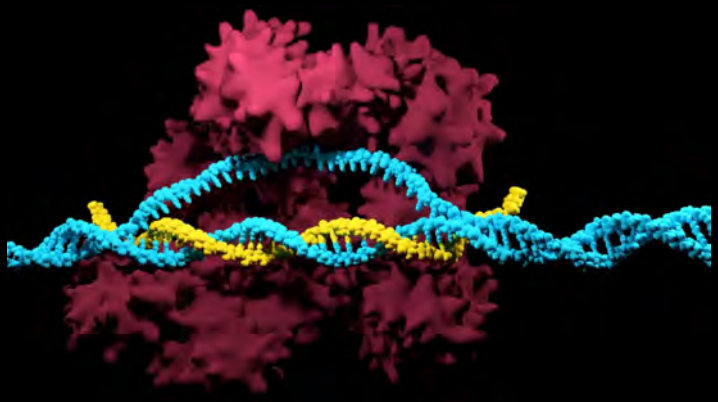
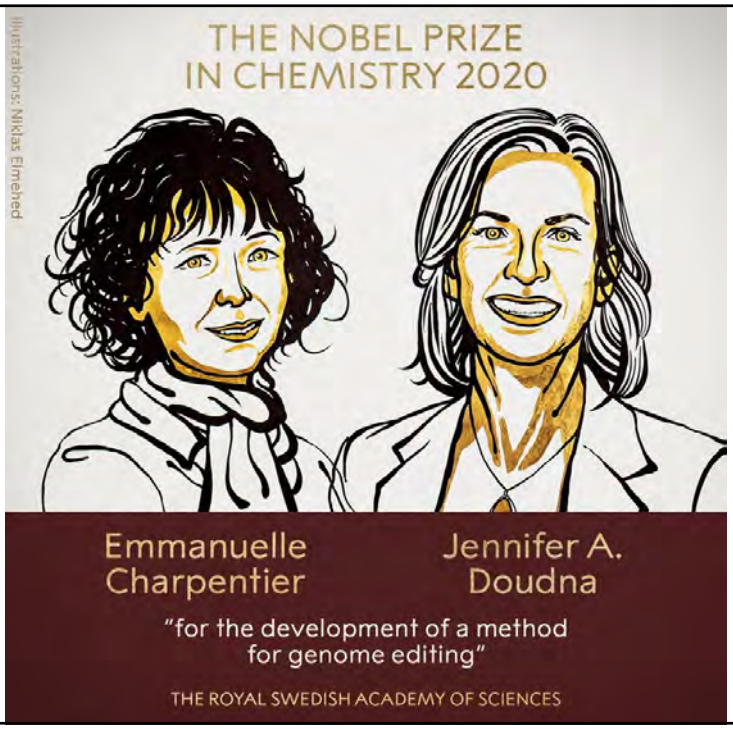
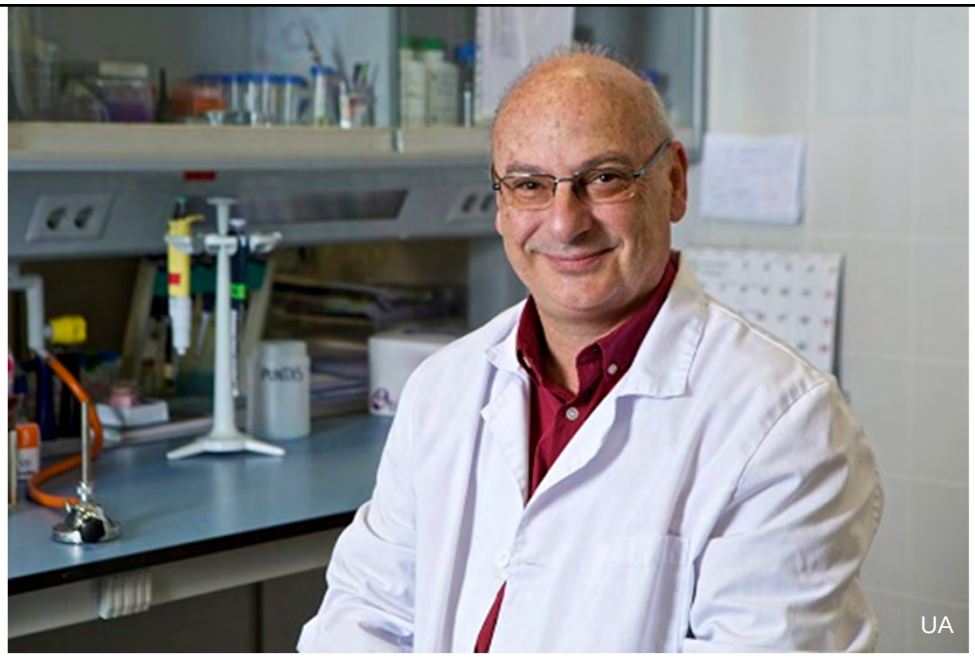


