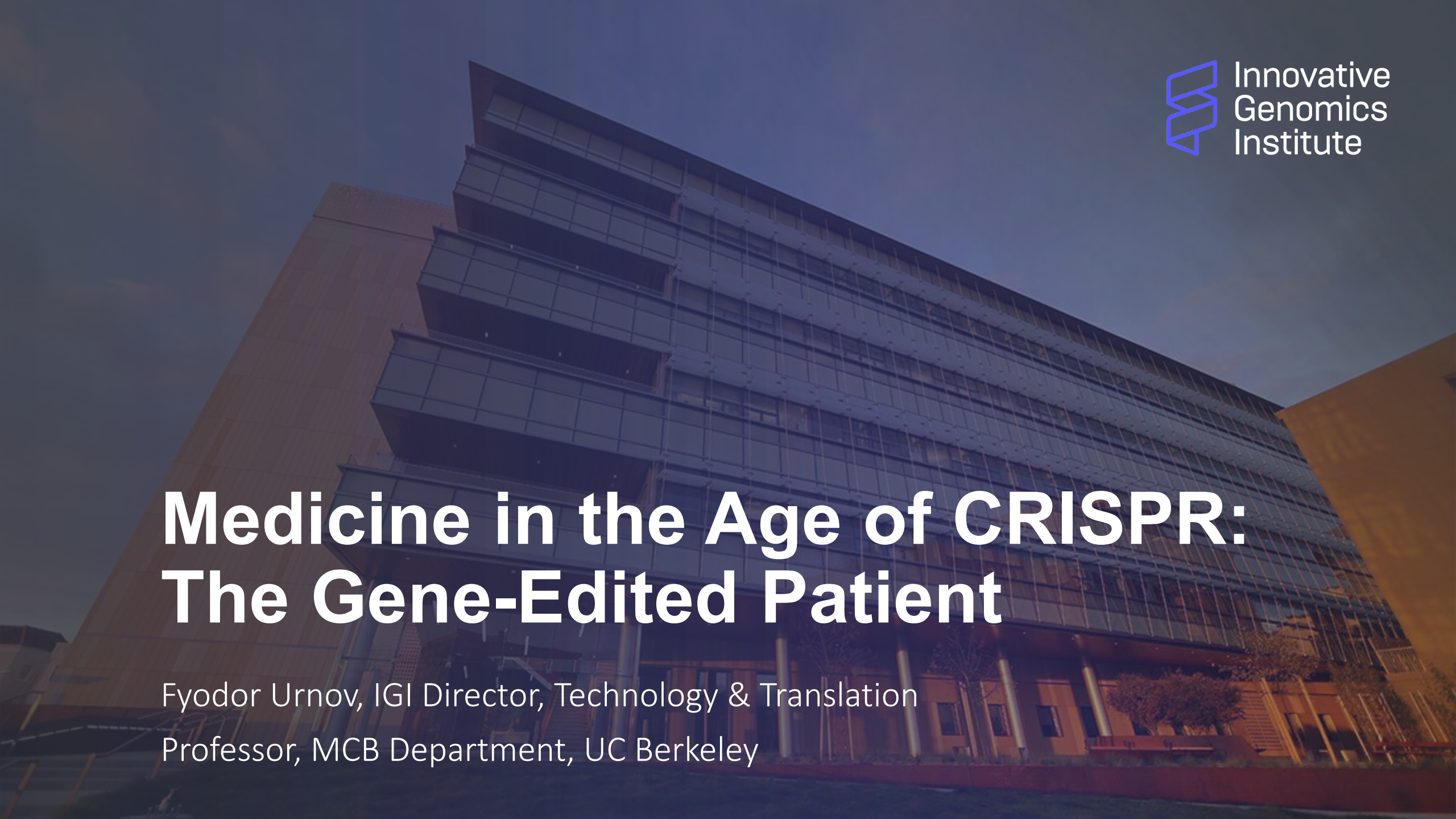


Innovative Genomics Institute

Medicine in the Age of CRISPR: The Gene-Edited Patient

Fyodor Urnov, IGI Director, Technology & Translation

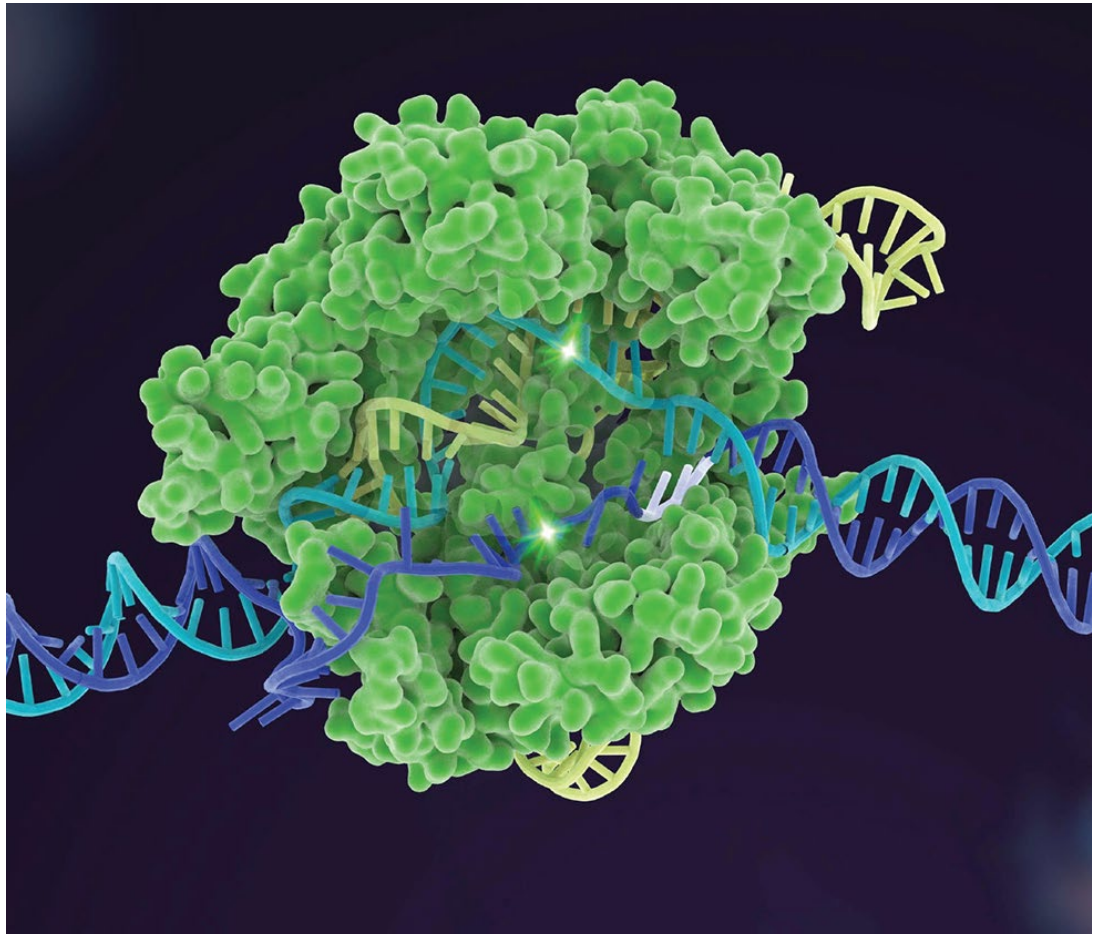
Professor, MCB Department, UC Berkeley

Fyodor Urnov – conflicts of interest

- Tune Therapeutics – scientific co-founder, paid consultant, hold equity
- GSK – paid advisor

2020 Nobel Prize: Jennifer Doudna, IGI, UC Berkeley

Basic science discovery: **2012 ->** CRISPR gene editing



Prize shared with Dr Emmanuelle Charpentier

CRISPR has enabled a fundamentally new kind of medicine

- CRISPR genome editing 101
- CRISPR as medicine – clinical trials and track record – September 2021
- CRISPR as target discovery engine AND as a medicine for that target
- CRISPR horizons – the challenge of “rare” genetic disease

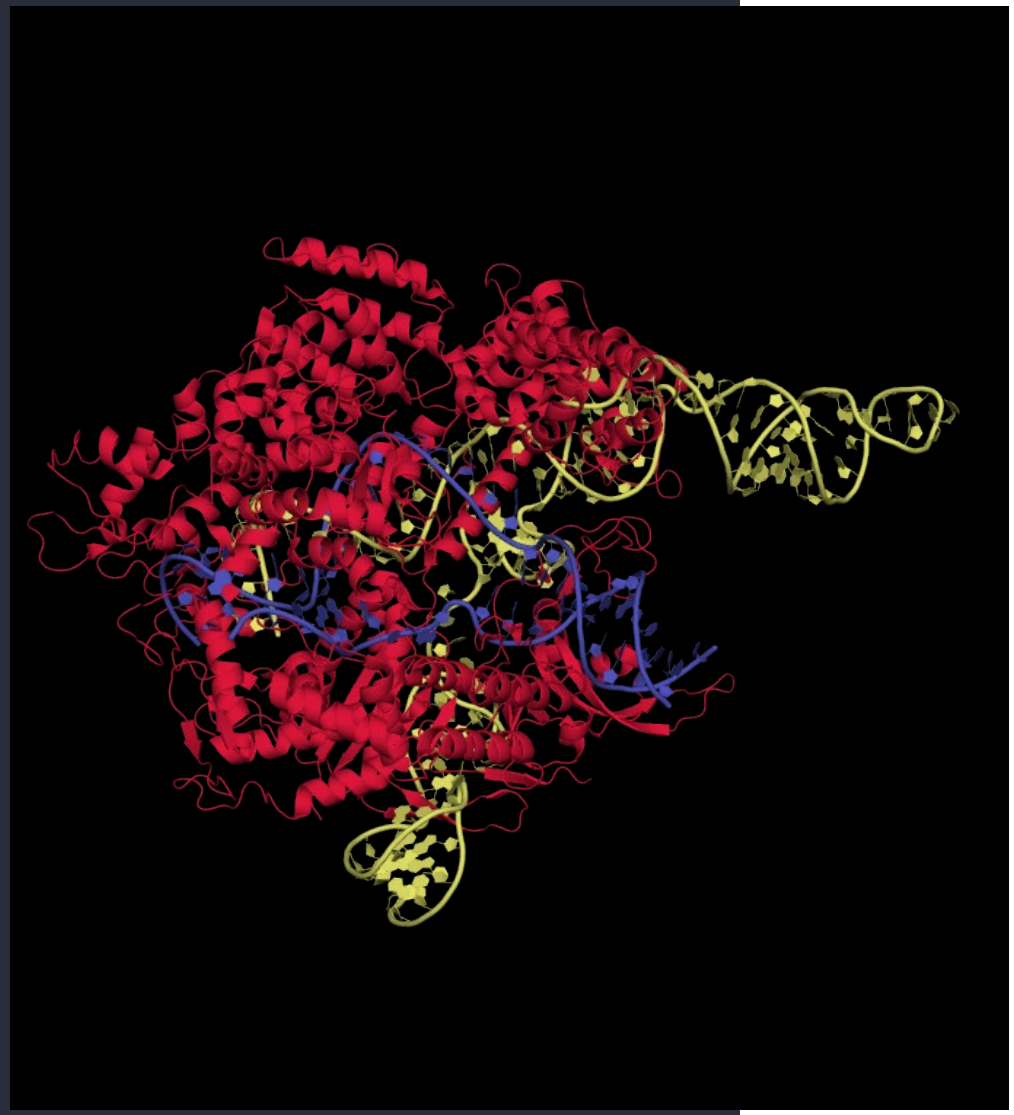
Two CRISPR-edited human beings

Victoria Gray (sickle cell disease)

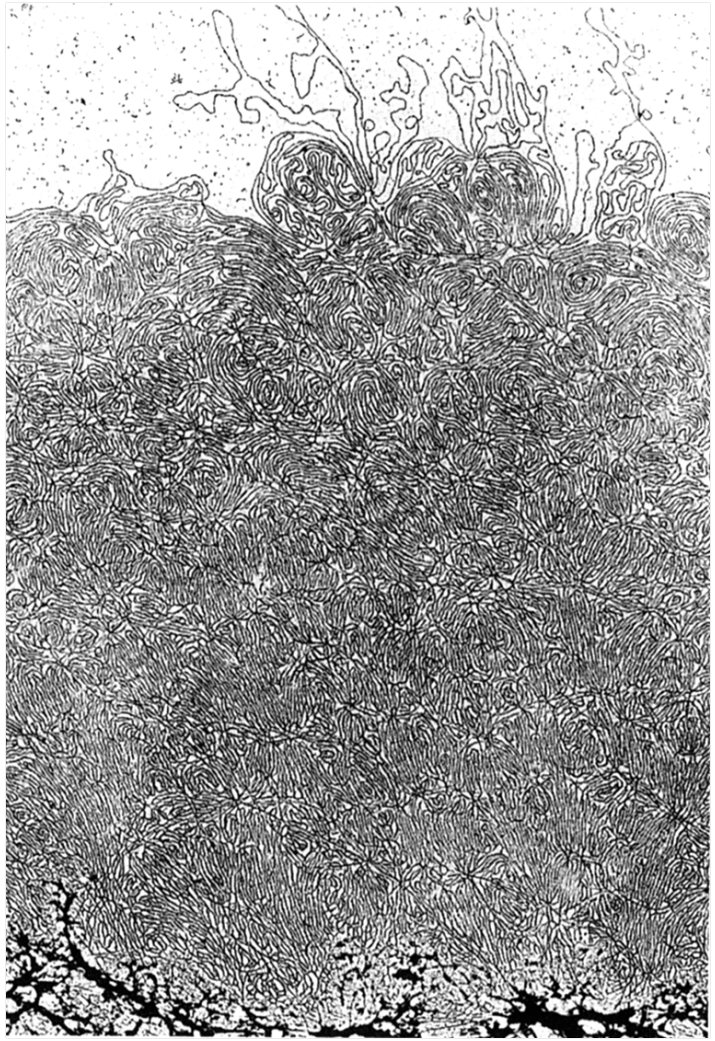
Patrick Doherty (TTR amyloidosis)

https://www.npr.org/sections/health-shots/2019/12/25/784395525/a-young-mississippi-womans-journey-through-a-pioneering-gene-editing-experiment
https://www.npr.org/sections/health-shots/2021/06/26/1009817539/he-inherited-a-devastating-disease-a-crispr-gene-editing-breakthrough-stopped-it

