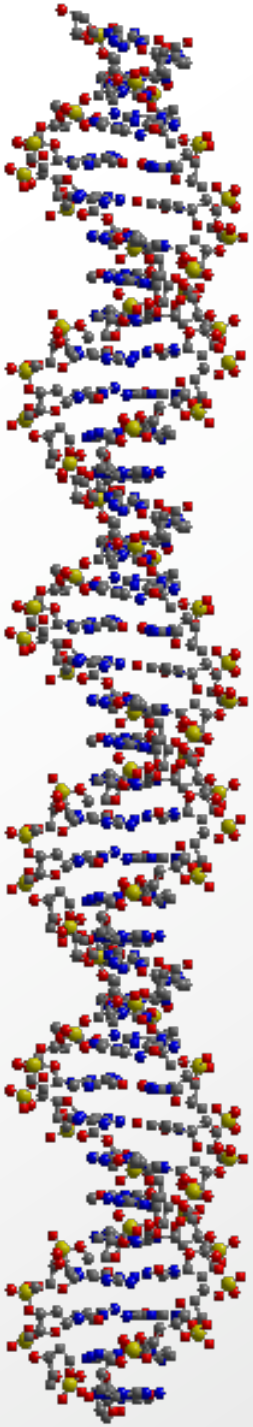
worldwide. In 2016, the medicinal product Strimvelis™ received marketing approval in Europe for patients affected by ADA-SCID without a suitable human leukocyte antigen-matched related donor. Positive safety and efficacy results have been

The price for the treatment was set at €594k, 2 times the annual cost of enzyme replacement therapy injections.[13] enzyme replacement therapy for ADA requires weekly injections and costs about $4.25 million for one patient over 10 years.[8]

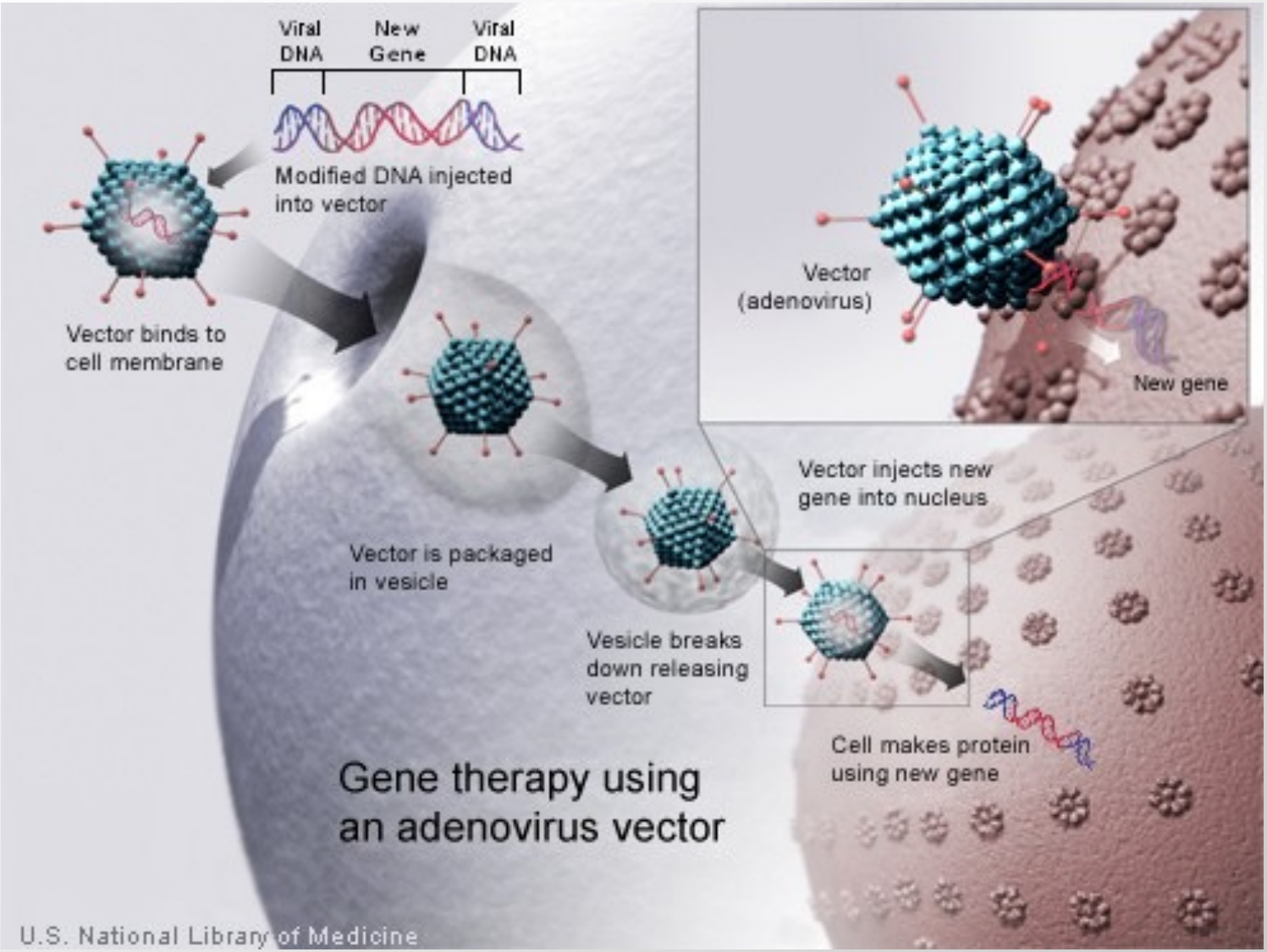
CAR-T gene therapy- KYMRIAH

Indo atrás e matando o tumor (linfoma) (lentivirus)

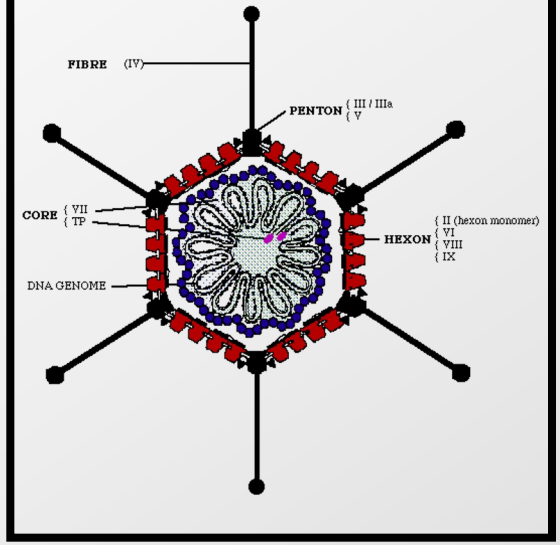


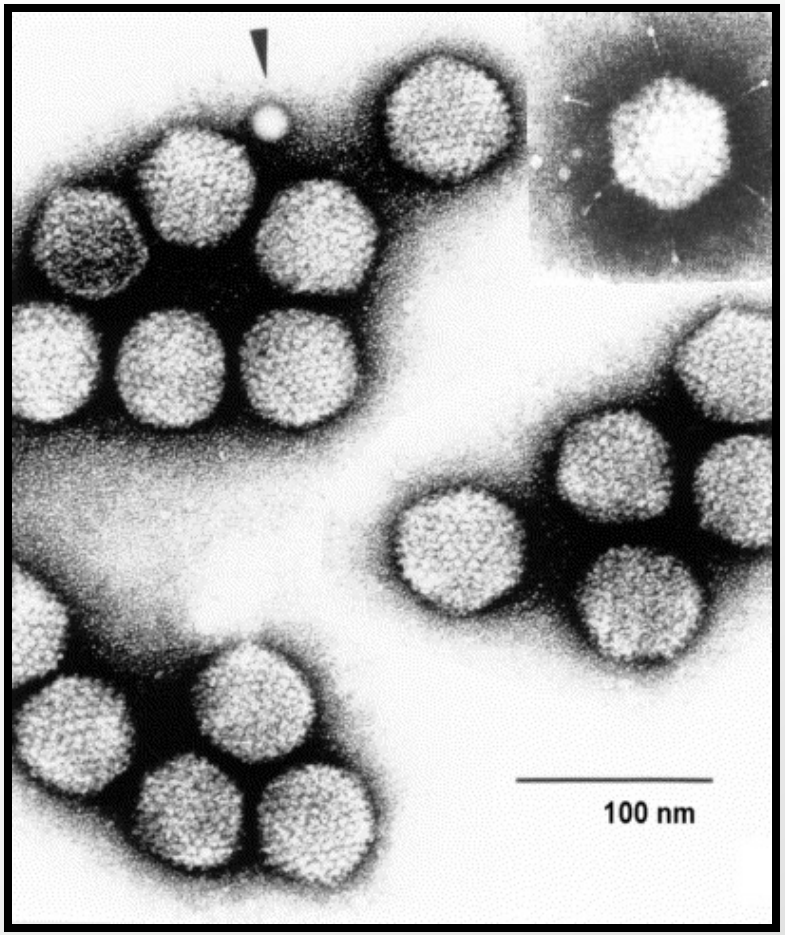


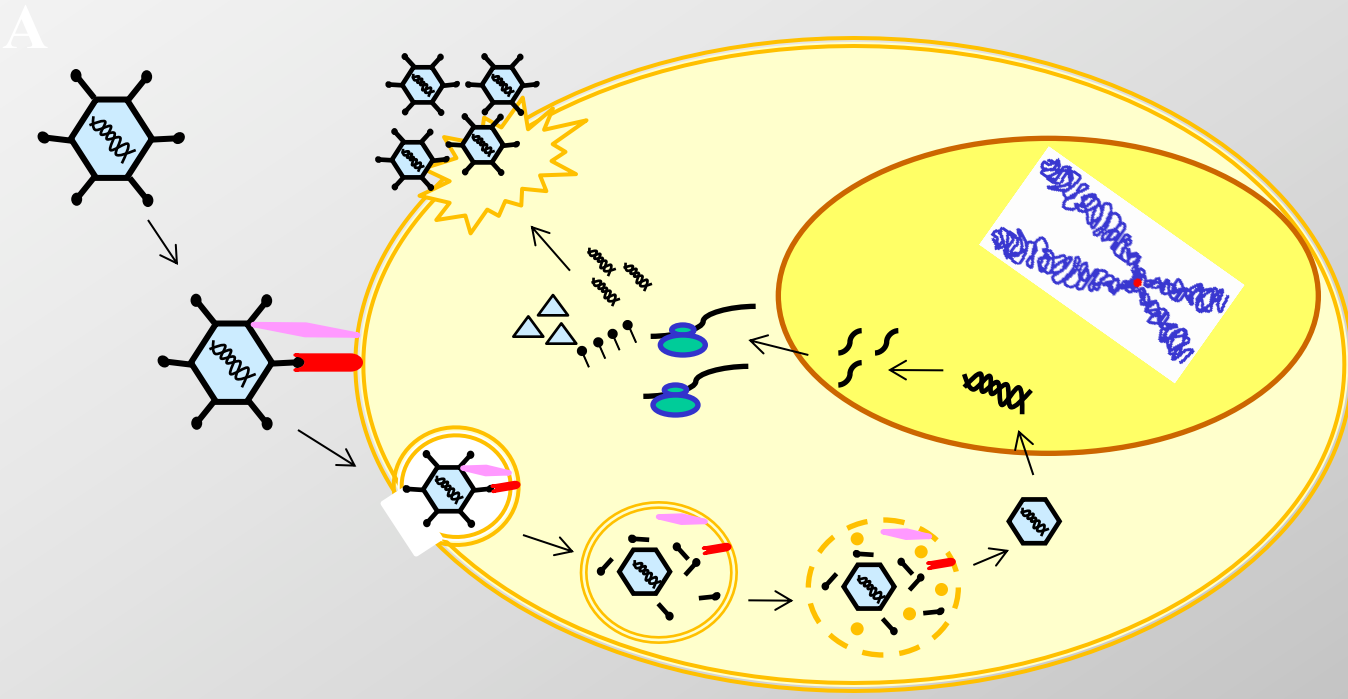
Uso de adenovírus para terapia gênica.

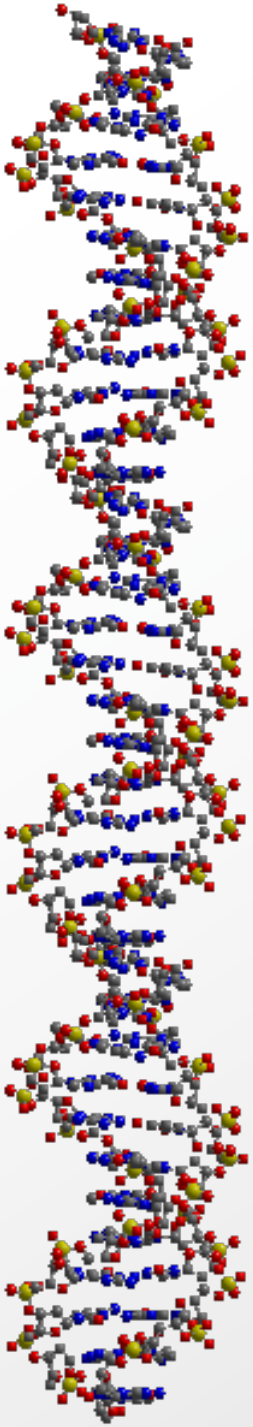


Uso de adenovírus para terapia gênica.









Vantagens dos adenovírus recombinantes:

*Alto título viral.

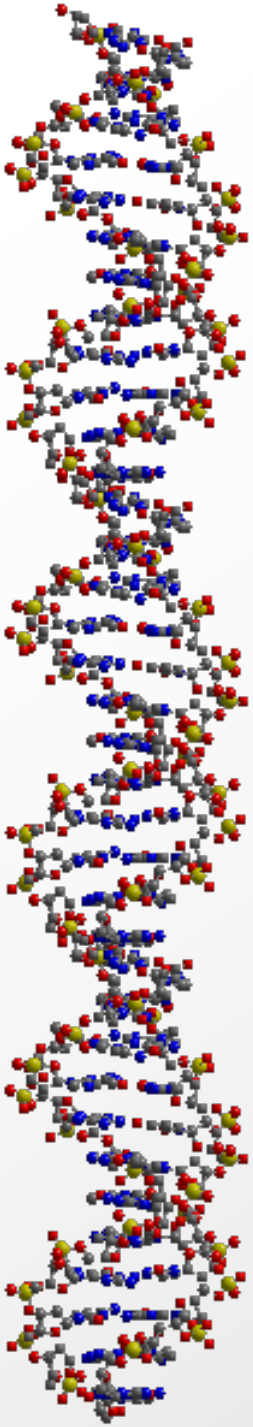
*Infecta uma grande variedade de células.

*Se mantém epissomal (não integra no genoma celular).

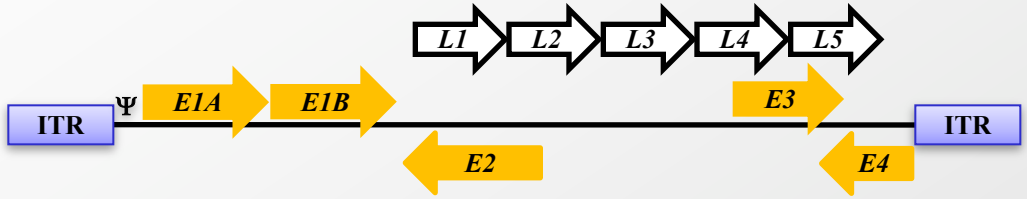
Desvantagens:

- Expressão Transiente (qual é o problema?)
- Forte resposta imune!
- Permite apenas uma aplicação (se tanto).

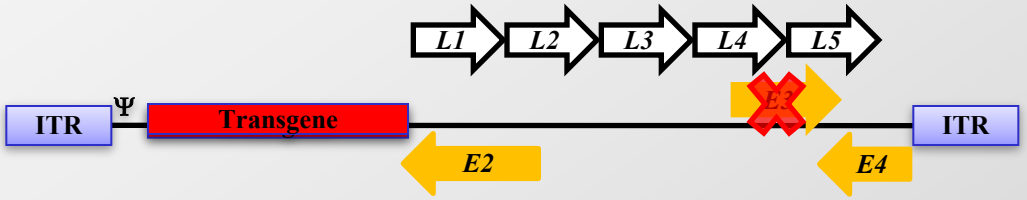
Construção de um vetor adenoviral.



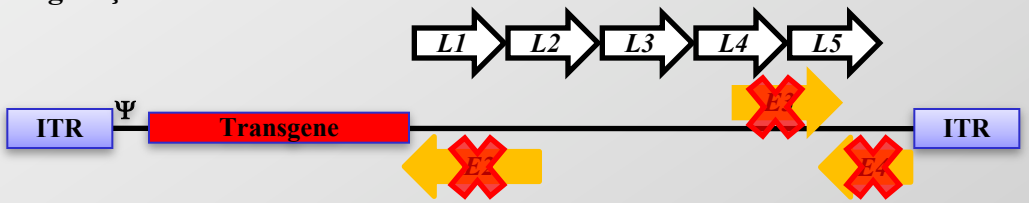
B



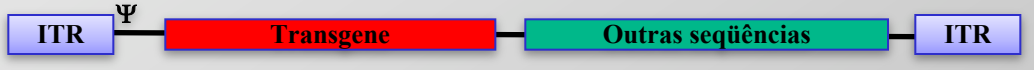
Vetores de primeira geração:

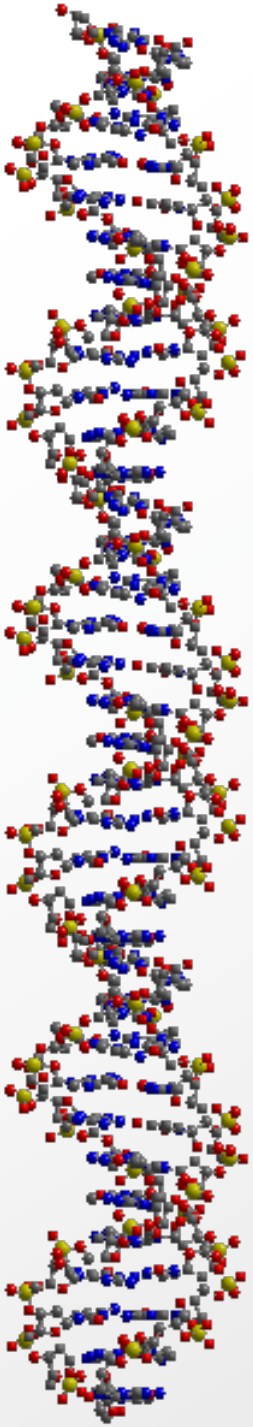


Vetores de segunda geração:

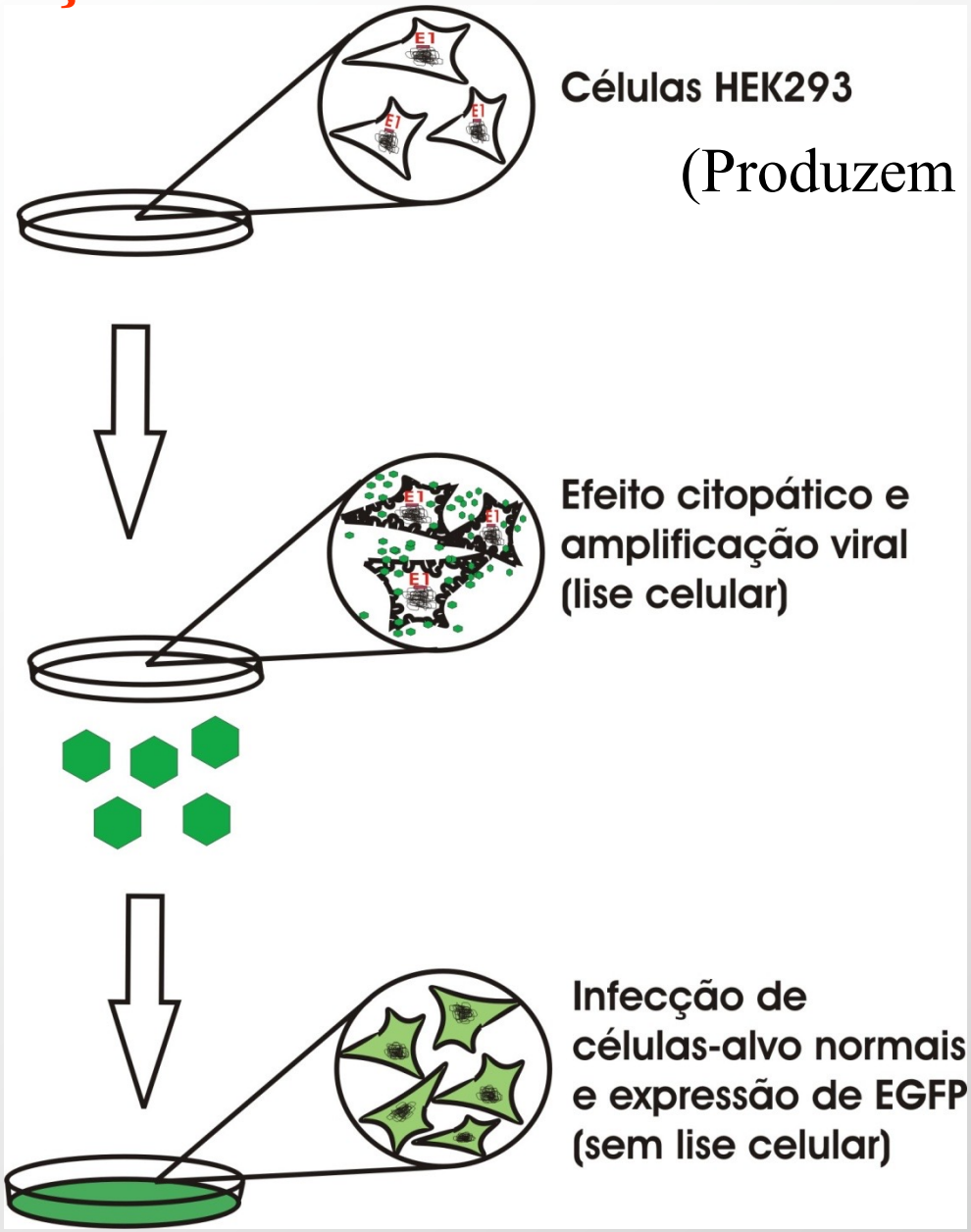


Vetores de terceira geração:

