Prime Medicine

41st Annual J.P. Morgan Healthcare Conference
January 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; our ability to demonstrate, and the timing of, preclinical proof-of-concept in vivo for multiple programs; our ability to advance any product candidates that we may identify and successfully complete any clinical studies, including the manufacture of any such product candidates; our ability to pursue our four strategic indication categories: immediate target indications, differentiation target indications, “blue sky” indications and “march up the chromosome” approaches; our ability to quickly leverage programs within our initial target indications and to progress additional programs to further develop our pipeline; the timing of our regulatory filings, including our investigational new drug applications submissions; the implementation of our strategic plans for our business, programs and technology; the scope of protection we are able to establish and maintain for intellectual property rights covering our Prime Editing technology; developments related to our competitors and our industry; our ability to leverage the clinical, regulatory, and manufacturing advancements made by gene therapy and gene editing programs to accelerate our clinical trials and approval of product candidates; our ability to identify and enter into future license agreements and collaborations; developments related to our Prime Editing technology; regulatory developments in the United States and foreign countries; our ability to attract and retain key scientific and management personnel; our estimates of our expenses, capital requirements, and needs for additional financing as well as our cash runway into 2025; and general economic, industry and market conditions, including rising interest rates and inflation.

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.

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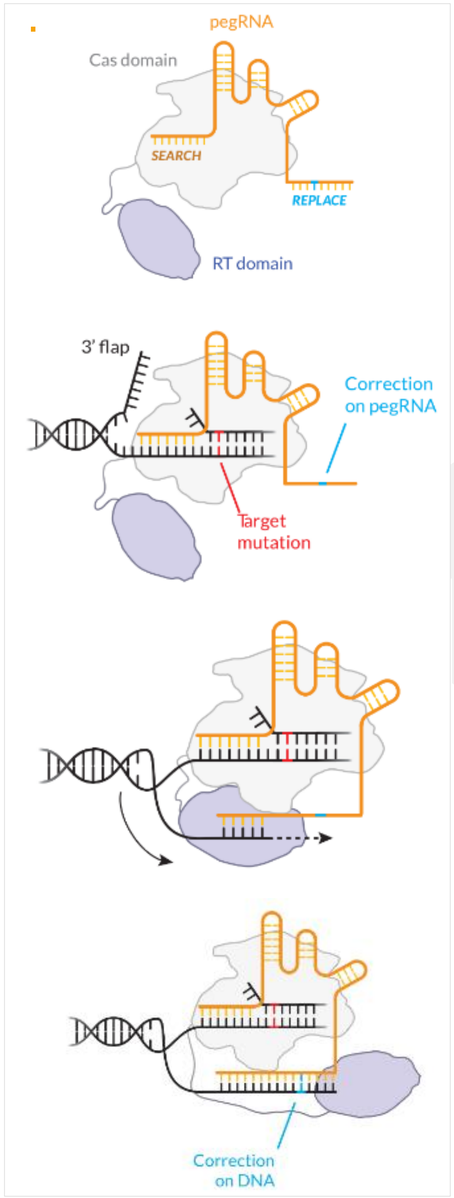
30 years after the first patient was treated with gene therapy, gene editing is only just beginning to demonstrate clinical benefit.

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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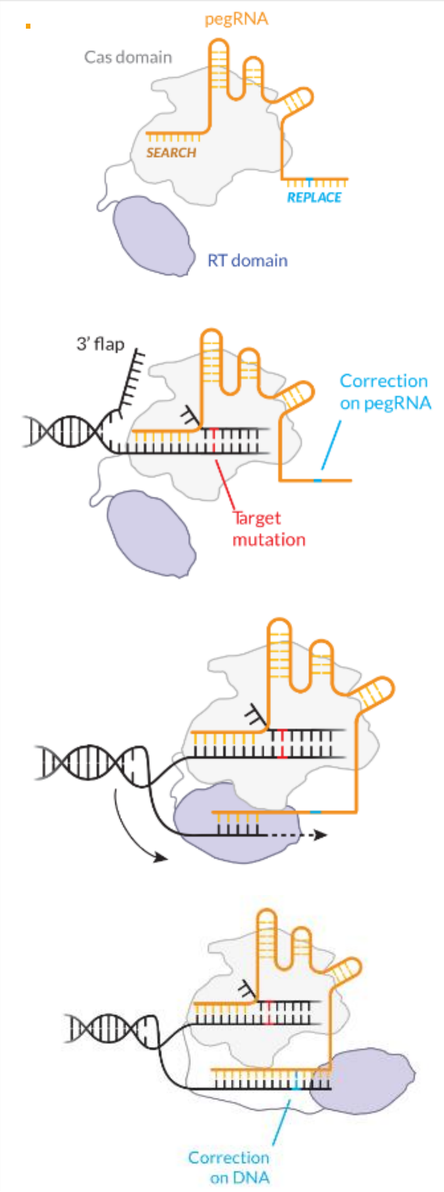