Genome editing and CRISPR

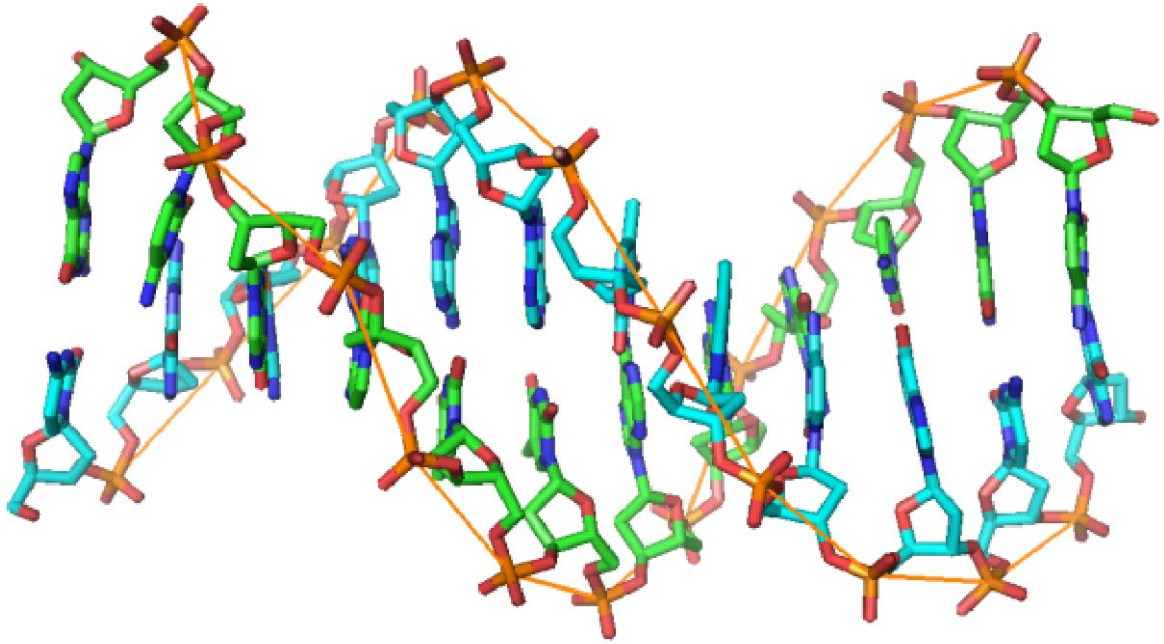


0.3% of human genome



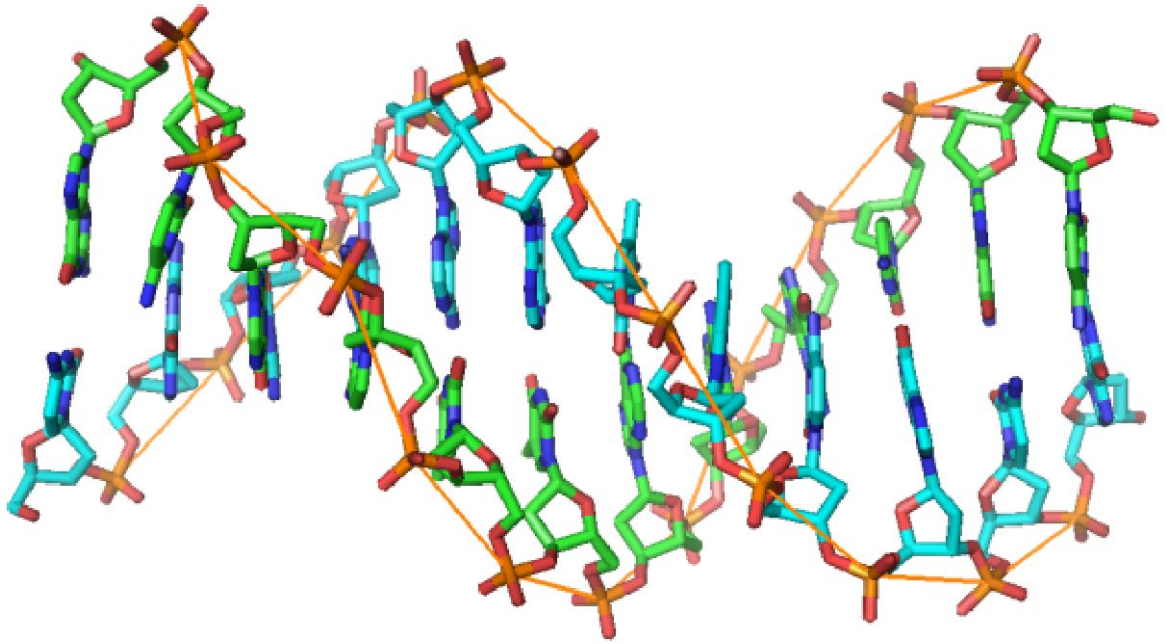
6.6e9 bp diploid

B-form DNA – 12 bp

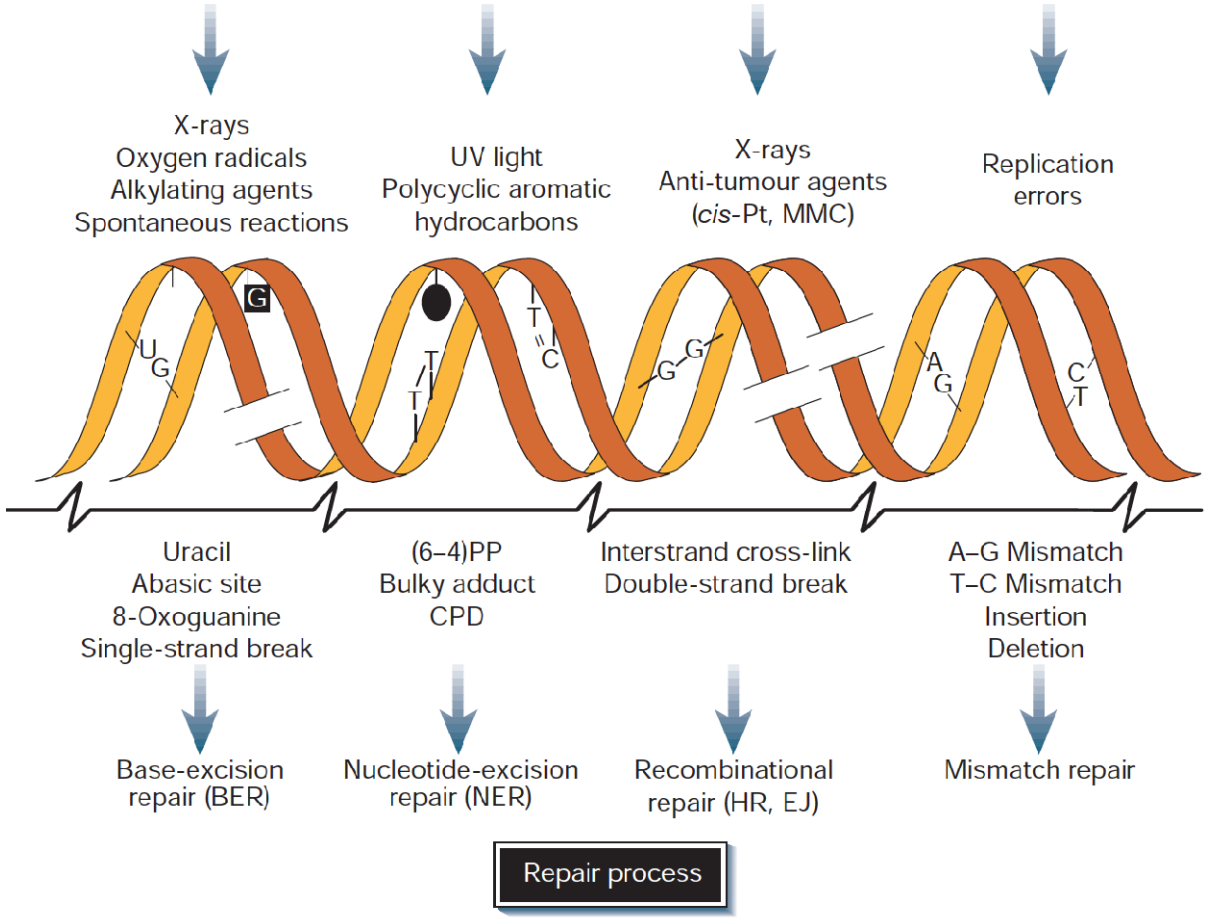


in contrast to bacteria and yeast, HIGHLY resistant to targeted change

B-form DNA – 12 bp



DNA repair

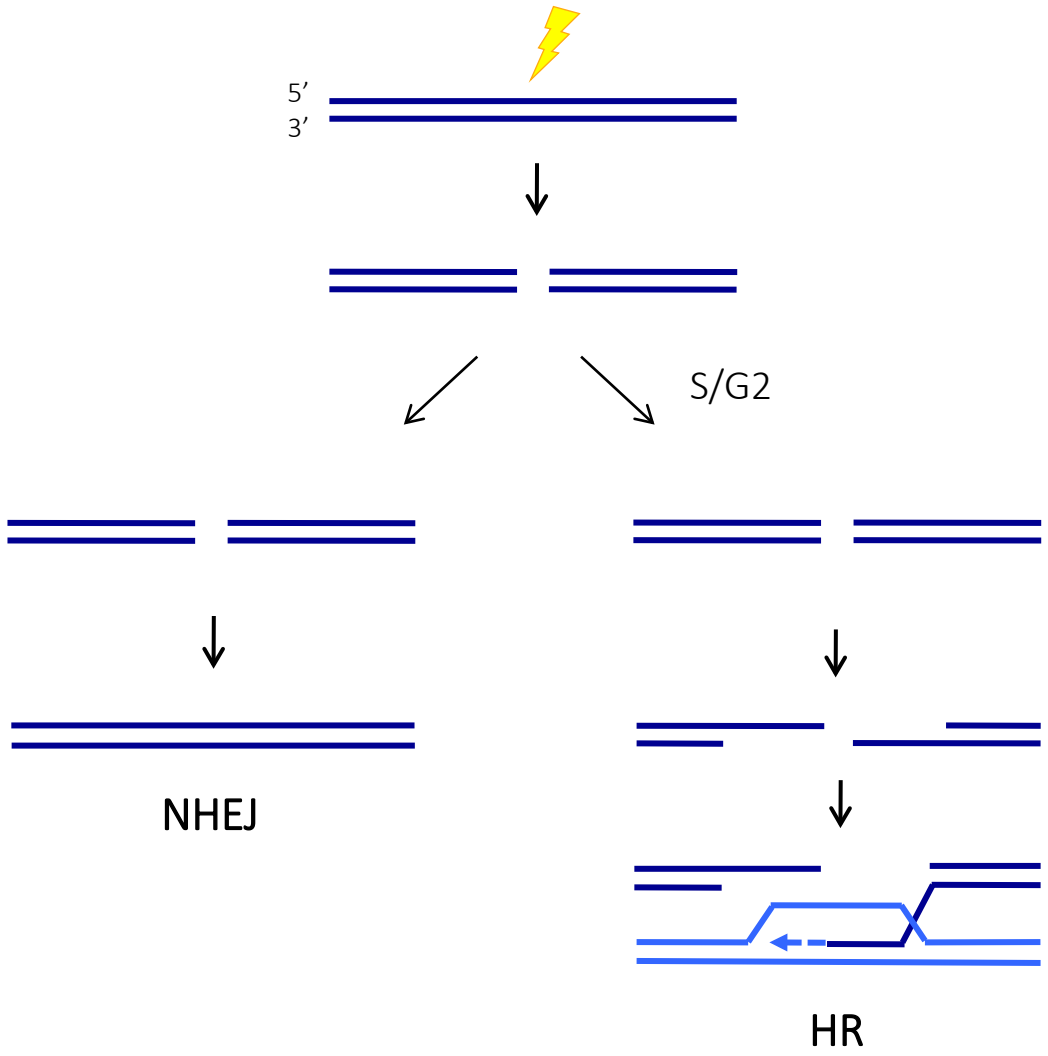


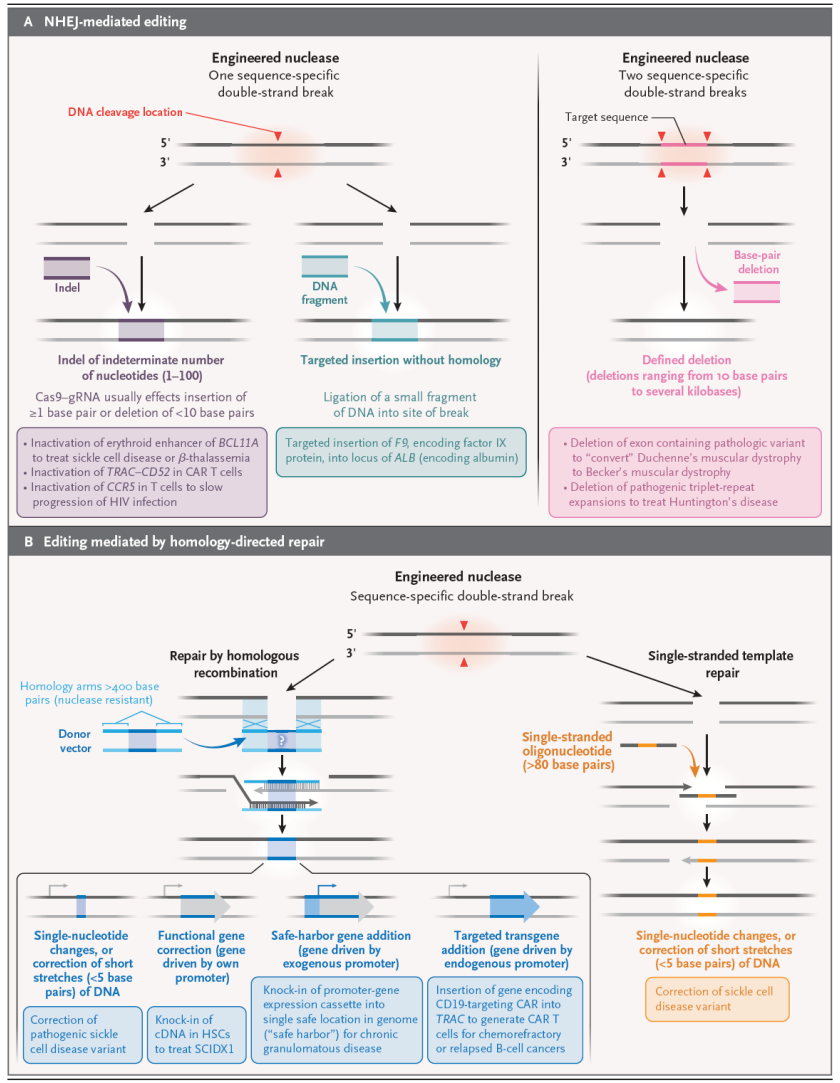
DSB – acutely genotoxic

Dividing human cells experience up to 50 DSBs per cell cycle

Multiple pathways of DSB-R highly conserved across evolution

Human cells use two DSB-R pathways





Schematic courtesy of Dr. Lorraine Symington, Columbia University

Porteus *NEJM* 2019

2012: Jennifer Doudna + Emmanuelle Charpentier
RNA-guided genome editing

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

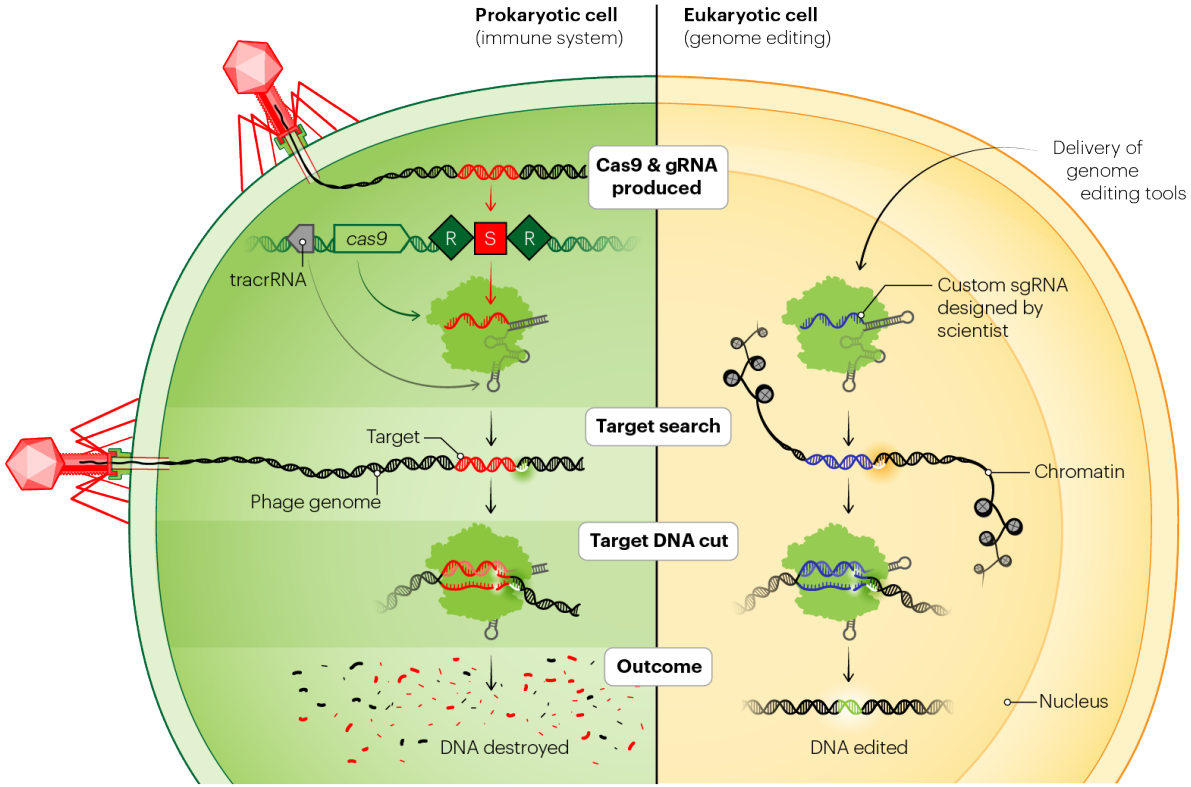
Martin Jinek,[1,2]* Krzysztof Chylinski,[3,4]* Ines Fonfara,[4] Michael Hauer,[2]†
Jennifer A. Doudna,[1,2,5,6]‡ Emmanuelle Charpentier[4]‡

The origin of Cas9 in CRISPR-type bacterial adaptive immune systems and its repurposing for genome editing

Genome editing requires a programmable nuclease: an enzyme that can induce a DSB at the locus of interest.

Bacteria have evolved an adaptive immune system that relies on such a nuclease.

It can be programmed to cut a given locus by “arming” it with an RNA complementary to the DNA of interest.

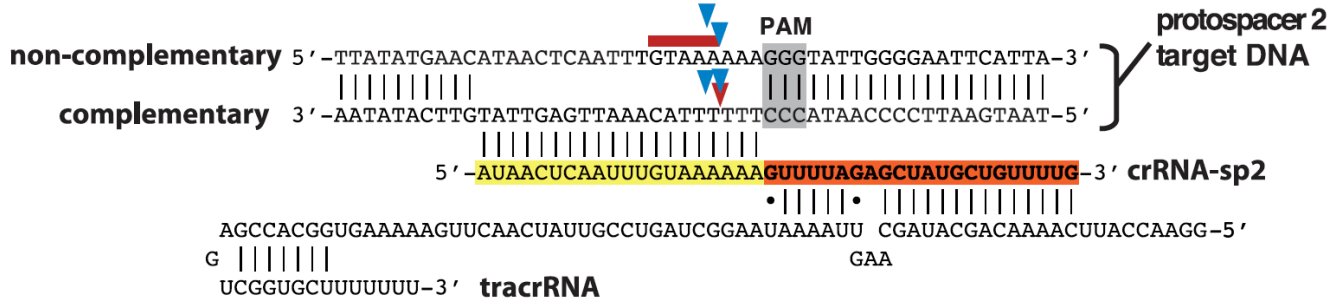


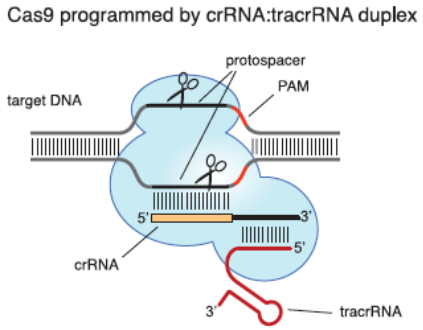
Innovative Genomics Institute | CRISPRpedia

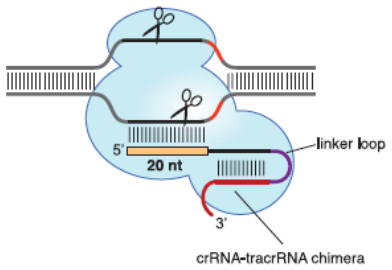
The most impactful experiment in biology in the 21st century

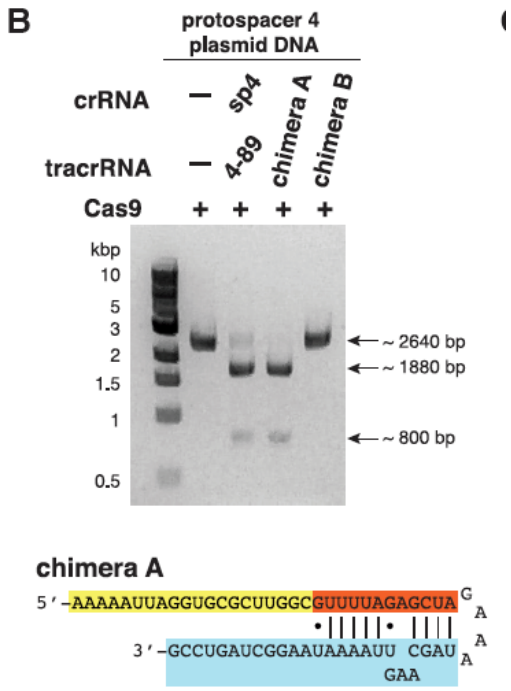
A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

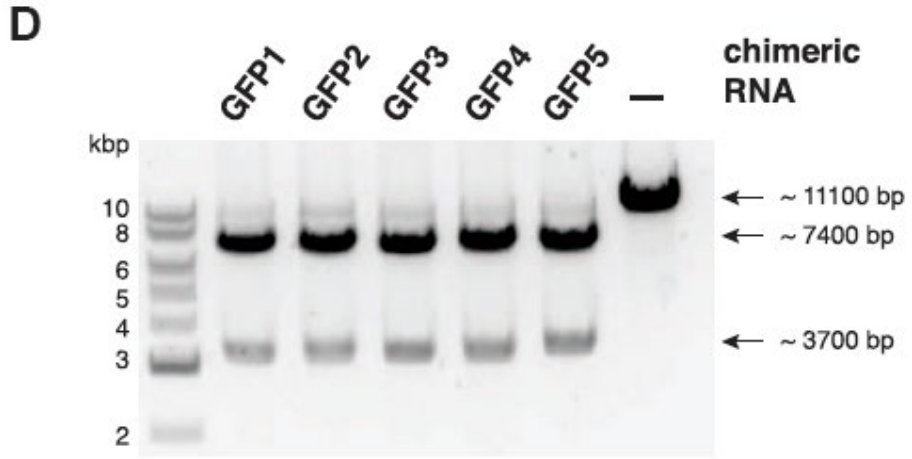
Martin Jinek,[1,2]* Krzysztof Chylinski,[3,4]* Ines Fonfara,[4] Michael Hauer,[2]† Jennifer A. Doudna,[1,2,5,6]‡ Emmanuelle Charpentier[4]‡



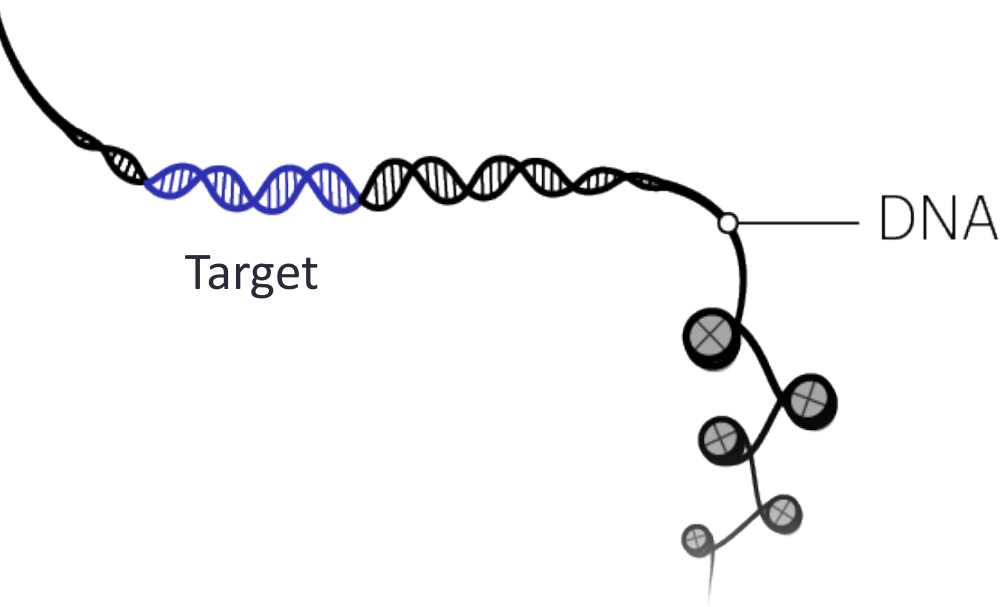




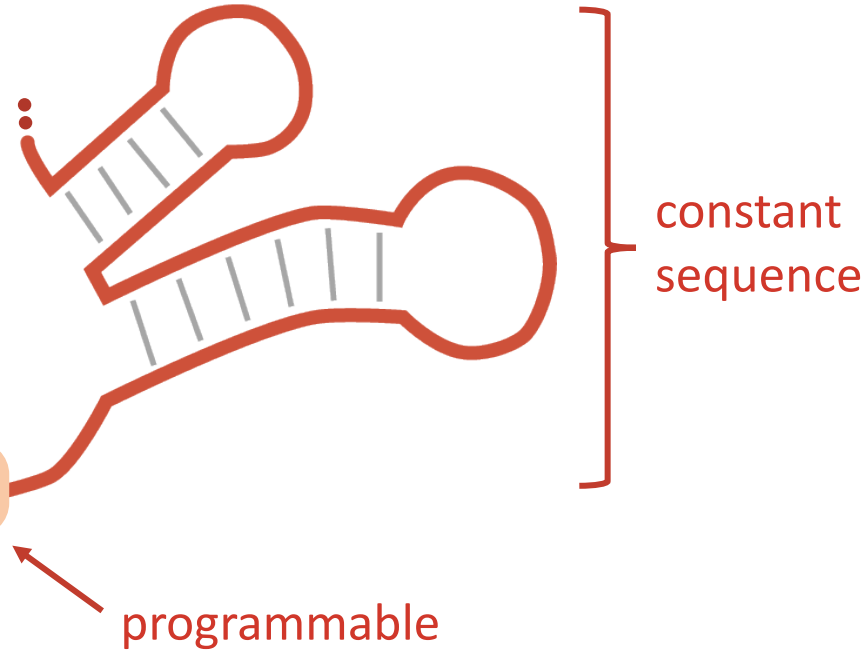




How to program Cas9



How to program Cas9

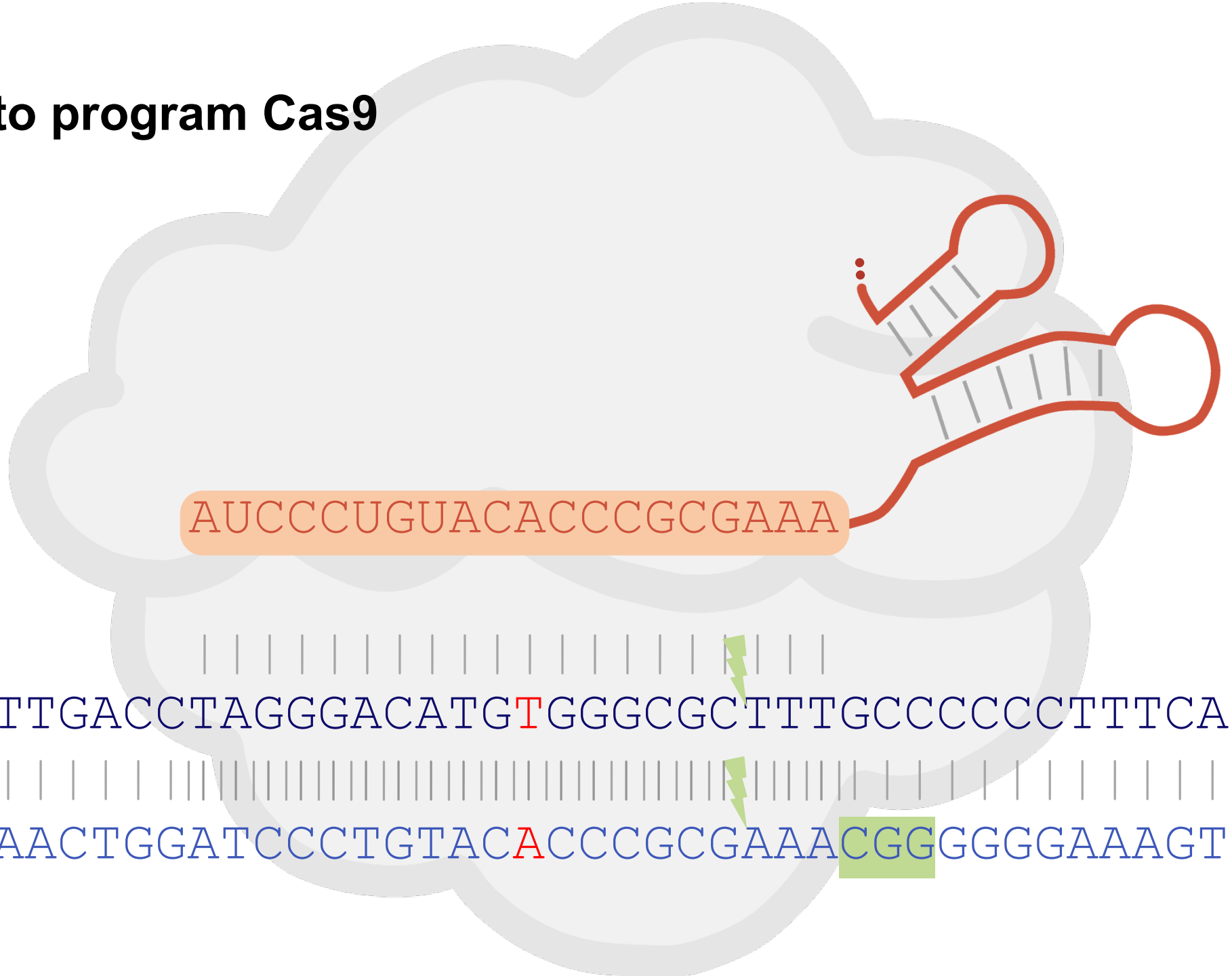


AATAACTATTGACC**TAGGGACATGTGGGCGCTTT**GCCCCCCTTTCAGGTAAACG

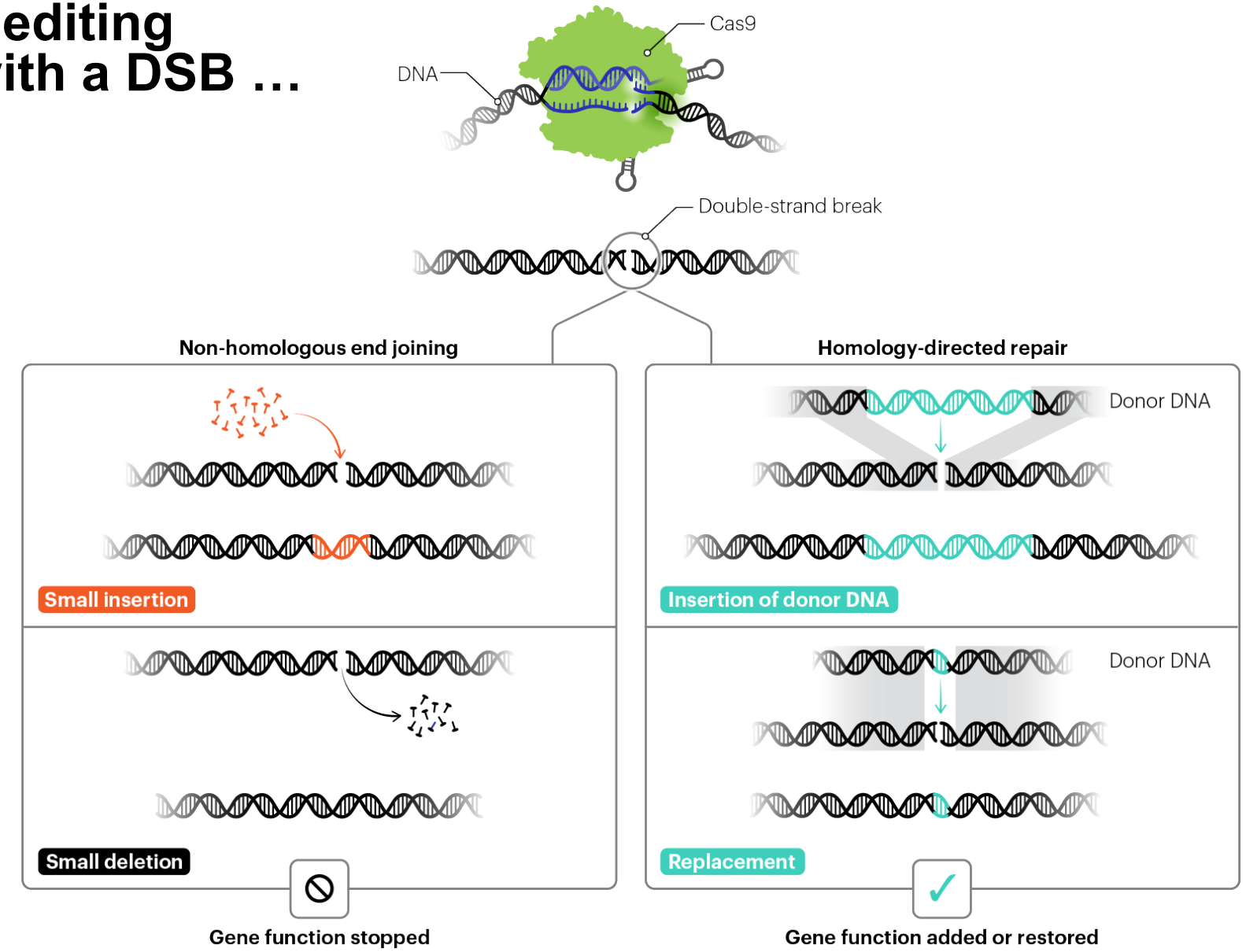
TTATTGATAACTGG**ATCCCTGTACACCCGCGAAA**CGGGGGGAAAGTCCATTTGC

SpyCas9 PAM: 5’ NGG 3’