Medicina personalizada desde la edición genética

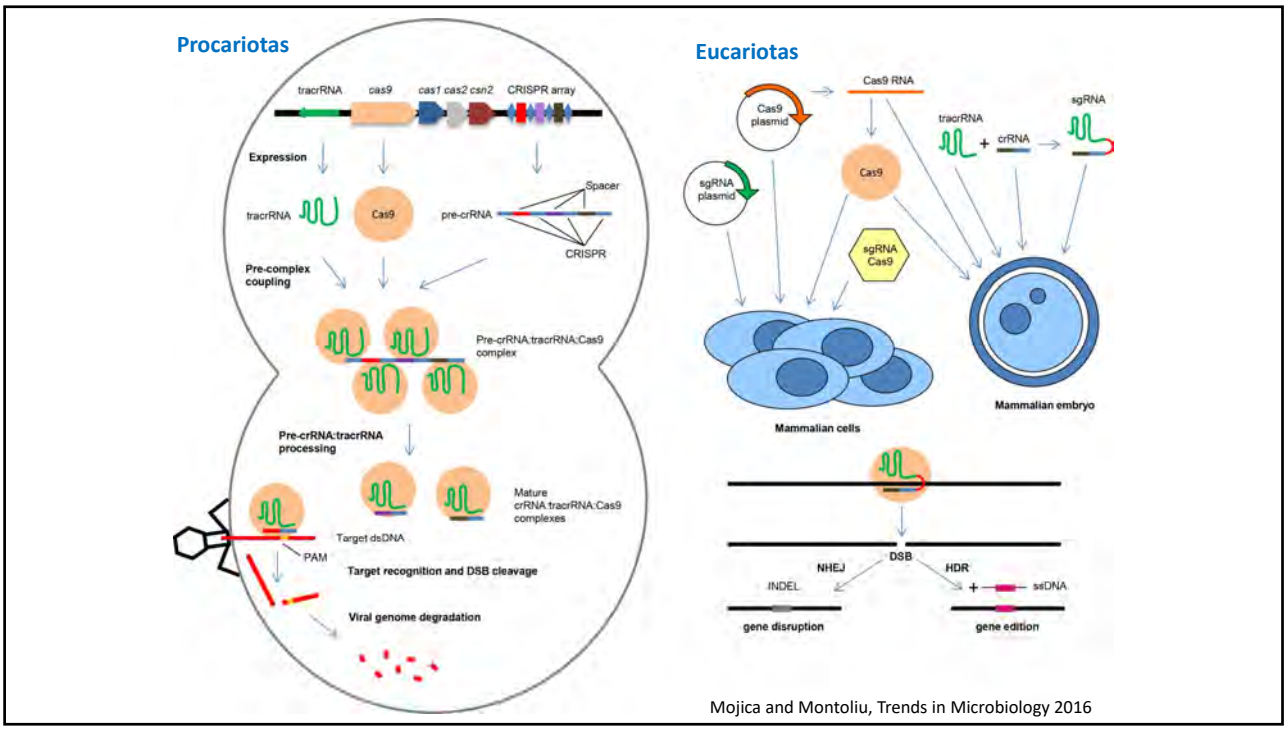
@LluisMontoliu

CNB-CSIC & CIBERER-ISCIII, Madrid



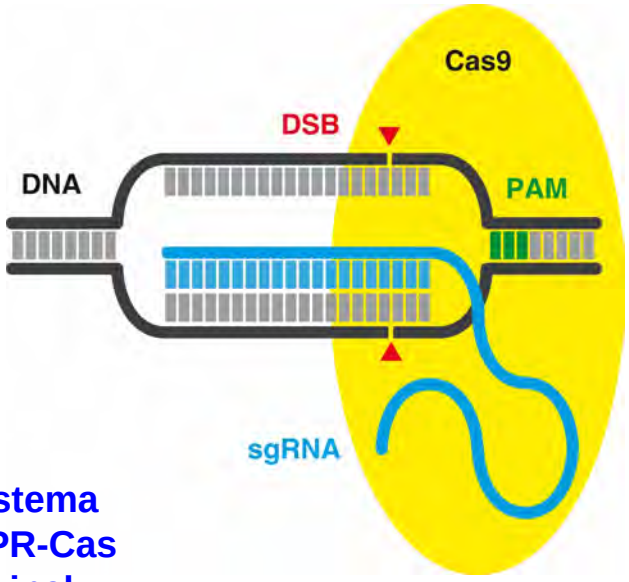


Francisco Juan Martínez Mojica



Mojica and Montoliu, Trends in Microbiology 2016

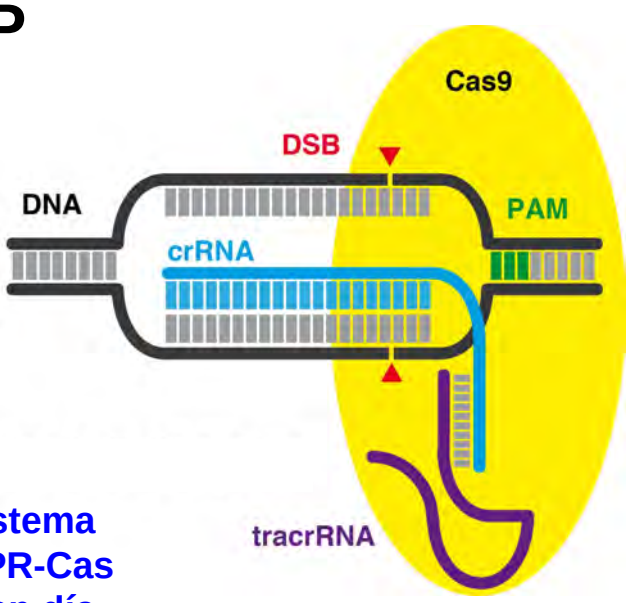
2012



El sistema CRISPR-Cas original

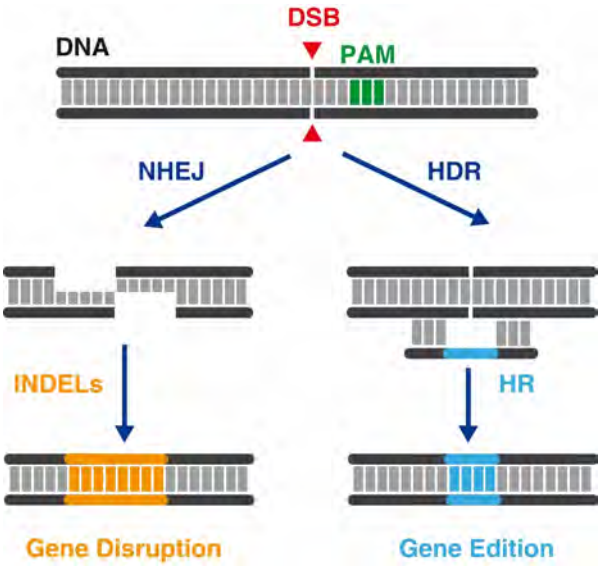
RNP

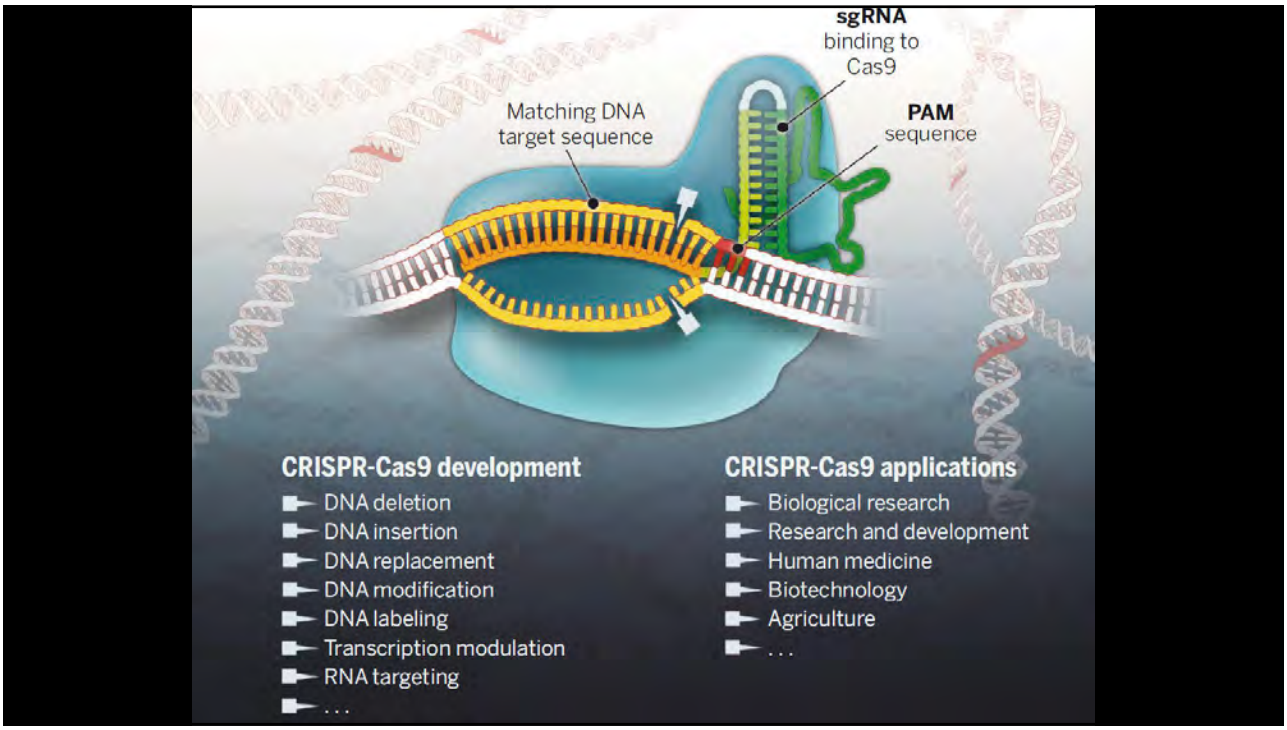
2021



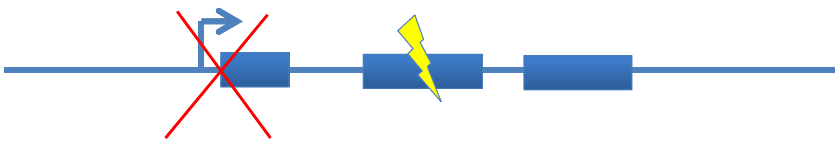
El sistema CRISPR-Cas hoy en día

Fixing the DSB: NHEJ vs HDR

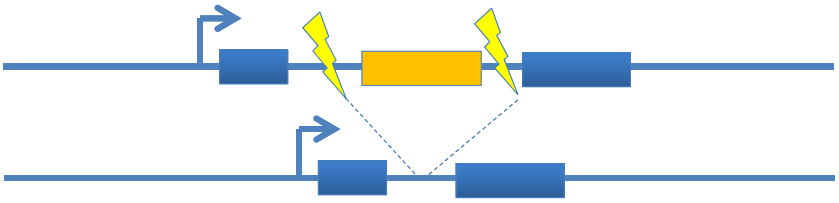




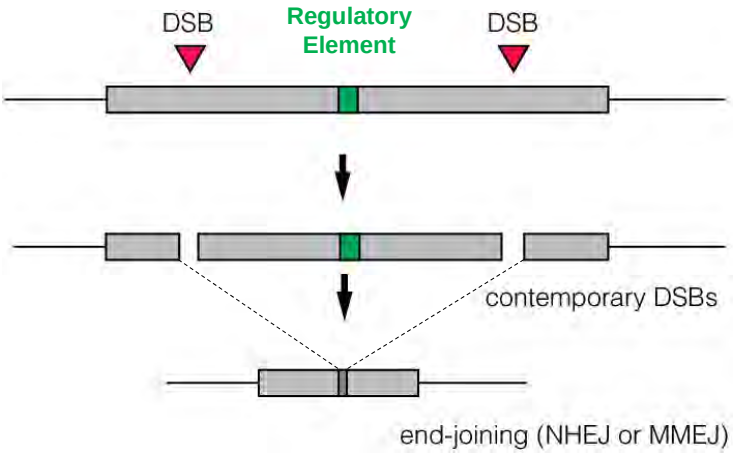
Disrupting a gene: KO



Deletions

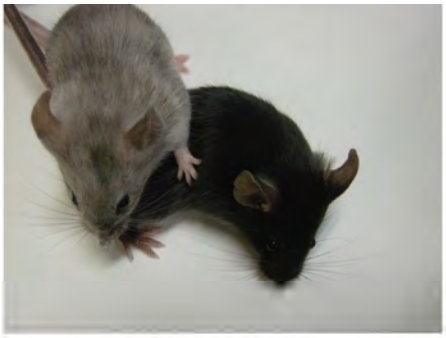


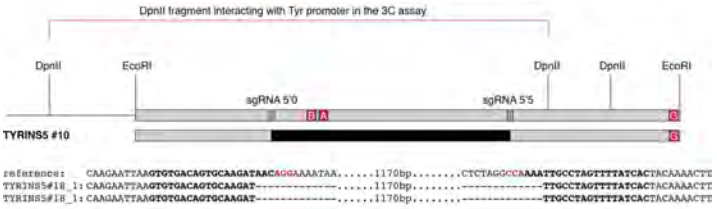
Using CRISPR-Cas9 genome editing to target *Tyr* regulatory elements



CRISPR-Cas9 genome editing

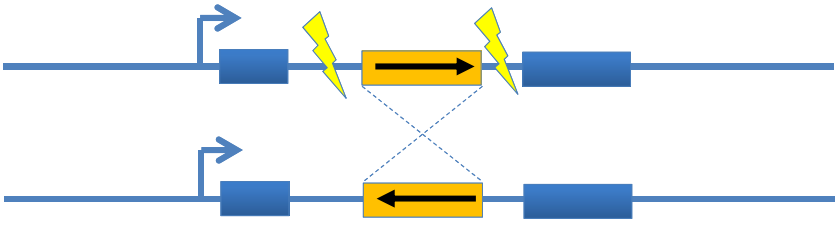
Deleting 5' *Tyr* regulatory elements with CRISPRs *in vivo* results in hypopigmentation



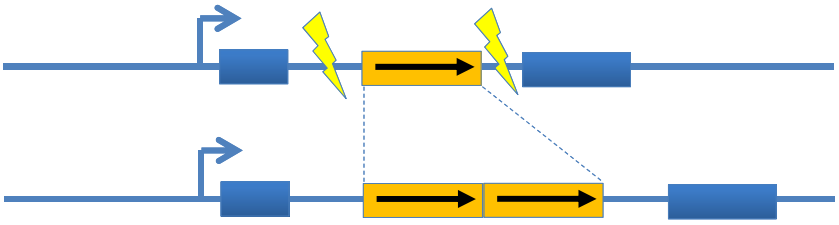


Seruggia et al. 2015 Nucleic Acids Research
Seruggia et al. 2020 Scientific Reports
Seruggia et al. 2021 Pigment Cell & Melanoma Res.

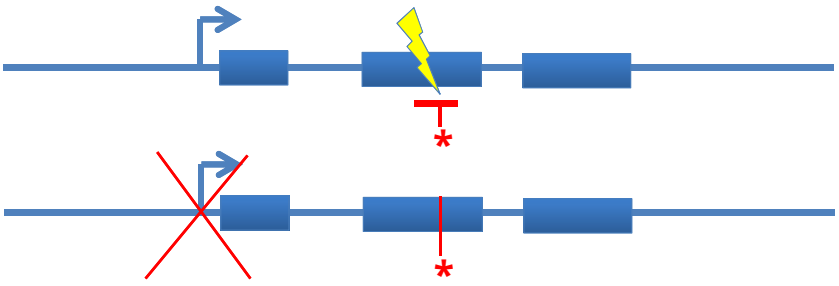
Inversions



Duplications



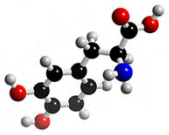
Point mutations



AVATAR CRISPR mice

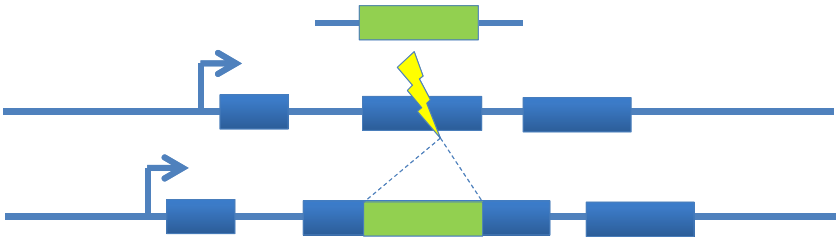
- Easier approach to reproduce human mutations in animal models

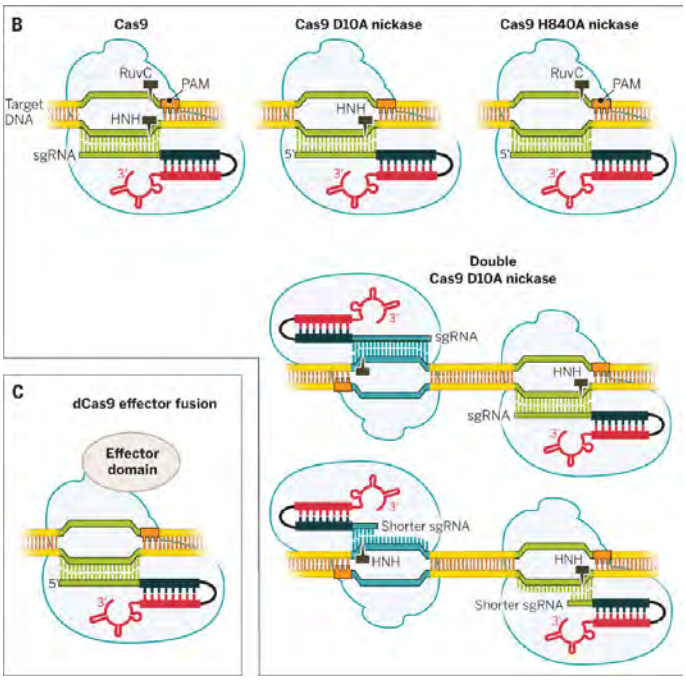
OCA4 (*SLC45A2*) c.986delC **Patty**



Validating treatments

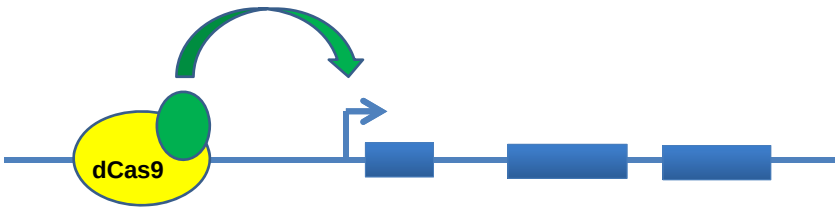
Knock-ins



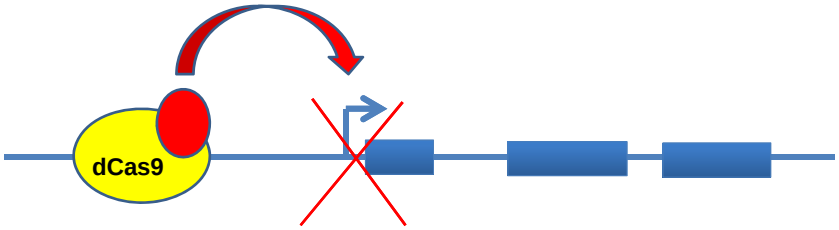


Doudna & Charpentier (2014) Science

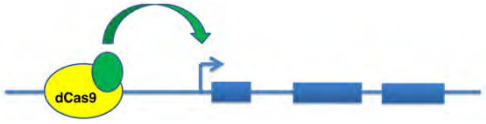
Activating a gene



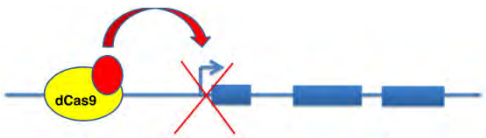
Inactivating a gene



Switching ON-OFF

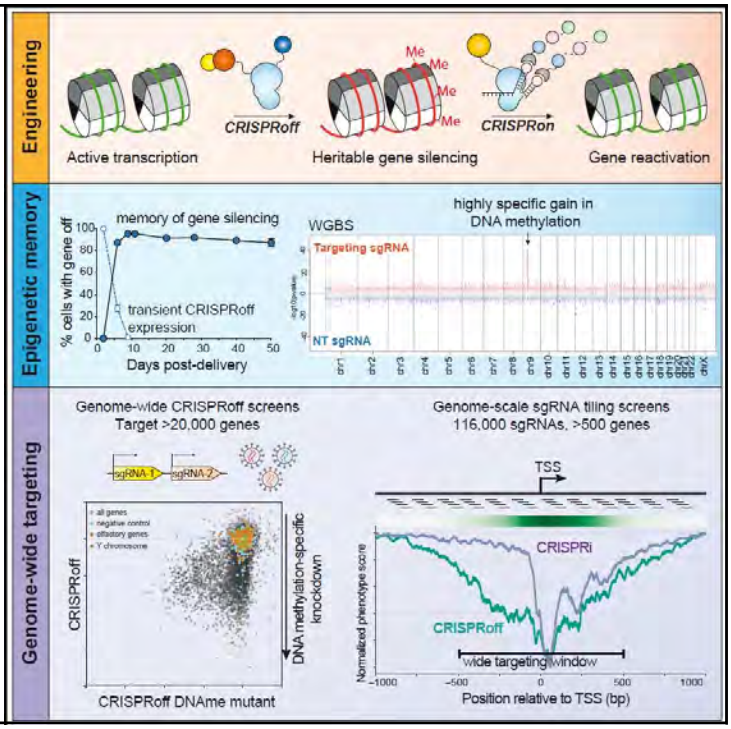


CRISPRon



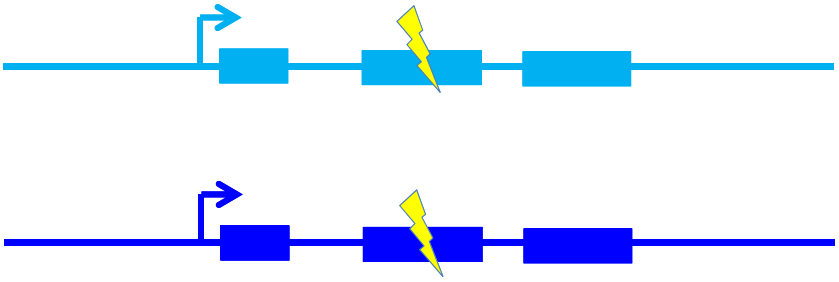
CRISPRoff

Nuñez *et al*. Cell (2021)



