Therapeutic Genome Editing

December 2019

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Today's Presenters

Natalia
Gomez-Ospina, MD, PhD

Kiran Musunuru,
MD, PhD, MPH, ML

Bruce Korf, MD, PhD
Moderator

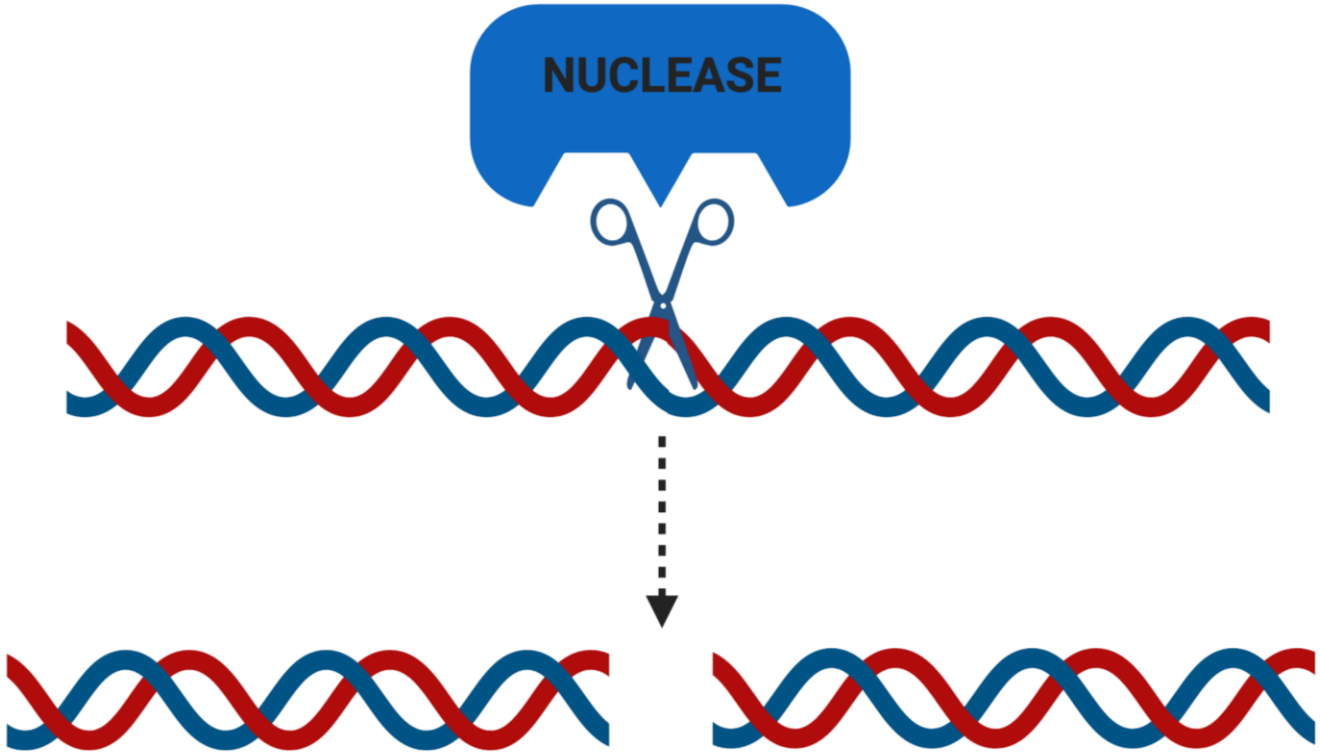
We will now hear from Dr. Natalia Gomez-Ospina.

The genome editing tool box

- Nuclease-based and non-nuclease-based genome editing
- Combining double-strand breaks and DNA repair for therapeutic genome editing
- Choosing your tools: how disease pathophysiology informs intended modifications

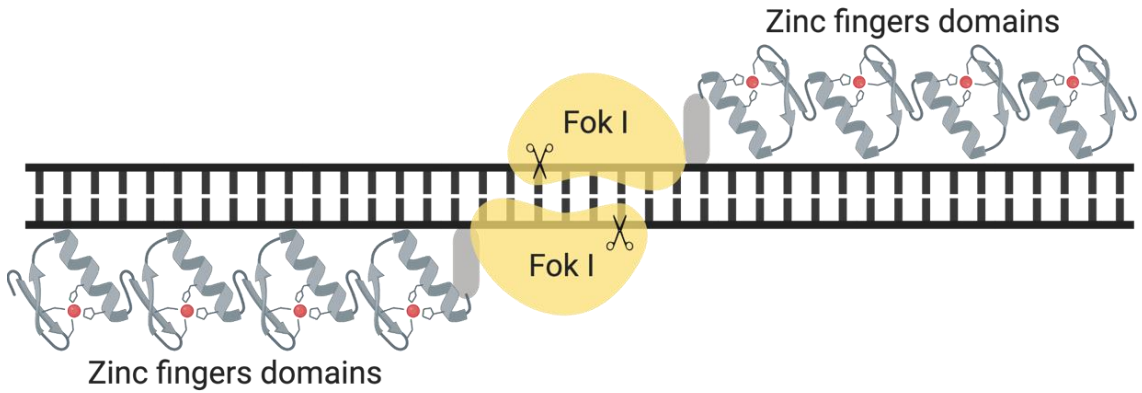
Nuclease-based genome editing

Creating double-strand DNA breaks at specific locations



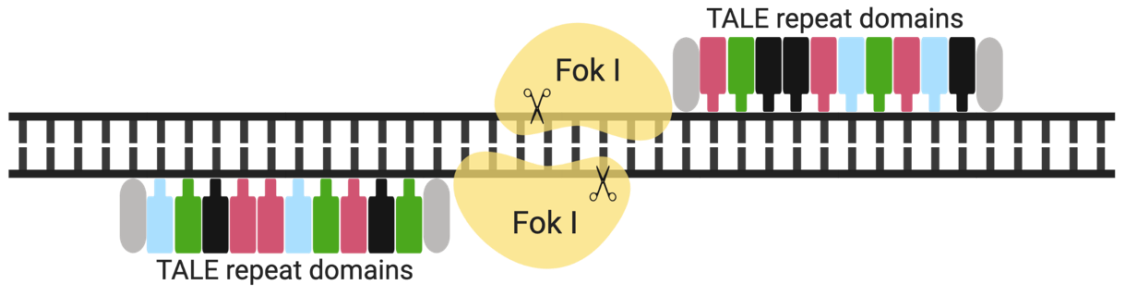
Nuclease-based genome editing: Protein-guided platforms

Zinc Finger Nucleases (ZFNs)



- **Nuclease**: Fok1
- **DNA recognition:** Array of zinc finger repeats

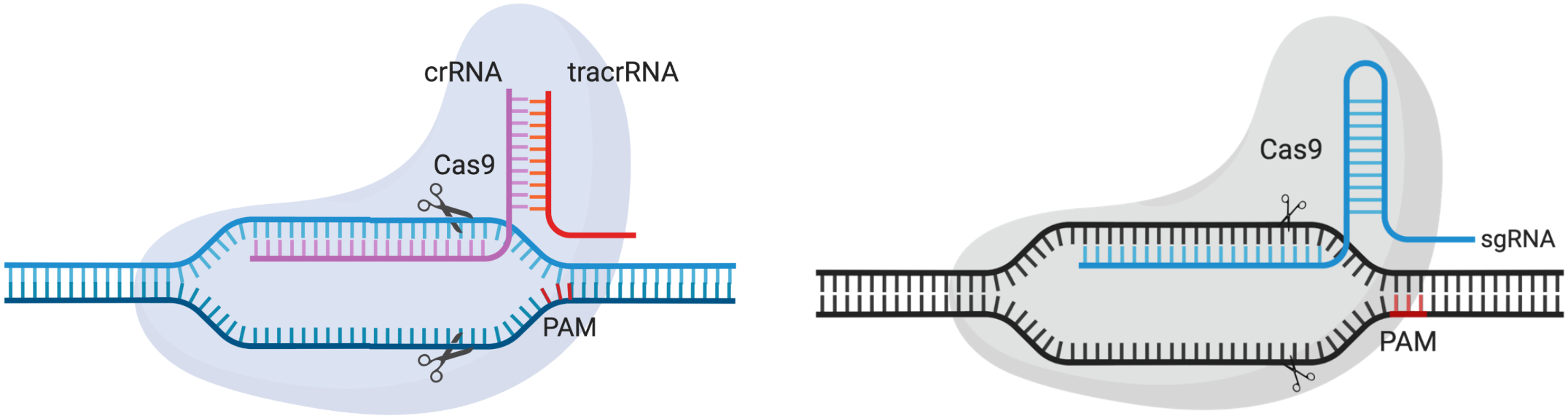
Transcription activator-like effector nucleases (TALENs)



- **Nuclease**: Fok1
- **DNA recognition:** Transcription activator-like effector DNA-binding domain

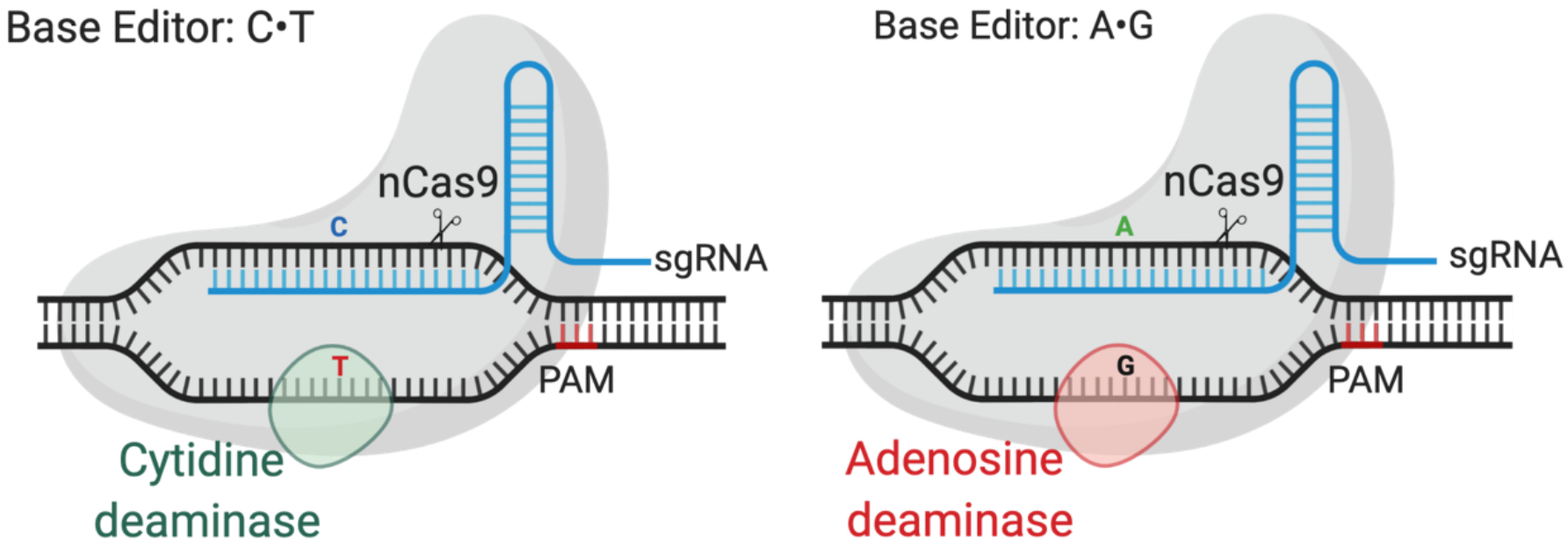
Nuclease-based genome editing: RNA-guided platforms

Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)–Cas9 system



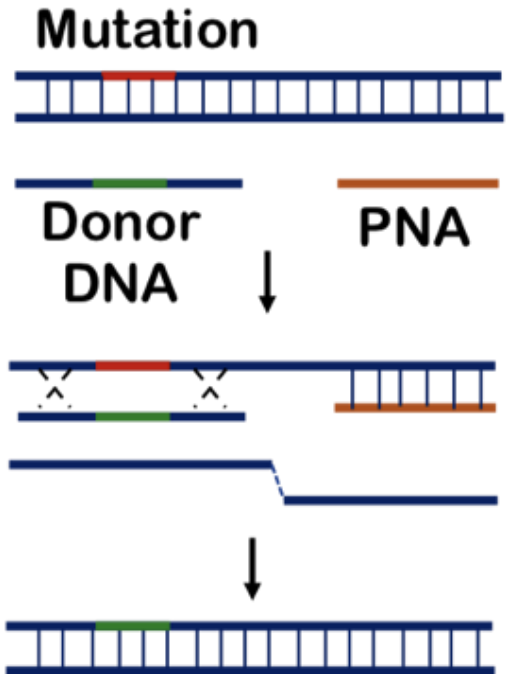
Nuclease-based genome editing: RNA-guided platforms

Base editors

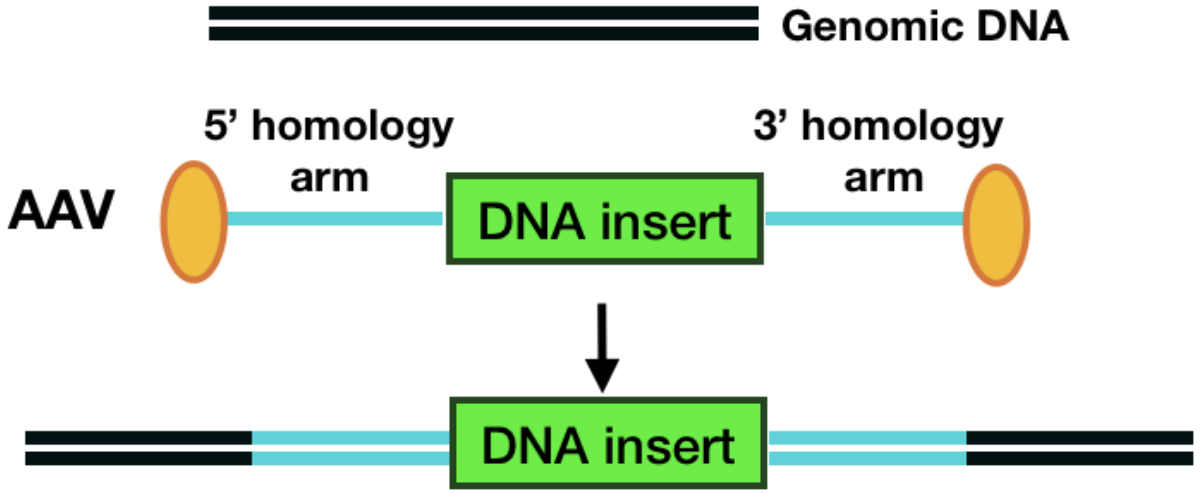


Nuclease-free genome editing

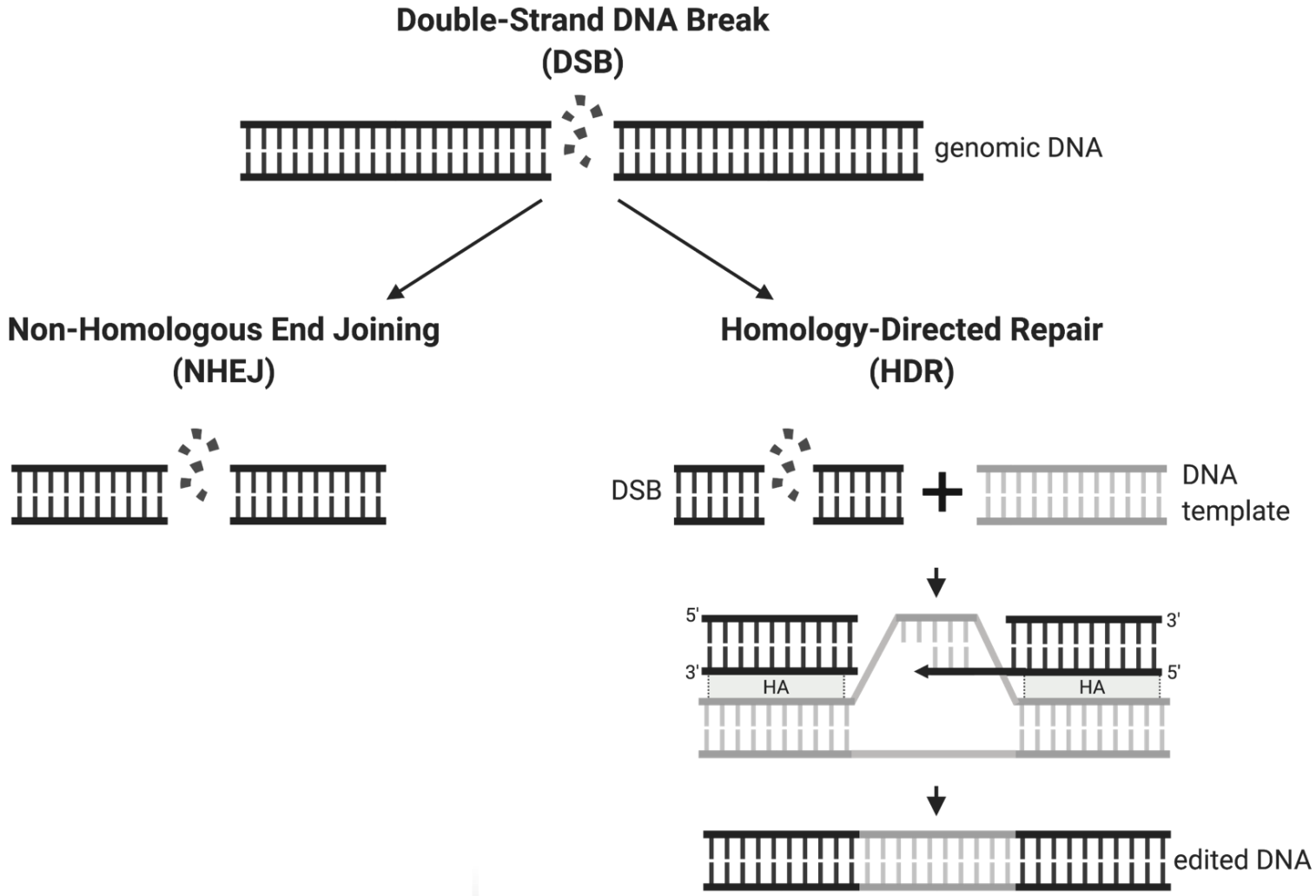
Peptide nucleic acids (PNAs)



Gene targeting without nucleases



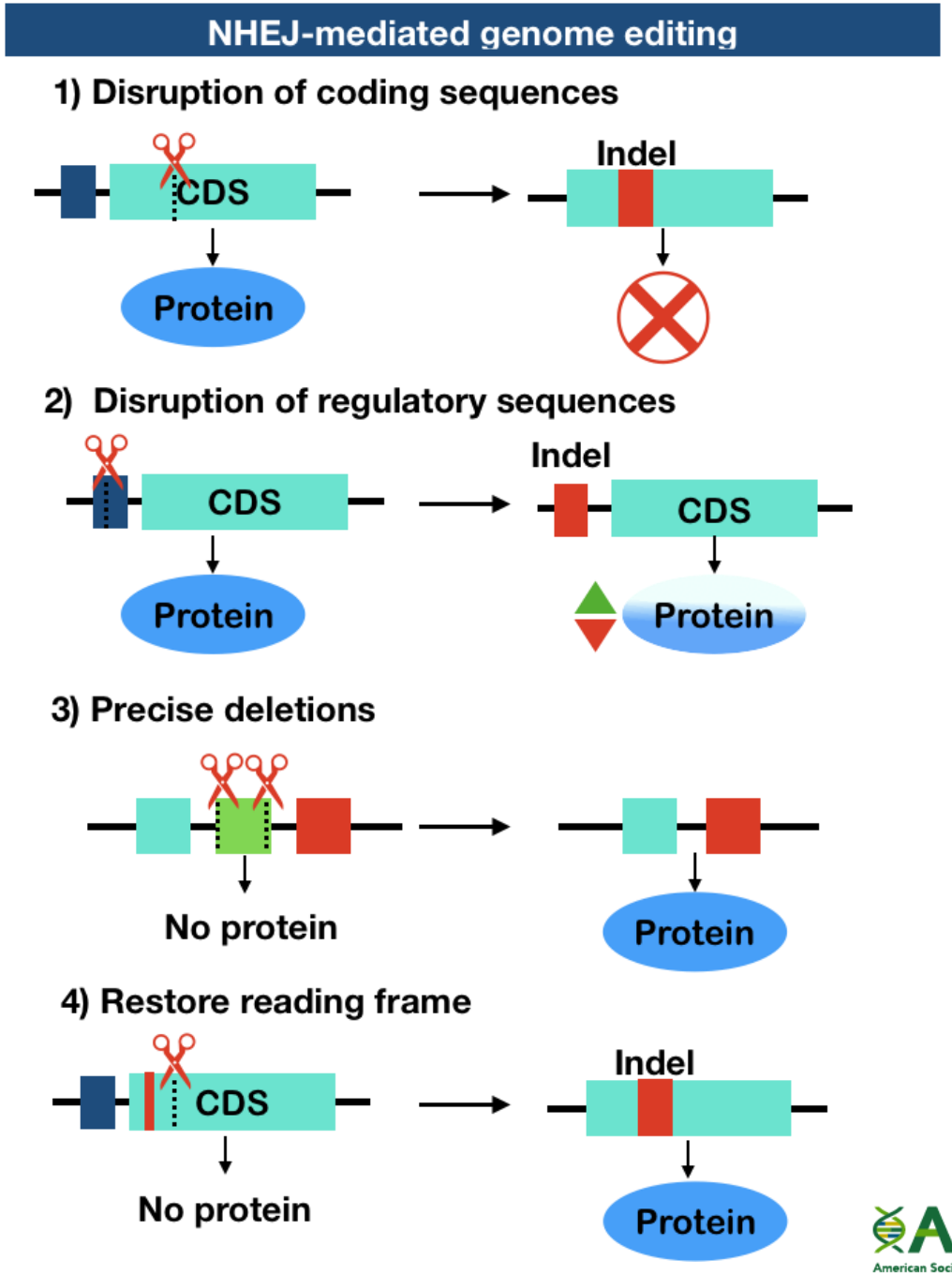
Combining double-strand breaks and DNA repair