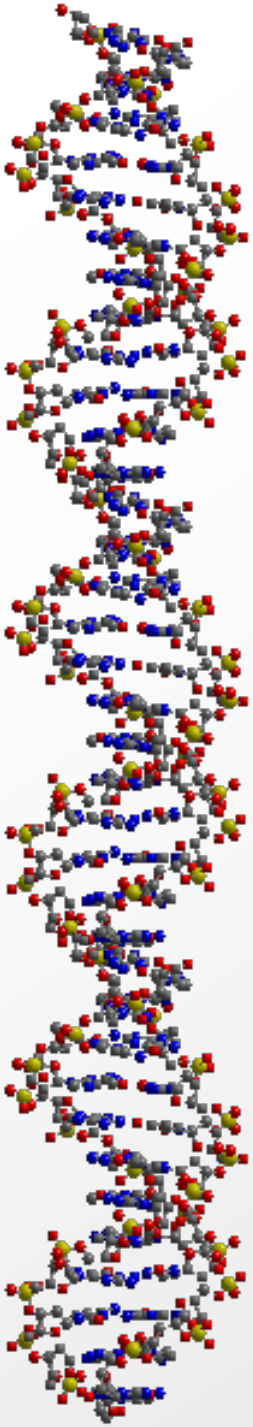




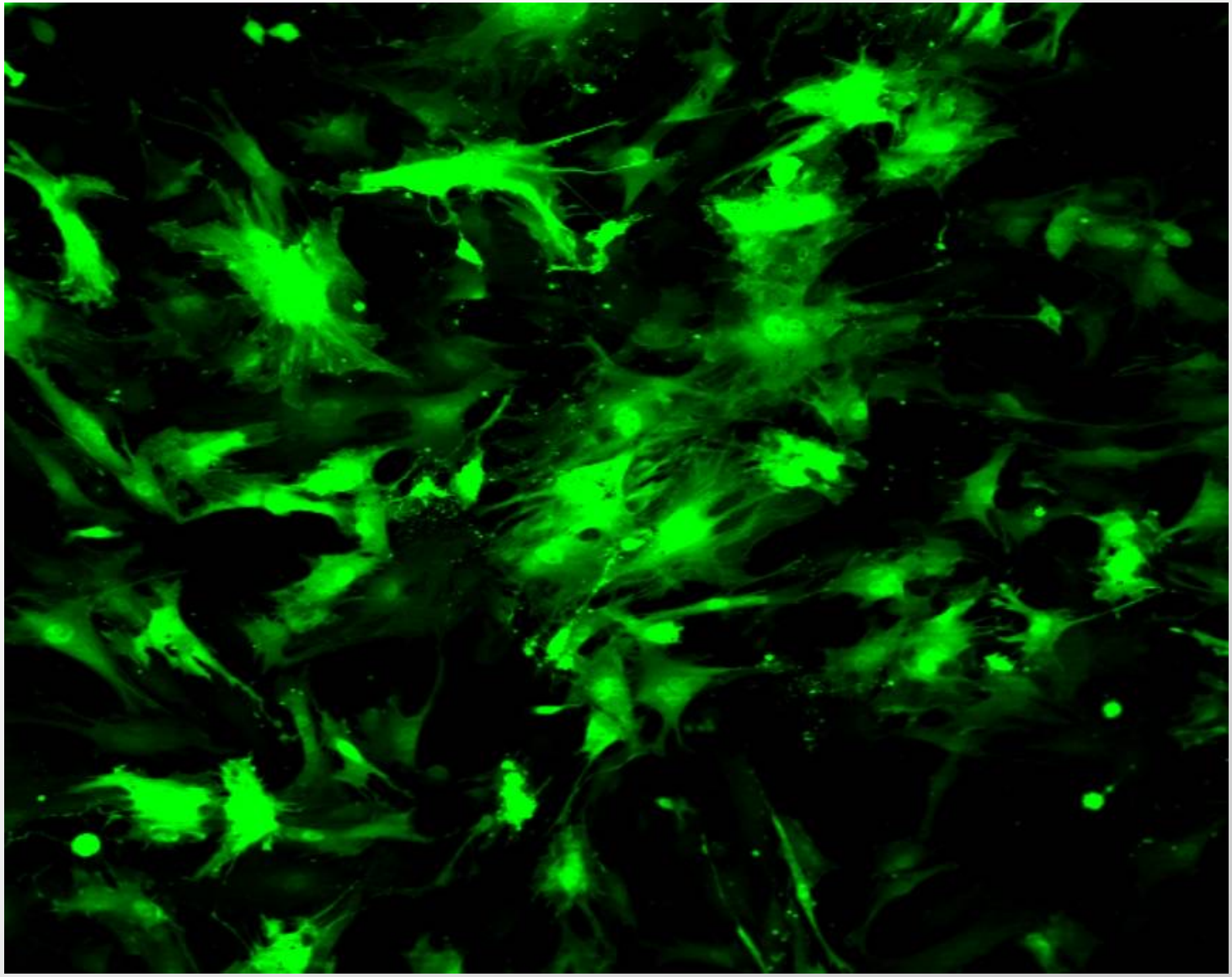
Produção de adenovírus recombinantes :



(Produzem E1Ae E1B)



Infecção de adenovírus recombinantes em células de camundongo:



Doença hereditária referente a reparo de DNA

Xeroderma pigmentosum (XP)

-rara (~1:200.000)

-fotossensibilidade

-alta incidência de câncer de pele.

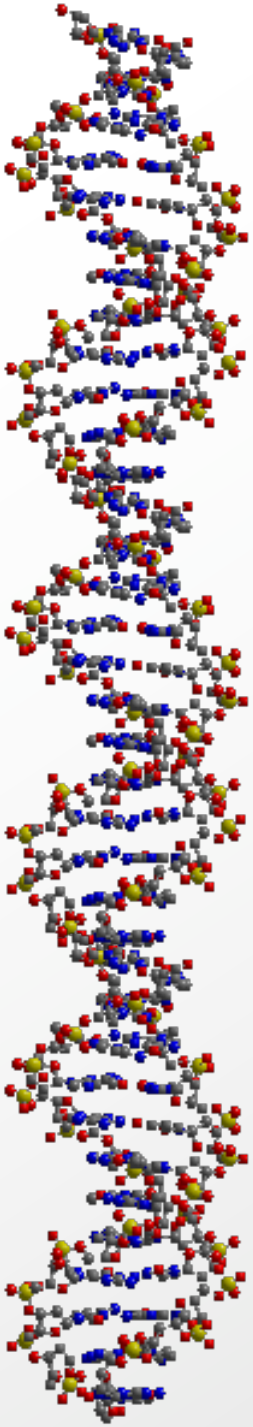
-anormalidades neurológicas.

-Vários genes envolvidos
(XPA to G and XPV)

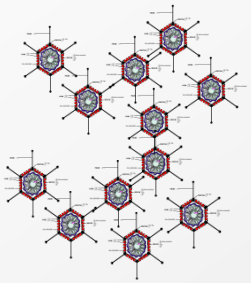
Síndrome XP nos ajudou a entender vários aspectos da Carcinogenesis e mesmo envelhecimento: será que podemos ajudá-los?

ABRAXP

ASSOCIAÇÃO BRASILEIRA DO XERODERMA PIGMENTOSO

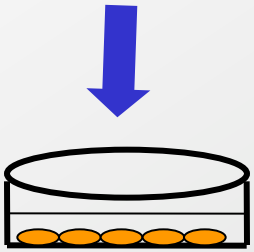


Vetores adenovirais: Desenho Experimental.



XPA adenovirus

Injeção subcutânea

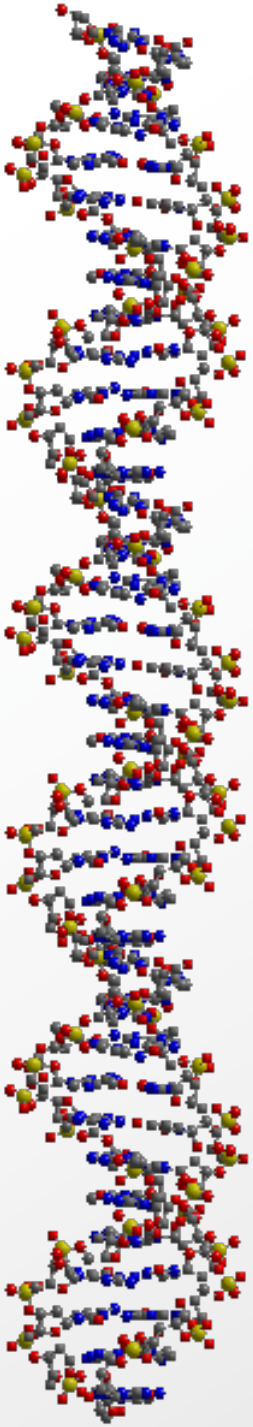


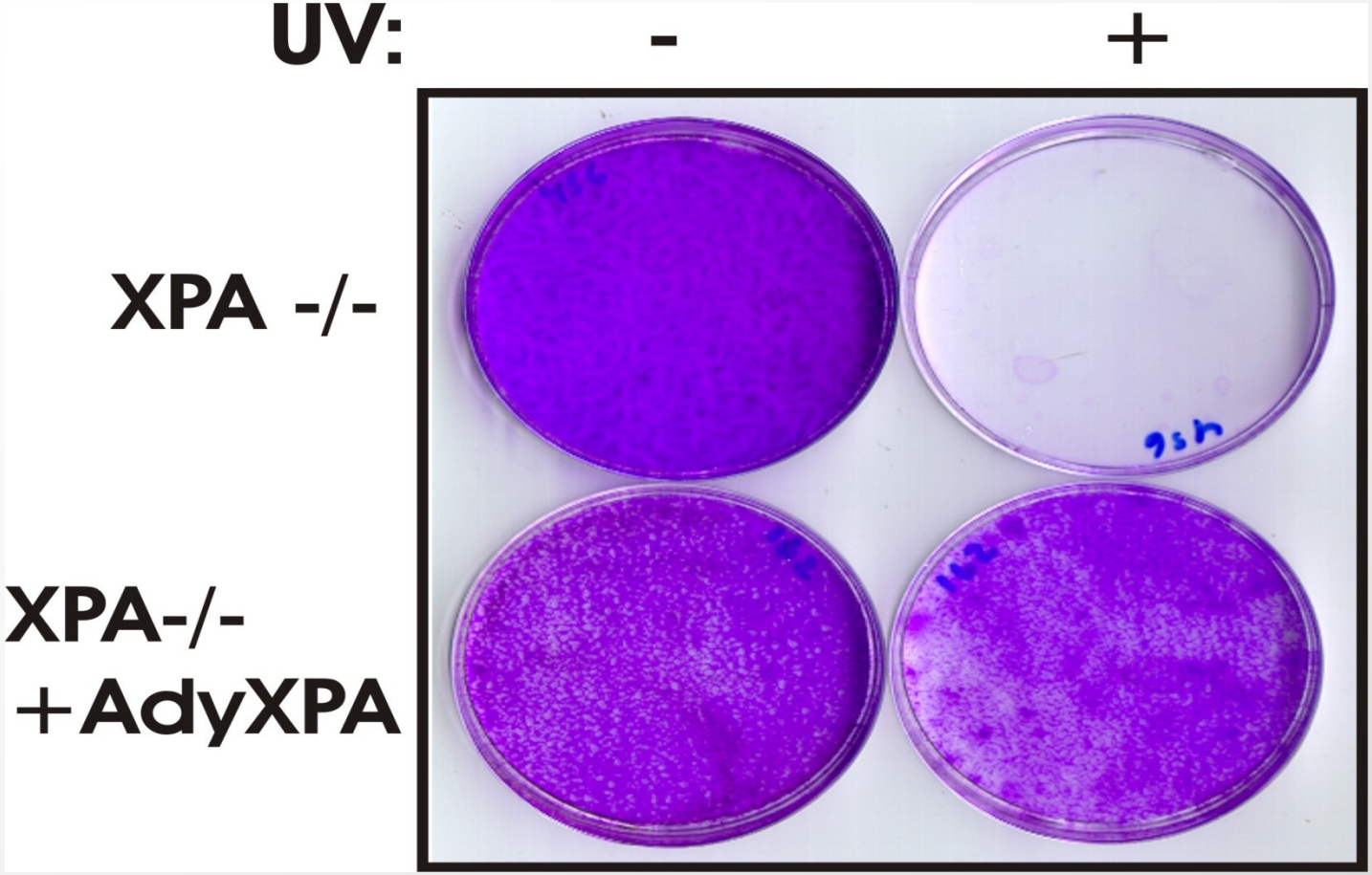
Células Xpa$^{-/-}$

Camundongo Xpa

- Expressão do Gene
  Fenótipo

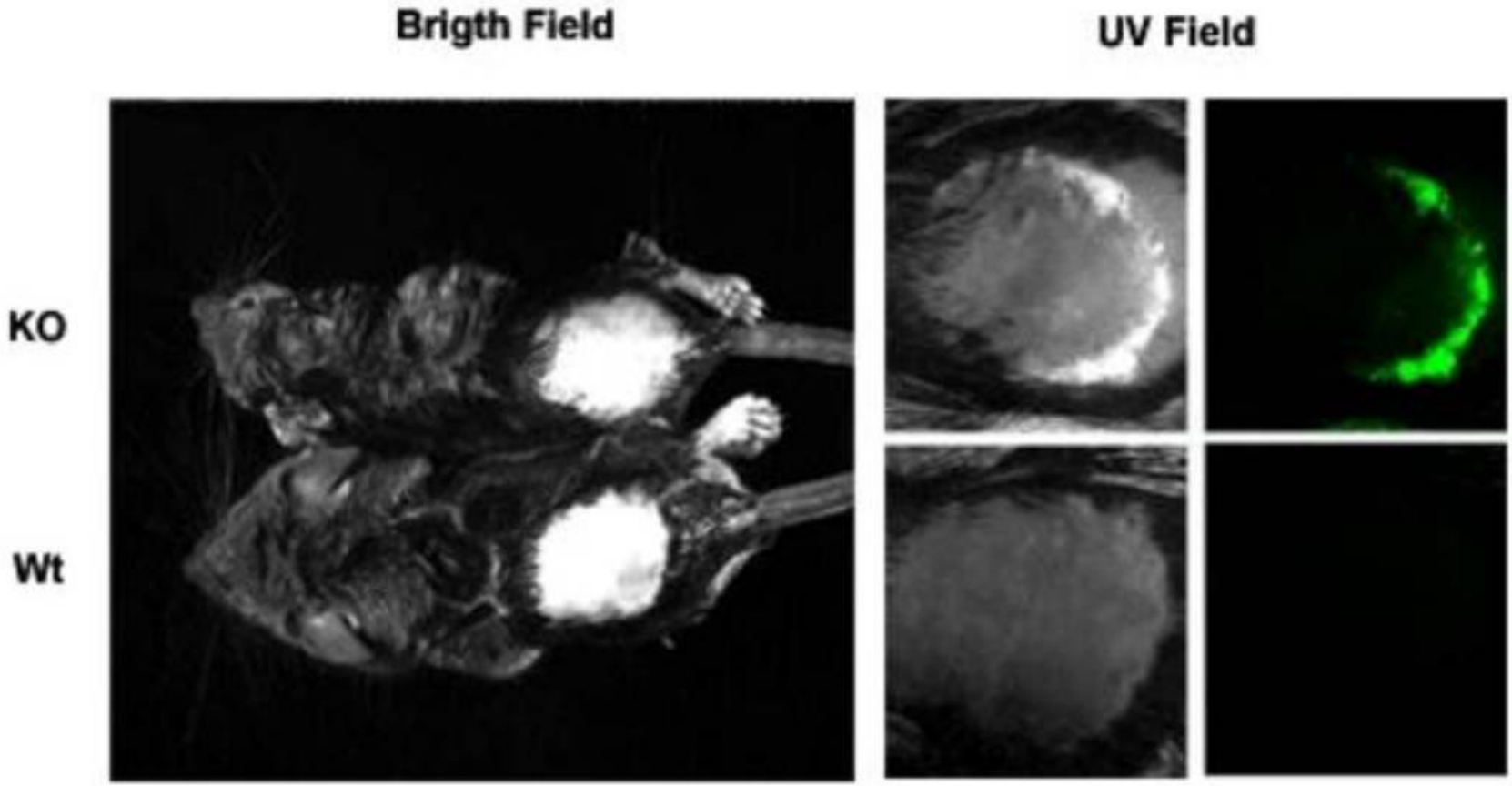
- Expressão gênica
- Sobrevivência UV
- Ensaios de reparo de DNA



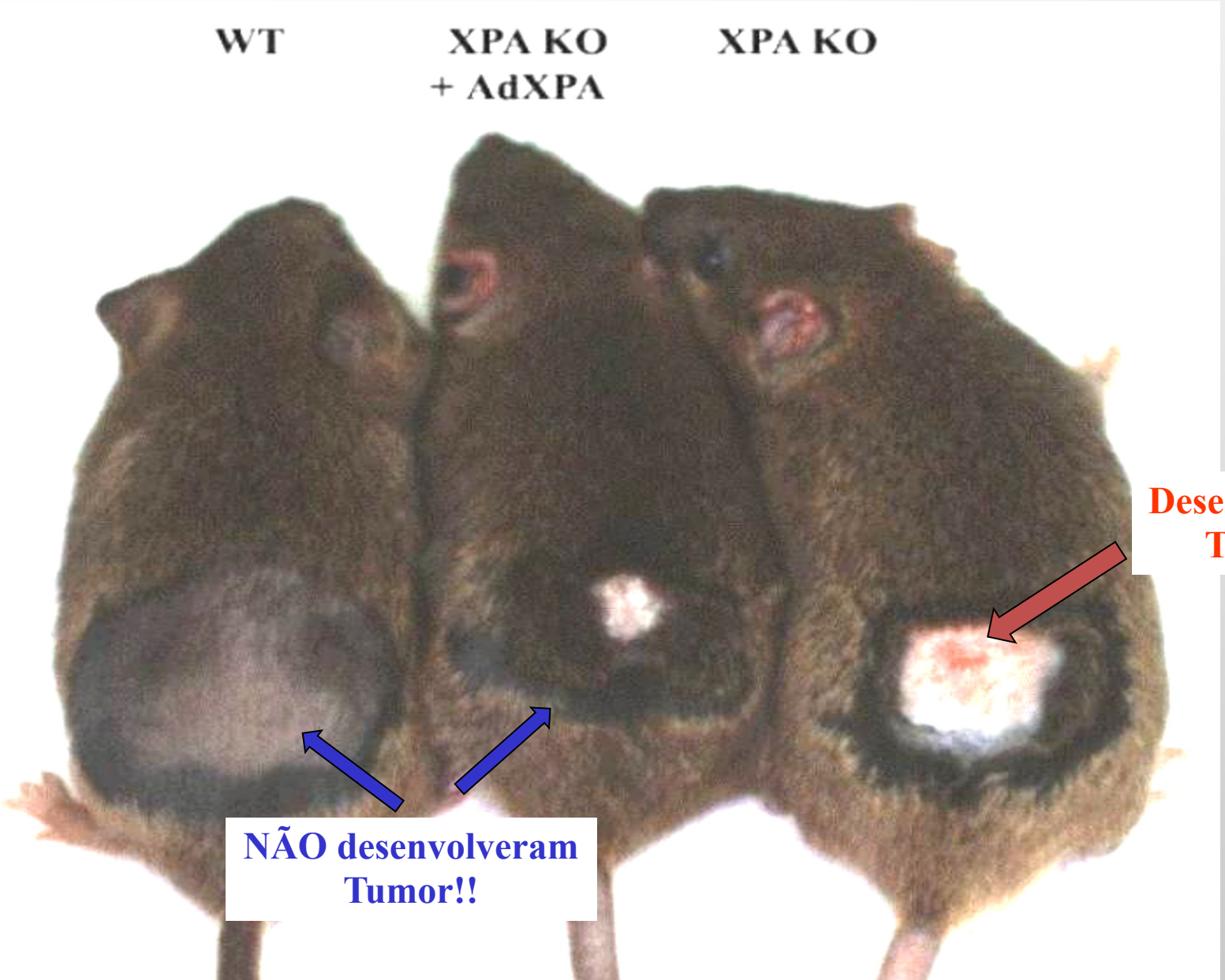


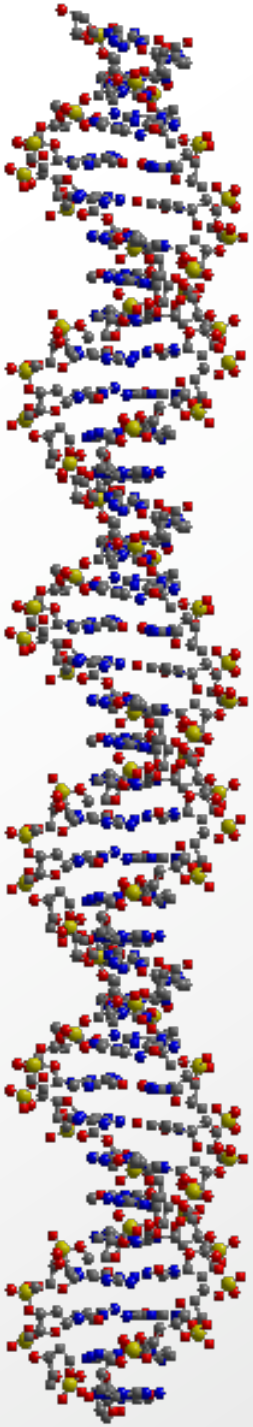
Recuperação da sobrevivência após UV, 2 meses após vírus

Injeção subcutânea!



3 semanas após a irradiação UV.





PERSPECTIVAS DESTE NOSSO TRABALHO

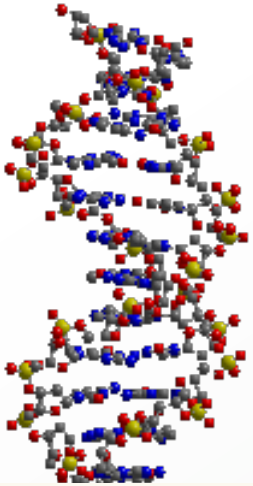
-Será que poderemos aplicar esses adenovírus direta-mente na pele de humanos?

-Quantas vezes? (e a reação imune contra o vírus?)