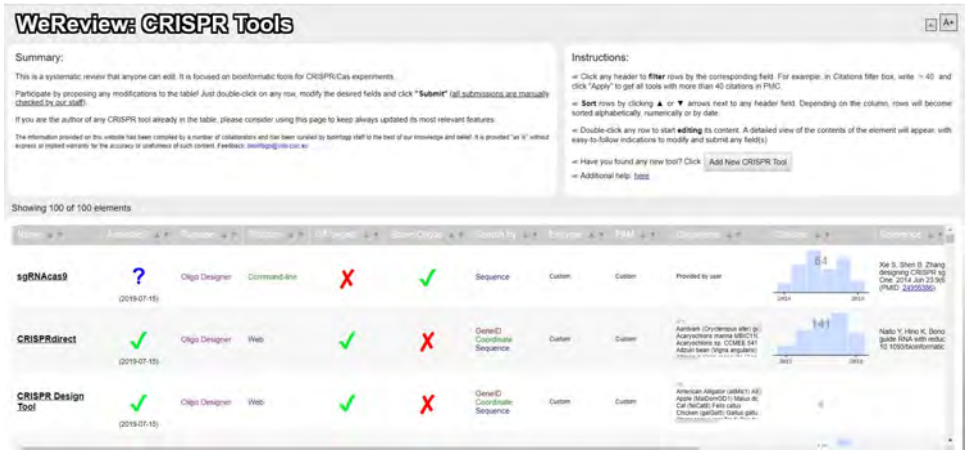
Current limitations of CRISPR-Cas9 tools

Inactivating similar genes



off target effects

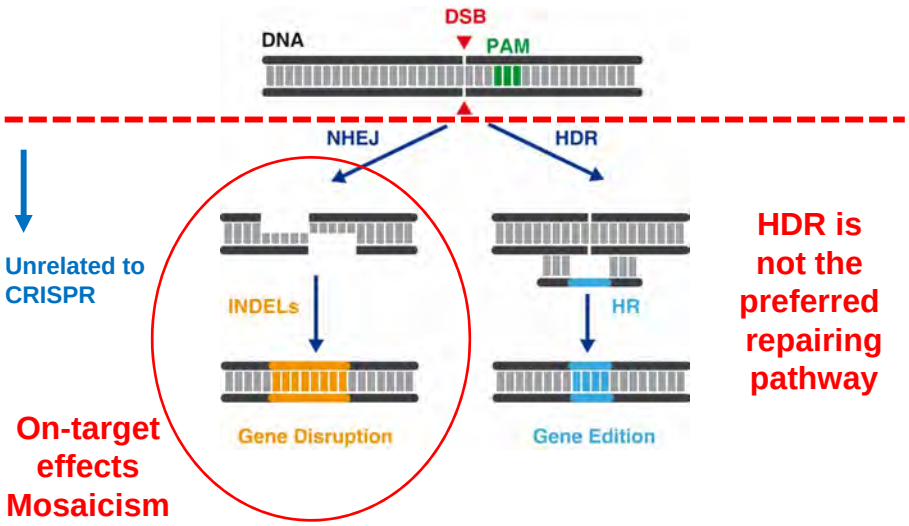
>100 programs available for designing sgRNA



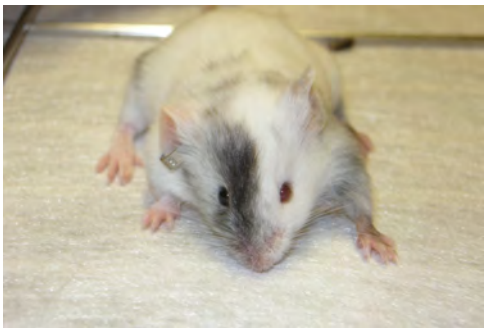
WeReview: CRISPR Tools

Torres-Perez *et al.* Bioengineering 2019

on target effects - mosaicism



On-targets: the real problem



- Founder animals are nearly always complex mosaic
- Many different alleles can be present
- Not all of them might transmit through germline

