

Prime Medicine

May 2023



Forward-Looking Statements

This presentation contains forward-looking statements of Prime Medicine, Inc. (“Prime”, “we” or “our”) within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements contain information about our current and future prospects and our operations and financial results, which are based on currently available information. All statements other than statements of historical facts contained in this presentation, including statements regarding our strategy, future financial condition, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “aim,” “anticipate,” “assume,” “believe,” “contemplate,” “continue,” “could,” “design,” “due,” “estimate,” “expect,” “goal,” “intend,” “may,” “objective,” “opportunity,” “plan,” “predict,” “positioned,” “potential,” “seek,” “should,” “target,” “will,” “would” and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, express or implied statements about Prime’s beliefs and expectations regarding: the initiation, timing, progress and results of our research and development programs, preclinical studies and future clinical trials, including the initiation of investigational new drug-enabling studies for chronic granulomatous disease (CGD) and our programs for Friedreich’s Ataxia and Cystic Fibrosis; the capacity of our PASSIGE technology to be used in cell therapy; our ability to demonstrate, and the timing of, preclinical proof-of-concept in vivo for multiple programs; our ability to pursue our strategic indication categories: immediate target indications, repeat expansion disorder indications and other differentiation target indications; the timing of our regulatory filings, including our investigational new drug applications submissions, including our anticipated initial IND submission as early as 2024 with additional filings anticipated in 2025; our ability to demonstrate superior off-target profiles for Prime Editing programs; our development and optimization of various non-viral and viral delivery systems; our expansion of Prime Editing using proprietary recombinase and/or retrotransposon and other proprietary technologies; the scope of protection we are able to establish and maintain for intellectual property rights covering our Prime Editing technology; the implementation of our strategic plans for our business, programs and technology, including our ability to identify and enter into future license agreements and collaborations; and our estimates of our expenses, capital requirements, and needs for additional financing as well as our cash runway into 2025.

Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make due to a number of risks and uncertainties. These and other risks, uncertainties and important factors are described in the section entitled “Risk Factors” in our most recent Quarterly Report on Form 10-Q, as well as any subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent our views only as of the date of this presentation and we undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, the occurrence of certain events or otherwise. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated the reasonableness or accuracy of our internal estimates or research and no reliance should be made on any information or statements made in this presentation relating to or based on such internal estimates and research.

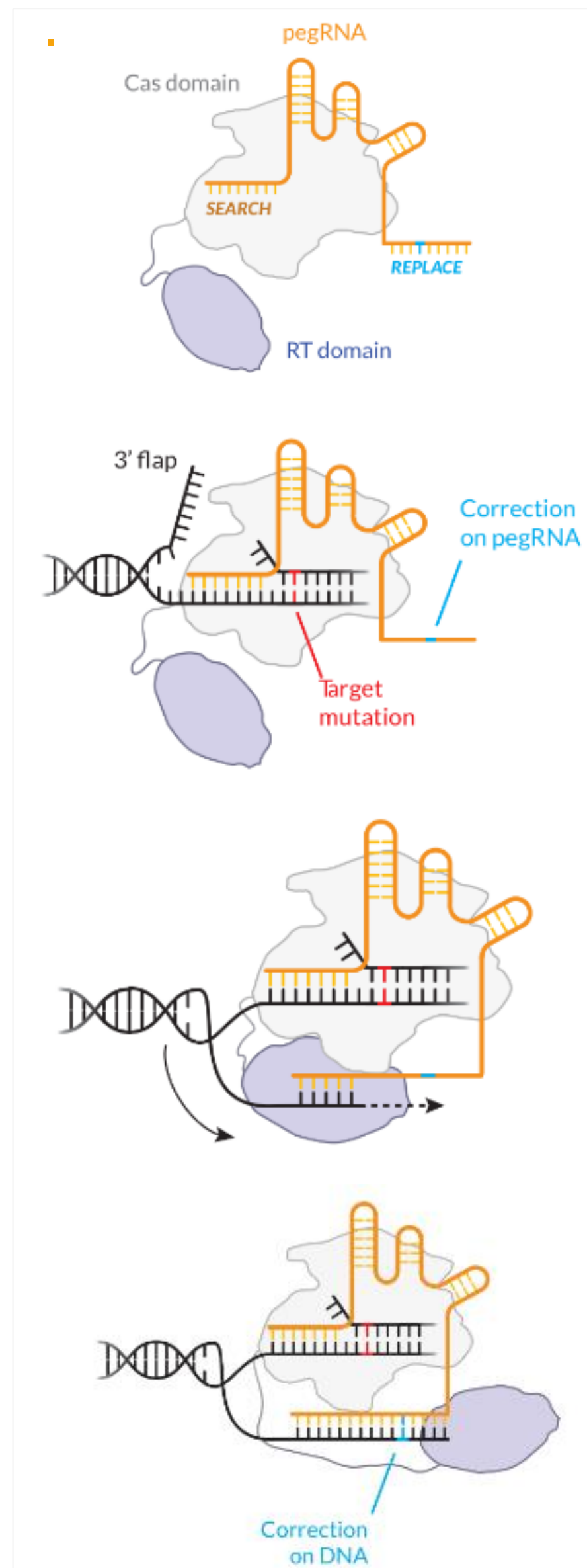
30 years after the first patient was treated with gene therapy,
gene editing is only just beginning to demonstrate clinical benefit.

Now is the moment for a revolution.

Prime Medicine brings together the
right people and the **right technology**
at the **right time**

with the aim to deliver the promise of one-time, curative
genetic therapies to address the widest spectrum of diseases.

Delivering the full promise of gene editing requires an extremely powerful technology



Prime Editing (PE) stands out as a best-in-class genetic medicine approach

Versatility: only gene editing technology with the capability to edit, correct, insert, and delete

- ✓ Performs and corrects insertions, deletions, and all twelve types of single base pair corrections
- ✓ Precisely targets to insert or delete kilobase-sized DNA
- ✓ Easily programmable to a unique target location and for a broad set of edits
- ✓ Restores gene function for multiple mutations with a single product (i.e., “hotspots”)

Precision: May be much safer with minimal, or no, off-target editing

- ✓ Does not create double stranded breaks: high specificity with low indels rate at targeted editing site
- ✓ Does not create double stranded breaks: minimal or no off-target activity
- ✓ Limited potential for “bystander editing” at target site

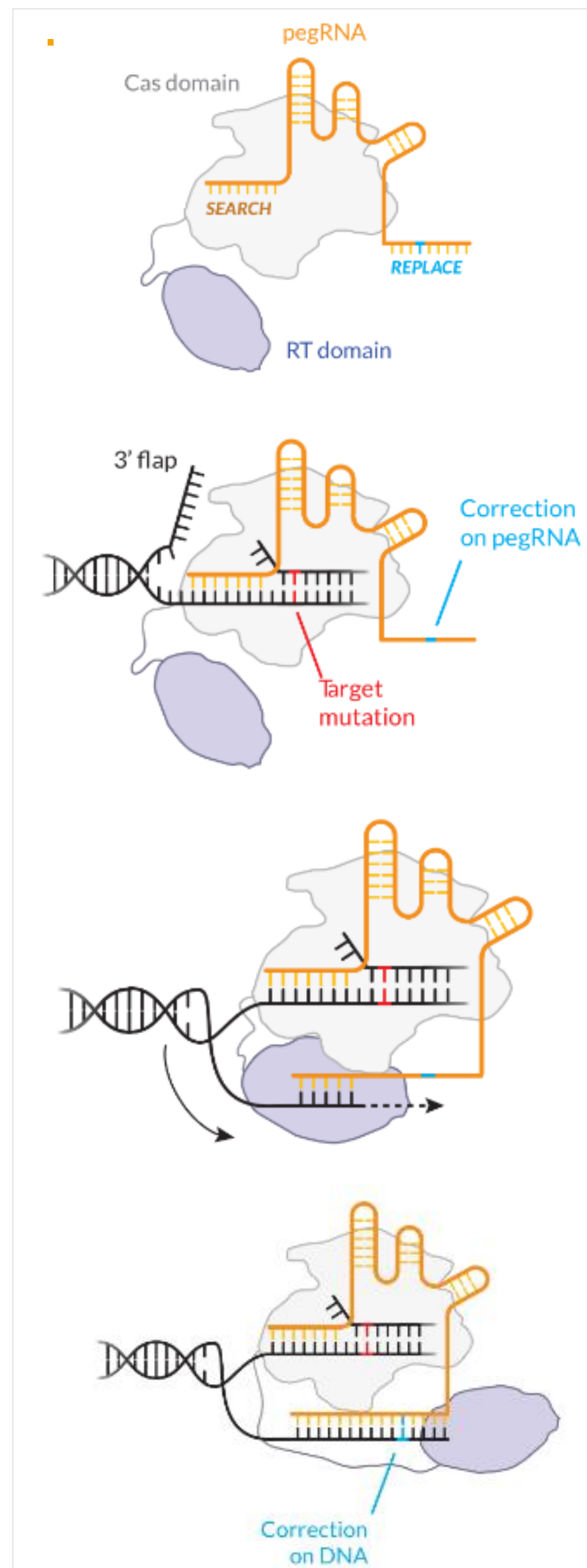
Efficiency: Durable and high-efficiency editing demonstrated across Prime Medicine portfolio

- ✓ Permanent edits that are passed along to daughter cells
- ✓ Corrects genes *in situ*, maintaining native gene control
- ✓ Single-dose, potentially curative correction to wild-type sequence

Breadth: Able to address ~90% of disease-causing mutations in multiple tissue types and cells

- ✓ Corrects mutations in dividing and non-dividing human cells
- ✓ 100's of potential indications already available in Prime Editing's toolbox

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Prime Medicine is well-positioned to maximize Prime Editing's broad therapeutic potential

In ~2.5 years since company inception:

Built and
advanced a
strategic
portfolio

Identified and progressed initial pipeline of 18 programs

- Focusing on indications with the fastest, most direct path to demonstrating technological success, as well as diseases that cannot be treated using other gene-editing approaches
- *In vivo* studies in progress across portfolio; multiple programs advancing toward development candidates, with first IND filing potentially as early as 2024

Demonstrated Prime Editing capabilities: established preclinical proof-of-concept and safety

- *In vivo* long-term engraftment of Prime Edited hematopoietic stem cell therapy for Chronic Granulomatous Disease
- Efficient removal of pathological repeats in Friedreich's Ataxia, a Repeat Expansion Disease, with phenotypic correction in patient organoids
- Efficient editing with phenotypic correction of cystic fibrosis patient organoids

Advanced CMC and delivery capabilities

- Efficient *in vivo* Prime Editing in rodent liver and central nervous system

Optimized and expanded Prime Editing platform, capabilities and IP

- One-step non-viral precise insertion of whole genes into the genome in primary human cells using PASSIGE technology
- Industrialized and automated Prime Editor screening capabilities
- Advanced and substantially improved Prime Editing
- Developed strong Intellectual Property position

Established
strong
corporate
position

Led by world-class, diverse team of researchers and drug developers; grew company to ~200 employees

Raised ~\$315M in Series A/B, and ~\$200M in IPO (Oct '22), from a blue-chip group of investors

Leveraging close relationship with founders David Liu and Andrew Anzalone to bring new innovation rapidly into Prime Medicine

Aim to create additional value and extend reach through BD and partnering in 2023

Our current portfolio of 18 programs leverages the versatility and breadth of Prime Editing



To be discussed in detail today

STRATEGIC CATEGORY	TARGET TISSUE	INDICATION	DELIVERY	DISCOVERY	LEAD OPTIMIZATION	IND-ENABLING	Phase 1/2
IMMEDIATE	BLOOD	Chronic Granulomatous Disease	ex vivo				
		Fanconi Anemia	ex vivo				
	LIVER	Wilson's Disease	LNP				
		Glycogen Storage Disease 1b	LNP				
	EYE	Retinitis Pigmentosa/Rhodopsin	AAV				
		Retinitis Pigmentosa/Usher Syndrome	AAV				
	EAR	Usher Syndrome Type 3	AAV				
		Non-Syndromic Hearing Loss – GJB2	AAV				
DIFFERENTIATION: REPEAT EXPANSION DISEASES	NEURO-MUSCULAR	Friedreich's Ataxia	AAV				
		Myotonic Dystrophy Type 1	viral/non-viral				
		Amyotrophic Lateral Sclerosis	viral/non-viral				
		Oculopharyngeal Muscular Dystrophy	LNP				
		Fragile X Syndrome	viral/non-viral				
		Huntington's Disease	TBD				
	EYE	Fuchs' Endothelial Corneal Dystrophy	viral/non-viral				
DIFFERENTIATION: OTHER	MUSCLE	Duchenne Muscular Dystrophy	AAV				
	LUNG	Cystic Fibrosis	LNP				

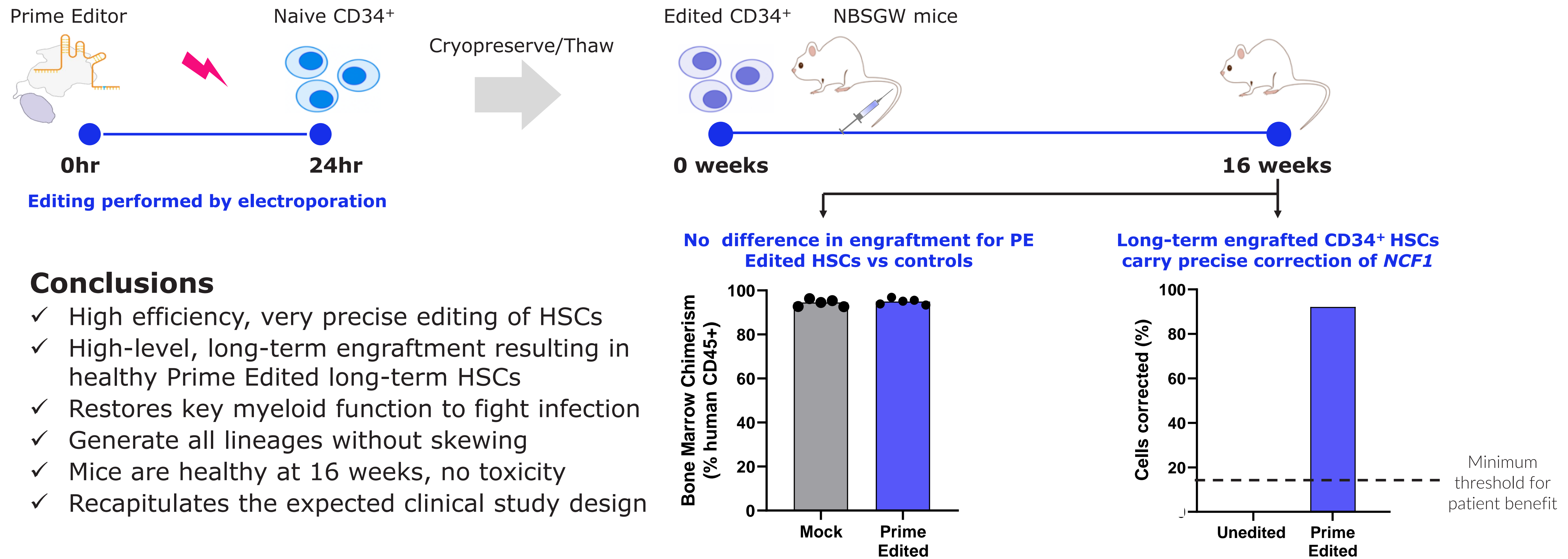
PARTNERED PROGRAMS	BLOOD	Sickle Cell Disease		ex vivo
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Initially focused on our first two strategic indication categories in diseases where Prime Editing could offer compelling advantages over current standard-of-care and novel therapeutic modalities in development

*Pipeline reflects the current development stage and will be updated quarterly

Successful Prime Editing in long-term HSC population: *in vivo* engraftment of Prime Edited CD34⁺ Cells

Maintenance of >92% corrected long-term HSCs following 16-week engraftment



Successful Prime Editing in long-term HSC population: Prime Editing is highly reproducible

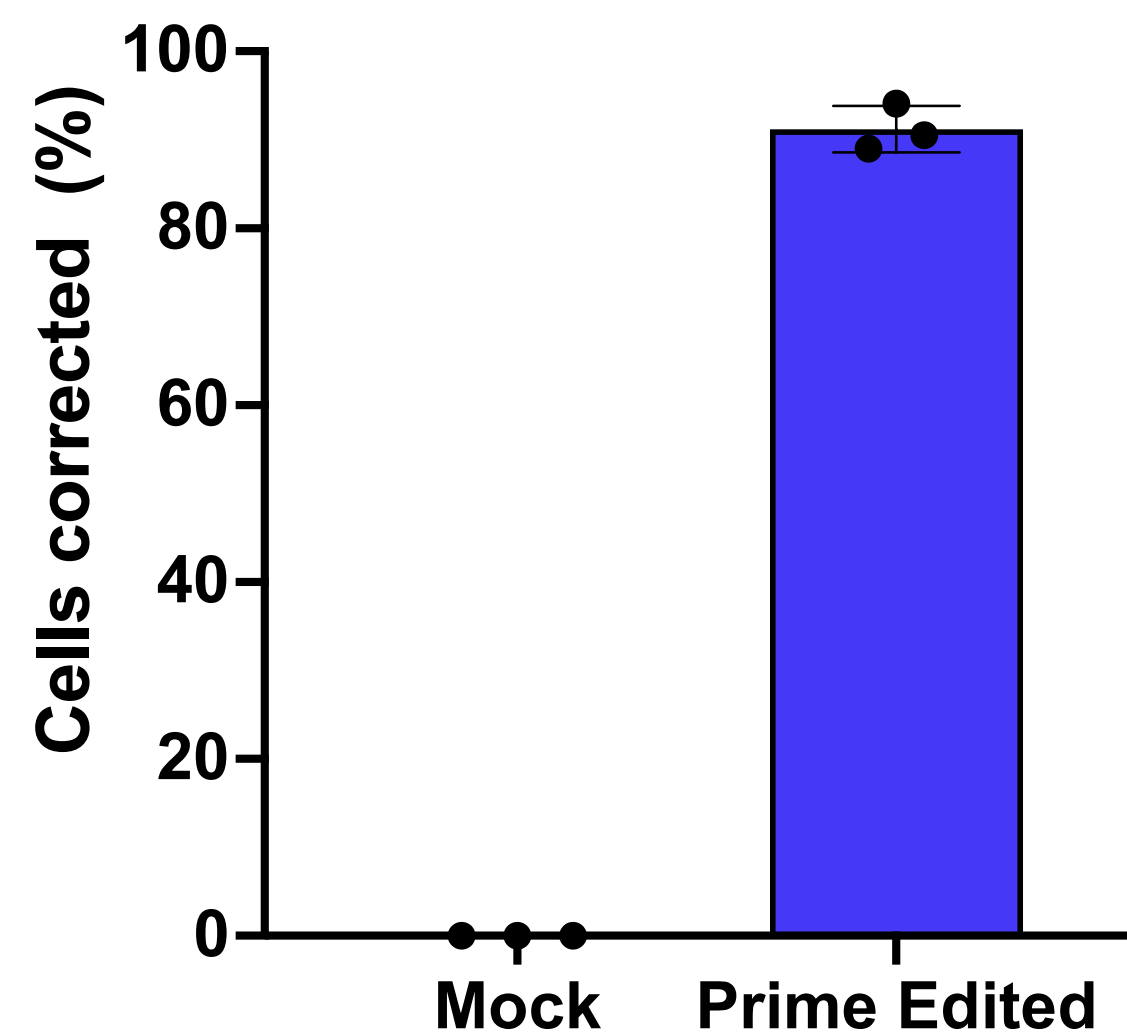
Greater than 90% Prime Editing in CD34+ cells from each of four donors following 16-week engraftment