Therapeutic NHEJ

Freq	Indel	Sequence
79.8%	+1	ACTGGGCGGCAGCATAGTGAGCCCA|NGAAGGGGACAGTAAGAAGGAAA
5.4%	0	ACTGGGCGGCAGCATAGTGAGCCCA| GAAGGGGACAGTAAGAAGGAAA
1.7%	-24	ACTGGGCGGCAG----------| ----------TAAGAAGGAAA
1.4%	-12	ACTGGGCGGCAGCATAGTGAGCCC-| ----------TAAGAAGGAAA
1.1%	-24	ACTGGGCGGCAGCAT----------| --------------GAAGGAAA
1.5%	-25	ACTGGGCGGC----------| ----------GTAAGAAGGAAA
0.9%	-20	ACTGGGCGGCAGCATA---------| ----------TAAGAAGGAAA
0.6%	-5	ACTGGGCGGCAGCATAGTGAG----| -AAGGGGACAGTAAGAAGGAAA
0.6%	-7	ACTGGGCGGCAGCATAGTGAG----| ---GGGGACAGTAAGAAGGAAA
0.6%	-19	ACTGGGCGGCAGCATAGTGA-----| --------------GAAGGAAA
0.6%	-1	ACTGGGCGGCAGCATAGTGAGCCC-| GAAGGGGACAGTAAGAAGGAAA
0.5%	-13	ACTGGGCGGCAGCATAGTG------| -------ACAGTAAGAAGGAAA
0.4%	-9	ACTGGGCGGCAGCATAGTGAGCCCA| ---------AGTAAGAAGGAAA
0.4%	-2	ACTGGGCGGCAGCATAGTGAGCCC-| -AAGGGGACAGTAAGAAGGAAA
0.4%	-1	ACTGGGCGGCAGCATAGTGAGCCCA| -AAGGGGACAGTAAGAAGGAAA
0.3%	-15	ACTGGGCGGCAGCATAGT-------| --------CAGTAAGAAGGAAA
0.3%	-21	ACTGGGCGGCAGCATA---------| ------------AAGAAGGAAA
0.3%	-25	ACTGGGCGGCAGCAT----------| ---------------AAGGAAA
0.3%	-14	ACTGGGCGGCAGCATAGTGAGCCC-| -------------AGAAGGAAA
0.3%	-15	ACTGGGCGGCAGCATAGTGAGCCC-| -------------GAAGGAAA
0.3%	-7	ACTGGGCGGCAGCATAGTGAGCCC-| ------GACAGTAAGAAGGAAA
0.2%	-14	ACTGGGCGGCAGCATAGTG------| --------CAGTAAGAAGGAAA
0.2%	-24	ACTGGGCGGCAGCATA---------| ---------------AAGGAAA
0.2%	-8	ACTGGGCGGCAGCATAGTGAGC---| -----GGACAGTAAGAAGGAAA
0.2%	-8	ACTGGGCGGCAGCATAGTGAGCCC-| -------ACAGTAAGAAGGAAA
0.1%	-22	ACTGGGCGGC----------| -------ACAGTAAGAAGGAAA
0.1%	-15	ACTGGGCGGC----------| GAAGGGGACAGTAAGAAGGAAA
0.1%	-14	ACTGGGCGGCAGCATAGTGAGC---| ----------TAAGAAGGAAA
0.1%	-23	ACTGGGCGGC----------| --------CAGTAAGAAGGAAA
0.1%	-15	ACTGGGCGGCA---------| -AAGGGGACAGTAAGAAGGAAA

The pattern of INDELs for any individual site is largely unpredictable and generates multiple loss-of-function alleles



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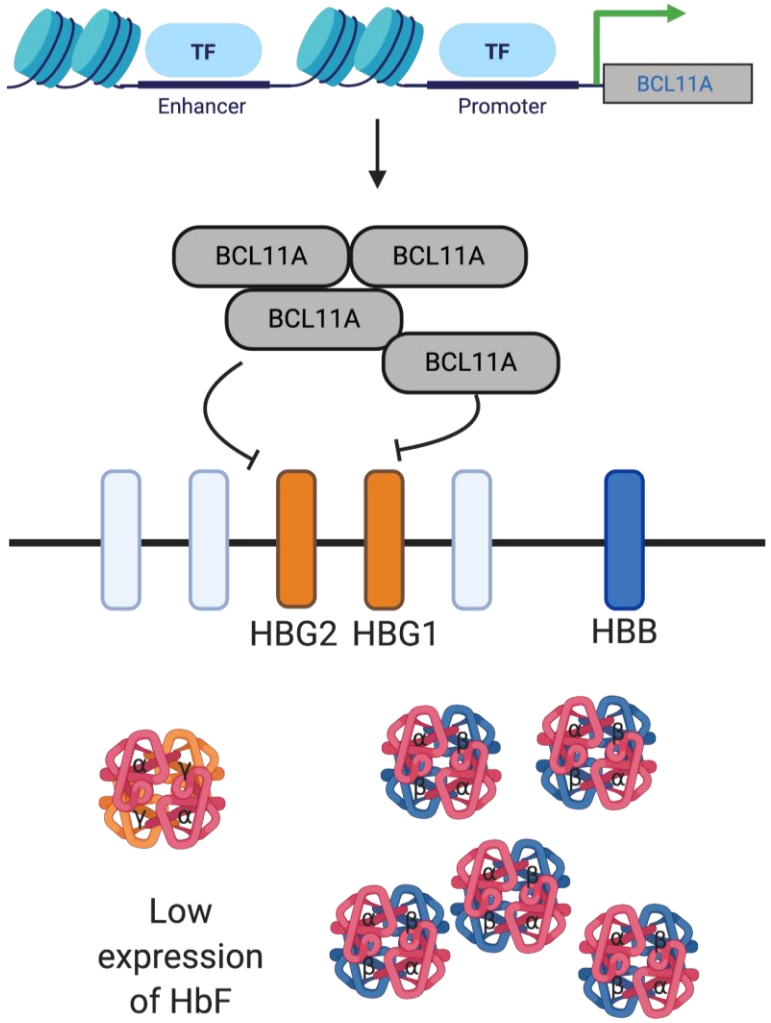
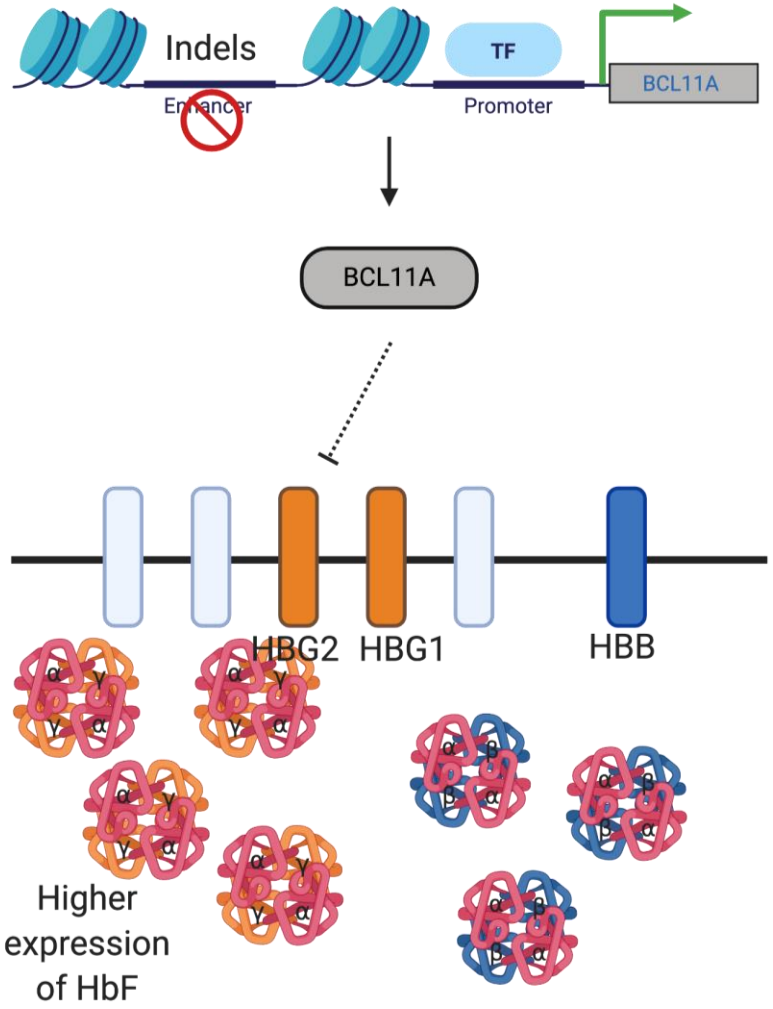
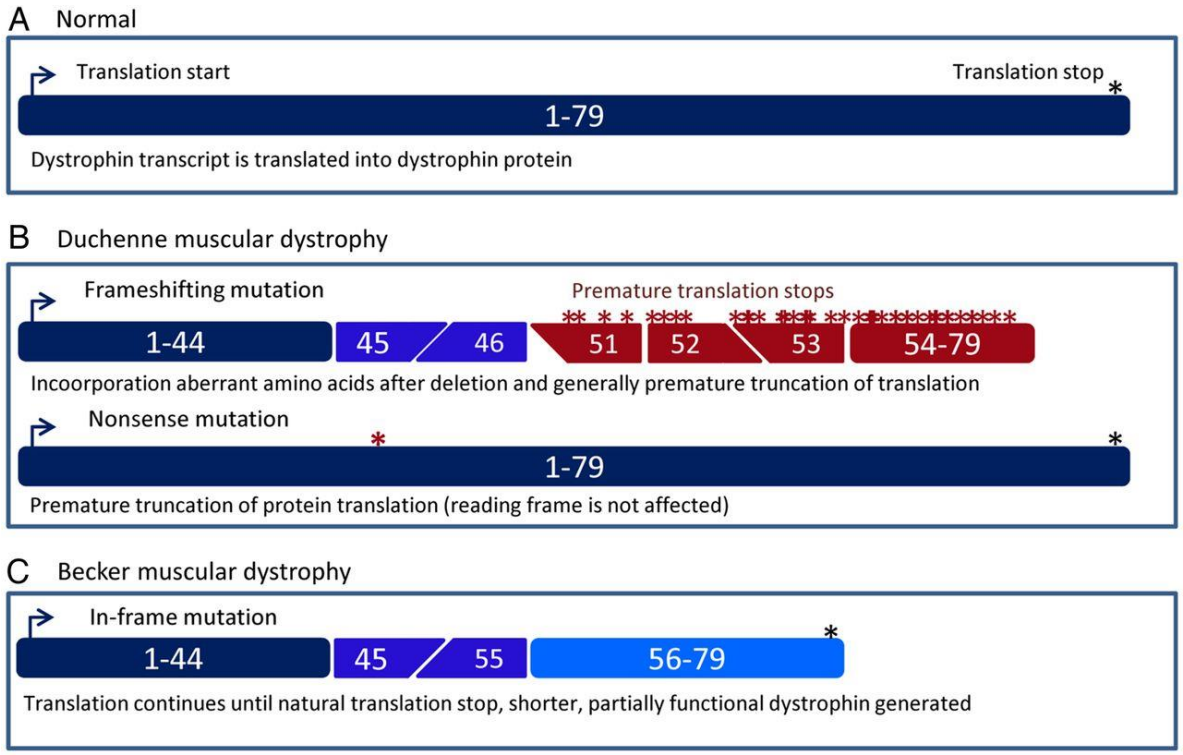
Therapeutic NHEJ: knock down of BCL11A for b-hemoglobinopathies



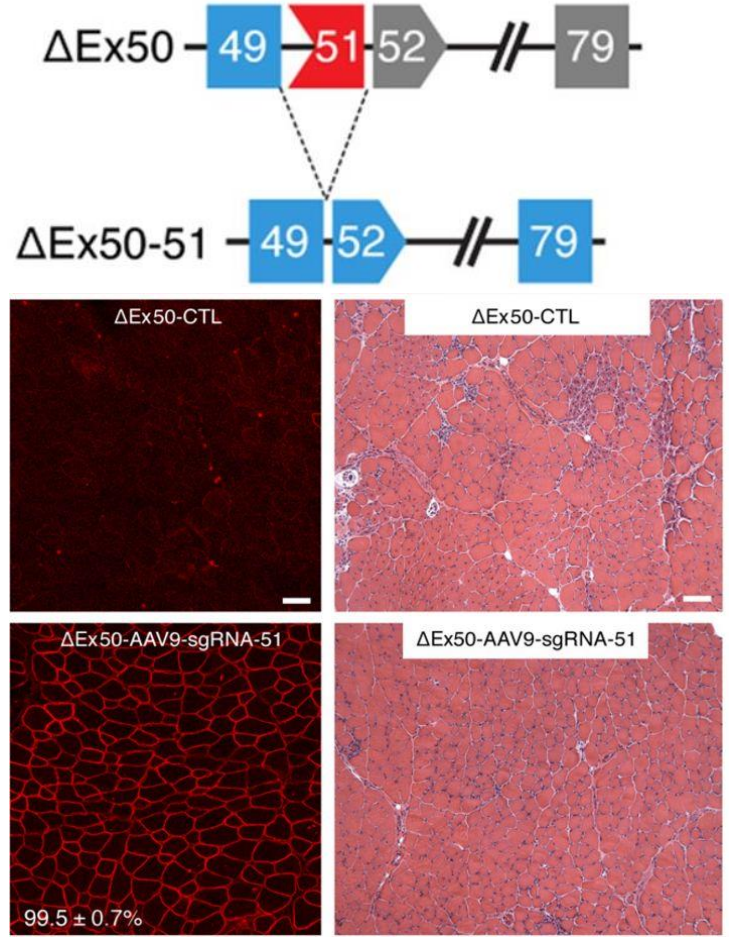


Therapeutic NHEJ: Restoring reading frames

Duchenne muscular dystrophy (DMD)



Annemieke Aartsma-Rus et al. J Med Genet 2016



Leonela Amoasii et al., Sci Transl Med 2017

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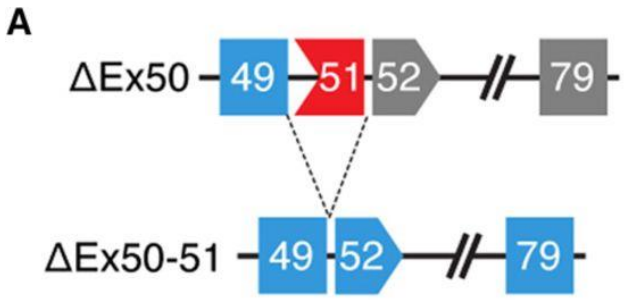
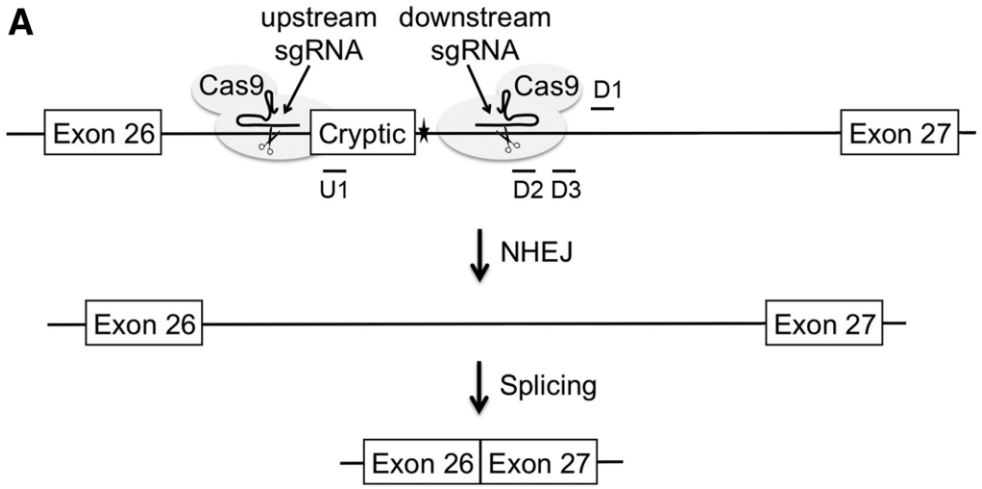
Therapeutic NHEJ: Restoring reading frames

Duchenne muscular dystrophy (DMD)



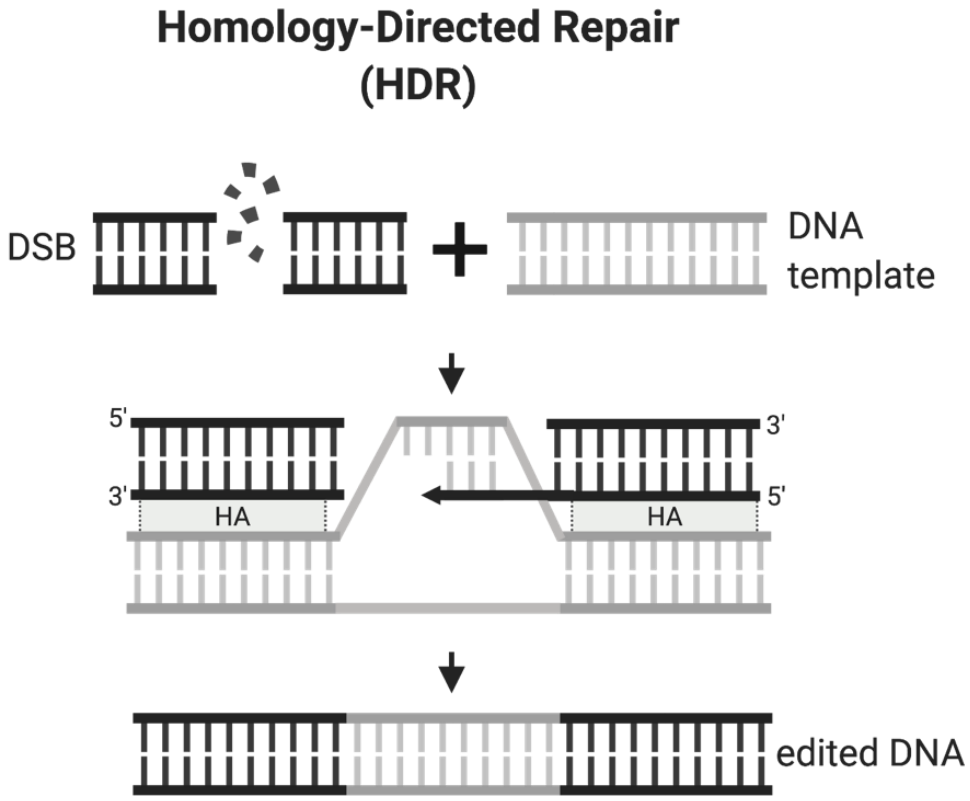
Leonela Amoasii et al., Sci Transl Med 2017

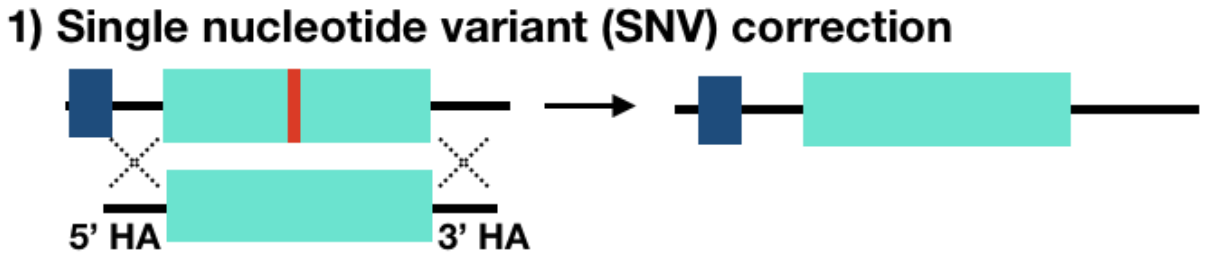
Leber congenital amaurosis 10 (LCA10)