One 8-cell embryo = 16 possible alleles

ON-TARGET genetic variations are the main challenge


```
Reference:  AACATTGGAGGAGCTGCCACTGCTATTGGGGACCCACCAAATGTTATCATTGTTTCCAATCAGGAGTTGAGAAAAATGGTAGGTAACAGCACGGTAGGGTTGATTTCAGGAAATGTAA
B9040.1     AACATTGGAGGAGCTGC ACTGCTATTGGGGACCCACCAAATGTTATCATTGTTTCCAATCAGGAGTTGAGAAAAATGGTAG----------GTAGGGTTGATTTCAGGAAATGTAA
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B9040.3     AACACTGGAGGAGCTGCCACTGCTATTGGGGACCCACCAAATGTTATCATTGTTTCCAATCAGGAGTTGAGAAAAATGGTAG----------GTAGGGTTGATTTCAGGAAATGTAA
B9040.4     AACATTGGAGGAGCTGCCACTGCTATTGGGGACCCACCAAATGTTATCATTGTTTCCAATCAGGAGTTGAGAAAAATGGTAGGTAACAGC-----AGGGTTGATTTCAGGAAATGTAA
B9040.5     CAAGCTCCTGCCCCACTTTCAAAGCTGTACTGAACTGCAGTTTCTTCTCCACCCAGATTCCTGCAAGACCTTGCACCGGGG----------(437bp)----------
B9040.6     ----------------------------------------------(561bp)----------------------------------------------------------------------------------------------------
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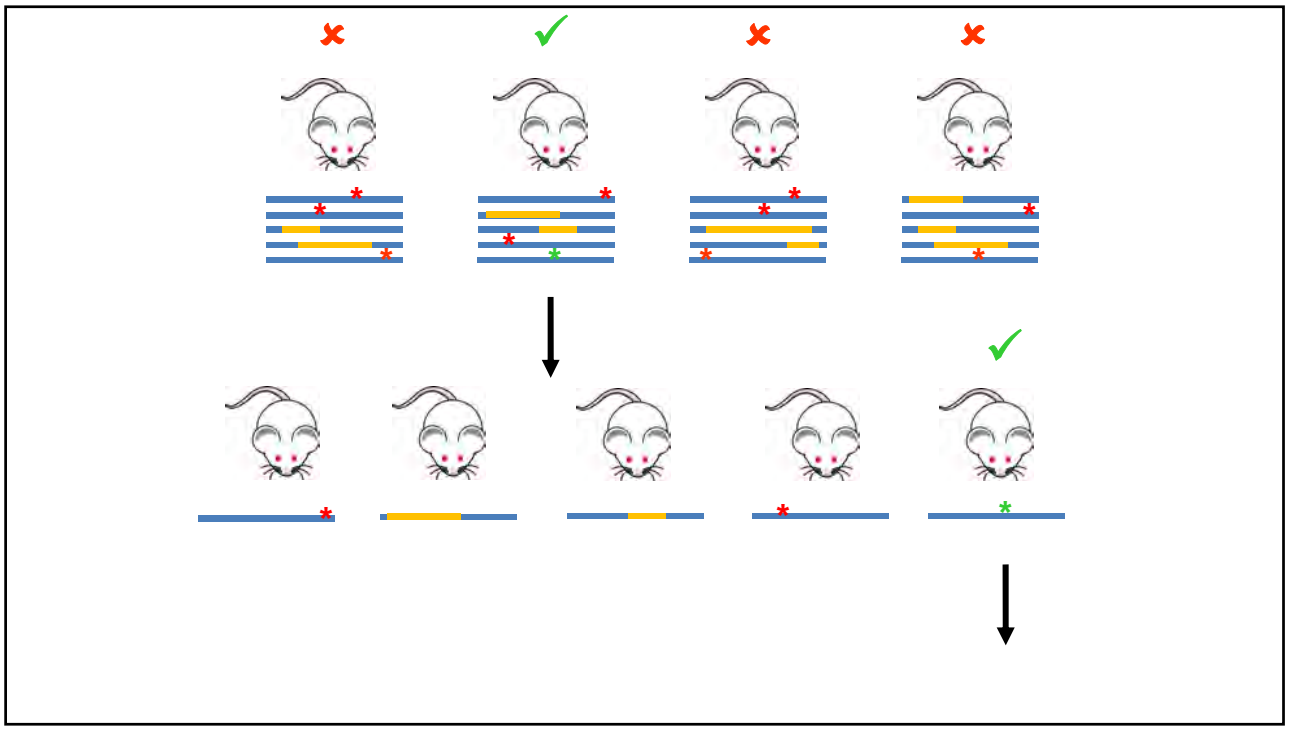
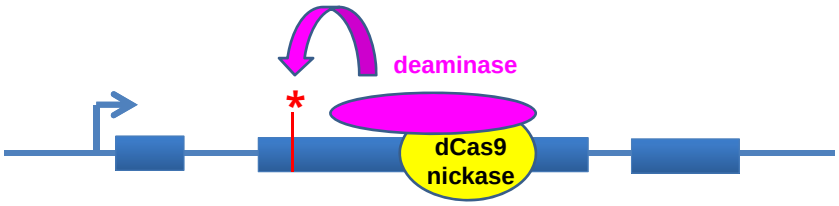


Solutions to the limitations of CRISPR-Cas9 genome editing tools

Base editing a gene

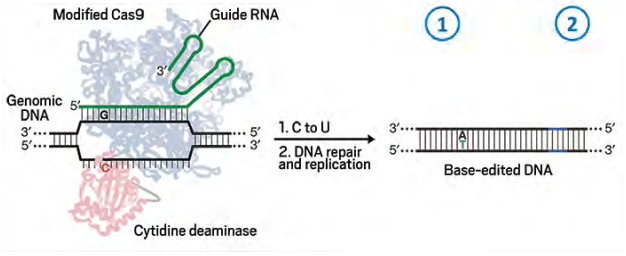


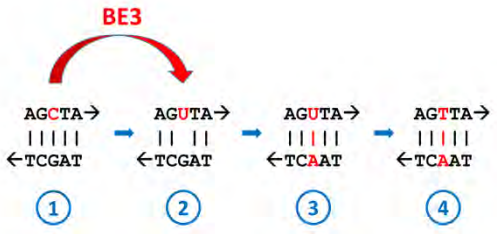
David Liu Lab

CRISPR-derived BASE EDITORS (BE3) CBE and ABE

CBE: C → U → T

ABE: A → I → G

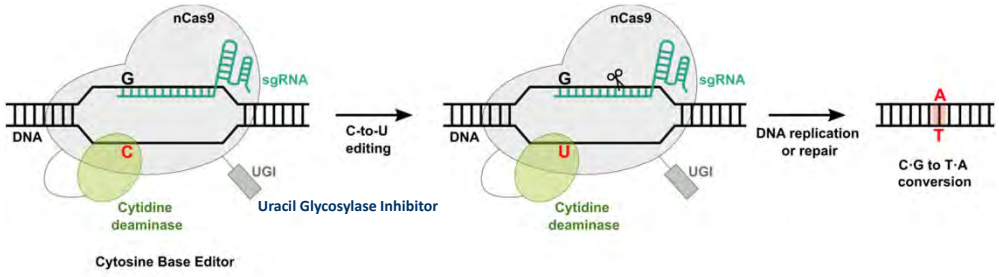




Komor et al. Nature 2016

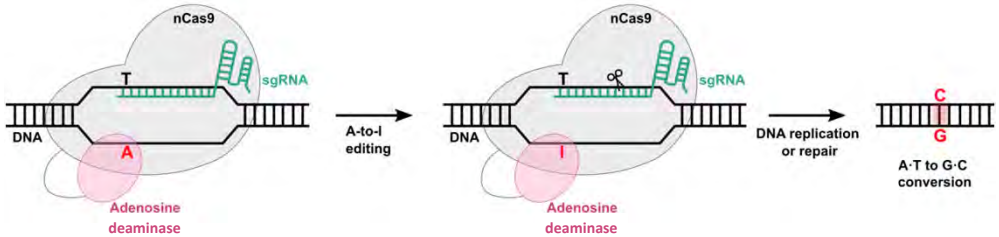
AGGATTAGAGCCGATAGCATACGATCAGTACGAT

CBE



Cytosine Base Editor

ABE



https://biotech.ucdavis.edu/news/dna-base-editors-genome-editing

New base editors: CGBE C→G

nature biotechnology

ARTICLES

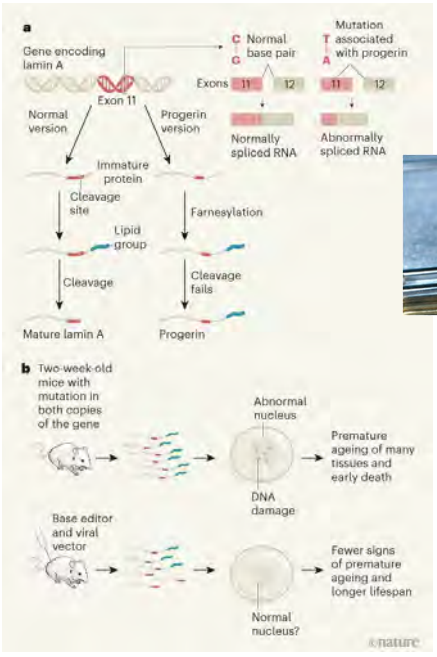
https://doi.org/10.1038/s41587-021-00938-z

Check for updates

Efficient C•G-to-G•C base editors developed using CRISPRi screens, target-library analysis, and machine learning

Luke W. Koblan[1,2,3,15], Mandana Arbab[1,2,3,15], Max W. Shen[1,2,3,4,15], Jeffrey A. Hussmann[5,6,7,13,14], Andrew V. Anzalone[1,2,3], Jordan L. Doman[1,2,3], Gregory A. Newby[1,2,3], Dian Yang[5,7,13,14], Beverly Mok[1,2,3], Joseph M. Replogle[5,7,8,9,13,14], Albert Xu[5,6,8,10], Tyler A. Sisley[2], Jonathan S. Weissman[5,7,8,13,14] ✉, Britt Adamson[5,7,11,12] ✉ and David R. Liu[1,2,3] ✉

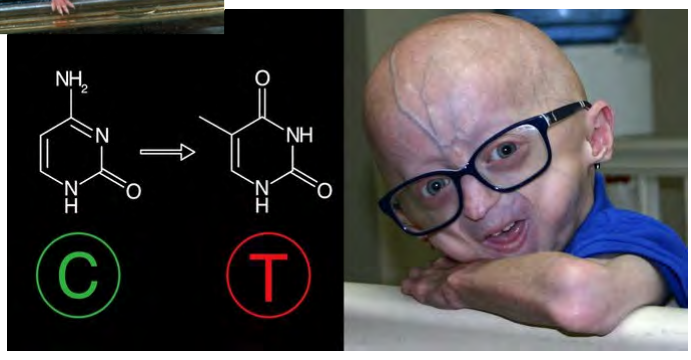
Koblan et al. Nat. Biotech. (2021)



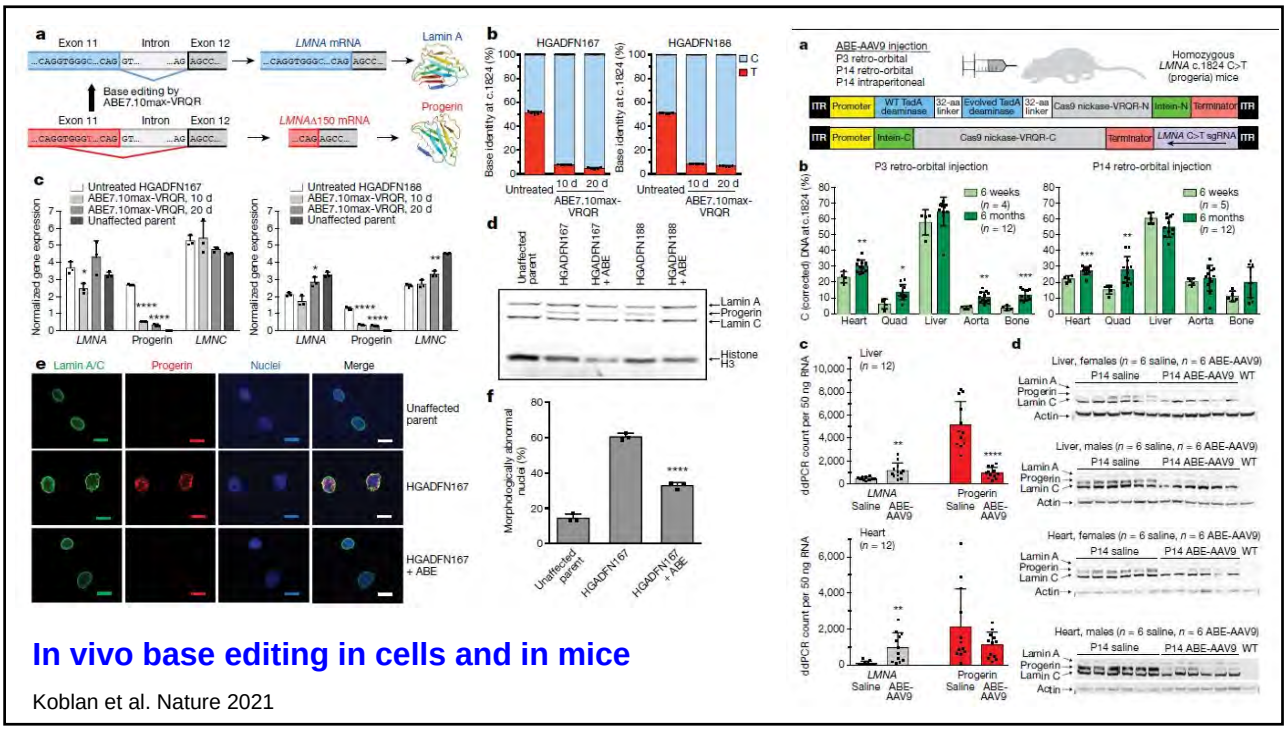
Article

In vivo base editing rescues Hutchinson–Gilford progeria syndrome in mice