How to program Cas9



Genome editing begins with a DSB …



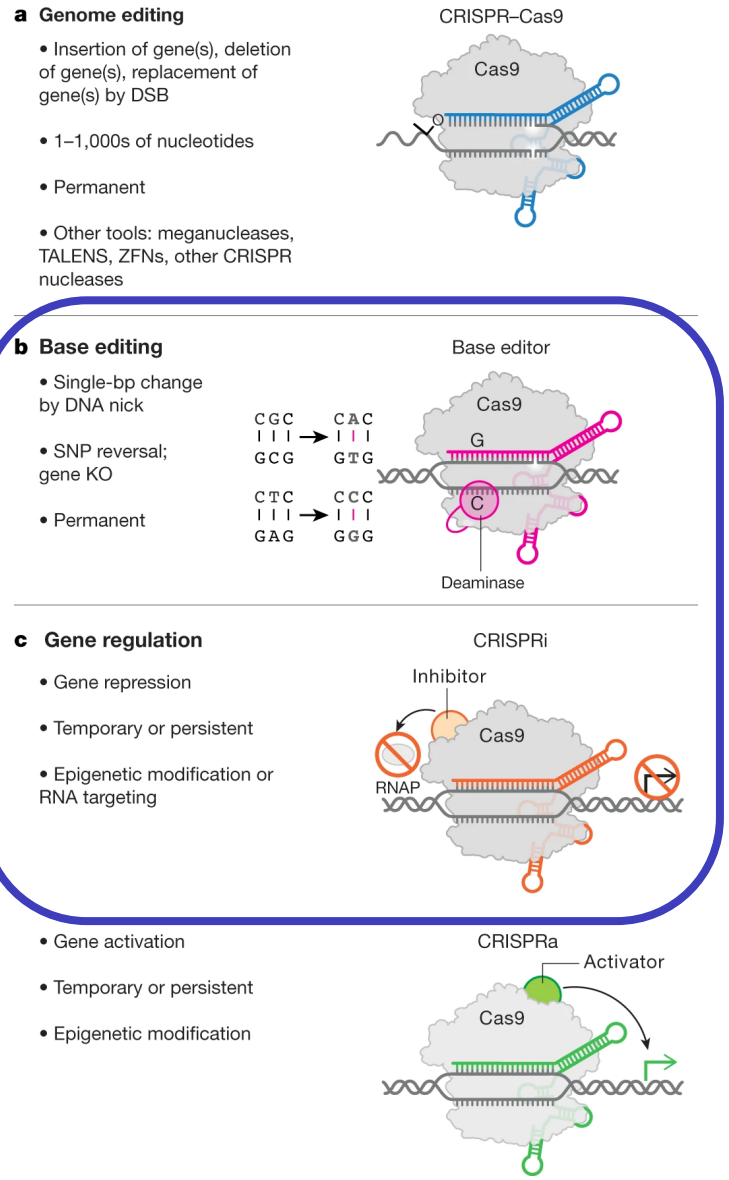
Innovative Genomics Institute | CRISPRpedia

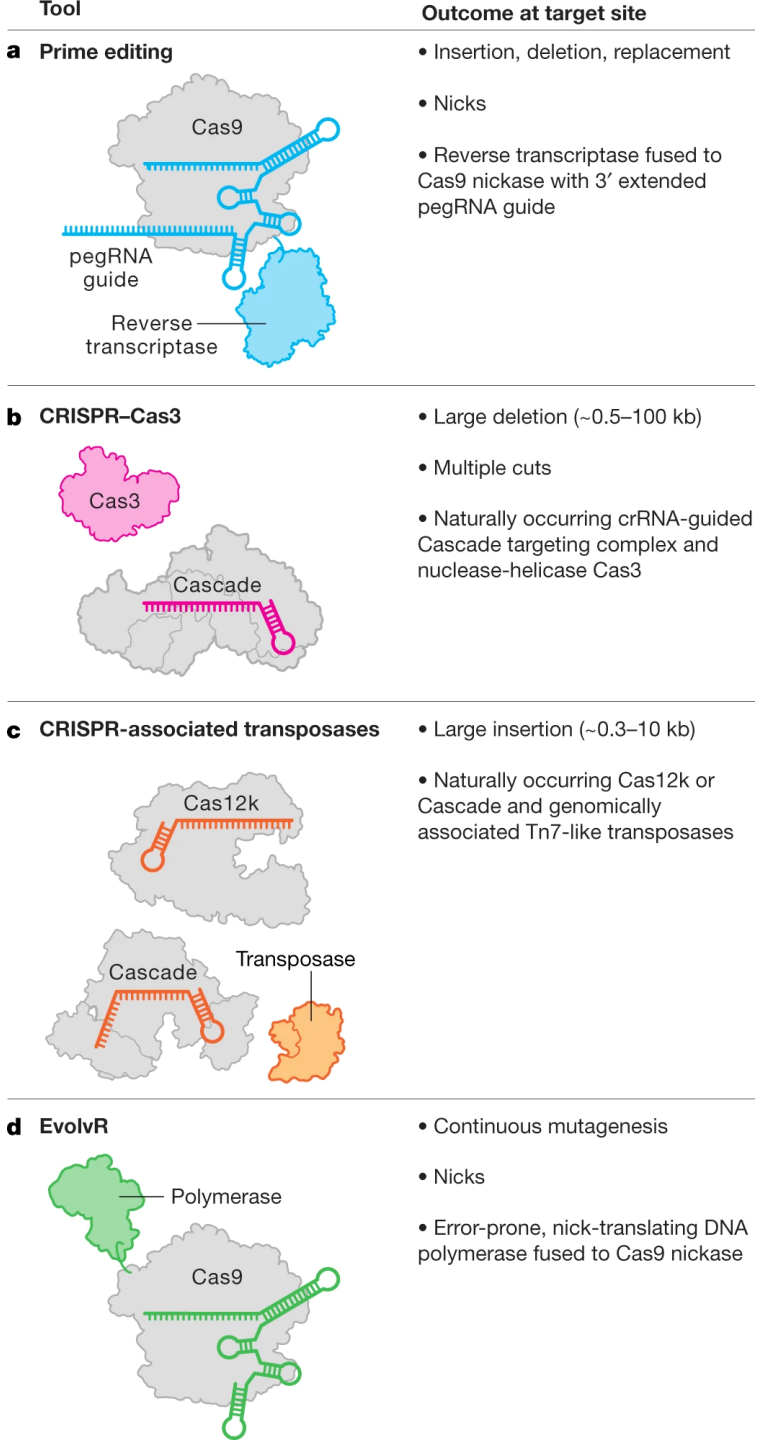
SCD
Amyloidosis
Congenital blindness
HIV
Cancer

SCD
Hemophilia
LSDs

Except when it doesn't

- CAD
- Pain





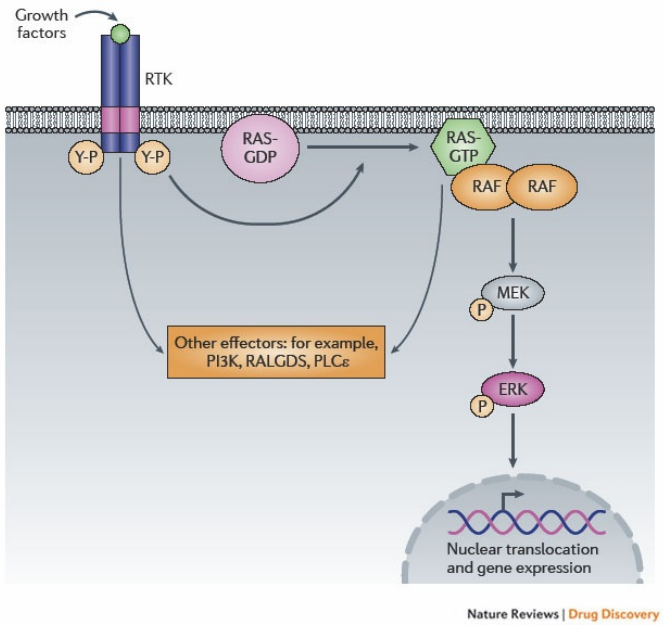
Doudna *Nature* 2019

The Age of CRISPR has redefined the meaning of the term “druggable target.”

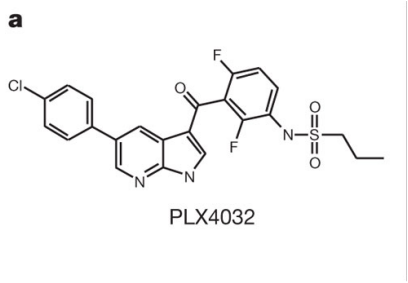
Inhibition of the kinase BRAF prolongs survival in melanoma

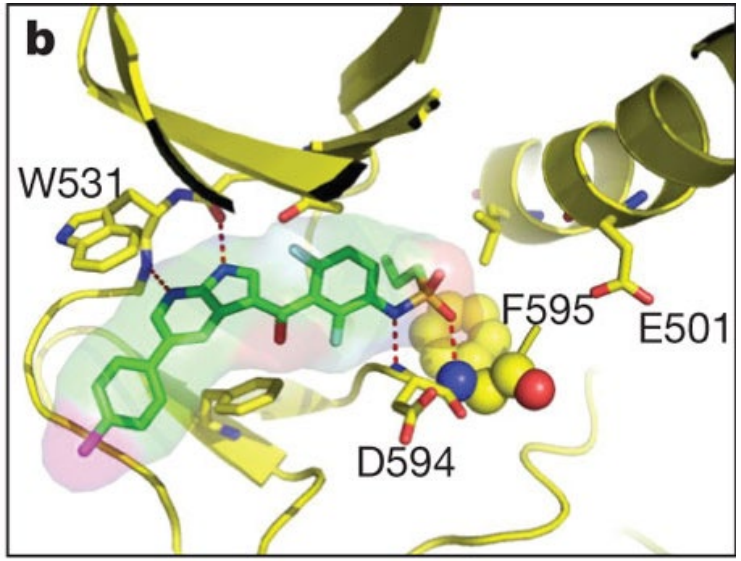
B-RAF V600E

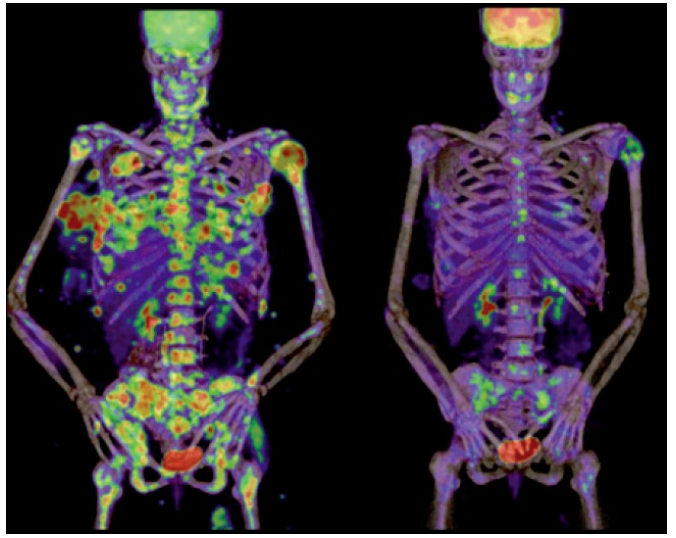
Melanoma driver

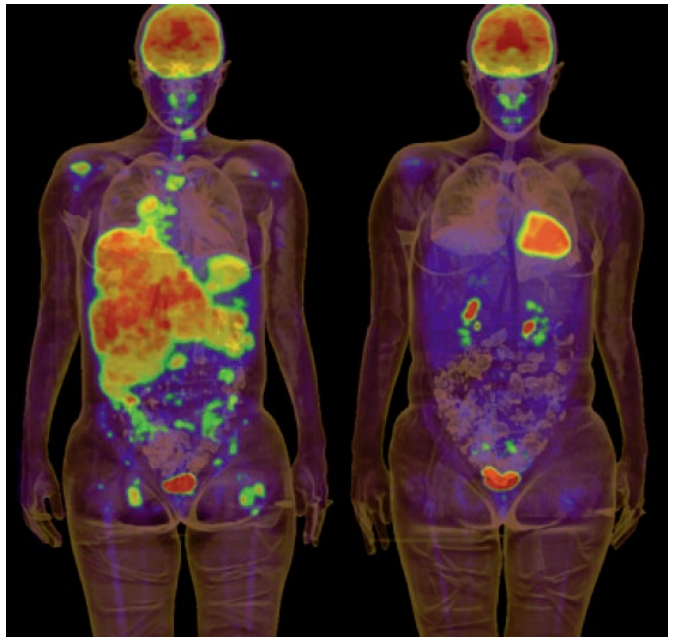


Plexxikon









The Age of CRISPR has redefined the meaning of the term “druggable target.”

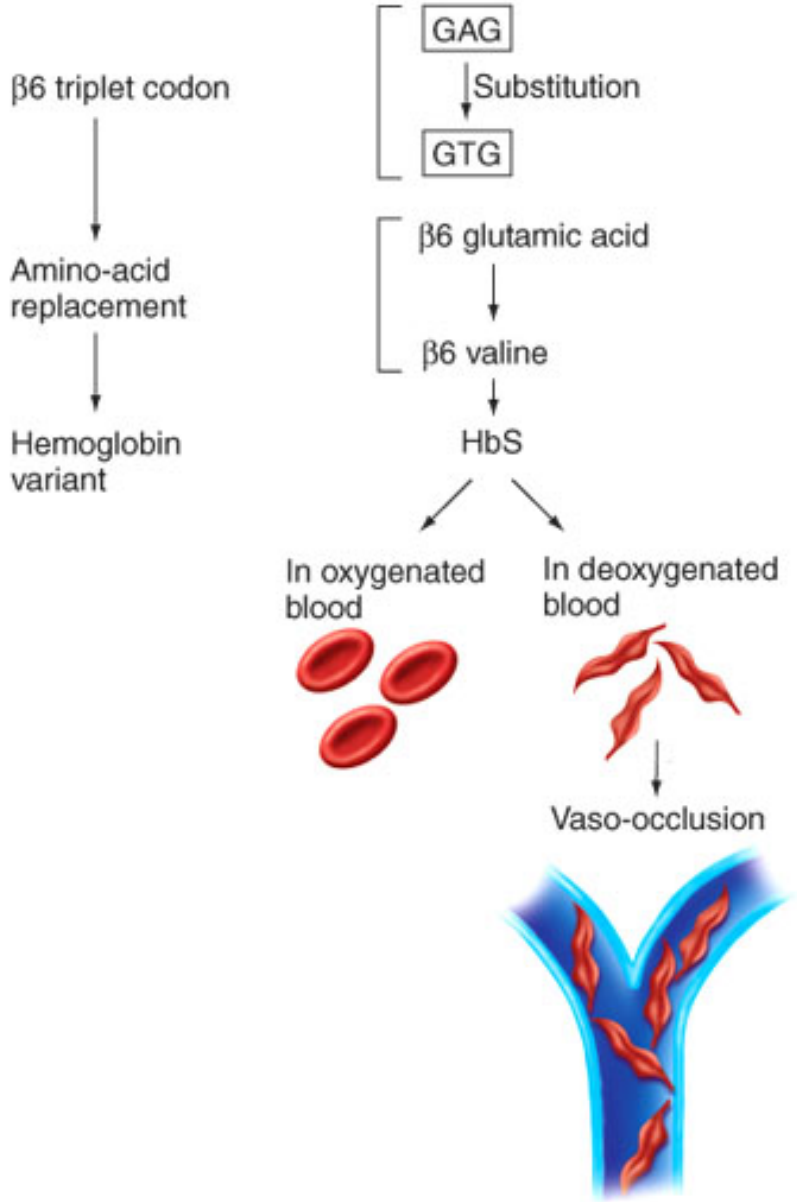
New definition: if it’s in the genome, it’s a druggable target

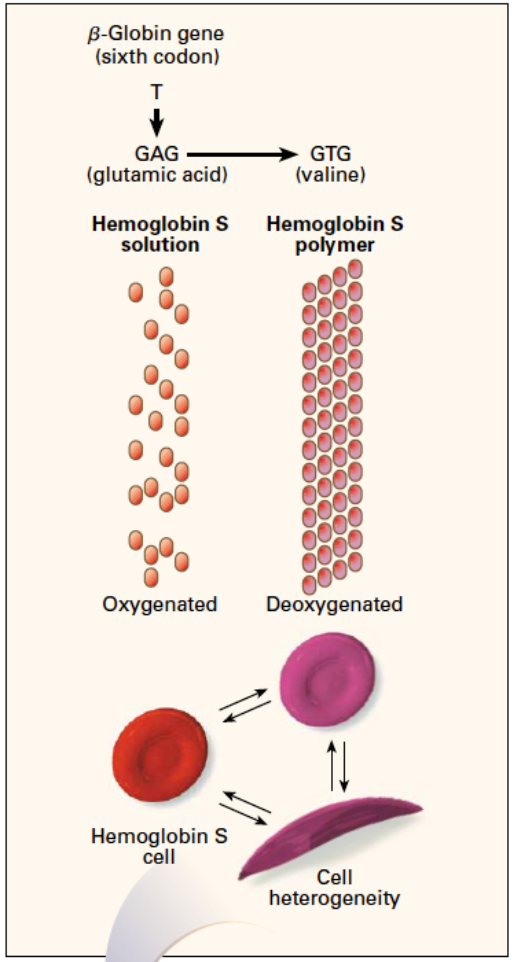
Drugging the undruggable for the hemoglobinopathies

Sickle cell disease

NIH:

“Sickle cell anemia is the most common inherited blood disorder in the United States, affecting about 100,000 Americans or 1 in 500 African Americans. SCA is characterized by episodes of pain, chronic hemolytic anemia and severe infections, usually beginning in early childhood.”





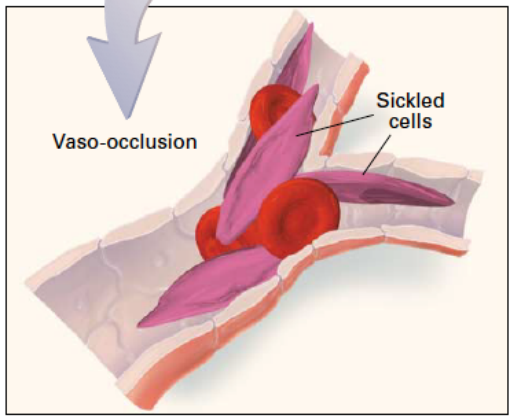


TABLE 1. CLINICAL FEATURES OF SICKLE CELL DISEASE.

TYPE OF COMPLICATION	FEATURES
Vaso-occlusive complications	
Painful episodes	In more than 70 percent of patients; very frequent in some, rare in others
Stroke	In about 10 percent of patients in childhood; "silent" central nervous system damage with cognitive impairment in 5 to 9 times as many patients
Acute chest syndrome	In 40 percent of all patients; more common in children; more severe in adults
Priapism	In 10 to 40 percent of men; severe cases cause erectile dysfunction
Liver disease	In <2 percent of patients; many causes (e.g., iron overload, hepatitis B or C)
Splenic sequestration	In children <6 yr old; often preceded by infection
Spontaneous abortion	In about 6 percent of pregnant women with sickle cell anemia; much less frequent in sickle cell–hemoglobin C disease
Leg ulcers	In about 20 percent of adults with sickle cell anemia; rare in sickle cell–hemoglobin C disease
Osteonecrosis	In 10 to 50 percent of adults with sickle cell anemia and sickle cell–hemoglobin C disease
Proliferative retinopathy	Rare in sickle cell anemia; in 50 percent of adults with sickle cell–hemoglobin C disease
Renal insufficiency	In 5 to 20 percent of adults; severe anemia often present
Complications of hemolysis	
Anemia	Hematocrit values of 15 to 30 percent in sickle cell anemia; higher values in sickle cell–hemoglobin C disease
Cholelithiasis	Present in most adults; often asymptomatic
Acute aplastic episodes	Due to parvovirus B19 infection; appears with rapidly occurring, severe anemia
Infectious complications	
Streptococcus pneumoniae sepsis	In 10 percent of children <5 yr old with sickle cell anemia
Osteomyelitis	Due to salmonella and *Staphylococcus aureus*
Escherichia coli sepsis	In adults, initiated by urinary tract infection

Pleiotropy

Steinberg M. N Engl J Med 1999;340:1021-1030

Clinical variability of SCD

"In a given year, about 60 percent of patients with sickle cell anemia will have an episode of severe pain. A small minority of patients have severe pain almost constantly. These differences are one manifestation of the heterogeneity of this disease, which complicates the choice of treatment. Episodes of pain are sometimes triggered by infection, extreme temperatures, or physical or emotional stress, but more often they are unprovoked and begin with little warning."