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Prime Medicine is well-positioned to maximize Prime Editing's broad therapeutic potential

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 Friedrich'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

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To be discussed in detail today

STRATEGIC CATEGORY	TARGET TISSUE	INDICATION	DELIVERY	DISCOVERY*	IND-ENABLING	CLINICAL TRIALS
IMMEDIATE	BLOOD	Sickle Cell Disease (Beam Therapeutics)	*ex vivo*			
		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	viral/non-viral			
		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			

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

AAV = adeno-associated viral vectors; LNP = lipid nanoparticles; TBD = to be determined

*As of IPO pricing, 10/19/22

Successful Prime Editing in long-term HSC population: *in vivo* engraftment in Chronic Granulomatous Disease mouse model

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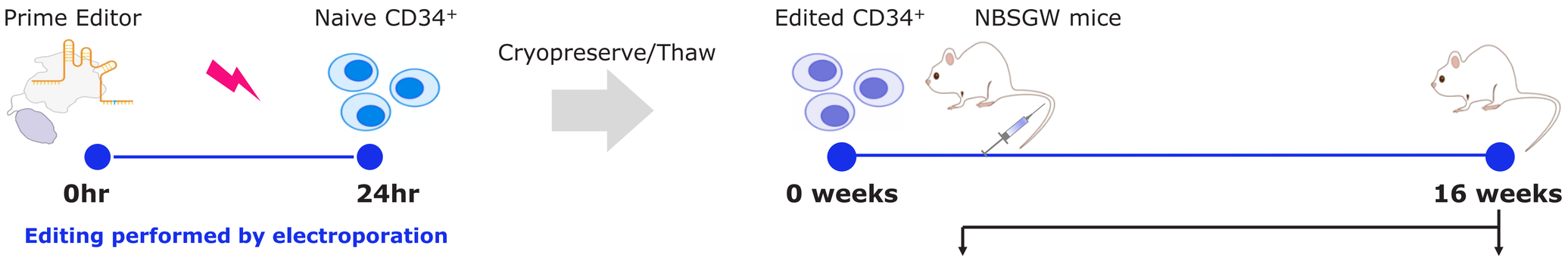
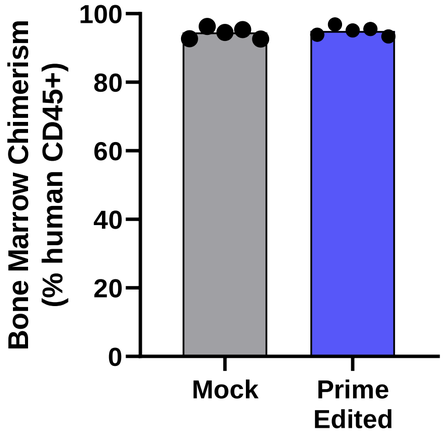
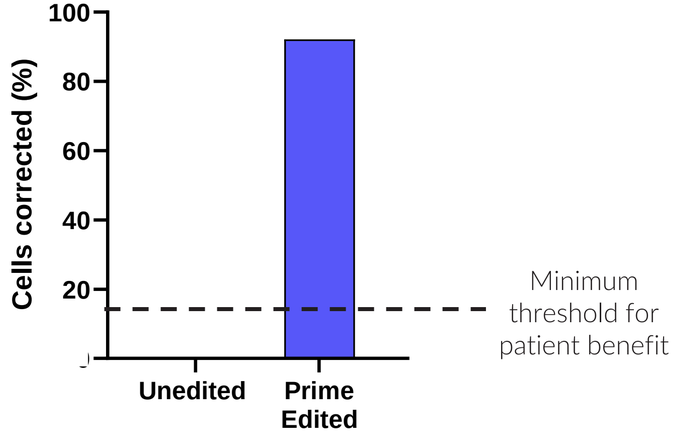
Maintenance of >92% corrected long-term HSCs following 16-week engraftment



No difference in engraftment for PE Edited HSCs vs controls



Long-term engrafted CD34+ HSCs carry precise correction of *NCF1*



Conclusions

- ✓ High efficiency, very precise editing of HSCs
- ✓ High-level, long-term engraftment resulting in healthy Prime Edited long-term HSCs
- ✓ Restores key myeloid function to fight infection
- ✓ Generate all lineages without skewing
- ✓ Mice are healthy at 16 weeks, no toxicity
- ✓ Recapitulates the expected clinical study design

NBSGW: NOD.Cg-*Kit*^{W41J} *Tyr* $^{+}$ *Prkdc*^{scid} *Il2rg*^{tm1Wjl}/ThomJ highly immunodeficient mice that support human CD34^{+} cell engraftment without irradiation. HSC: hematopoietic stem cell. PE: Prime Edited.