Luke W. Koblan[1,2,3,15], Michael R. Erdos[4,15], Christopher Wilson[1,2,3], Wayne A. Cabral[4], Jonathan M. Levy[1,2,3], Zheng-Mei Xiong[4], Urraca L. Tavarez[4], Lindsay M. Davison[5], Yantenew G. Gete[6], Xiaojing Mao[6], Gregory A. Newby[1,2,3], Sean P. Doherty[5], Narisu Narisu[4], Quanhu Sheng[7], Chad Krilow[4], Charles Y. Lin[8,9,12], Leslie B. Gordon[10,11], Kan Cao[6], Francis S. Collins[4] ✉, Jonathan D. Brown[1,2,3] ✉ & David R. Liu[1,2,3] ✉



Koblan et al. Nature 2021



In vivo base editing in cells and in mice

Koblan et al. Nature 2021

Article

In vivo CRISPR base editing of *PCSK9* durably lowers cholesterol in primates

https://doi.org/10.1038/s41586-021-03534-y

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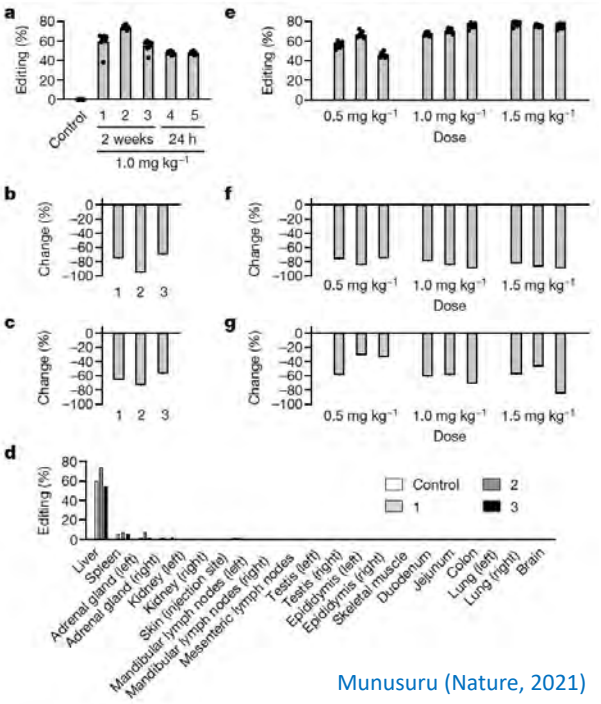
Nature (2021)



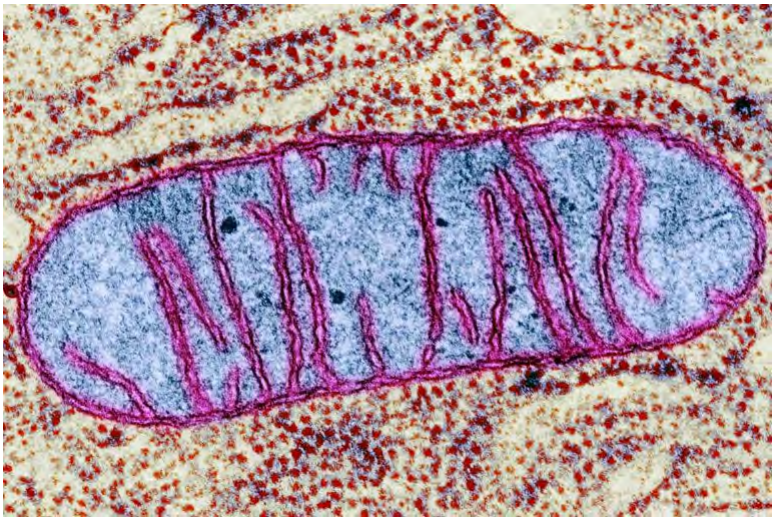
Munusuru (Nature, 2021)

PCSK9 ⊣ LDL receptor ↑

LDL ↓

Reduced risk of aterosclerosis & cardiovascular diseases

CRISPR genome editing and mitochondria



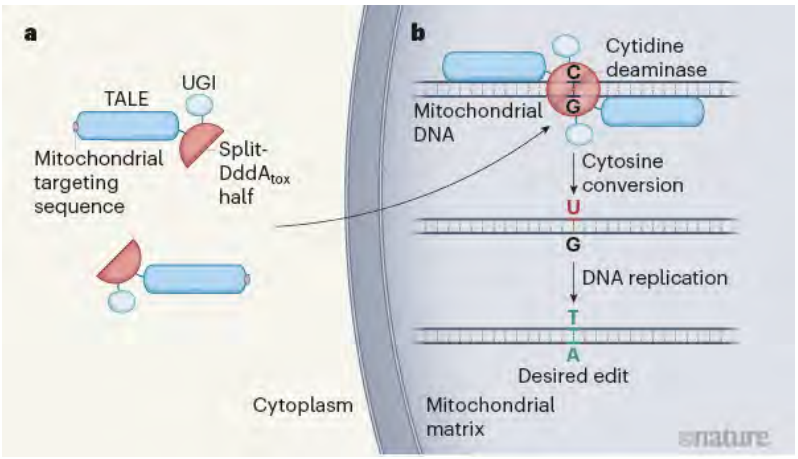
Article | Published: 08 July 2020

A bacterial cytidine deaminase toxin enables CRISPR-free mitochondrial base editing

Beverly Y. Mok, Marcos H. de Moraes, Jun Zeng, Dustin E. Bosch, Anna V. Kotrys, Aditya Raguram, FoSheng Hsu, Matthew C. Radey, S. Brook Peterson, Vamsi K. Mootha, Joseph D. Mougous & David R. Liu

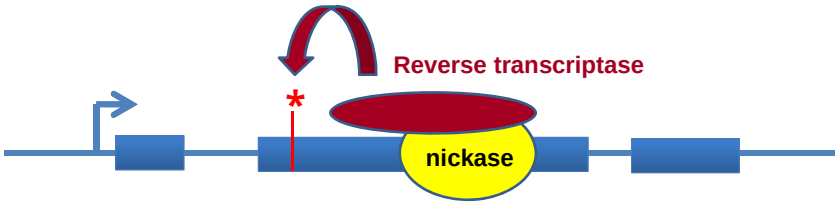
Nature **583**, 631–637(2020) | Cite this article

July 2020

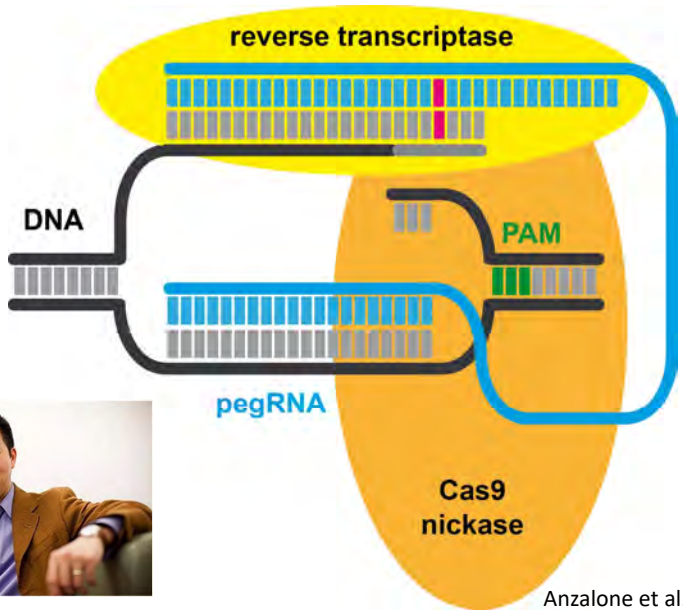


Mok et al. 2020

Prime editing a gene



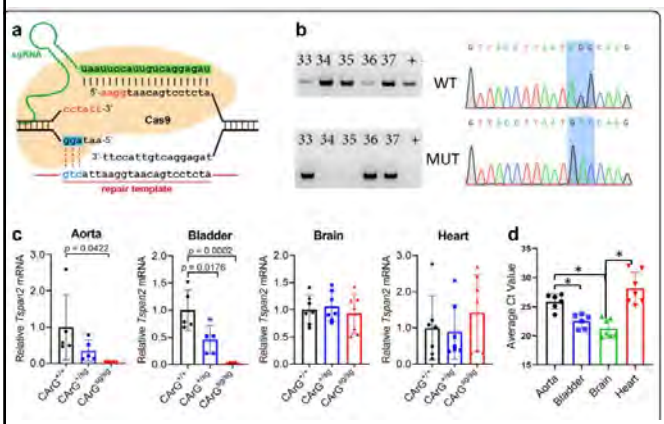
Prime editing a gene

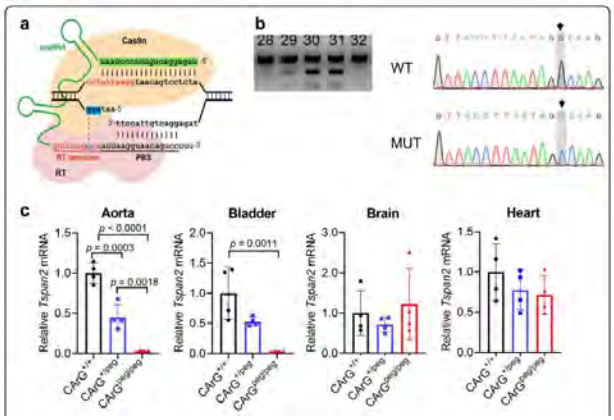


David Liu Lab

Anzalone et al. Nature 2019

CRISPR-Cas9 mediated gene editing **vs** **Prime-mediated gene editing**





56% correct on-targeting
40% INDELS (mosaicism)

21% correct on-targeting
0% INDELS (mosaicism)

Gao et al. 2021 Genome Biol

nature biotechnology

ARTICLES

https://doi.org/10.1038/s41587-021-01039-7

Check for updates

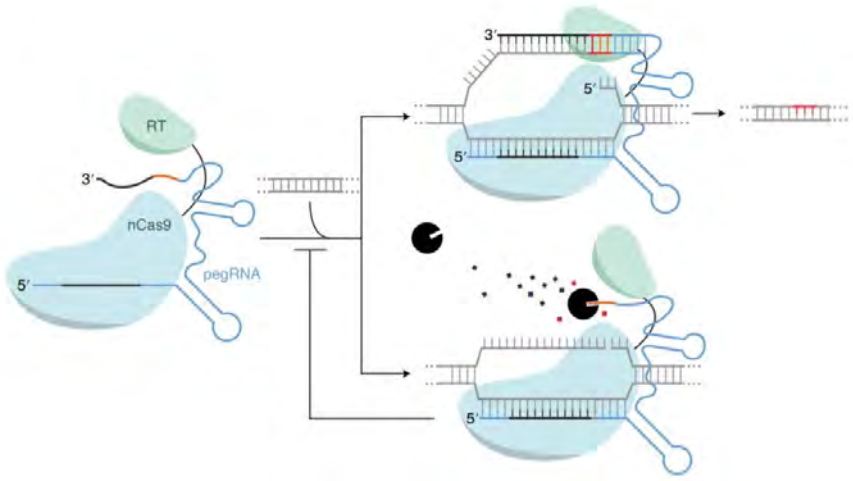
Engineered pegRNAs improve prime editing efficiency

James W. Nelson[1,2,3,4], Peyton B. Randolph[1,2,3,4], Simon P. Shen[1,2,3], Kelcee A. Everette[1,2,3], Peter J. Chen[1,2,3], Andrew V. Anzalone[1,2,3], Meirui An[1,2,3], Gregory A. Newby[1,2,3], Jonathan C. Chen[1,2,3], Alvin Hsu[1,2,3] and David R. Liu[1,2,3]✉