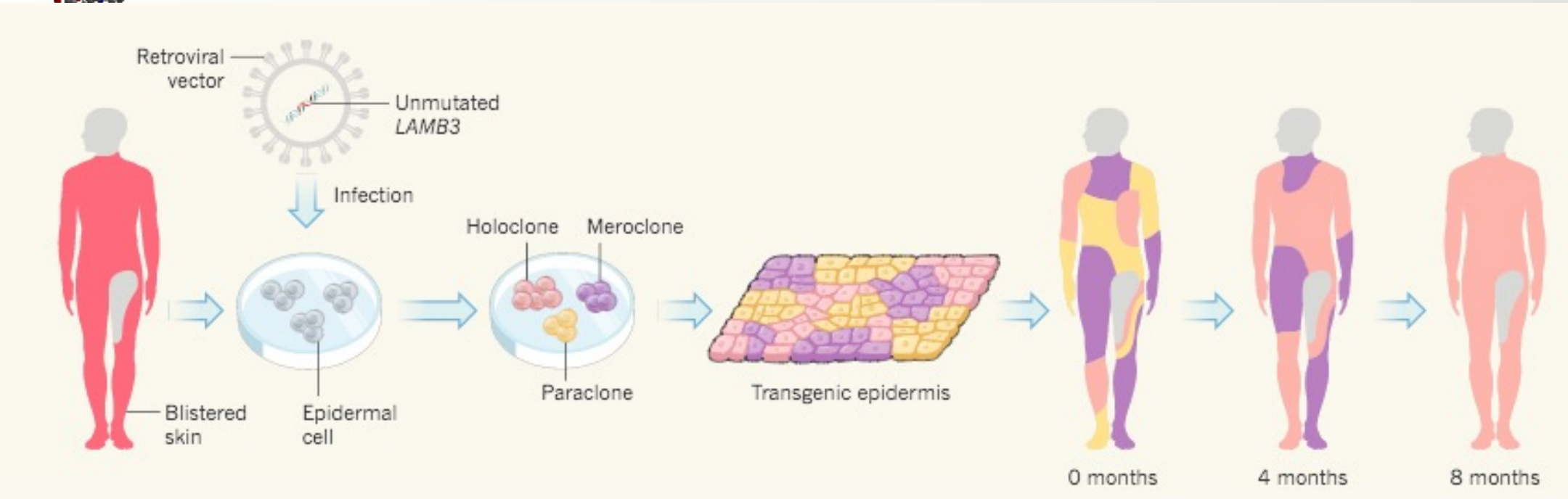
-De que vale uma terapia por apenas 2 meses?

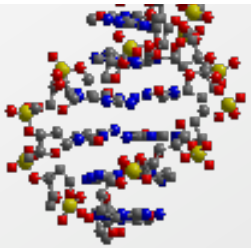
- Vale a pena mudar para um tipo de vírus que não induz tanta reação imune (vetor adeno-associado).

- uso de imunossupressores no momento da aplicação.



Podemos recuperar totalmente a pele terapia para epidermolysis bullosa – Publicado em 2017 na Nature!





Problemas com adenovirus

- Morte de um garoto de 18-19 anos!

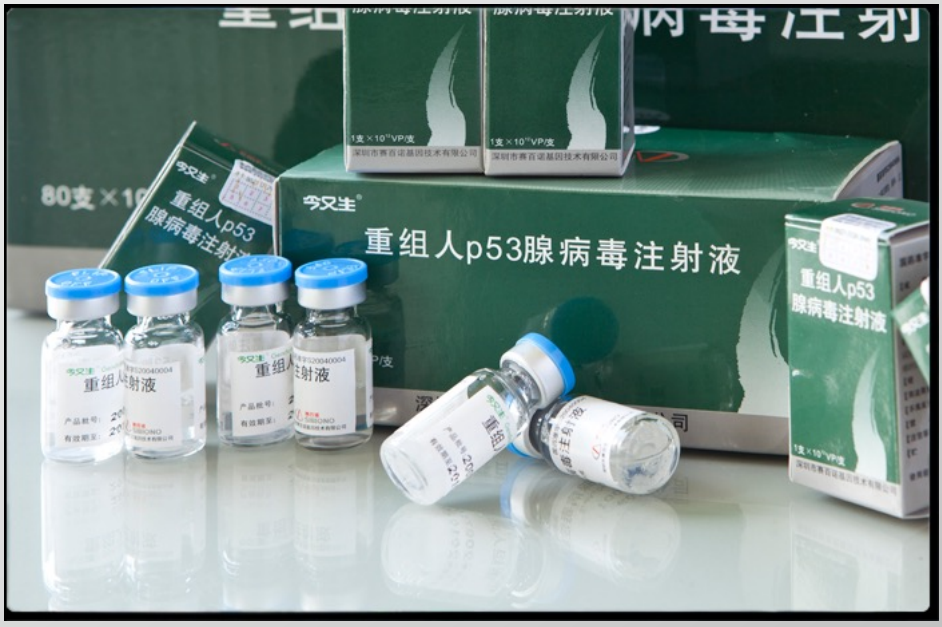
Jesse Gelsinger's death from a gene therapy clinical trial in 1999 raised many questions concerning the safety of experimental gene therapy treatments.

Gendicine:
o primeiro remédio de terapia gênica aprovado para uso clínico, Em 2004 na China!!!

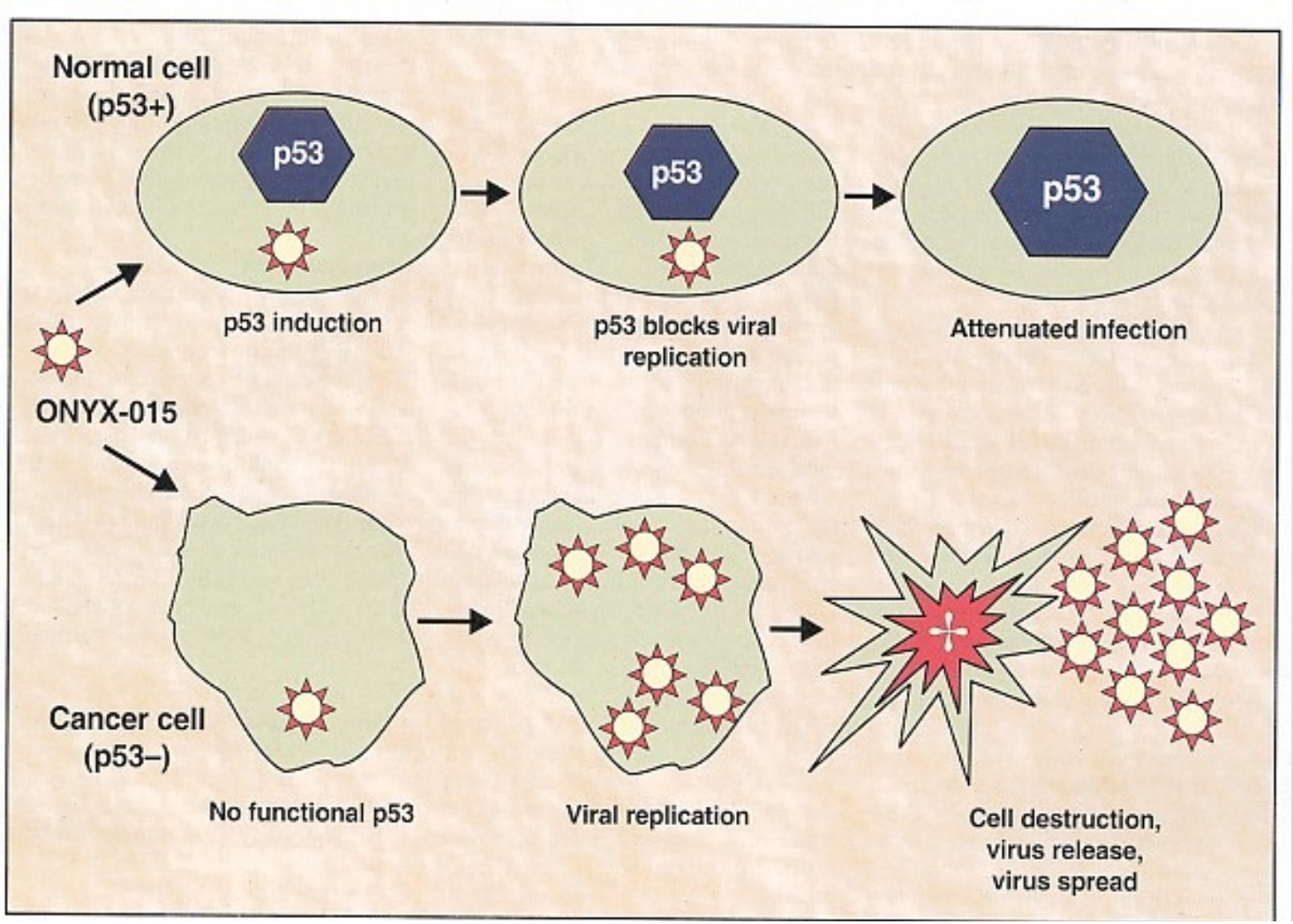
Gendicina propõe o uso combinado de radio ou quimioterapia e terapia gênica com Adenovírus –p53! (usado principalmente em cancer cabeça/pescoço).

Os estudos clínicos têm demonstrado um melhor prognóstico em pacientes tratados com a terapia combinada!

SiBiono claims dramatic improvements in patients treated with Gendicine after just two months (right)



Como funciona?
Direcionando e matando células tumorais p53 negativas!



Como é a terapia: o p53 ajuda no processo de morte da célula tumoral, aumentando a eficiência do tratamento.

GENDICINE- fase II/III clinical protocol!

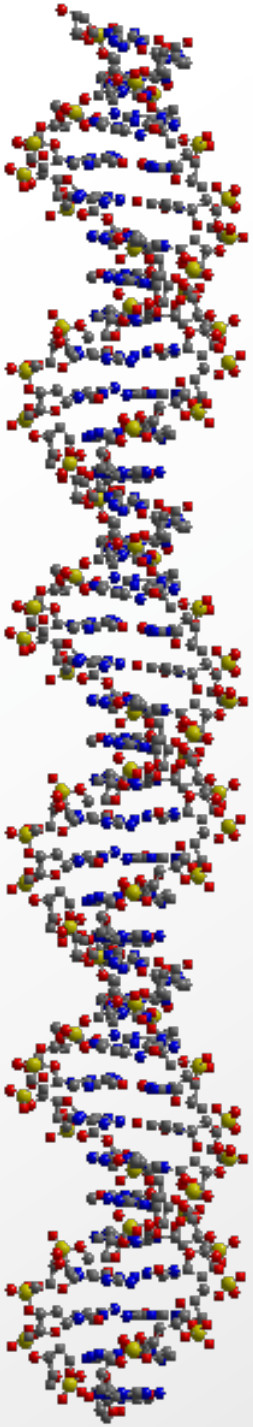
Group	No.
GTRT	63
RT	72

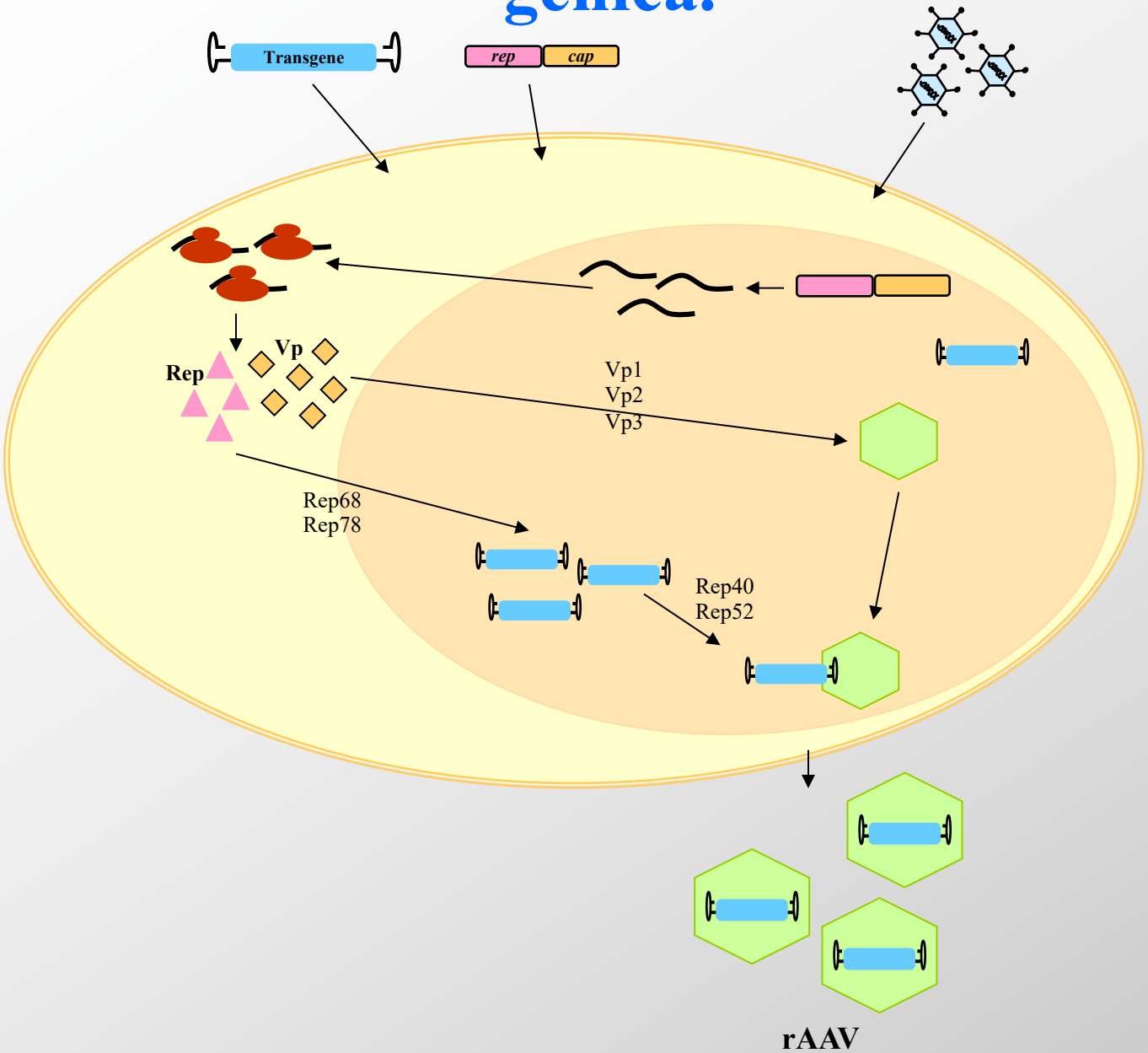
12 weeks (confirmation)				
No.	CR	PR	SD	PD
56	36 (64%)	16 (29%)	4 (7%)	0 (0%)
63	12 (19%)	38 (60%)	13 (21%)	0 (0%)

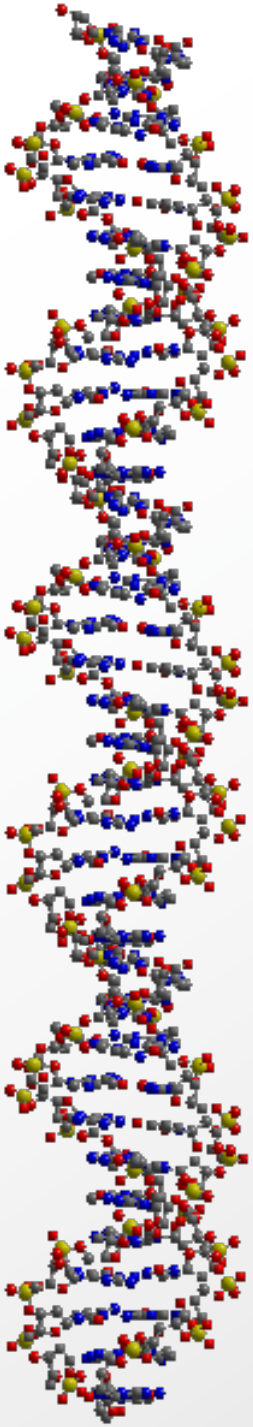
No número de pacientes
CR: Complete remission
PR: Partial remission

GENDICINE- prolongando a vida e melhorando qualidade de vida de pacientes!

Uso de vetores adeno-associado para terapia gênica.







Vantagens dos vetores Adeno-associados

- Fácil produção.

- Não patogênicos em humanos.

-Longo tempo de expressão in vivo (pouca estimulação do sistema imune)

Corrigindo distrofia muscular

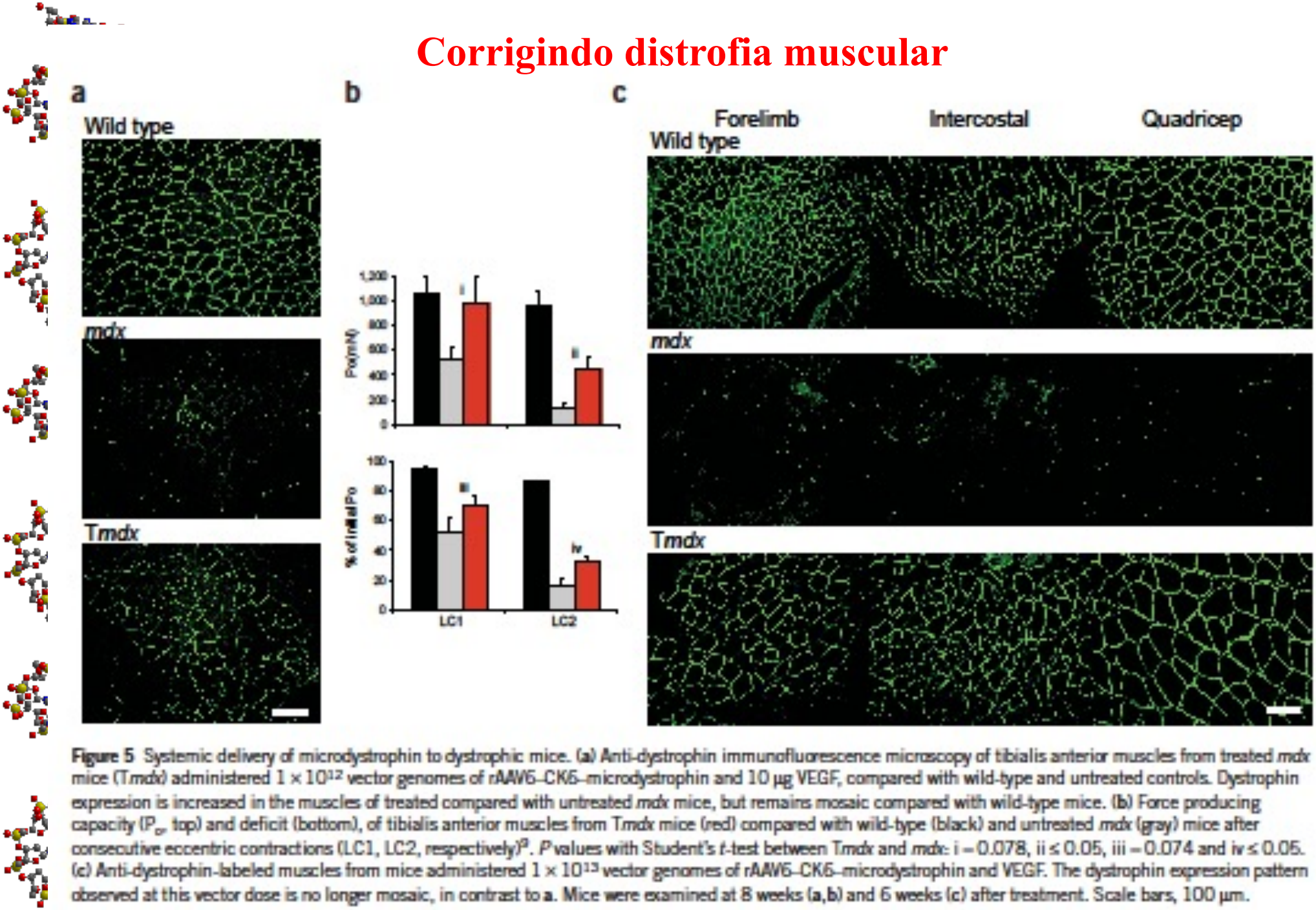


Figure 5 Systemic delivery of microdystrophin to dystrophic mice. (**a**) Anti-dystrophin immunofluorescence microscopy of tibialis anterior muscles from treated *mdx* mice (T*mdx*) administered 1×10^{12} vector genomes of rAAV6–CK6–microdystrophin and 10 μg VEGF, compared with wild-type and untreated controls. Dystrophin expression is increased in the muscles of treated compared with untreated *mdx* mice, but remains mosaic compared with wild-type mice. (**b**) Force producing capacity (P_o, top) and deficit (bottom), of tibialis anterior muscles from T*mdx* mice (red) compared with wild-type (black) and untreated *mdx* (gray) mice after consecutive eccentric contractions (LC1, LC2, respectively)[9]. *P* values with Student's *t*-test between T*mdx* and *mdx*: i = 0.078, ii ≤ 0.05, iii = 0.074 and iv ≤ 0.05. (**c**) Anti-dystrophin-labeled muscles from mice administered 1×10^{13} vector genomes of rAAV6–CK6–microdystrophin and VEGF. The dystrophin expression pattern observed at this vector dose is no longer mosaic, in contrast to **a**. Mice were examined at 8 weeks (**a**,**b**) and 6 weeks (**c**) after treatment. Scale bars, 100 μm.

GLYBERA:
o primeiro remédio de terapia gênica aprovado no mundo ocidental!!!