ex vivo >90% cells corrected

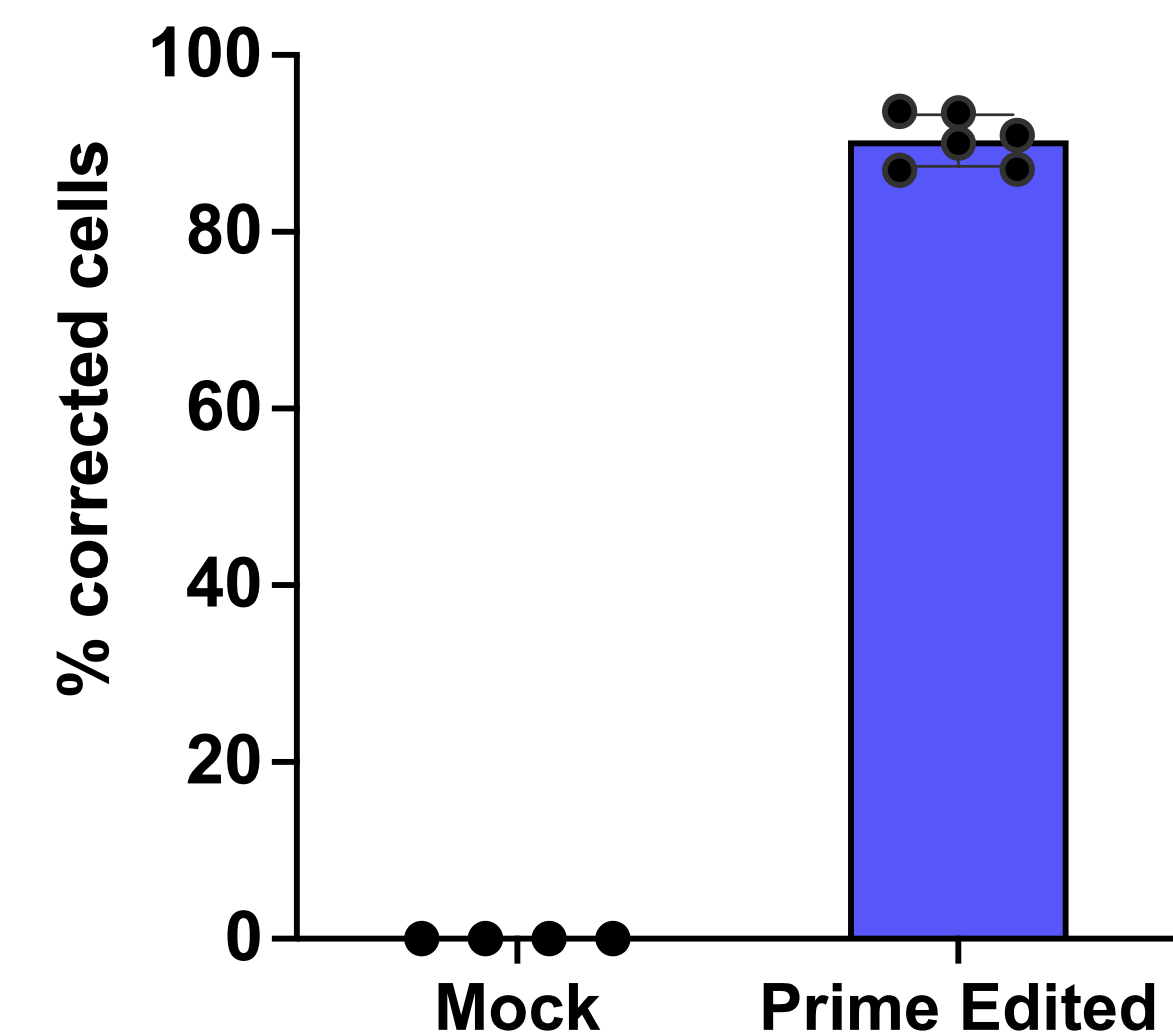
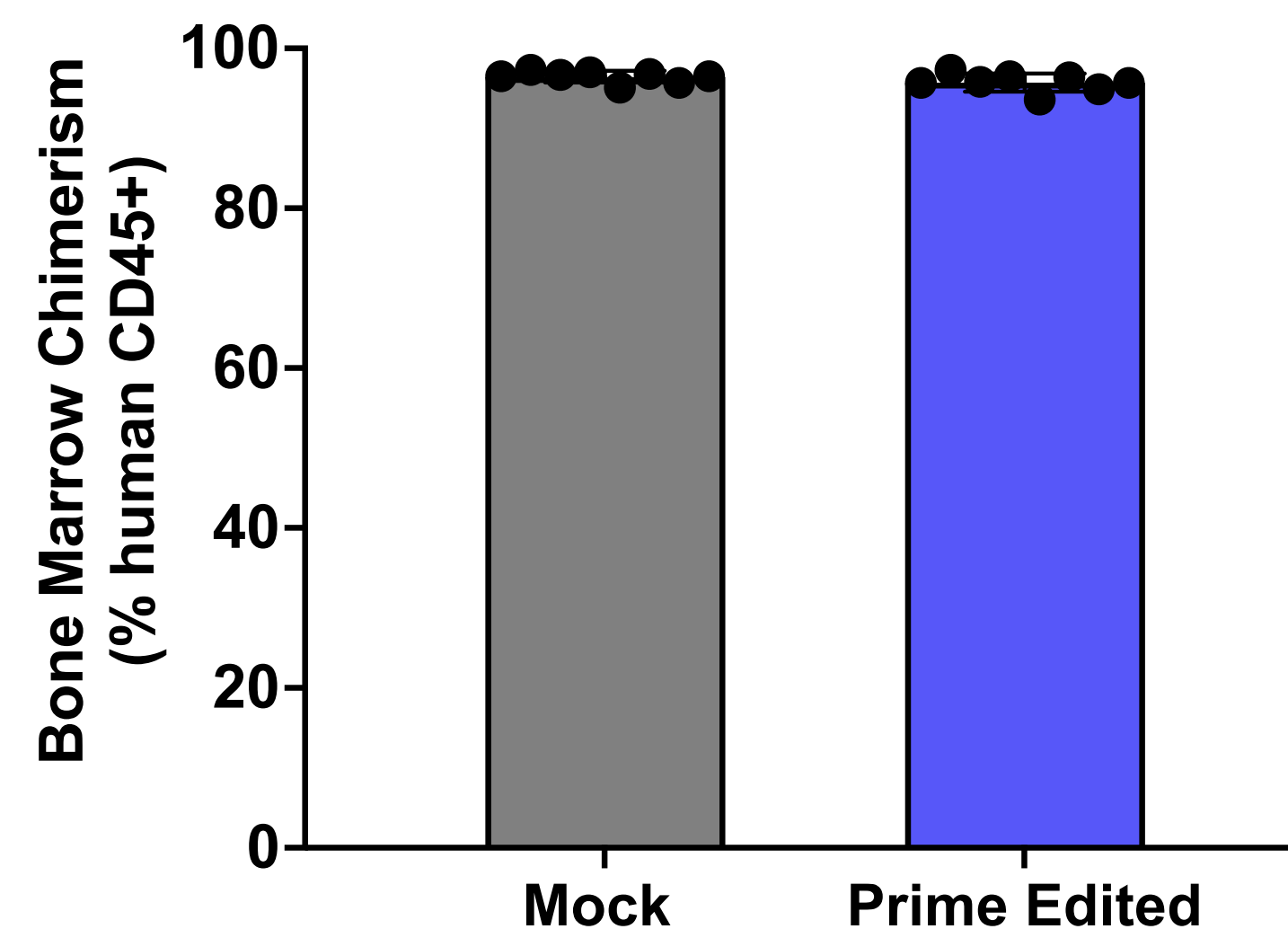
in vivo analysis shows:

>95% human cell engraftment

>90% editing in LT-HSCs



Donor 2

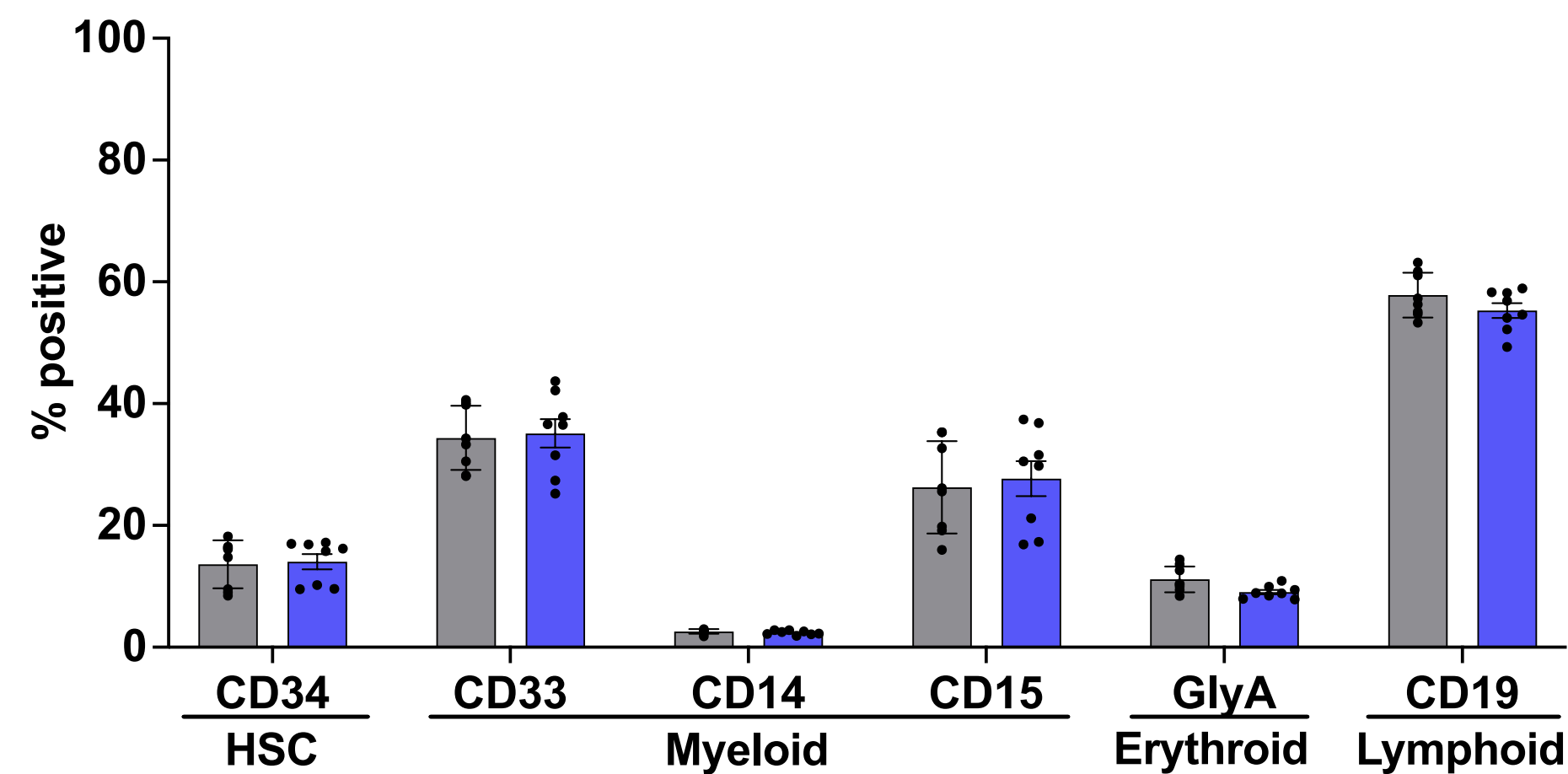


Successful Prime Editing: 16-week engrafted Prime Edited long-term HSCs support multilineage blood production, biodistribution *in vivo*

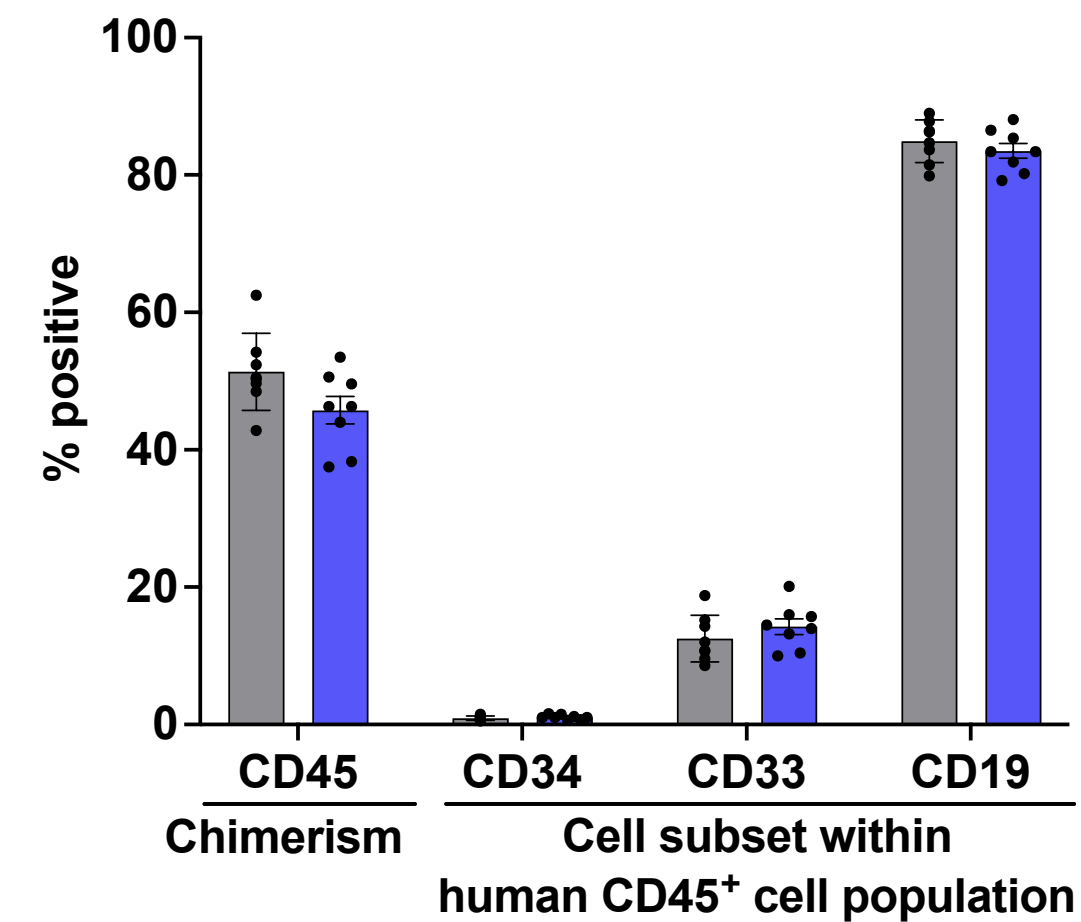
prime_
medicine

No significant difference between mock and Prime Edited LT-HSC in hematopoietic reconstitution