Prime editing enables the installation of virtually any combination of point mutations, small insertions or small deletions in the DNA of living cells. A prime editing guide RNA (pegRNA) directs the prime editor protein to the targeted locus and also encodes the desired edit. Here we show that degradation of the 3′ region of the pegRNA that contains the reverse transcriptase template and the primer binding site can poison the activity of prime editing systems, impeding editing efficiency. We incorporated structured RNA motifs to the 3′ terminus of pegRNAs that enhance their stability and prevent degradation of the 3′ extension. The resulting engineered pegRNAs (epegRNAs) improve prime editing efficiency 3–4-fold in HeLa, U2OS and K562 cells and in primary human fibroblasts without increasing off-target editing activity. We optimized the choice of 3′ structural motif and developed pegLIT, a computational tool to identify non-interfering nucleotide linkers between pegRNAs and 3′ motifs. Finally, we showed that epegRNAs enhance the efficiency of the installation or correction of disease-relevant mutations.

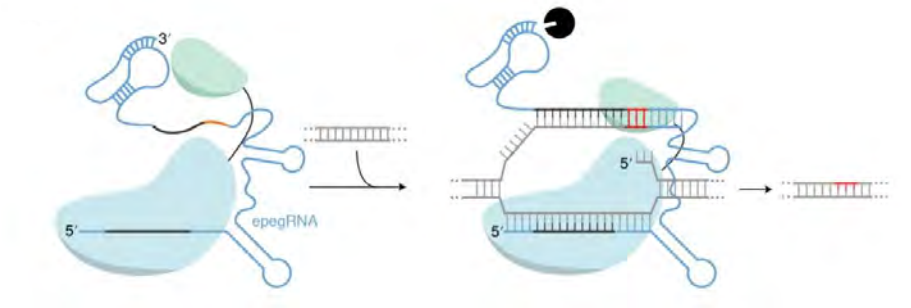
4 October 2021

3’ degradation of pegRNA inhibits prime editing



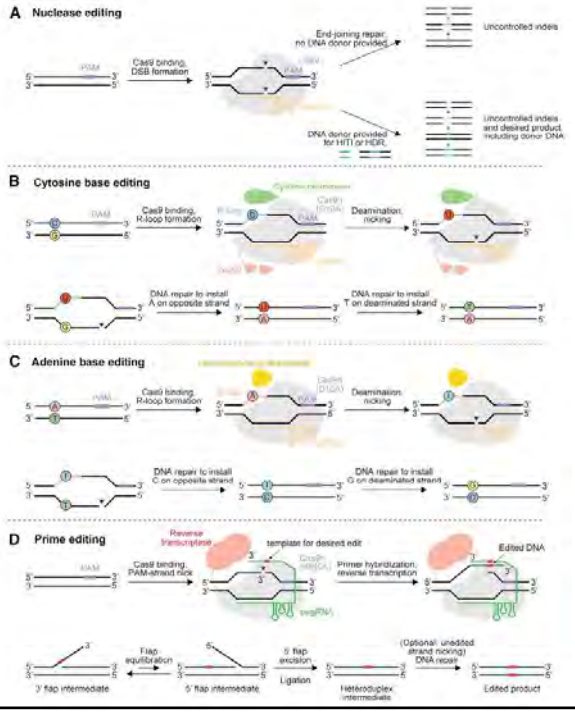
Nelson et al. (2021) Nature Biotechnology

3’ structure protection of pegRNA enhances prime editing



epegRNA “enhanced pegRNA”

Nelson et al. (2021) Nature Biotechnology



Current CRISPR variants to be used in gene therapy approaches

- **CRISPR-Cas9**
- **Base editors**
- **Prime editors**

Newby & Liu, Mol. Therapy (2021)

CRISPR-Cas is the future

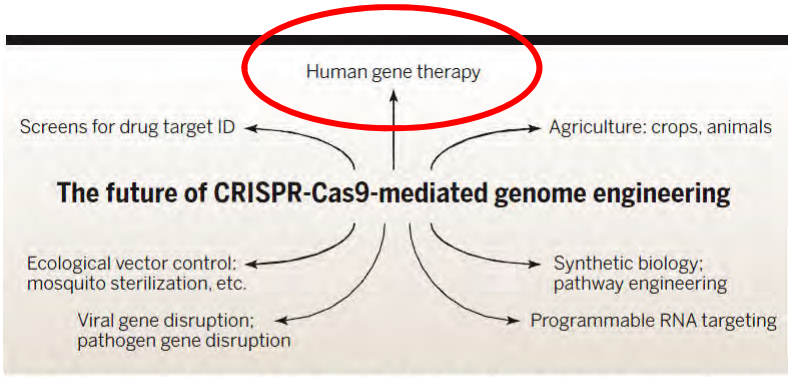
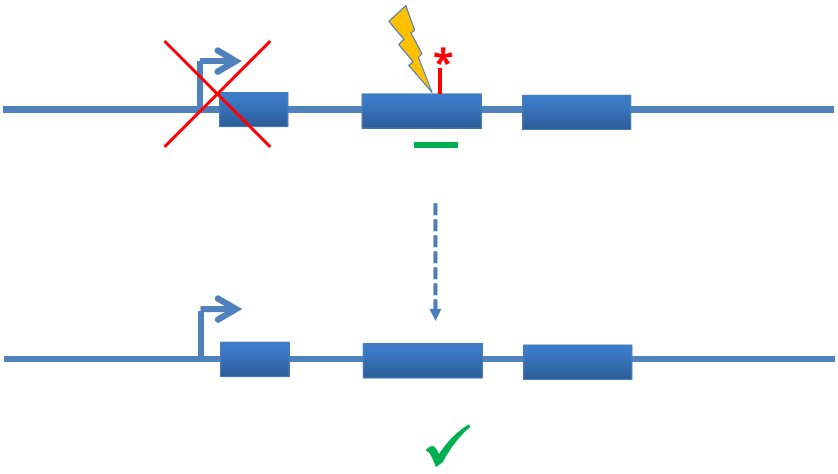
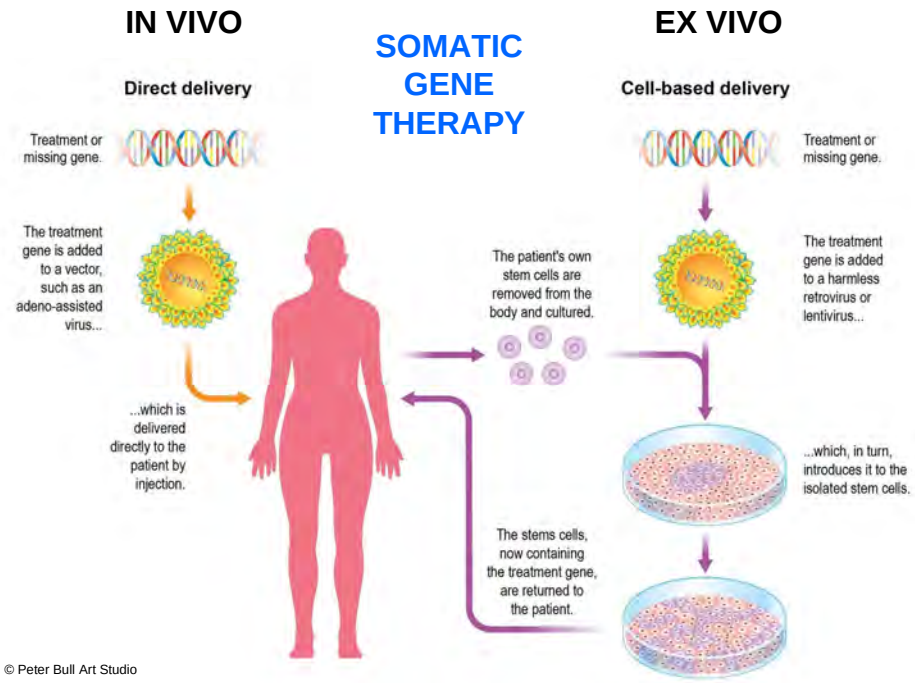


Fig. 6. Future applications in biomedicine and biotechnology. Potential developments include establishment of screens for target identification, human gene therapy by gene repair and gene disruption, gene disruption of viral sequences, and programmable RNA targeting.

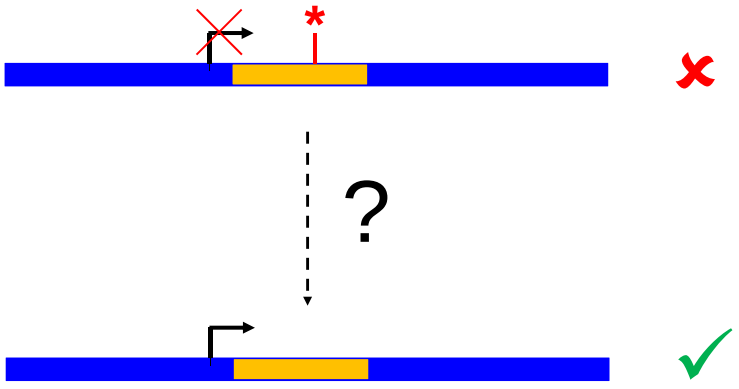
Doudna & Charpentier (2014) *Science*

Gene Therapy with CRISPR

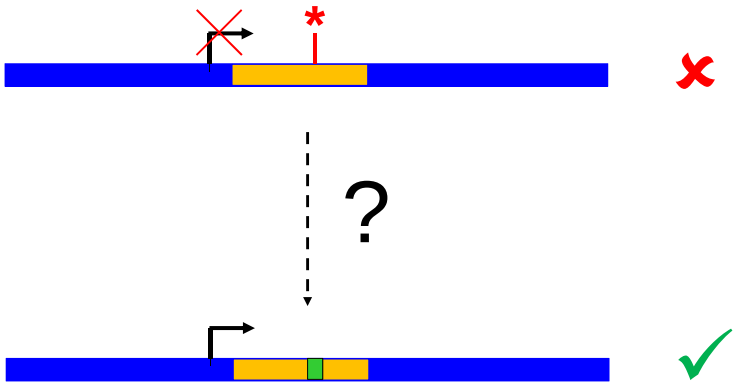




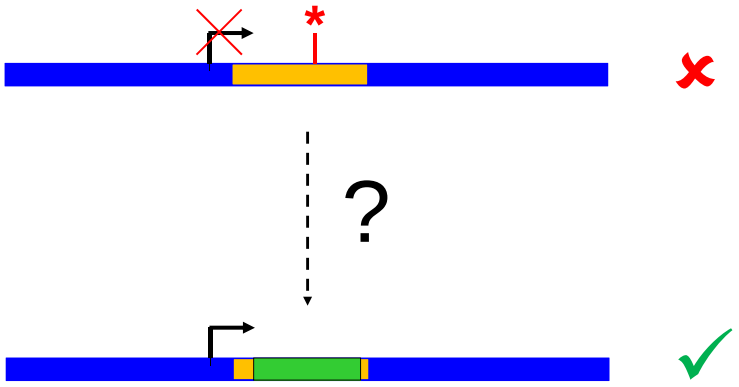
Gene Therapy



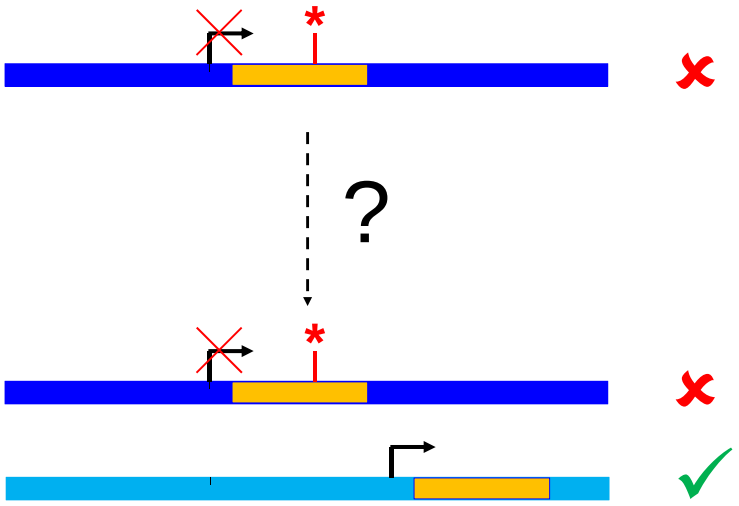
Gene Therapy



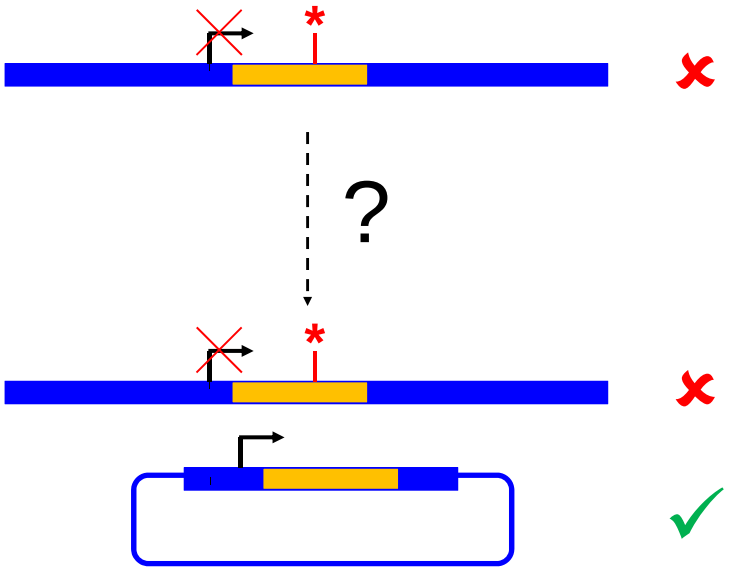
Gene Therapy



Gene Therapy

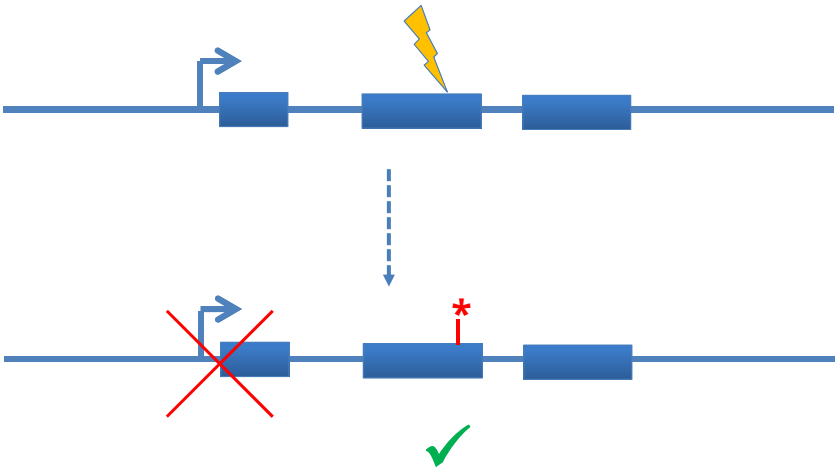


Gene Therapy

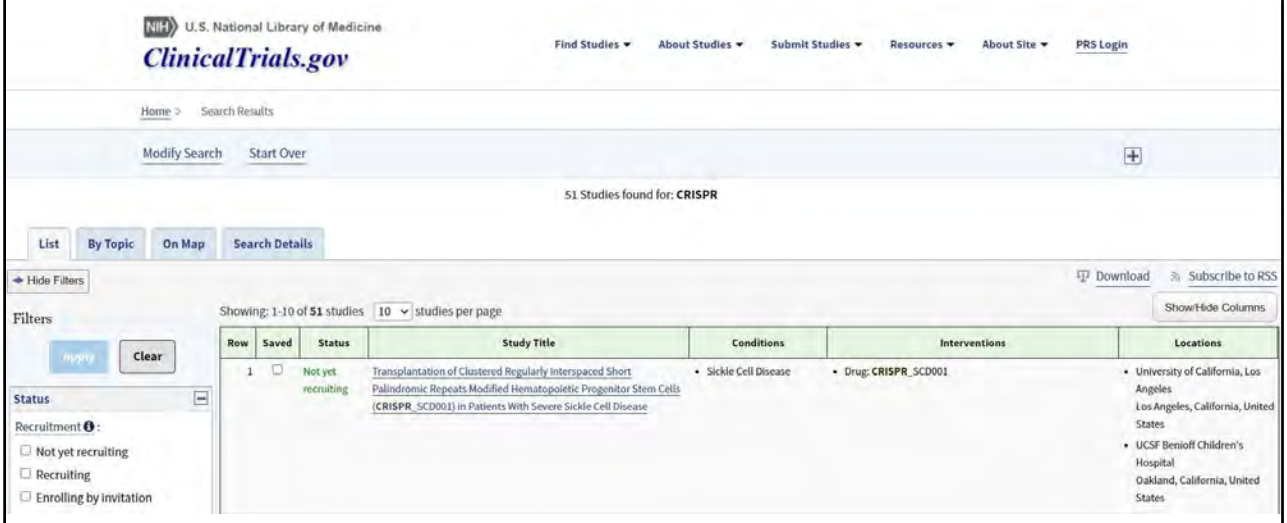


Luxturna (Spark Therapeutics, Inc.)
Treatment of retinal degenerative diseases (RPE65 gene)

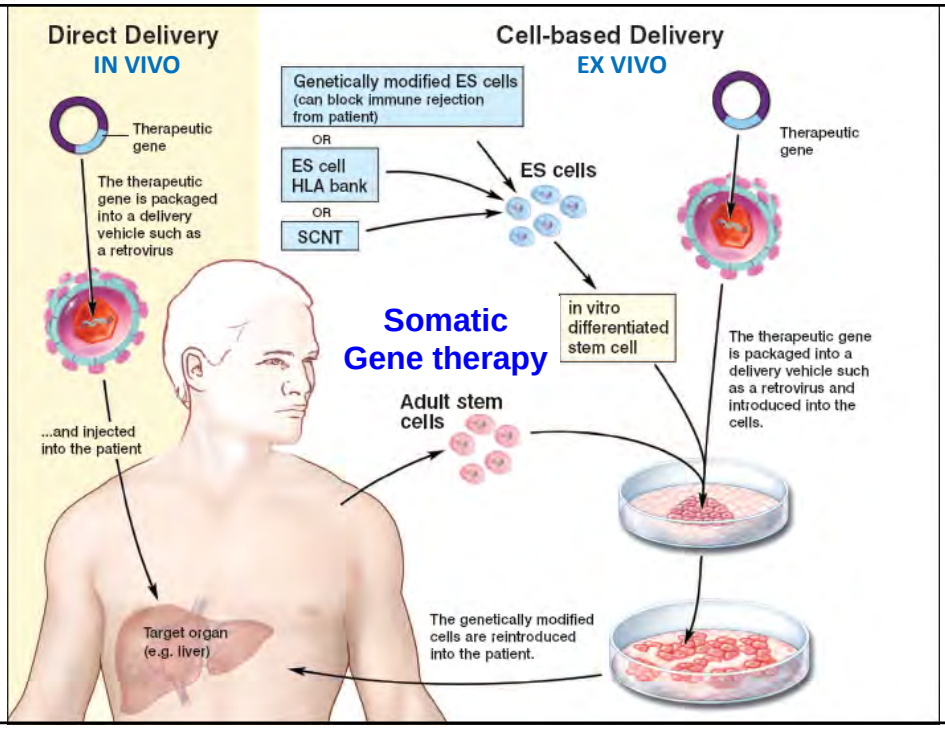