VARIABLE EXPRESSIVITY

Steinberg M. N Engl J Med 1999;340:1021-1030

Mutually reinforcing progress

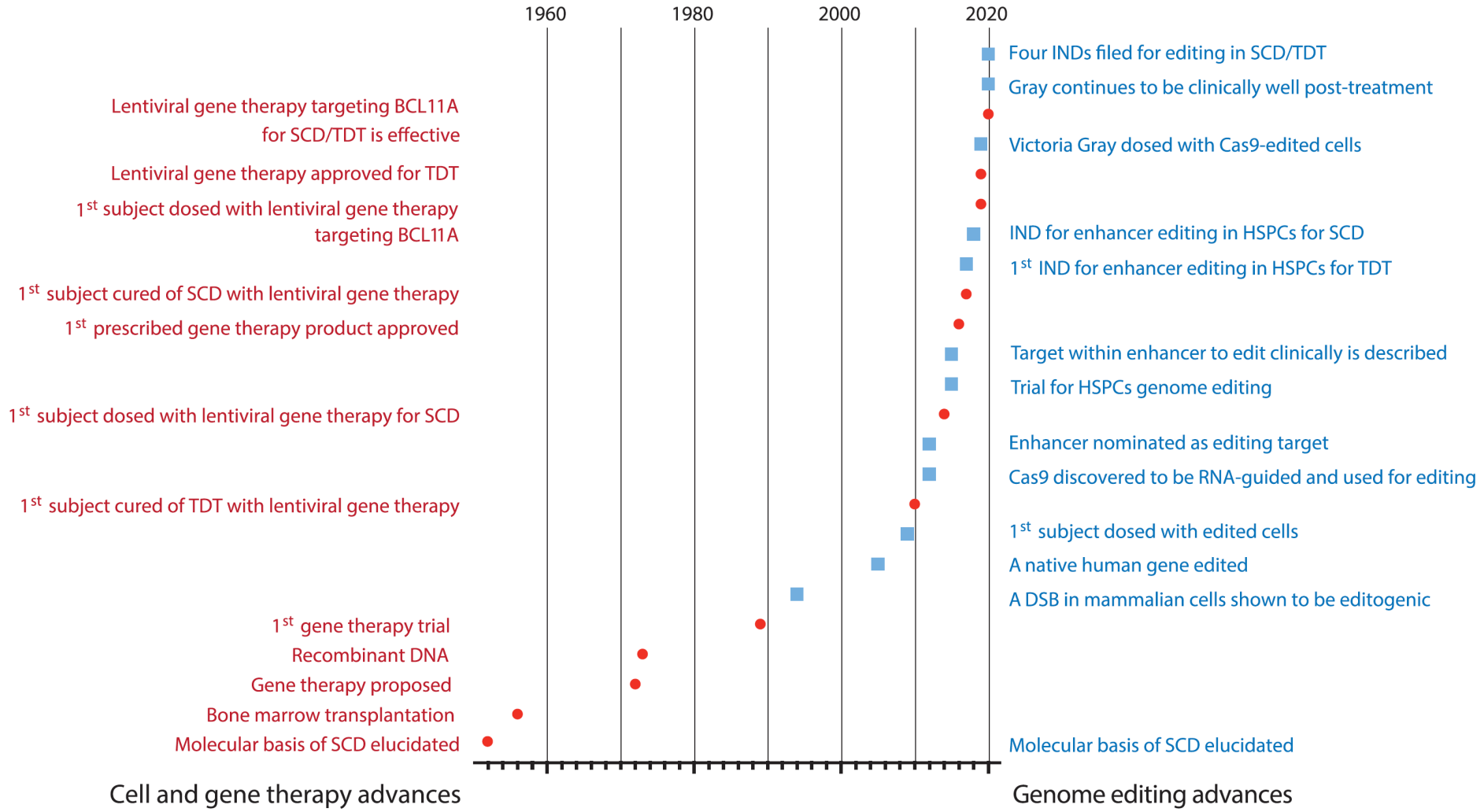
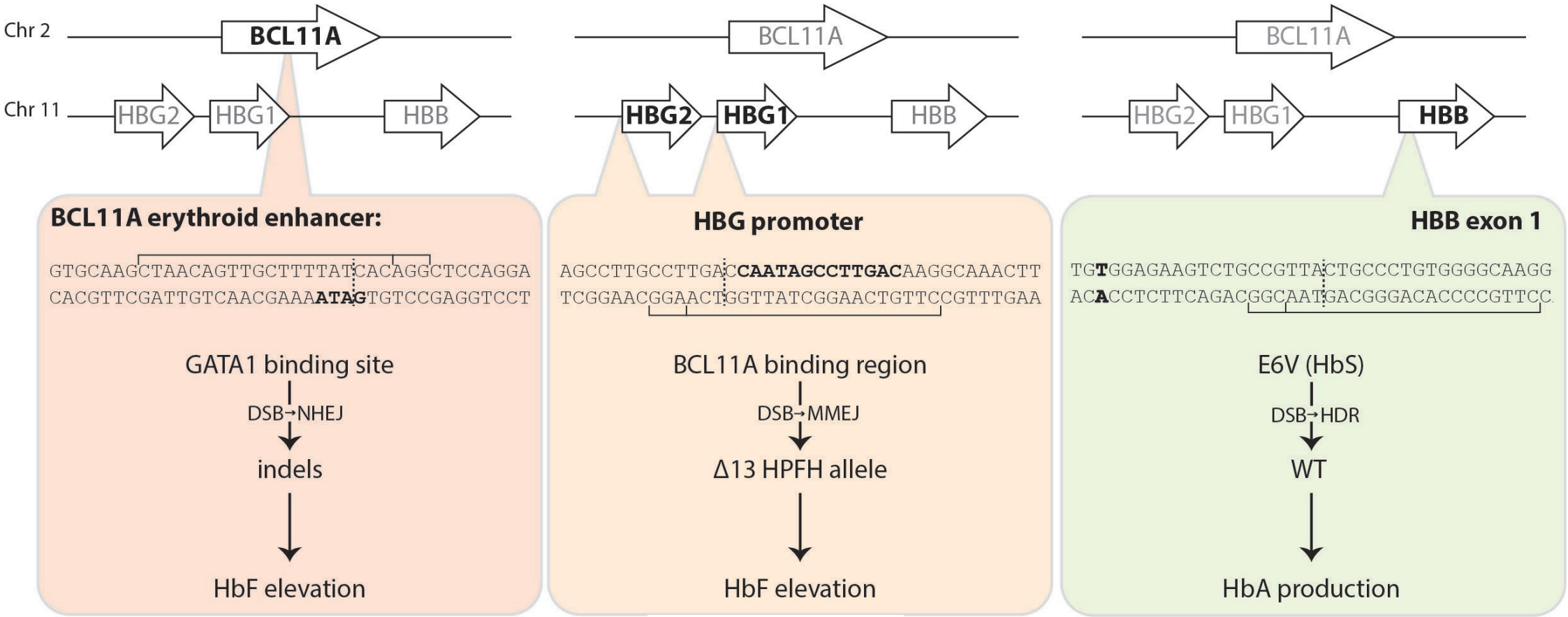


FIG. 2. A timeline of technology developments in cell and gene therapy (left), and in clinic-directed genome editing both broadly and for SCD/TDT specifically (right), that enabled the clinical trial data reported by Frangoul *et al.*

Genome editing for SCD/TDT in the clinic and on approach



Urnov *CRISPR Journal* 2021

LentiGlobin for SCD gene therapy overview

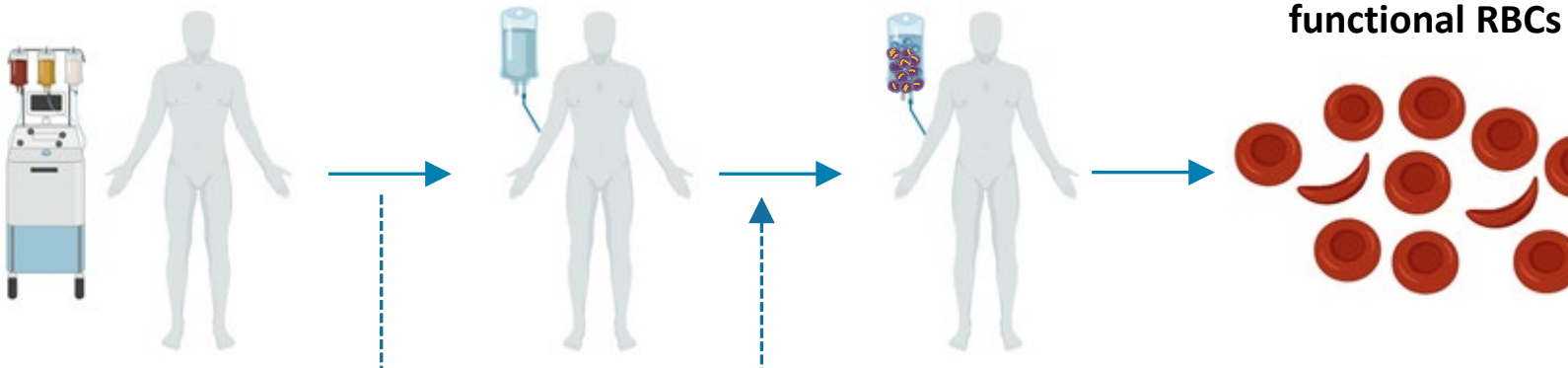
HSC collection
Mobilization with plerixafor & apheresis

Busulfan myeloablative conditioning

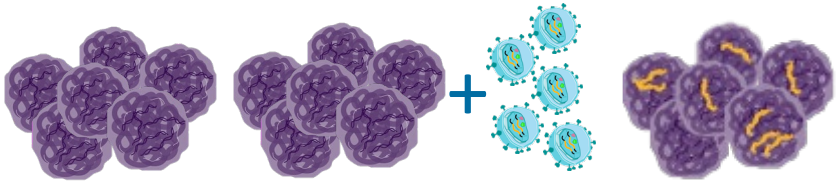
DP infusion

Transduced HSCs engraft and contribute to reconstitution of functional RBCs

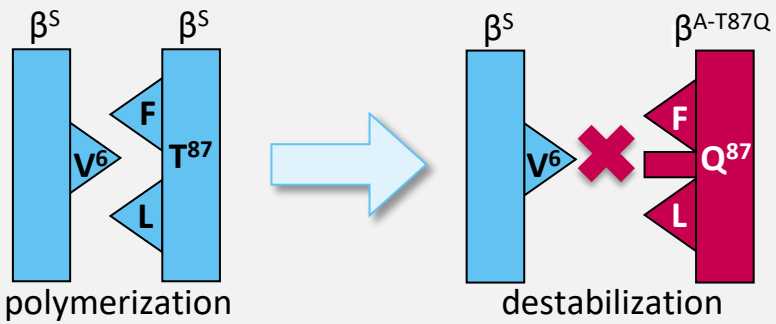
2-year follow-up → **Long-term follow-up study (NCT02633943)**



LentiGlobin DP centralized manufacturing



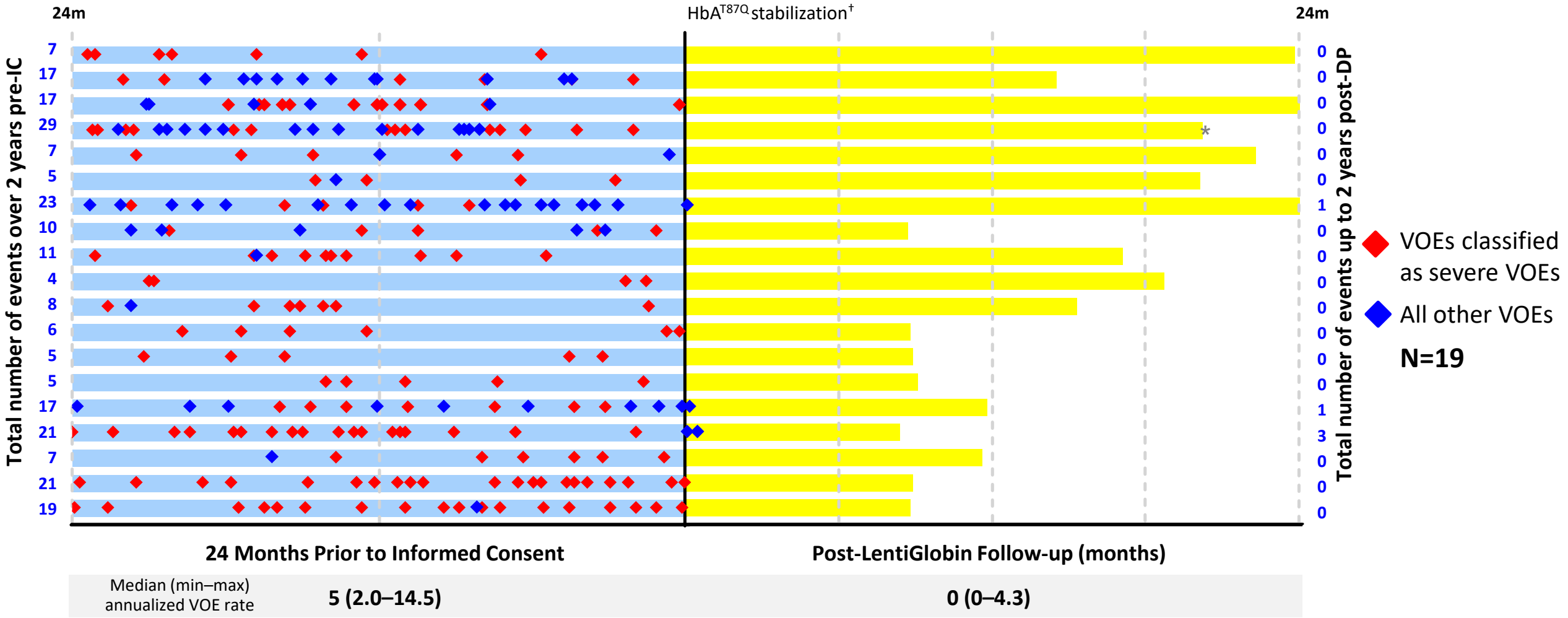
Select CD34+ cells — *Transduce with BB305 lentiviral vector* — *Cryopreserve, test, release DP*



Modified RBCs express gene therapy-derived HbA^{T87Q}

DP, drug product; Hb, hemoglobin; HSCs, hematopoietic stem cells; RBCs, red blood cells SCD, sickle cell disease.

HGB-206 Group C: Complete resolution of VOEs ≥6 months post-LentiGlobin treatment



Protocol VOE are shown; Patients with ≥ 4 sVOE at baseline before IC and with ≥ 6 months of follow-up post-DP infusion are included. A VOE includes episodes of acute pain with no medically determined cause other than a vaso-occlusion, lasting more than 2 hours and severe enough to require care at a medical facility, a VOE includes acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration; †HbA^{T87Q} expression stabilizes within 6 months; *One death, unlikely related to LentiGlobin, > 18 months post treatment in a patient with significant baseline SCD-related cardiopulmonary disease.
Note: In the last datacut, one patient had a non-serious VOC at Day 107. The event is recorded as an investigator reported VOE but does not meet the definition of a protocol VOE

Thompson, et al. ASH 2020

DP, drug product; IC, informed consent; max, maximum; min, minimum; sVOEs, severe VOEs; VOE, vaso-occlusive event; VOC, vaso-occlusive crisis.

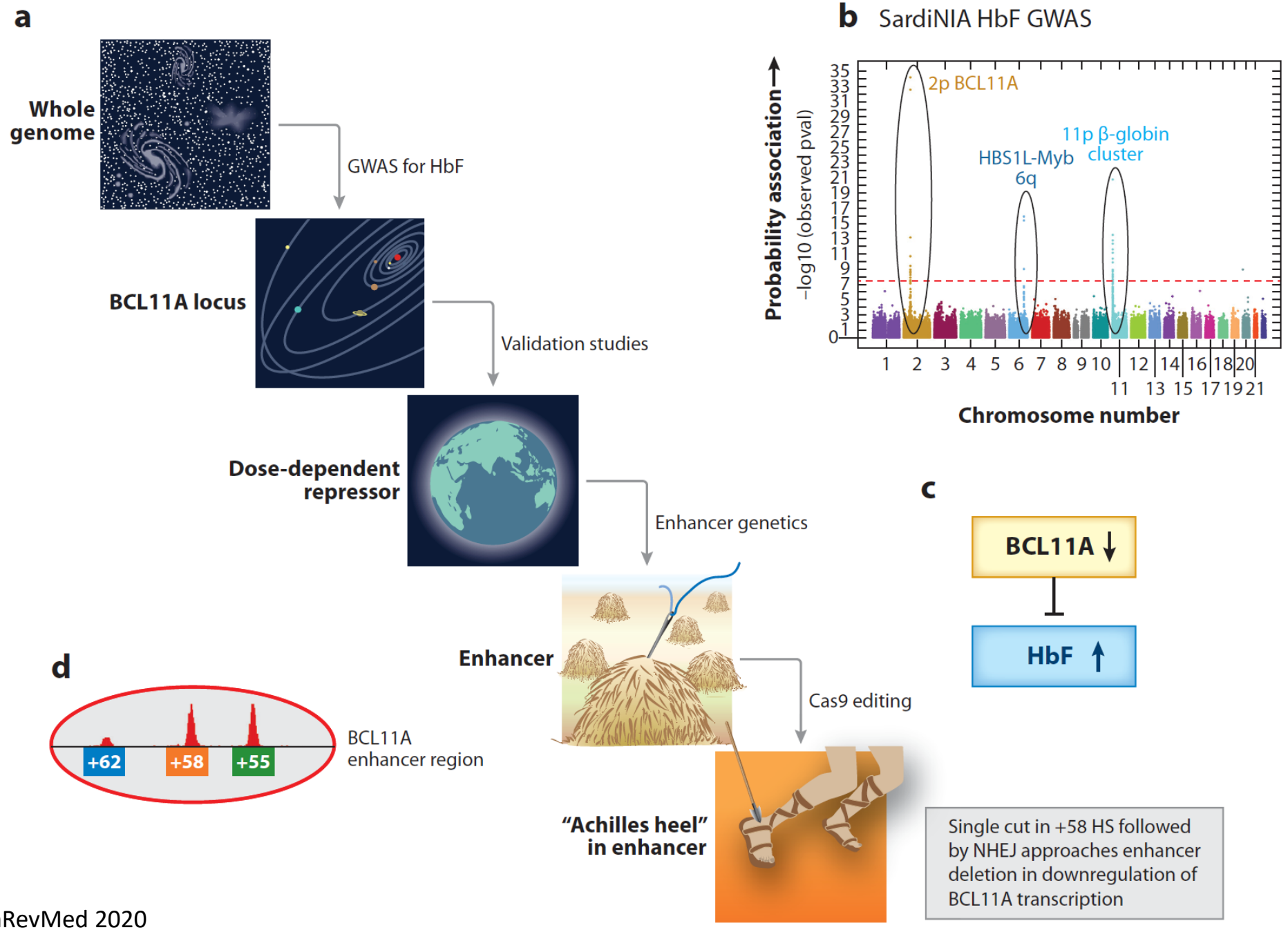
A teachable moment

1st Patients To Get CRISPR Gene-Editing Treatment Continue To Thrive

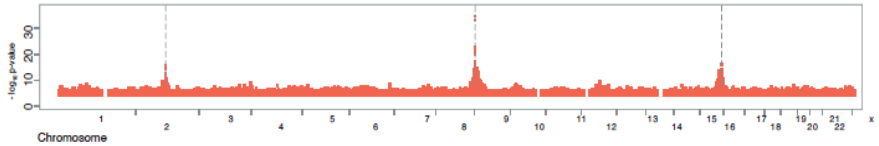
December 15, 2020 · 5:02 AM ET
Heard on Morning Edition