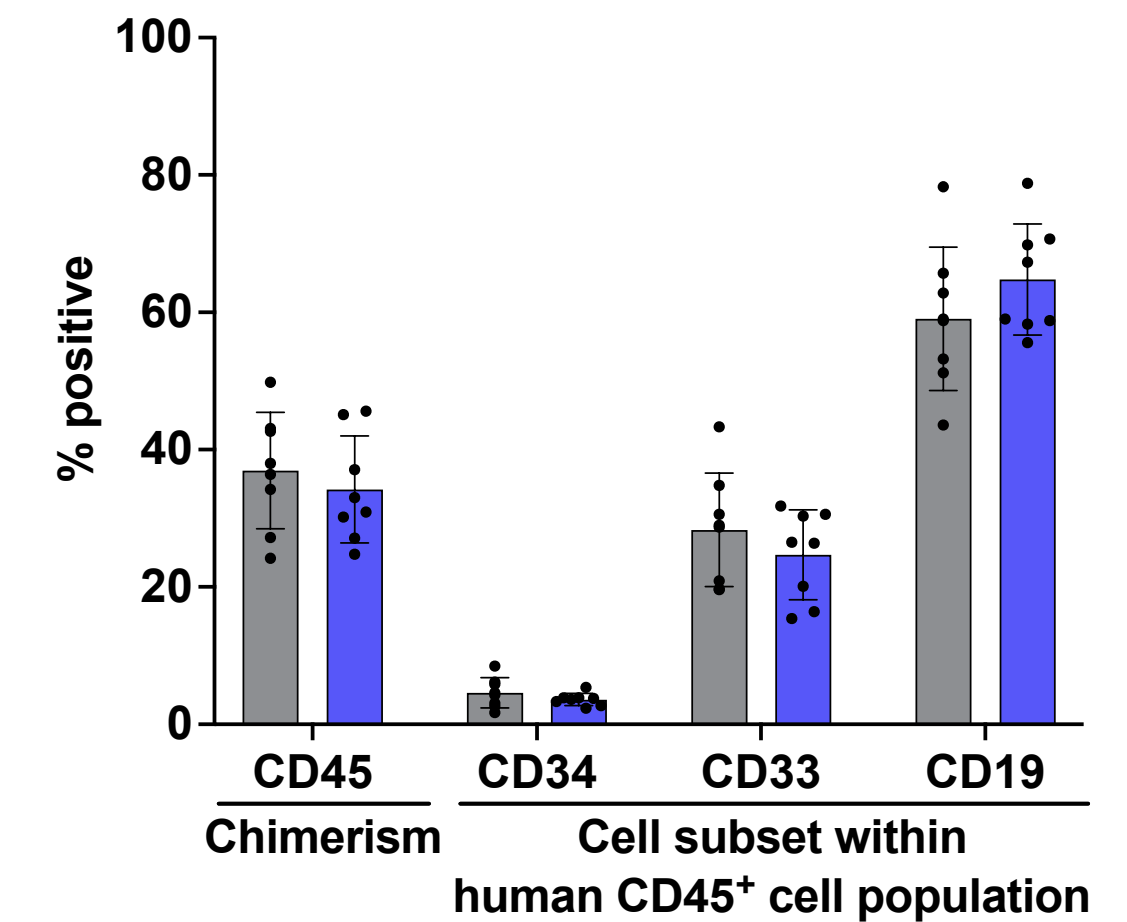
Bone marrow



Spleen



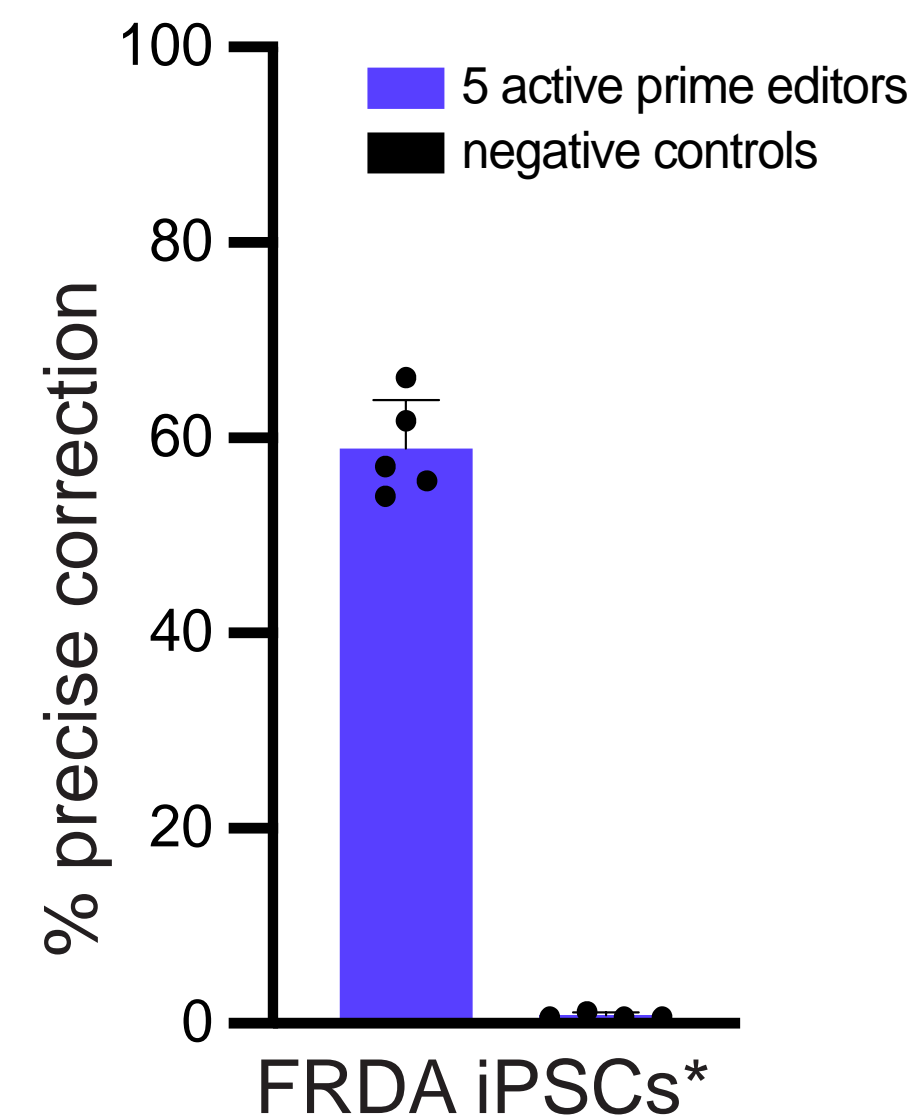
Peripheral blood



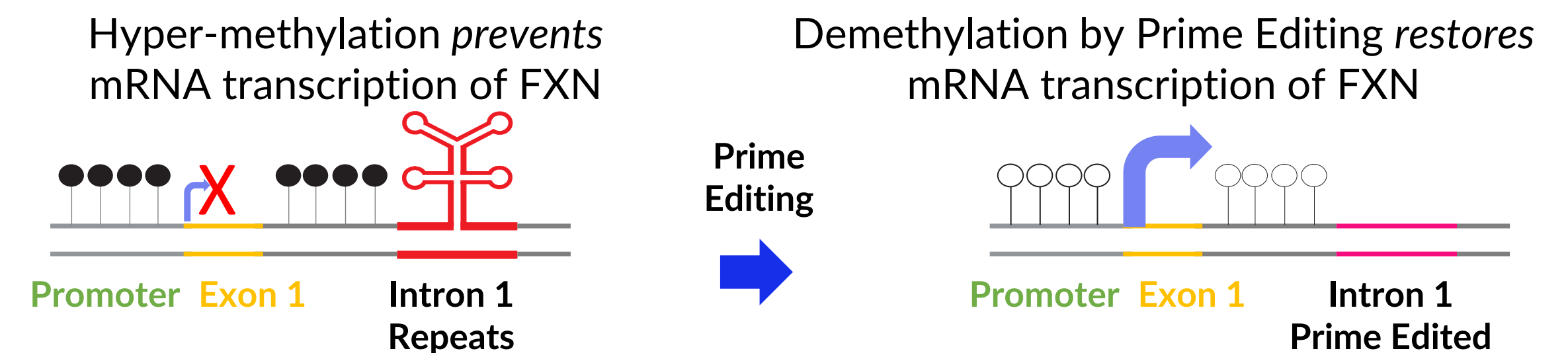
Mock Prime Edited

Successful Prime Editing removal of pathogenic repeats: Friedreich's ataxia

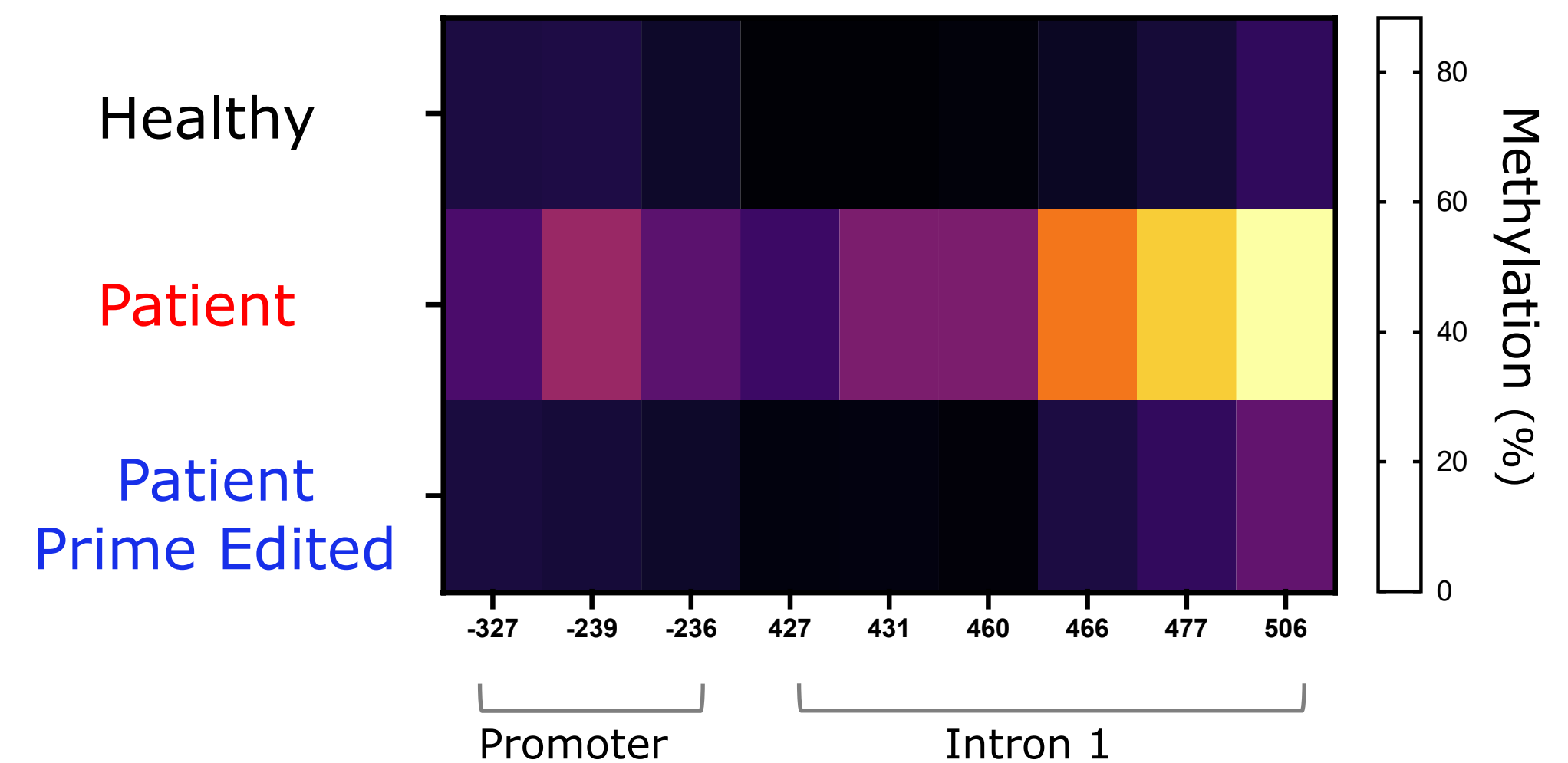
High efficiency Prime Editing removes the GAA pathological repeats and hyper-methylation at the Frataxin (FXN) gene in Friedreich's Ataxia patient cells



- ✓ High efficiency, very precise editing of patient cells without double strand breaks
- ✓ Restores normal methylation of FXN gene



Removal of Hyper-Methylation¹

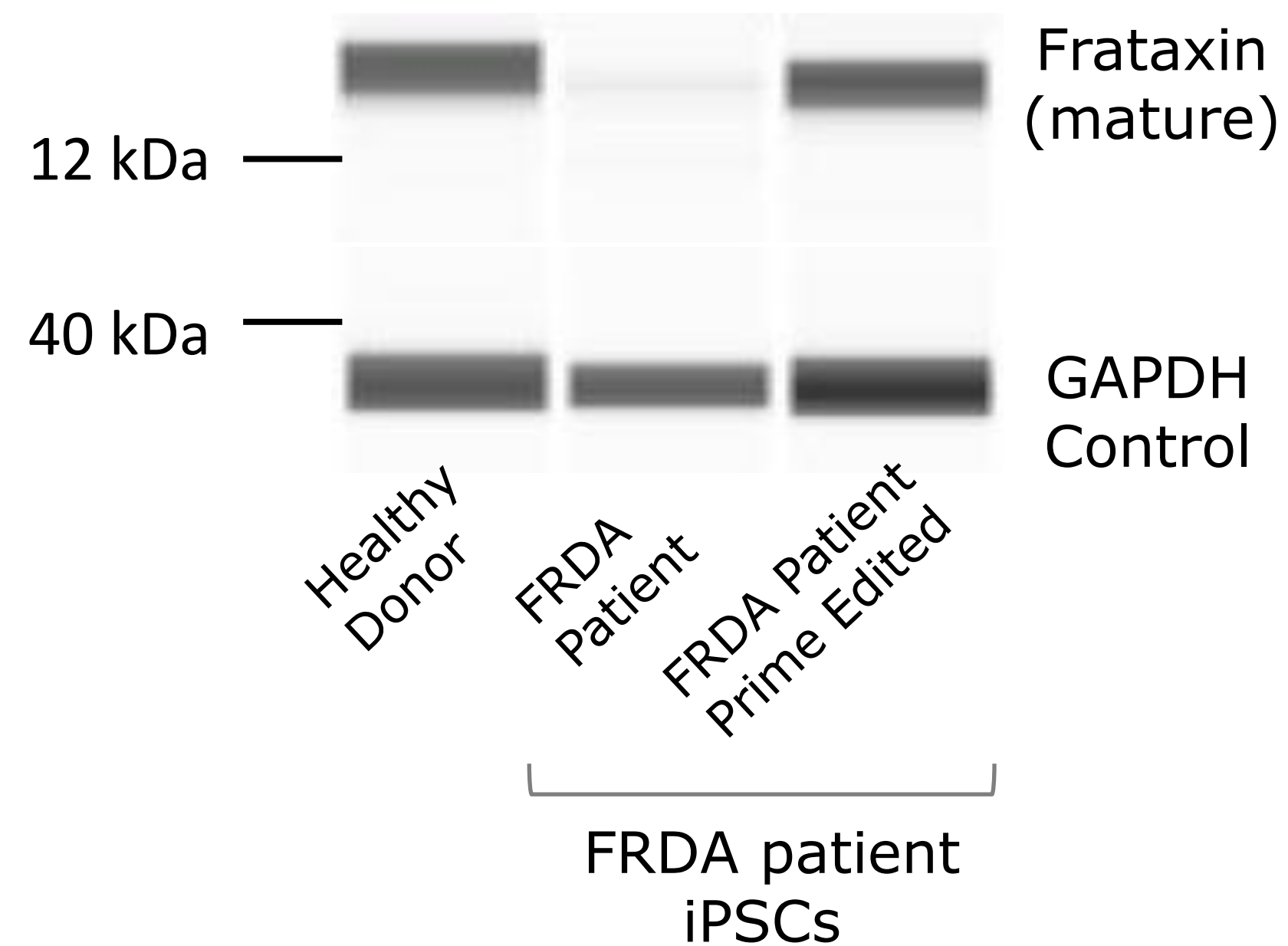


Many repeat expansion diseases exhibit hyper-methylation as a key feature of the underlying pathogenesis

Successful Prime Editing removal of pathogenic repeats

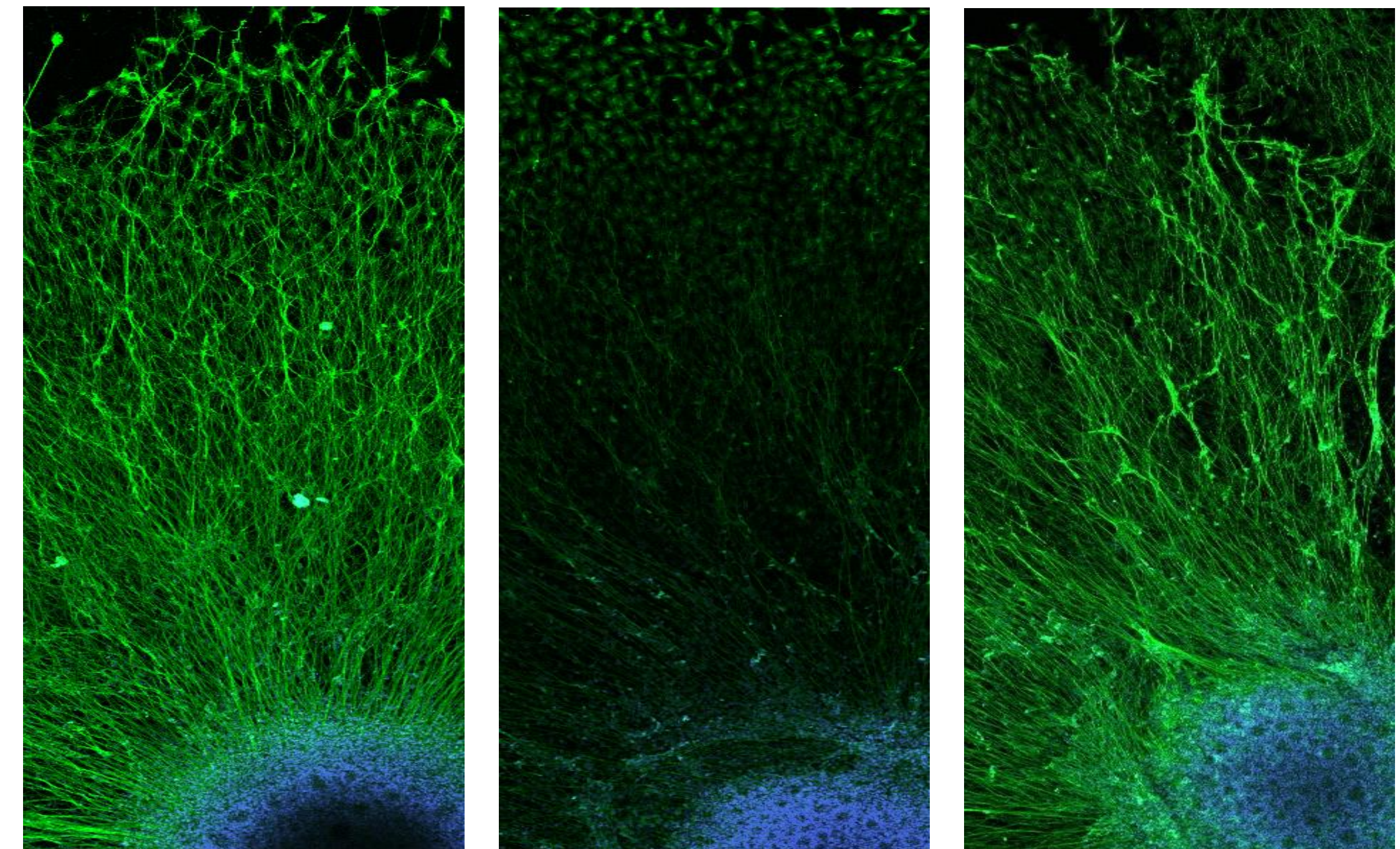
High efficiency Prime Editing restores FXN protein expression and sensory neuron function in Friedreich's Ataxia patients' dorsal root ganglia

Restoration of Frataxin protein expression after Prime Editing



Restoration of axonal projections after Prime Editing

β III-TUB
DAPI



Healthy Donor

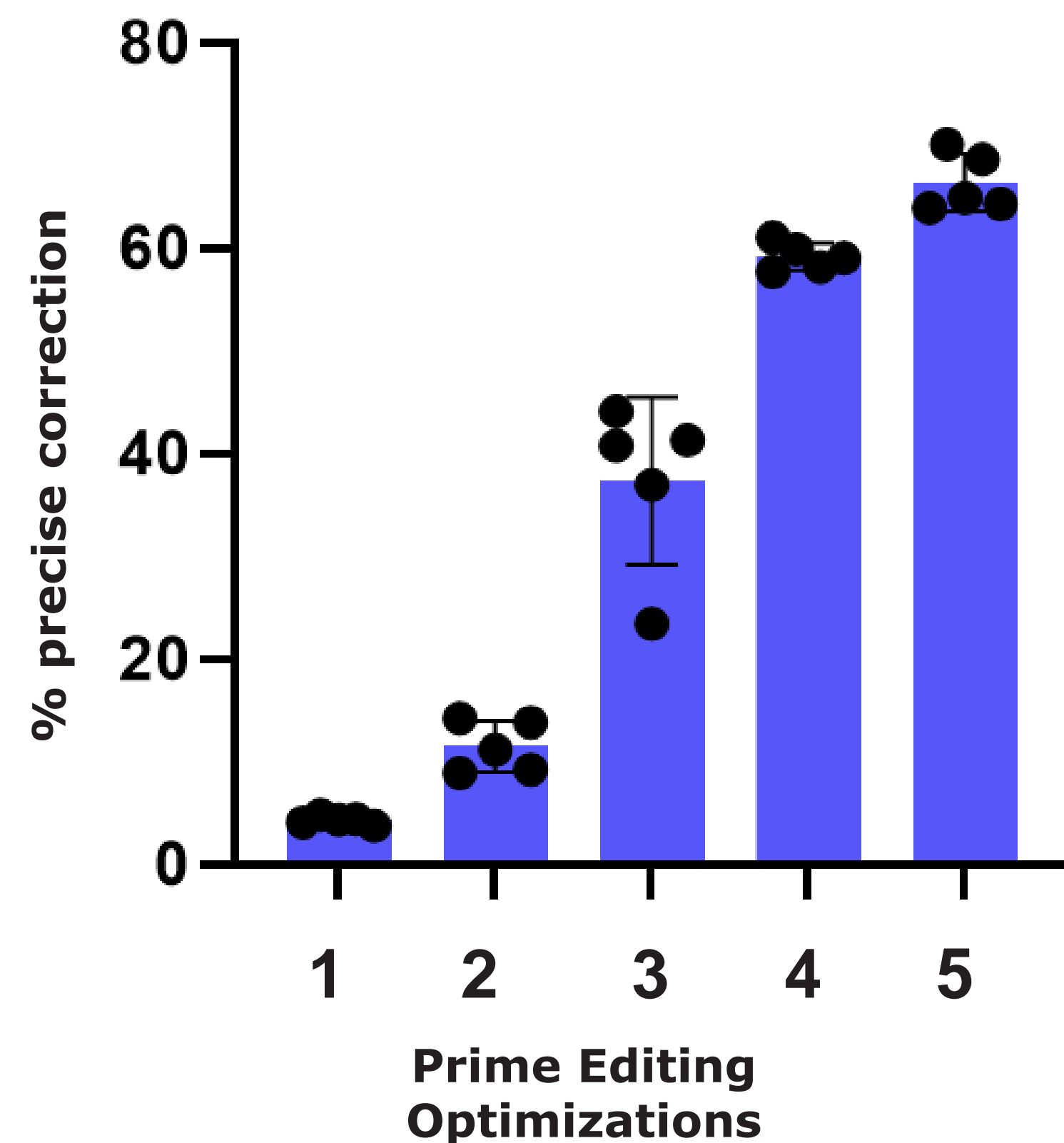
FRDA Patient

FRDA Patient
Prime-Edited

Unmet needs in Cystic Fibrosis: Potential to restore CFTR function in patients with G542X mutation

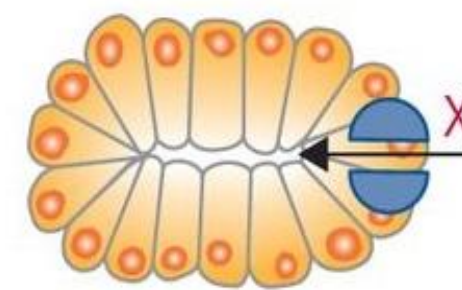
One-time, non-viral delivery to patient intestinal organoids restores CFTR function

Optimization results in high efficiency Prime Editors that precisely correct G542X mutation