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

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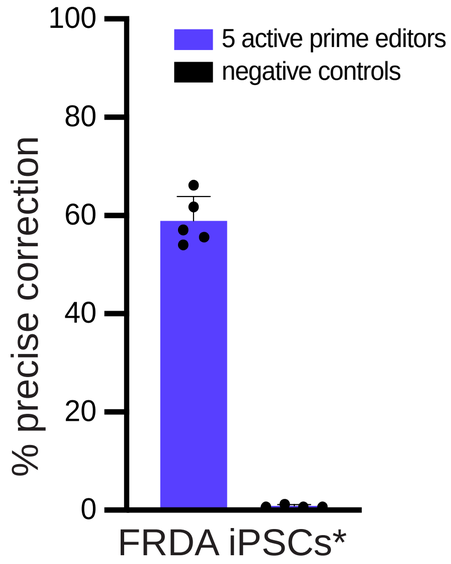
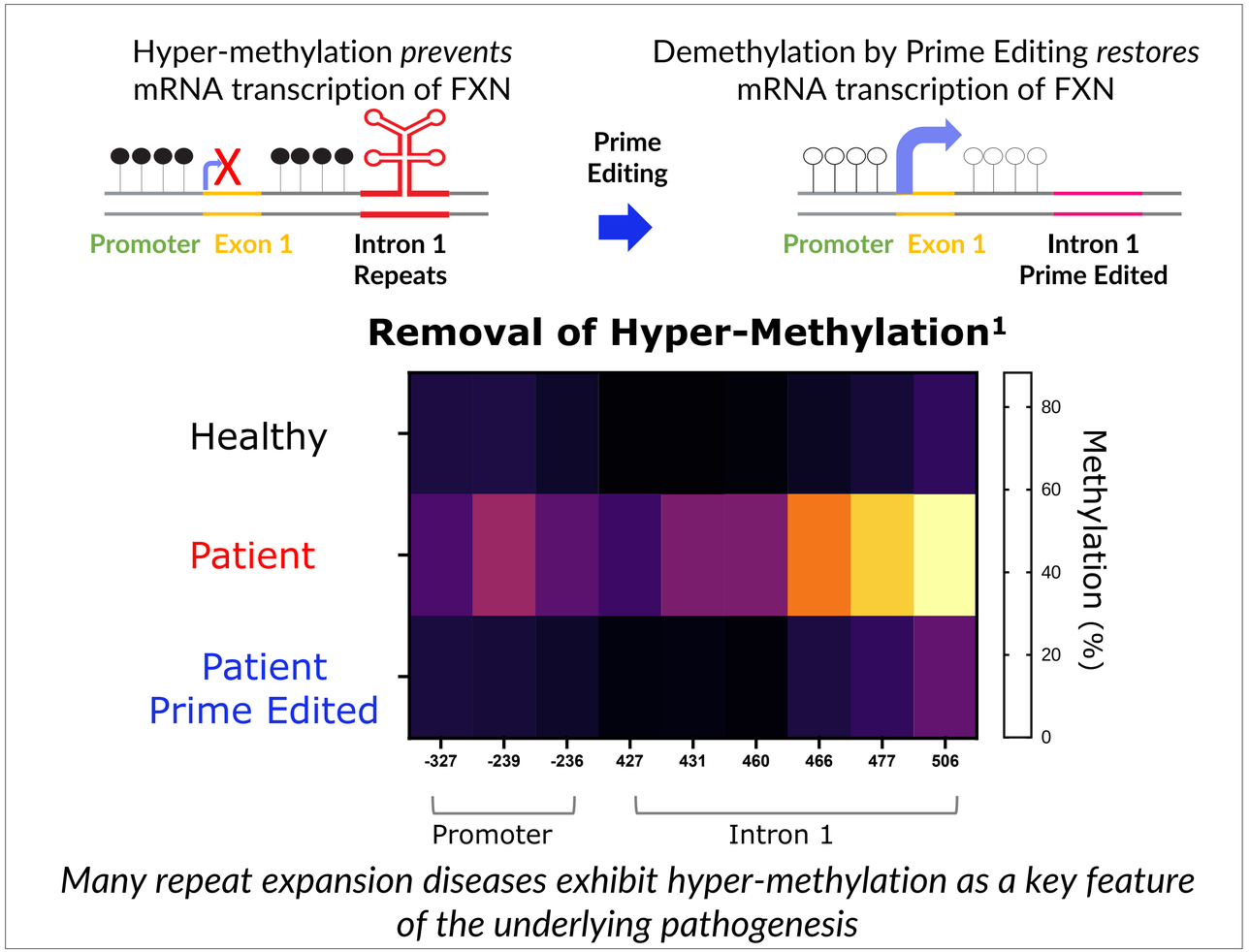
High efficiency Prime Editing removes the GAA pathological repeats and hyper-methylation at the Frataxin (FXN) gene in Friedreich's Ataxia patients



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



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

FXN: frataxin gene: FRDA: Friedreich's ataxia; iPSCs: induced pluripotent stem cells. 1 Methylation quantified by bisulfite sequencing