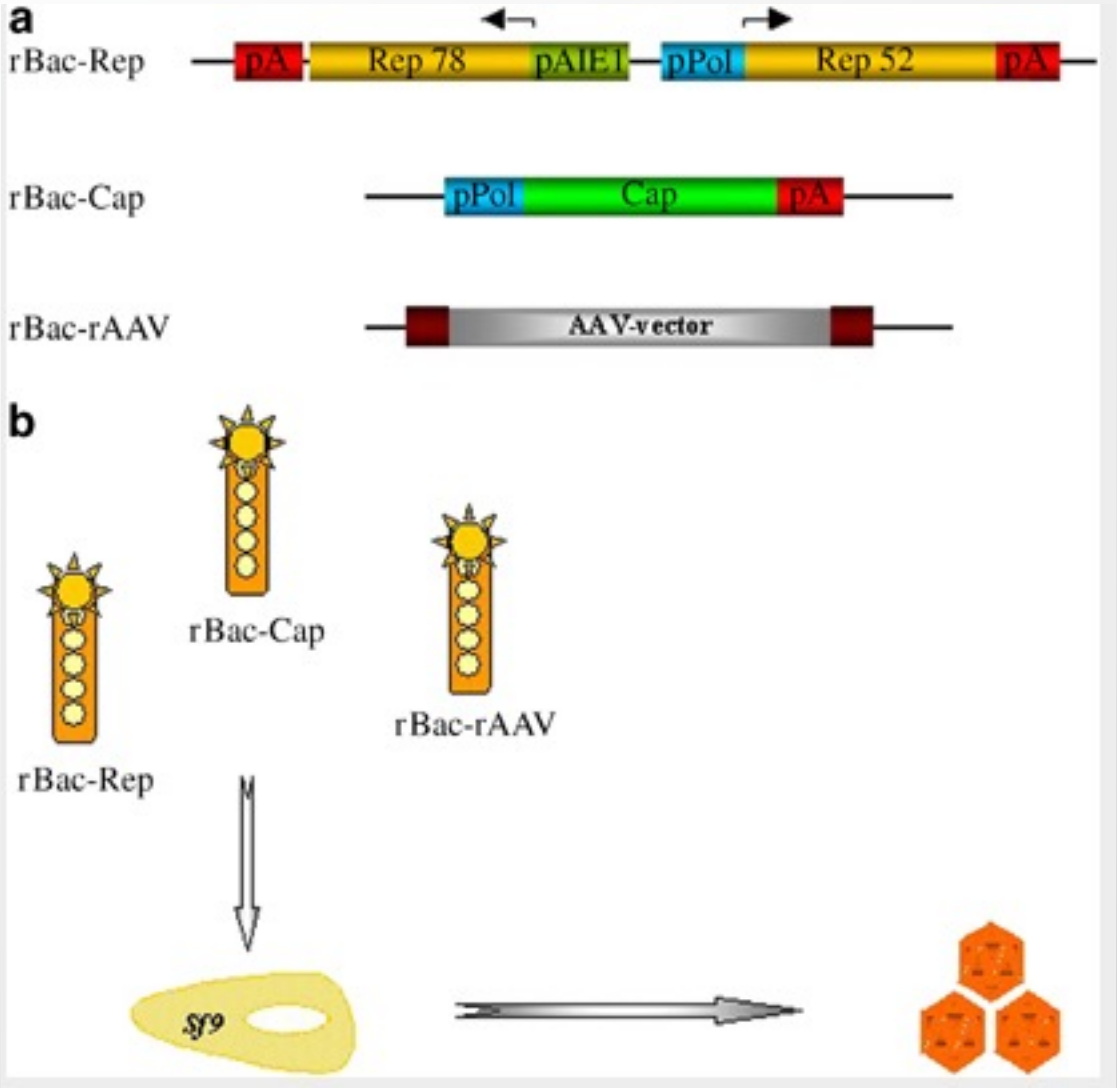
Na cura de "lipoprotein lipase deficiency" (LPLD)!!

A ausência dessa lipase (LPL) causa aumento de gordura no sangue, causando episódios de pancreatite aguda.

Como é a terapia: rAAV carregando o gene LPL, sendo aplicado (série de injeções) no músculo da perna..... Pacientes têm melhoras rápidas no nível de gordura e menor frequencia de pancreatite.

http://www.uniqure.com/flash/gene.swf

GLYBERA:
Como produzir vírus em alta escala:



Outros produtos da UNIQURE:

Hemofilia A e B- fases 1 e 2

Porfiria aguda intermitente

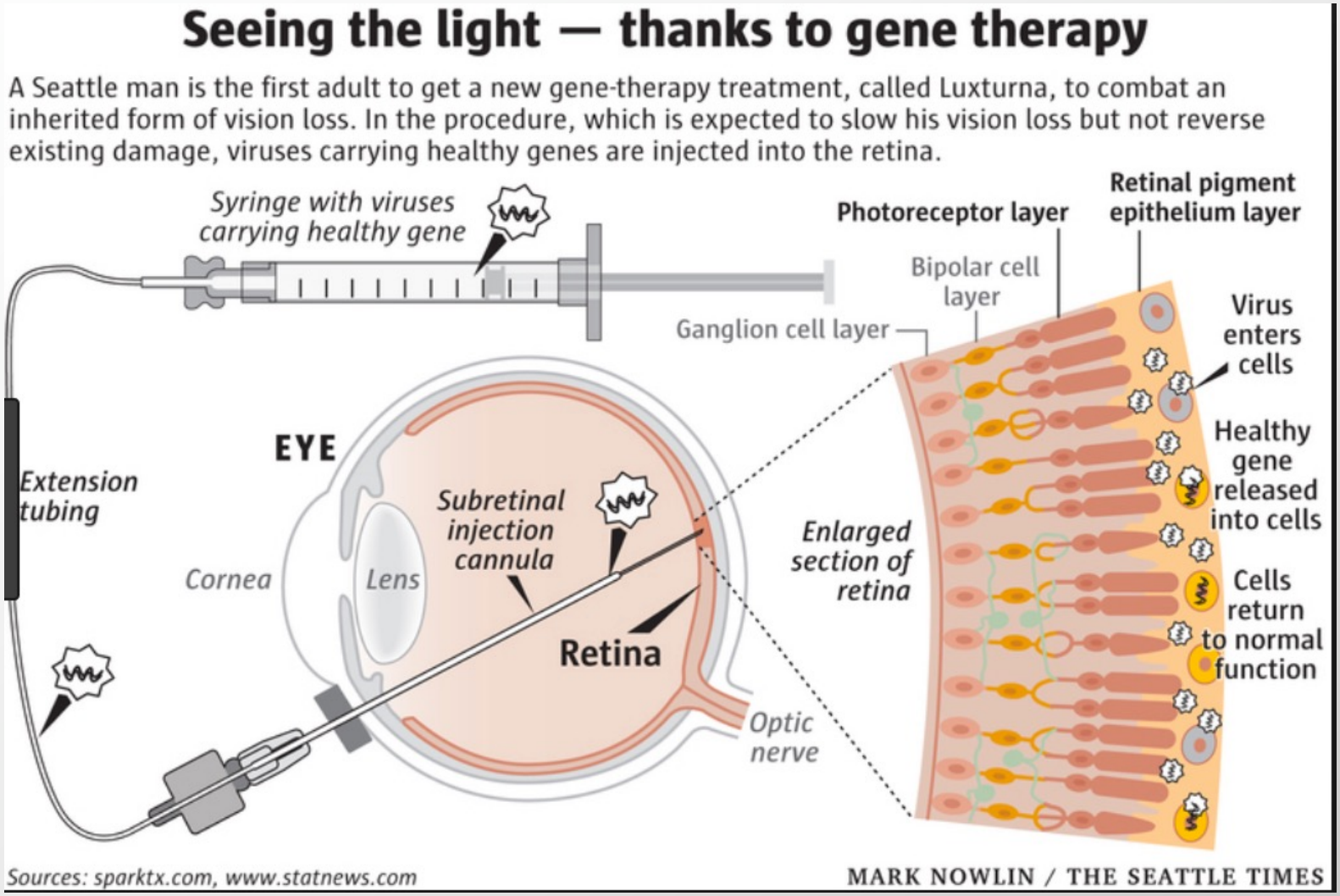
Doença de Parkinson

Doença de Huntington

Insuficiência cardíaca (Congestive Heart Failure)
(cardiac deficiency of the calcium-binding protein S100A1, a master regulator of myocardial function)

http://www.uniqure.com/

Luxturna (Spark Therapeutics):
Para "*RPE65* mutation-associated retinal dystrophy"
Primeiro produto aprovado pelo FDA!!



O remédio “mais caro do mundo”
Atrofia muscular espinhal (gene SMN1)

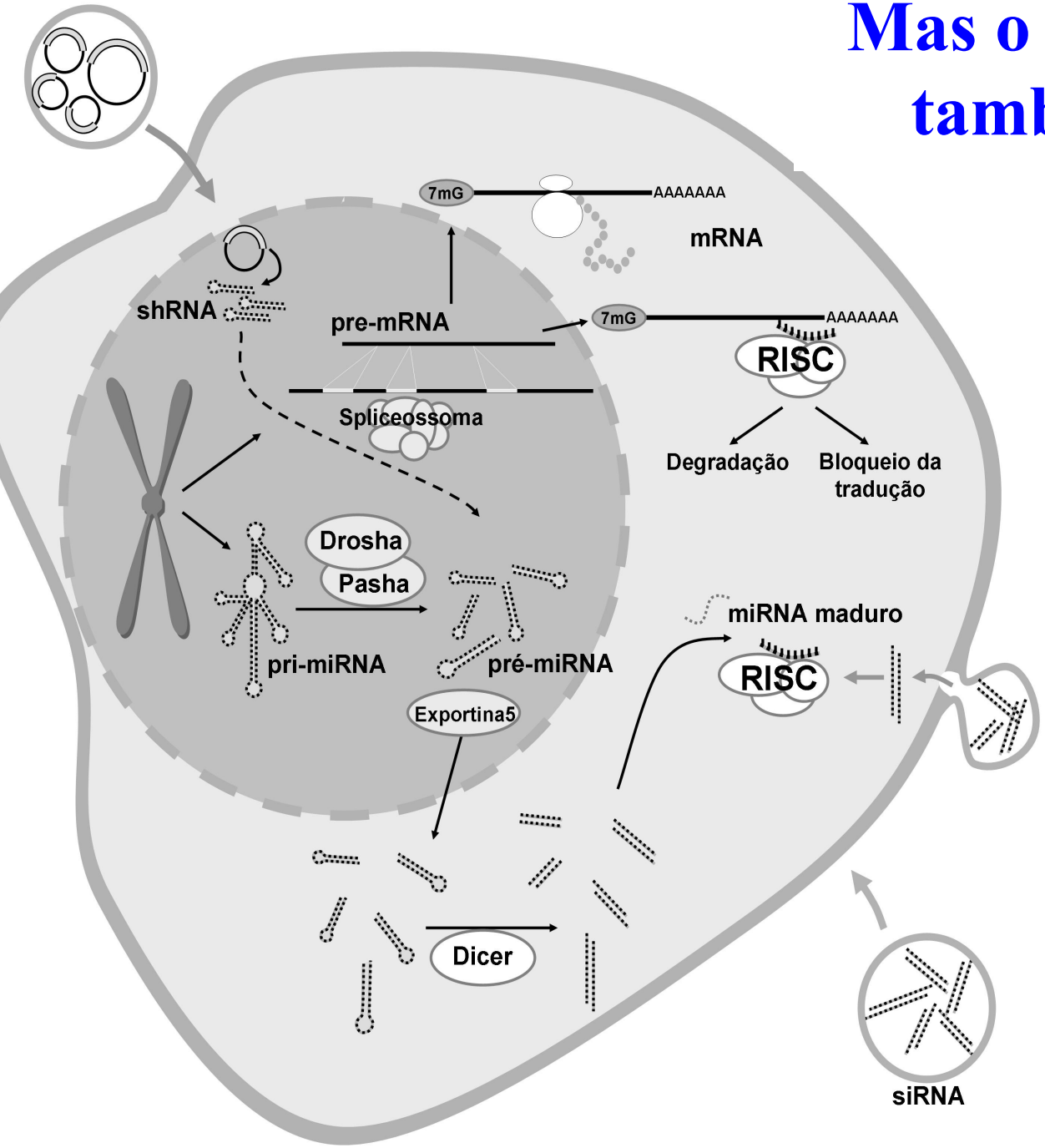
Mas casos fatais associado ao tratamento estão Gerando preocupação de segurança.

A Novartis Biociências S.A., Brasil, conforme comunicado à ANVISA, gostaria de informá-lo sobre o seguinte:

- **O objetivo desta carta é informá-lo sobre informações importantes de segurança para ZOLGENSMA® (onasemnogeno abeparvoveque) para infusão intravenosa.**
- **Recentemente, foram relatados dois casos fatais de insuficiência hepática aguda associados ao ZOLGENSMA®.**

We report a fatal case of systemic thrombotic microangiopathy (TMA) predisposition in the *complement factor I* gene. Other cases of TMA have recently been reported after onasemnogene abeparvovec and after AAV9 minidystrophin therapy in Duchenne muscular dystrophy. The risk-benefit ratio of this therapy must therefore be assessed. Early recognition of TMA and targeted immunotherapy are fundamental to ensure the safety of patients treated with AAV gene therapies.

Mas o duplex de RNA pode ser também externo da célula!



O uso de RNAi no silenciamento gênico

Mello, SS ; Andrade, L. N. d. S. ; MENCK CF. Biologia Molecular e Evolução. 2 ed. Ribeirão Preto, SP, Brasil: Holos/SBG, 2012

É possível usar na clínica?

Ciência *In Foco*

Microbiologia in foco, 2007

RNA INTERFERÊNCIA

A nova corrida do ouro.

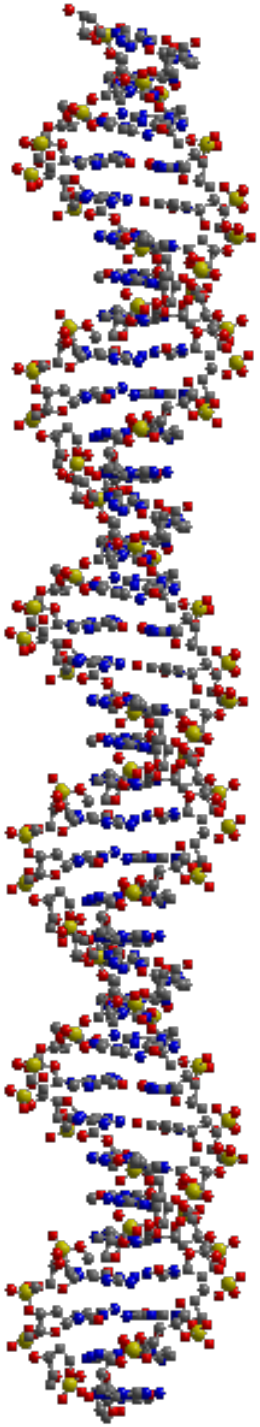
Carlos F. M. Menck
Depto. de Microbiologia,
Professor Titular do Instituto de Ciências Biomédicas
Av. Prof. Lineu Prestes 1374 - CEP 05508-900
São Paulo- SP - Brasil

SiRNA: inovação tecnológica

-Fácil design (basta saber a sequencia do gene!)

-Síntese simplificada (oligonucleotídeos 21-27 bp)

MENCK, Carlos Frederico Martins. RNA interferência: a nova corrida do ouro. ***Microbiologia in Foco***, São Paulo, v. 1, n. 1, p. 17-21, 2007.



Mas o desafio de uso clínico de siRNA já começou:

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

Adams, D. et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N. Engl. J. Med. 379, 11–21 (2018).

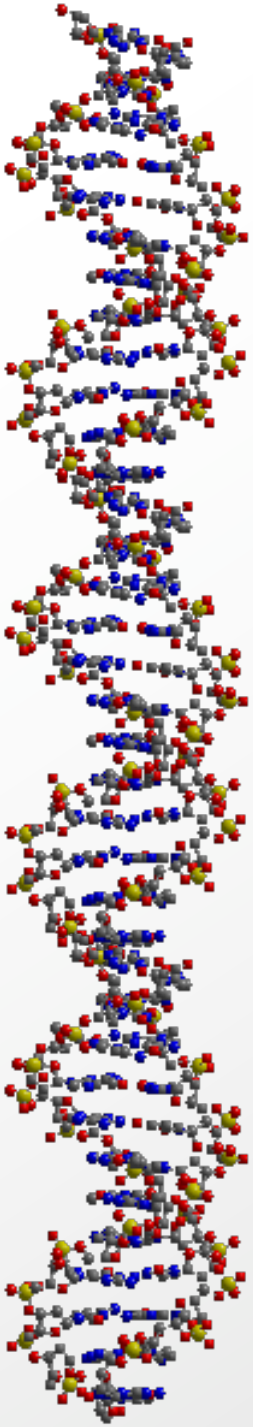
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2020 VOL. 382 NO. 24

Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria

M. Balwani, E. Sardh, P. Ventura, P.A. Peiró, D.C. Rees, U. Stölzel, D.M. Bissell, H.L. Bonkovsky, J. Windyga, K.E. Anderson, C. Parker, S.M. Silver, S.B. Keel, J.-D. Wang, P.E. Stein, P. Harper, D. Vassiliou, B. Wang, J. Phillips, A. Ivanova, J.G. Langendonk, R. Kauppinen, E. Minder, Y. Horie, C. Penz, J. Chen, S. Liu, J.J. Ko, M.T. Sweetser, P. Garg, A. Vaishnaw, J.B. Kim, A.R. Simon, and L. Gouya, for the ENVISION Investigators*

Balwani, M. *et al.* Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N. Engl. J. Med.* **382**, 2289–2301 (2020).



Gene Therapy-based drugs in the market

Imlygic™
Melanoma
Amgen Inc.
Europe and USA

Strimvelis™
Bubble Boy Syndrome
GlaxoSmithKline Plc.
Europe

Glybera™
Lipoprotein Lipase Deficiency
UniQure Inc.
Europe

Rexin-G™
Pancreatic Cancer
Epeius Biotechnologies Corp
Philippines

Gendicine™
Head and Neck Cancer
Shenzhen SiBiono GeneTech
China

Neovasculgen™
Peripheral Artery Diseases
Human Stem Cells Institute
Russia

Kymriah™
Lymphoblastic Leukemia
Novartis International AG
USA

Luxturna™
Inherited Blind Diseases
Spark Therapeutic Inc.
USA

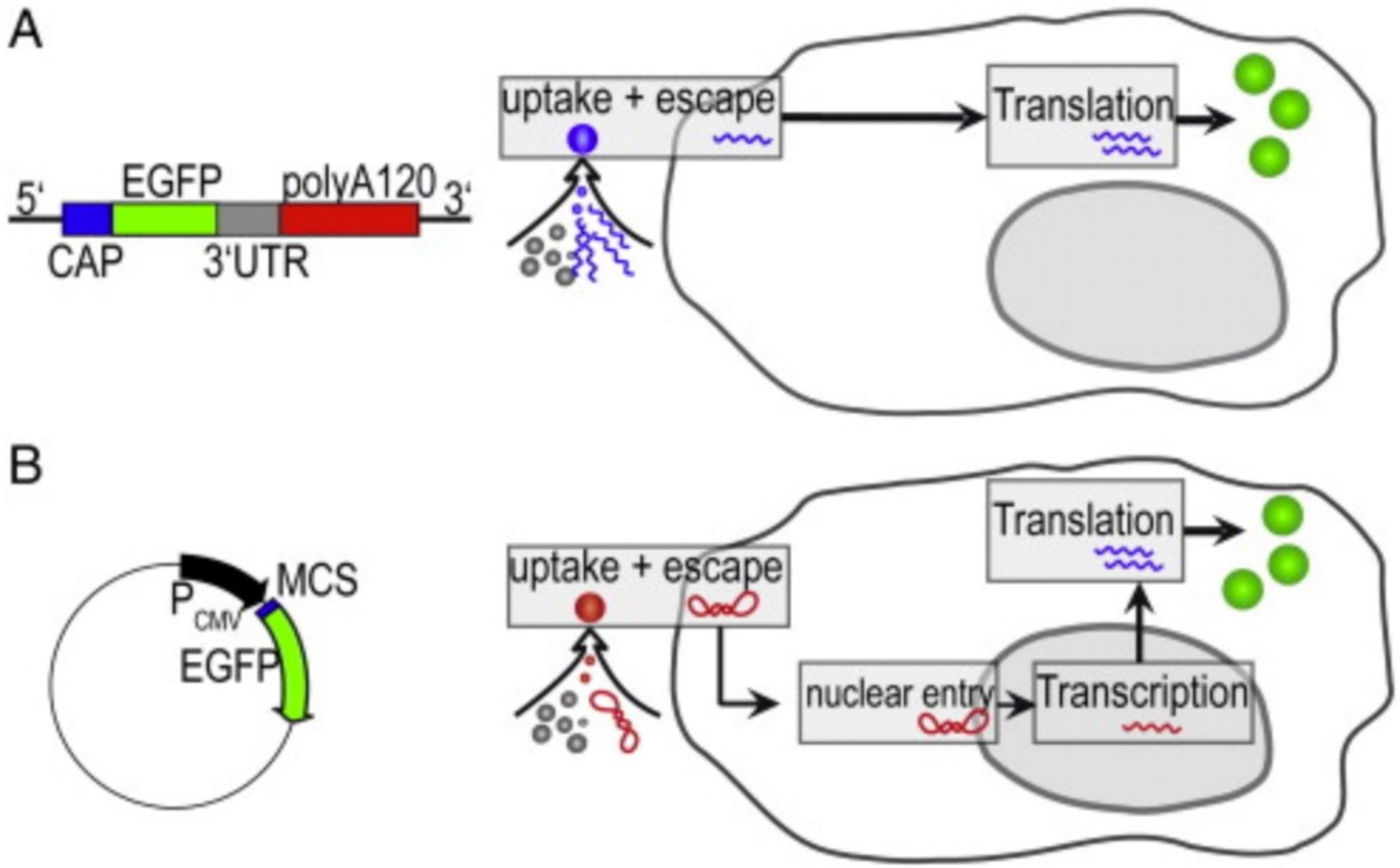
Yescarta™
Non-Hodgkin's Lymphoma
Gilead
USA