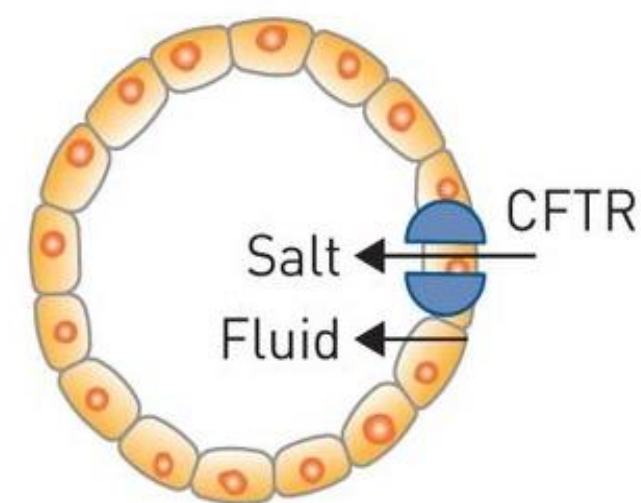


Intestinal organoids swelling assay for CFTR function

Cystic fibrosis



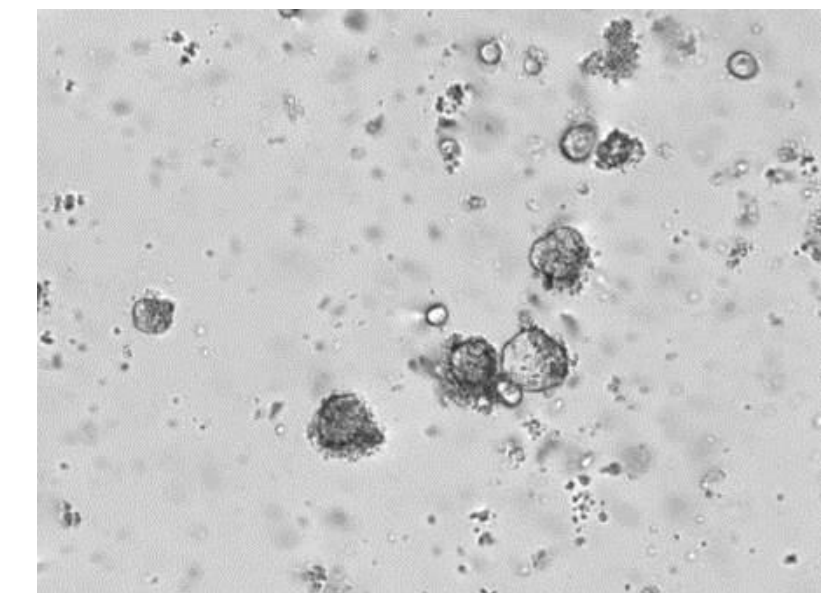
Healthy control



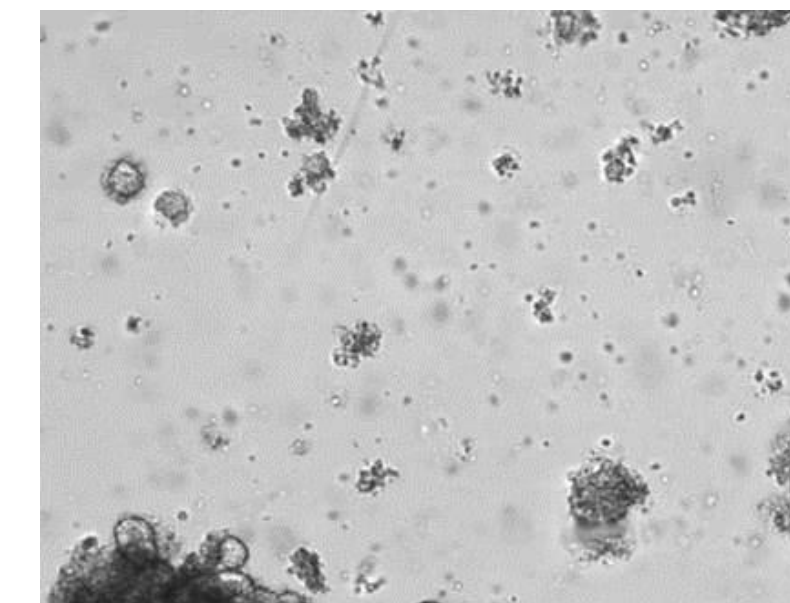
Prime Editing of patient intestinal organoids restores swelling and CFTR function



Healthy control



G542X with mock treatment

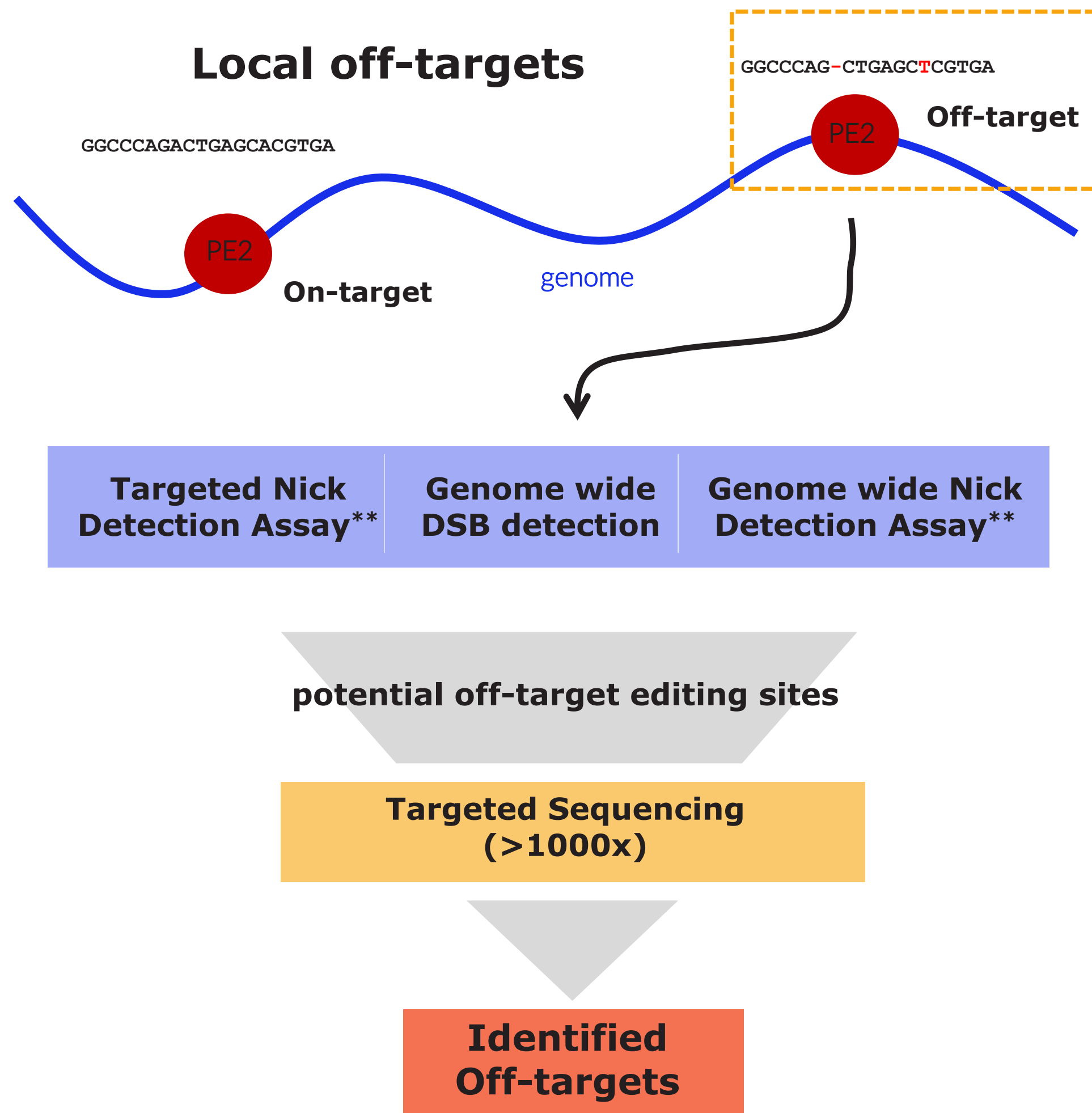


G542X with TRIKAFTA® treatment

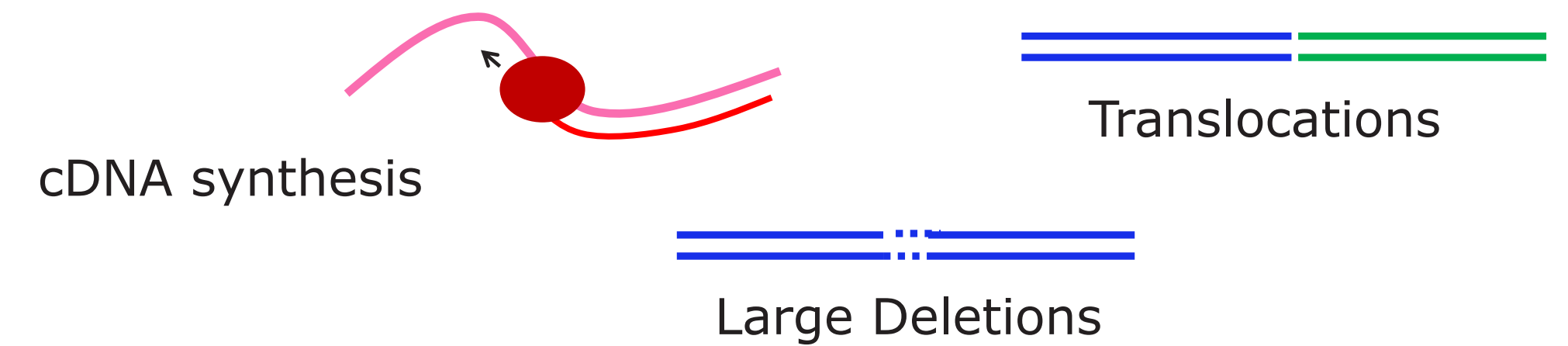


G542X with Prime Editing correction

Safety: Prime's comprehensive suite of assays for off-target discovery*



Chromosome scale or structural off-targets



Reverse Trans. Assay

mRNAseq
PEG integration

Chromosomal Integrity Assays

Imaging

Sequencing based

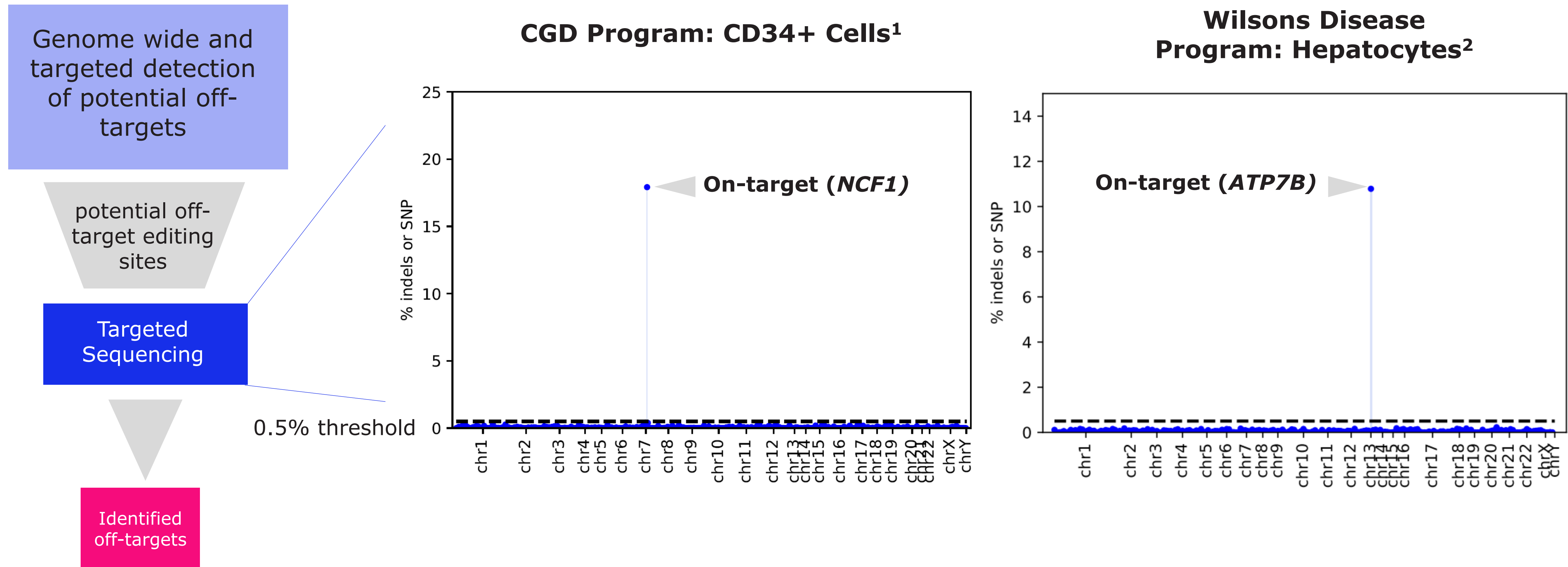
Whole Genome
Sequencing

Vector Integration
Analysis

Identified
Off-targets

Safety: Preliminary off-target analyses demonstrate minimal or no off-target editing

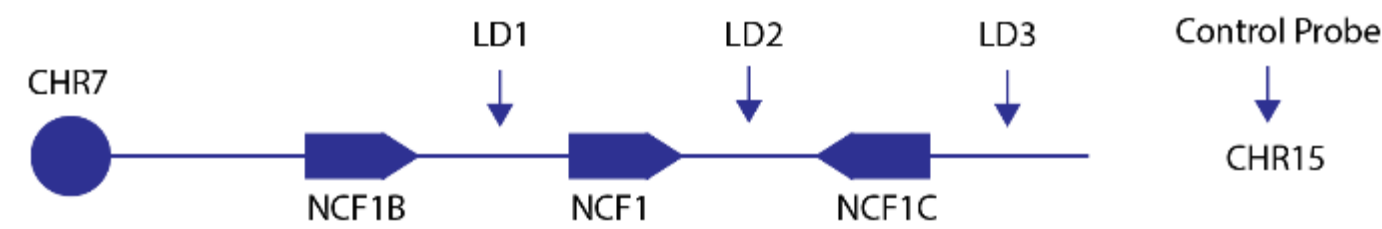
Data expands the demonstration of no off-target editing detected across multiple prime edited cell types



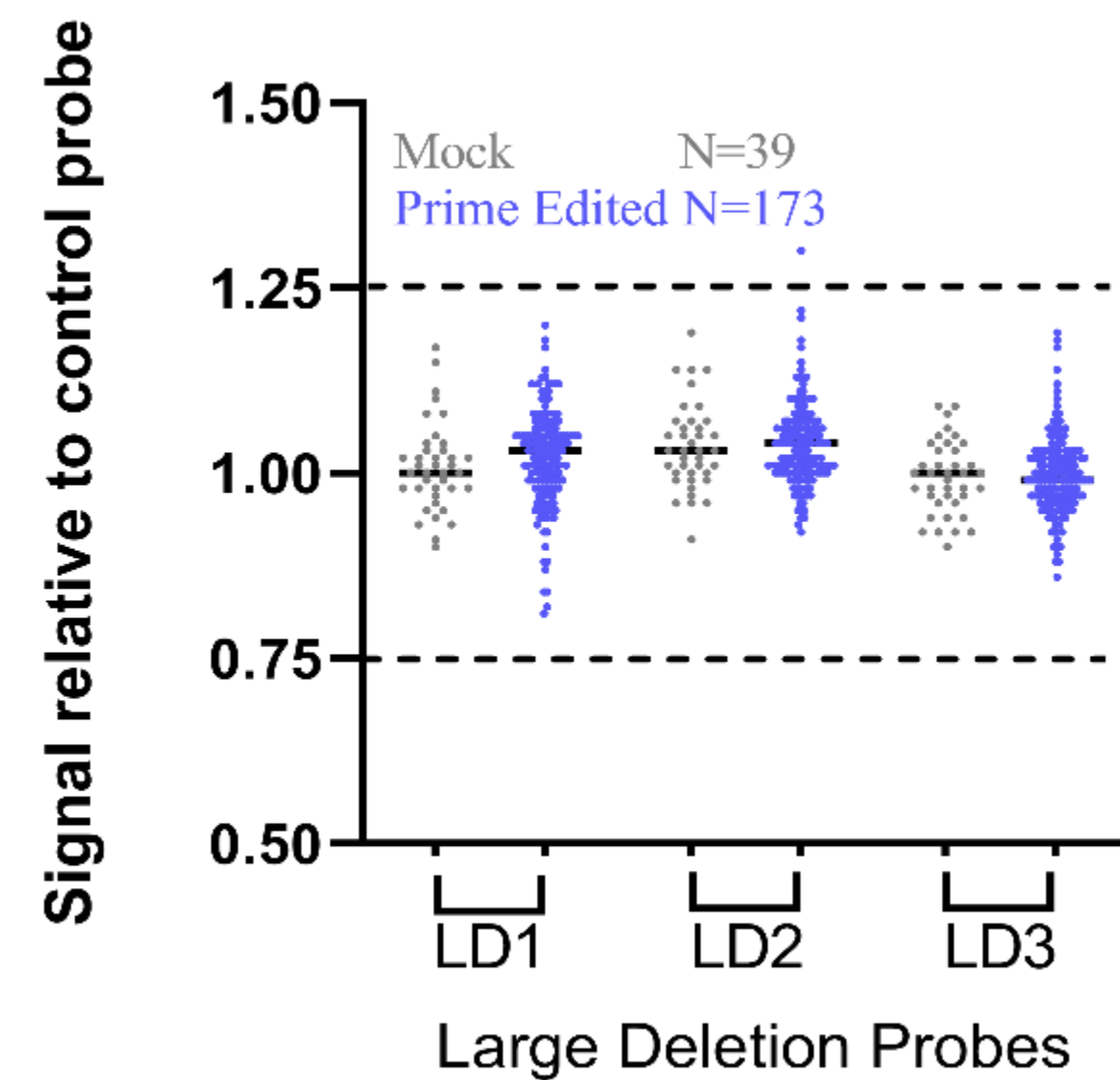
¹Analysis of edited CD34+ cells from CGD program: Targeted Analysis of 550 potential off-target sites of off-target editing. ²Analysis of edited iHEP (iPSG hepatocyte) cells from the Wilsons Disease program: Targeted Analysis of 170 potential off-target sites. SNP: Single nucleotide polymorphisms