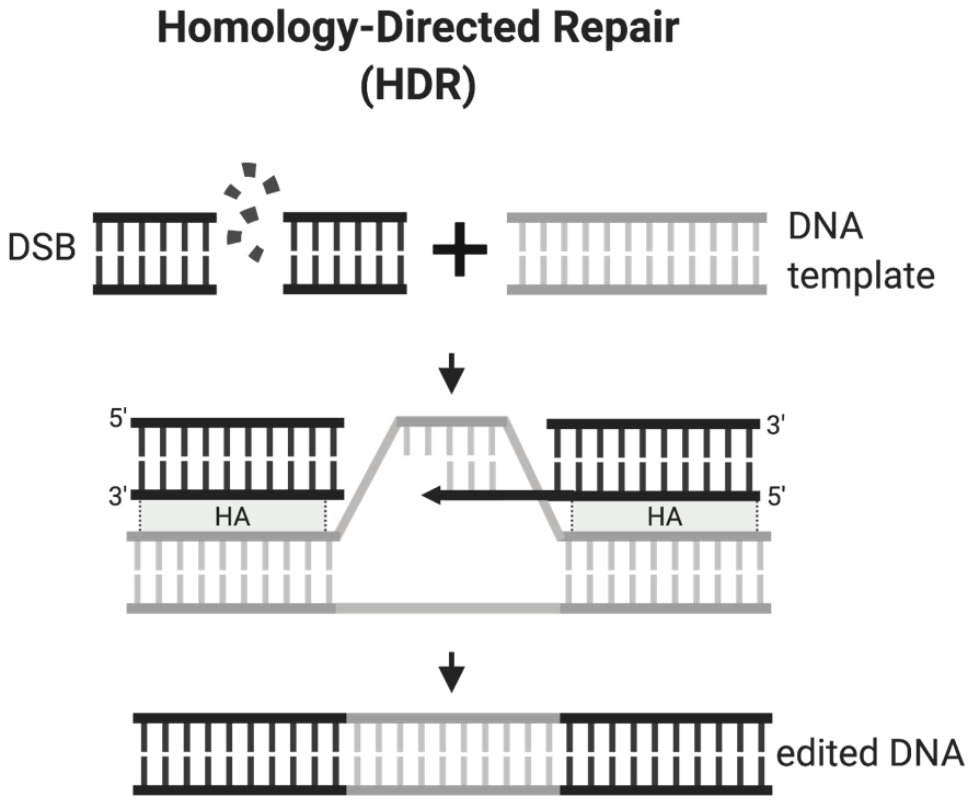
Ruan et al., Mol Ther 2017

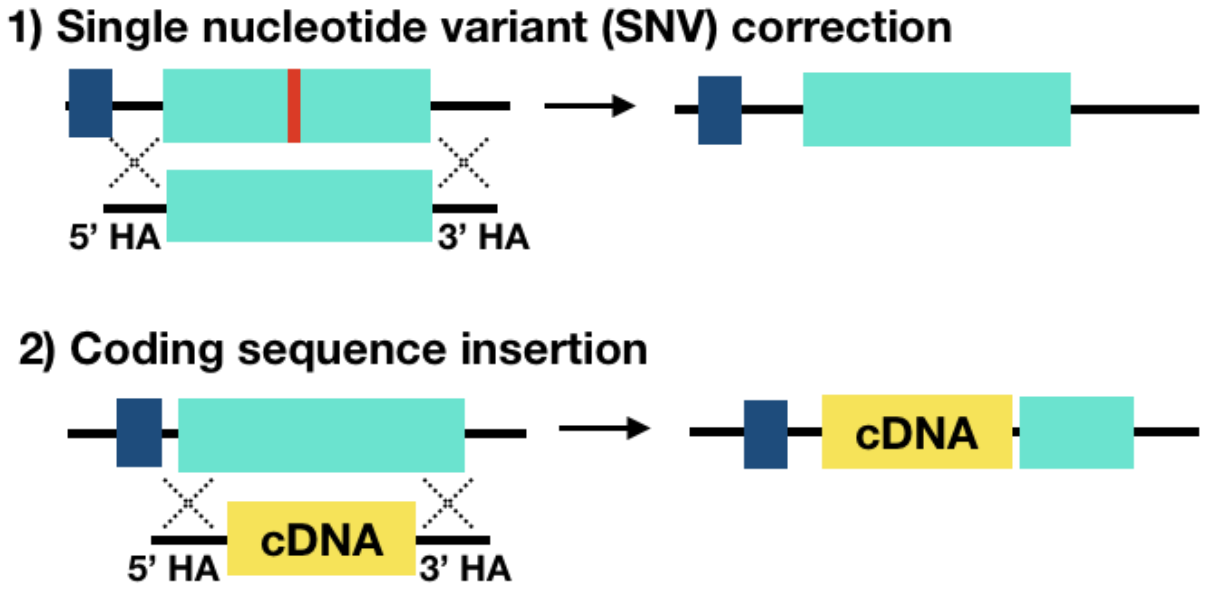
HDR-mediated genome editing



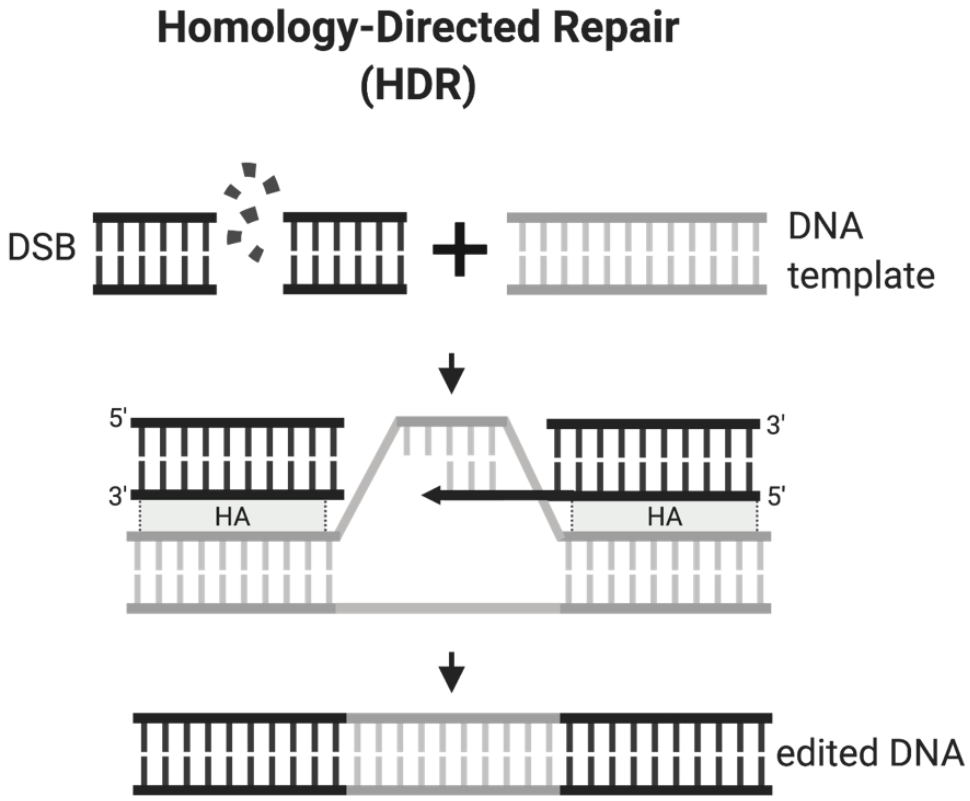


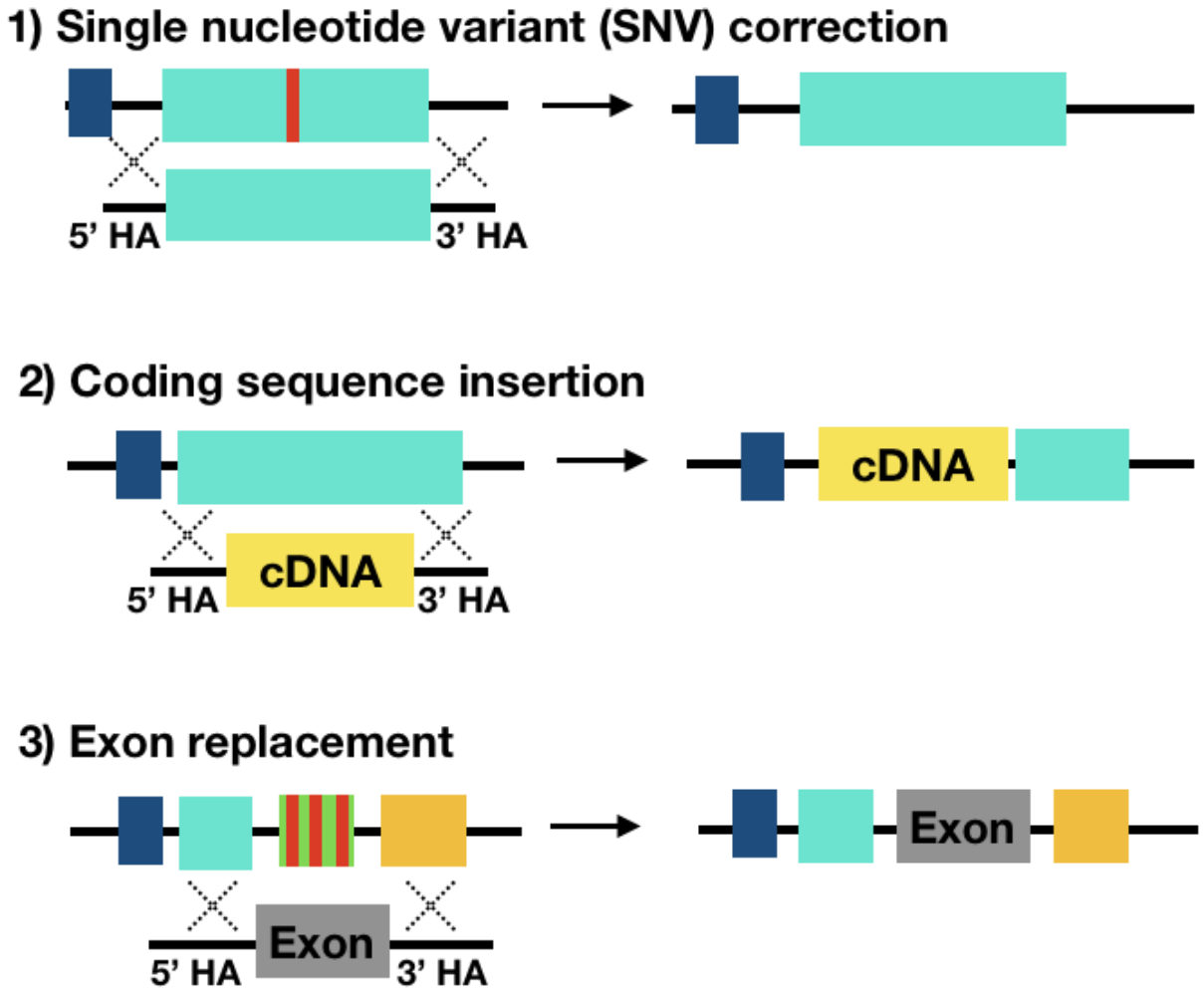
HDR-mediated genome editing





HDR-mediated genome editing





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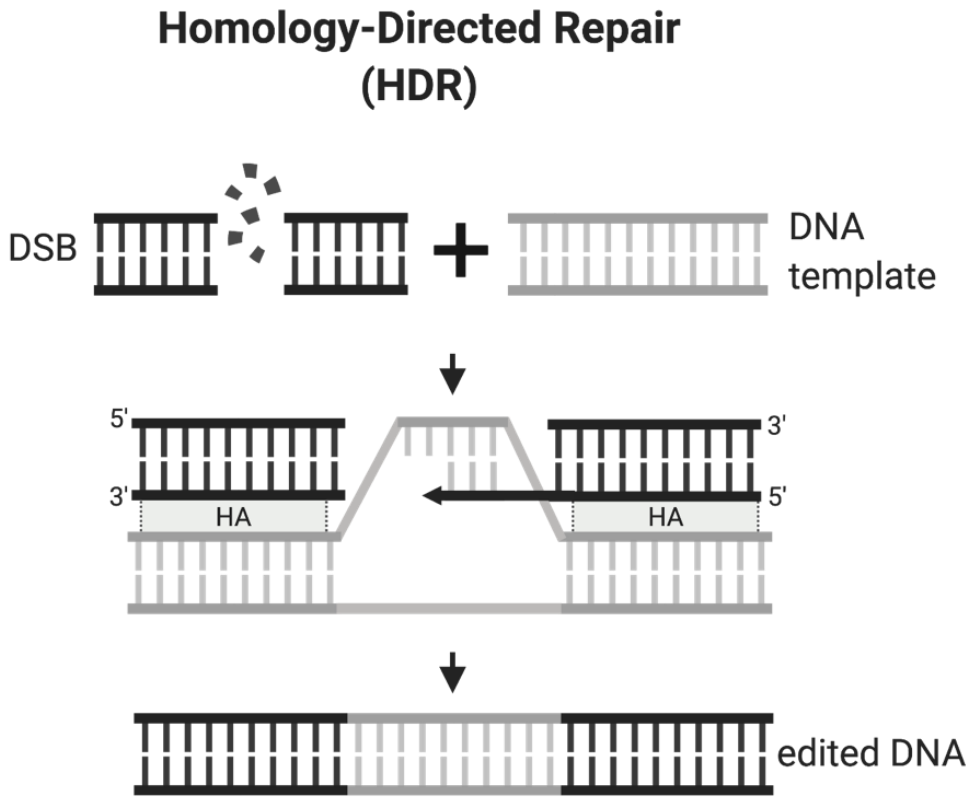
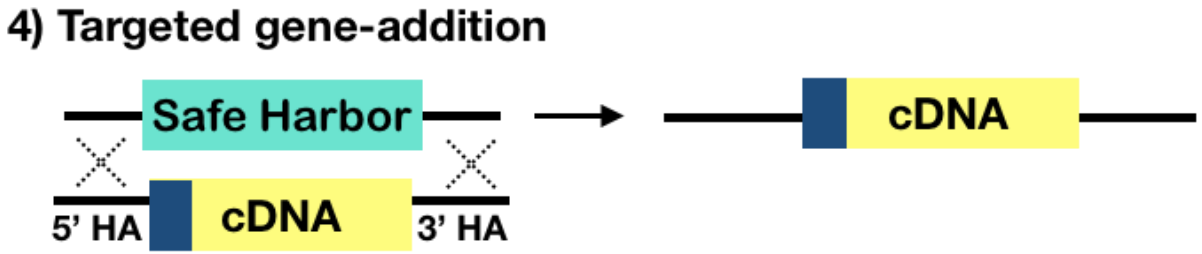
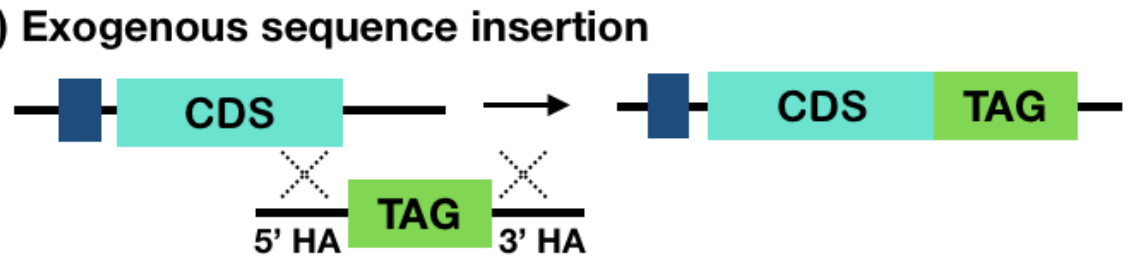
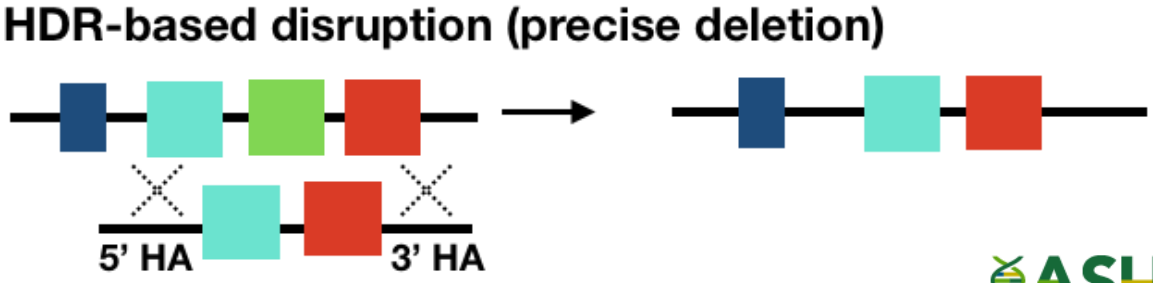
HDR-mediated genome editing









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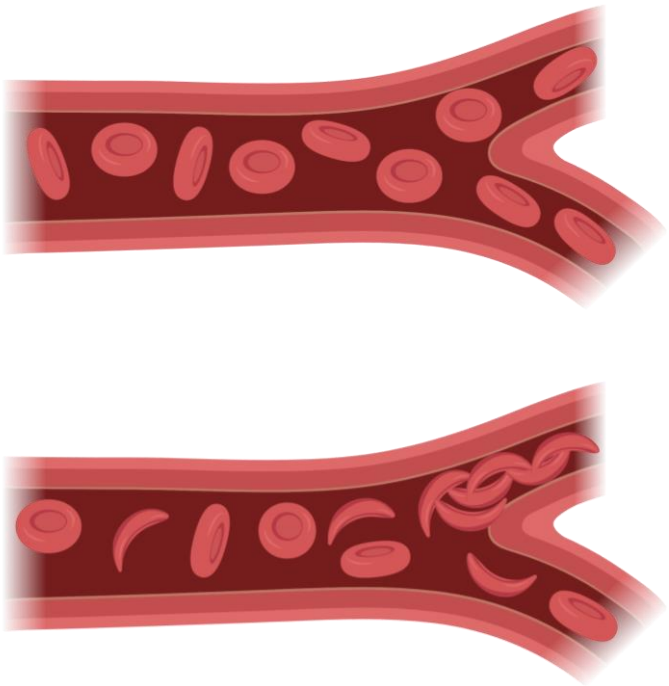
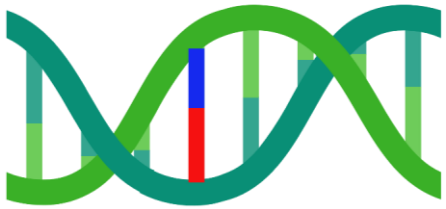
Choosing your tools: how disease pathophysiology informs intended modifications:

1) Sickle cell disease
2) Lysosomal storage disorders

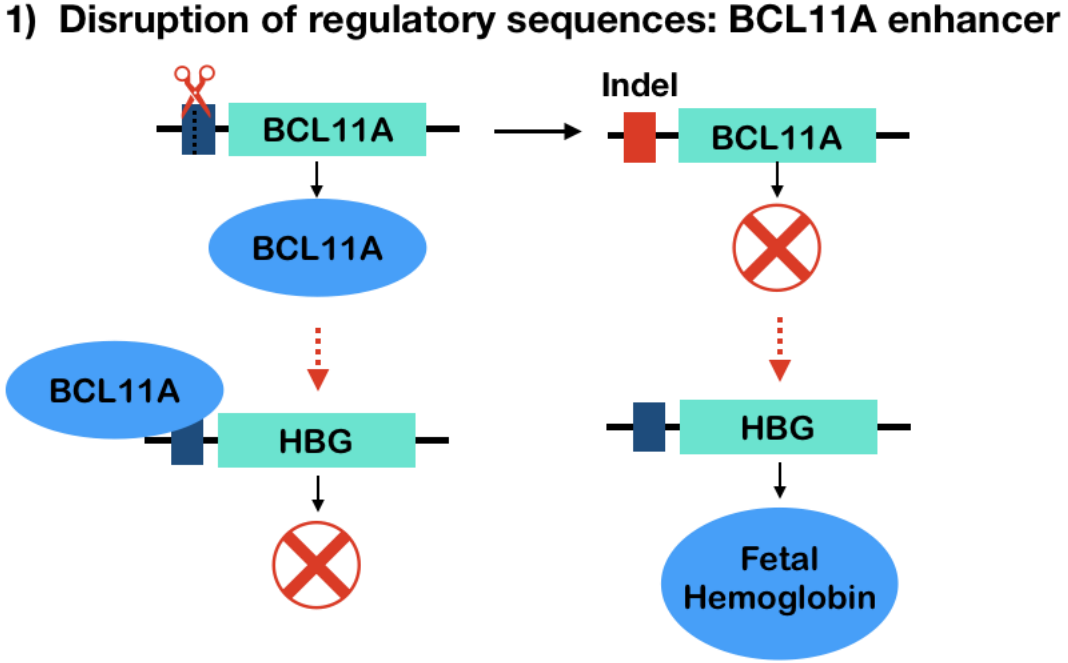
Therapeutic NHEJ in sickle cell disease



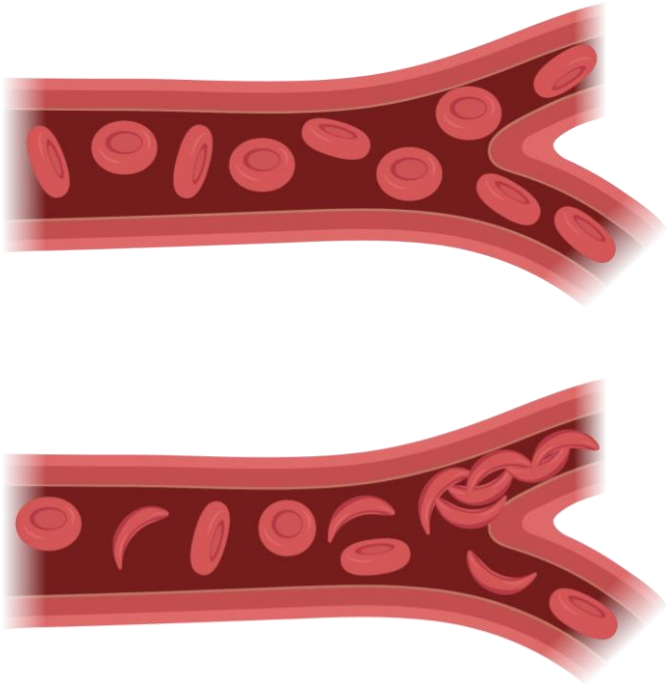
CAG ---> CTG
Glu ---> Val



Universal SNV:
p. Glu6Val in *HBB*



Therapeutic HDR in sickle cell disease



CAG ---> CTG
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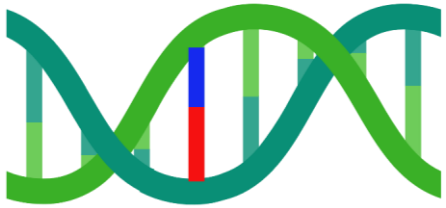

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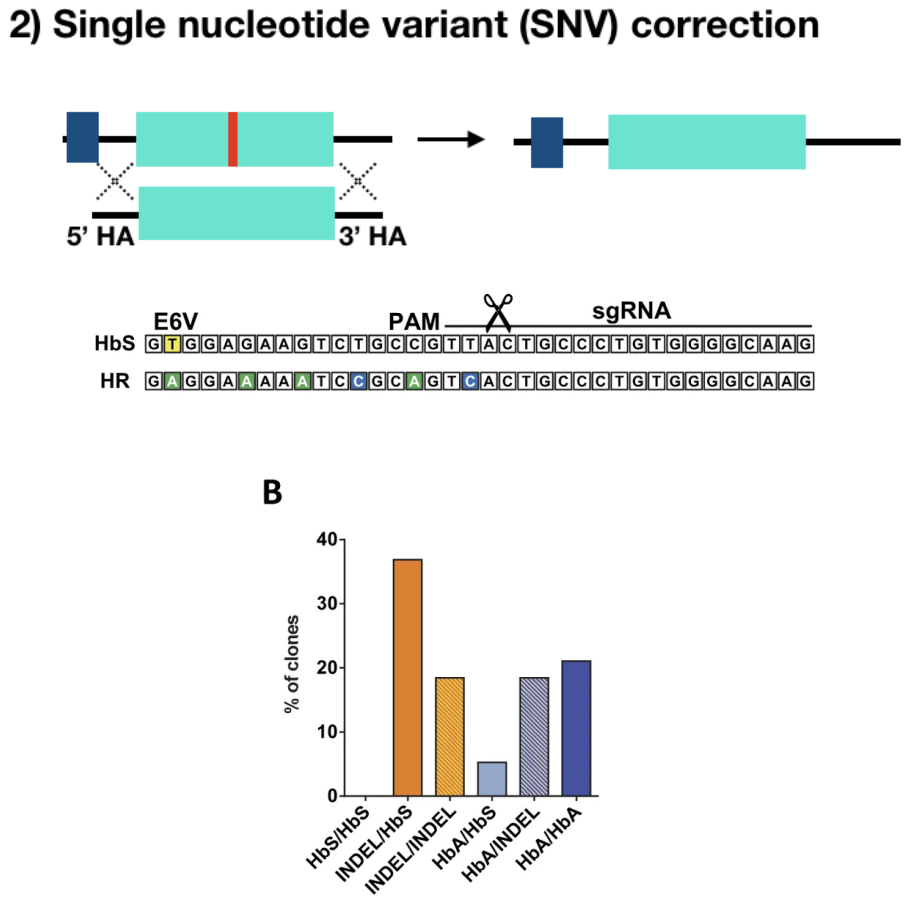

D P Dever *et al. Nature* 1–6 (2016) doi:10.1038/nature20134

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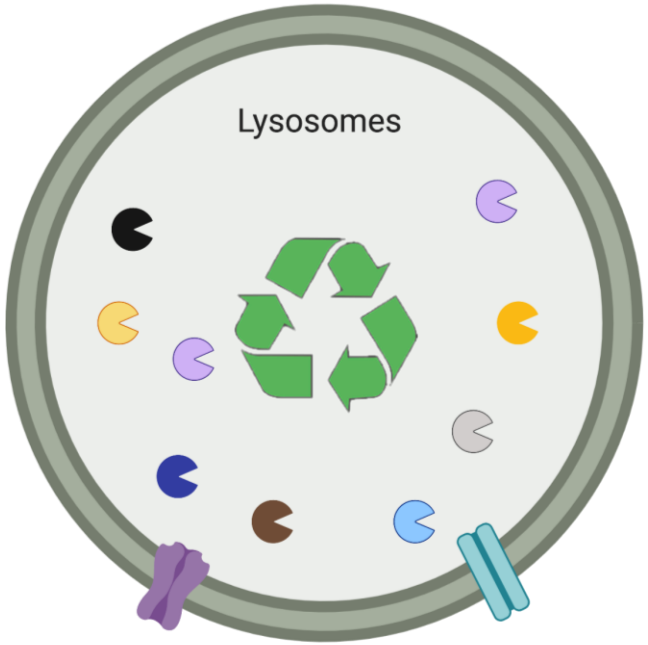
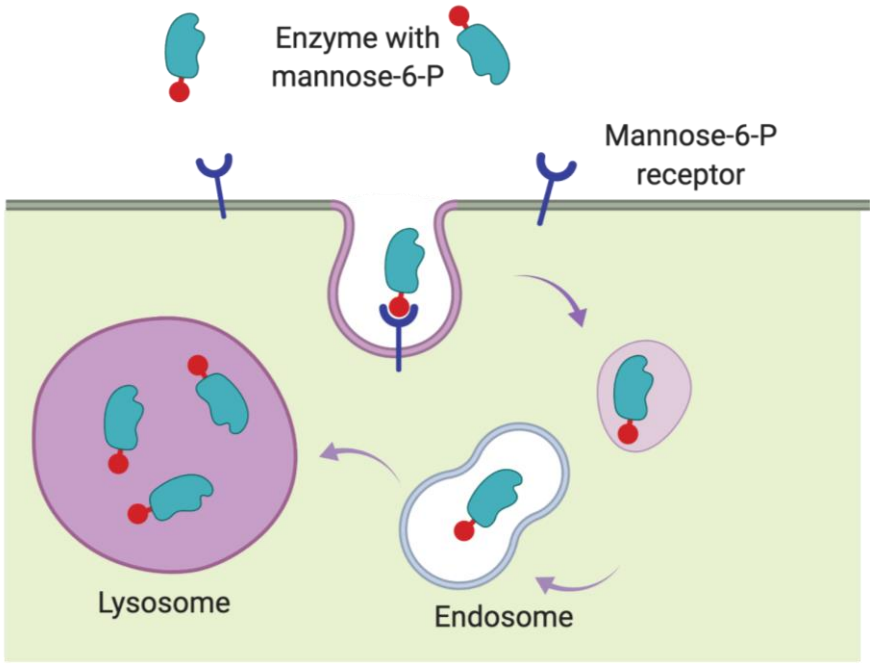
Therapeutic HDR for lysosomal storage disorders