Oncorine™
Nasopharyngeal carcinoma
Shanghai Sunway Biotech Co.
China

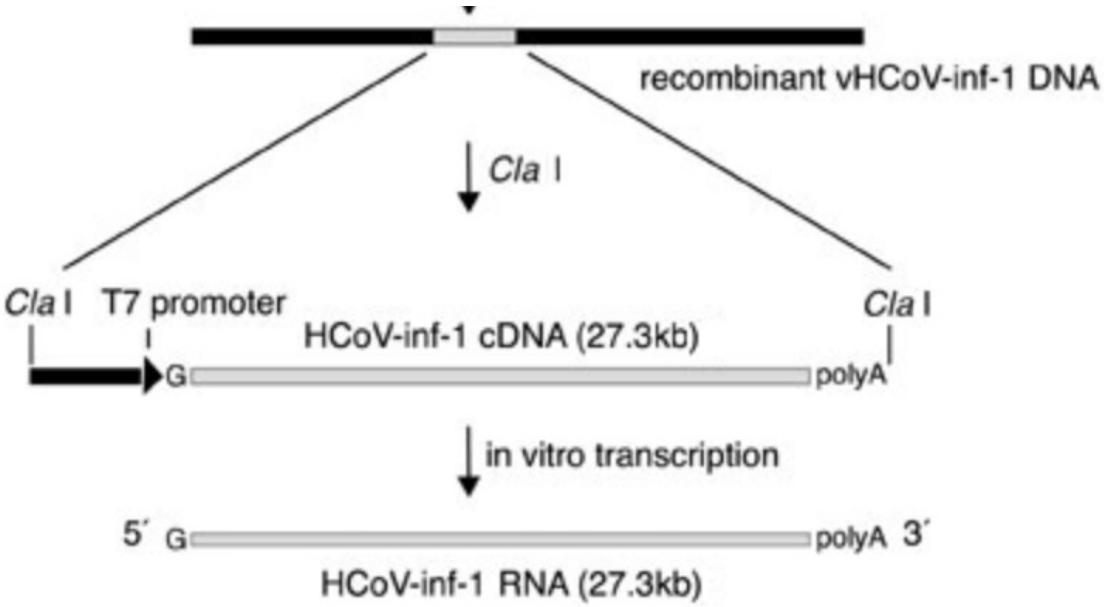
Spinraza®
Spinal Muscular Atrophy
Biogen Inc.
USA, Canada, Japan, Brasil

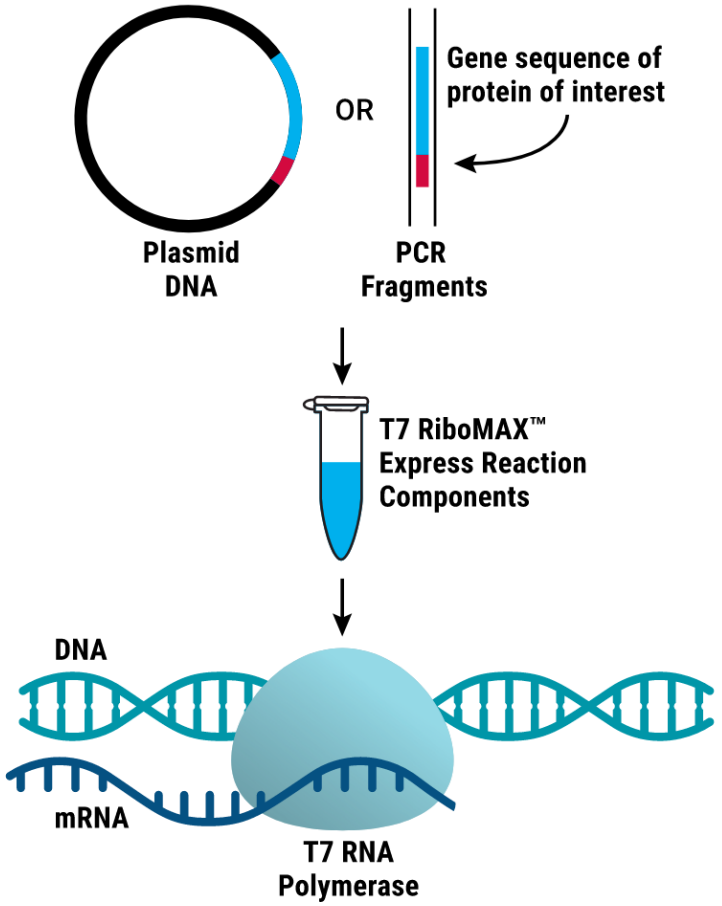
Zalmoxis
Leukemia
MolMed S.p.A
Europe

A revolução da vacina de mRNA.... Mas não é só Vacina!! (Dr. Katalin Karikó)

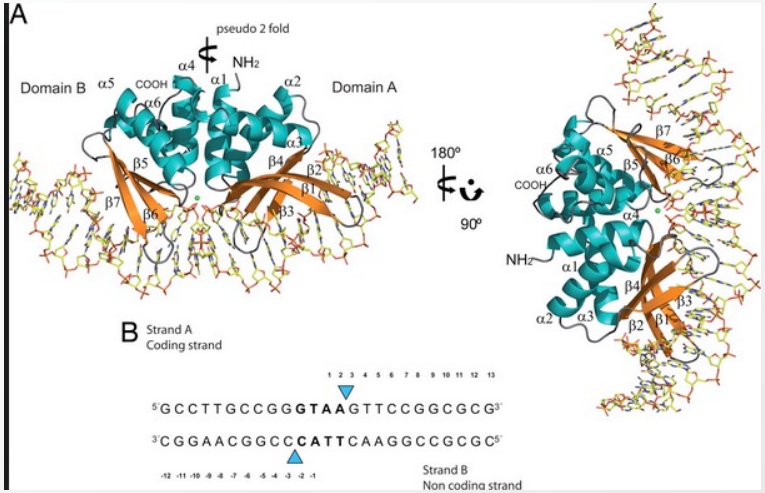


Síntese in vitro de mRNA- clonagem em vetor específico com promotor T7, poli A e depois capear! Síntese com pseudo-uridine!!!

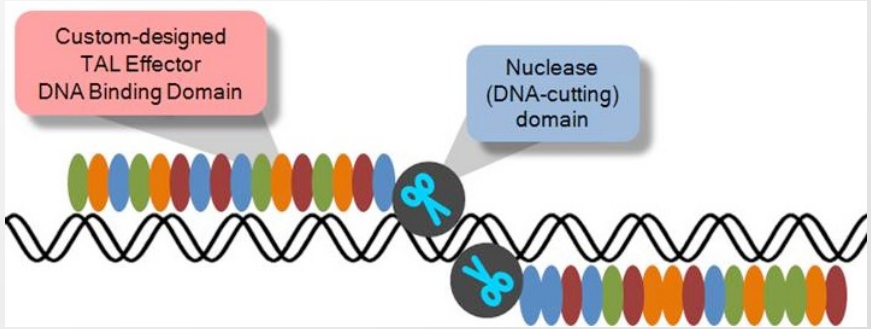




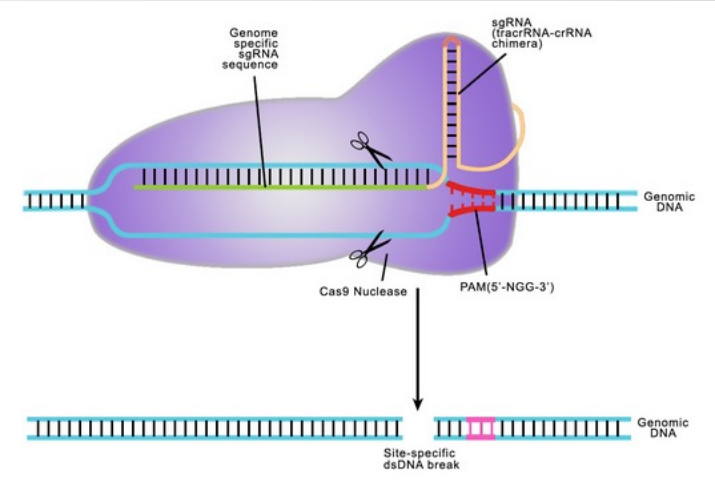
Meganucleases



Talen Enzymes



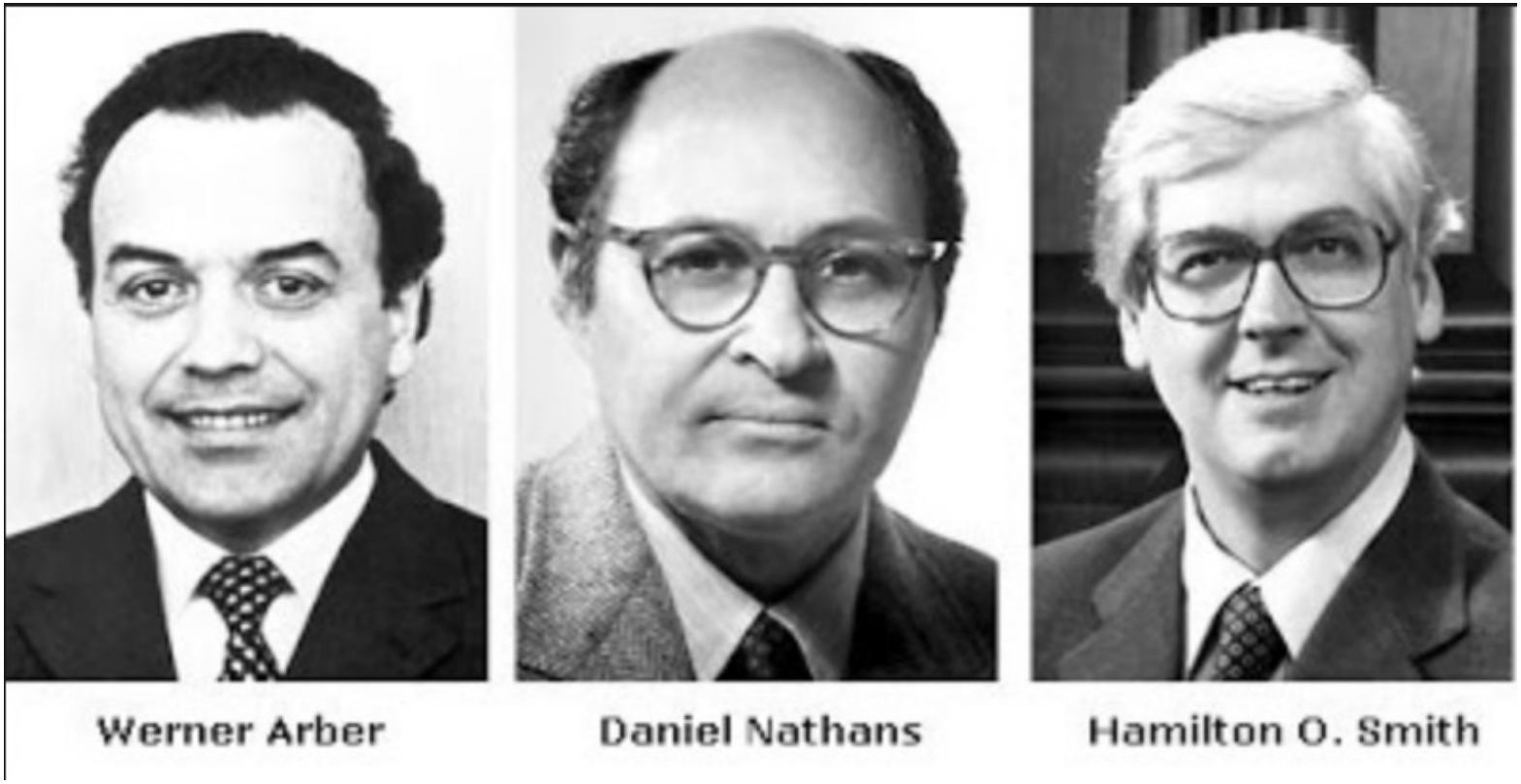
CRISPR/Cas9



A descoberta das enzimas de Restrição na década de ’60 e publicado em 1971!

Defesa de bactérias a bacteriófagos!

O Início da Engenharia Genética!

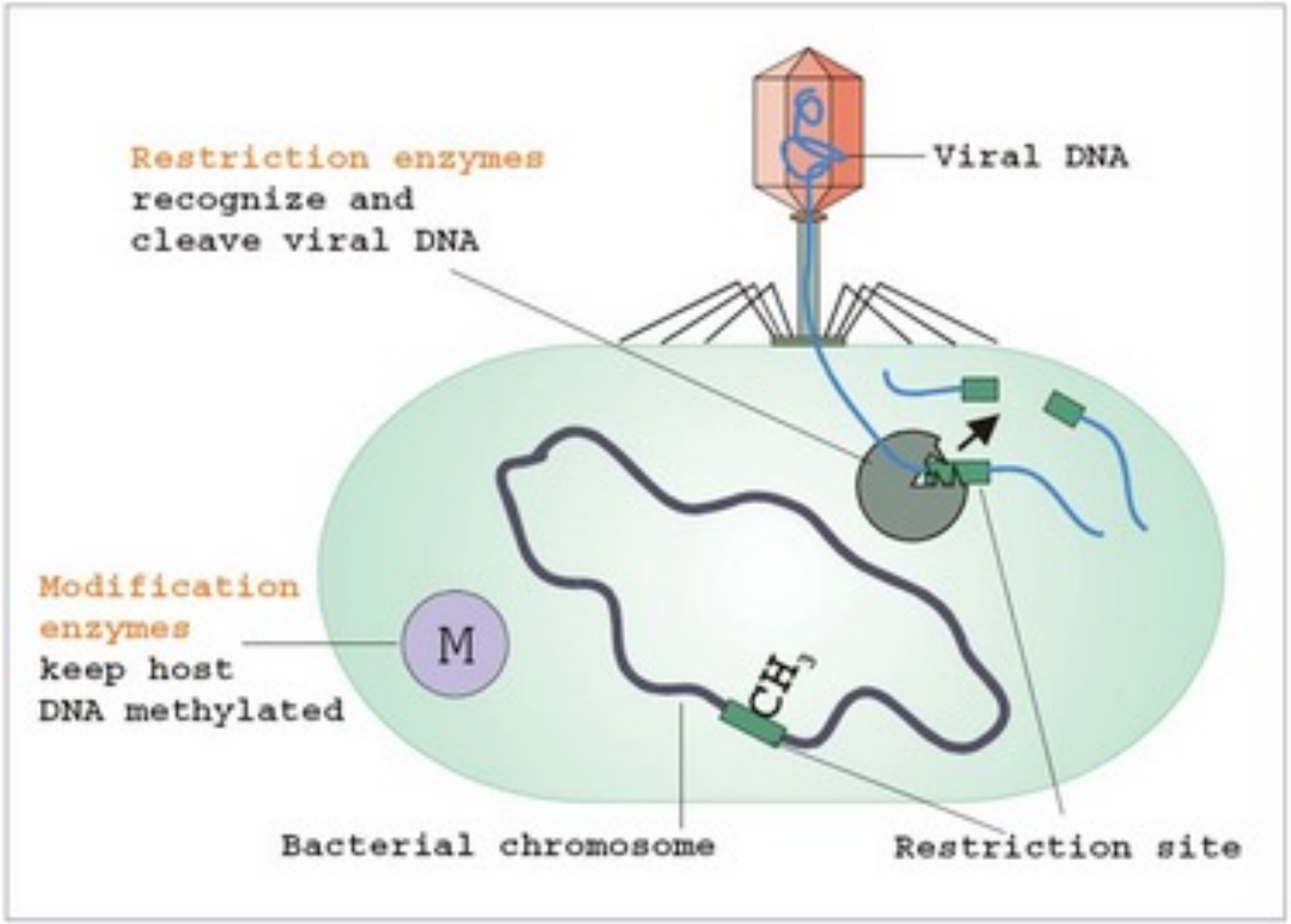


Prêmio Nobel de 1978

Defesa de bactérias a bacteriófagos!

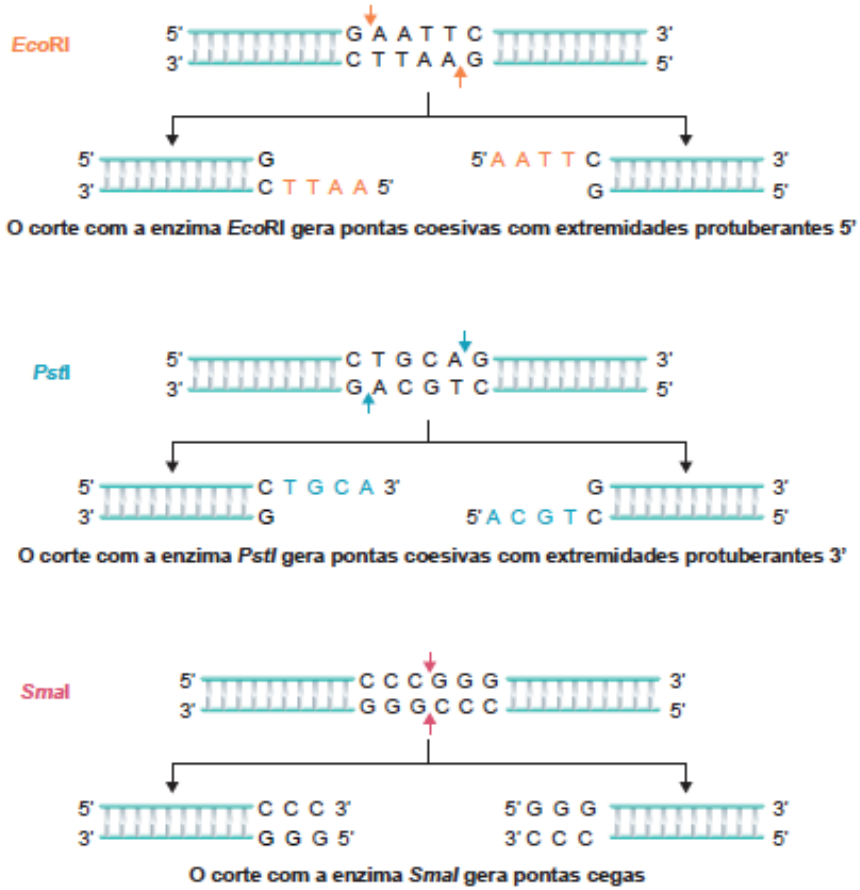
Restriction Enzymes

Bacterial defense against viral infection
by restriction-modification complexes



• Início da Engenharia Genética!

• corta

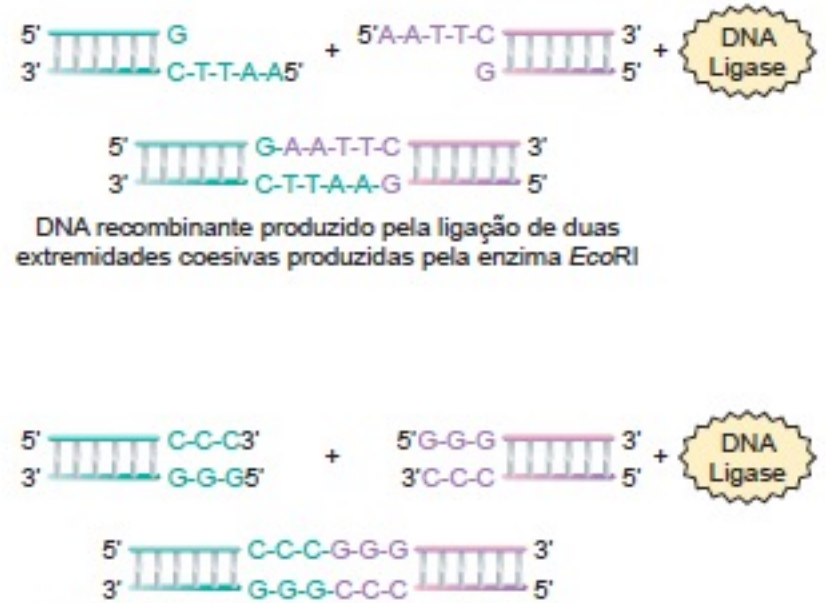


O corte com a enzima *EcoRI* gera pontas coesivas com extremidades protuberantes 5'

O corte com a enzima *PstI* gera pontas coesivas com extremidades protuberantes 3'

O corte com a enzima *SmaI* gera pontas cegas

liga

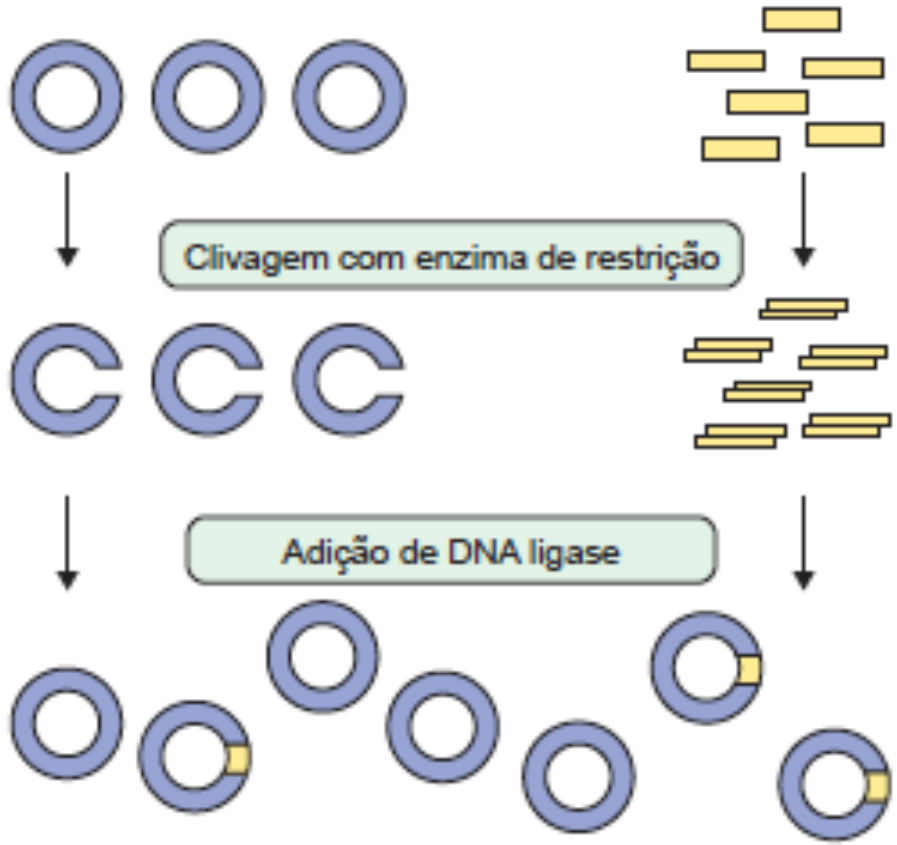


DNA recombinante produzido pela ligação de duas extremidades coesivas produzidas pela enzima *EcoRI*

DNA recombinante produzido pela ligação de duas extremidades cegas produzidas pela enzima *SmaI*

Livro GMB: dos Genes aos Genomas cap. 11

- **Início da Engenharia Genética!**
  - **Plasmídeos recombinantes**



Livro GMB: dos Genes aos Genomas cap. 11

A História se repete 40 anos depois!