Safety: No large deletions or translocations detected in Prime Edited LT-HSCs

Digital PCR Large Deletion Assay

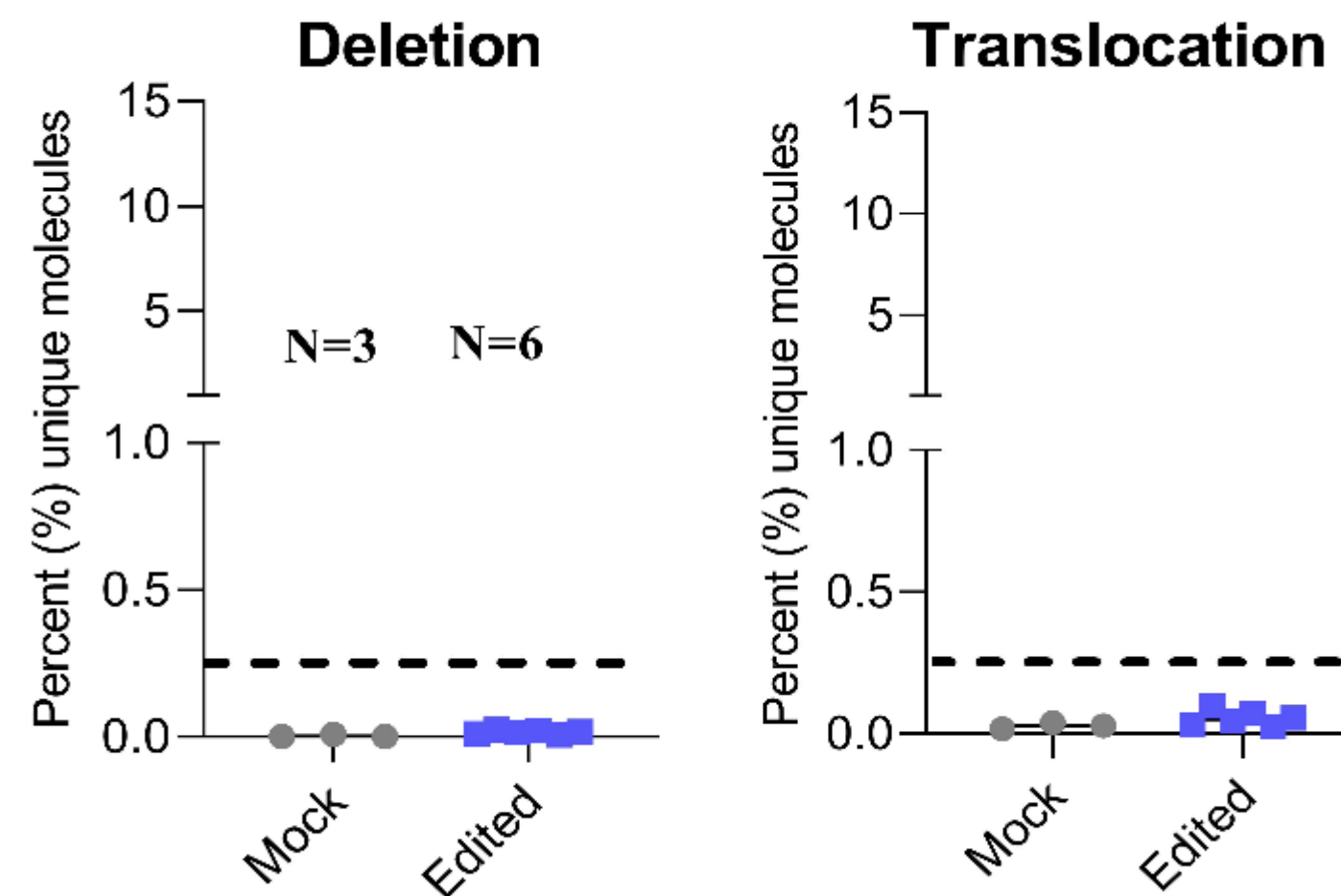


**No large deletions
in pre-infusion CD34⁺ cell clones**

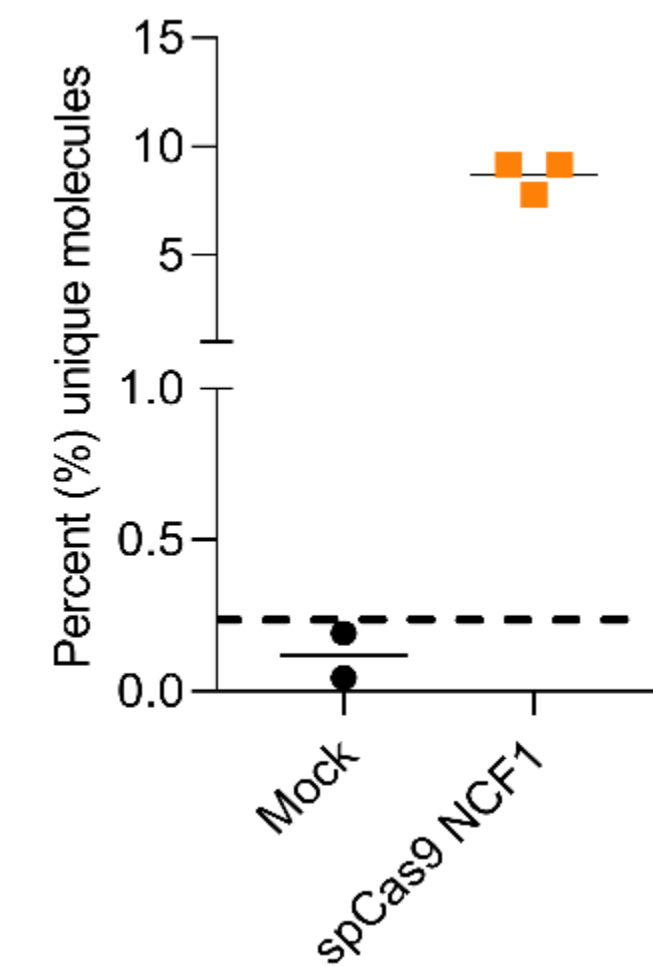


One-sided PCR Chromosomal alterations assay

**No large deletions or translocations in
bone marrow engrafted LT-HSC**



**Translocation Positive Control:
Cas9 nuclease edited cells**



Data from analysis of total human material from mouse bone marrow harvested 16 weeks after engraftment

dPCR: CD34⁺ population was sorted and expanded in colony forming media, individual colonies were picked and presence of the indicated chromosomal segments measured, N=number of colonies measured

One-Sided PCR: total material was amplified using a one-sided pcr protocol to identify genomic sequence changes adjacent to the edit site. Positive control sample was generated by transfecting HEK293T with sgRNA against NCF1 and SpCAS9 mRNA.

Data presented at ASGCT 26th Annual Meeting, May 2023.

LNP Delivery: Optimization of mRNA increases Prime Editing efficiency and leads to reduction of PCSK9 protein in serum

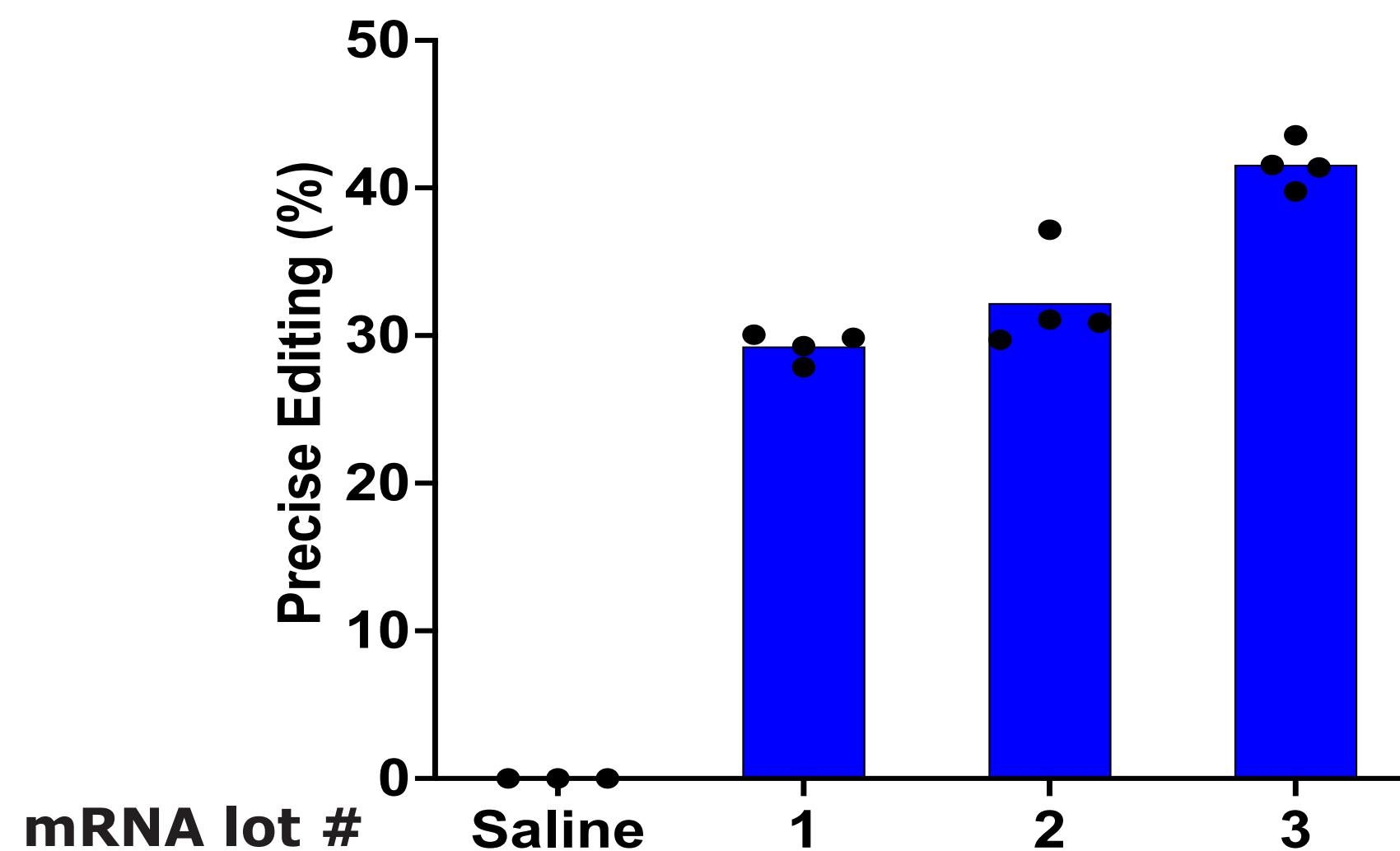
Prime Editor LNP delivered to the liver a **precisely introduced stop codon** in PCSK9 gene in mice

Prime Editor LNP delivered systemically

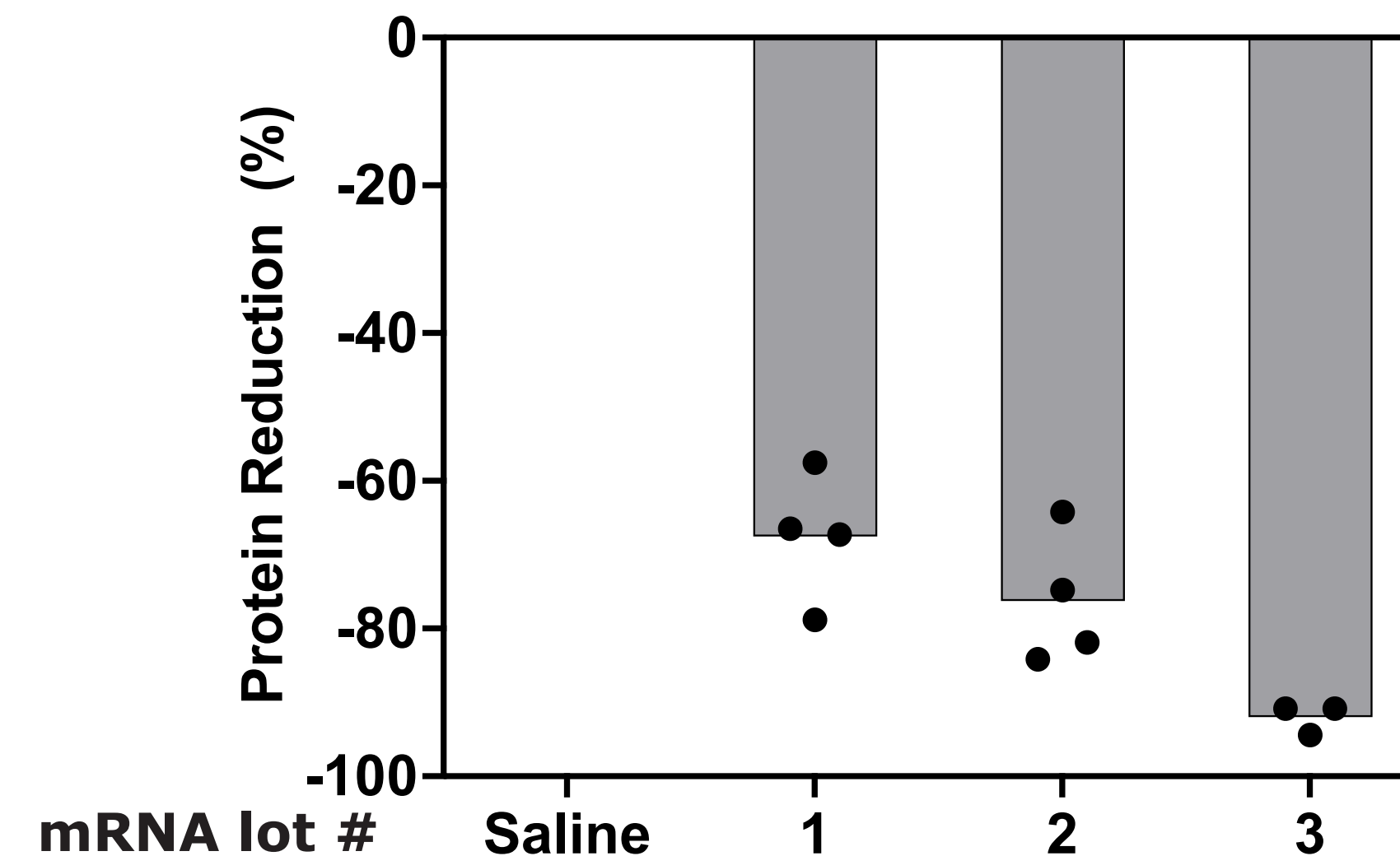
- Prime Editor mRNA
- Prime editor guide RNA



Optimized mRNA
increases Prime Editing



Optimized mRNA
decreases PCSK9 protein



LNP delivery to mice results in 42% PCSK9 Prime Editing and 92% serum protein reduction

Prime Editing Delivery: CSF and Local Administration to CNS via dual AAV achieves high efficiency in mouse brain

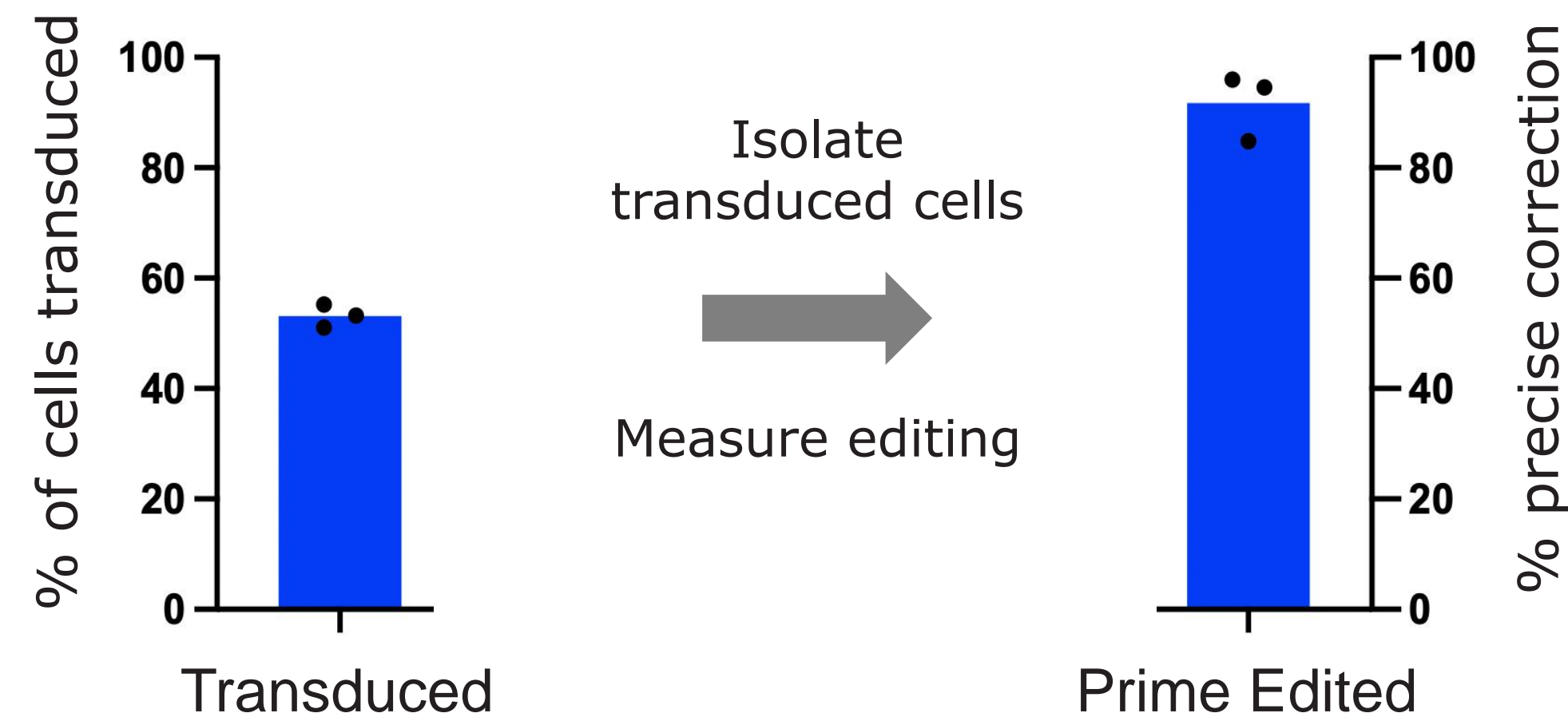
Dual AAV² effectively delivers to ~ 95%, and precisely edits ~80%, of neurons in adult mice

Prime Editor dual AAV

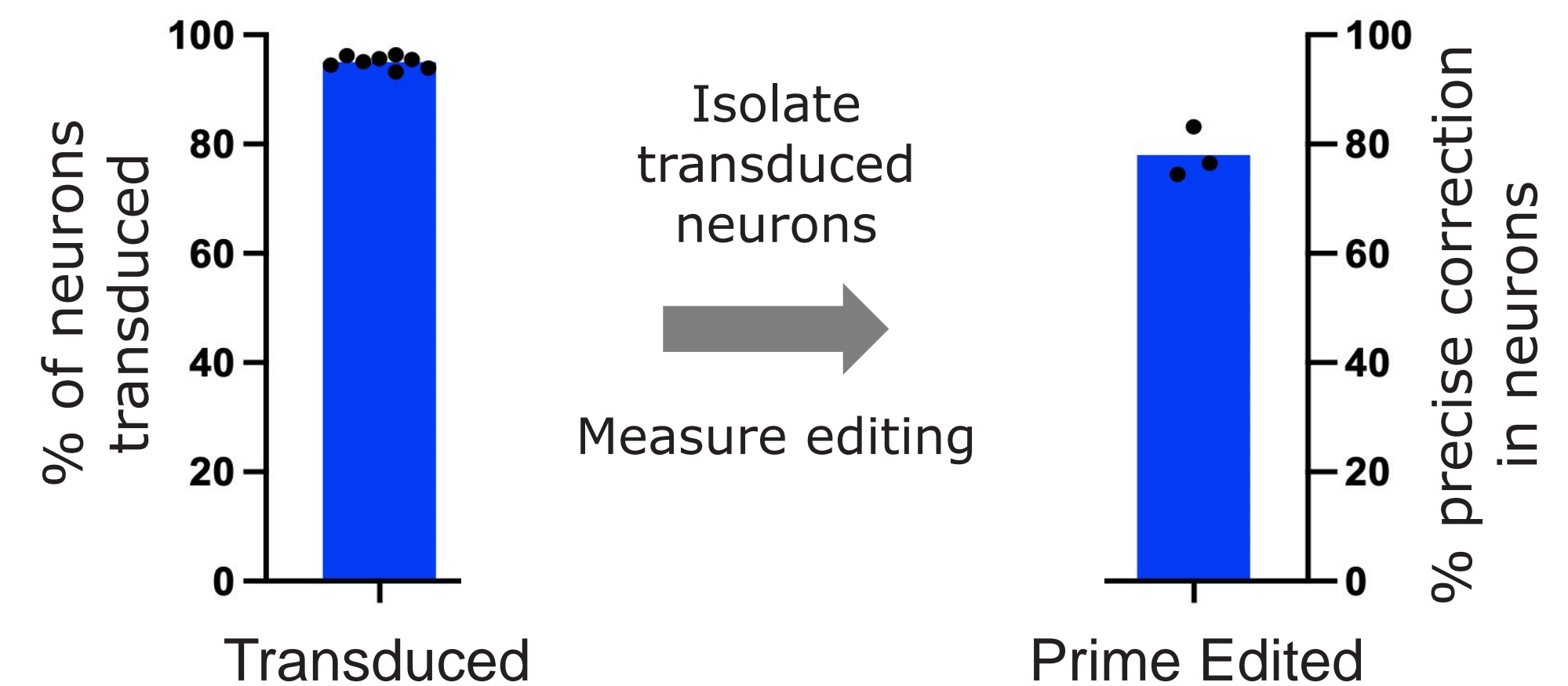
- Prime Editor
- Prime editor dual guide RNA



Neonatal mice – ICV infusion¹
transduced cortex (left) and precisely
edited cortical cells (right)



Adult mice – local administration¹
transduced neurons (left) and precisely
edited neurons² (right)

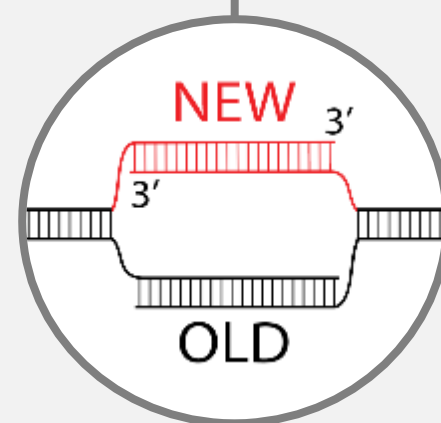
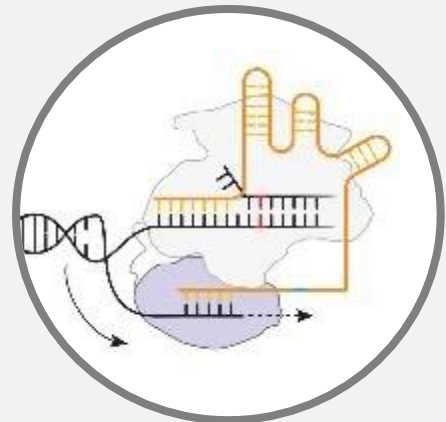


¹Three weeks in neonatal mice via intra-cerebral infusion (ICV); 5 weeks in adult mice via local administration into cerebellum or cortex. ²Prime Editor cassette with neuron-specific promoter. All experiments shown are Proof of Concept delivery experiments using a control Prime Editor site.