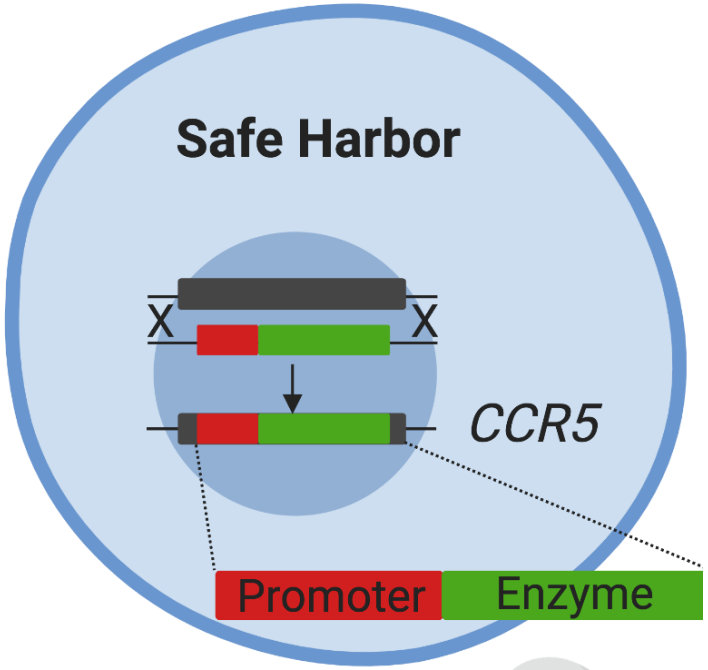


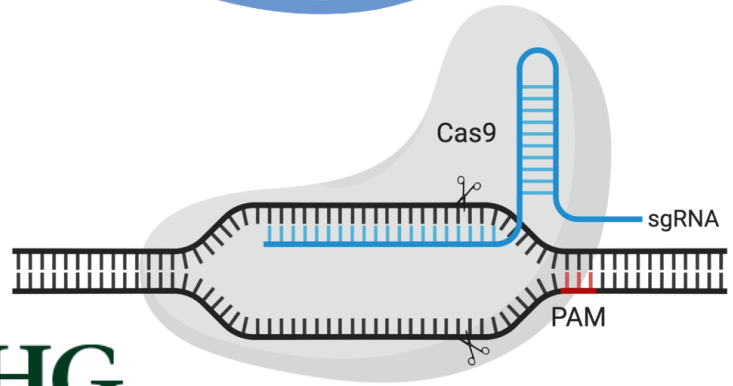
1. > 50 proteins

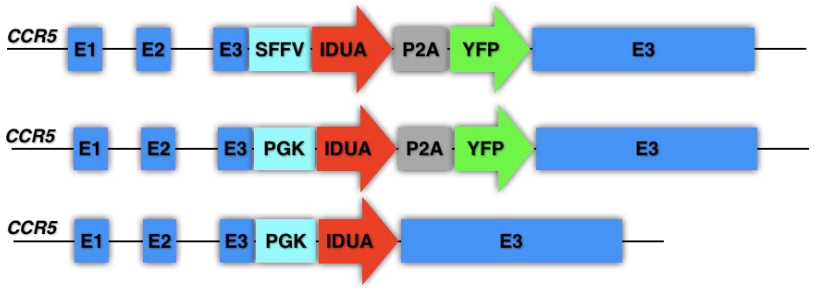
2. Most are enzymes

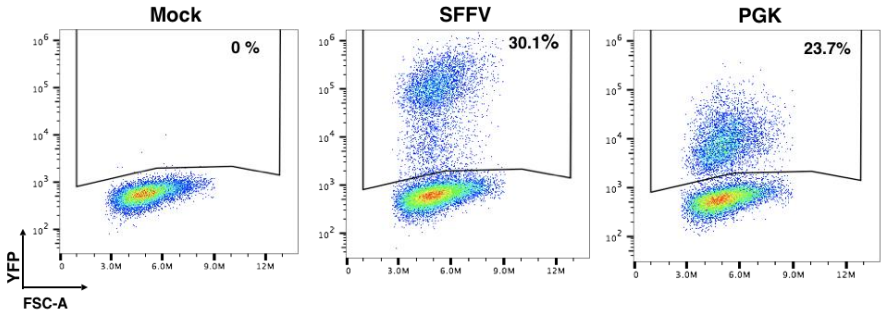
3. Property of cross-correction enables cells to become enzyme depots

Targeted gene addition into a safe harbor

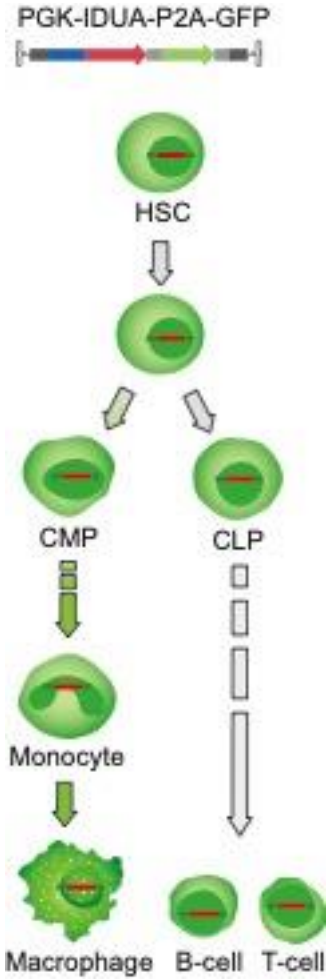








Gomez-Ospina et al, Nature Communications, 2019



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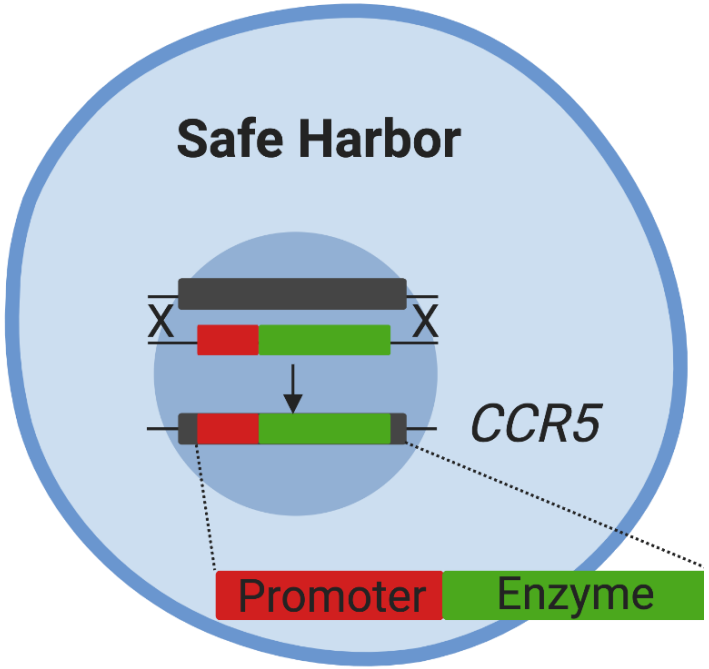
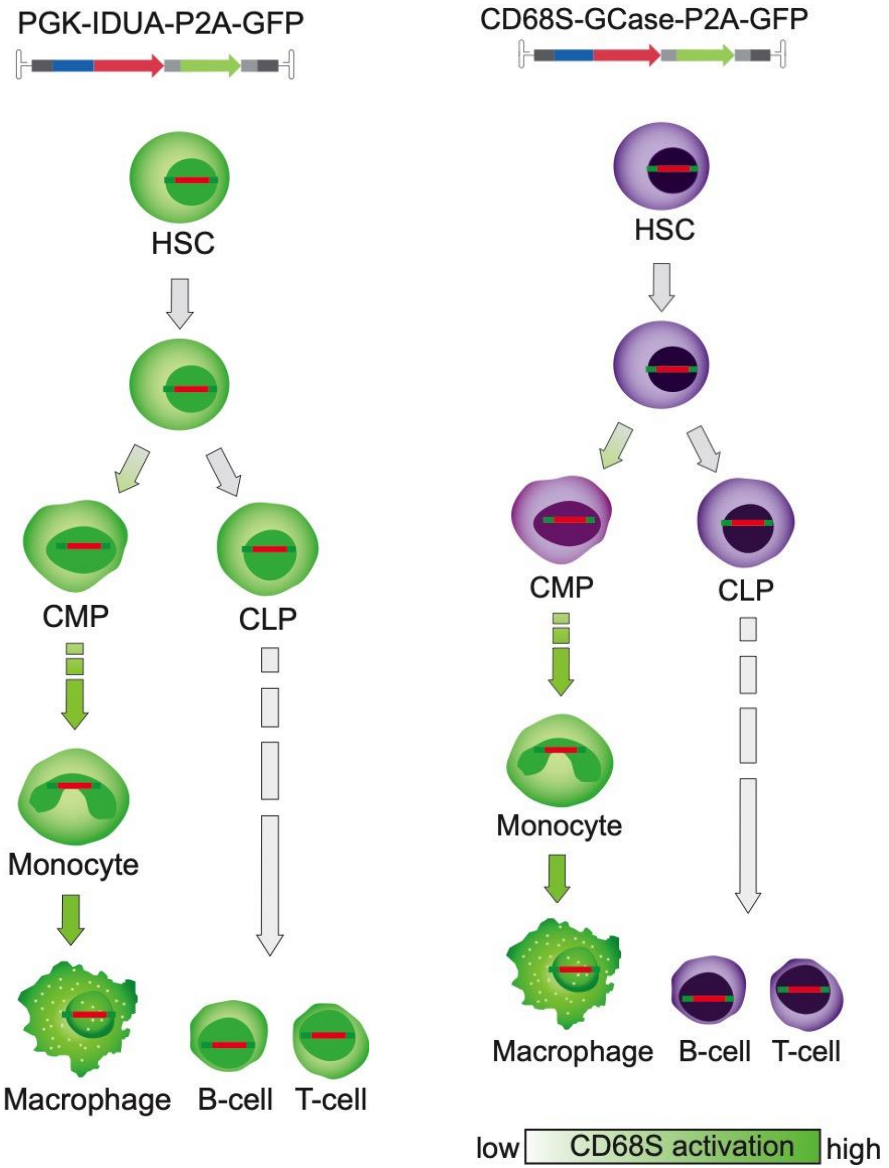
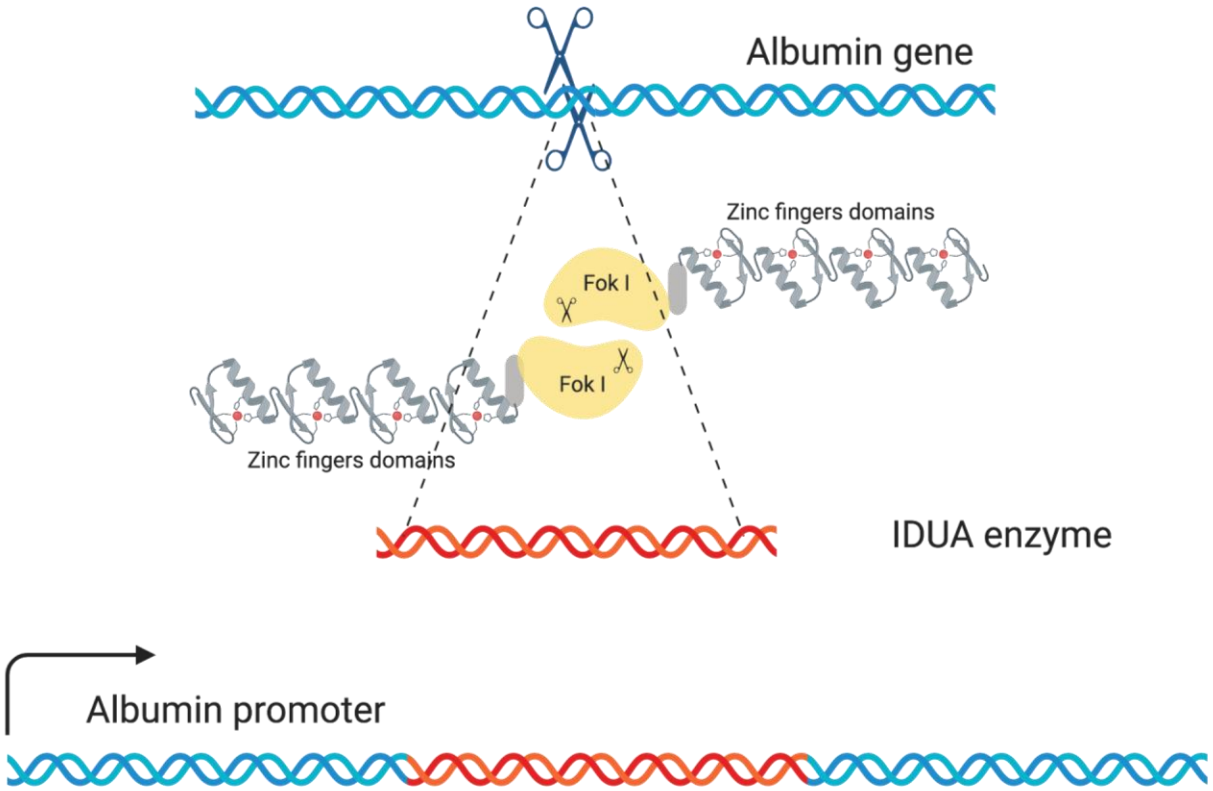
A safe harbor is a flexible platform





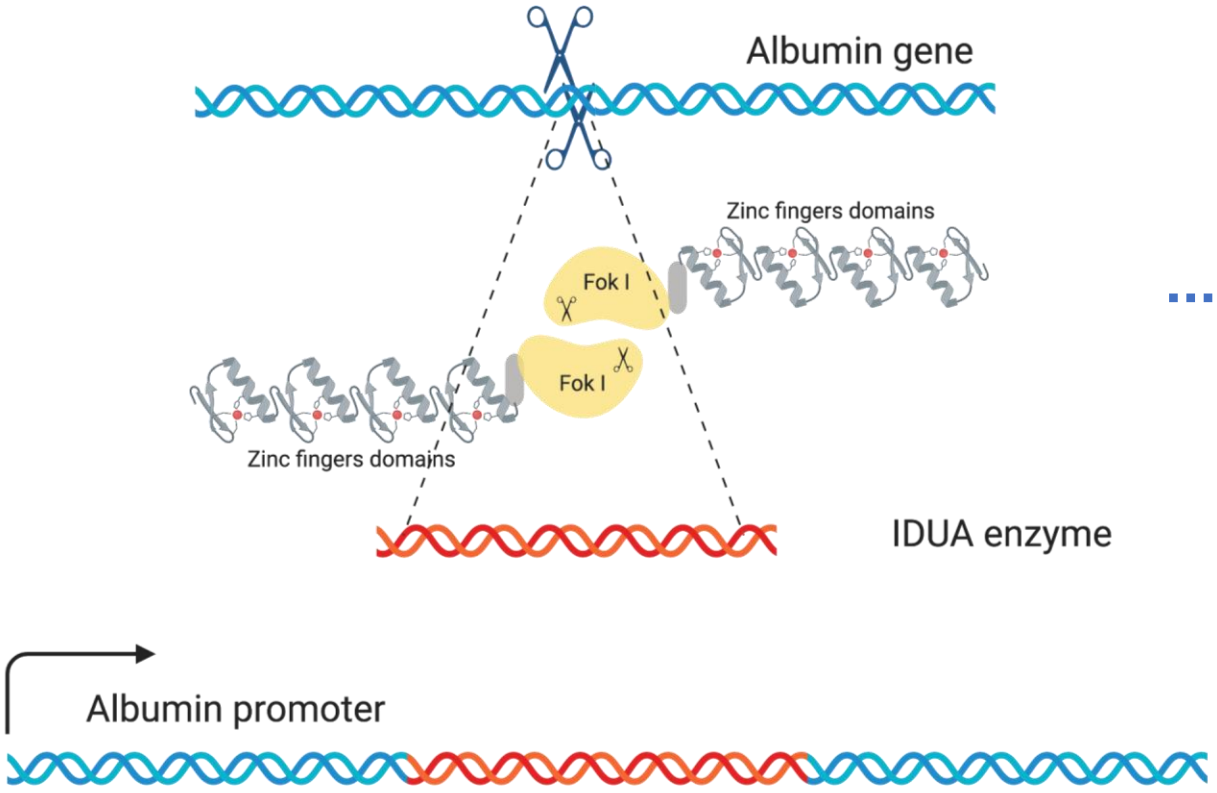
Scharenberg et al,
Under review

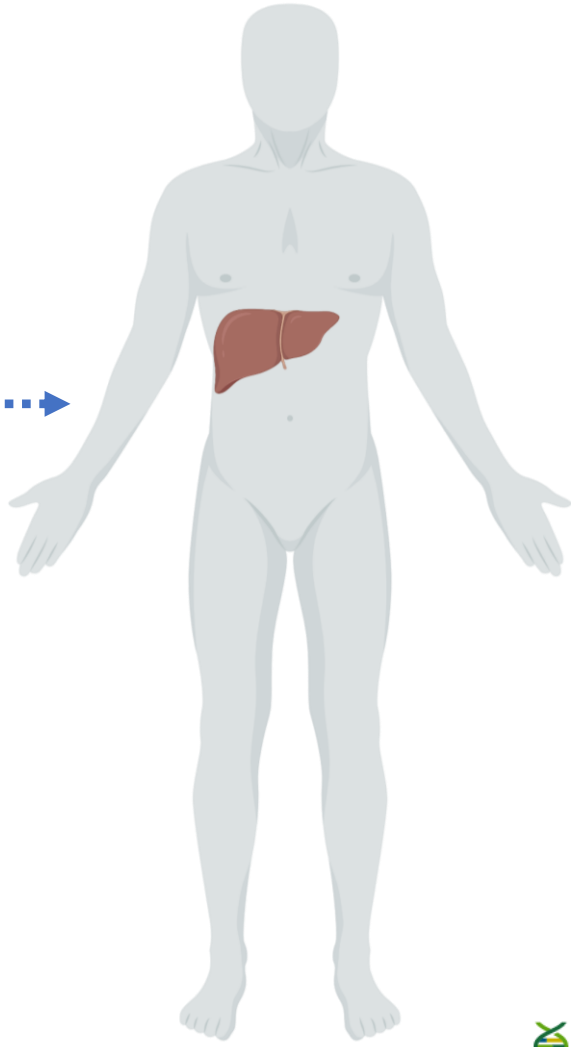
Coding sequence insertion into the albumin locus



Sharma et al, blood 2015
Ou et al, Molecular Therapy 2019

Coding sequence insertion into the albumin locus





Sharma et al, blood 2015
Ou et al, Molecular Therapy 2019

We will now hear from Dr. Kiran Musunuru.