Nomeou CRISPR e identificou que Essas regiões eram parte de um sistema De defesa contra fagos!

Francisco Mojica Univ de Alicante Espanha 2005

J Mol Evol (2005) 60:174–182
DOI: 10.1007/s00239-004-0046-3

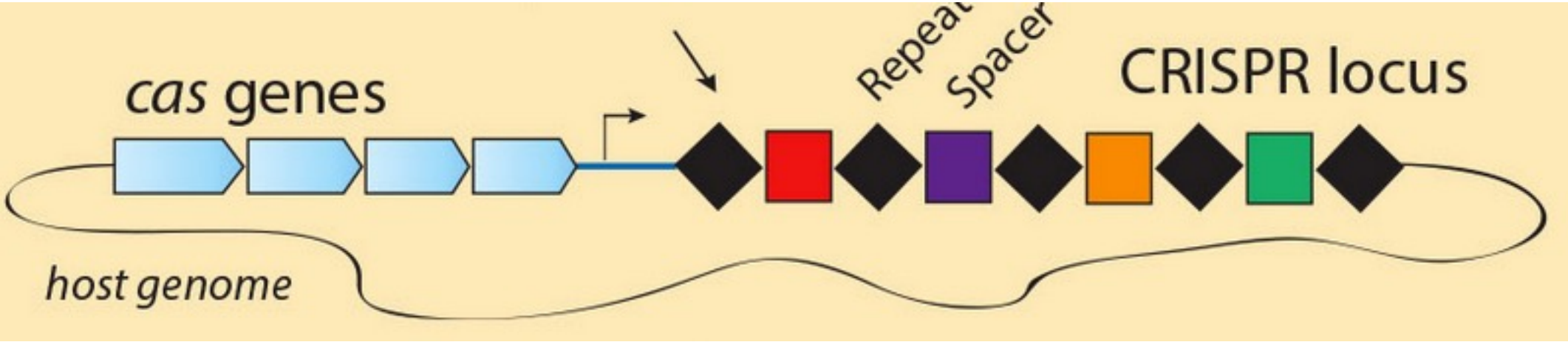
JOURNAL OF MOLECULAR EVOLUTION

© Springer Science+Business Media, Inc. 2005

Intervening Sequences of Regularly Spaced Prokaryotic Repeats Derive from Foreign Genetic Elements

Francisco J.M. Mojica, César Díez-Villaseñor, Jesús García-Martínez, Elena Soria

División de Microbiología, Departamento de Fisiología, Genética y Microbiología, Universidad de Alicante, Campus de San Vicente, E-03080, Spain



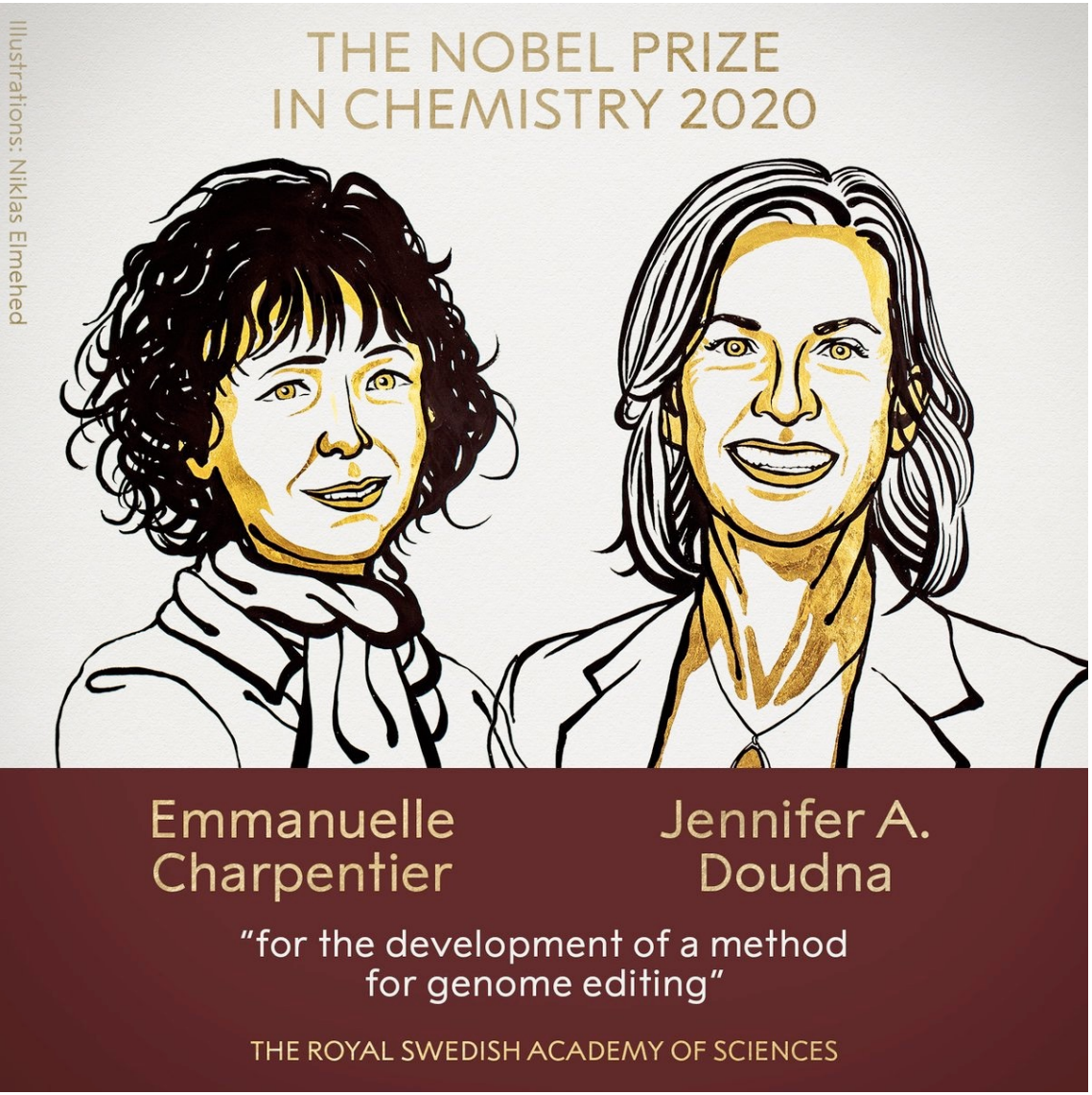
CRISPR = Clustered Regularly Interspaced Short Palindromic Repeat (identificada em 1987 nos genomas bacterianos)

Associada a imunidade bacteriana (2005)

Cas- CRISPR ASsociated - uma nuclease de DNA sítio específica (2012)

Edição de genomas (2013)- in vitro Doudna e Charpentier
em células Zhang

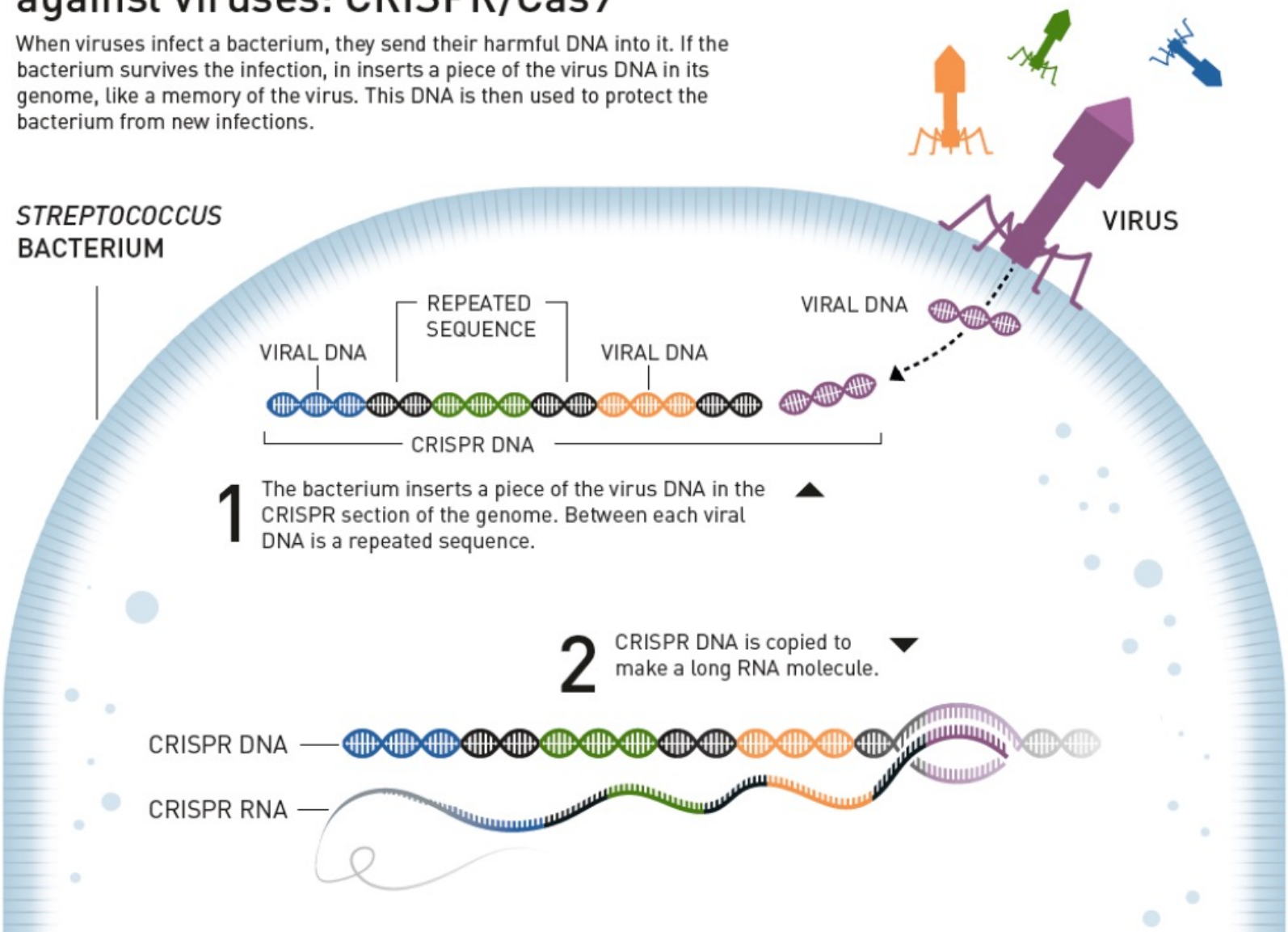
Prêmio Nobel de Química 2020
(primeira vez duas mulheres dividem o prêmio!)



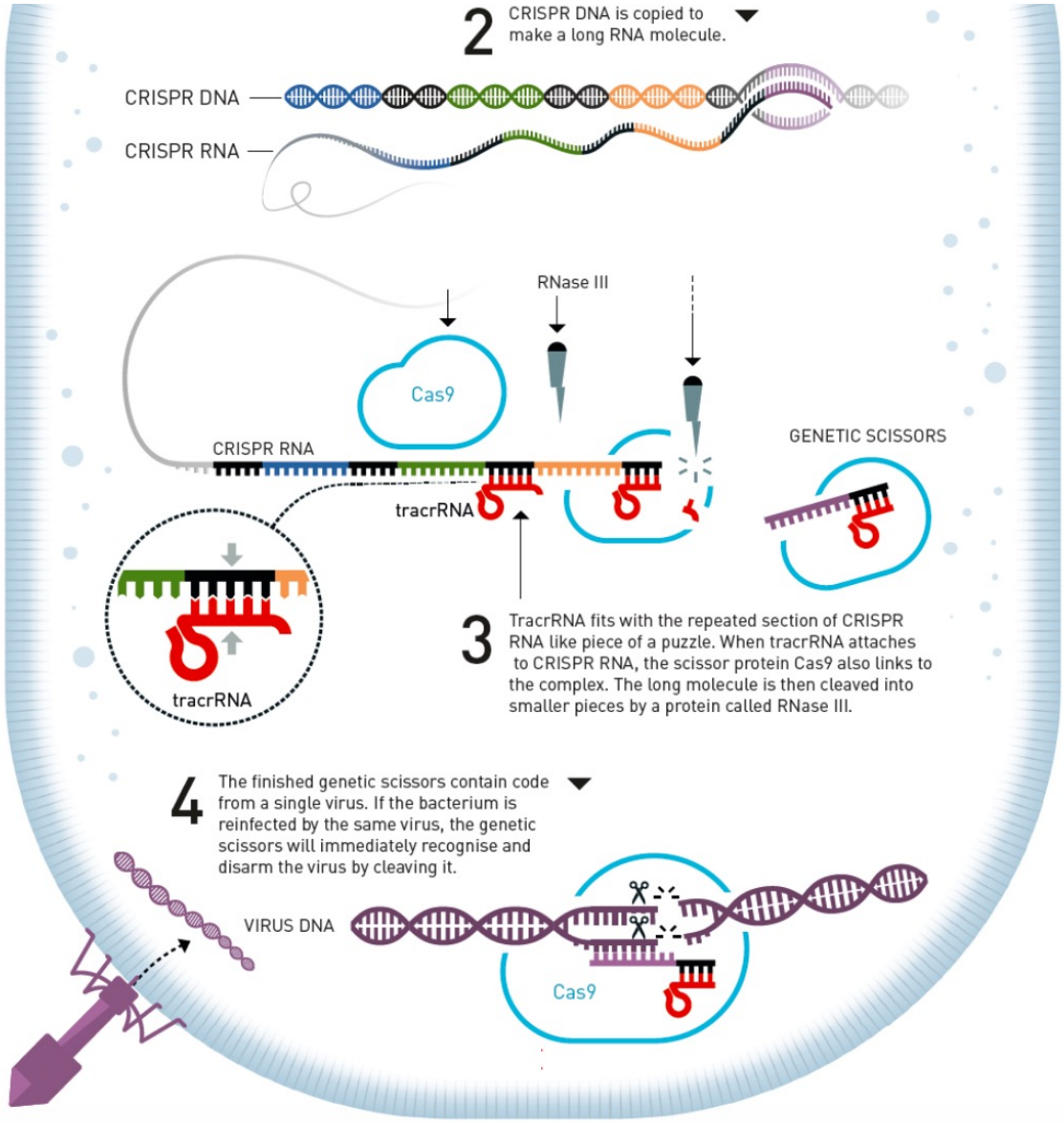
Imunidade bacteriana

Streptococcus' natural immune system against viruses: CRISPR/Cas9

When viruses infect a bacterium, they send their harmful DNA into it. If the bacterium survives the infection, in inserts a piece of the virus DNA in its genome, like a memory of the virus. This DNA is then used to protect the bacterium from new infections.



Imunidade bacteriana



©Johan Jarnestad/The Royal Swedish Academy of Sciences

RESEARCH ARTICLE

A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek[1,2,*], Krzysztof Chylinski[3,4,*], Ines Fonfara[4], Michael Hauer[2,†], Jennifer A. Doudna[1,2,5,6,‡], Emmanuelle Charpentier[4,‡]

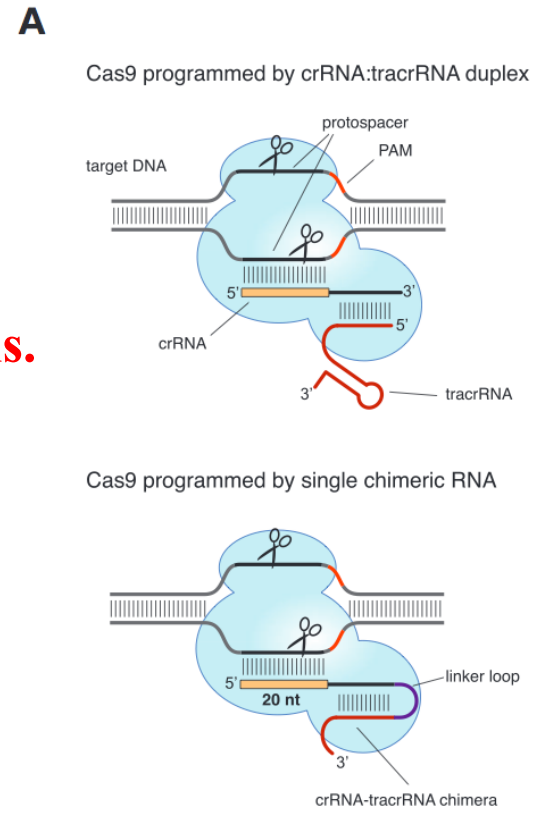
A ação da endonuclease (Cas)

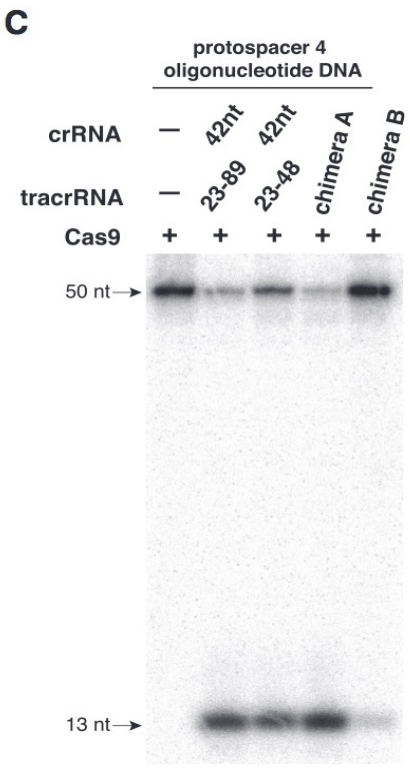
é guiada pelos RNAs Tracking e guia.

Fizeram a quimera dos dois RNAs.

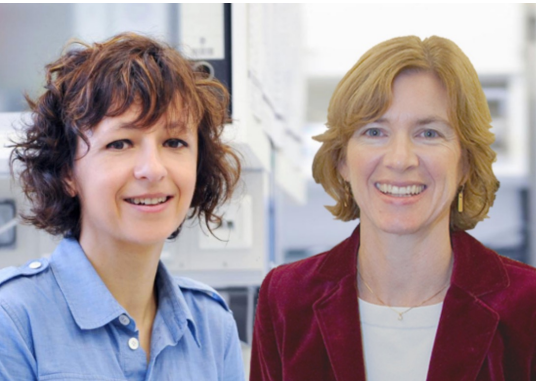
In vitro!

Sequência PAM!





Science 17 Aug 2012:



Emmanuelle Charpentier e Jennifer Doudna! (in vitro)

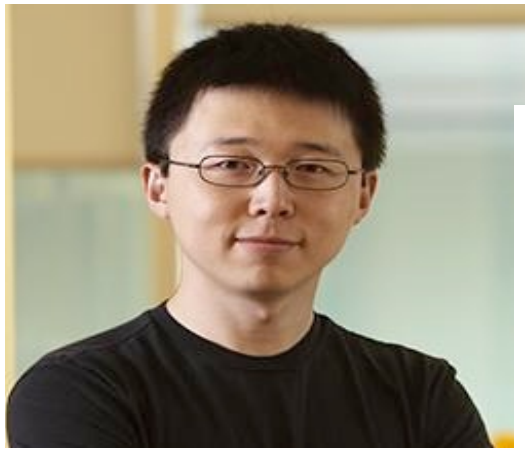
Multiplex Genome Engineering Using CRISPR/Cas Systems

Science
AAAS

Le Cong[1,2,*], F. Ann Ran[1,4,*], David Cox[1,3], Shuailiang Lin[1,5], Robert Barretto[6], Naomi Habib[1], Patrick D. Hsu[1,4], Xuebing Wu[7], Wenyan Jiang[8], Luciano A. Marraffini[8], and Feng Zhang[1,†]

' 03 January 2013;

CRISPR-Cas9 podem clivar genoma em células humanas e de camundongo!
- enzima pode ser modificada: nicking pode ajudar a fazer recombinação homóloga