Prime Medicine has rapidly advanced and substantially improved Prime Editing

Seminal Prime Editing Publication¹

- All base pair edits, insertions of 40+ bp, deletions of 80+ bp
- Efficiencies ranging from ~10%-60%
- Targeted introduction of recombinase site

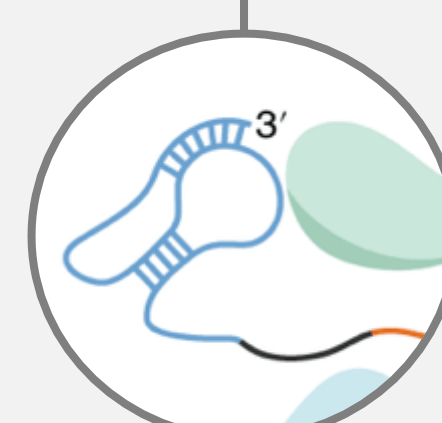
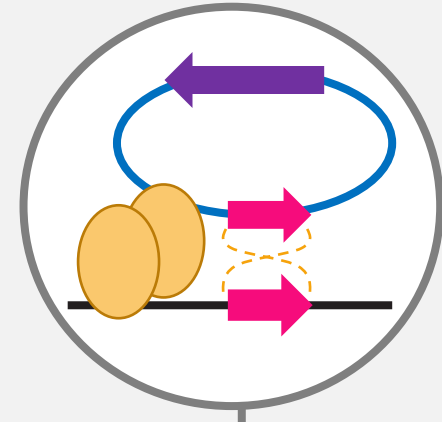


Dual Flap Prime Editing²

- Efficiencies $\geq 80\%$
- Hotspot editing and larger insertions
- Synergies with recombinase enzymes (>5-kb targeted DNA integration)

PASSIGE System

- Advanced PE+ recombinase approach
- Targeted whole gene insertions with up to 60% efficiency

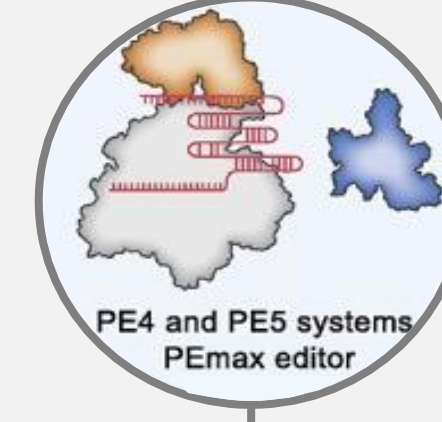


Engineered pegRNAs⁴

- Improved pegRNA stability
- Up to 4-fold increase in editing

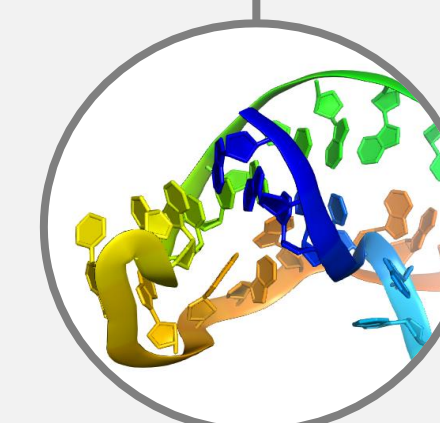
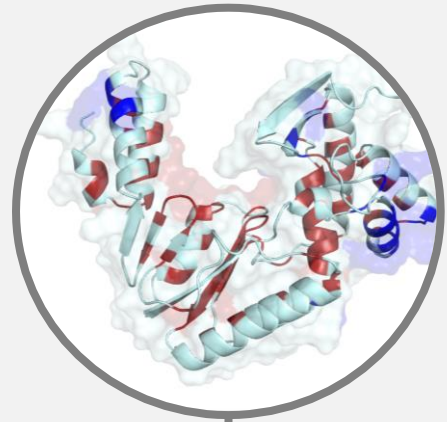
PE4, PE5, and PEmax³

- Up to 7-fold increase in editing
- Up to 2-fold decrease in byproducts



Novel PE Proteins

- 80+ active RT domains
- RT domains up to 60% smaller
- Up to 2-fold increase in editing



pegRNA Enhancements

- New classes of efficiency-increasing pegRNAs enhancements

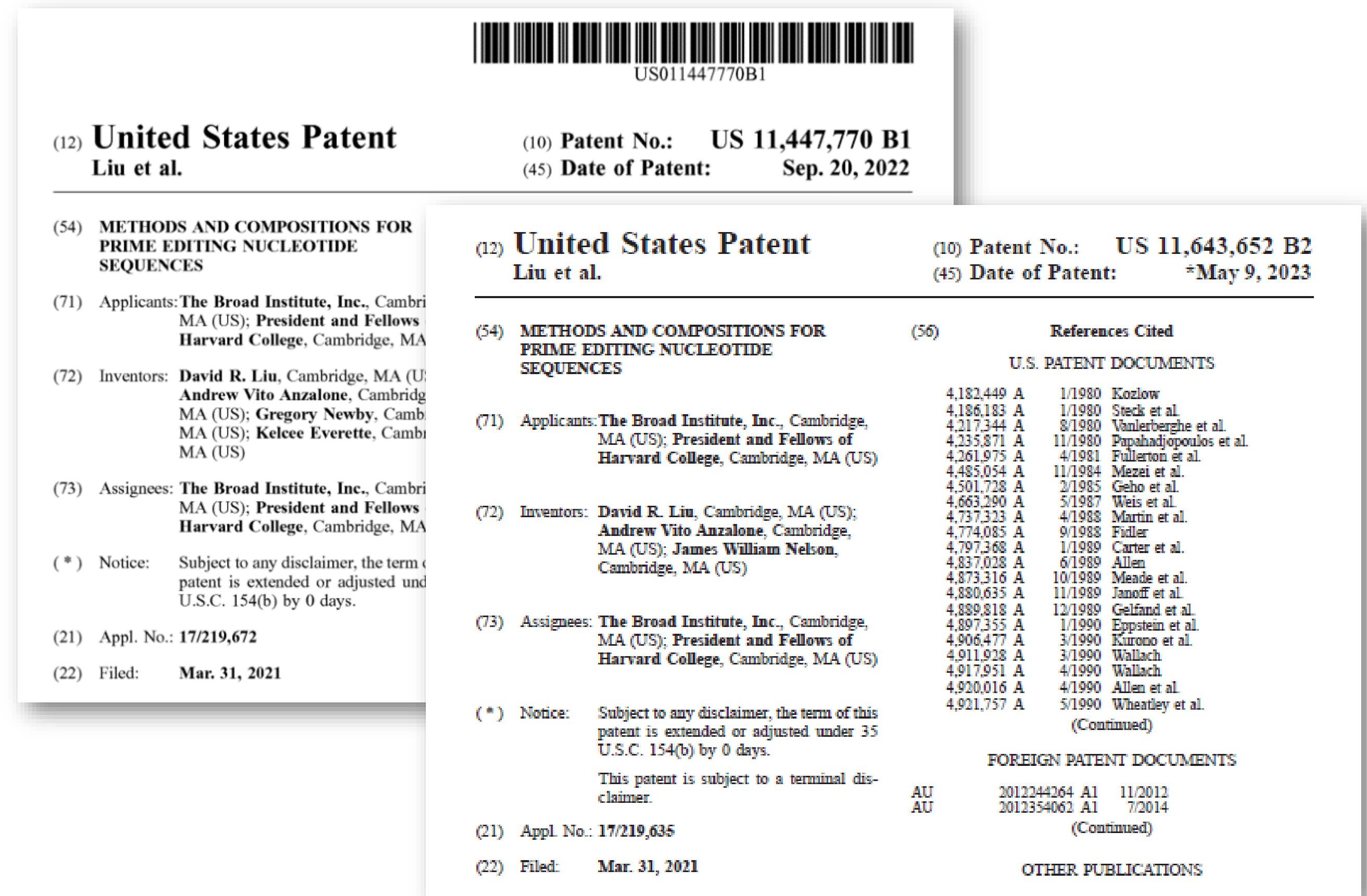
Prime Medicine holds foundational IP for Prime Editing

Committed to securing broadest IP protection for platform technology, programs and advances

Patent portfolio includes:

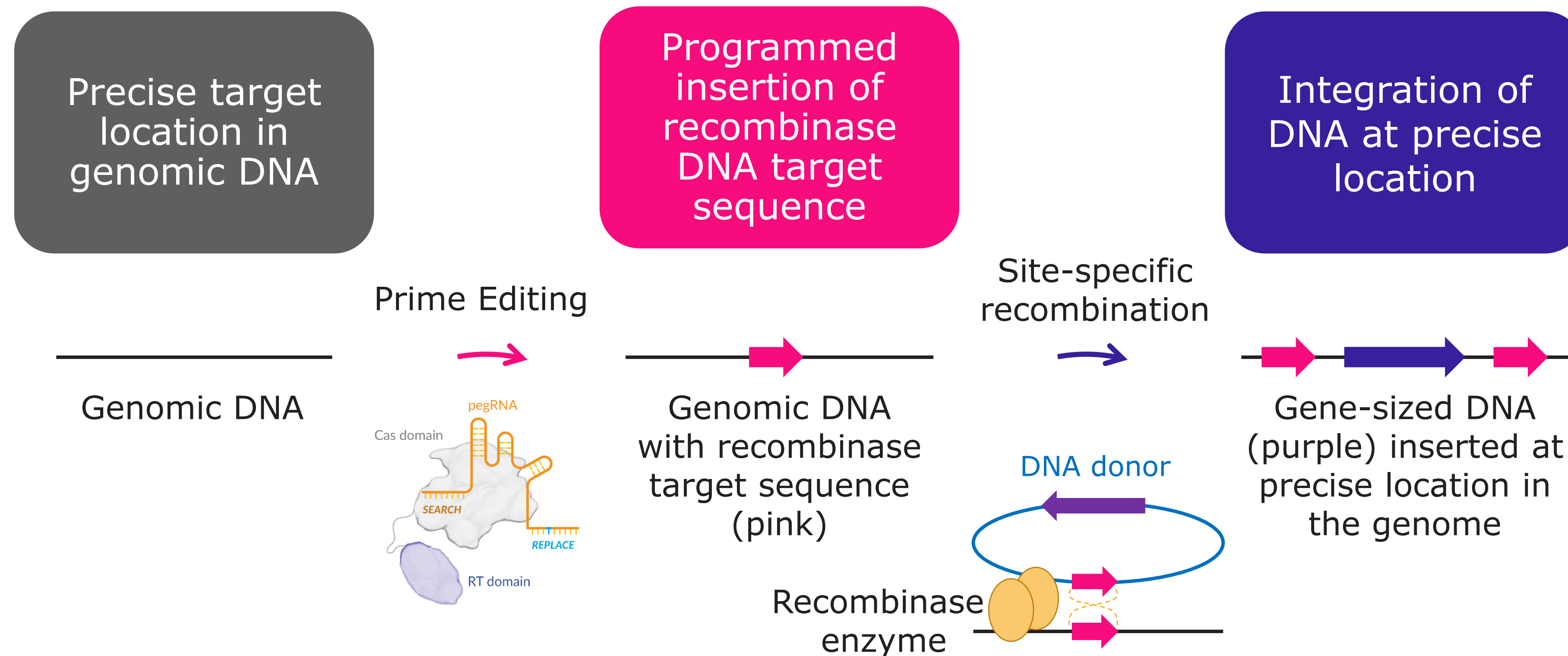
- U.S. Patent 11,447,770, covering methods of using Prime Editors
- U.S. Patent 11,643,652, covering composition of matter for Prime editor guide RNAs (PEgRNAs)
- U.S. allowed application 17/751,599, covering Prime Editing systems that include PEgRNA, Prime Editor protein and, optionally, recombinase (expected to issue Q2-Q3 2023)

Prime Medicine has filed for additional IP protection for technological advancements



Prime Assisted Site-Specific Integrase Gene Editing

PASSIGE™: Applying Prime Editing to insert gene sized sequences precisely in the genome



One step non-viral kilobase-size gene editing approach – without double stranded breaks

PASSIGE: Efficient insertion of anti-CD19 CAR at the *TRAC* locus in human primary T cells

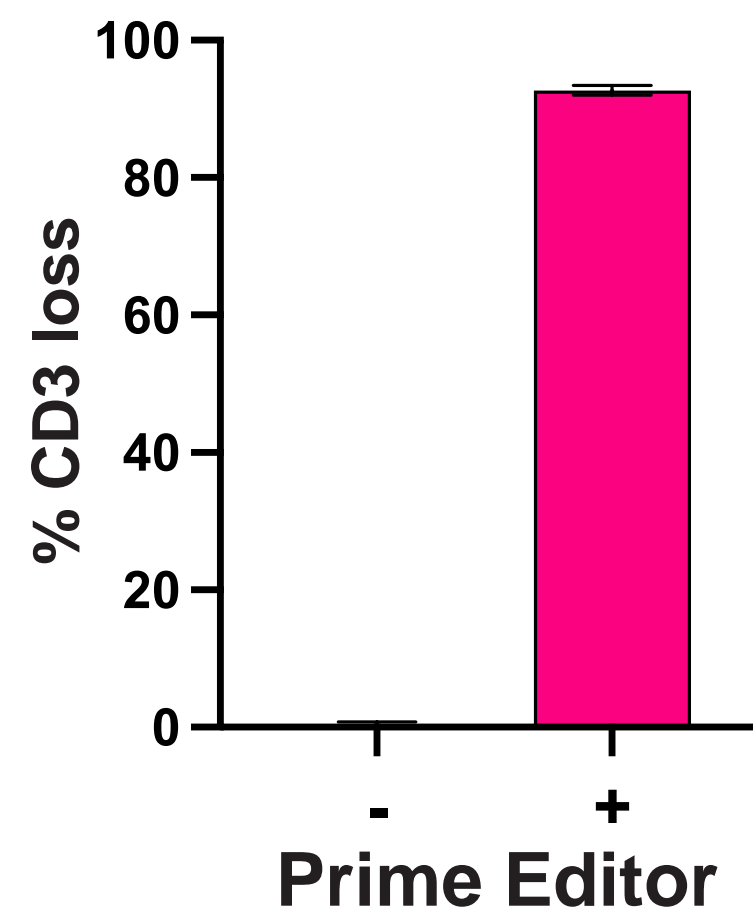
PASSIGE **one-step non-viral** approach for precise introduction of genetic cargo into the genome

Prime Editing to insert **recombinase site**

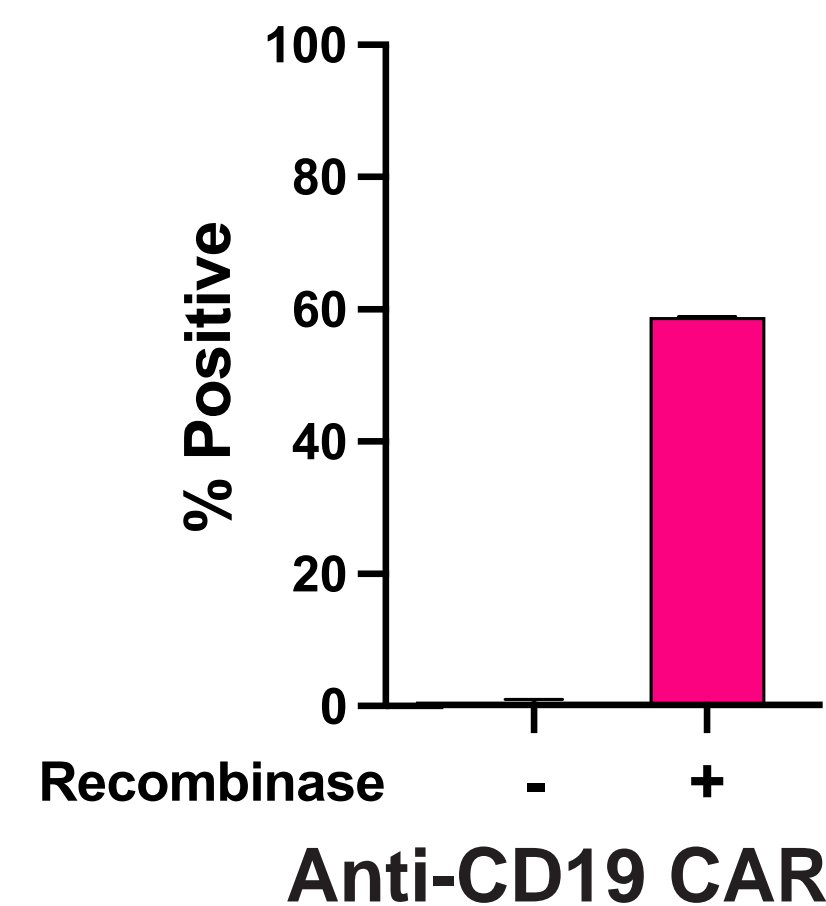
Recombinase to integrate **anti-CD19 CAR**