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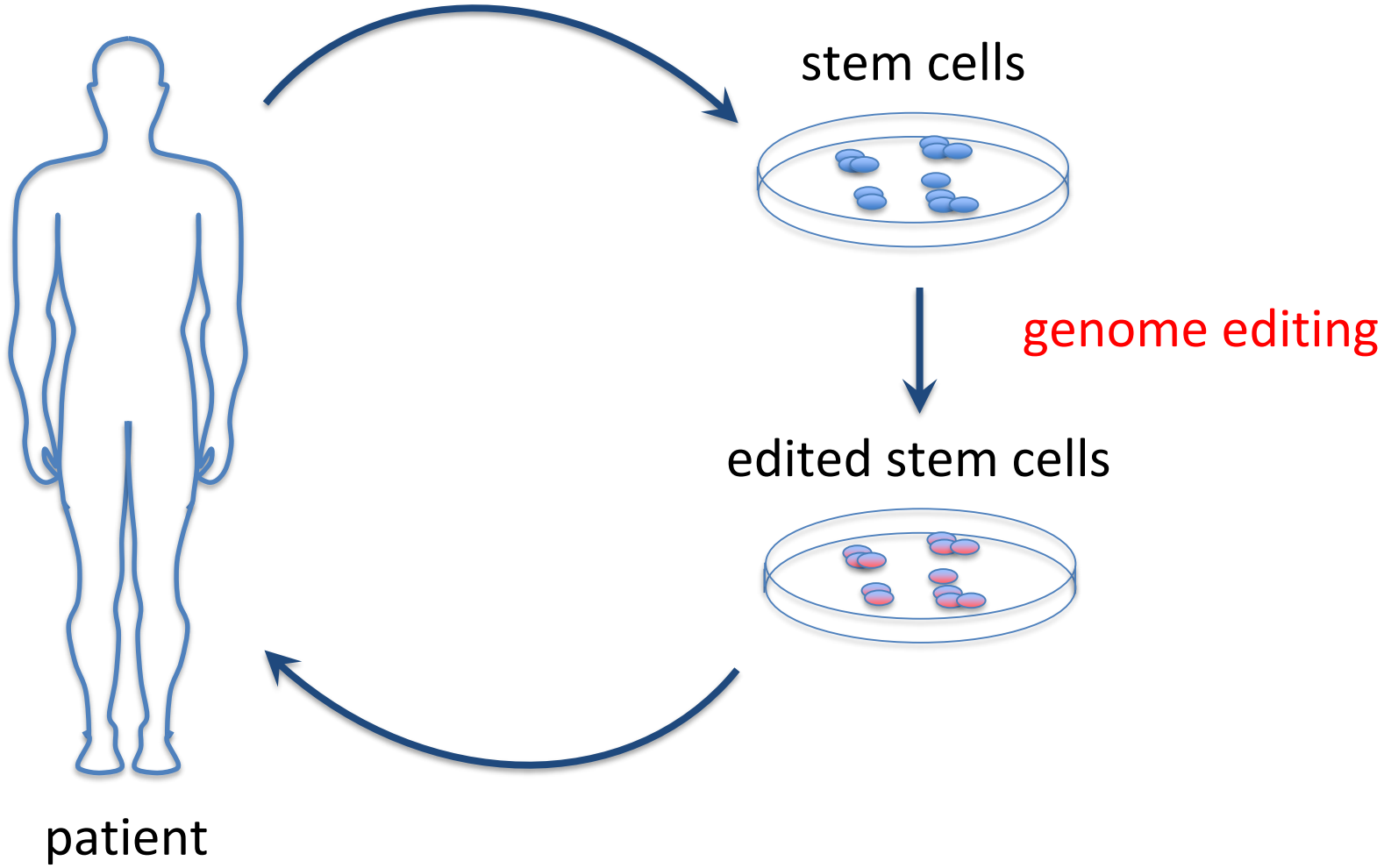
Choosing your tools: how disease pathophysiology dictates delivery

1) Ex vivo modification
2) In vivo modification

Ex vivo genome editing for therapy



CCR5 and HIV infection

Cell, Vol. 86, 367–377, August 9, 1996, Copyright ©1996 by Cell Press

Homozygous Defect in HIV-1 Coreceptor Accounts for Resistance of Some Multiply-Exposed Individuals to HIV-1 Infection

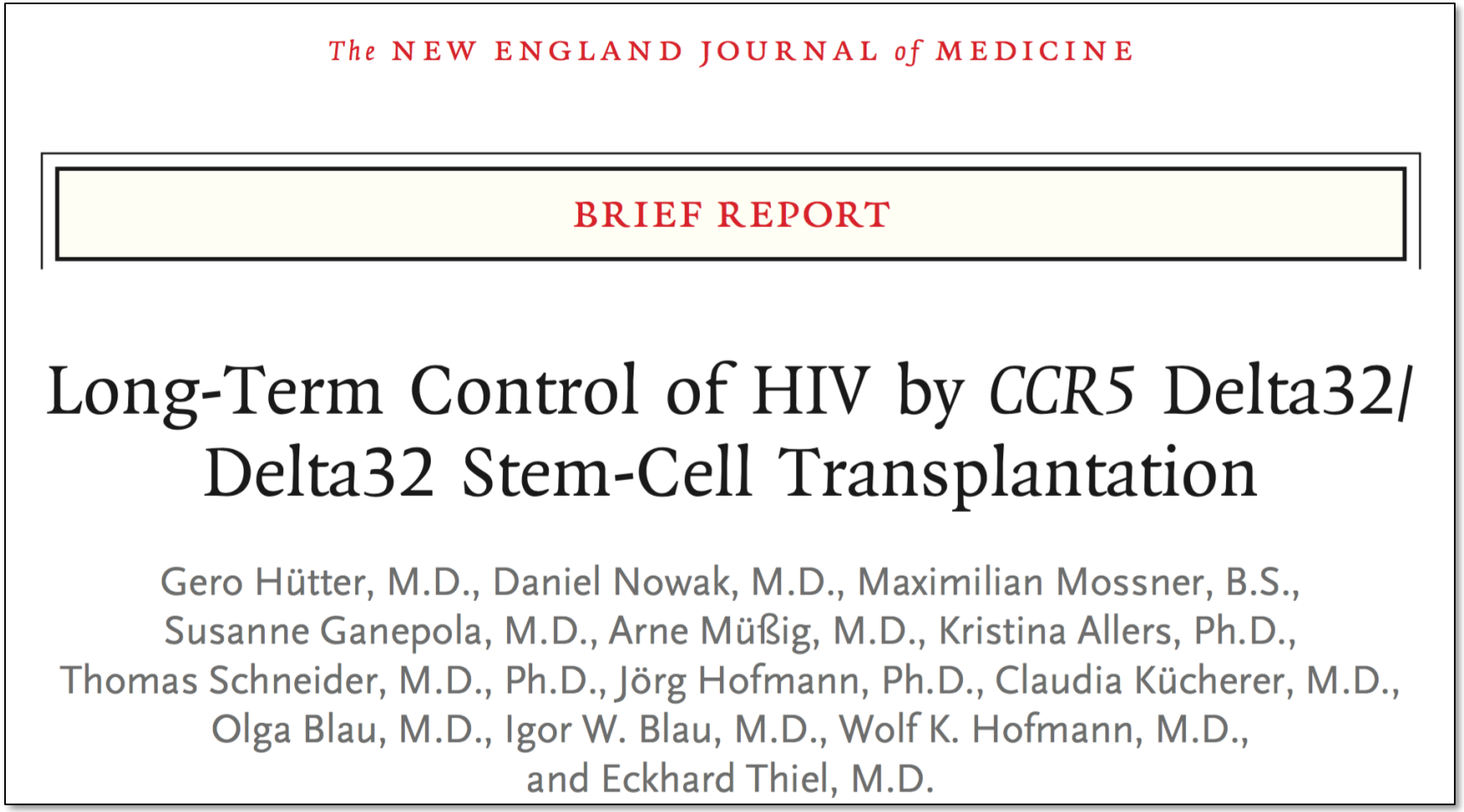
Rong Liu,* William A. Paxton,* Sunny Choe,*
Daniel Ceradini,* Scott R. Martin,* Richard Horuk,†
Marcy E. MacDonald,‡ Heidi Stuhlmann,§
Richard A. Koup,* and Nathaniel R. Landau*
*Aaron Diamond AIDS Research Center
The Rockefeller University
New York, New York 10016
†Department of Immunology
Berlex Biosciences
Richmond, California 94080
‡Molecular Neurogenetics Unit
Massachusetts General Hospital
Charlestown, Massachusetts 02129
§Brookdale Center for Molecular Biology
Mount Sinai School of Medicine
New York, New York 10029

designated EU2 and EU3, required about 1000-fold more virus to establish infection than contol cells from unexposed donors. While a small fraction of the cells did become infected with this high inoculum, the virus failed to replicate further. Analysis of the early events of the viral replication cycle showed that macrophage-tropic HIV-1 isolates failed to enter or fuse to the $CD4^+$ cells of these two individuals (Dragic et al., 1996). Thus, the resistance of these individuals to sexual transmission of HIV-1 was likely to have resulted from the inability of their cells to support entry of macrophage-tropic virus.

HIV-1 can broadly be divided into macrophage- or T-tropic isolates (Gartner et al., 1986; Koyanagi et al., 1987; Fisher et al., 1988). Macrophage-tropic nonsyncytium-inducing (NSI) isolates infect primary macrophages but fail to infect transformed T-cell lines, while T-tropic syncytium-inducing (SI) strains have the reciprocal tro-

Liu et al. *Cell* 1996; 86:367-77

CCR5 and HIV infection



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Long-Term Control of HIV by *CCR5* Delta32/Delta32 Stem-Cell Transplantation

Gero Hütter, M.D., Daniel Nowak, M.D., Maximilian Mossner, B.S., Susanne Ganepola, M.D., Arne Müßig, M.D., Kristina Allers, Ph.D., Thomas Schneider, M.D., Ph.D., Jörg Hofmann, Ph.D., Claudia Kücherer, M.D., Olga Blau, M.D., Igor W. Blau, M.D., Wolf K. Hofmann, M.D., and Eckhard Thiel, M.D.

AJHG

"Berlin patient"

Hütter et al. *N Engl J Med* 2009; 360:692-8

ASHG American Society of Human Genetics

Genome editing of *CCR5* in human cells

Establishment of HIV-1 resistance in CD4+ T cells by genome editing using zinc-finger nucleases

Elena E Perez[1,2], Jianbin Wang[3], Jeffrey C Miller[3], Yann Jouvenot[3,4], Kenneth A Kim[3], Olga Liu[1], Nathaniel Wang[3], Gary Lee[3], Victor V Bartsevich[3], Ya-Li Lee[3], Dmitry Y Guschin[3], Igor Rupniewski[3], Adam J Waite[3], Carmine Carpenito[1], Richard G Carroll[1], Jordan S Orange[2], Fyodor D Urnov[3], Edward J Rebar[3], Dale Ando[3], Philip D Gregory[3], James L Riley[1], Michael C Holmes[3] & Carl H June[1]

Homozygosity for the naturally occurring *Δ32* deletion in the HIV co-receptor *CCR5* confers resistance to HIV-1 infection. We generated an HIV-resistant genotype *de novo* using engineered zinc-finger nucleases (ZFNs) to disrupt endogenous *CCR5*. Transient expression of CCR5 ZFNs permanently and specifically disrupted ~50% of *CCR5* alleles in a pool of primary human

Human hematopoietic stem/progenitor cells modified by zinc-finger nucleases targeted to *CCR5* control HIV-1 *in vivo*

Nathalia Holt[1], Jianbin Wang[2], Kenneth Kim[2], Geoffrey Friedman[2], Xingchao Wang[3], Vanessa Taupin[3], Gay M Crooks[4], Donald B Kohn[4], Philip D Gregory[2], Michael C Holmes[2] & Paula M Cannon[1]

CCR5 is the major HIV-1 co-receptor, and individuals homozygous for a 32-bp deletion in *CCR5* are resistant to infection by CCR5-tropic HIV-1. Using engineered zinc-finger nucleases (ZFNs), we disrupted *CCR5* in human CD34+ hematopoietic stem/progenitor cells (HSPCs) at a mean frequency of 17% of the total alleles in a population. This procedure produces both mono- and

AJHG

Perez et al. *Nat Biotechnol* 2008; 26:808-16

Holt et al. *Nat Biotechnol* 2008; 28:839-47

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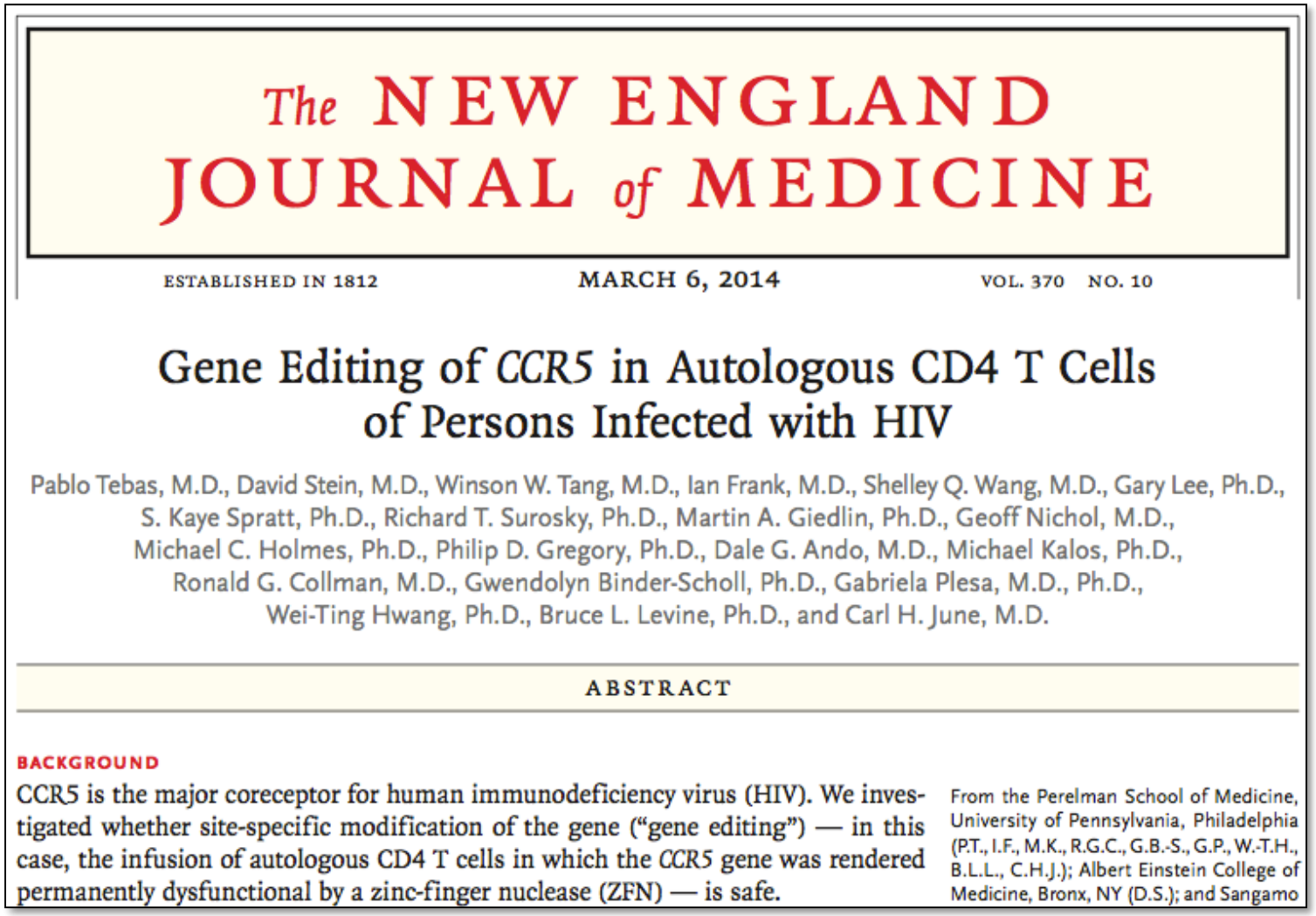
Genome editing of *CCR5* in human cells



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 6, 2014 VOL. 370 NO. 10

Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

Pablo Tebas, M.D., David Stein, M.D., Winson W. Tang, M.D., Ian Frank, M.D., Shelley Q. Wang, M.D., Gary Lee, Ph.D., S. Kaye Spratt, Ph.D., Richard T. Surosky, Ph.D., Martin A. Giedlin, Ph.D., Geoff Nichol, M.D., Michael C. Holmes, Ph.D., Philip D. Gregory, Ph.D., Dale G. Ando, M.D., Michael Kalos, Ph.D., Ronald G. Collman, M.D., Gwendolyn Binder-Scholl, Ph.D., Gabriela Plesa, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

ABSTRACT

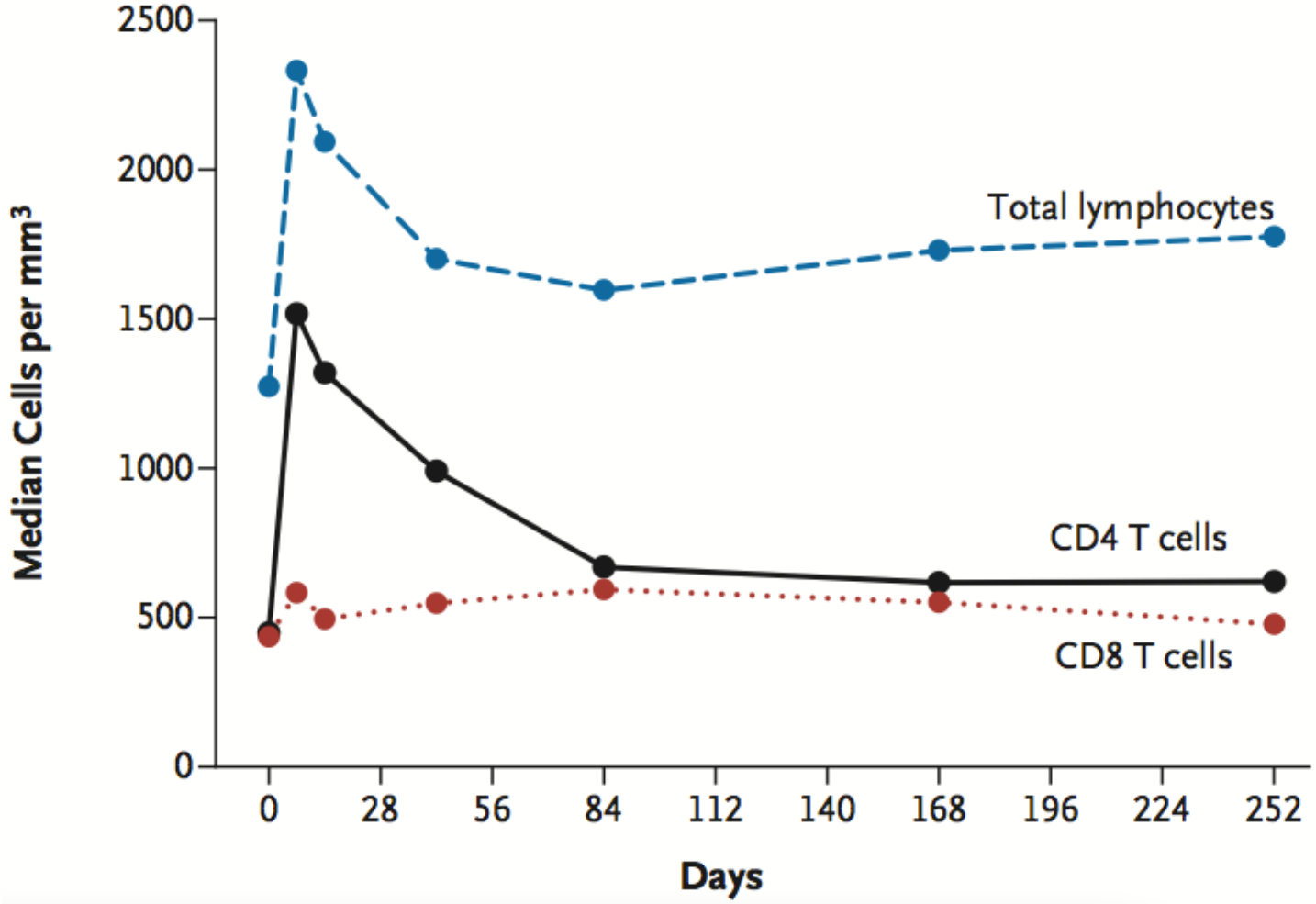
BACKGROUND

CCR5 is the major coreceptor for human immunodeficiency virus (HIV). We investigated whether site-specific modification of the gene ("gene editing") — in this case, the infusion of autologous CD4 T cells in which the *CCR5* gene was rendered permanently dysfunctional by a zinc-finger nuclease (ZFN) — is safe.

From the Perelman School of Medicine, University of Pennsylvania, Philadelphia (P.T., I.F., M.K., R.G.C., G.B.-S., G.P., W.-T.H., B.L.L., C.H.J.); Albert Einstein College of Medicine, Bronx, NY (D.S.); and Sangamo

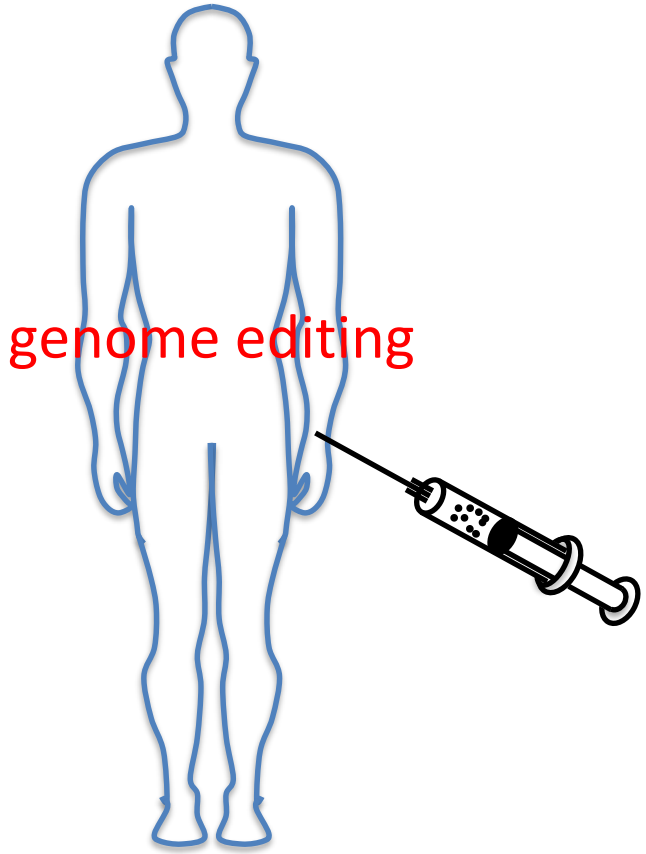
Tebas et al. *N Engl J Med* 2014; 370:901-10

Genome editing of *CCR5* in human cells



Tebas et al. *N Engl J Med* 2014; 370:901-10

In vivo genome editing for therapy



patient

The Philadelphia Inquirer

10-year-old's cholesterol was over 800. Can CRISPR fix the problem?

by Tom Avril, Updated: June 10, 2019- 10:00 AM

LESLIE BARBARO

Rare Gene Mutations Inspire New Heart Drugs

By GINA KOLATA MAY 24, 2017

Anna Feurer learned she had unusually low triglyceride levels after having bloodwork at a corporate health fair. The discovery prompted researchers to recruit her and her family for a research study of their genetic makeup.
Jess T. Dugan for The New York Times

What if you carried a genetic mutation that left you nearly impervious to heart disease? What if scientists could bottle that miracle and use it to treat everyone else?

In a series of studies, the most recent published on Wednesday, scientists have described two rare genetic mutations that reduce levels of triglycerides, a type of blood fat, far below normal. People carrying these genes seem invulnerable to heart disease, even if they have other risk factors.

Drugs that mimic the effects of these mutations are already on the way, and many experts believe that one day they will become the next blockbuster heart treatments. Tens of millions of Americans have elevated triglyceride levels. Large genetic studies have consistently suggested a direct link to heart disease.

PCSK9 and coronary heart disease (CHD)

Individuals with total loss-of-function mutations in *PCSK9*:

SINGLE mutation → LDL-C ↓ 30-40%; CHD risk ↓ 80-90%

TWO mutations → LDL-C ↓ ~80%; CHD risk eliminated?

No apparent adverse health consequences

3% in populations have loss-of-function *PCSK9* mutations

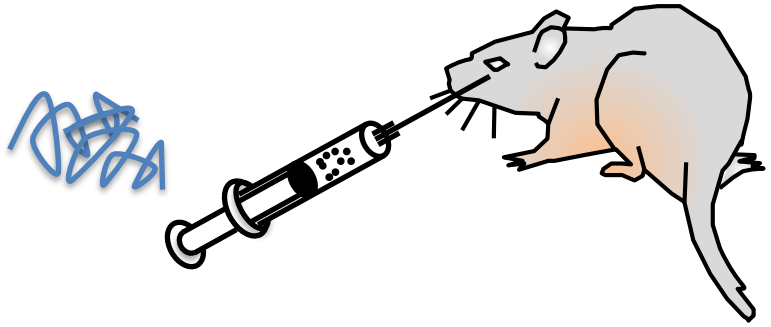
Cohen et al. *Nat Genet* 2005; 37:161-5

Cohen et al. *N Engl J Med* 2006; 356:1264-72

Zhao et al. *Am J Hum Genet* 2006; 79:514-23

Hooper et al. *Atherosclerosis* 2007; 193:445-8

Targeting mouse *Pcsk9* with somatic genome editing



→ cholesterol ↓ ?