CRISPR gene therapy (currently)



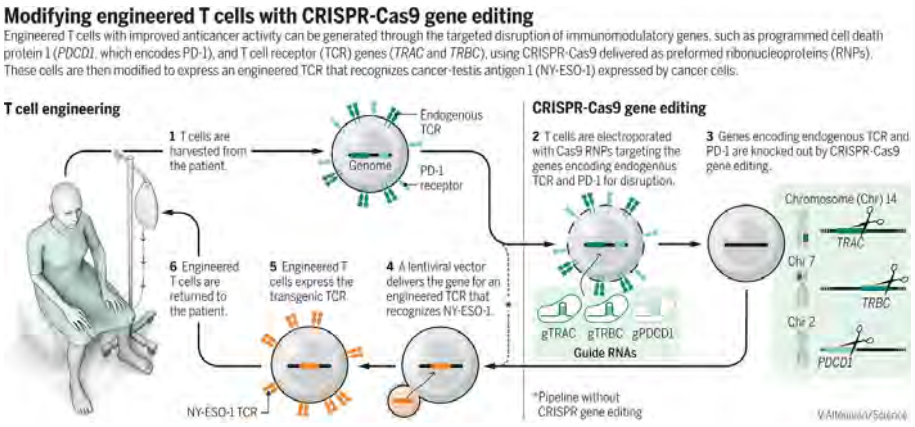
51 clinical trials today with CRISPR



Most of them are EX-VIVO



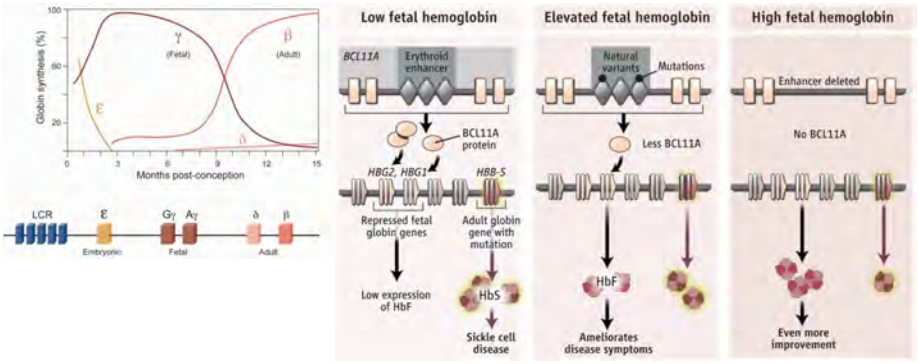
Cancer Immunotherapy with CRISPR



6 Feb 2020

Hamilton & Doudna (Science, 2020)
Stadtmauer et al. (Carl June Lab, Science 2020)

Treating sickle-cell anemia and beta-thalassemia withn CRISPR



Bauer Lab (Dana Farber-Boston Children's)

CRISPR THERAPEUTICS

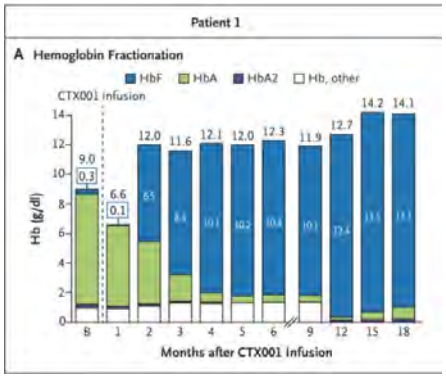
VERTEX

First ex-vivo CRISPR therapy approved in Europe

November 2019

First CRISPR-treated Sickle Cell Anemia patients cured (2020)

Victoria Gray (treated July 2, 2019)

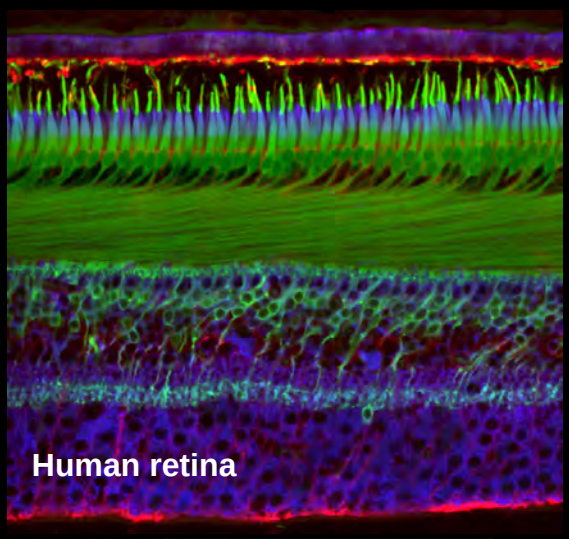


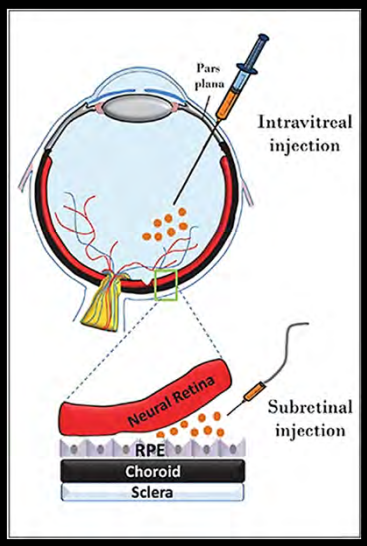
Frangoul *et al.* NEJM (5 December 2020)

NPR

Correcting mutations in CEP290 gene with CRISPR

Leber Congenital Amaurosis type 10



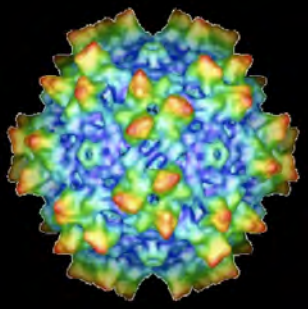


editas MEDICINE Allergan

In vivo

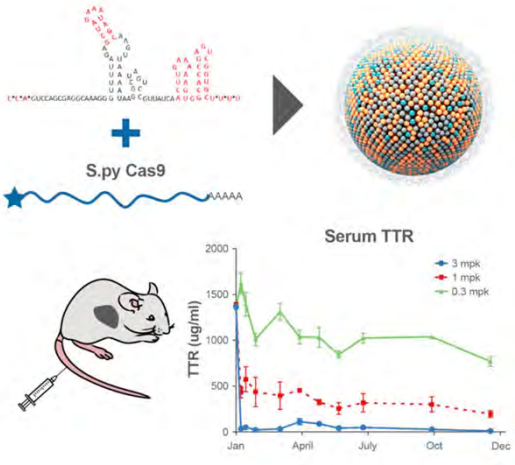
Dec 2018

Adenoassociated virus (AAV) to bring CRISPR to cells



AAV

Transthyretine Amylodosis congenital (ATTR)
NANOTECNOLOGY - Nanoparticles



Finn et al. Cell Reports 2018 22, 2227-2235DOI: (10.1016/j.celrep.2018.02.014)

October 2020

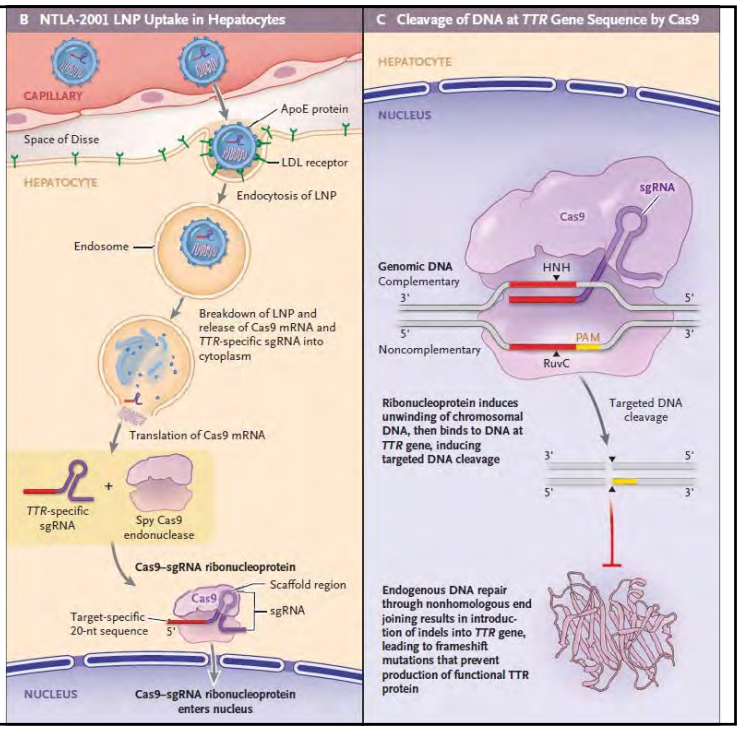
The NEW ENGLAND JOURNAL of MEDICINE

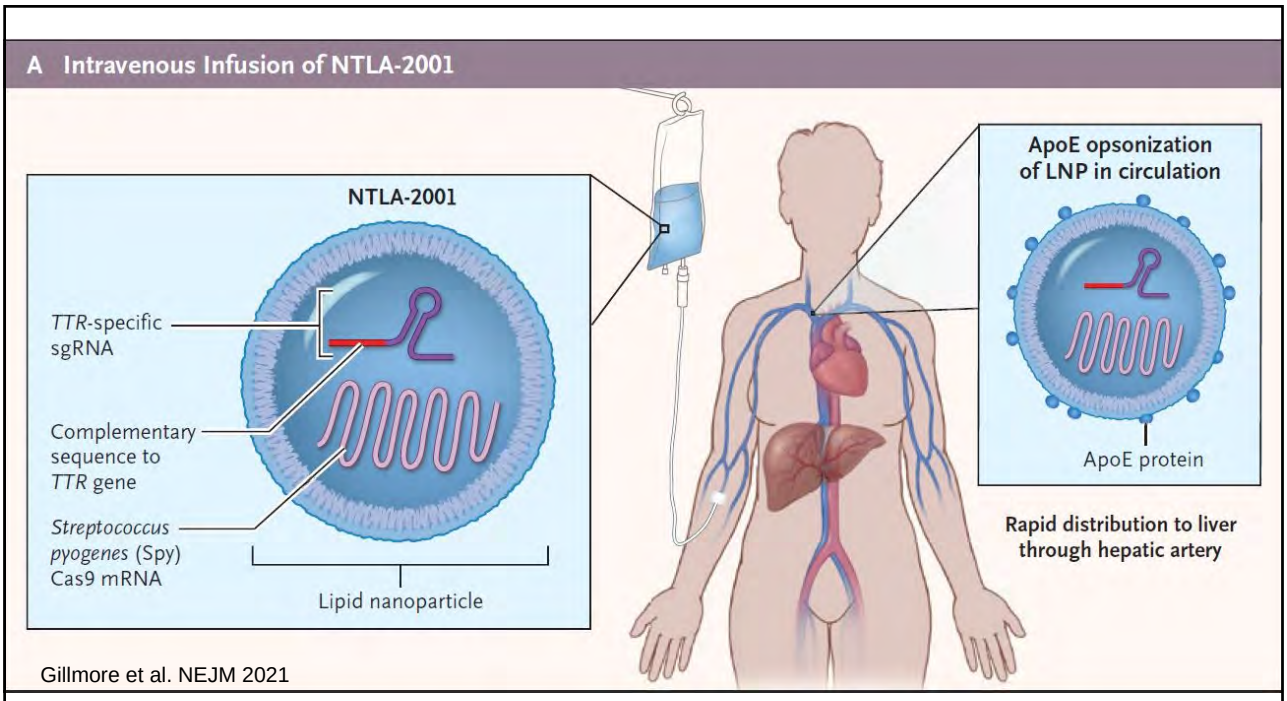
ORIGINAL ARTICLE

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

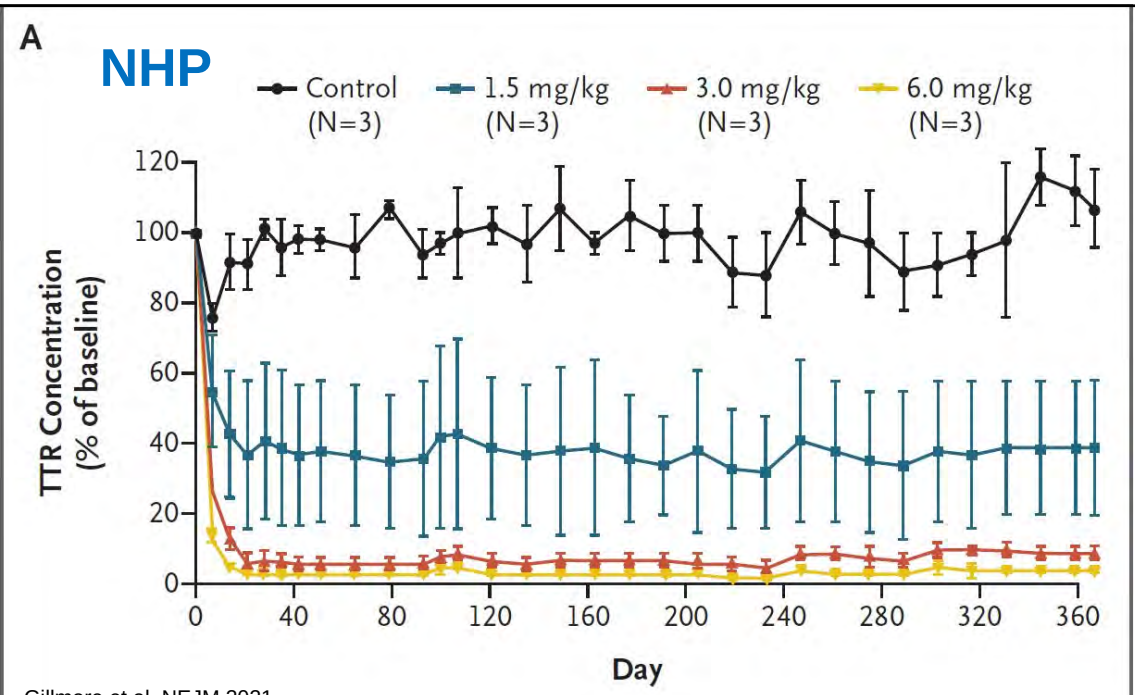
Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.

26 June 2021

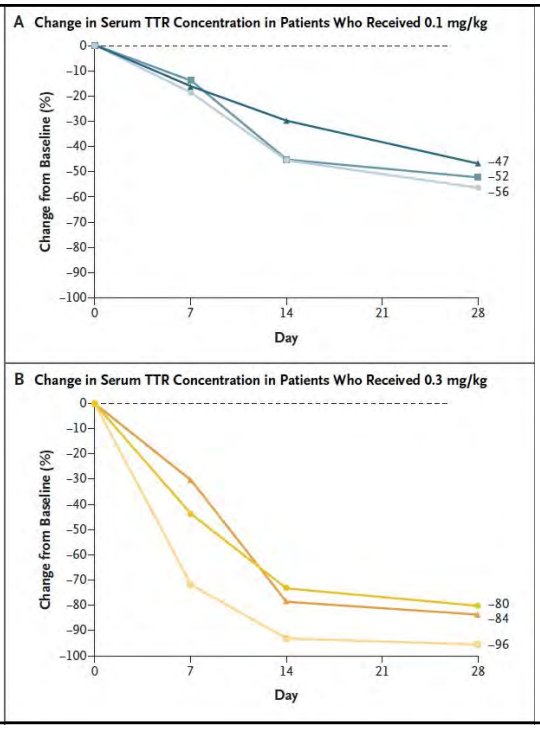




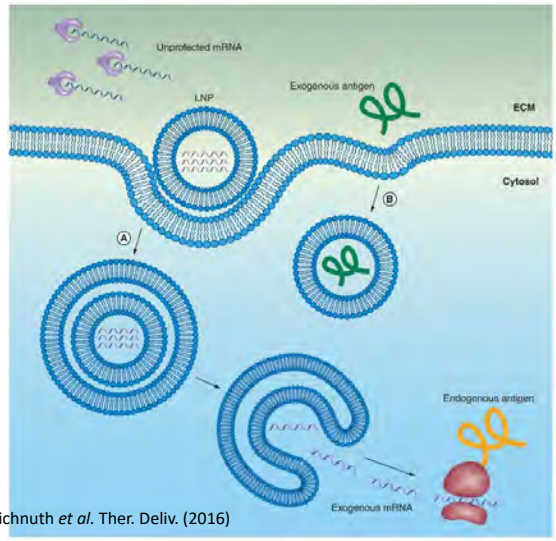
Gillmore et al. NEJM 2021



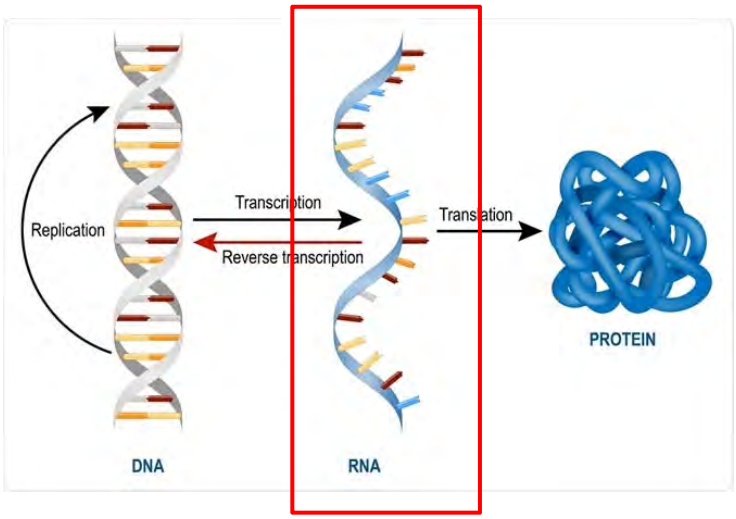
Gillmore et al. NEJM 2021

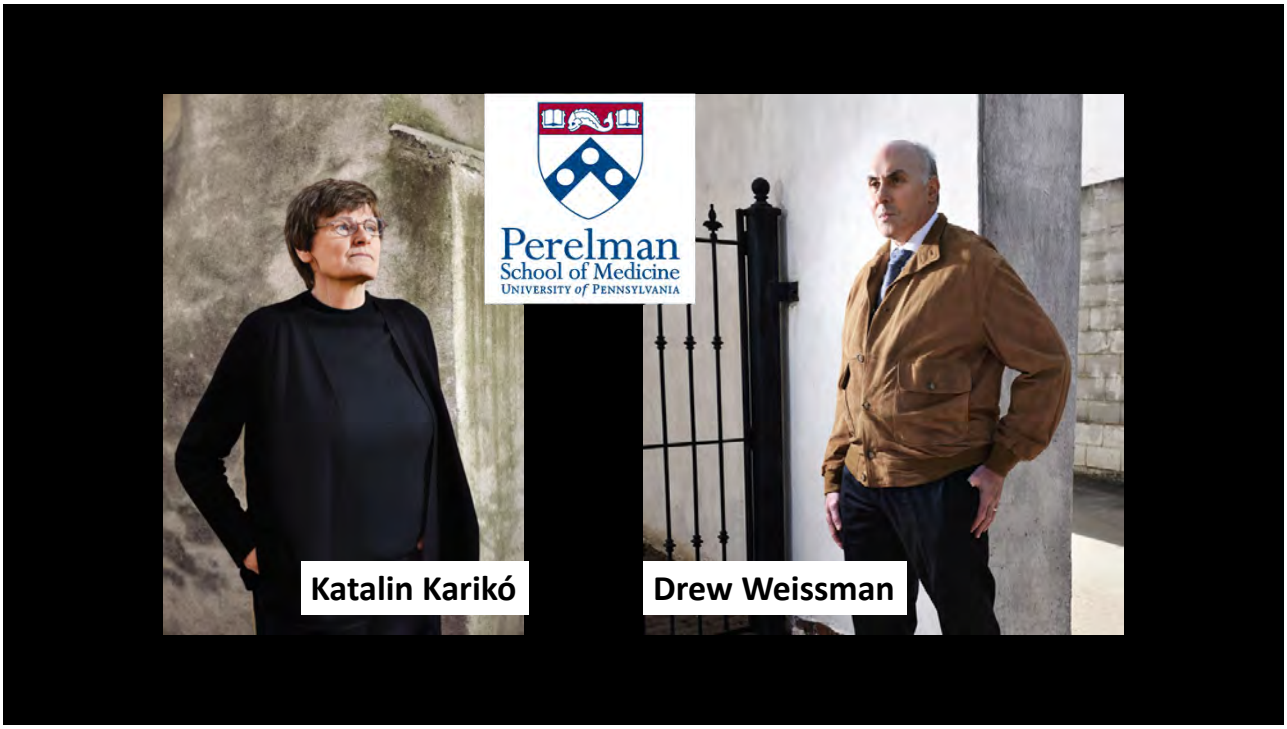


Gillmore et al. NEJM 2021



Reichnuth *et al.* Ther. Deliv. (2016)


Replication
Transcription
Reverse transcription
Translation
PROTEIN
DNA
RNA

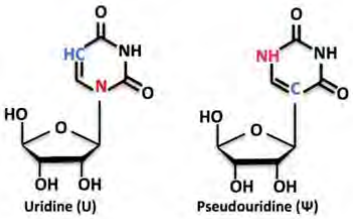

Perelman
School of Medicine
University of Pennsylvania
Katalin Karikó
Drew Weissman

Immunity, Vol. 23, 165–175, August, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.06.008

2005

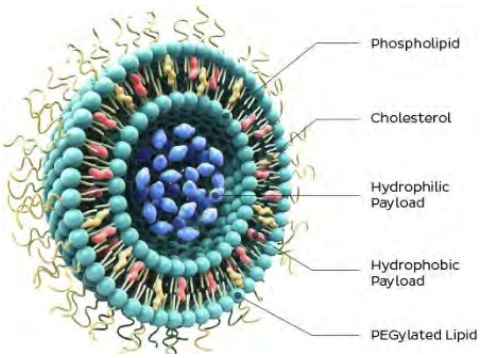
Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

Katalin Karikó,[1,*] Michael Buckstein,[2] Houping Ni,[2] and Drew Weissman[2]
[1]Department of Neurosurgery
[2]Department of Medicine
University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania 19104



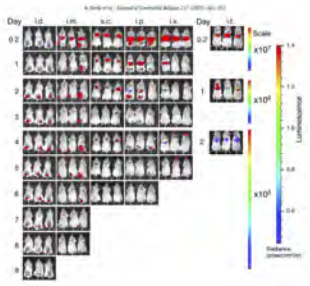