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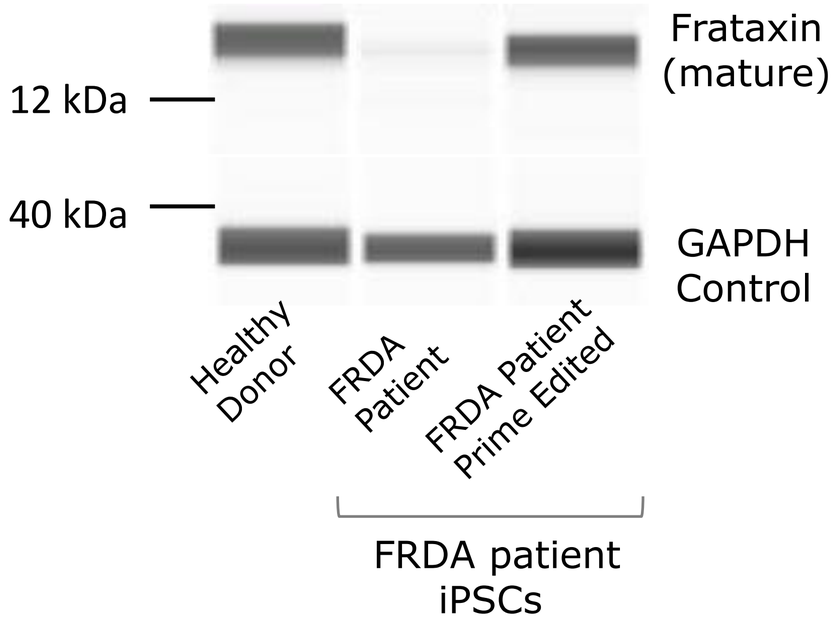
Successful Prime Editing removal of pathogenic repeats

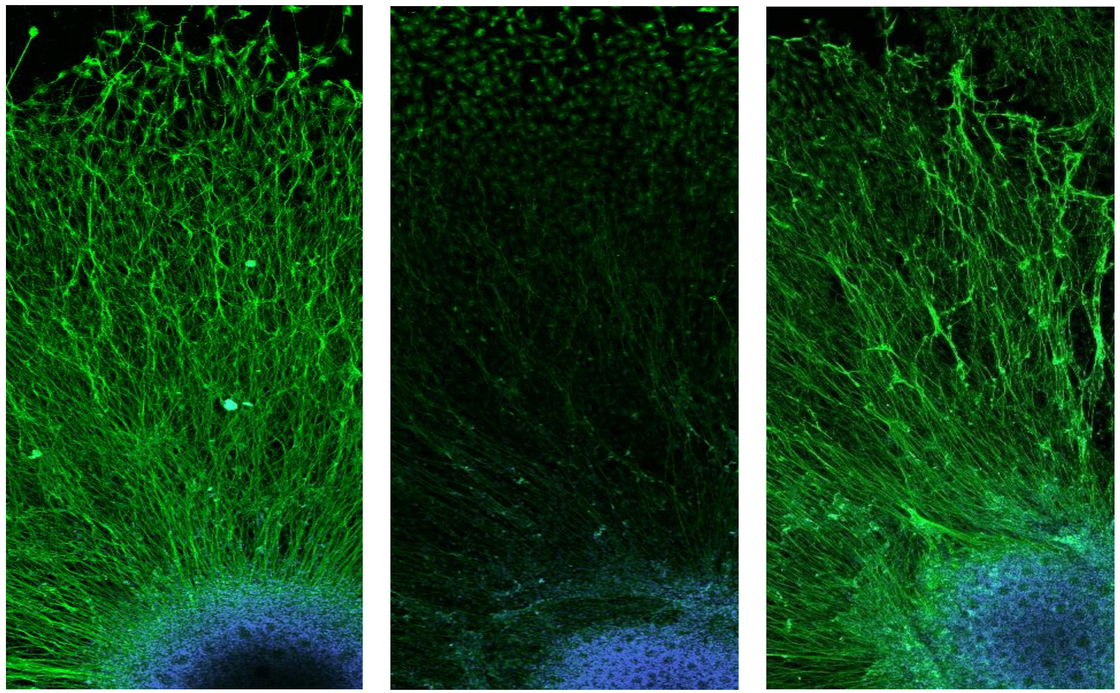
High efficiency Prime Editing restores FXN protein expression and sensory neuron function in Friedreich's Ataxia patients' dorsal root ganglia

Restoration of Frataxin protein expression after Prime Editing



Restoration of axonal projections after prime editing

βIII-TUB
DAPI



Healthy Donor | FRDA Patient | FRDA Patient Prime-Edited

FXN: Frataxin; FRDA: Friedreich's Ataxia; iDRG: iPSC-derived dorsal root ganglia. DAPI: nuclear staining; βIII-TUB: axonal projection staining