CRISPR-Cas9 targeting *Pcsk9* in the mouse liver using virus

Qiurong Ding
Harvard University
(now Shanghai)

Molecular Medicine

Permanent Alteration of PCSK9 With In Vivo CRISPR-Cas9 Genome Editing

Qiurong Ding, Alanna Strong, Kevin M. Patel, Sze-Ling Ng, Bridget S. Gosis, Stephanie N. Regan, Chad A. Cowan, Daniel J. Rader, Kiran Musunuru

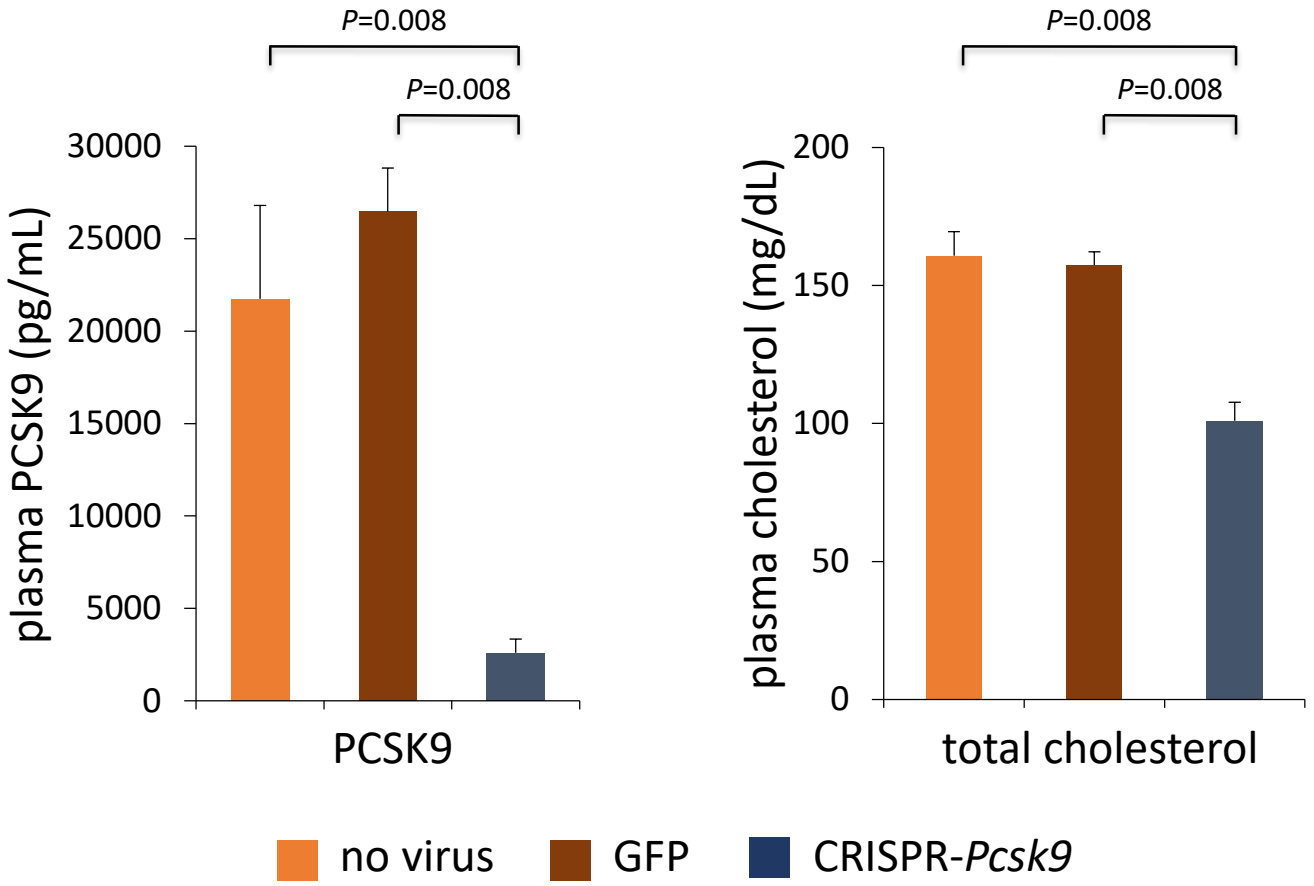
AJHG

Ding et al. *Circ Res* 2014; 115:488-92

ASHG
American Society of Human Genetics

Targeting mouse *Pcsk9* with somatic genome editing

>90% reduction



35%–40% reduction

N = 5 per group, 4 days after injection

Ding et al. *Circ Res* 2014; 115:488-92

In vivo genome editing for therapy

Traditional therapies	Genome-editing therapy
• Repeated dosing	• One-time therapy
• Short-term effect	• Permanent effect

In vivo genome editing for therapy

Traditional therapies	Genome-editing therapy
• Repeated dosing	• One-time therapy
• Short-term effect	• Permanent effect

Big concern is safety – what is the extent of off-target mutagenesis elsewhere in the genome? Risk of cancer?

Unbiased genome-wide assessment for safety (off-target mutations)

LETTER

https://doi.org/10.1038/s41586-018-0500-9

In vivo CRISPR editing with no detectable genome–wide off–target mutations

Pinar Akcakaya[1,13], Maggie L. Bobbin[2,3,4,13], Jimmy A. Guo[2,3], Jose Malagon–Lopez[2,3,4], Kendell Clement[2,3,4], Sara P. Garcia[2], Mick D. Fellows[5], Michelle J. Porritt[1], Mike A. Firth[6], Alba Carreras[1,9], Tania Baccega[1,10], Frank Seeliger[7], Mikael Bjursell[1], Shengdar Q. Tsai[2,3,4,11], Nhu T. Nguyen[2,3], Roberto Nitsch[8], Lorenz M. Mayr[1,12], Luca Pinello[2,4], Mohammad Bohlooly–Y[1], Martin J. Aryee[2,4], Marcello Maresca[1]* & J. Keith Joung[2,3,4]*

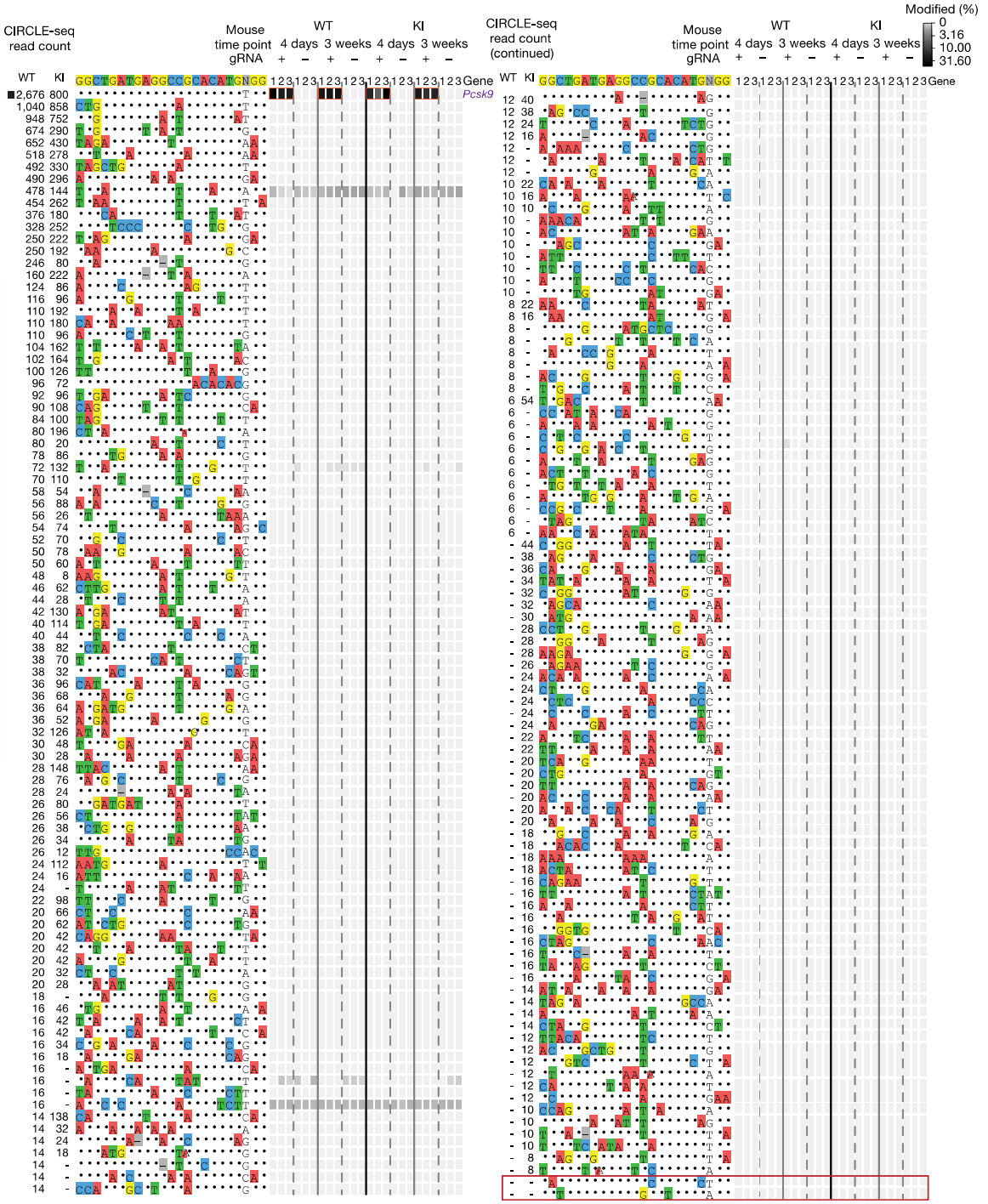
CRISPR–Cas genome-editing nucleases hold substantial promise for developing human therapeutic applications[1–6] but identifying unwanted off-target mutations is important for clinical translation[7].

Having established the efficacy of gP–Cas9 for on-target *Pcsk9* modification in vivo, we conducted the first screening step of VIVO by performing CIRCLE-seq with gP–Cas9 on liver genomic DNA from

J. Keith Joung, MGH

Akcakaya et al.
Nature 2018

AJHG

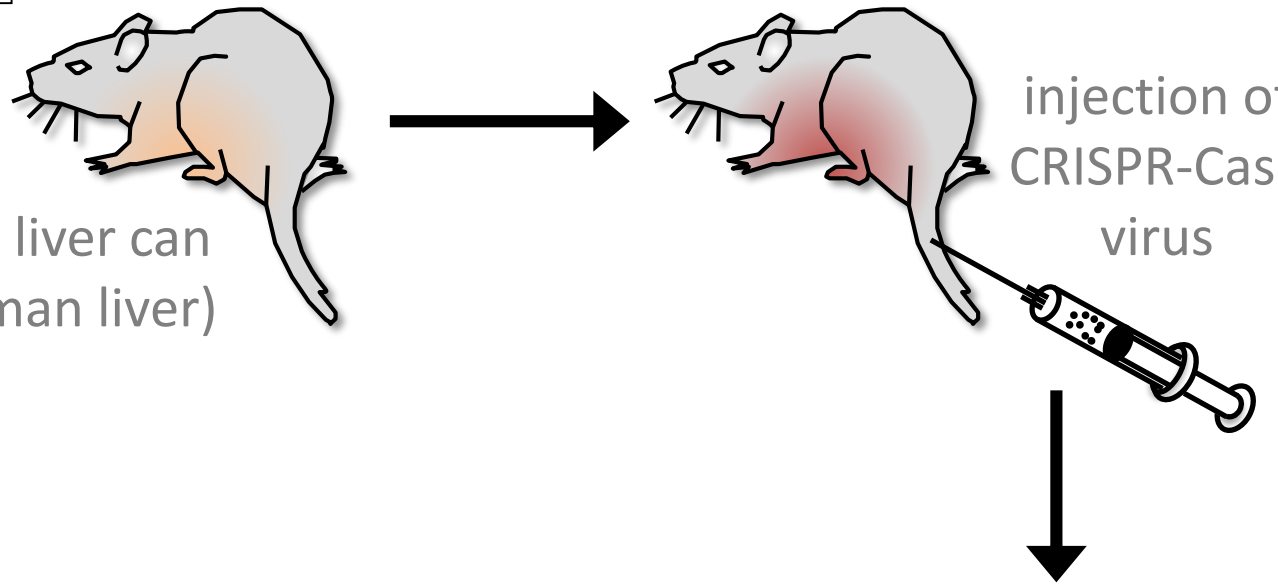


What about human therapy?

Targeting human *PCSK9* in liver-humanized mice

"Humanized" mouse model

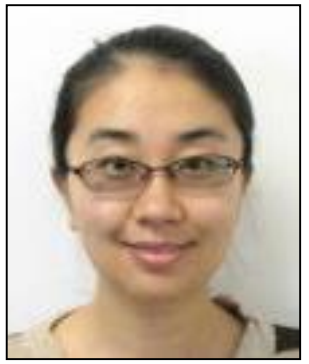
transplantation of primary human hepatocytes



FRG KO mice (mouse liver can be replaced with human liver)

injection of CRISPR-Cas9 virus

changes in **human** characteristics



Xiao Wang
UPENN

Wang et al., *Arterioscler Thromb Vasc Biol* 2016; 36:783-6

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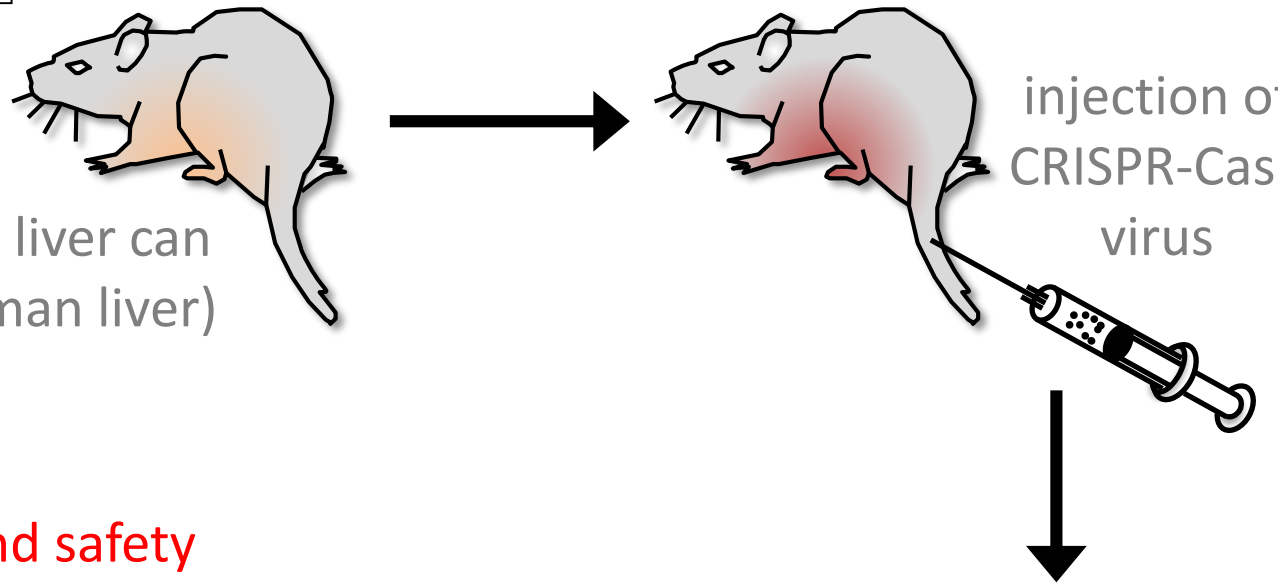

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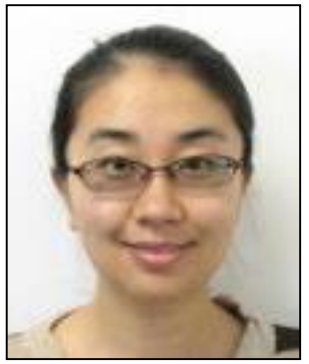

Xiao Wang
UPENN

can gauge efficacy and safety
in authentic human cells,
with human genomes,
in a living animal

Wang et al., *Arterioscler Thromb Vasc Biol* 2016; 36:783-6

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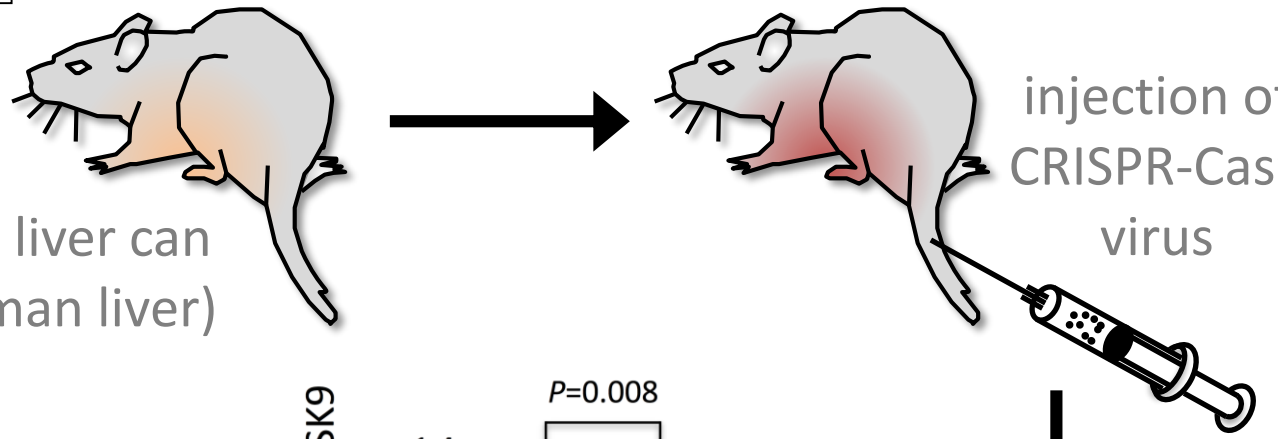

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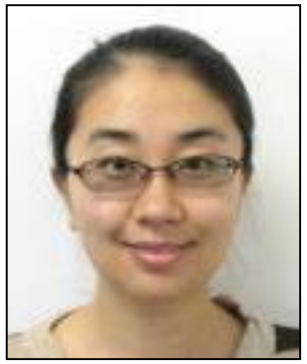

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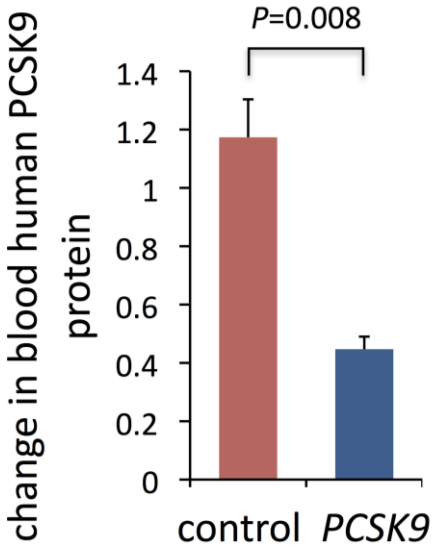

changes in **human** characteristics

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Wang et al., *Arterioscler Thromb Vasc Biol* 2016; 36:783-6

ASHG American Society of Human Genetics

ANGPTL3 as a therapeutic target is similar to *PCSK9*

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ANGPTL3 Deficiency and Protection Against Coronary Artery Disease

Nathan O. Stitziel, MD, PhD,[a] Amit V. Khera, MD,[b,c,d] Xiao Wang, PhD,[e] Andrew J. Bierhals, MD, MPH,[f] A. Christina Vourakis, BA,[g] Alexandra E. Sperry, BA,[g] Pradeep Natarajan, MD,[b,c,d] Derek Klarin, MD,[b,c,h] Connor A. Emdin, DPhil,[b,c,d] Seyedeh M. Zekavat, BSc,[d] Akihiro Nomura, MD,[b,c,d] Jeanette Erdmann, PhD,[i,j] Heribert Schunkert, MD,[k,l] Nilesh J. Samani, MD,[m,n] William E. Kraus, MD,[o] Svati H. Shah, MD, MPH,[o] Bing Yu, PhD,[p,q] Eric Boerwinkle, PhD,[p,q] Daniel J. Rader, MD,[e,r] Namrata Gupta, PhD,[d] Philippe M. Frossard, PhD,[s] Asif Rasheed, MBBS,[s] John Danesh, DPhil,[t,u,v] Eric S. Lander, PhD,[d] Stacey Gabriel, PhD,[d] Danish Saleheen, MBBS, PhD,[s,w] Kiran Musunuru, MD, PhD, MPH,[e] Sekar Kathiresan, MD,[b,c,d] for the PROMIS and Myocardial Infarction Genetics Consortium Investigators

ABSTRACT

BACKGROUND Familial combined hypolipidemia, a Mendelian condition characterized by substantial reductions in all 3 major lipid fractions, is caused by mutations that inactivate the gene angiopoietin-like 3 (*ANGPTL3*). Whether ANGPTL3 deficiency reduces risk of coronary artery disease (CAD) is unknown.

OBJECTIVES The study goal was to leverage 3 distinct lines of evidence—a family that included individuals with complete (compound heterozygote) ANGPTL3 deficiency, a population based-study of humans with partial (heterozygote) ANGPTL3 deficiency, and biomarker levels in patients with myocardial infarction (MI)—to test whether ANGPTL3 deficiency is associated with lower risk for CAD.