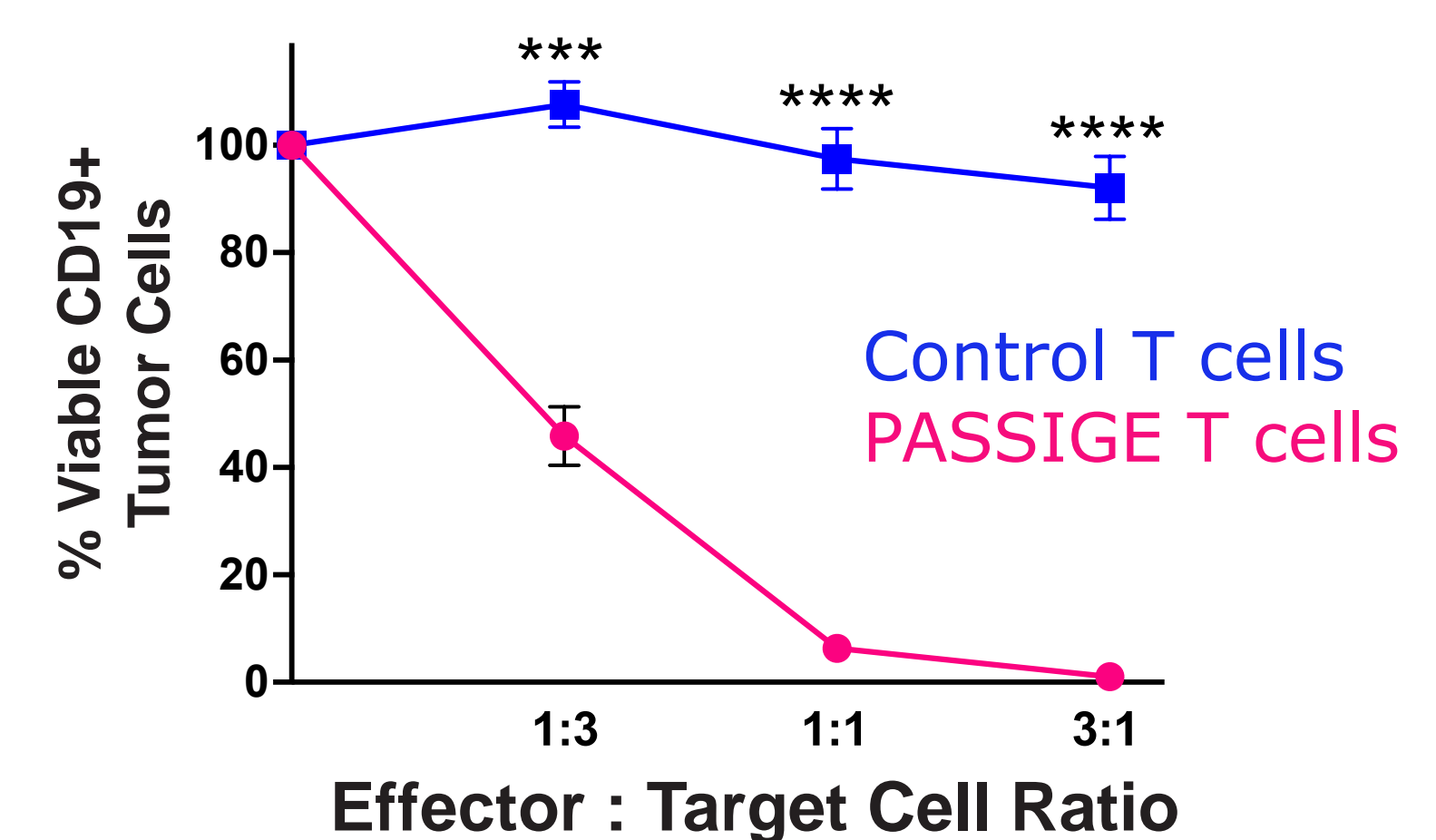
Insertion of recombbinase site - over 90% efficiency



Integration of CAR at *TRAC* in 60% of T cells



Tumor cell killing at 72 hours

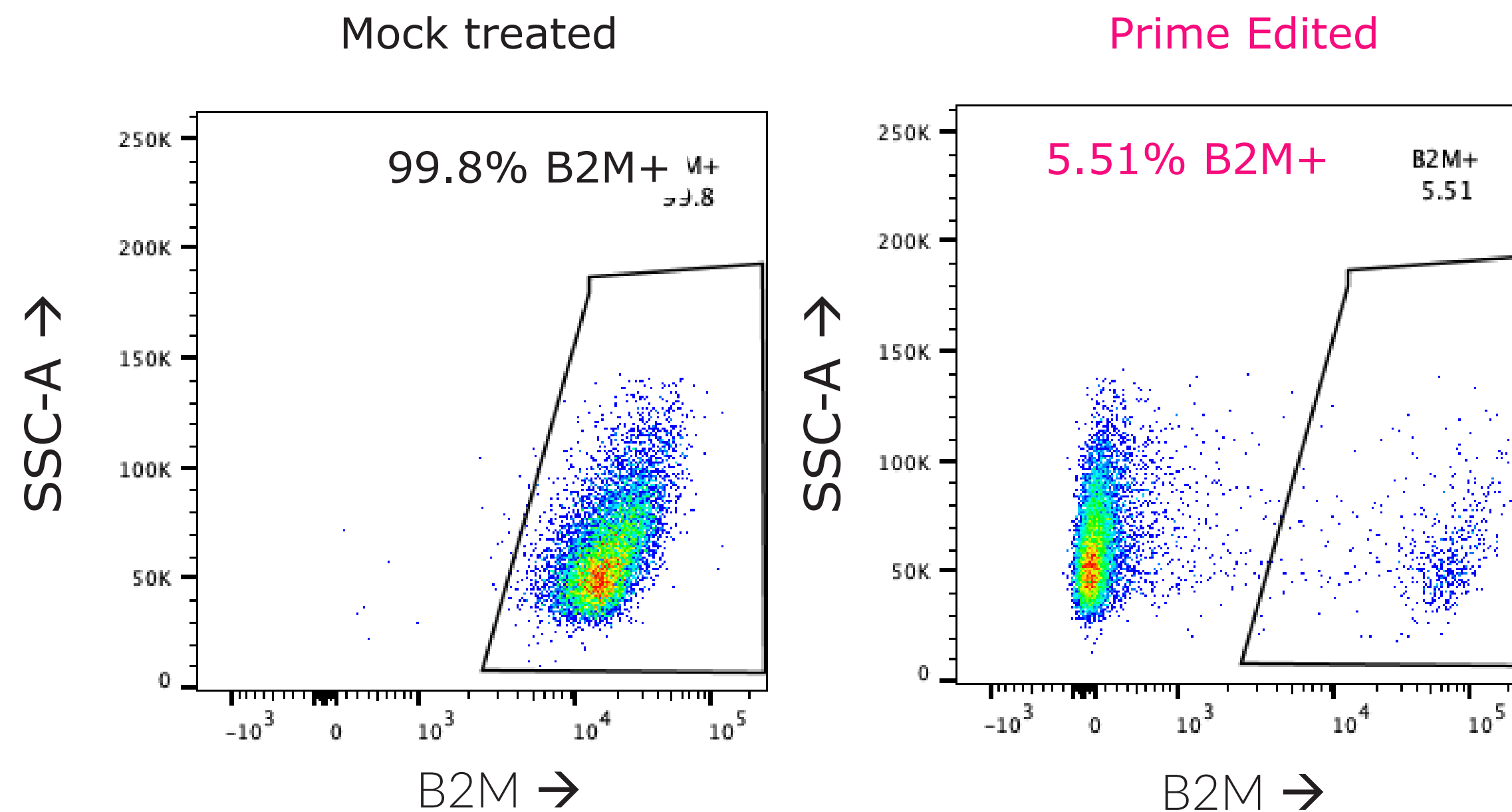


Targeted integration of the anti-CD19 CAR provides potent tumor killing function

PASSIGE: Knockout of *B2M* can be achieved in 95% of Prime-Edited T cells and PASSIGE CAR-T cells reduce tumor burden *in vivo*

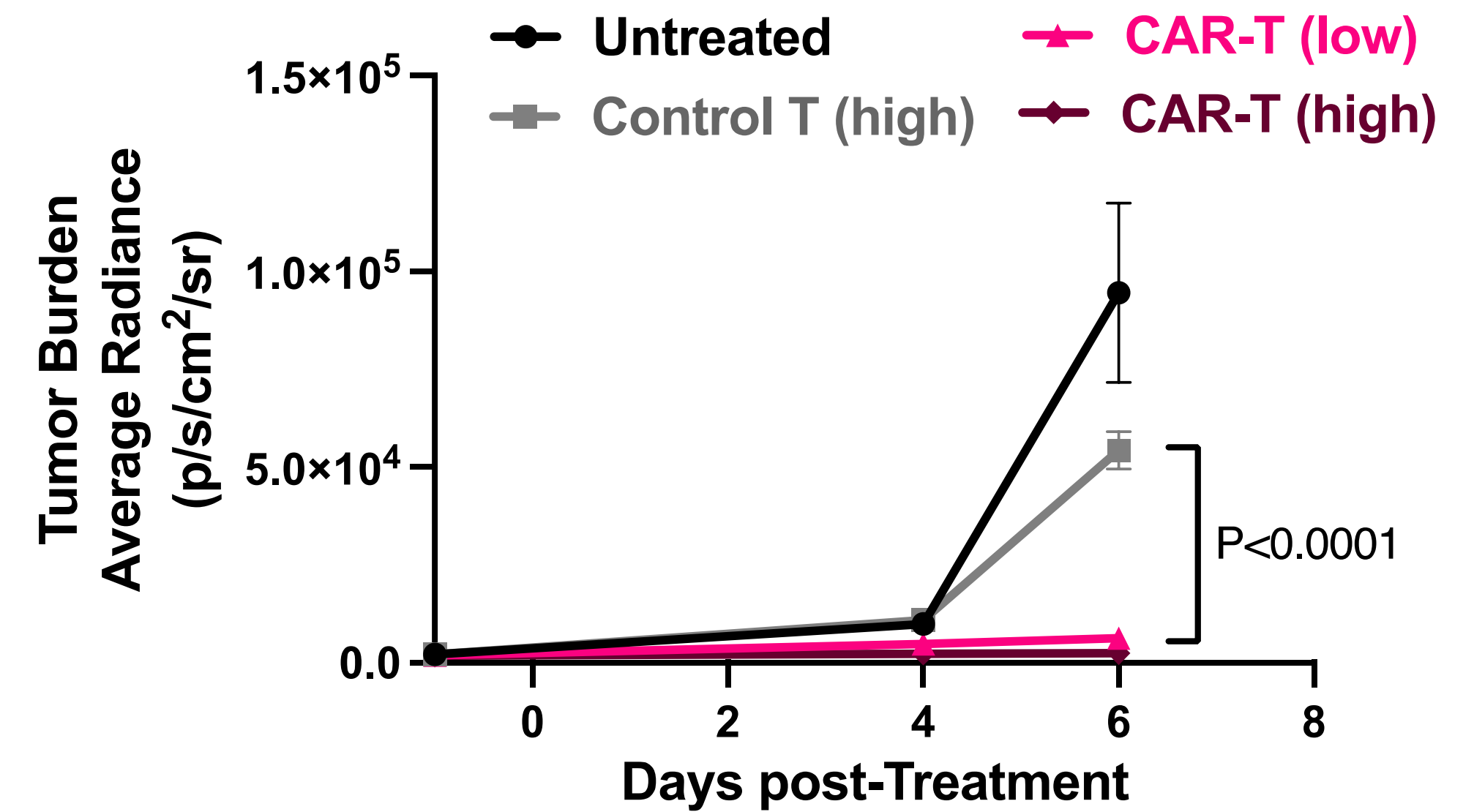
Prime Editing technologies can be used to introduce multiple genomic modifications in cell therapies

$\beta 2$ microglobulin expression on day 7 post-EP



Knockout with Prime Editing is efficient in T cells and can be done in multiplex

Anti-CD19 CAR-T cells generated with PASSIGE show reduce tumor burden *in vivo*



Business Development and Partnering: A major focus for 2023

We aim to maximize PE's broad therapeutic potential and create value by:

1

Independently developing and commercializing in **appropriate disease areas** (our pipeline)

2

Entering strategic collaborations to **extend the reach and impact of PE, provide funding**, and create value in areas we may not enter ourselves in the near-term but may enter later

3

Partnering and licensing to access **enabling technologies**, including delivery, manufacturing and technologies synergistic with Prime Medicine products

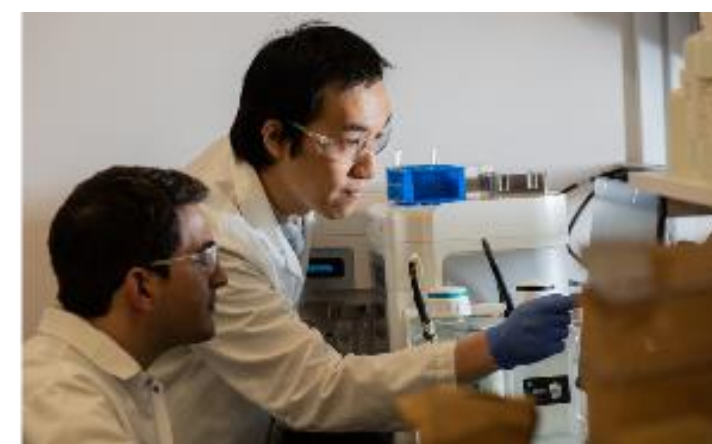
This strategy aims to **fully exploit the richness of our potential to create programs and address indications**, while **focusing our internal resources** on what we do best, ultimately accelerating our efforts to translate PE into new medicines for patients worldwide.

Building the Company

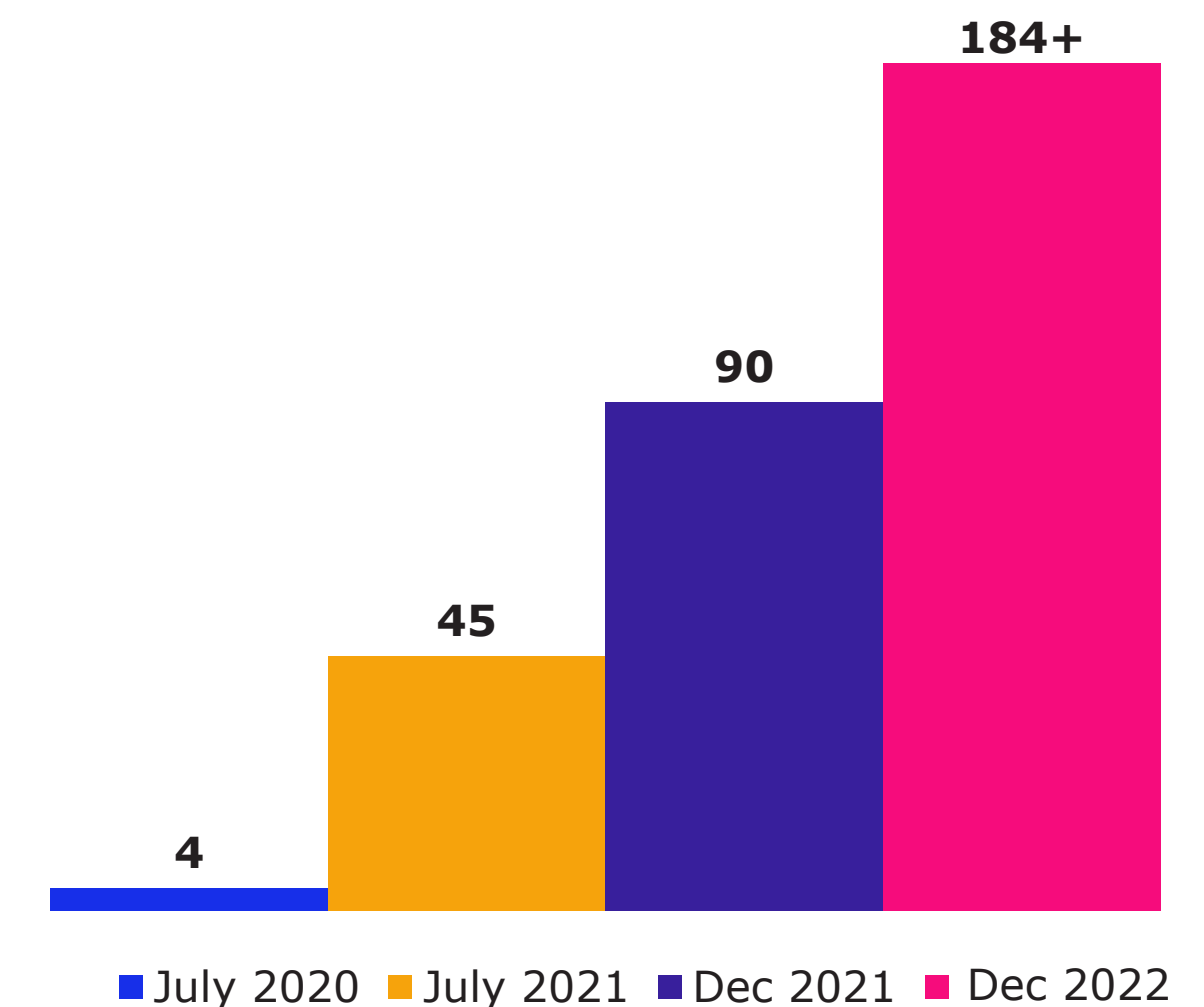
Currently

- ~200 employees; approximately 85% across Research & Technical Development
- Key leadership and staff across all departments of the organization in place
- Built out core capabilities across the company, from IP strategy to automation and AI to RNA technologies
- Established strong external relationships
- 3 locations in Cambridge, MA and a chemistry facility in Watertown, MA, with buildout of 150,000 square feet permanent space in an additional Cambridge facility, target for move in 2024
- Successful IPO in Oct 2022, with >\$500M raised to date

Critical Milestones Achieved



Successful Growth of Talent



¹ Anzalone et al., Nature, 2019

Key upcoming events will continue to drive the Prime Medicine platform forward

Summary of select ongoing activities and next steps for Prime Medicine

Pipeline

- ✓ Nominated first Development Candidate for Chronic Granulomatous Disease (CGD) in 1Q 2023.
- Initiate investigational new drug (IND)-enabling studies in CGD in 2023.
- Expand preclinical proof-of-concept *in vivo*, including sharing data from *in vivo* rodent studies and large animal studies in several programs in 2H 2023.
- Share *in vitro* preclinical data in additional liver, eye and neuromuscular programs.
- First IND filing expected as early as 2024 and additional IND filings anticipated in 2025.

Platform

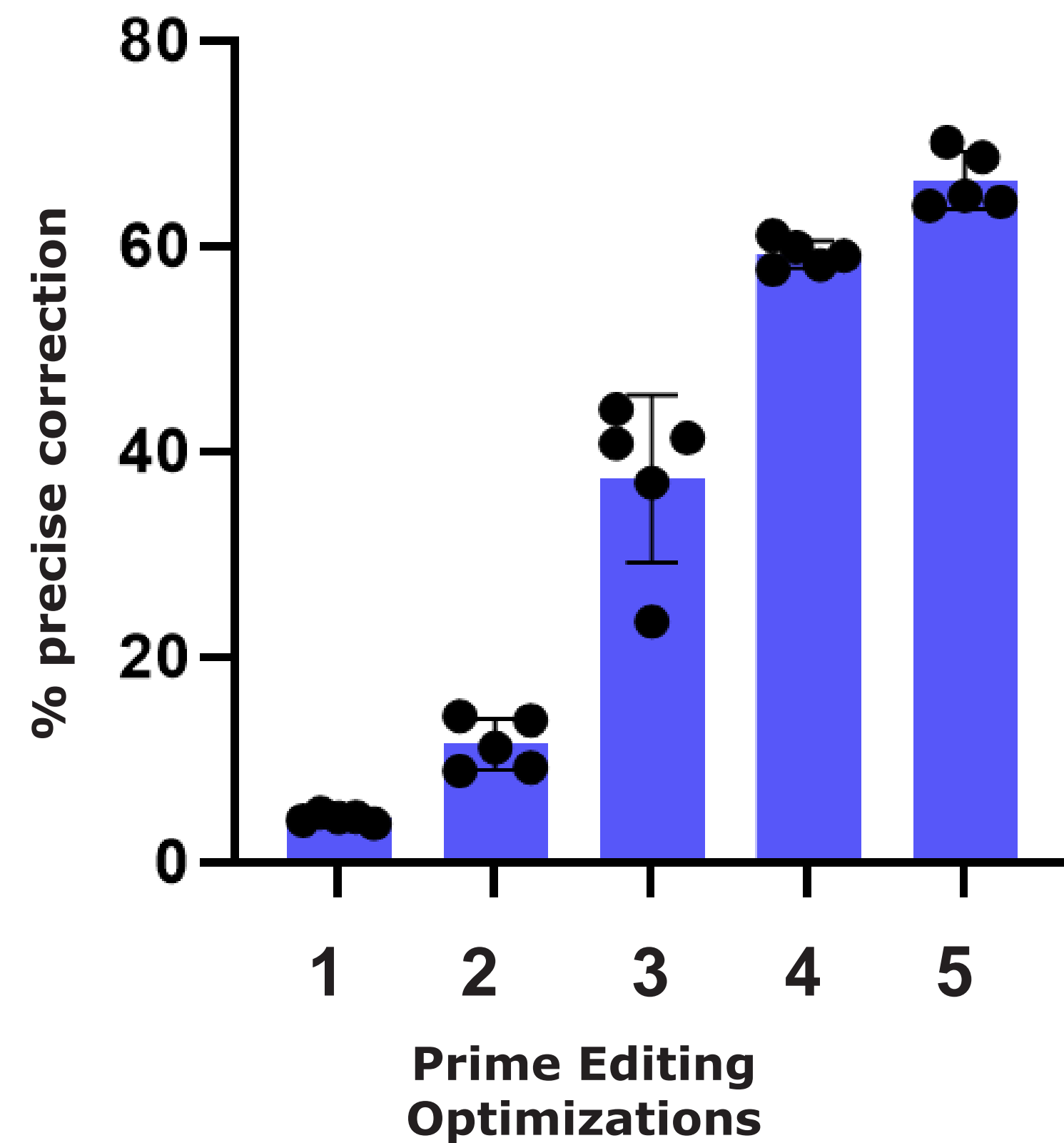
- Continue to develop and optimize non-viral and viral delivery systems and share additional proof-of-concept data from *in vivo* rodent and large animal studies in 2H 2023.
- Further demonstrate superior “off-target” profile for Prime Editing programs.
- Extend Prime Editing using proprietary recombinase and/or retrotransposon technologies for new and existing programs.