Unmet needs in Cystic Fibrosis: Restoring CFTR function in patients with G542X mutation

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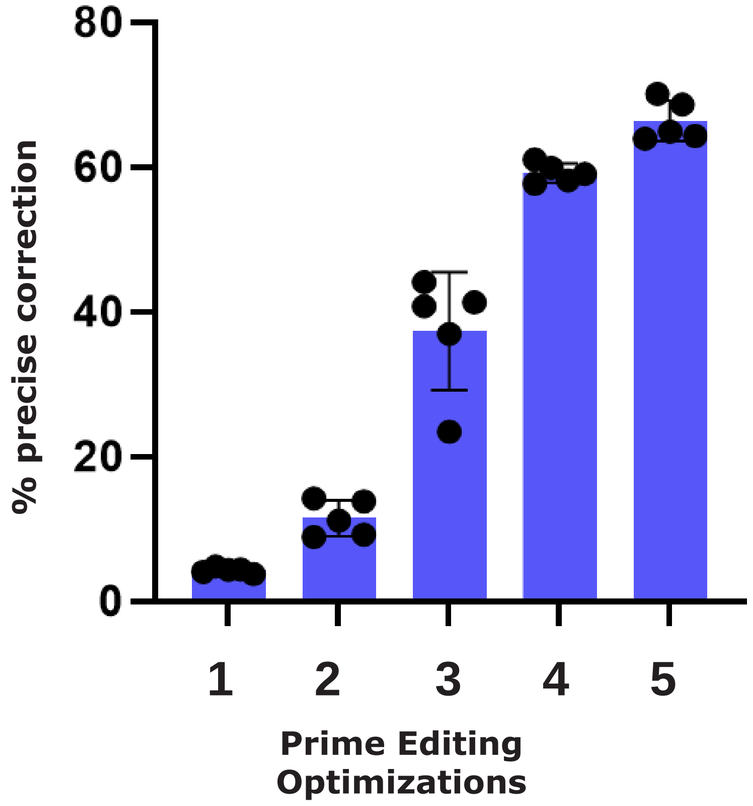
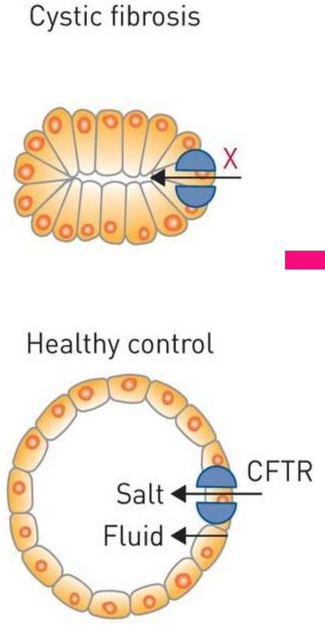
One-time, non-viral delivery to patient intestinal organoids restores CFTR function

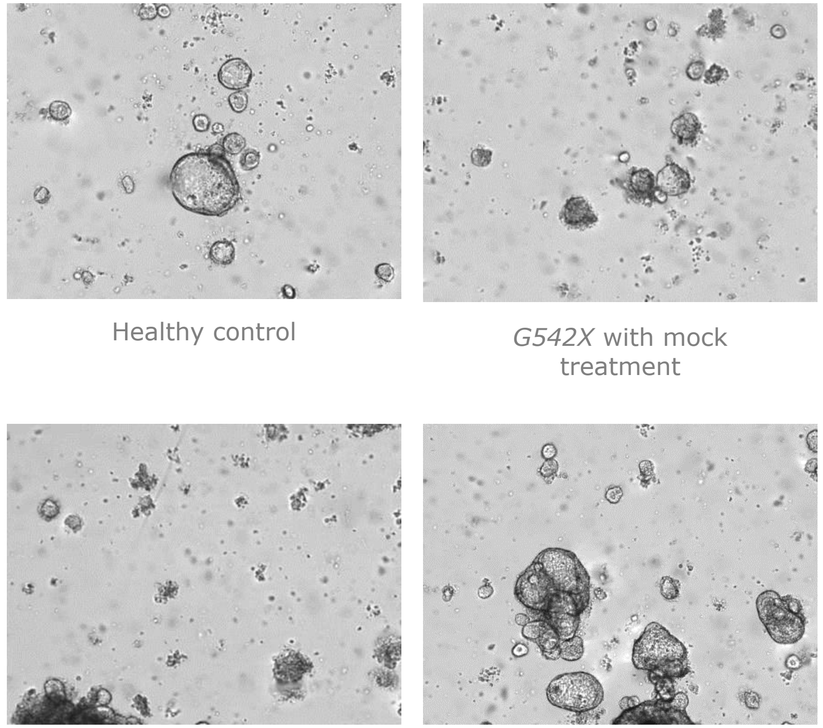
Optimization results in high efficiency Prime Editors that precisely correct G542X mutation



Intestinal organoids swelling assay for CFTR function



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

Van Mourik et al., 2019. Actual time course: 24 hours. TRIKAFTA® is a registered trademark of Vertex Pharmaceuticals, Incorporated.