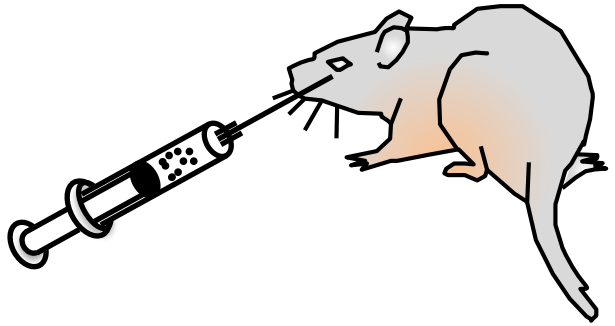
Individuals with one loss-of-function mutation in *ANGPTL3*:

LDL-C, TG ↓ 30%
CHD risk ↓ 35-40%

Individuals with two loss-of-function mutations in *ANGPTL3*: totally healthy

Musunuru et al. *N Engl J Med* 2010; 363:2220-7
Stitziel et al. *J Am Coll Cardiol* 2017; 69:2054-63
Dewey et al. *N Engl J Med* 2017; 377:211-21

Base editing of *Angptl3* in mouse model of FH



BE3 targeting *Angptl3* in the mouse liver using virus:
Q135X (**C**AA→**T**AA)

Alex Chadwick
UPENN

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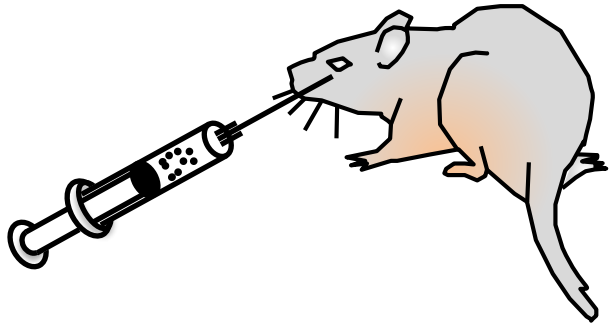

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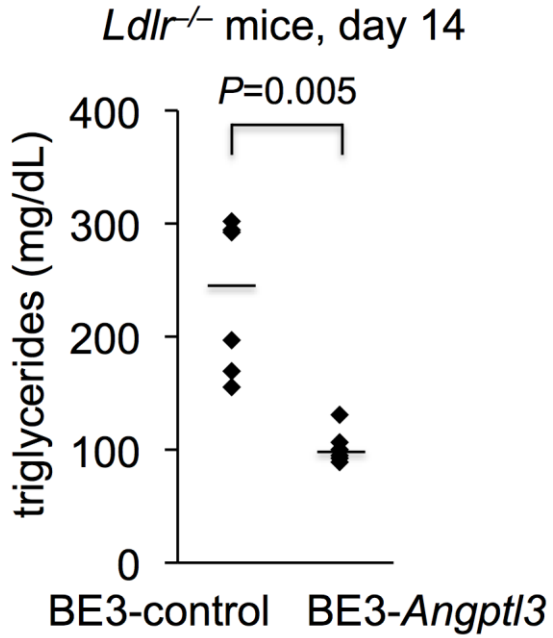

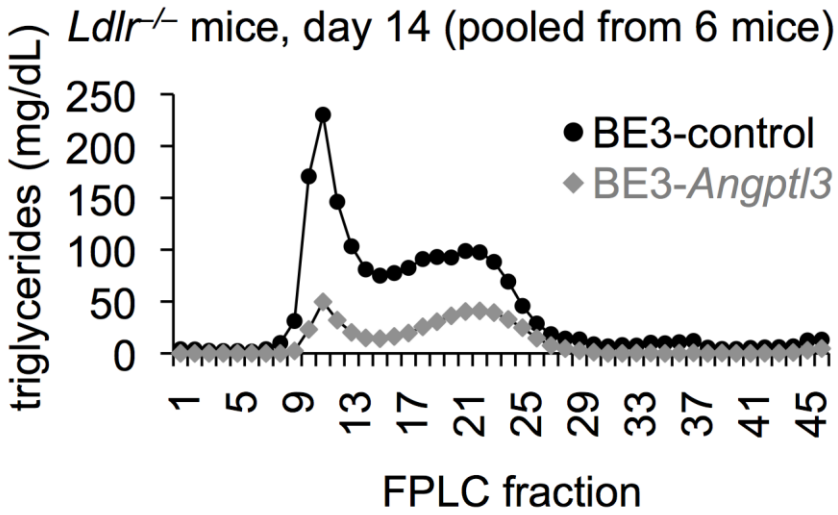

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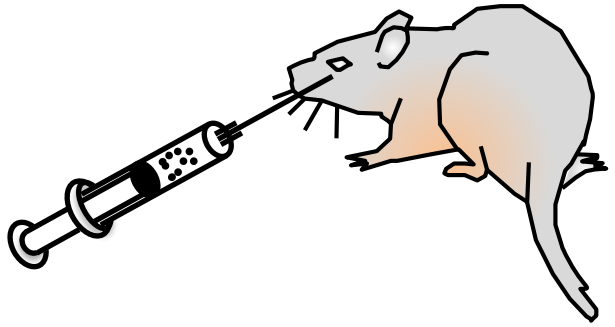

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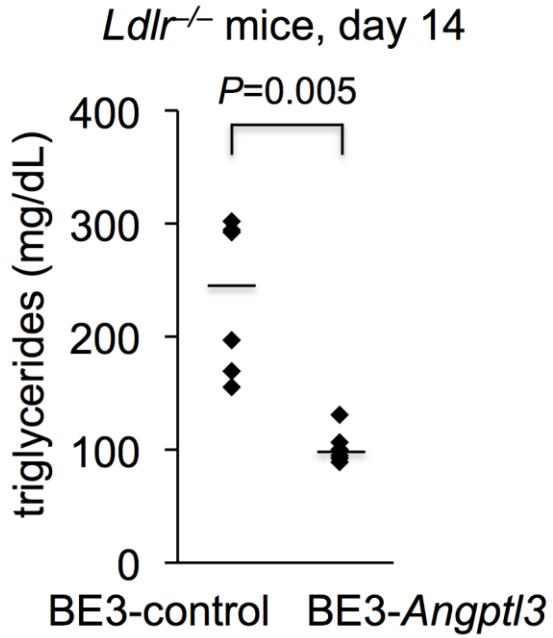

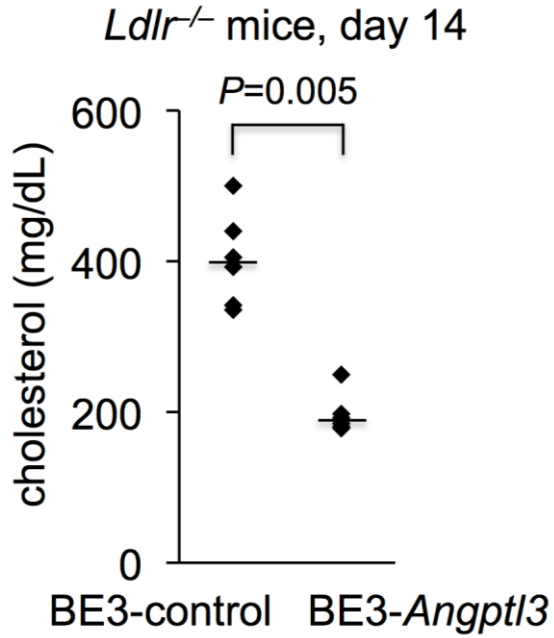

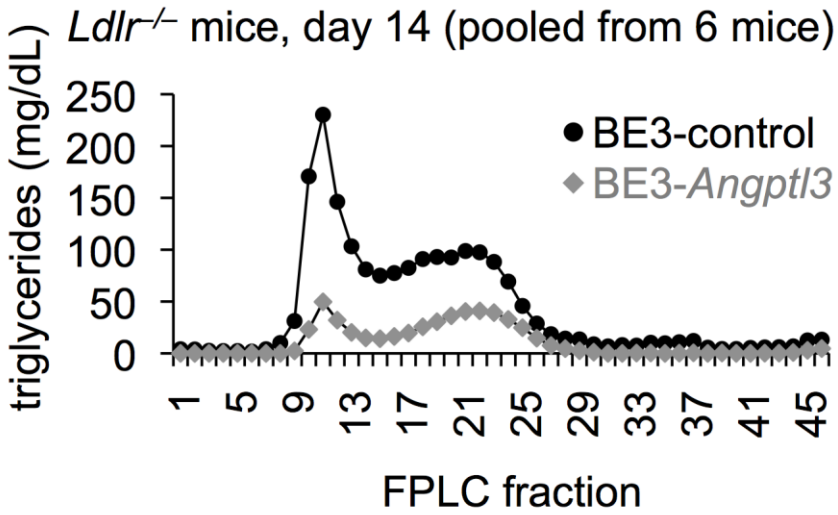

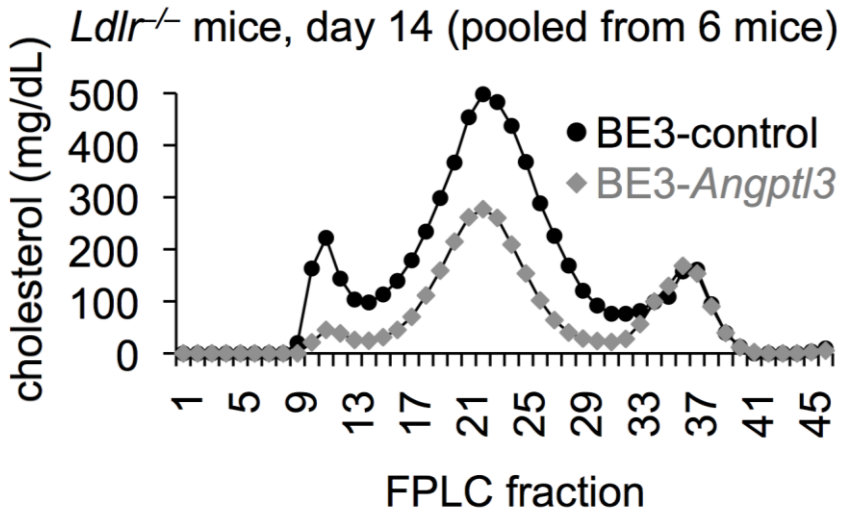

AJHG

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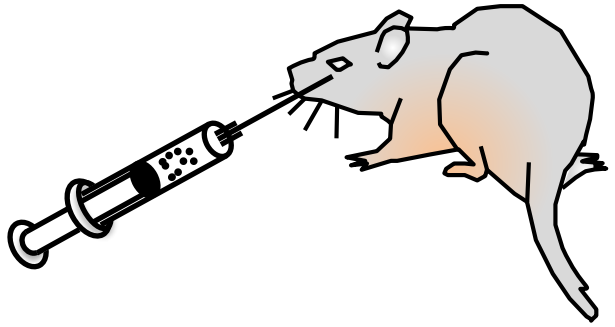

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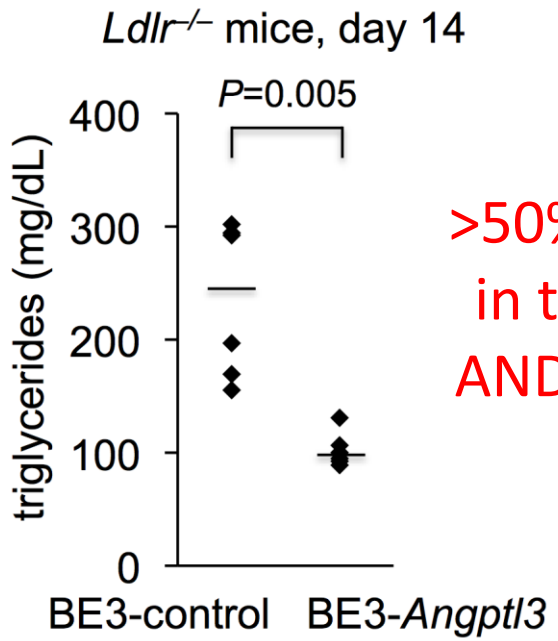
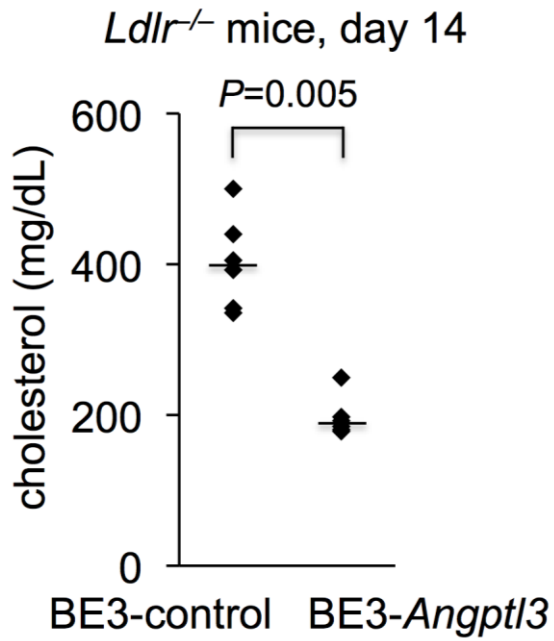
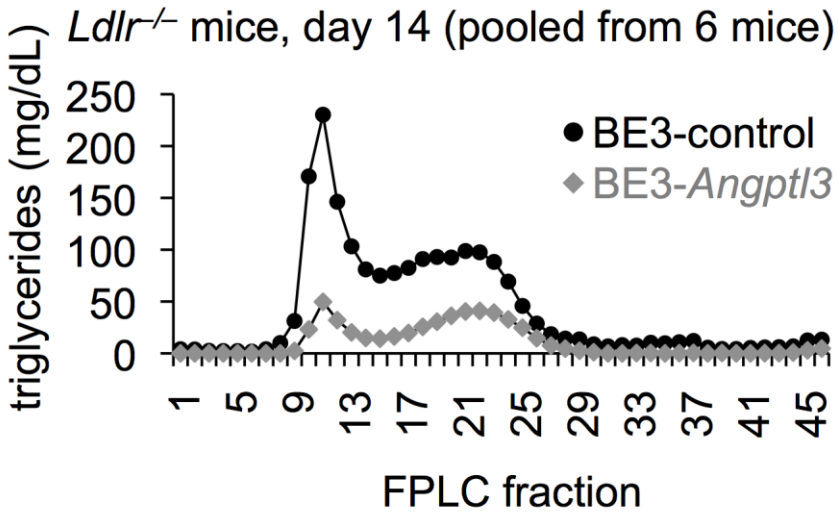
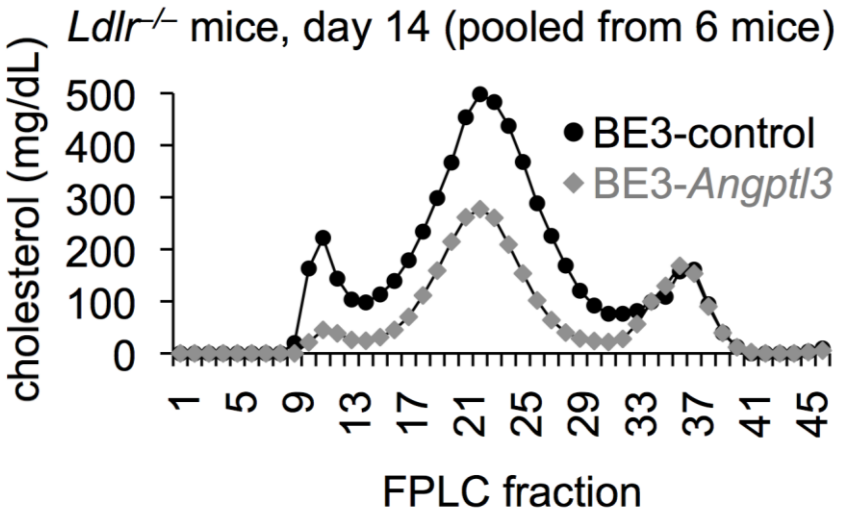


>50% reductions in triglycerides AND cholesterol







AJHG

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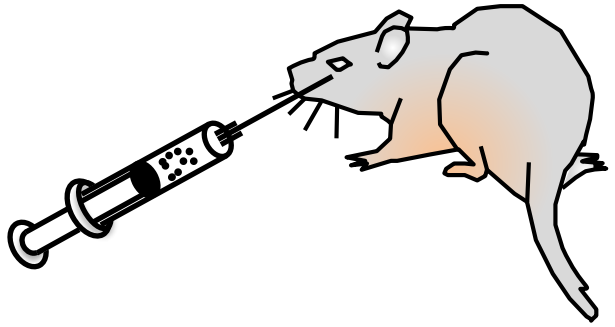

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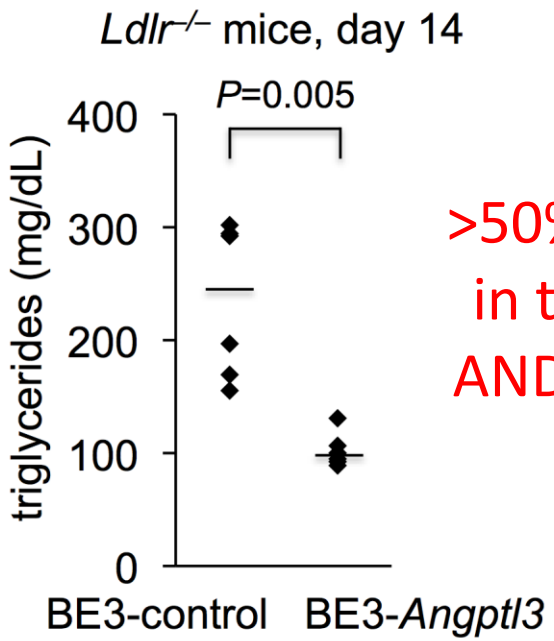

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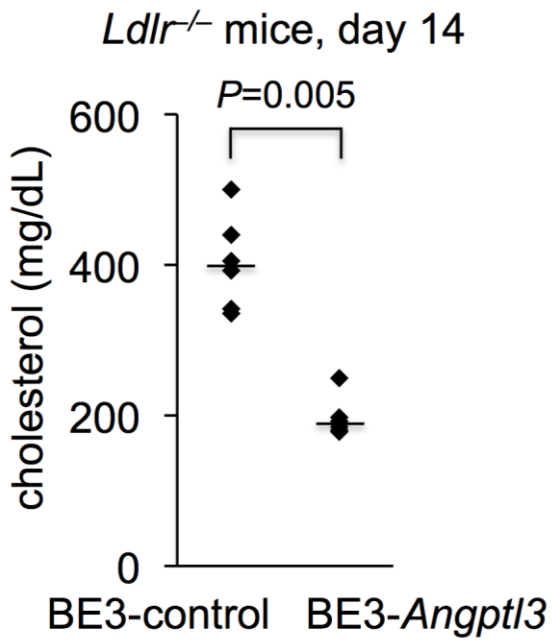
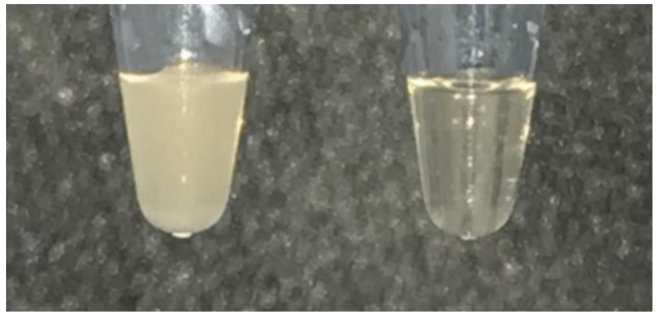
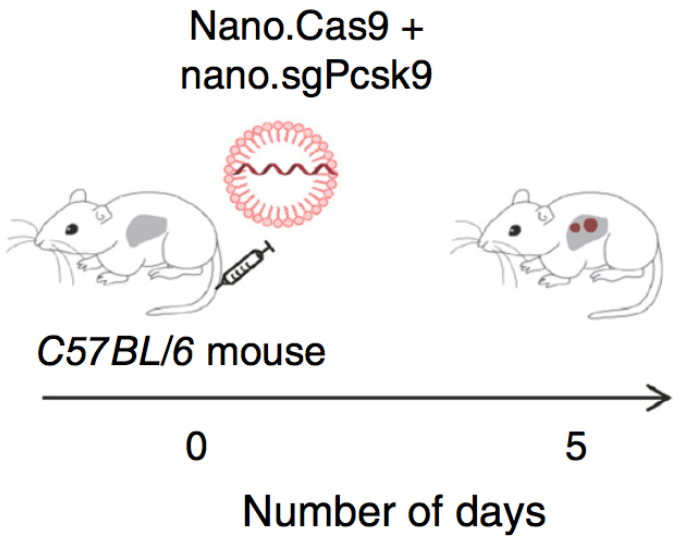


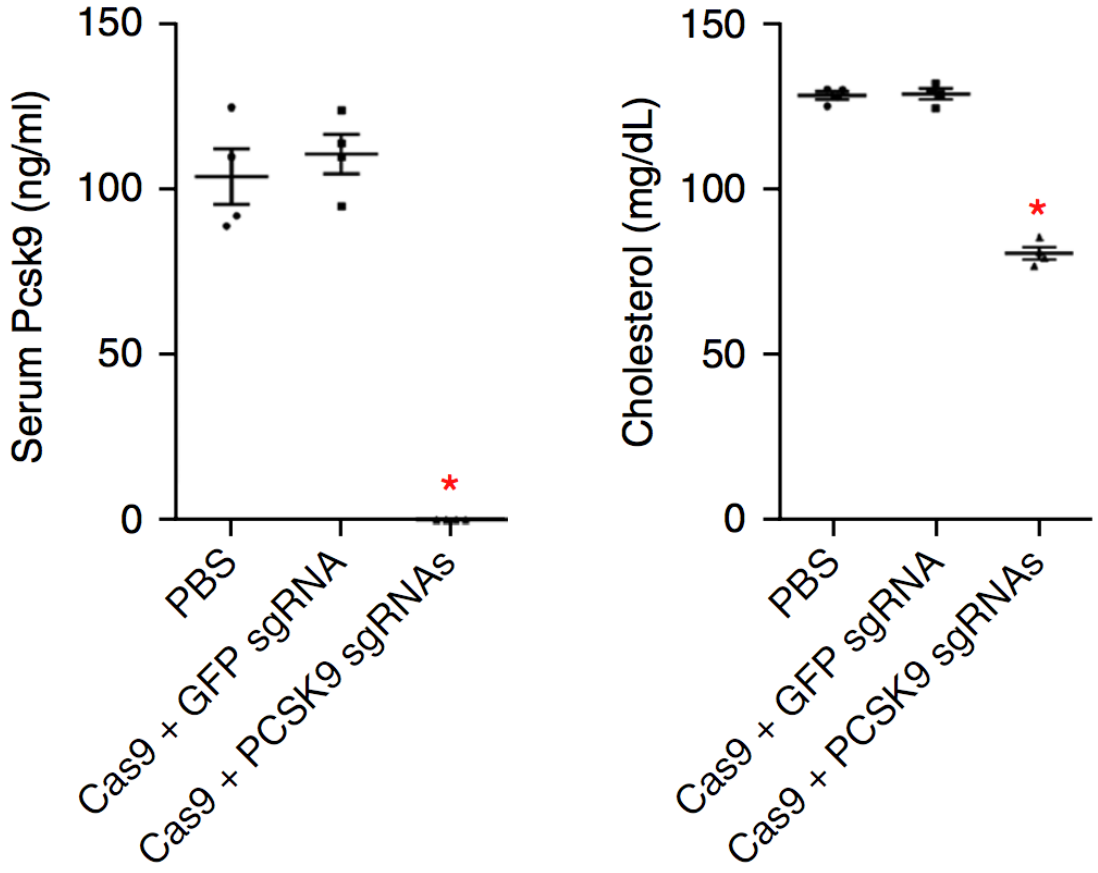
mouse plasma samples, day 14



BE3-control BE3-*Angptl3*

Lipid nanoparticle delivery of genome-editing tool





Yin et al. *Nat Biotechnol* 2017; 35:1179-87

PCSK9/ANGPTL3 and coronary heart disease (CHD)

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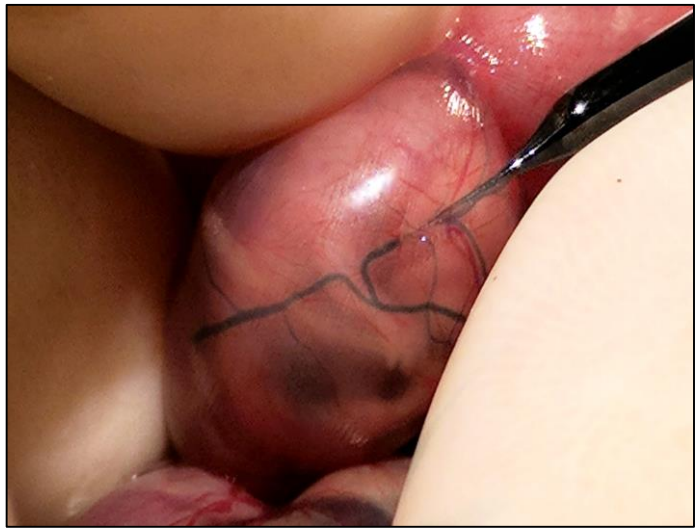
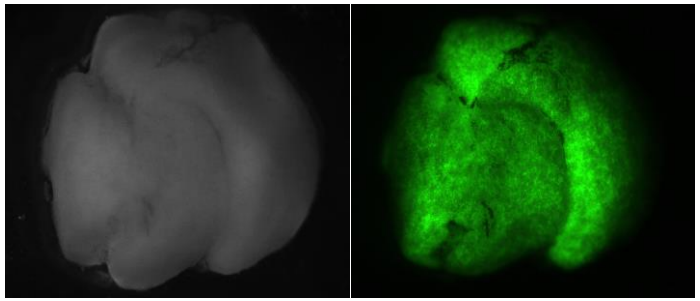
In utero base editing of mouse *Pcsk9*



day E16.5 intravenous injection



greyscale, 5 ms GFP filter, 5 ms
liver on day P0 post injection

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Rossidis, Stratigis, Chadwick, Hartman et al., *Nat Med* 2018; 24:1513-8