ROB STEIN

4-Minute Listen + PLAYLIST



Bauer and Orkin AnnRevMed 2020

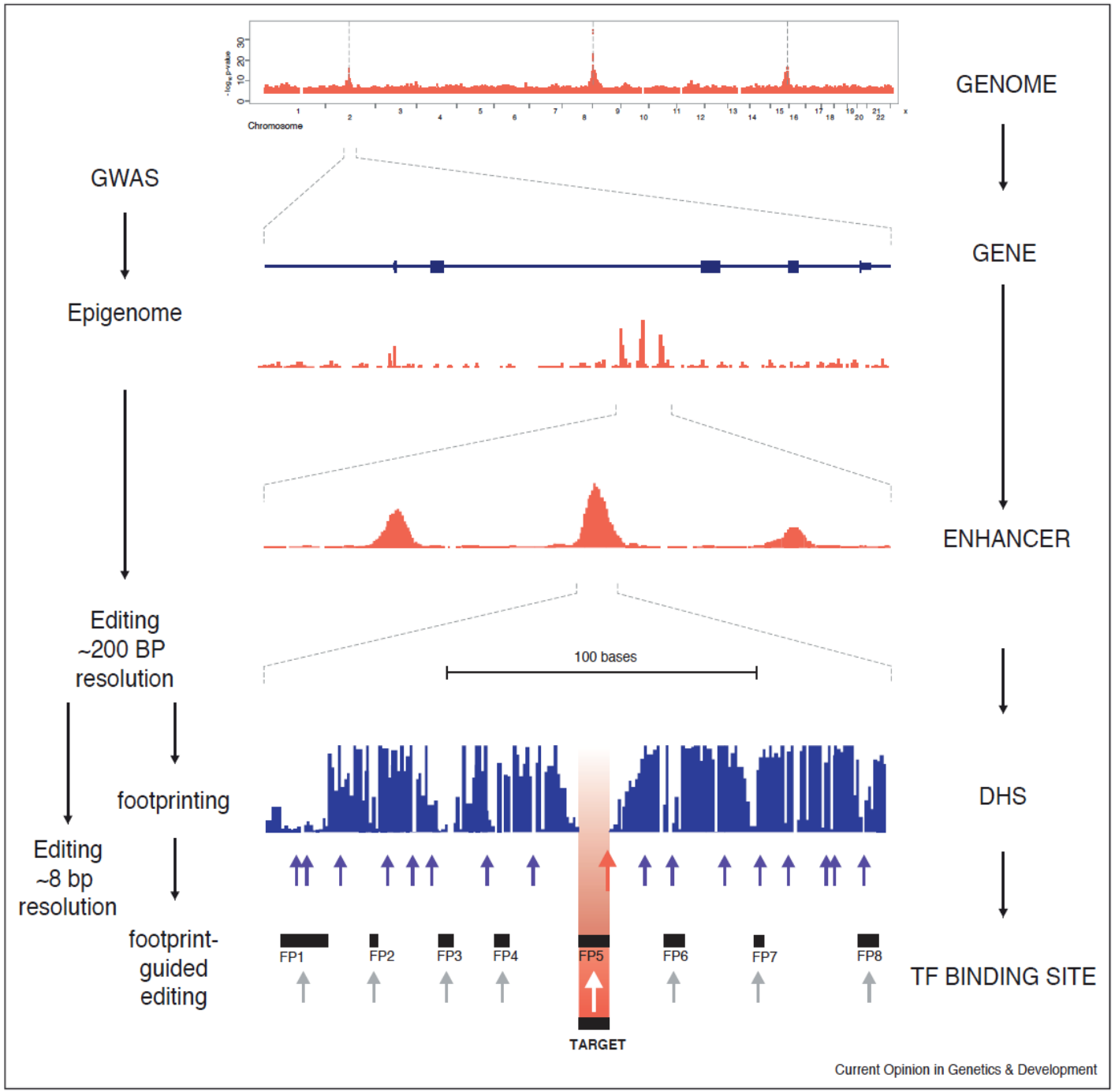


re

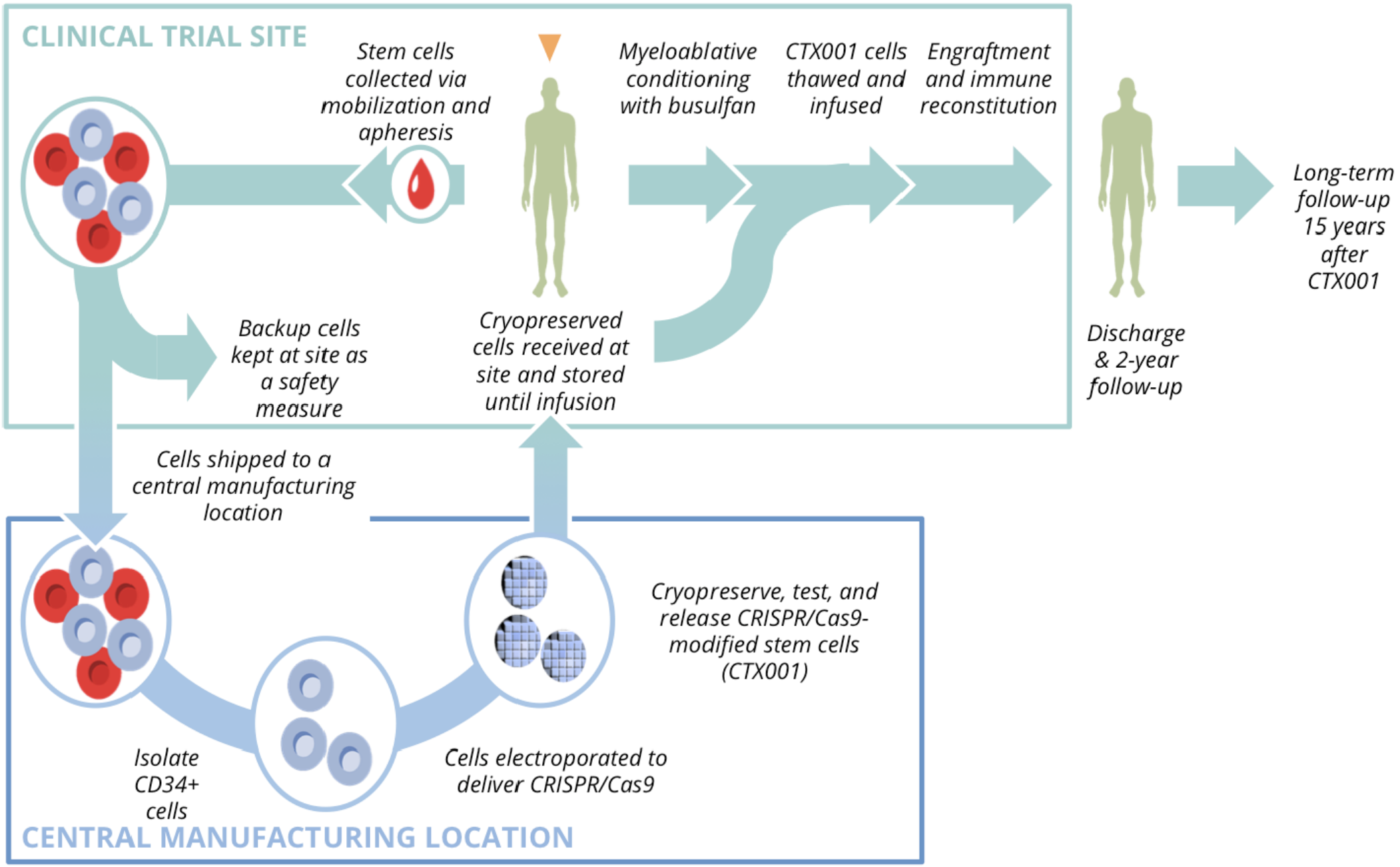
TARGET

Current Opinion in Genetics & Development

Urnov *COGD* 2018



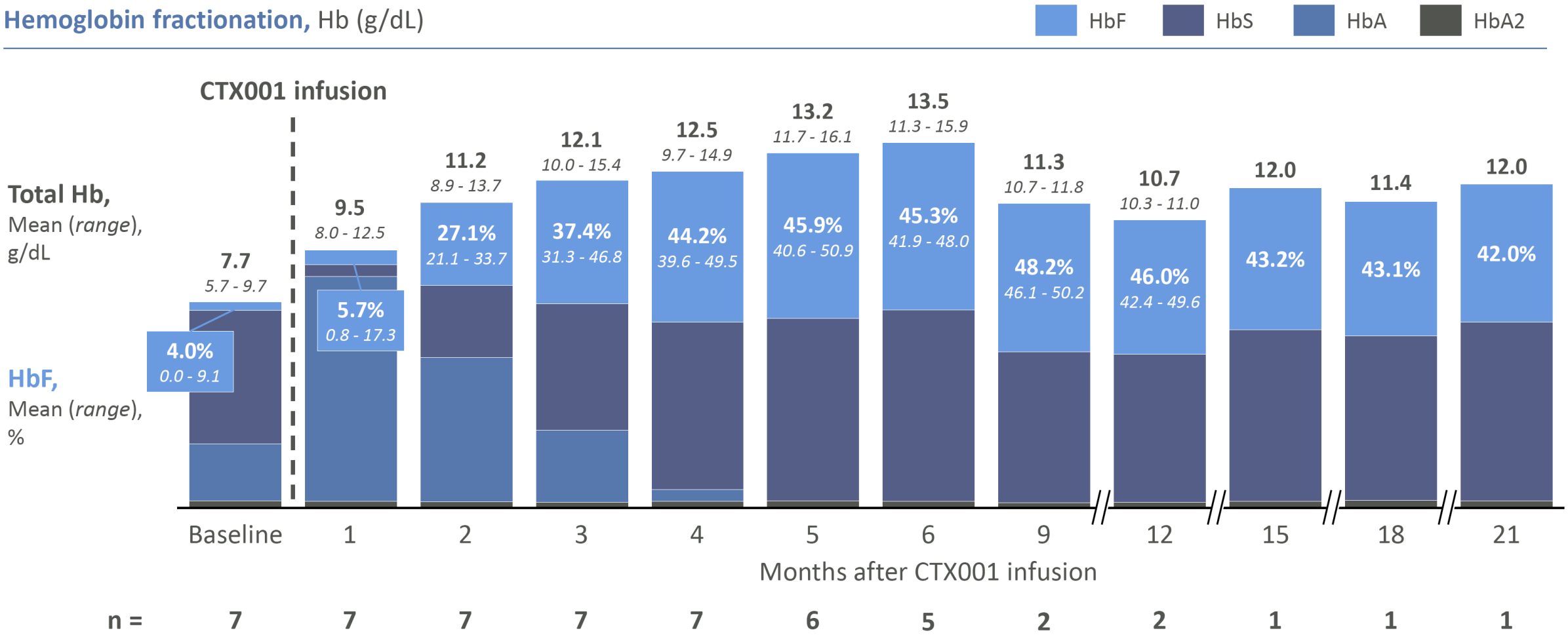
Urnov *COGD* 2018



Frangoul *NEJM* 2021

SCD: Clinically Meaningful HbF and Total Hb Are Achieved Early and Maintained

Hemoglobin fractionation, Hb (g/dL)



Data as of March 15, 2021

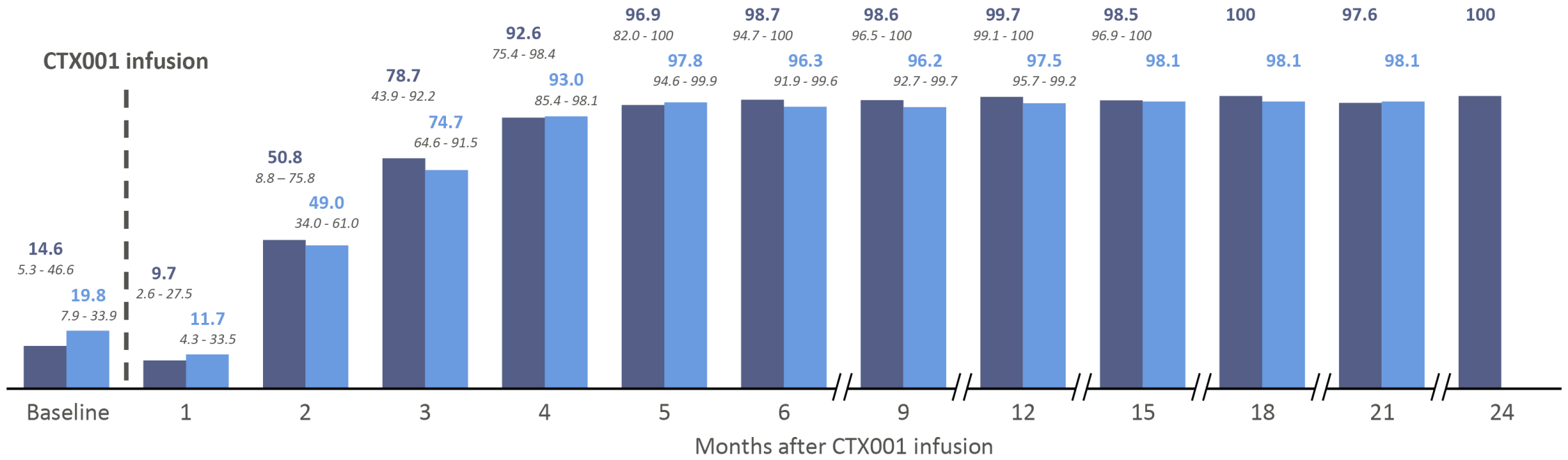
Pancellular HbF Expression and Durable Editing

TDT
SCD

CRISPR THERAPEUTICS

Pancellular expression of HbF maintained

Mean % peripheral F-cells (*range*), % circulating RBCs expressing HbF



n (TDT):	15	15	15	14	13	11	10	5	5	2	1	1	1
n (SCD):	7	7	7	7	6	4	4	2	2	1	1	1	0

Durable BCL11A editing in the bone marrow[1]

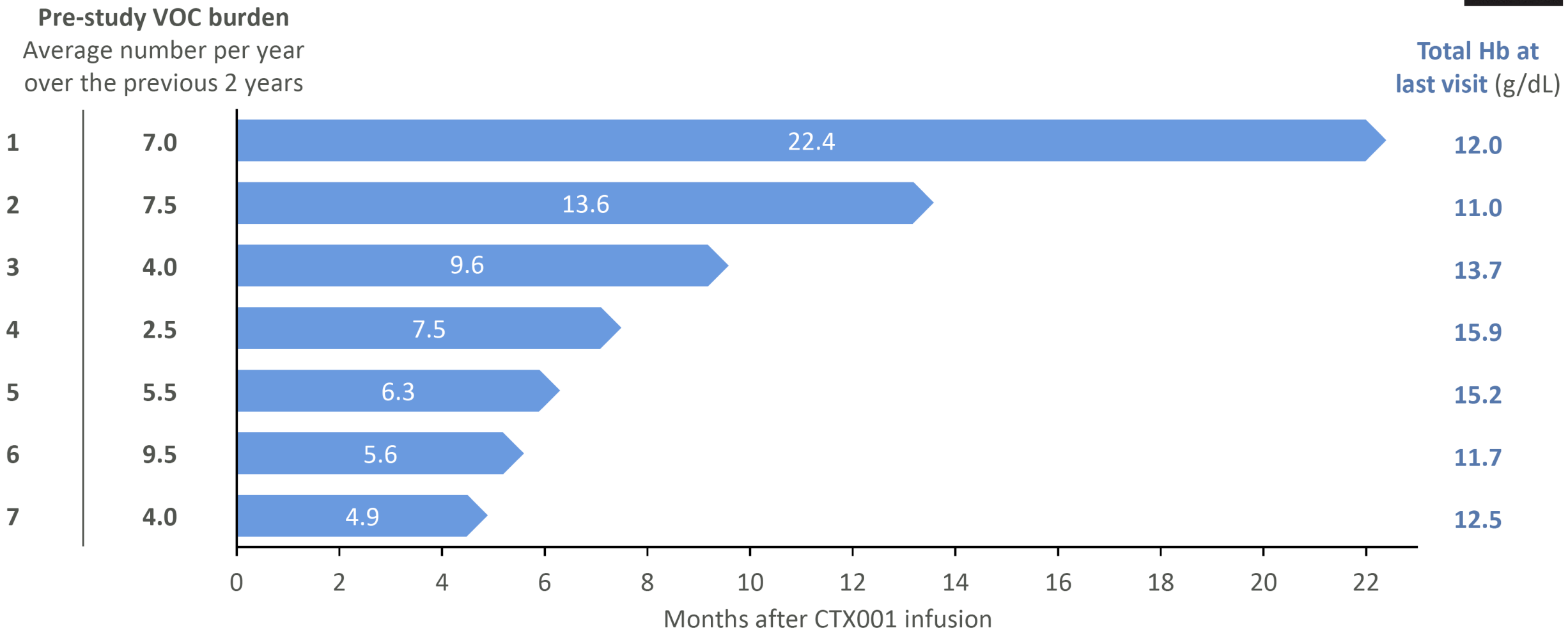
Mean allelic editing in CD34⁺ bone marrow cells (*range*), %

70.5 *41.8 - 91.4*	73.6 *53.3 - 88.2*		80.9
85.5 *80.4 - 93.1*	83.8 *80.4 - 87.1*		

Data as of March 30, 2021 for TDT and March 15, 2021 for SCD

(1) Bone marrow editing assessments performed starting at 6 months, 12 months, and 24 months of follow-up

SCD: Duration VOC-Free After CTX001



Improvements in markers of hemolysis (serum lactate dehydrogenase and haptoglobin) observed; haptoglobin detectable by Month 6 in all 4 patients with Month 6 values

Data as of March 15, 2021

UCSF-UCLA-IGI SCD: technology innovation (2016) to IND (2020)

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

SICKLE CELL DISEASE

Selection-free genome editing of the sickle mutation in human adult hematopoietic stem/progenitor cells

Mark A. DeWitt,[1,2] Wendy Magis,[3] Nicolas L. Bray,[1,2] Tianjiao Wang,[1,2] Jennifer R. Berman,[4] Fabrizia Urbinati,[5] Seok-Jin Heo,[3] Therese Mitros,[2] Denise P. Muñoz,[3] Dario Boffelli,[3] Donald B. Kohn,[5] Mark C. Walters,[3,6] Dana Carroll,[1,7]* David I. K. Martin,[3]* Jacob E. Corn[1,2]*

Genetic diseases of blood cells are prime candidates for treatment through ex vivo gene editing of $CD34^+$ hematopoietic stem/progenitor cells (HSPCs), and a variety of technologies have been proposed to treat these disorders. Sickle cell disease (SCD) is a recessive genetic disorder caused by a single-nucleotide polymorphism in the β-globin gene (*HBB*). Sickle hemoglobin damages erythrocytes, causing vasoocclusion, severe pain, progressive organ damage, and premature death. We optimize design and delivery parameters of a ribonucleoprotein (RNP) complex comprising Cas9 protein and unmodified single guide RNA, together with a single-stranded DNA oligonucleotide donor (ssODN), to enable efficient replacement of the SCD mutation in human HSPCs. Corrected HSPCs from SCD patients produced less sickle hemoglobin RNA and protein and correspondingly increased wild-type hemoglobin when differentiated into erythroblasts. When engrafted into immunocompromised mice, ex vivo treated human HSPCs maintain SCD gene edits throughout 16 weeks at a level likely to have clinical benefit. These results demonstrate that an accessible approach combining Cas9 RNP with an ssODN can mediate efficient HSPC genome editing, enables investigator-led exploration of gene editing reagents in primary hematopoietic stem cells, and suggests a path toward the development of new gene editing treatments for SCD and other hematopoietic diseases.

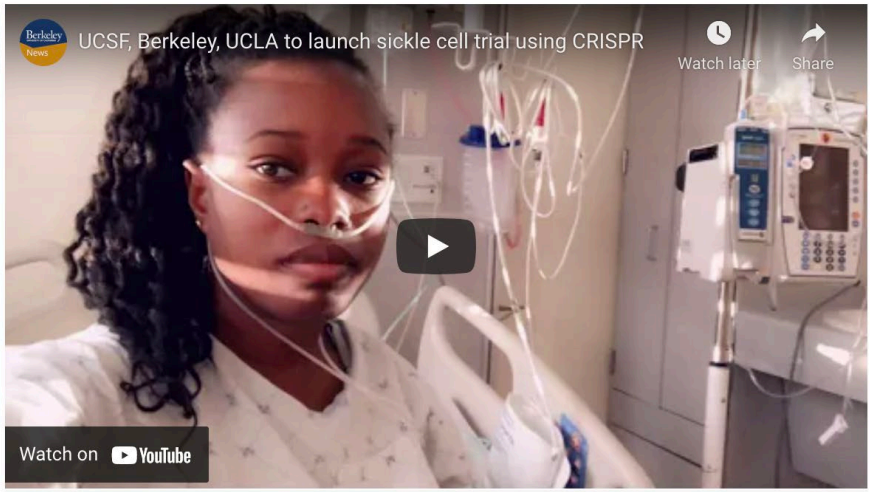
Berkeley News Research People Campus & community

MIND & BODY, RESEARCH

FDA approves first test of CRISPR to correct genetic defect causing sickle cell disease

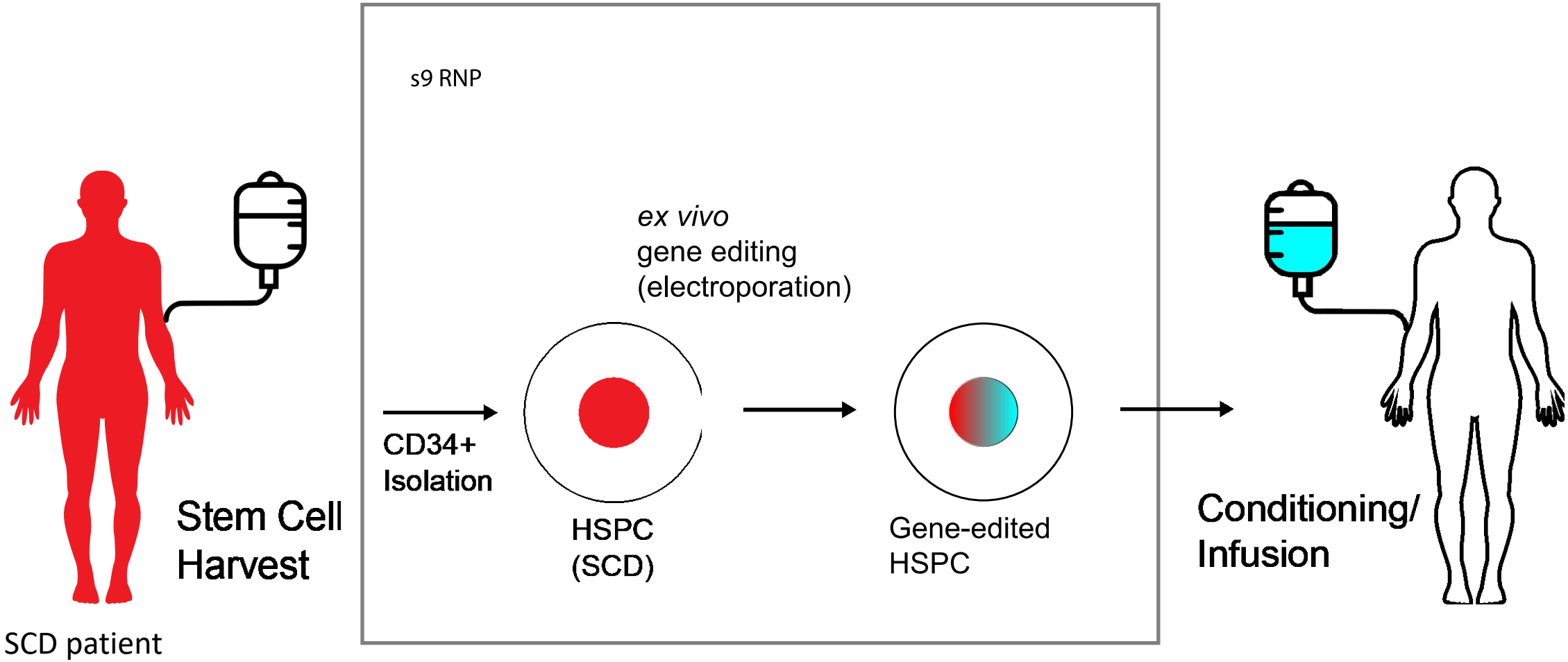
By Robert Sanders, Media relations | MARCH 30, 2021

Tweet Share 1.2K Email Print



Sickle cell patients such as Cassandra Trimnell and Evie James Junior and UCSF physician Mark Walters talk about the severe pain experienced by those with the disease and the potential benefits of a CRISPR cure. (Video by UC Berkeley Public Affairs; video of Evie Junior by Colin Weatherby, courtesy UCLA's Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research)

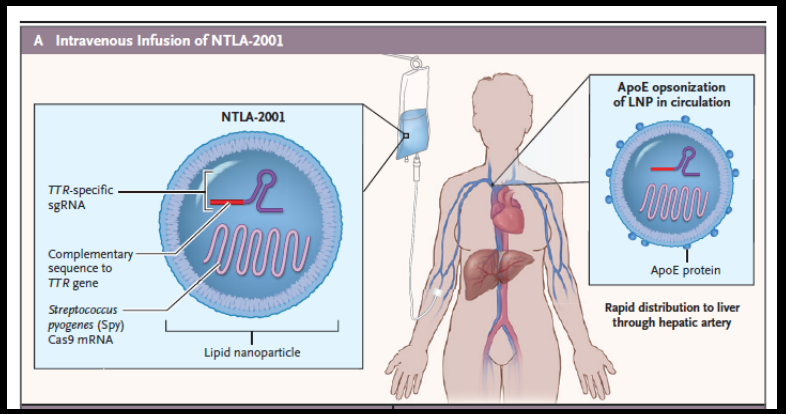
We * have developed a GMP-compliant manufacturing protocol that uses non-viral gene editing to correct the SCD mutation



IGI: Mark DeWitt, Jacob Corn
UCSF: Mark Walters
UCLA: Don Kohn

Autologous Cell Product Manufacturing

CRISPR as in vivo medicine



Intellia Therapeutics – CRISPR KO for amyloidosis

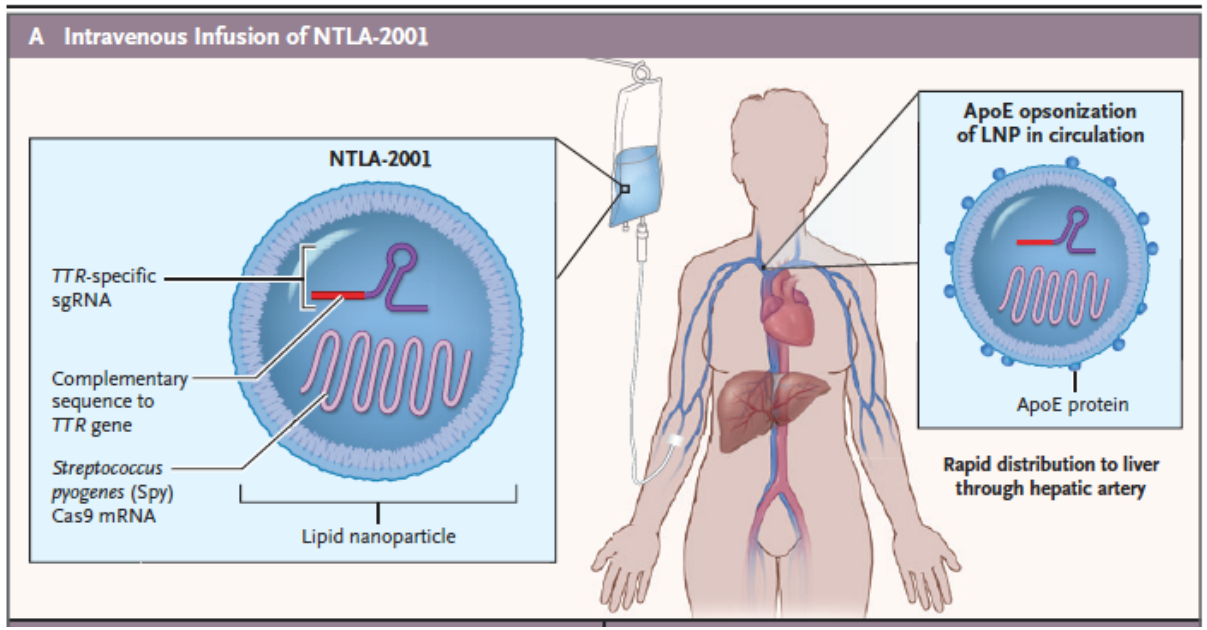
The NEW ENGLAND JOURNAL of MEDICINE

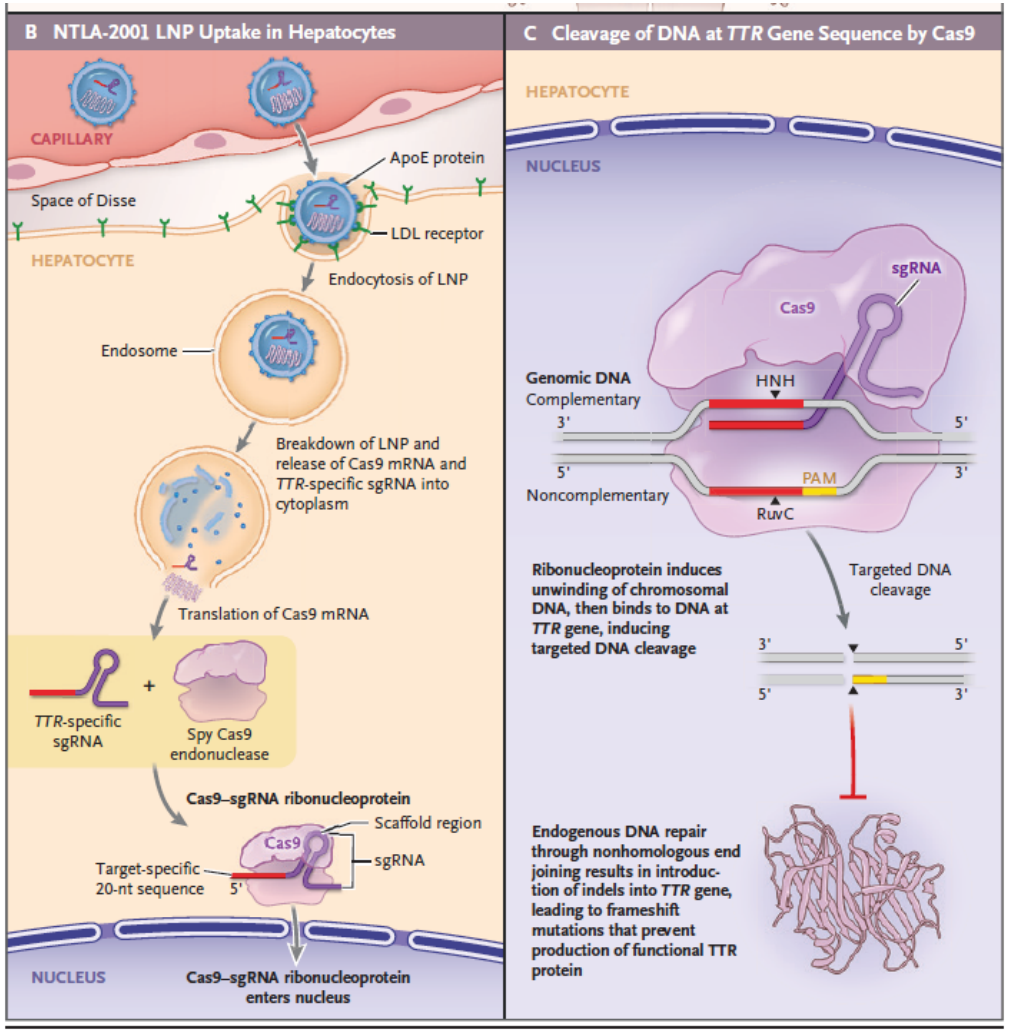
ESTABLISHED IN 1812 AUGUST 5, 2021 VOL. 385 NO. 6

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

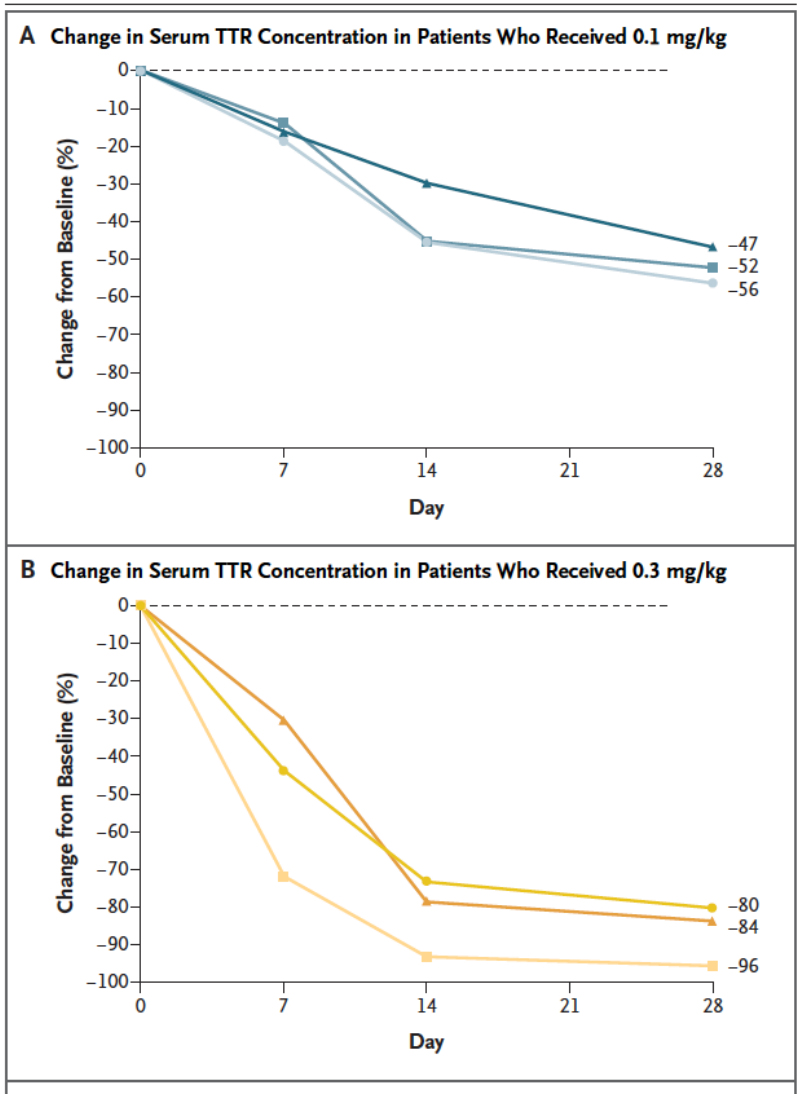
Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., 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.