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

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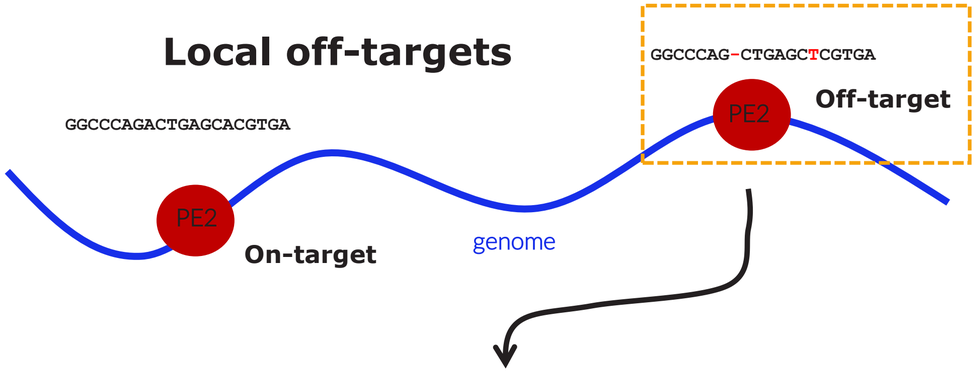
Local off-targets



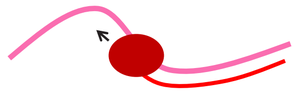
Targeted Nick Detection Assay**	Genome wide DSB detection	Genome wide Nick Detection Assay**

potential off-target editing sites

Targeted Sequencing (>1000x)

Identified Off-targets

Chromosome scale or structural off-targets



cDNA synthesis

Translocations

Large Deletions

Reverse Trans. Assay

mRNAseq PEG integration

Chromosomal Integrity Assays

Imaging	Sequencing based

Whole Genome Sequencing

Vector Integration Analysis

Identified Off-targets

*Preliminary plans pending discussions with regulatory agencies; **Proprietary assay developed by Prime