Modified nucleosides does not trigger an immune response

Lipid NanoParticles (LNP)



RNA

2015



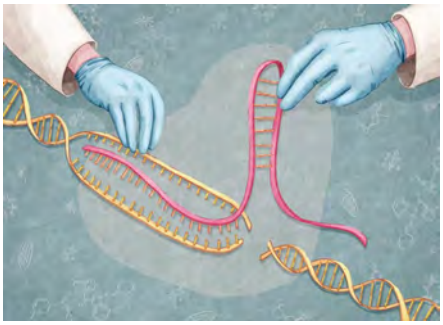
Journal of Controlled Release

Expression kinetics of nucleoside-modified mRNA delivered in lipid nanoparticles to mice by various routes

Encapsulating modified mRNA in LNPs extends the translation period

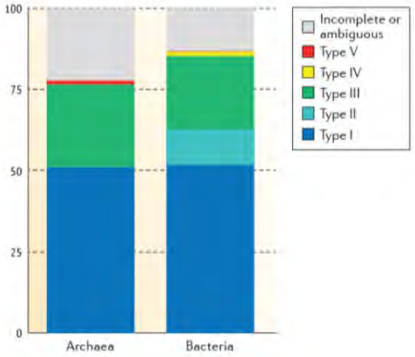
CRISPR & gene therapy (today) – clinical trials

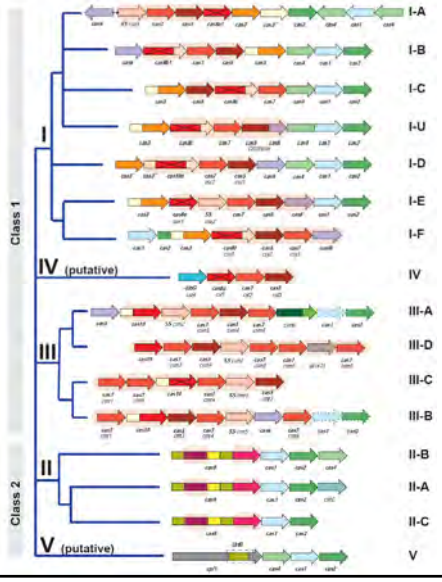
- **Inactivating genes** → CRISPR-Cas9 or base editors
- **Correcting genes** → Base editors
- **Technologies used** → mRNA + lipid nanoparticles (LNPs)



Diversity of CRISPR-Cas systems

An updated evolutionary classification of CRISPR–Cas systems
Makarova *et al.* **Nature Rev. Microbiol. 2015**

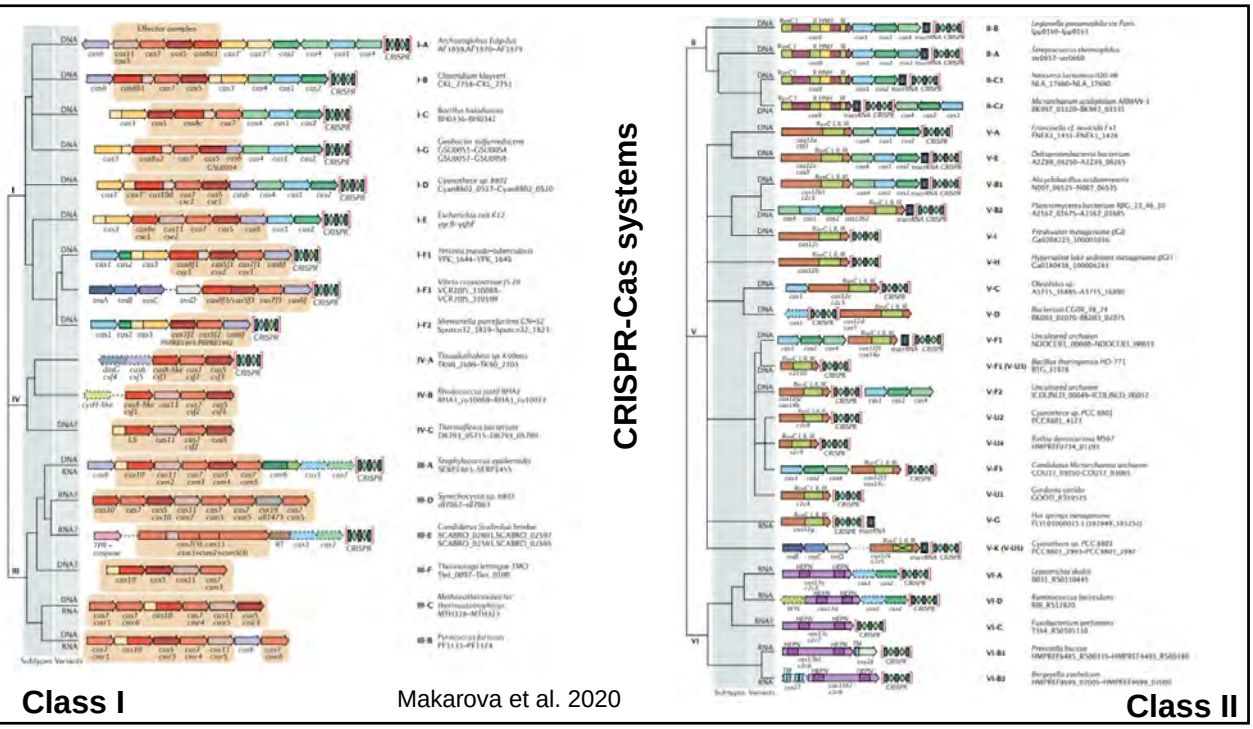




REVIEWS

Evolutionary classification of CRISPR–Cas systems: a burst of class 2 and derived variants

*Kira S. Makarova[1], Yuri I. Wolf[1], Jaime Iranzo[1], Sergey A. Shmakov[1], Omer S. Alkhnbashi[2], Stan J. J. Brouns[3], Emmanuelle Charpentier[4], David Cheng[5], Daniel H. Haft[1], Philippe Horvath[6], Sylvain Moineau[7], Francisco J. M. Mojica[8], David Scott[5], Shiraz A. Shah[9], Virginijus Siksnys[10], Michael P. Terns[11], Česlovas Venclovas[10], Malcolm F. White[12], Alexander F. Yakunin[13,14], Winston Yan[5], Feng Zhang[15,16,17,18], Roger A. Garrett[19], Rolf Backofen[2,20], John van der Oost[21], Rodolphe Barrangou[22] and Eugene V. Koonin[1]**



The widespread IS200/605 transposon family encodes diverse programmable RNA-guided endonucleases

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CRISPR

Las 'tatarabuelas' de las tijeras moleculares CRISPR harán más sencilla la edición genética

Investigadores de EE UU liderados por Feng Zhang, uno de los pioneros del corta-pega genético, han descubierto una clase de nucleasas que podrían ser los ancestros de las más utilizadas, Cas9 y Cas12. Su pequeña longitud permitiría facilitar el proceso.

Ana Hernando 9/9/2021 20:00 CEST

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ALBA Asociación de ayuda a personas con albinismo

feder

frA FUNDACIÓN RAMÓN ARECES

mid Un lugar para la ciencia y la tecnología

CSIC Consejo Superior de Investigaciones Científicas

CNB Centro Nacional de Biotecnología

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EMMA mouse repository

INFRAFRONTIER mouse disease models

Horizon 2020 European Union Funding for Research & Innovation