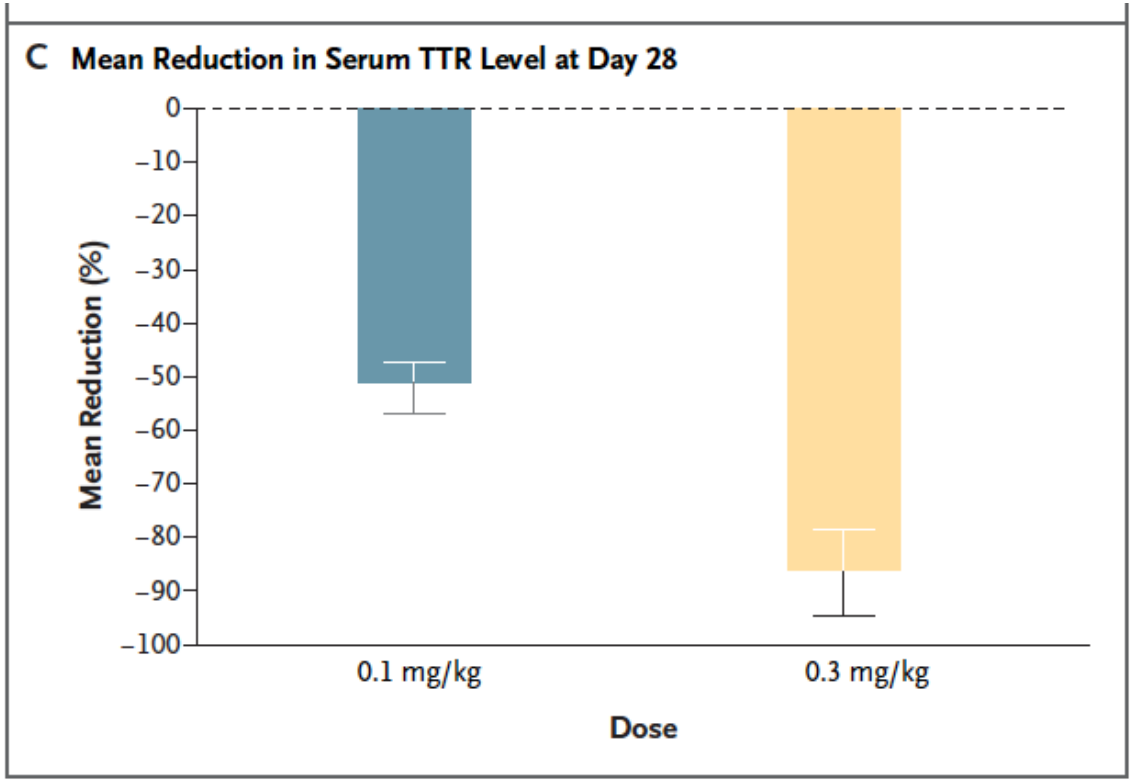
Intellia Therapeutics – CRISPR KO for amyloidosis





Intellia Therapeutics – CRISPR KO for amyloidosis





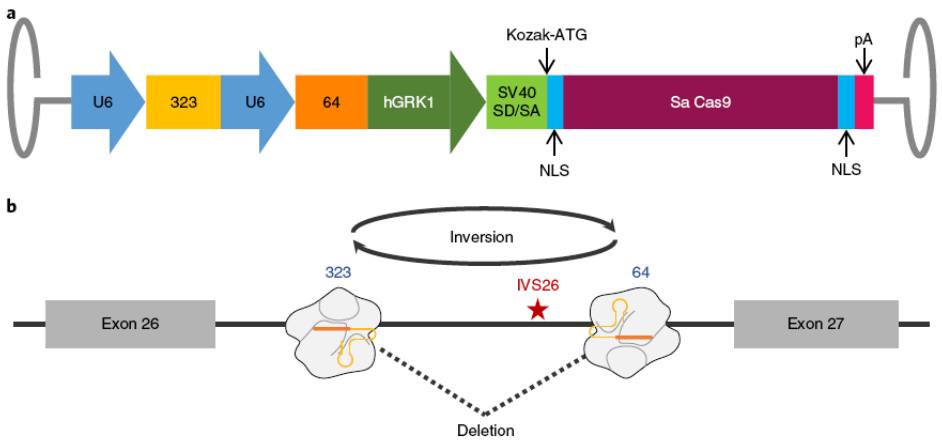
Editas Medicine – CRISPR KO for congenital blindness

Use of adeno-associated virus (AAV) to deliver Cas9 to the eye to restore gene function.

nature medicine
LETTERS
https://doi.org/10.1038/s41591-018-0327-9

Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10

Morgan L. Maeder[1,3]*, Michael Stefanidakis[1,3], Christopher J. Wilson[1], Reshica Baral[1], Luis Alberto Barrera[1], George S. Bounoutas[1], David Bumcrot[1], Hoson Chao[1], Dawn M. Ciulla[1], Jennifer A. DaSilva[1], Abhishek Dass[1], Vidya Dhanapal[1], Tim J. Fennell[2], Ari E. Friedland[1], Georgia Giannoukos[1], Sebastian W. Gloskowski[1], Alexandra Glucksmann[1], Gregory M. Gotta[1], Hariharan Jayaram[1], Scott J. Haskett[1], Bei Hopkins[1], Joy E. Horng[1], Shivangi Joshi[1], Eugenio Marco[1], Rina Mepani[1], Deepak Reyon[1], Terence Ta[1], Diana G. Tabbaa[1], Steven J. Samuelsson[1], Shen Shen[1], Maxwell N. Skor[1], Pam Stetkiewicz[1], Tongyao Wang[1], Clifford Yudkoff[1], Vic E. Myer[1], Charles F. Albright[1] and Haiyan Jiang[1]



Oral Presentation:

Title: BRILLIANCE: A Phase 1/2 Single Ascending Dose Study of EDIT-101, an *in vivo* CRISPR Gene Editing Therapy, in *CEP290*-Related Retinal Degeneration

Session Title: Platform Session V: Clinical Trials

Date and Time: Wednesday, September 29, 2021, 9:05 – 9:35 a.m. CT

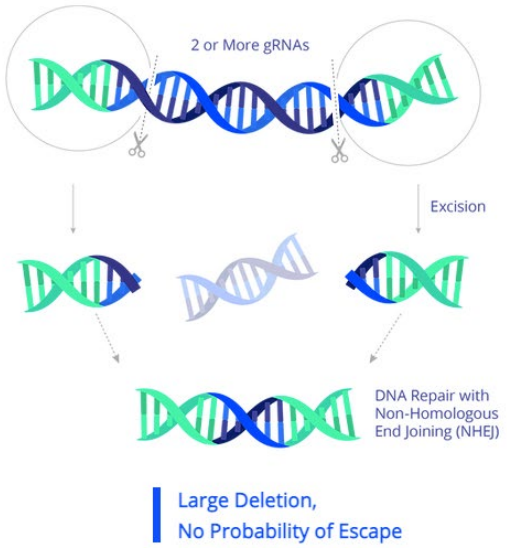
Presenter: Dr. Mark Pennesi, M.D., Ph.D., Professor of Molecular and Medical Genetics, Kenneth C. Swan Endowed Professor of Ophthalmology, Paul H. Casey Ophthalmic Genetics Division Chief, Casey Eye Institute, Oregon Health & Science University.

The FDA's increasing levels of comfort for in vivo editing

EXCISION

Approach

Dual gRNAs excise large sections of viral DNA, eliminating viral escape and reproduction. **The result is curative.**



EXCISION

Excision Receives FDA Clearance of IND for Phase 1/2 Trial of EBT-101 CRISPR-Based Therapeutic for Treatment of HIV

September 15, 2021 08:00 ET | Source: Excision BioTherapeutics

- ***EBT-101, first-in-human CRISPR-based one-time gene therapy to be evaluated in individuals with HIV***
- ***Initiation of EBT-101 Phase 1/2 clinical trial expected later this year***

SAN FRANCISCO, Sept. 15, 2021 (GLOBE NEWSWIRE) -- Excision BioTherapeutics, Inc., the developer of CRISPR-based therapies intended to cure viral infectious diseases, today announced that the U.S. Food and Drug Administration (FDA) has accepted the Investigational New Drug (IND) application for EBT-101, a CRISPR-based therapeutic candidate in development as a potential functional cure for chronic HIV. The IND clearance enables Excision to initiate a first-in-human Phase 1/2 clinical trial to evaluate the safety, tolerability, and efficacy of EBT-101 in individuals living with human immunodeficiency virus type 1 (HIV).

Sangamo Therapeutics and Intellia Therapeutics – in vivo editing

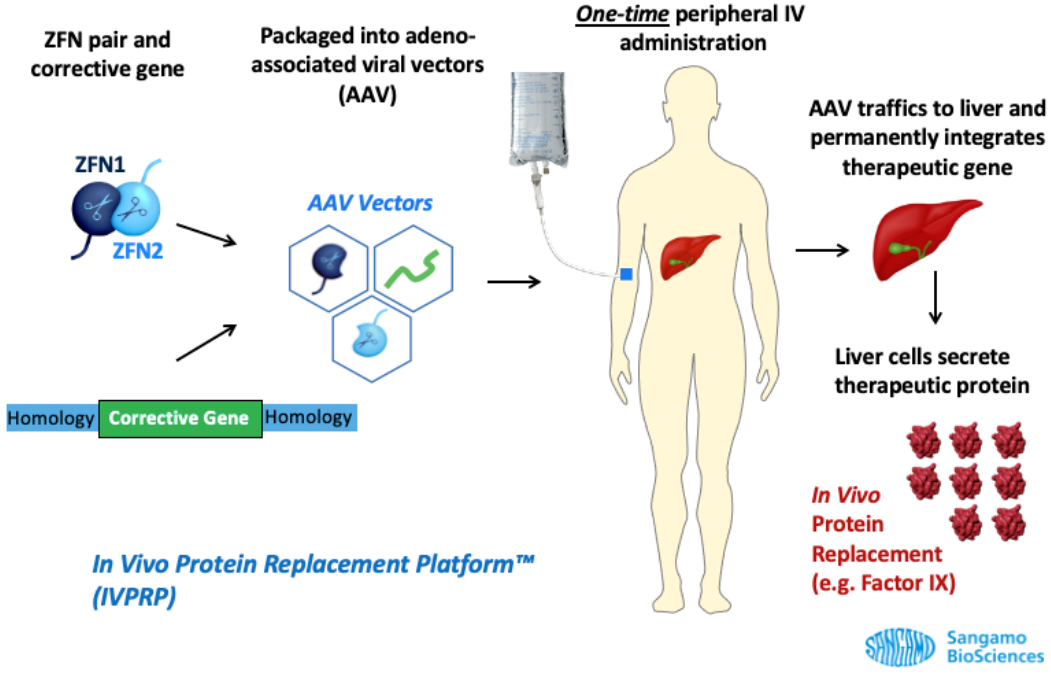
2011

In vivo genome editing restores haemostasis in a mouse model of haemophilia

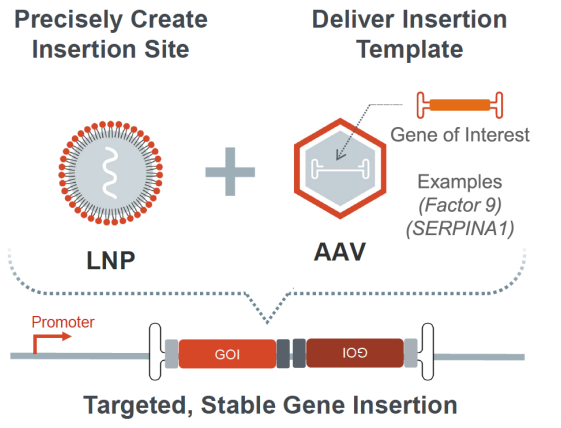
Hojun Li[1], Virginia Haurigot[1], Yannick Doyon[2], Tianjian Li[2], Sunnie Y. Wong[2], Anand S. Bhagwat[1], Nirav Malani[3], Xavier M. Anguela[1], Rajiv Sharma[1], Lacramiora Ivanciu[1], Samuel L. Murphy[1], Jonathan D. Finn[1], Fayaz R. Khazi[1], Shangzhen Zhou[1], David E. Paschon[2], Edward J. Rebar[2], Frederic D. Bushman[3], Philip D. Gregory[2], Michael C. Holmes[2] & Katherine A. High[1,4]

2015

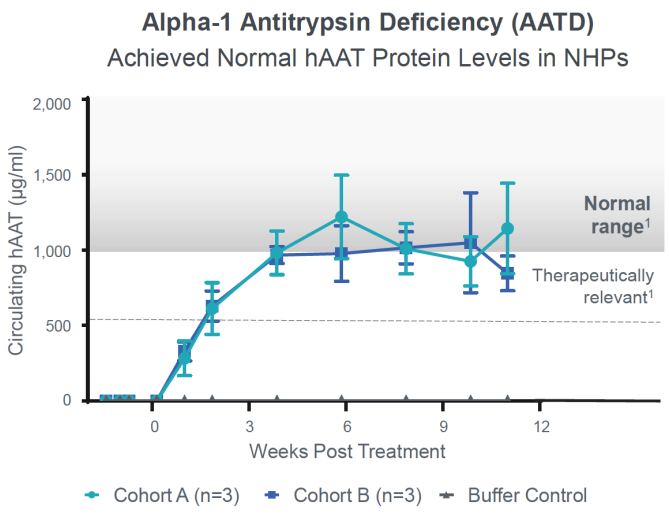
Systemic delivery of ZFP Therapeutics via AAV vectors allows *in vivo* correction of monogenic disease



Beyond Knockout: Insertion Technology Enables Production of High Levels of Therapeutic Protein



Potential best-in-class modality for a gain of function



[1] Stoller & Aboussouan *The Lancet*, 2005

Intellia THERAPEUTICS

Verve Therapeutics – CRISPR base editing for CAD

Article

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

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

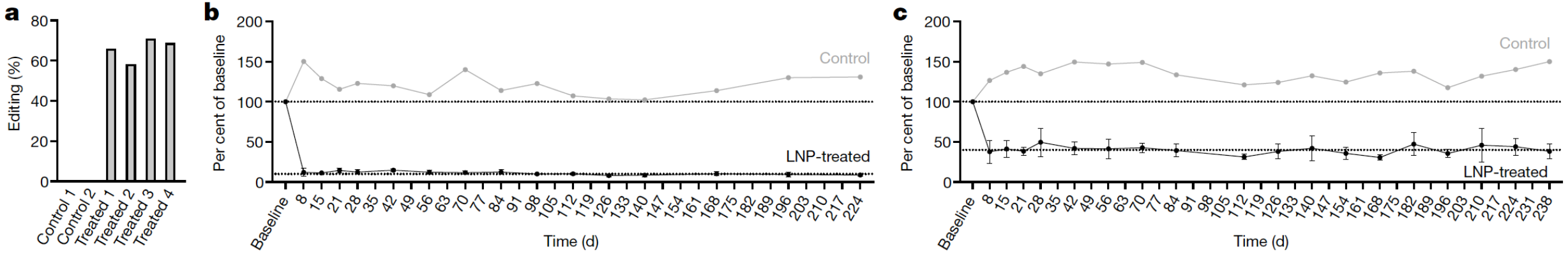
Received: 6 December 2020

Accepted: 11 April 2021

Published online: 19 May 2021

Check for updates

Kiran Musunuru[1,2,3], Alexandra C. Chadwick[4], Taiji Mizoguchi[4], Sara P. Garcia[4], Jamie E. DeNizio[4], Caroline W. Reiss[4], Kui Wang[4], Sowmya Iyer[4], Chaitali Dutta[4], Victoria Clendaniel[4], Michael Amaonye[4], Aaron Beach[4], Kathleen Berth[4], Souvik Biswas[4], Maurine C. Braun[4], Huei-Mei Chen[4], Thomas V. Colace[4], John D. Ganey[4], Soumyashree A. Gangopadhyay[4], Ryan Garrity[4], Lisa N. Kasiewicz[4], Jennifer Lavoie[4], James A. Madsen[4], Yuri Matsumoto[4], Anne Marie Mazzola[4], Yusuf S. Nasrullah[4], Joseph Nneji[4], Huilan Ren[4], Athul Sanjeev[4], Madeleine Shay[4], Mary R. Stahley[4], Steven H. Y. Fan[5], Ying K. Tam[5], Nicole M. Gaudelli[6], Giuseppe Ciaramella[6], Leslie E. Stolz[4], Padma Malyala[4], Christopher J. Cheng[4], Kallanthottathil G. Rajeev[4], Ellen Rohde[4], Andrew M. Bellinger[4] & Sekar Kathiresan[4]



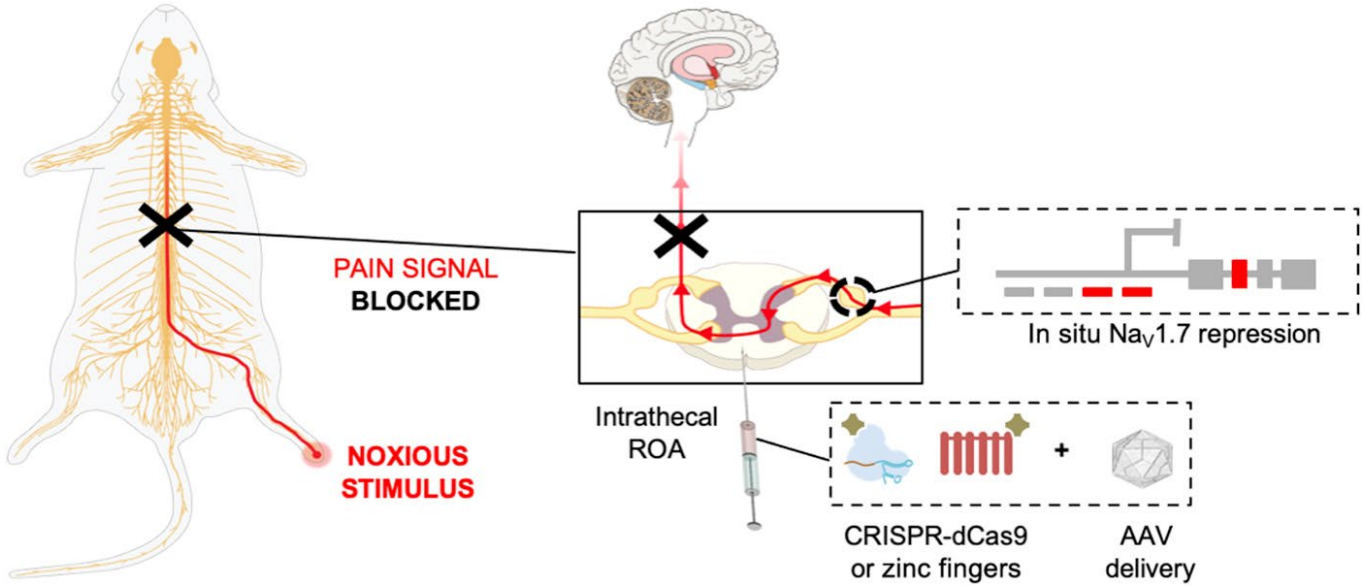
Navega: CRISPRi for pain

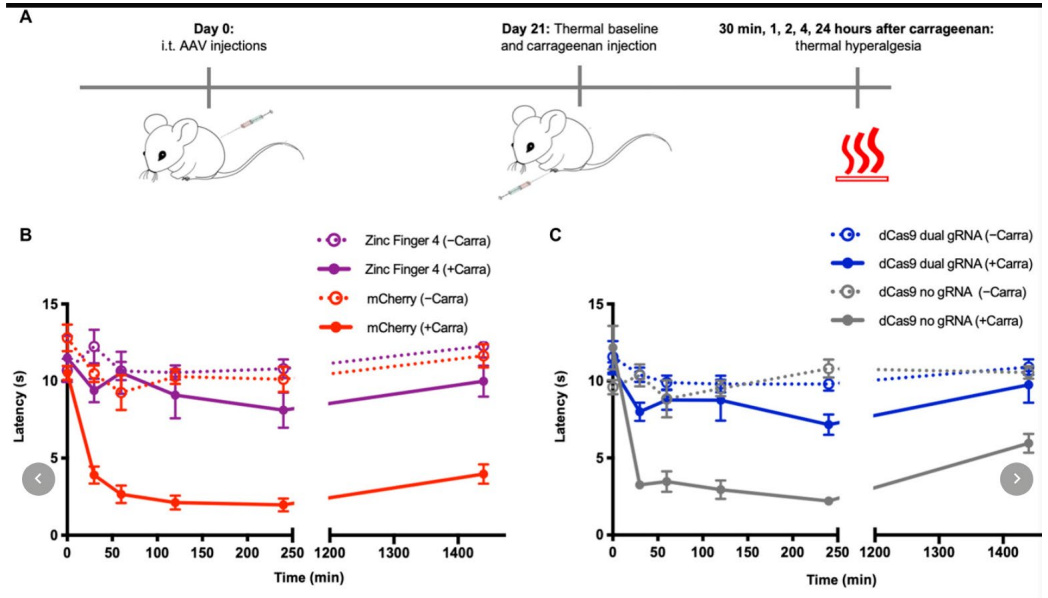
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PAIN