Strong cash position: Cash, cash equivalents and investments as of 3/31/2023 sufficient to fund anticipated operating expenses and capital expenditure requirements into 2025.

Unmet needs in Cystic Fibrosis: Potential to restore CFTR function in patients with G542X mutation

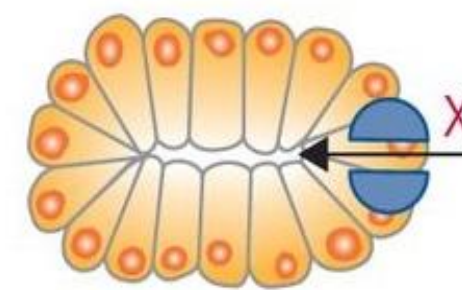
One-time, non-viral delivery to patient intestinal organoids restores CFTR function

Optimization results in high efficiency Prime Editors that precisely correct G542X mutation

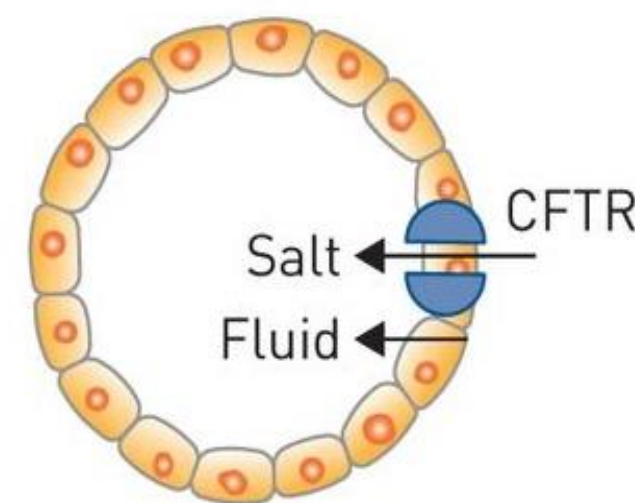


Intestinal organoids swelling assay for CFTR function

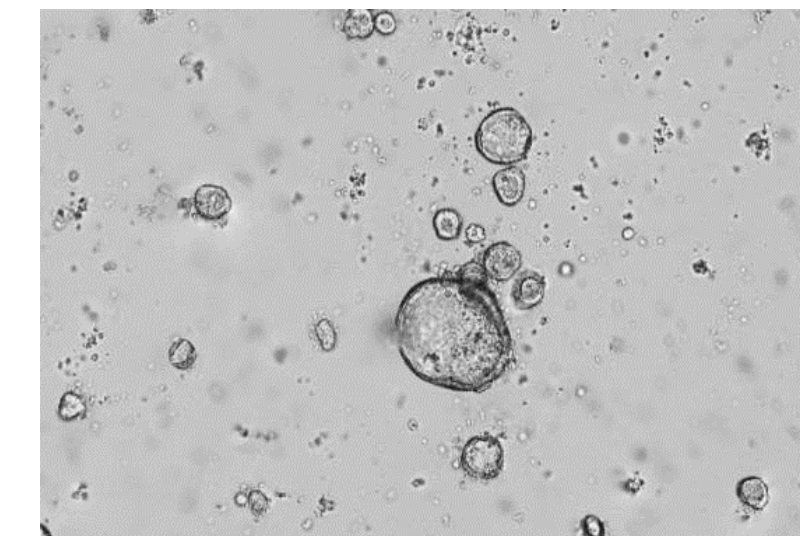
Cystic fibrosis



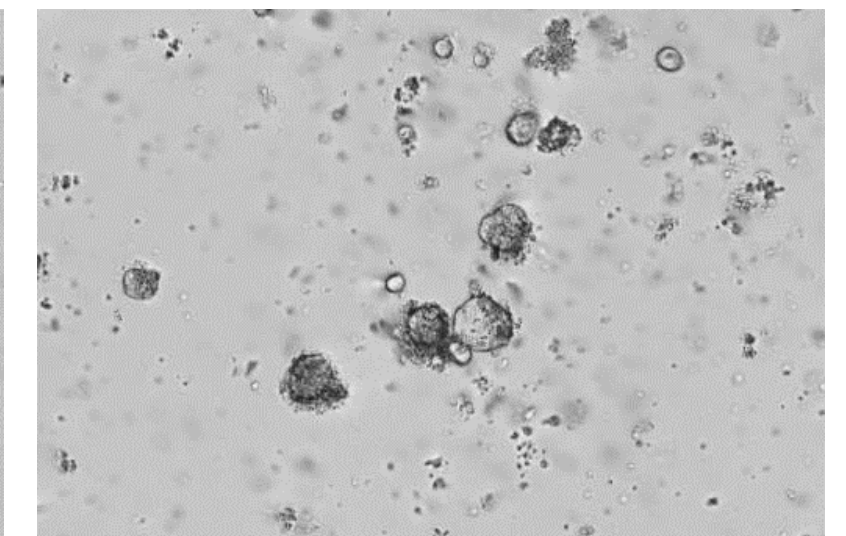
Healthy control



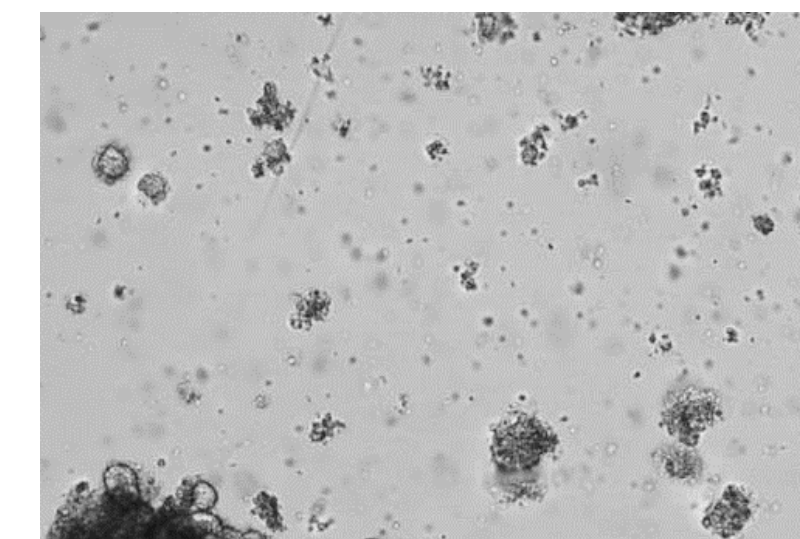
Prime Editing of patient intestinal organoids restores swelling and CFTR function



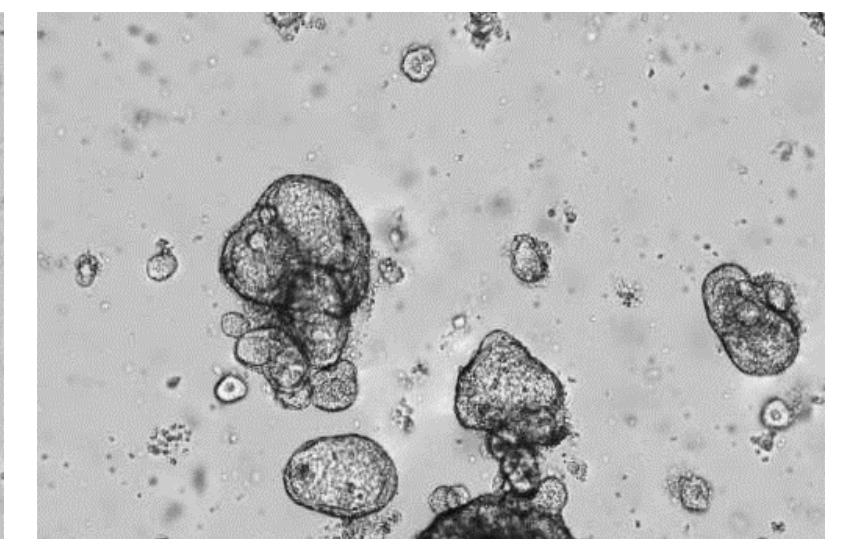
Healthy control



G542X with mock treatment



G542X with TRIKAFTA® treatment

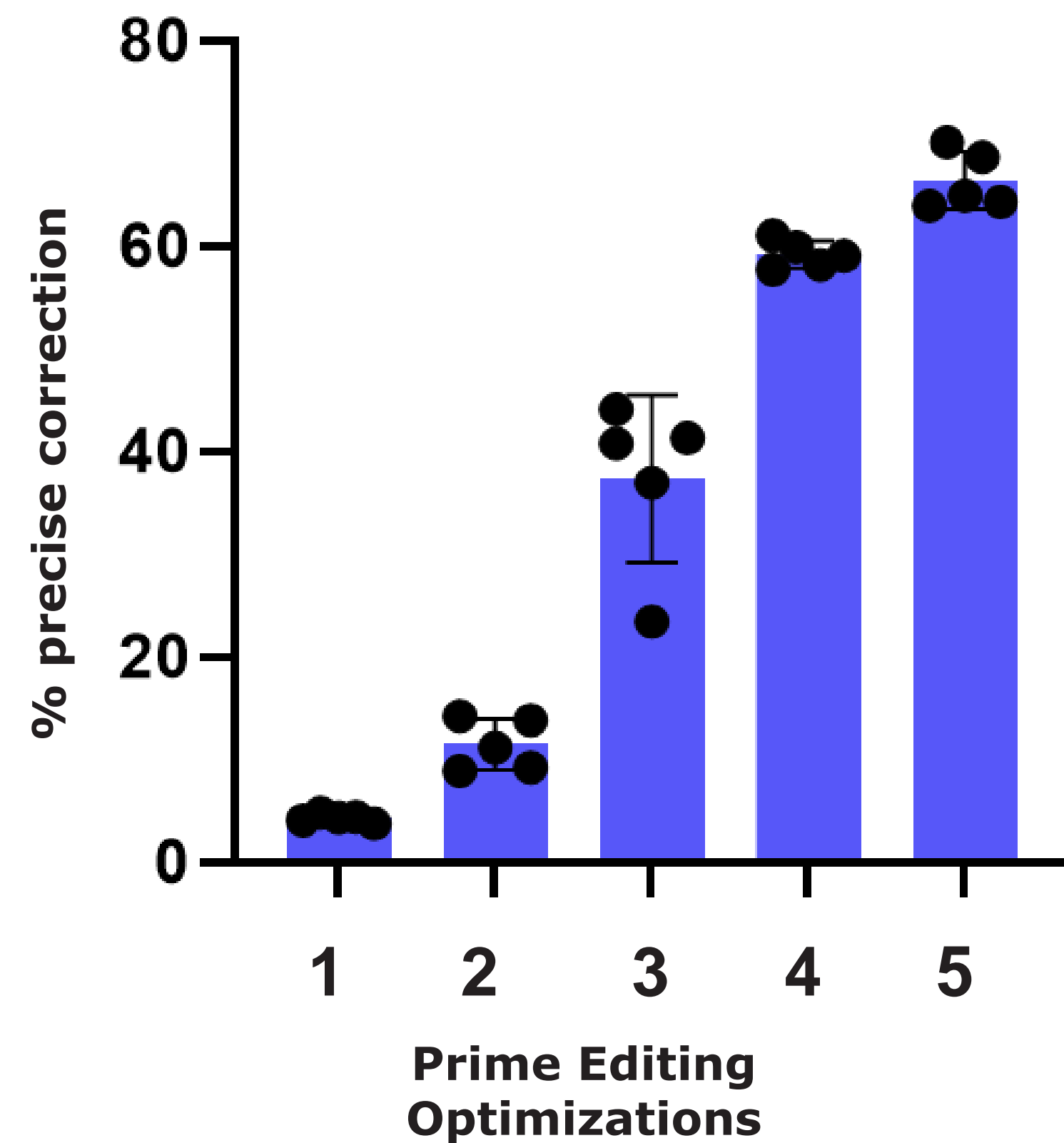


G542X with Prime Editing correction

Unmet needs in Cystic Fibrosis: Potential to restore CFTR function in patients with G542X mutation

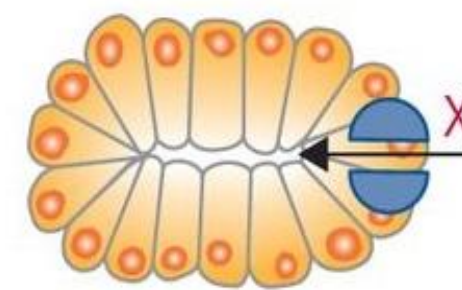
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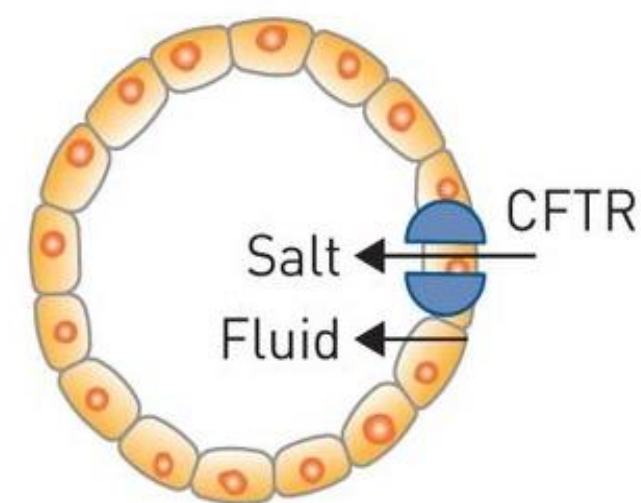


Intestinal organoids swelling assay for CFTR function

Cystic fibrosis



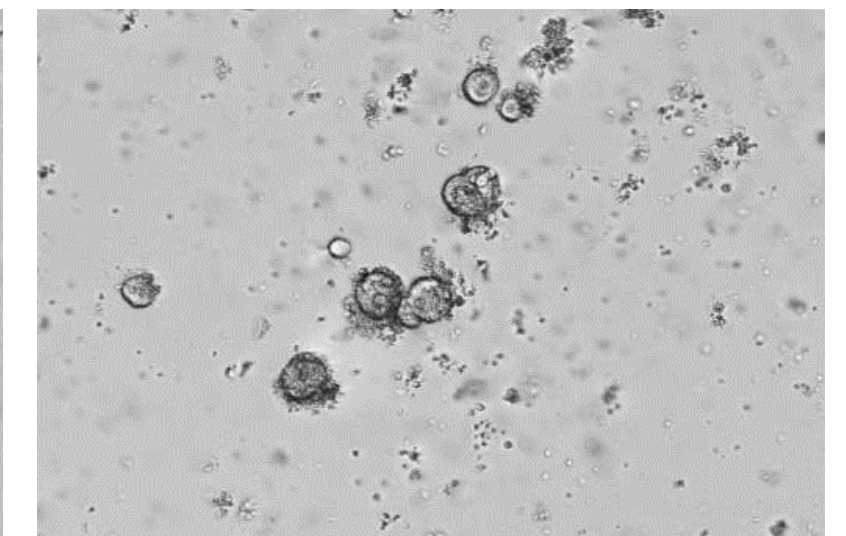
Healthy control



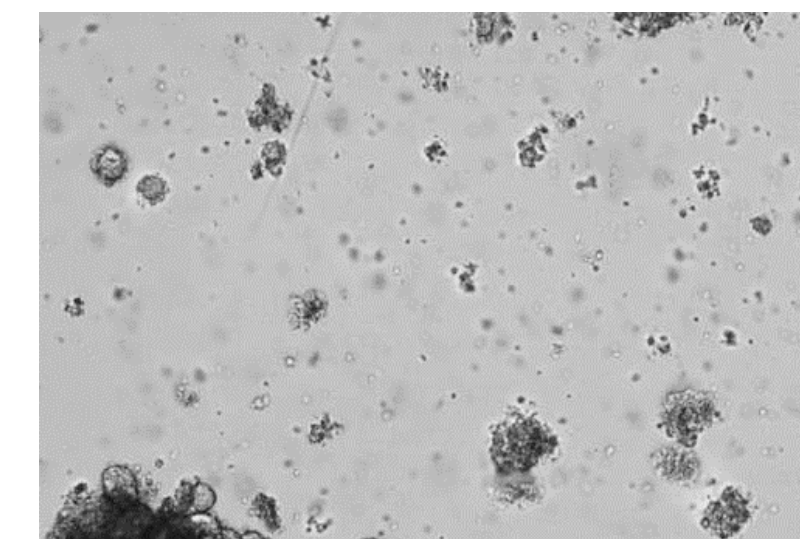
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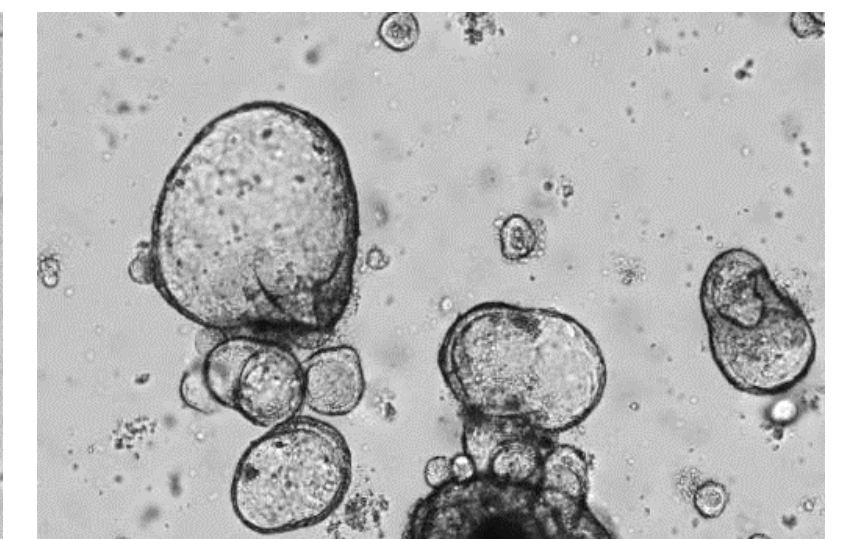
Healthy control



G542X with mock treatment



G542X with TRIKAFTA® treatment



G542X with Prime Editing correction