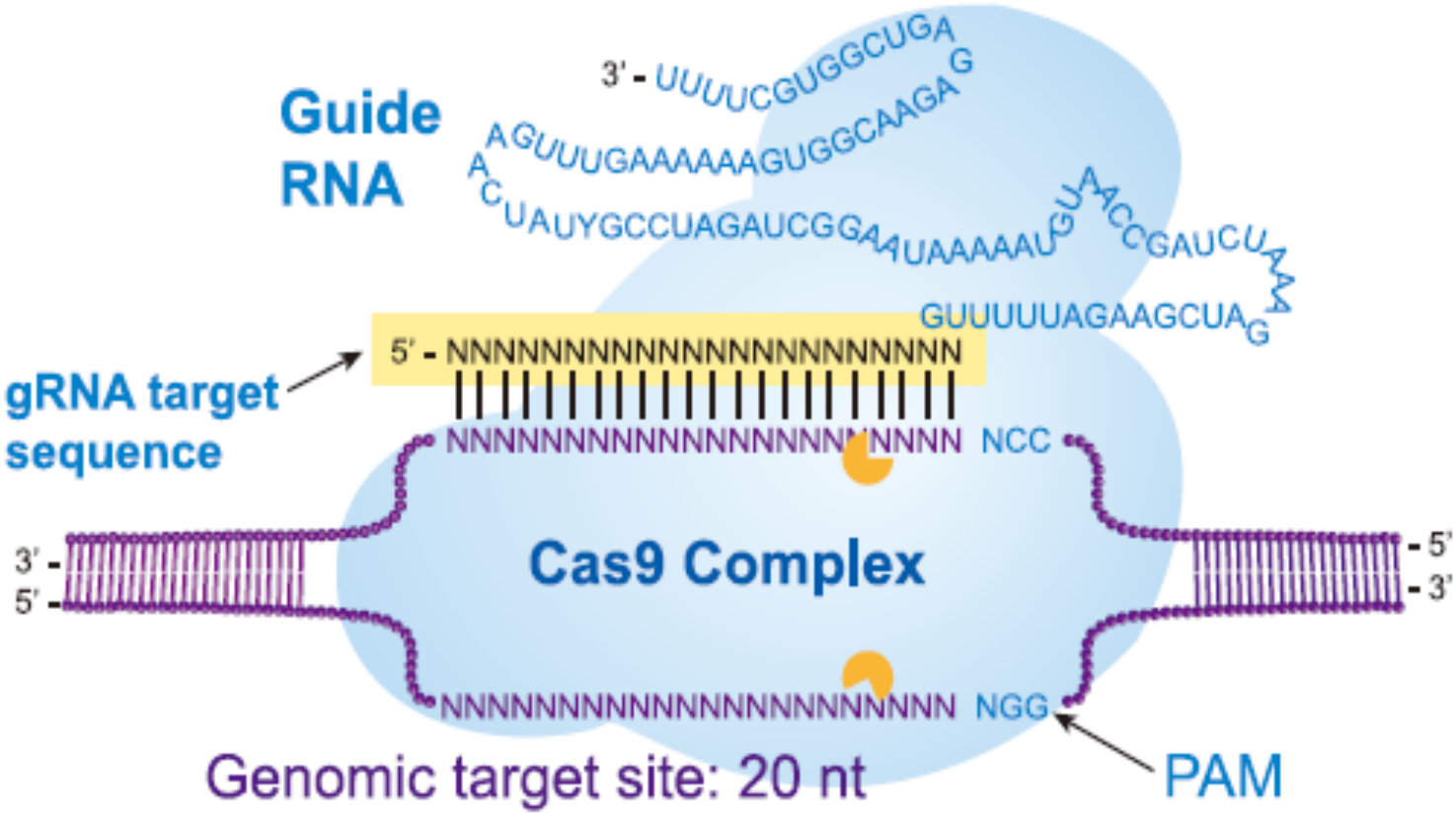


indels in human *EMX1* locus

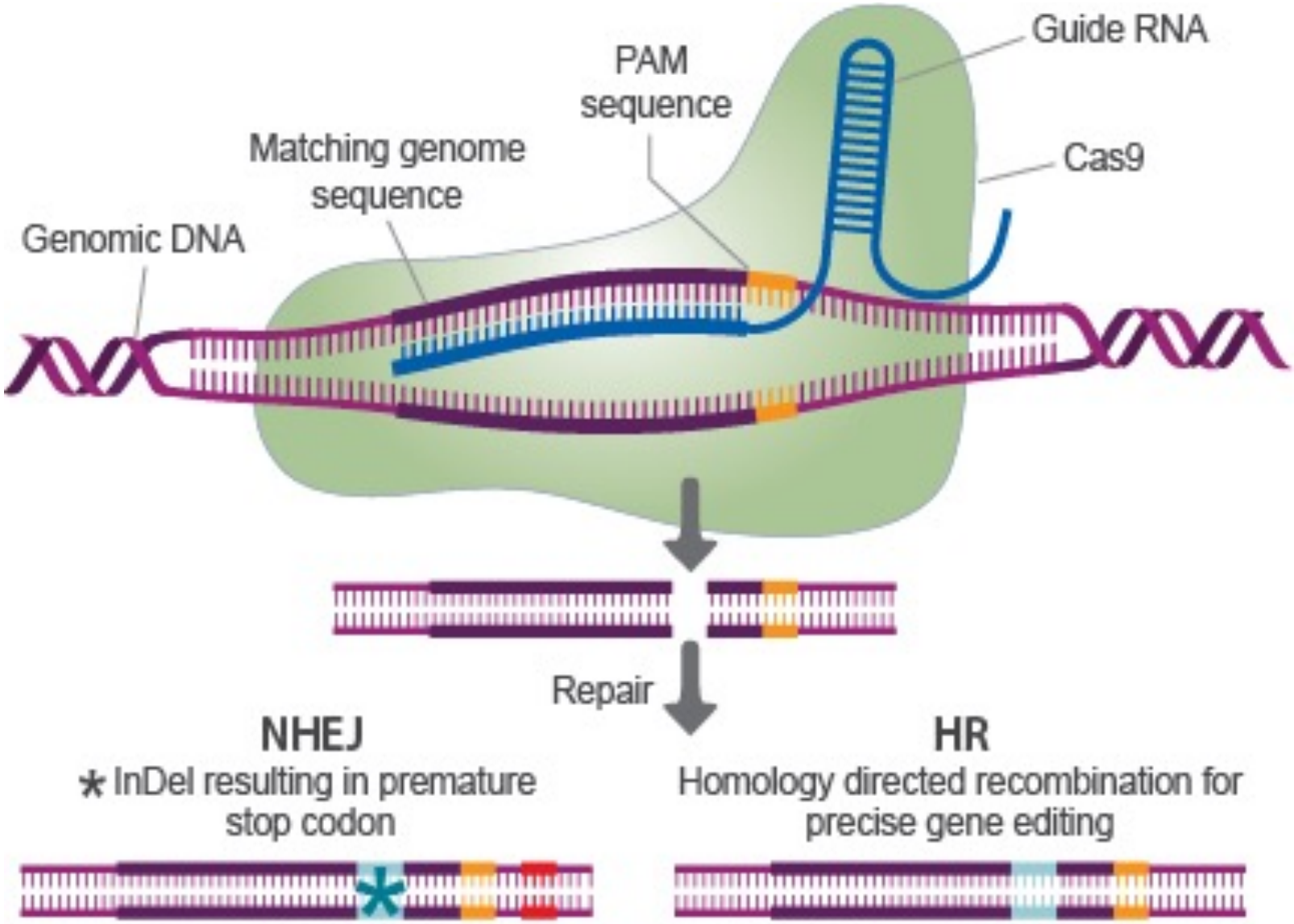
PAM

WT	5'-..GGAGGAAGGGCCTGAGTCCGAGCAGAAG-AAGAAGGGCTC..-3'
D1	GGAGGAAGGGCCTGAGTCCGAGCAGAAG--AGAAGGGCTC
+1	GGAGGAAGGGCCTGAGTCCGAGCAGAAGAAAGAAGGGCTC
D2	GGAGGAAGGGCCTGAGTCCGAGCAGAAG---GAAGGGCTC
D3	GGAGGAAGGGCCTGAGTCCGAGCAGAAG----AAGGGCTC
D6	GGAGGAAGGGCCTGAGTCCGAGCAGAAG-------GGCTC
m1, D6	GGAGGAAGGGCCTGAGCCCGAGCAGAAG-------GGCTC

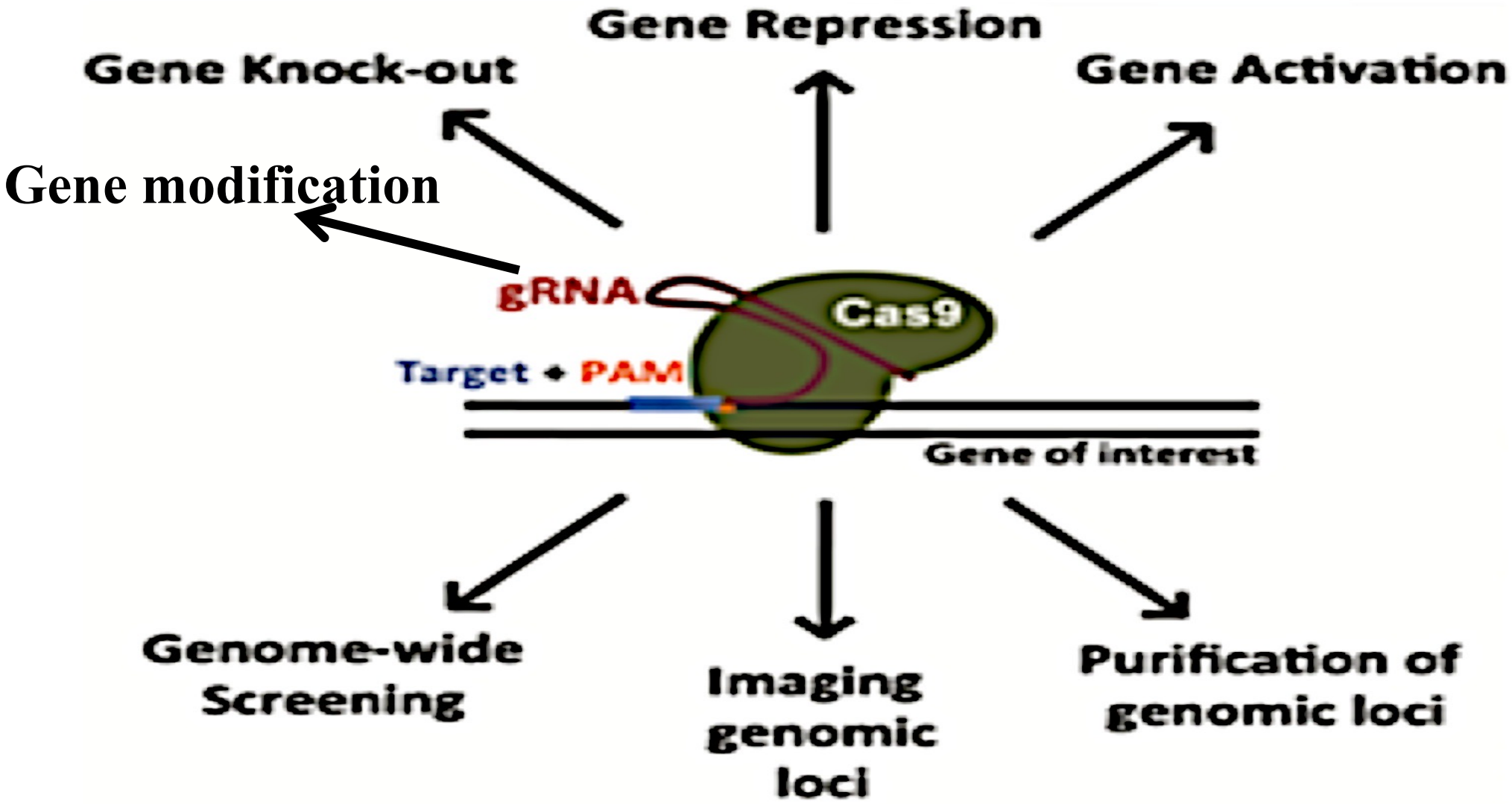
Como funciona a CRISPR-Cas
Clivando o DNA!



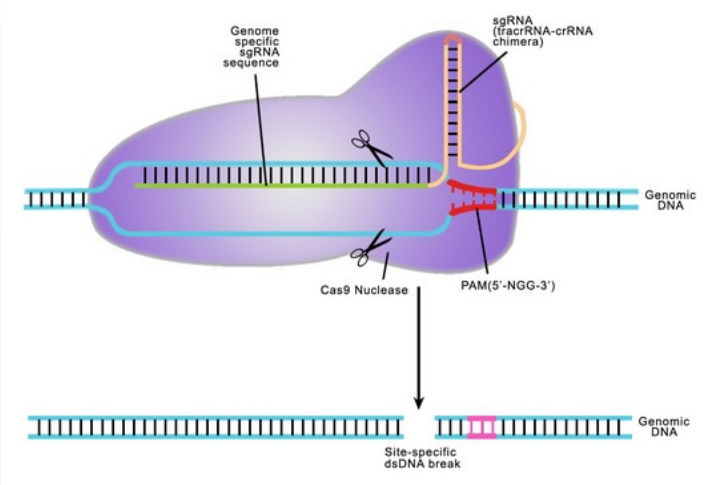
Mas depende do reparo celular para atuar na célula:
Mutar ou corrigir!



Mas serve para que????



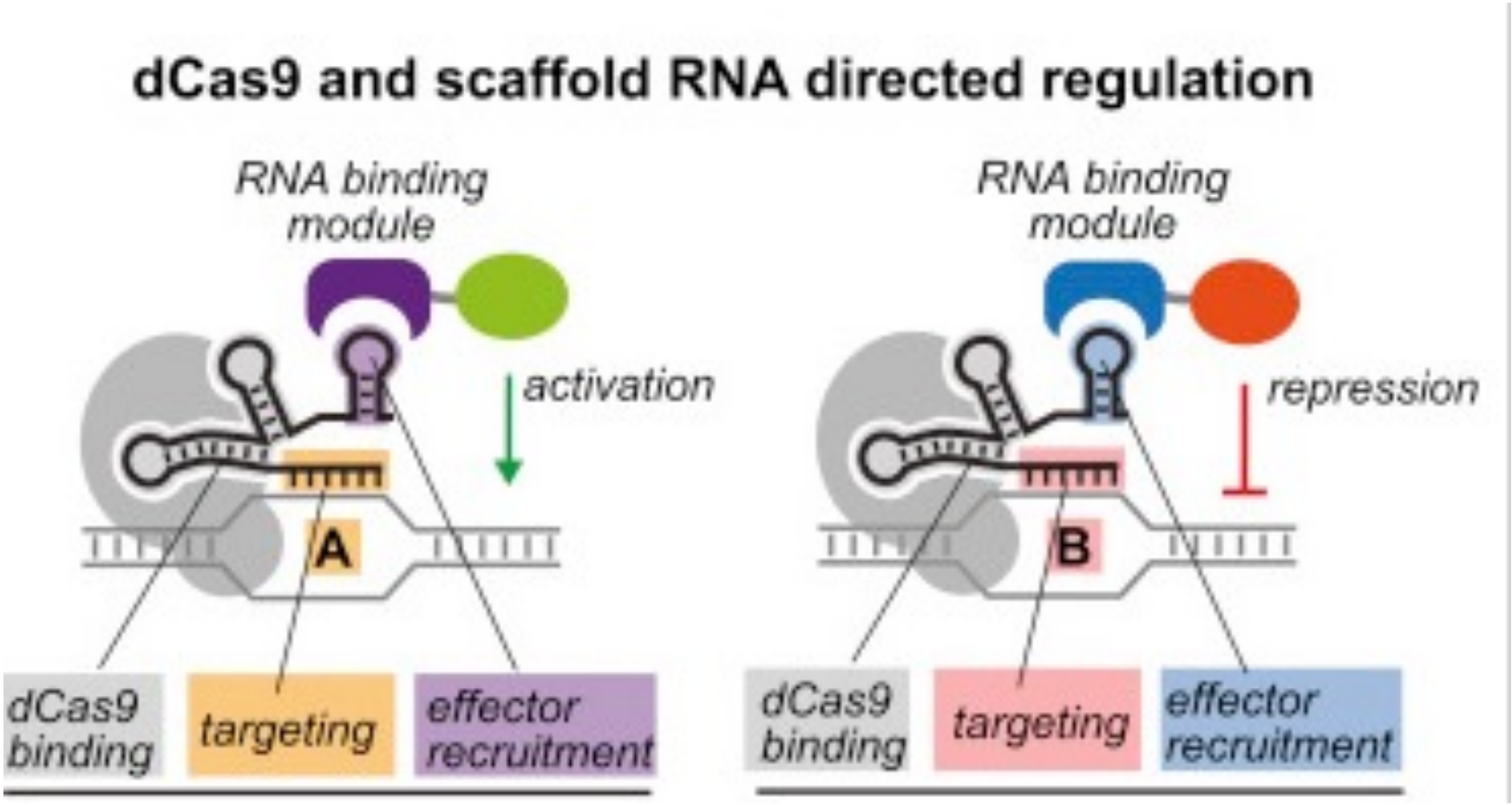
CRISPR/Cas9



https://www.youtube.com/watch?v=2pp17E4E-O8

https://www.youtube.com/watch?reload=9&v=4YKFw2KZA5o

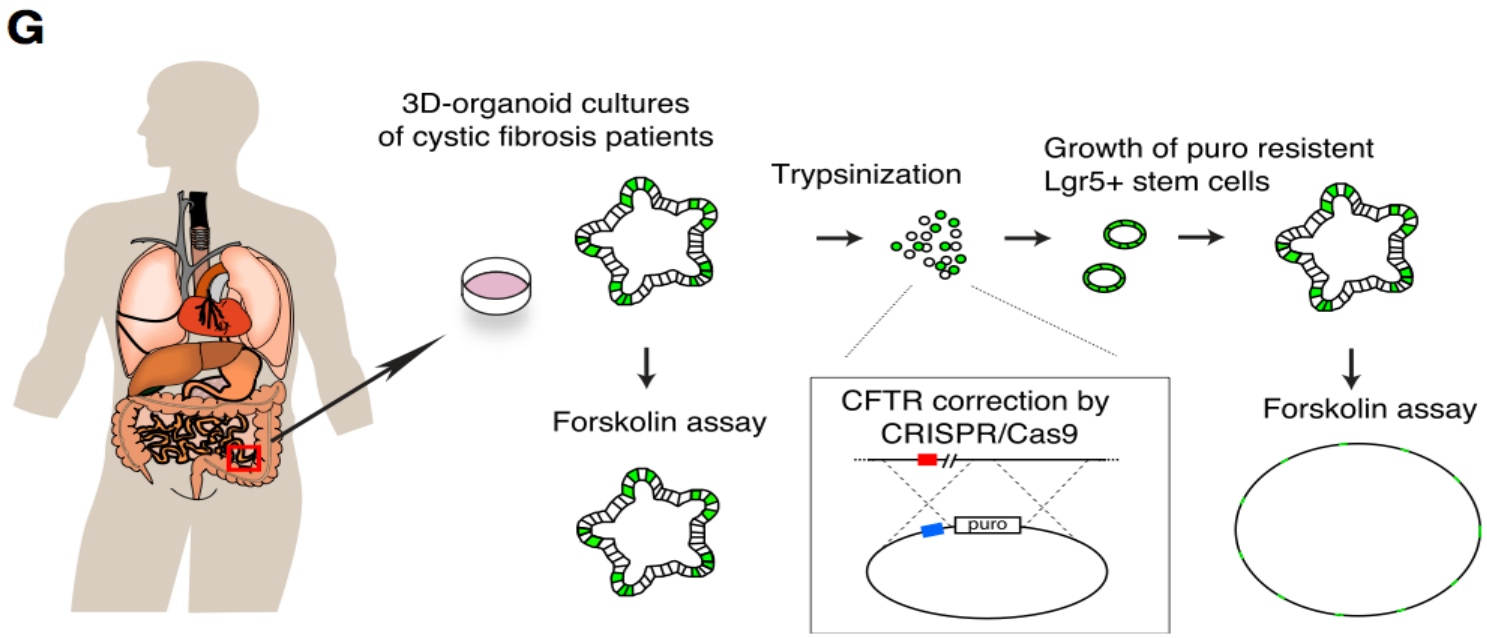
Controle gênico



Zalatan et al, Cell 2014

Cell Stem Cell
Brief Report

Functional Repair of CFTR by CRISPR/Cas9 in Intestinal Stem Cell Organoids of Cystic Fibrosis Patients

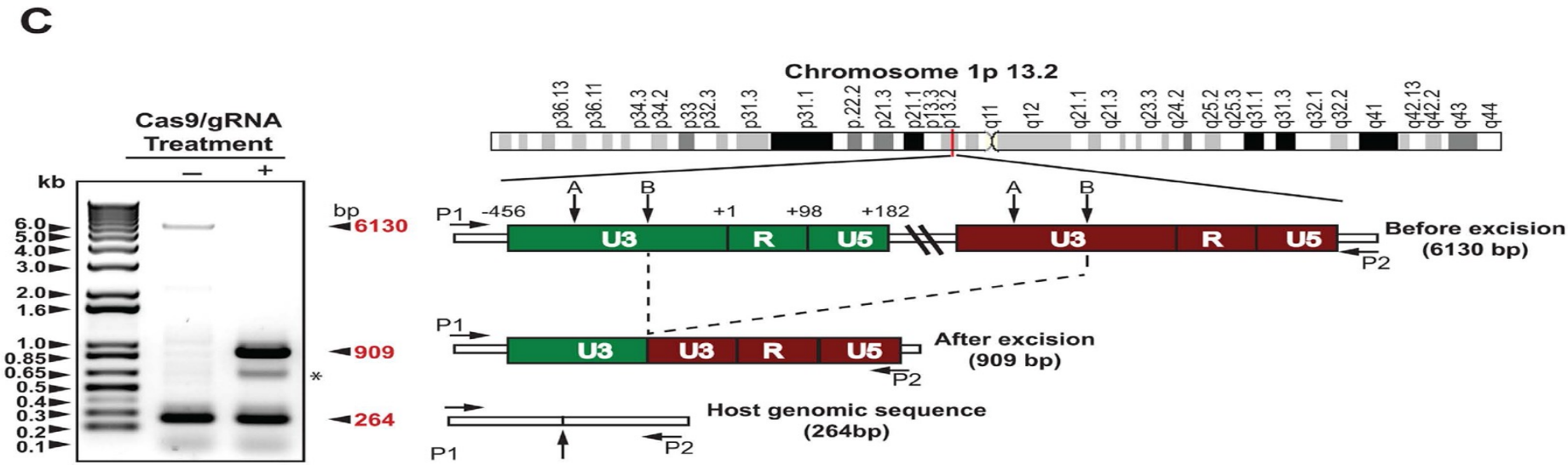


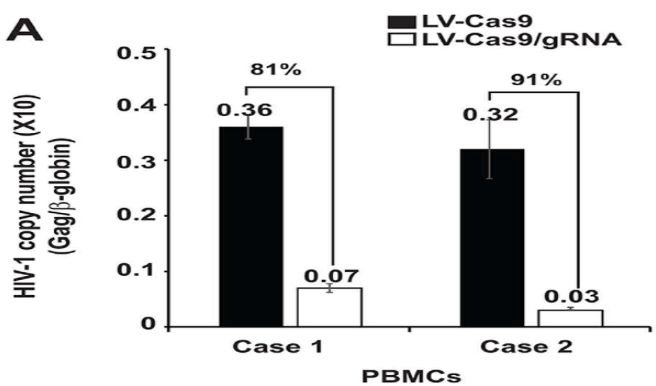
OPEN

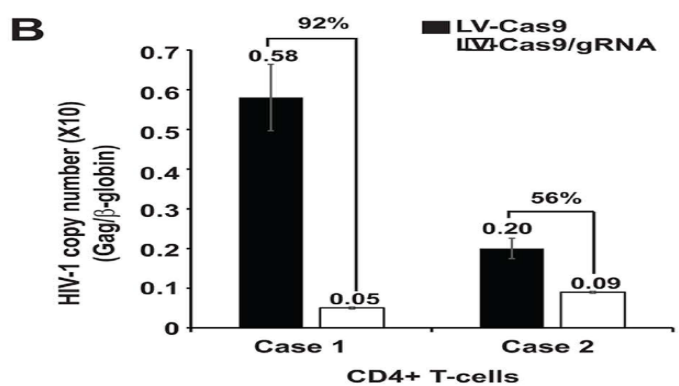
Elimination of HIV-1 Genomes from Human T-lymphoid Cells by CRISPR/Cas9 Gene Editing