Long-lasting analgesia via targeted in situ repression of $Na_V1.7$ in mice

Ana M. Moreno[1]*, Fernando Alemán[1]*, Glaucilene F. Catroli[2], Matthew Hunt[2], Michael Hu[1], Amir Dailamy[1], Andrew Pla[1], Sarah A. Woller[2†], Nathan Palmer[3], Udit Parekh[4], Daniella McDonald[1,5], Amanda J. Roberts[6], Vanessa Goodwill[7], Ian Dryden[7], Robert F. Hevner[7], Lauriane Delay[2], Gilson Gonçalves dos Santos[2], Tony L. Yaksh[2‡], Prashant Mali[1‡]





“The delivery challenge: fulfilling the promise of therapeutic genome editing”

nature biotechnology

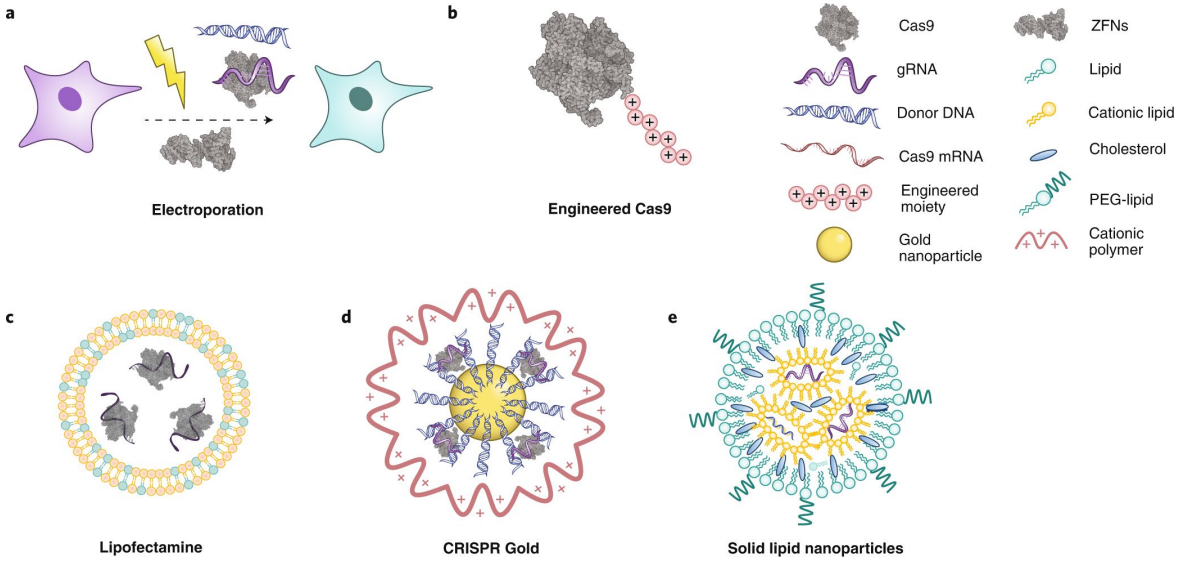
FOCUS | REVIEW ARTICLE

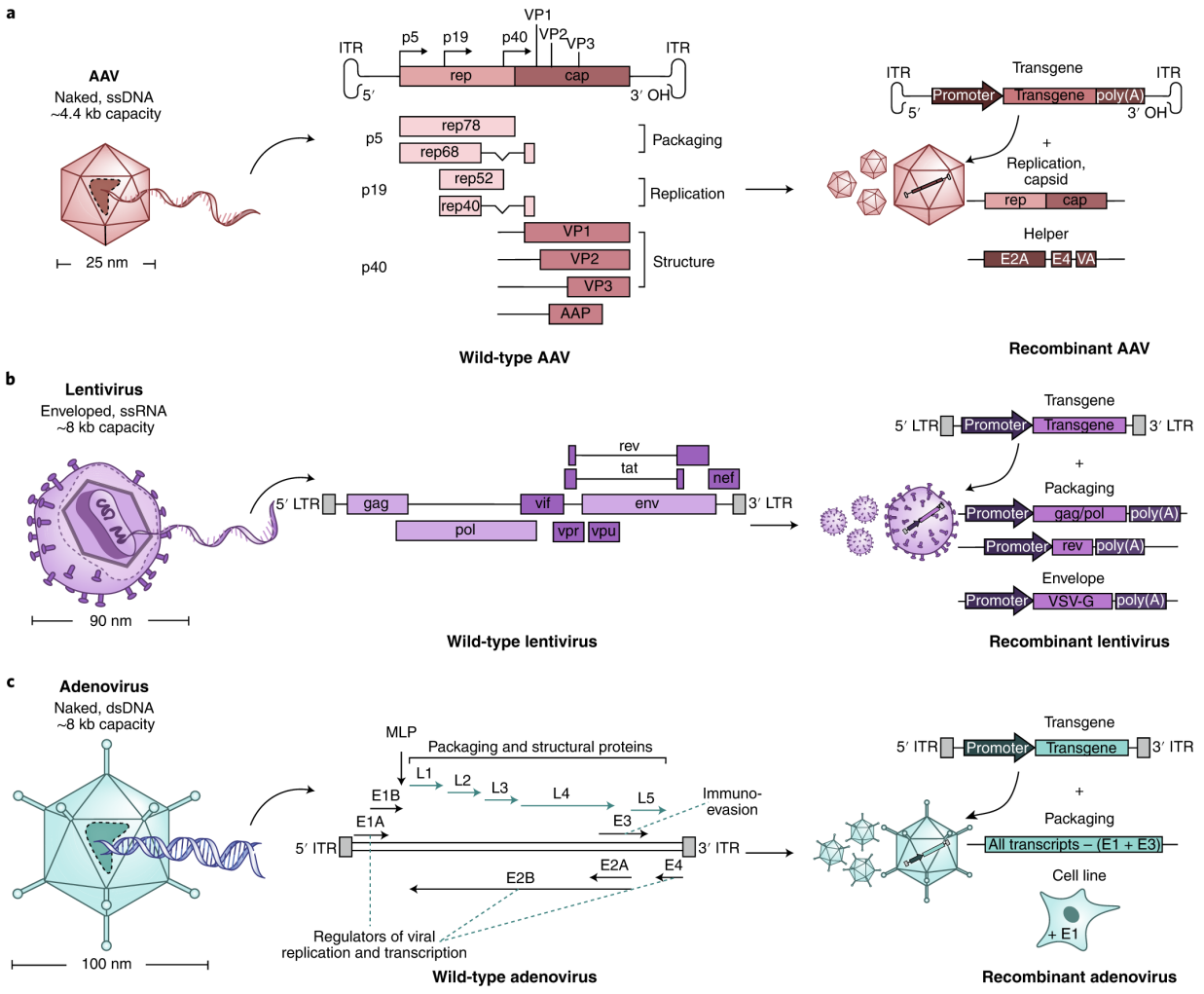
https://doi.org/10.1038/s41587-020-0565-5

Check for updates

The delivery challenge: fulfilling the promise of therapeutic genome editing

Joost van Haasteren[1,7], Jie Li[2,3,7], Olivia J. Scheideler[2,7], Niren Murthy[1,2,3] ✉ and David V. Schaffer[1,2,3,4,5,6] ✉





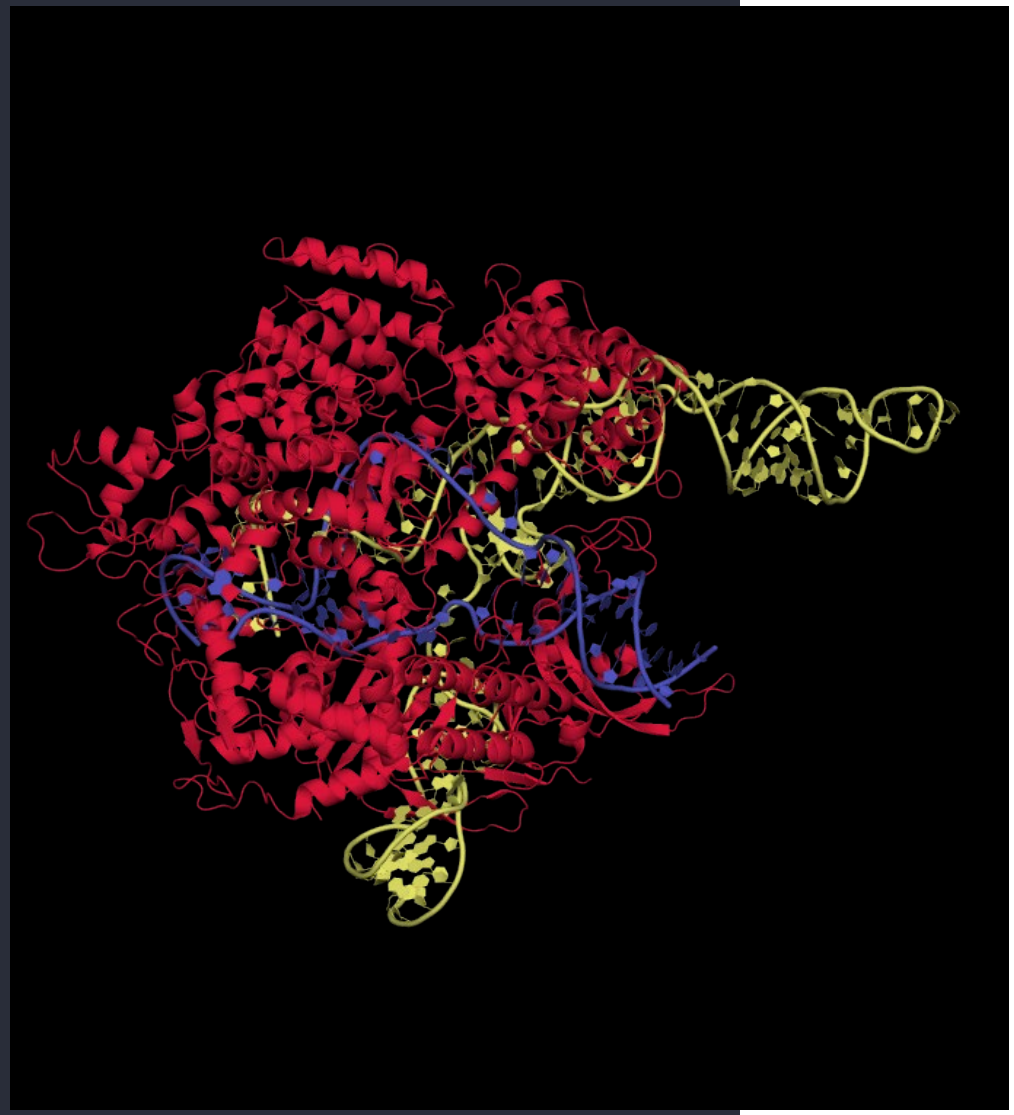
CRISPR as a therapeutic – key takeaways

- Ex vivo, CRISPR editing of primary cells has an established and fully charted regulatory path to first-in-human clinical trials, with formidable early-stage promise demonstrated in the hemoglobinopathies space
- Multiple additional trials ongoing in the cancer space

- Expanded toolbox of CRISRP-based effectors (base editing, epiediting) is expanding range of disease indications

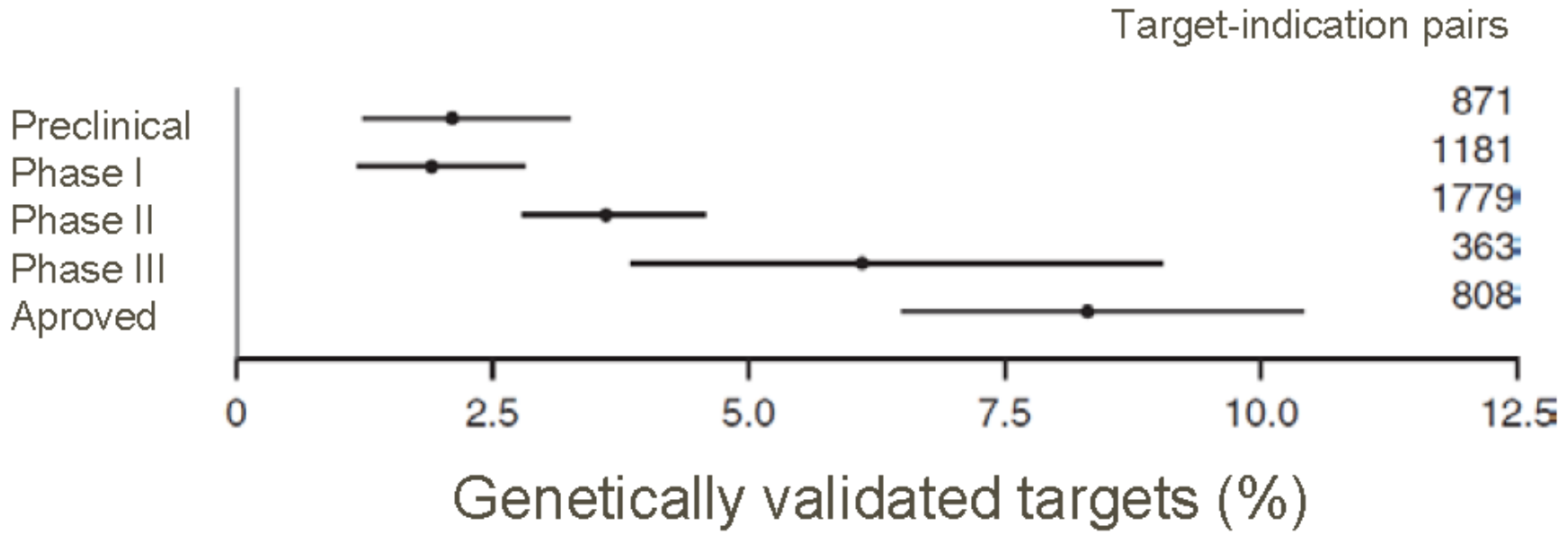
- In vivo, targeted gene knockout in the liver using transient (nonviral) delivery has demonstrated formidable early-stage promise with respect to biomarker knockdown
- Clinical precedent exists, and clinical development is ongoing, for an “in vivo protein replacement platform” approach where the liver acts as a protein synthesis factory

CRISPR as a target discovery engine



Slide from Hal Barron's presentation Jul. 2018

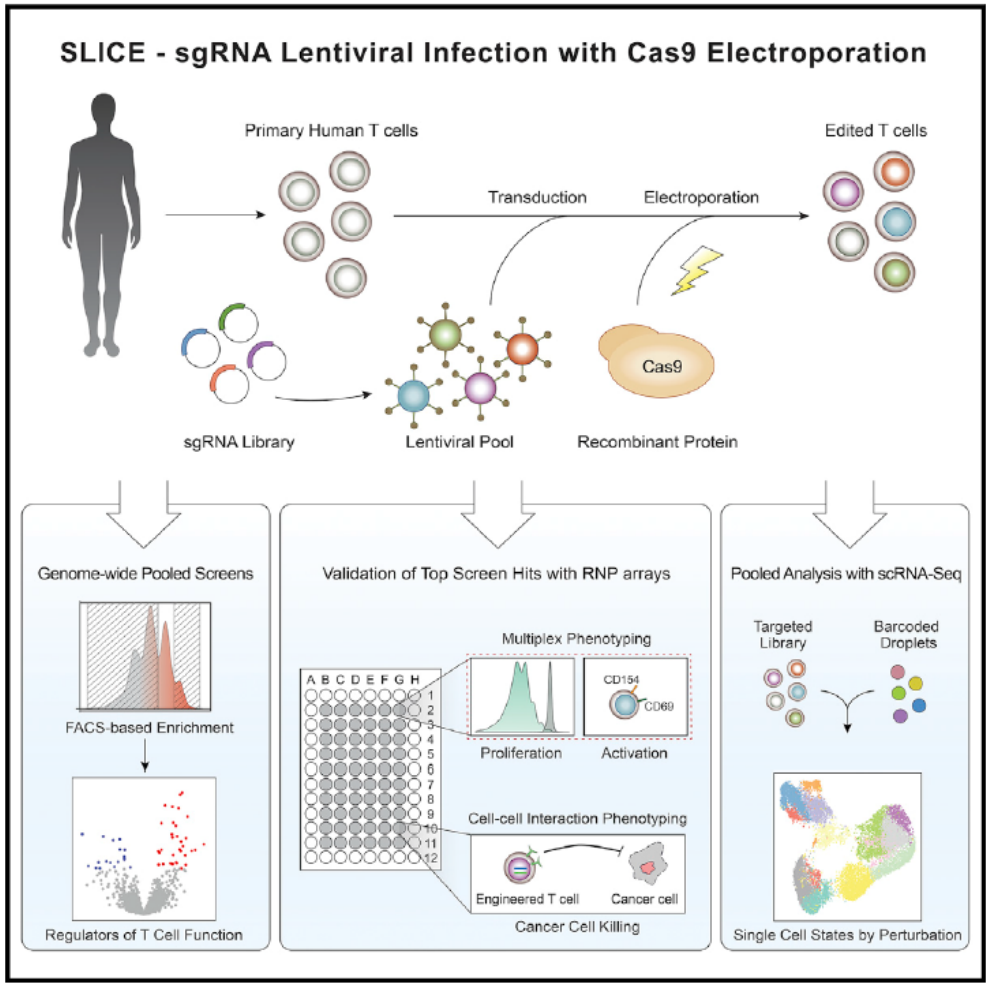
Drugs with human genetic evidence nearly 2x more likely to be successful[1]



Nelson et al Nature Genetics 2015

New screening system -> new disease area -> new target

Graphical Abstract



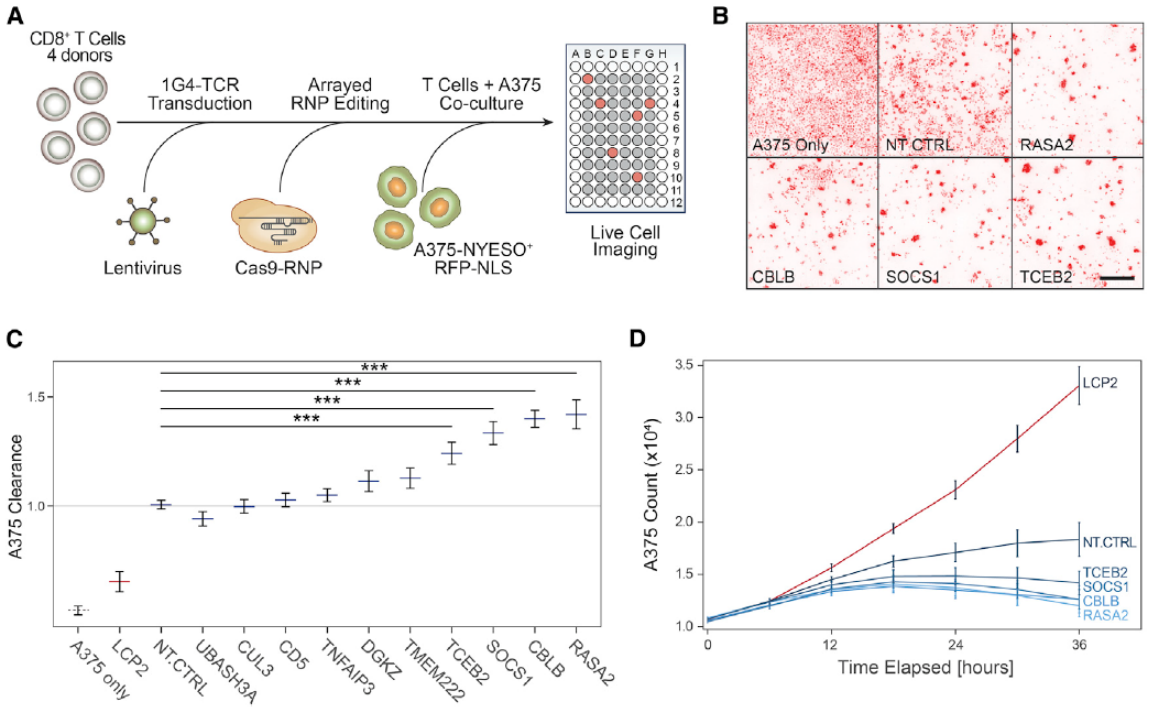
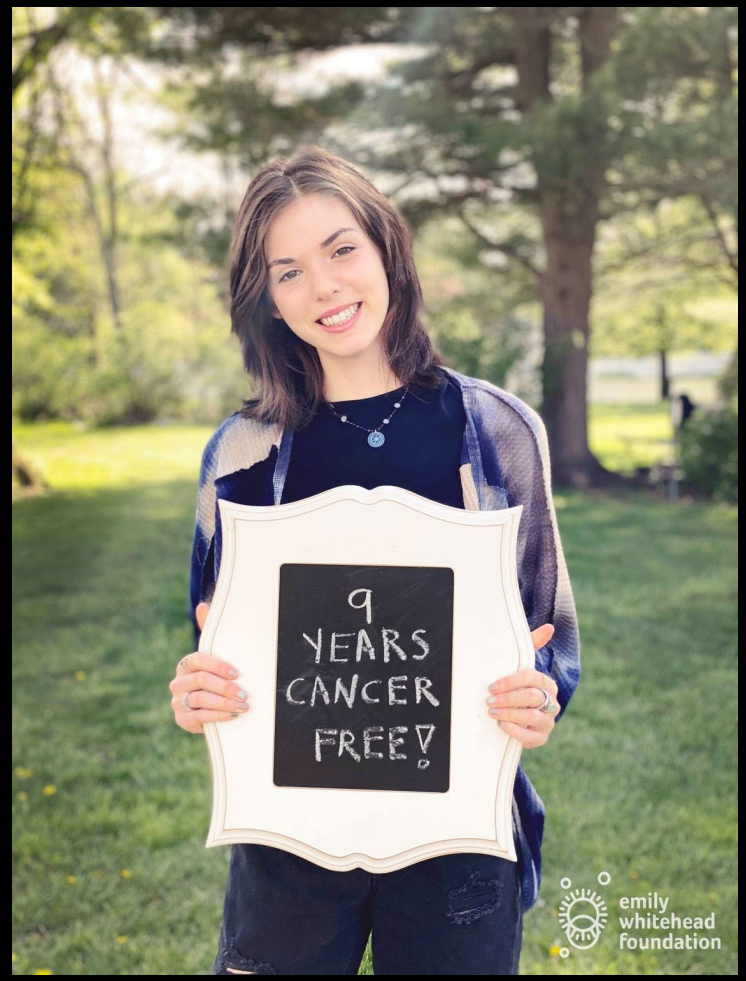


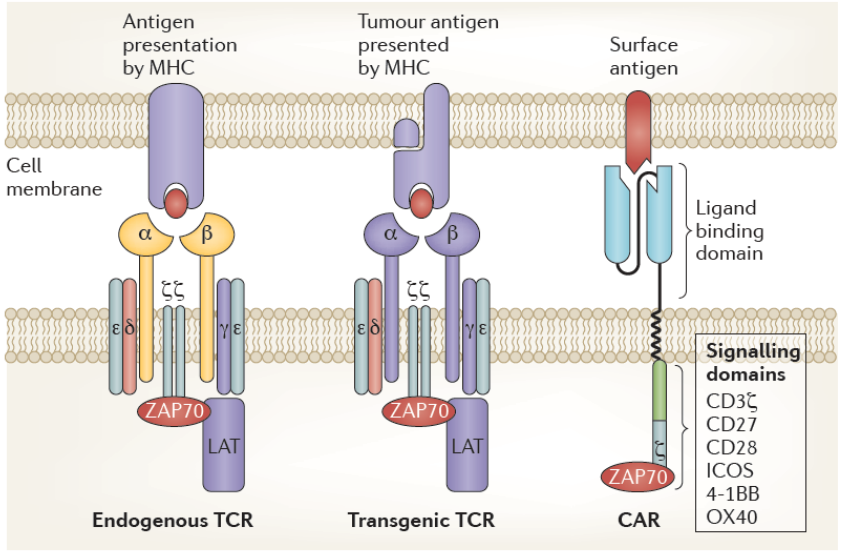
Figure 5. Genome-wide Screen Hits Boost *In Vitro* Cancer Cell Killing by Engineered Antigen-Specific Human T Cells