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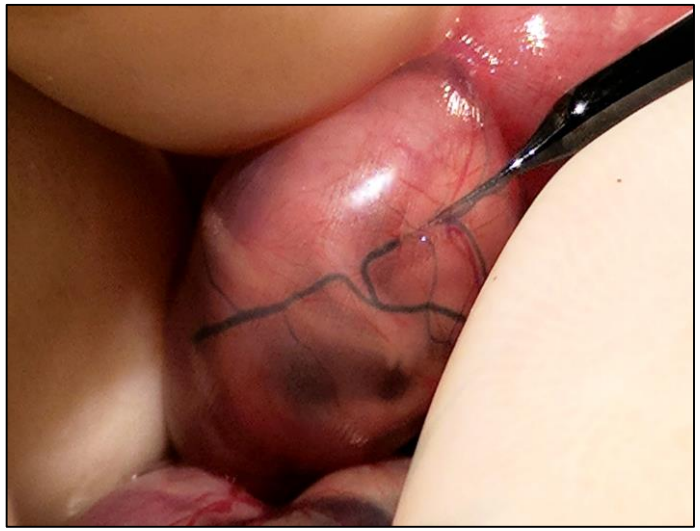
In utero base editing of mouse Pcsk9



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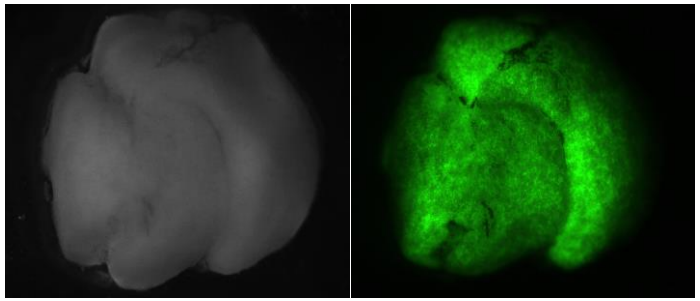

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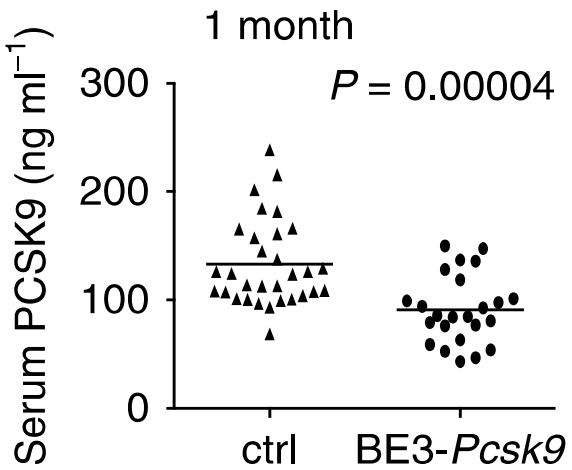

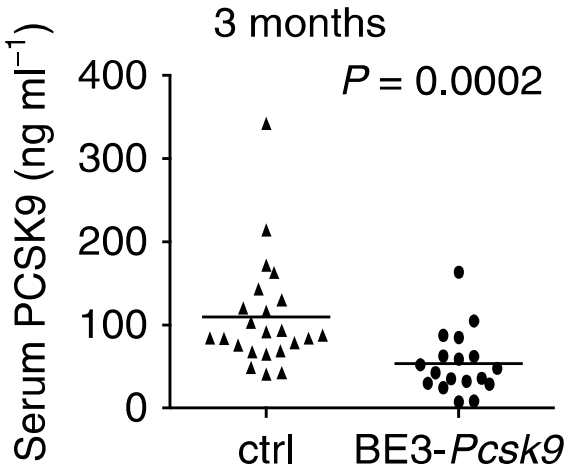

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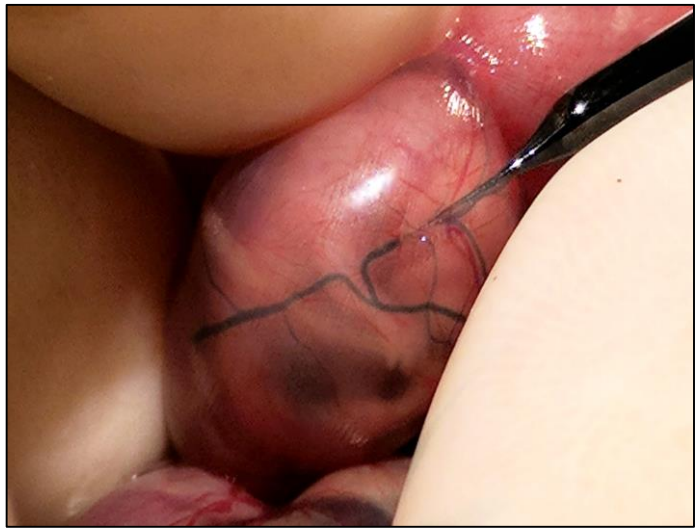

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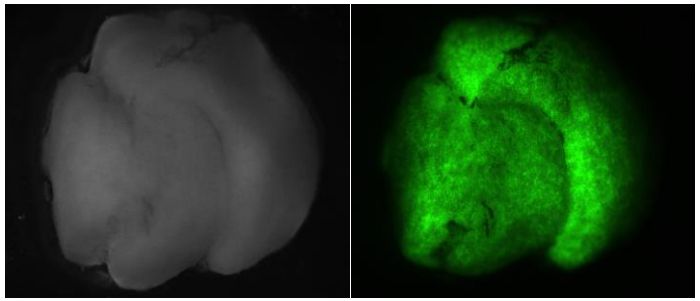

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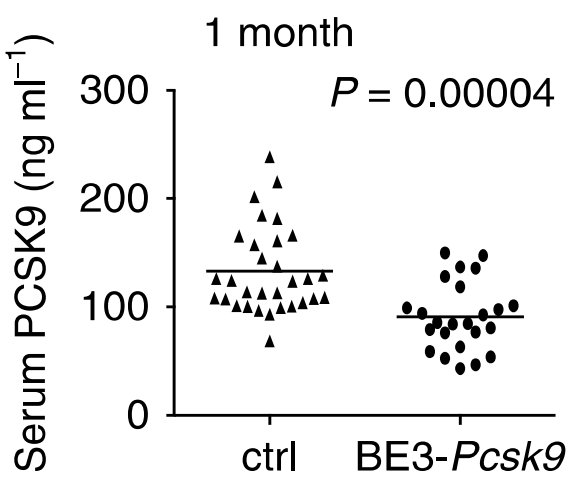

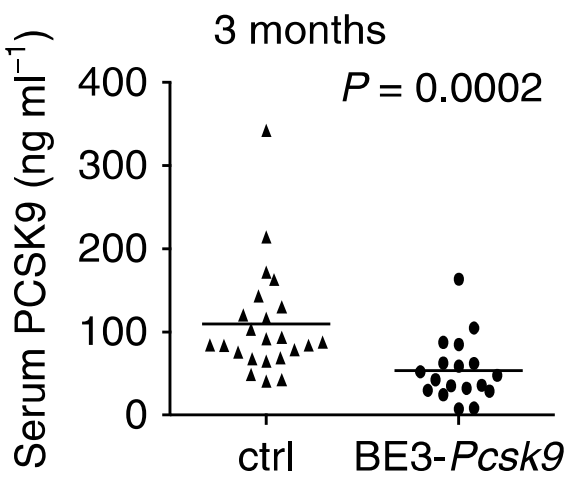

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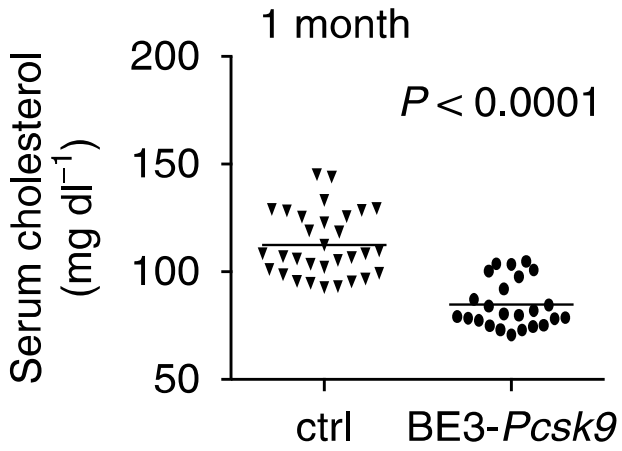

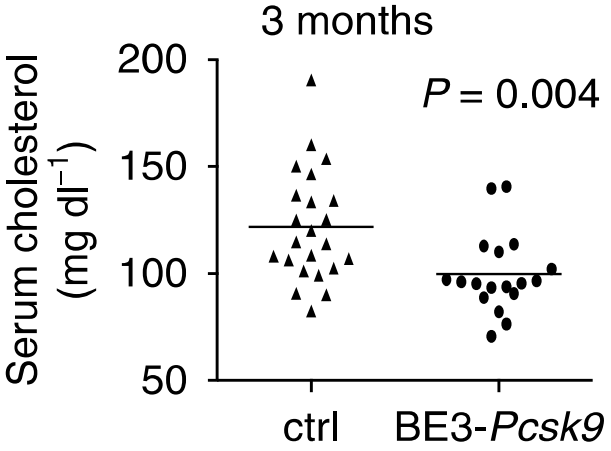

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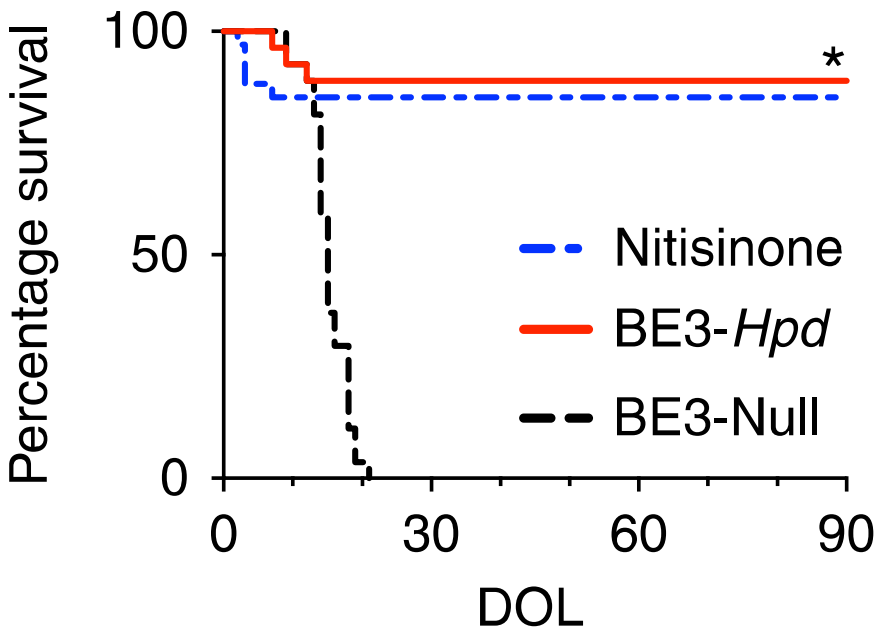
In utero base editing to cure tyrosinemia



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black = untreated
blue = postnatal medication
red = *in utero* base editing

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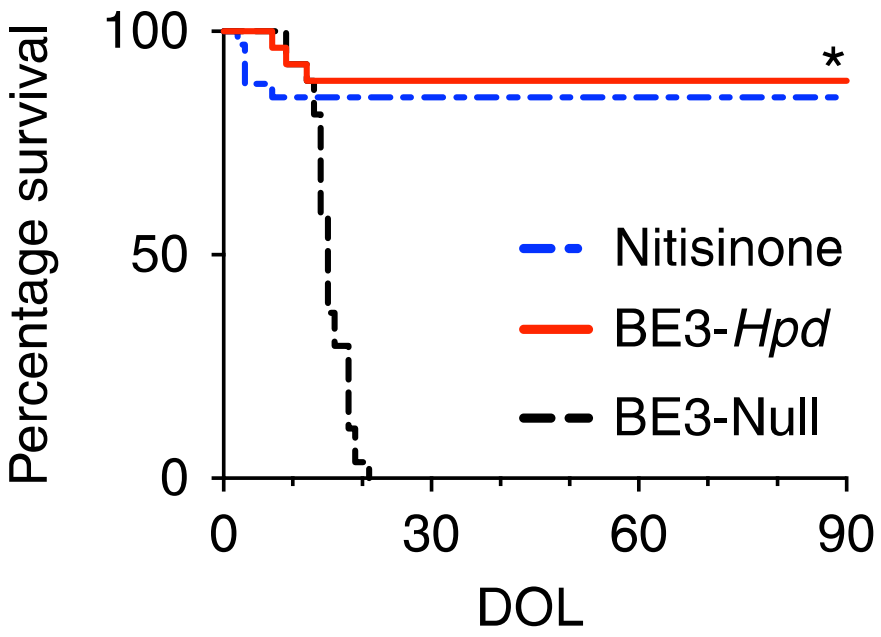

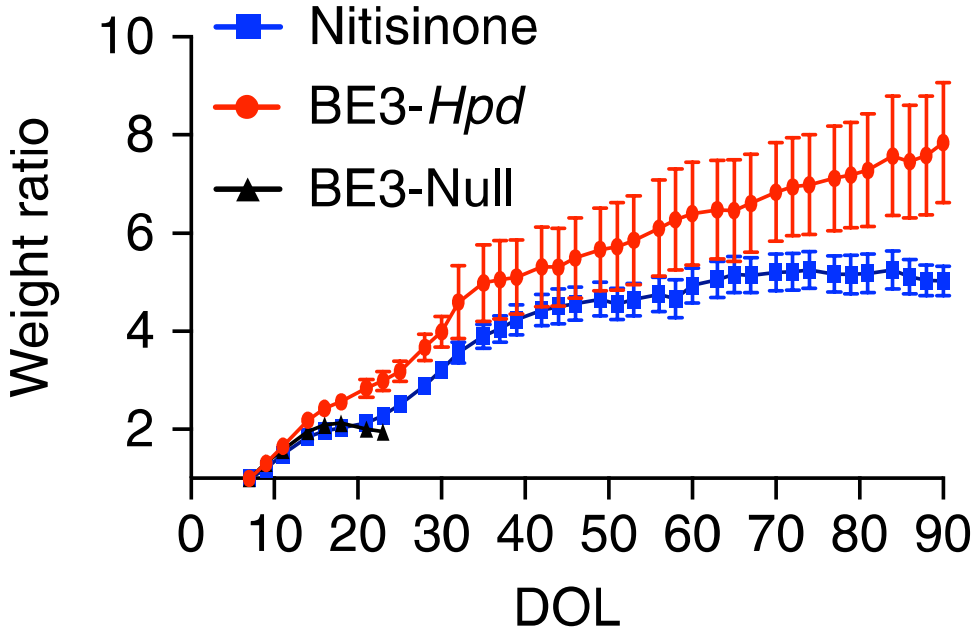

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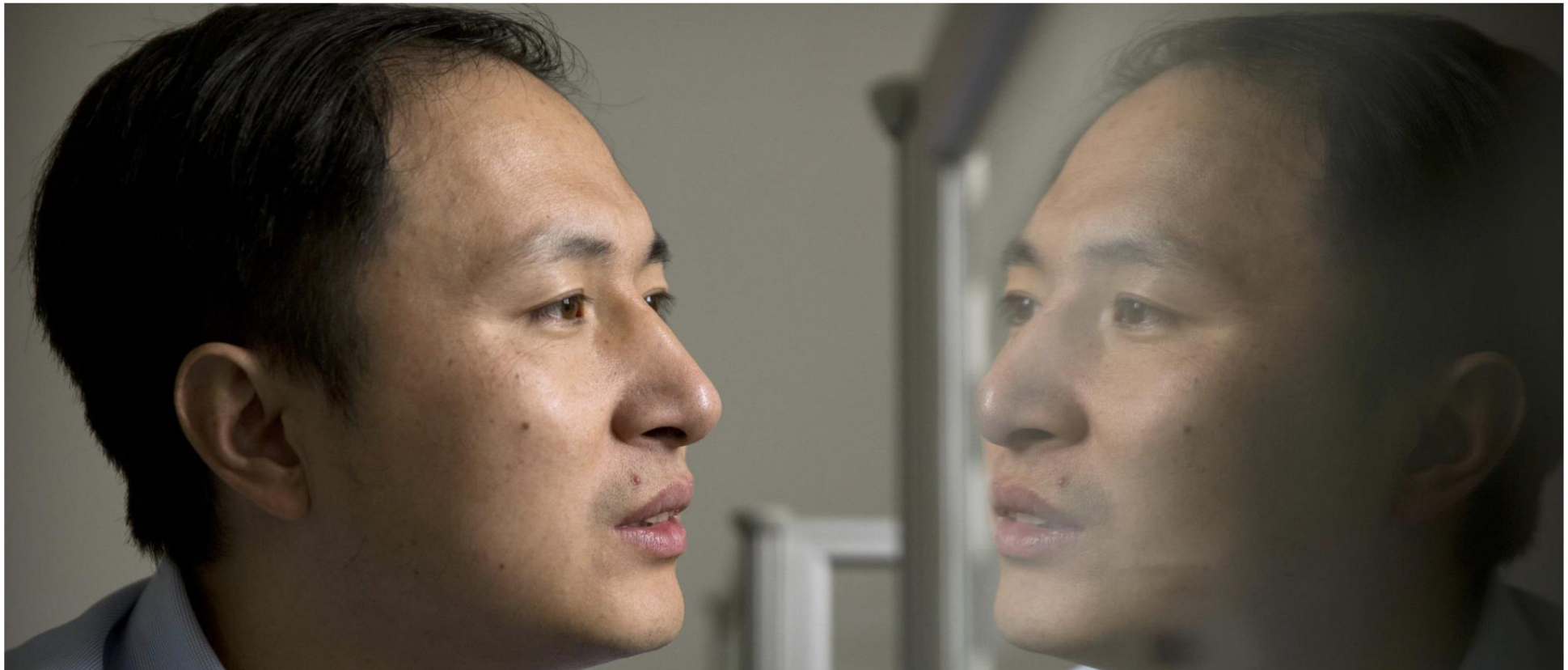
EXCLUSIVE

STAT+

Ethical issues plagued newly surfaced paper by 'CRISPR babies' scientist

By SHARON BEGLEY @sxbegle / DECEMBER 10, 2018



EXCLUSIVE

‘CRISPR babies’ lab asked U.S. scientist for help to disable cholesterol gene in human embryos

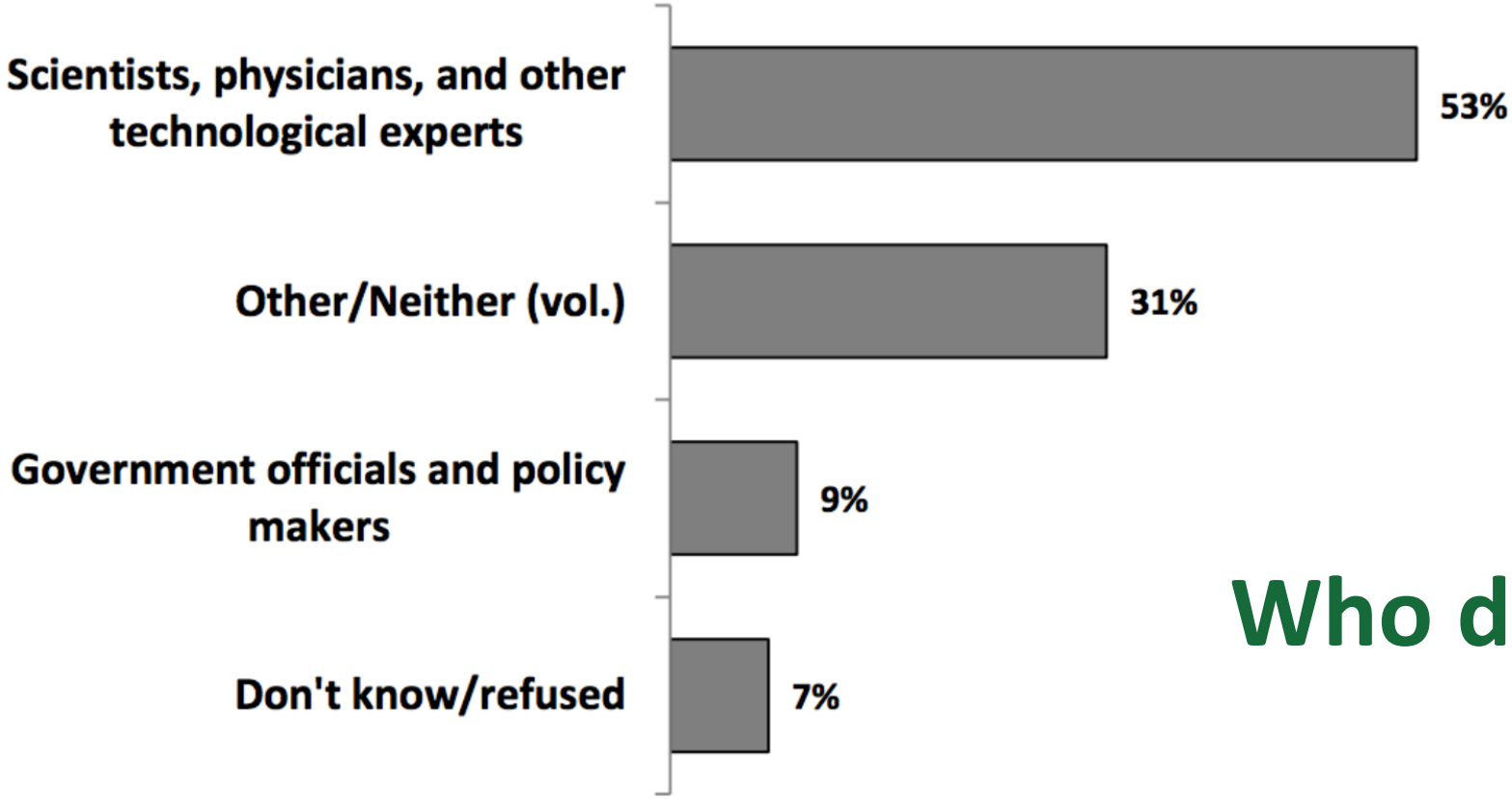
By SHARON BEGLEY @sxbegle / DECEMBER 4, 2018

Potential clinical uses of germline genome editing

- Pre-empting severe genetic disorders
- Addressing genetic causes of infertility (e.g., block in gamete development)
- Reducing risk of common/complex diseases
- “Enhancement”

FIGURE 3: Who Should Decide Whether or Not to Allow Changing the Genes of Unborn Babies?

For decisions on whether or not to allow changing the genes of unborn babies to improve their healthy, physical traits, or intelligence, do you think we should leave it up to...



Who decides?

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https://www.statnews.com/2016/02/11/stat-harvard-poll-gene-editing/

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Q&A with Speakers

Natalia
Gomez-Ospina, MD, PhD

Kiran Musunuru,
MD, PhD, MPH, ML

Bruce Korf, MD, PhD
Moderator

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