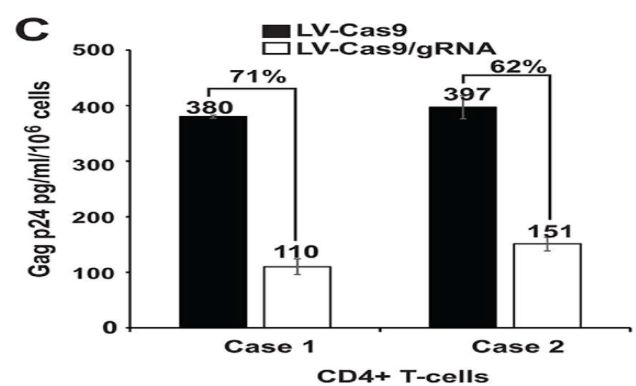
Received: 21 December 2015
Accepted: 16 February 2016
Published: 04 March 2016

Rafal Kaminski[1,2], Yilan Chen[1,2], Tracy Fischer[1,2], Ellen Tedaldi[2,3], Alessandro Napoli[1,2], Yonggang Zhang[1,2], Jonathan Karn[4], Wenhui Hu[1,2] & Kamel Khalili[1,2]



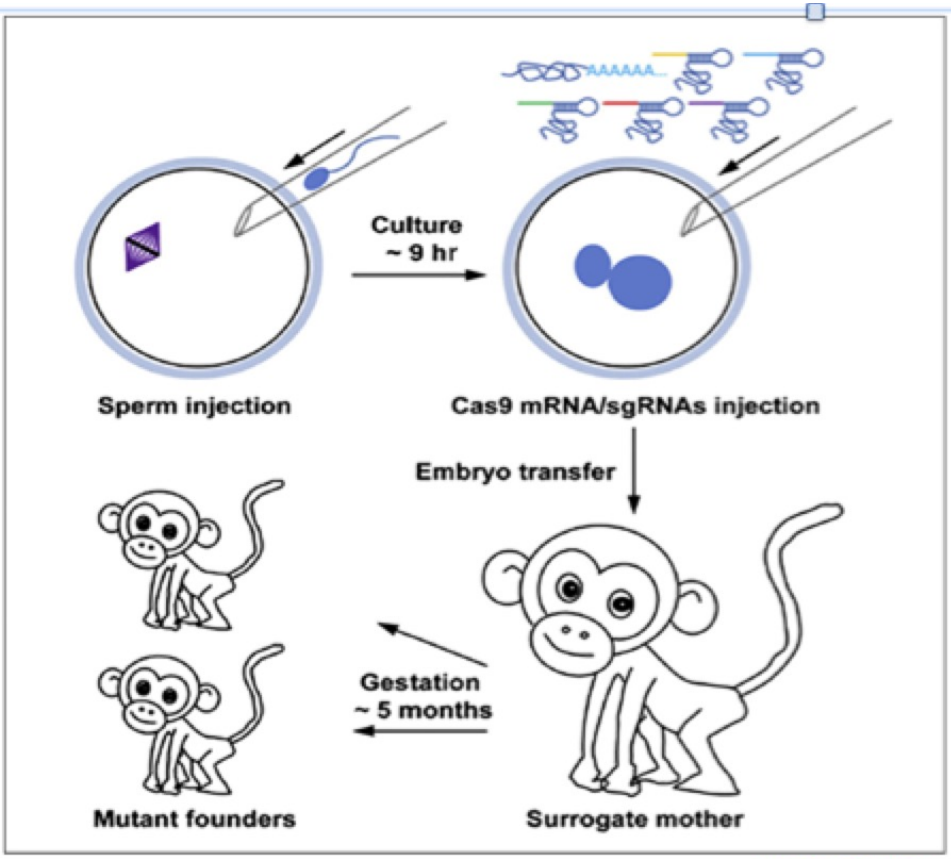






CRISPR: Editando genoma de primatas

PARP and RAG1 genes,
Involved in immune system-
Good scientific model!



Niu et al. *Cell* 2014

Cell

Volume 156, Issue 4, 13 February 2014, Pages 836–843

Resource

Generation of Gene-Modified Cynomolgus Monkey via Cas9/RNA-Mediated Gene Targeting in One-Cell Embryos

Yuyu Niu[1,5,7], Bin Shen[2,7], Yiqiang Cui[3,7], Yongchang Chen[1,5,7], Jianying Wang[2], Lei Wang[3], Yu Kang[1,5], Xiaoyang Zhao[4], Wei Si[1,5], Wei Li[4], Andy Peng Xiang[6], Jiankui Zhou[2], Xuejiang Guo[3], Ye Bi[3], Chenyang Si[1,5], Bian Hu[2], Guoying Dong[3], Hong Wang[1,5], Zuomin Zhou[3], Tianqing Li[1,5], Tao Tan[1,5], Xiuqiong Pu[1,5], Fang Wang[1,5], Shaohui Ji[1,5], Qi Zhou[4], Xingxu Huang[2], Weizhi Ji[1,5], Jiahao Sha[3]

Niu et al., *Cell*

Twin cynomolgus monkeys born in China are the first with mutations in specific target genes.

CRISPR gene-editing tested in a person for the first time

The move by Chinese scientists could spark a biomedical duel between China and the United States.

David Cyranoski

15 November 2016

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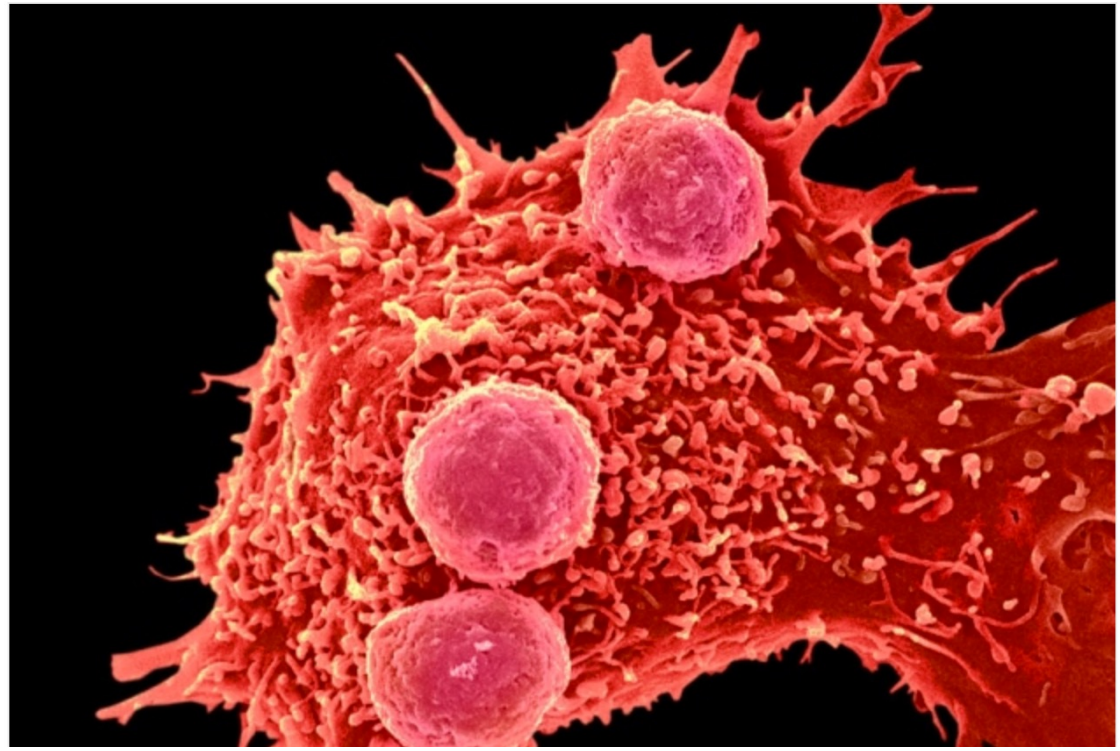


PD-1 gene, to accelerate immune responses against lung cancer!

Edição Genômica e terapia Gênica!!

Está sendo testada (com ZN-Finger nuclease) para doença metabólica como mucopolissacaridose!

Por simples infusão de vírus
Carregando a enzima de edição!!!!

Scientists make first ever attempt at gene editing inside the body

New therapy will permanently alter DNA, with no way to alter mistakes editing may cause - but offers chance to tackle currently incurable metabolic diseases

▲ Brian Madeux, 44, sits with his girlfriend Marcie Humphrey, waiting to receive the first human gene editing

NEWS | 29 June 2021

Landmark CRISPR trial shows promise against deadly disease

Administering gene-editing treatment directly into the body could be a safe and effective way to treat a rare, life-threatening condition.

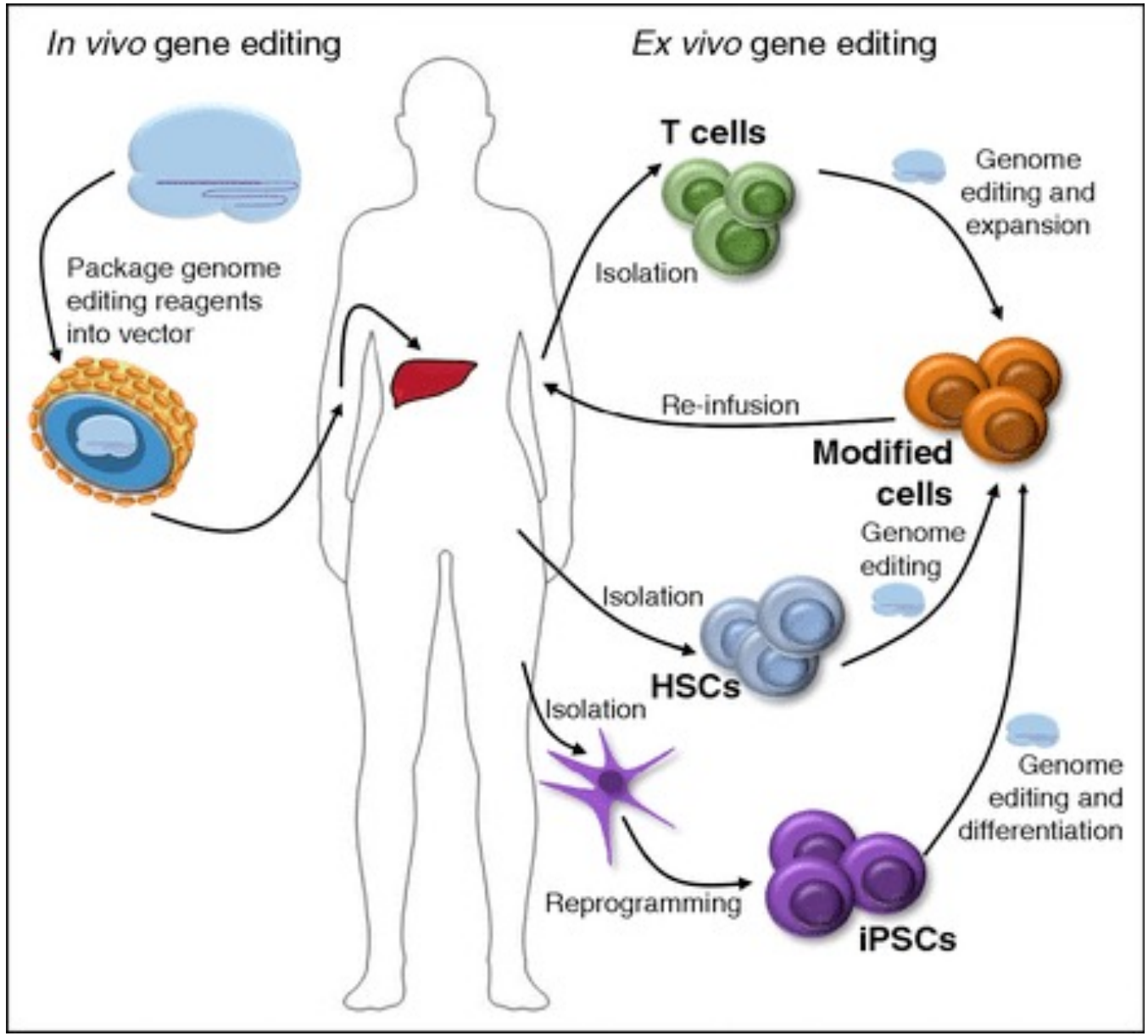
Heidi Ledford

Intellia therapeutics – Cambridge, UK

Amiloidose transthyretin: doença genética rara
condição dominante de expressão de
alelo tóxico.

Seis pacientes foram tratados (fígado)- redução da proteína!

Terapia Gênica com Edição do Genoma, como será (ou está sendo)?



Terapia Gênica com Edição do Genoma, como será (ou está sendo)?

HOME » NEWS AND TRENDS

Study says gene editing with CRISPR/Cas9 can lead to cell toxicity and genome instability

BY JIM CORNALL
AUGUST 9, 2022 - 3 MINUTES

BIOTECH

Scientists Breed Pigs Resistant to a Devastating Infection Using CRISPR

And the race to develop commercial applications for the revolutionary gene-editing tool is off and running

Credit: COURTESY OF NIC BENNER University of Missouri

egenesis

ENGINEERING LIFE

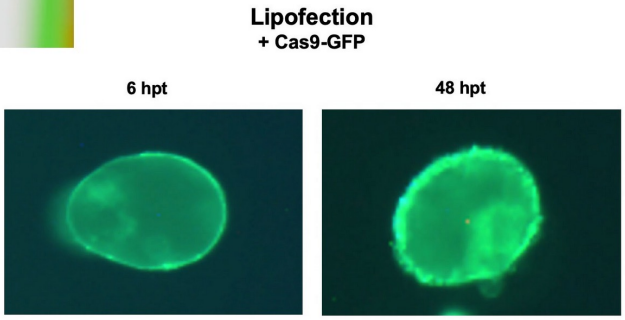
News › Science

Pig organs could soon be transplanted into humans after major 'xenotransplantation' breakthrough

The shortage of organs for transplants is one of the biggest challenges to modern medicine

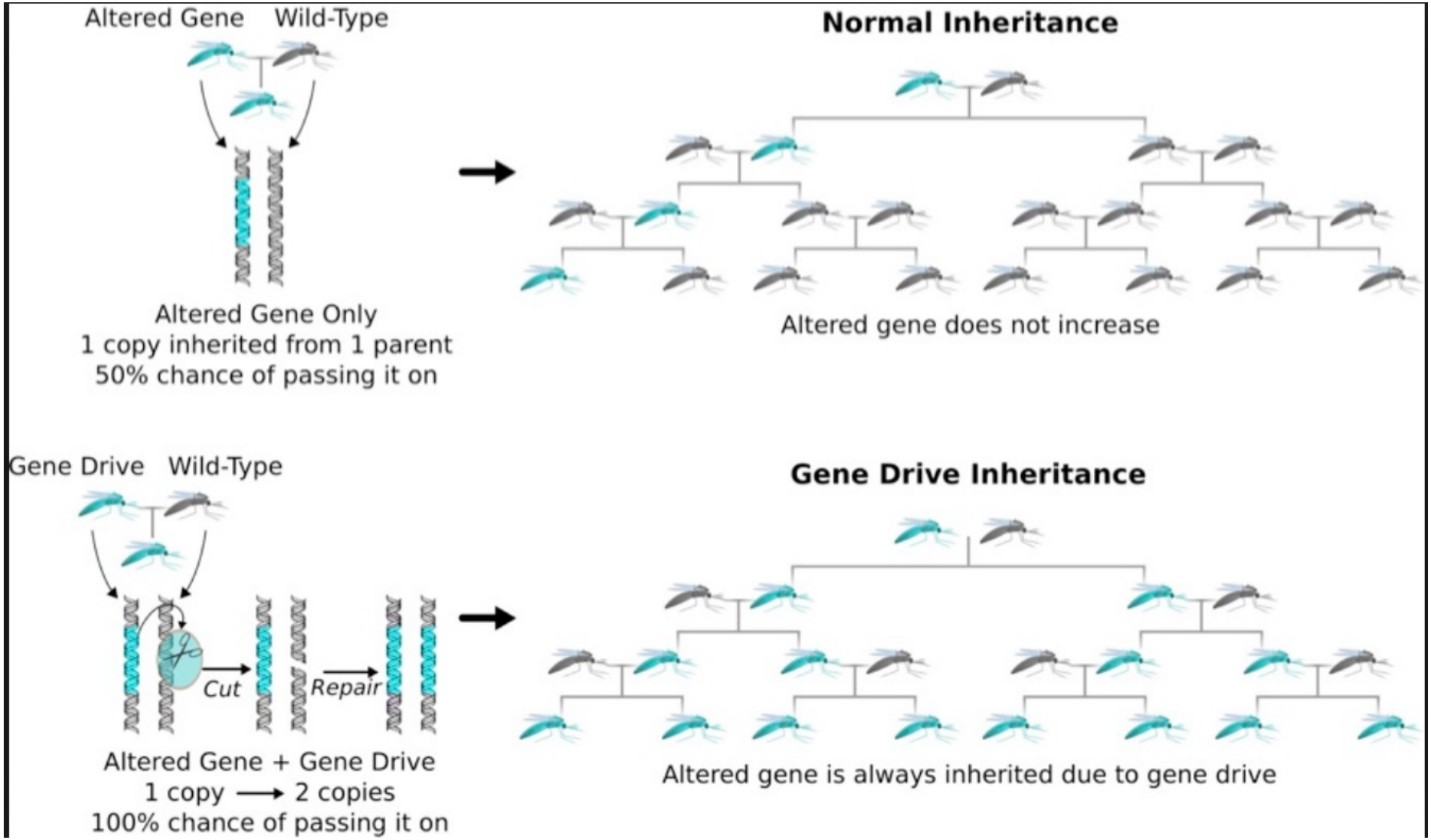
CRISPR Plants: New Non-GMO Method to Edit Plants

May 11, 2020 | Mollie Rappe



An image showing CRISPR/Cas9 protein — labeled with a green fluorescent protein — inside a plant cell after 6 and 48 hours. Image courtesy Wusheng Liu.

GENE DRIVE: como mudar uma população inteira!



GENE DRIVE: como mudar uma população inteira!

https://www.youtube.com/watch?v=75iP50LEHrU

CRISPR/CAS9

Problemas éticos….

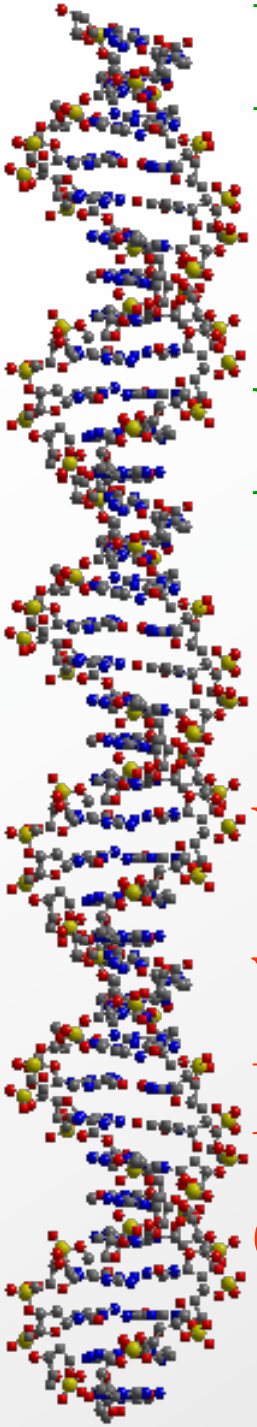
Devemos usar em humanos? Todo e qualquer gene?

Em embriões humanos?

Plantas deixariam de ser transgênicas?

GENE DRIVE em mosquitos?

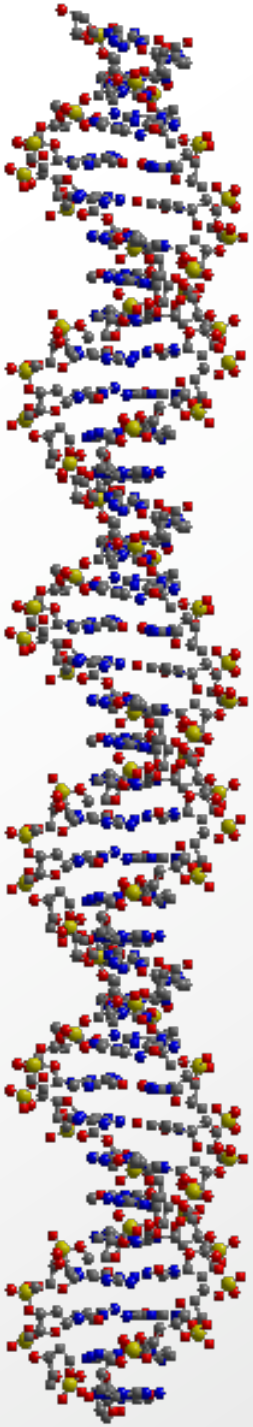
Outros organismos?



Revolução na Medicina!

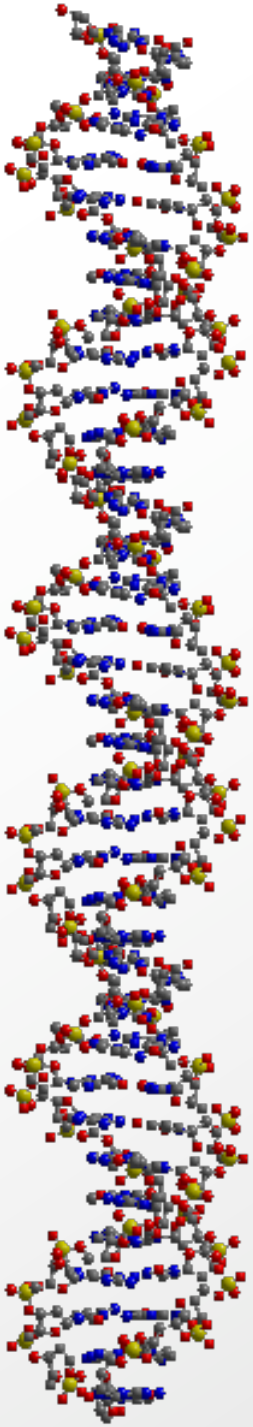
Na agropecuária…

Vamos participar do processo, ou vamos simplesmente comprar os Medicamentos e produtos feitos no exterior?



"I hear this guy really cleans up."

© 2009 Jonny Hawkins



Obrigado pela atenção!

cfmmenck@usp.br