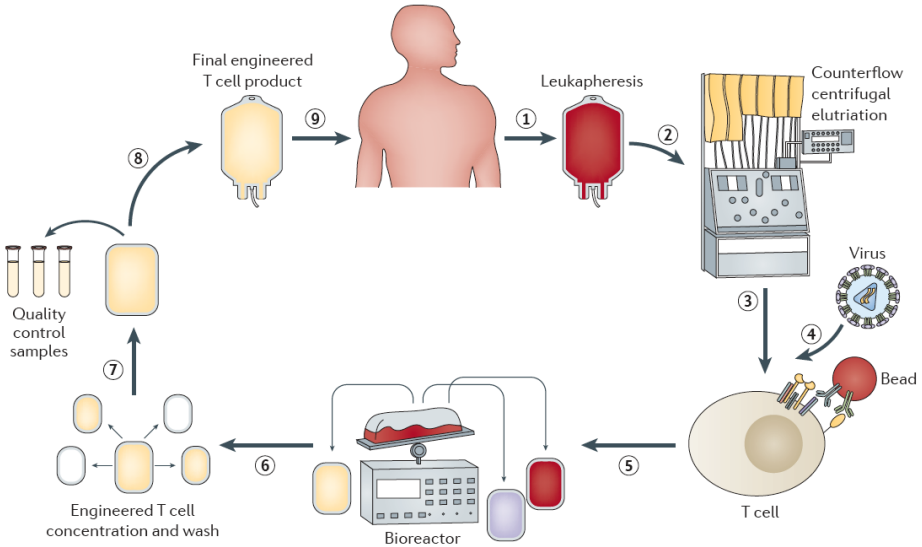
Shifrut, Marson et al Cell 2018

CRISPR for cancer immunotherapy

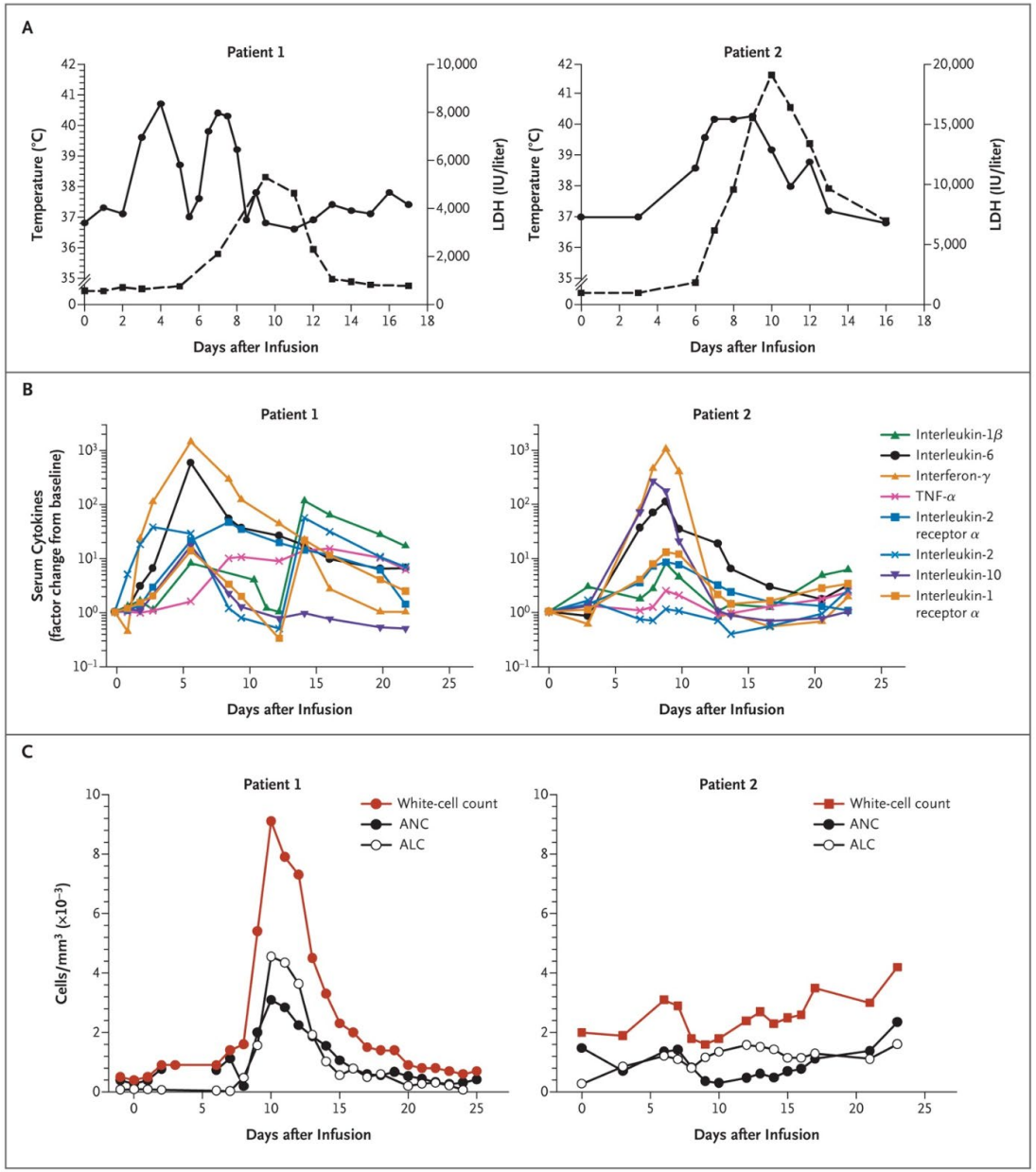


How Emily was saved





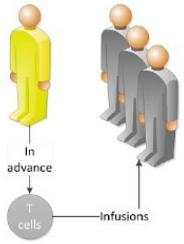
Fesnak, June, Levine *Nature Reviews Cancer* 2016



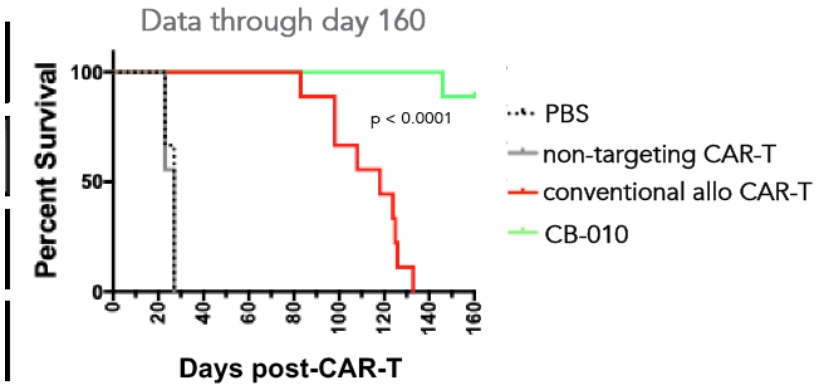
Grupp et al *NEJM* 2013

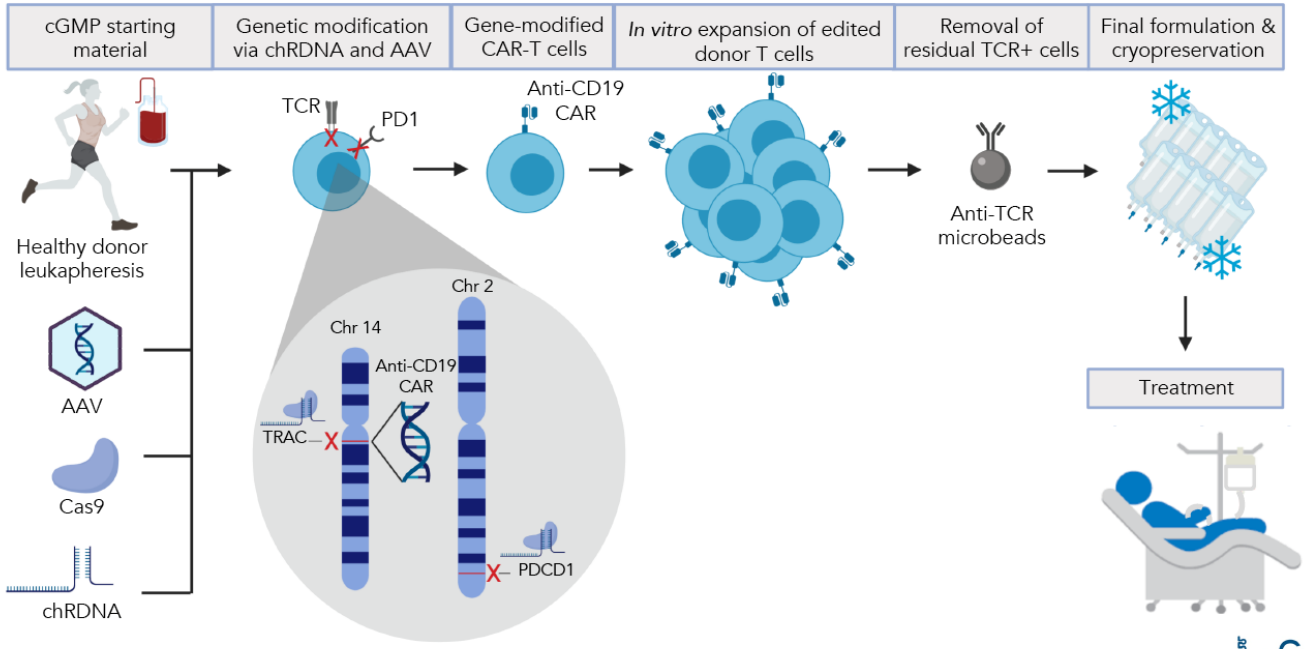
CRISRP-enhanced CAR-T therapy for cancer

Allogeneic therapy



- Off-the-shelf to patients, inventory build up
- Bridging therapy not required
- More uniform T cells from healthy donors
- Efficient manufacturing
- Patients ineligible for autologous
- Repeat dosing opportunity





CARIBOU BIOSCIENCES

Slides courtesy of Rachel Haurwitz, Caribou Biosciences

The Innovative Genomics Institute – CRISPR Cures for All

Karly Koch, 20, Muncie, Ind.

“She has a rare genetic immune disorder, and has written about her end-of-life plans”

https://well.blogs.nytimes.com/2015/03/28/teen-advance-directive-end-of-life-care/

There is a giant gap between commercially viable products (eg allo CAR-T, SCD/TDT, hemophilia), and N=1 indications where the NPV is such that it makes no commercial sense for a for-profit-entity to take it on.

The fact that editing represents an approach to the majority of monogenic disease *in principle* does not mean that some biotech will take on disease #823 in practice (and there are 5,000 monogenic conditions on OMIM). We need a fundamentally new N=1 framework

IGI: Cutting-Edge Science with Social Purpose

- Founded in 2014 by Nobel Laureate Jennifer Doudna, co-discoverer of CRISPR genome editing, as a non-profit institute in partnership with UC Berkeley and UCSF.
- The IGI's mission is to bridge revolutionary genome-editing tool development to affordable and accessible solutions in human health, climate, and agriculture.
- The IGI is working toward a world where genomic technology is routinely applied to treat genetic disease, enable sustainable agriculture, and help achieve a carbon-neutral economy.

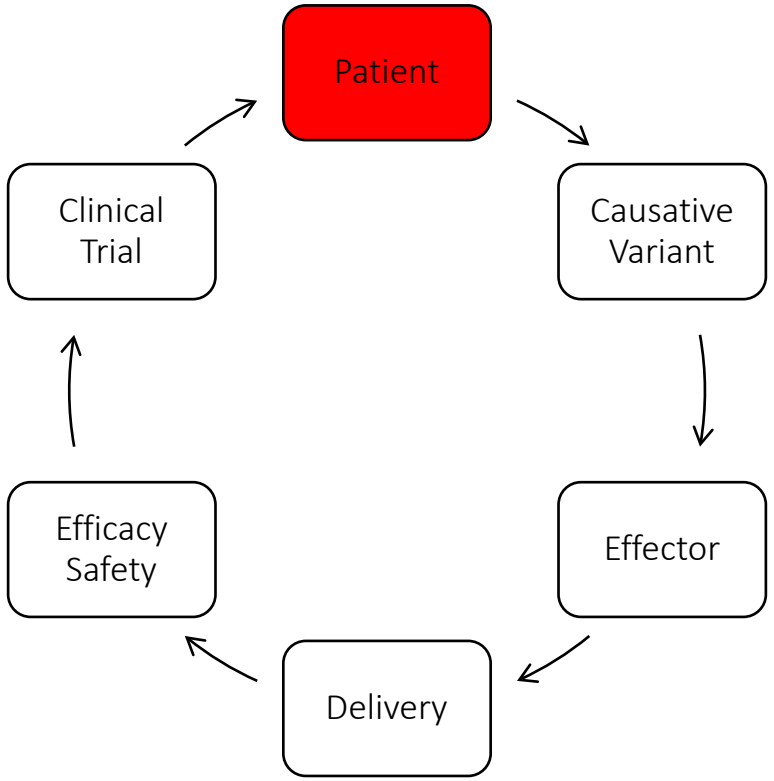
IGI's impact comes from the unique integration of:

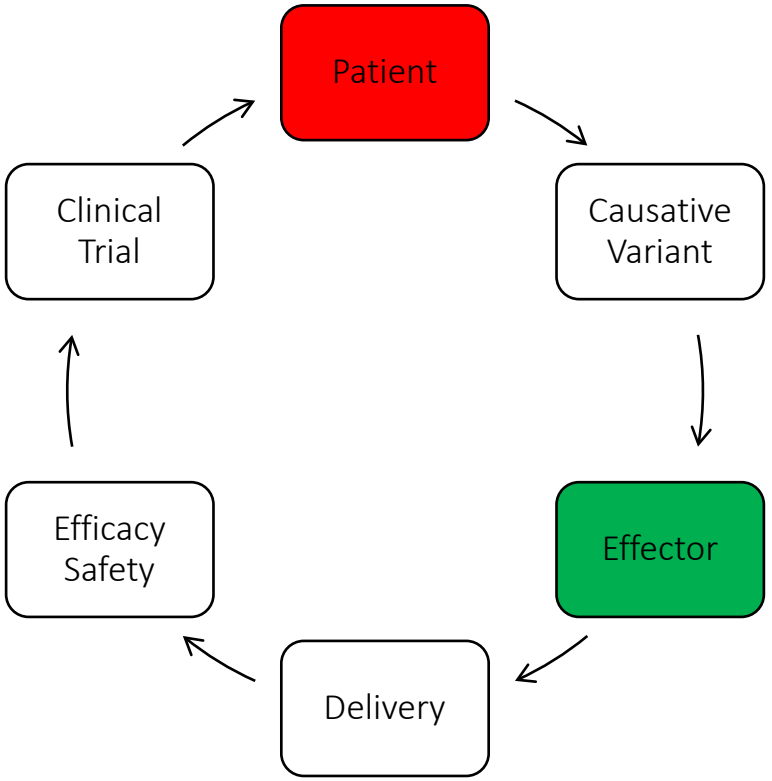
- Advancing CRISPR genome engineering to optimize the technology for real-world applications
- Solving targeted global problems of human health, agriculture, and climate change
- Focusing on public impact and solutions that are ethical, accessible, and affordable

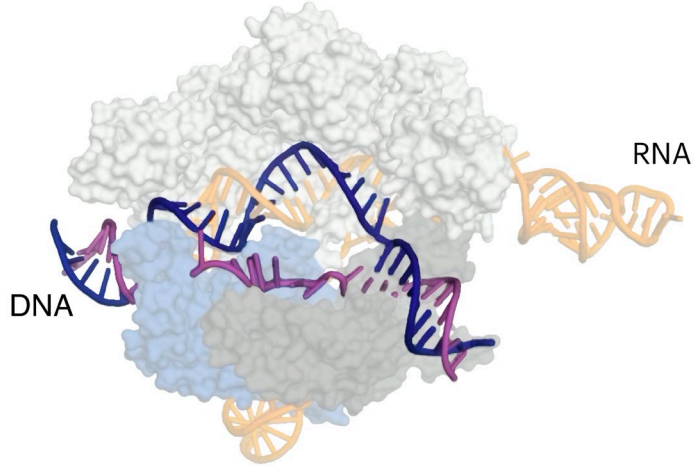
"We have a responsibility to pursue CRISPR's enormous potential to achieve previously impossible solutions to some of the world's big challenges — solutions that will be available to anyone."

— Jennifer Doudna

Taking on the challenge of N=1 genetic disease

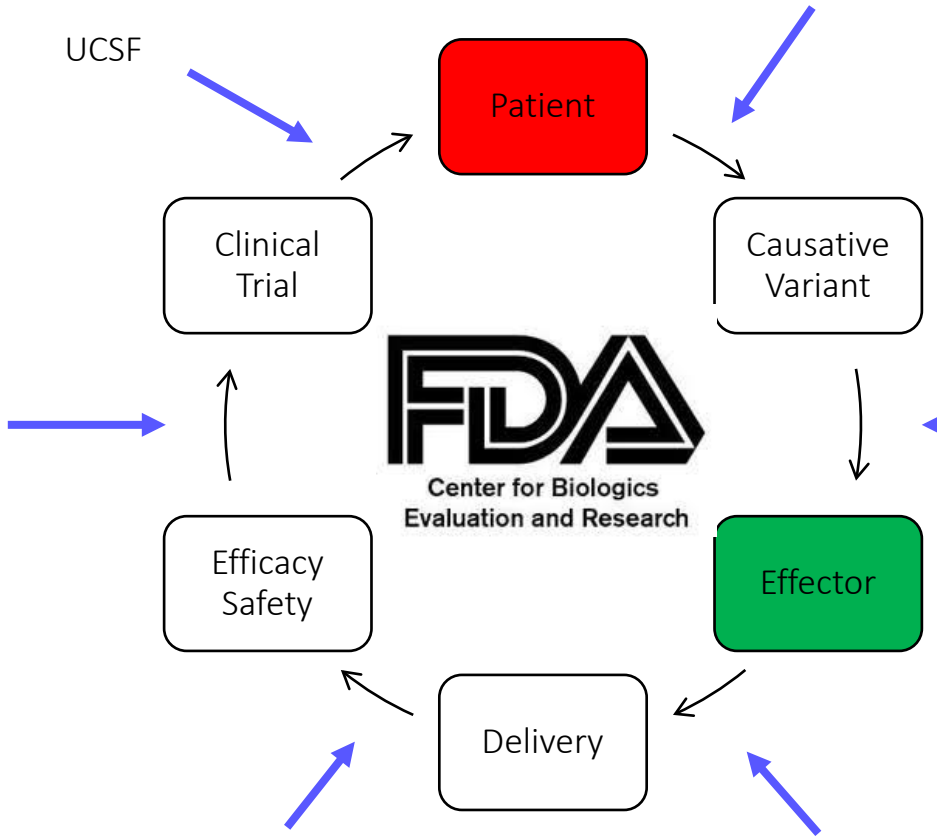



Patient
Causative Variant
Effector
Delivery
Efficacy Safety
Clinical Trial


RNA
DNA

The Center for Translational Genomics at IGI

Genome-scale platform for reverse and forward genetics in hPSCs
and clinically relevant primary human cells and organoids
coupled to HT phenotyping



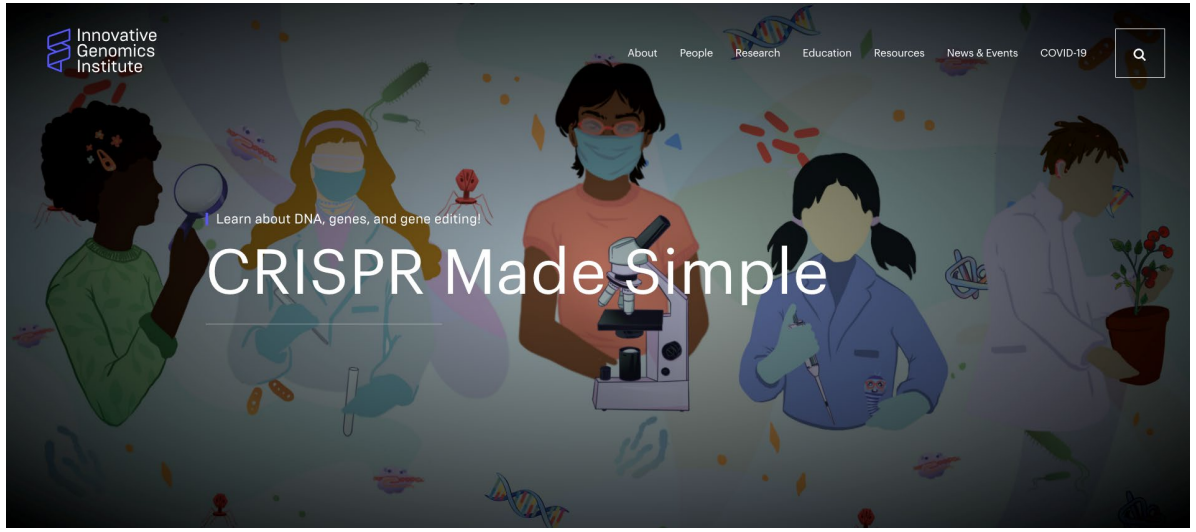
Carefully chosen
paradigm-establishing
programs

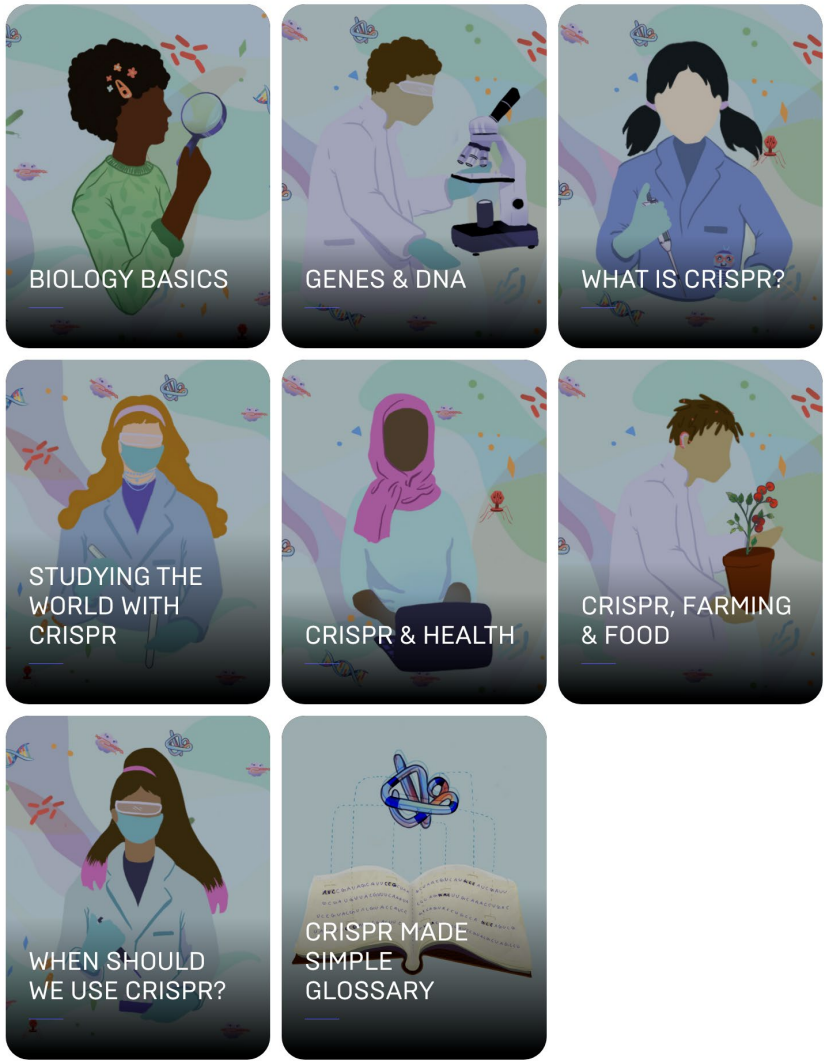
Library of CRISPR:
Every “Cas” ready to use
so we forget about “PAM deserts”

HT NGS
Definitive bioinformatic solution
to “target to optimal guide” problem

Viral and nonviral
solutions for key cell types
and organs

https://innovativegenomics.org/crispr-made-simple/





https://innovativegenomics.org/news/crispr-clinical-trials-2021/

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