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

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

Genome wide and targeted detection of potential off-targets

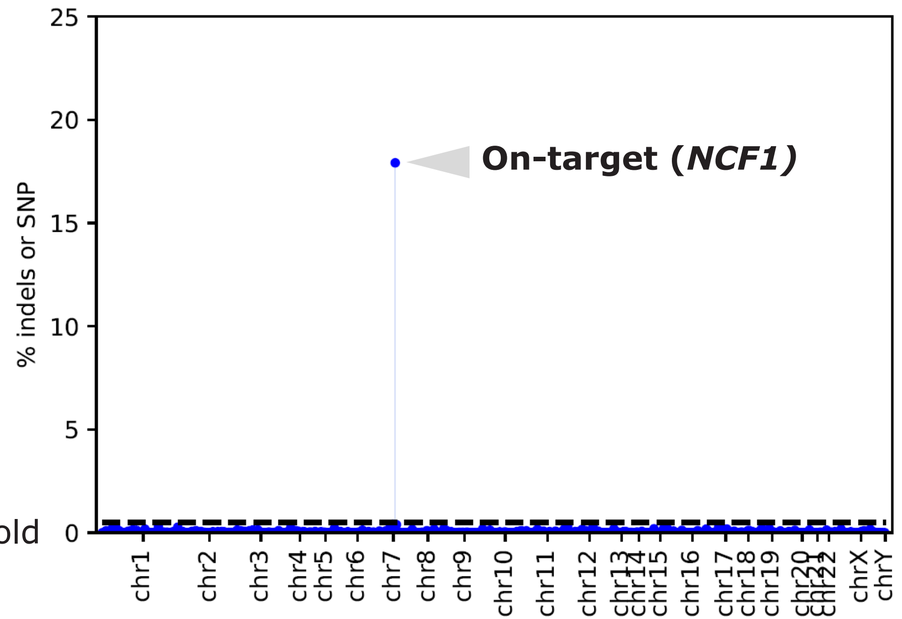
potential off-target editing sites

Targeted Sequencing

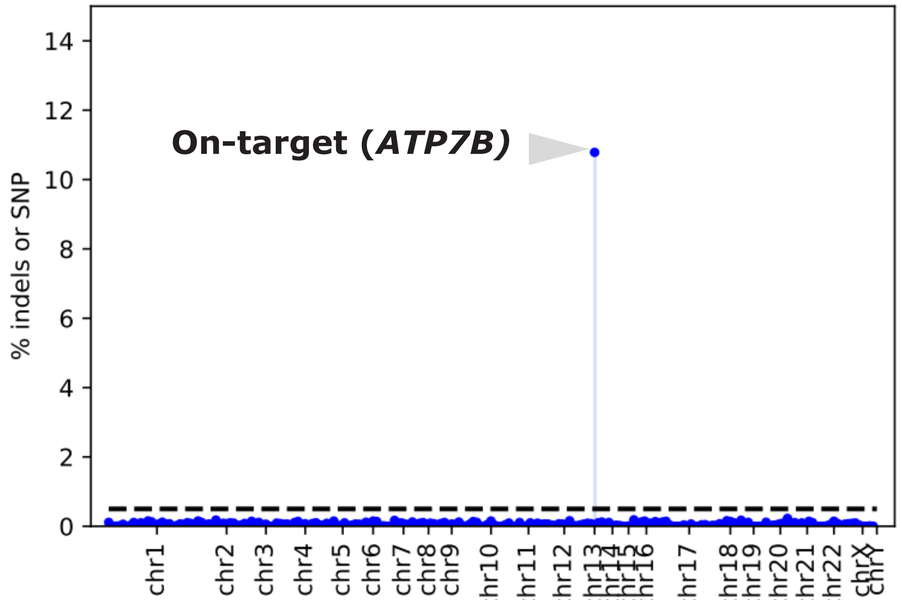
Identified off-targets

0.5% threshold

CGD Program: CD34+ Cells[1]



Wilsons Disease Program: Hepatocytes[2]



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

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

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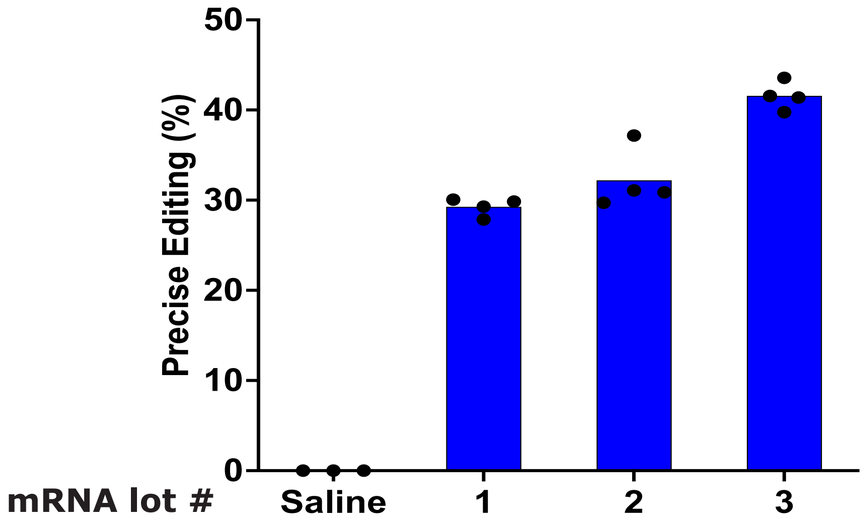
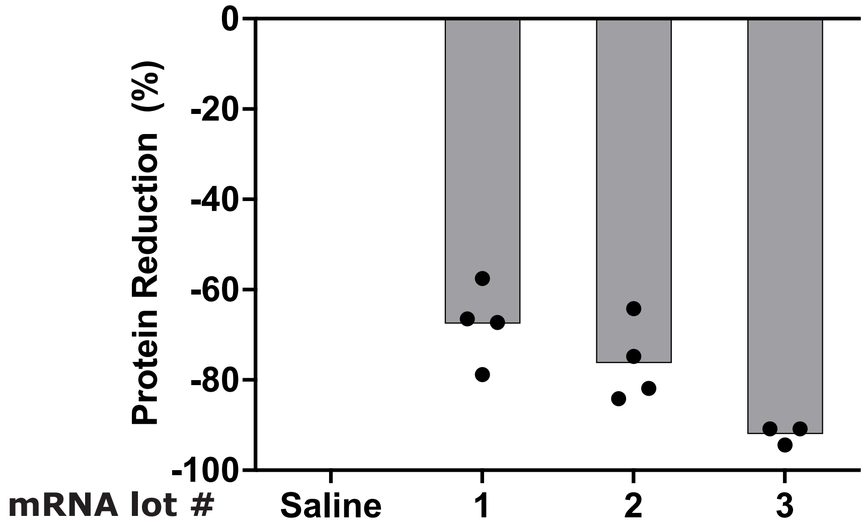
Prime Editor LNP delivered to the liver a **precisely introduced stop codon** in PCSK9 gene in mice

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

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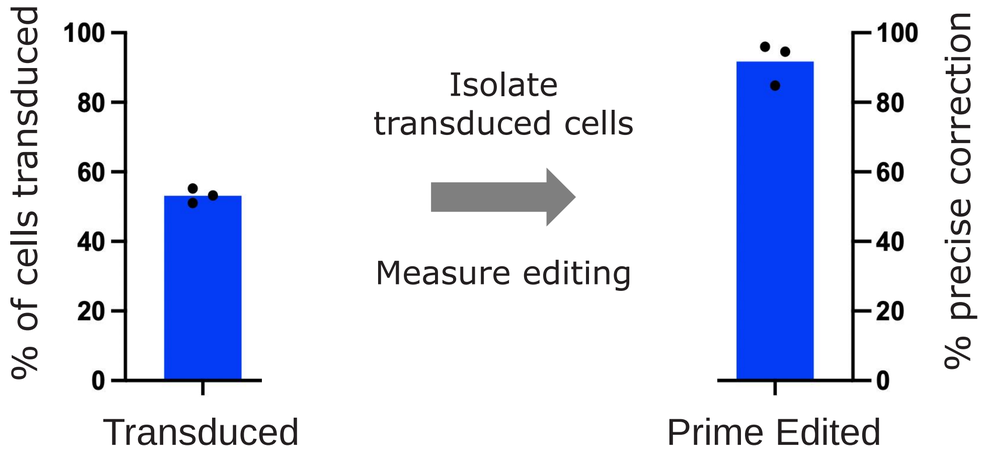
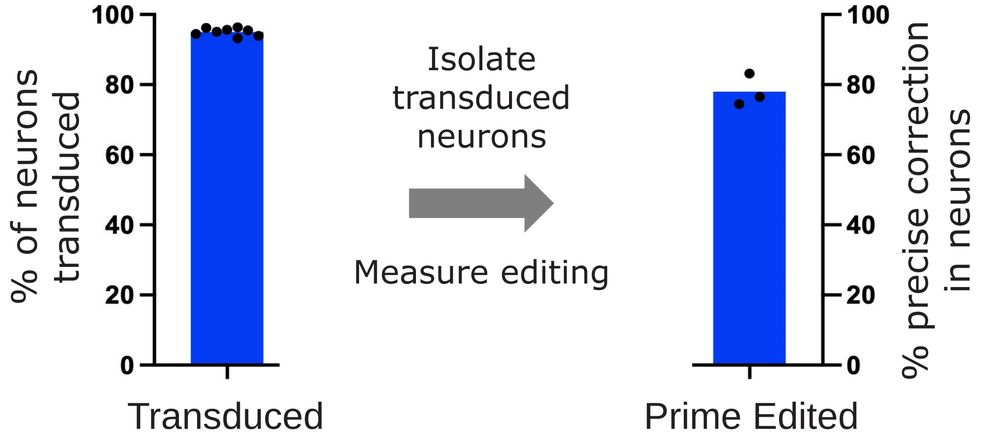
Dual AAV[2] effectively delivers to ~ 95%, and precisely edits ~80%, of neurons in adult mice

Prime Editor dual AAV
- Prime Editor
- Prime editor dual guide RNA

Neonatal mice – ICV infusion[1]
transduced cortex (left) and precisely edited cortical cells (right)



Adult mice – local administration[1]
transduced neurons (left) and precisely edited neurons[2] (right)



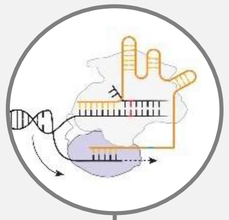
[1]Three weeks in neonatal mice via intra-cerebral infusion (ICV); 5 weeks in adult mice via local administration into cerebellum or cortex. [2]Prime Editor cassette with neuron-specific promoter. All experiments shown are Proof of Concept delivery experiments using a control Prime Editor site.

Prime Medicine has rapidly advanced and substantially improved Prime Editing

- Prime Medicine holds foundational IP and has filed for IP protection for technological advancements
- Patent portfolio includes U.S. Patent 11,447,770 covering methods of using Prime Editors, and US allowed application 17/219,635 covering pegRNAs (expected to issue Q1 2023)

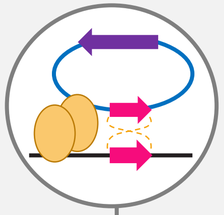
Seminal Prime Editing Publication[1]

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



PASSIGE System

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

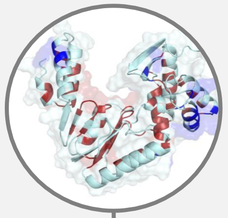


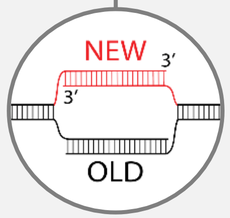
PE4, PE5, and PEmax[3]

- 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



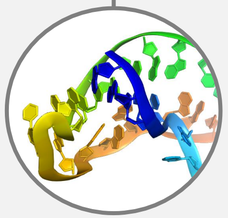


Dual Flap Prime Editing[2]

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

Engineered pegRNAs[4]

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



pegRNA Enhancements

- New classes of efficiency-increasing pegRNAs enhancements

Peer reviewed publications: [1] Anzalone, et al, Nature 2019. [2] Anzalone, et al, Nat. Biotechnol. 2021. [3] Chen, et al, Cell 2021. [4] Nelson, et al, Nat. Biotechnol. 2021.

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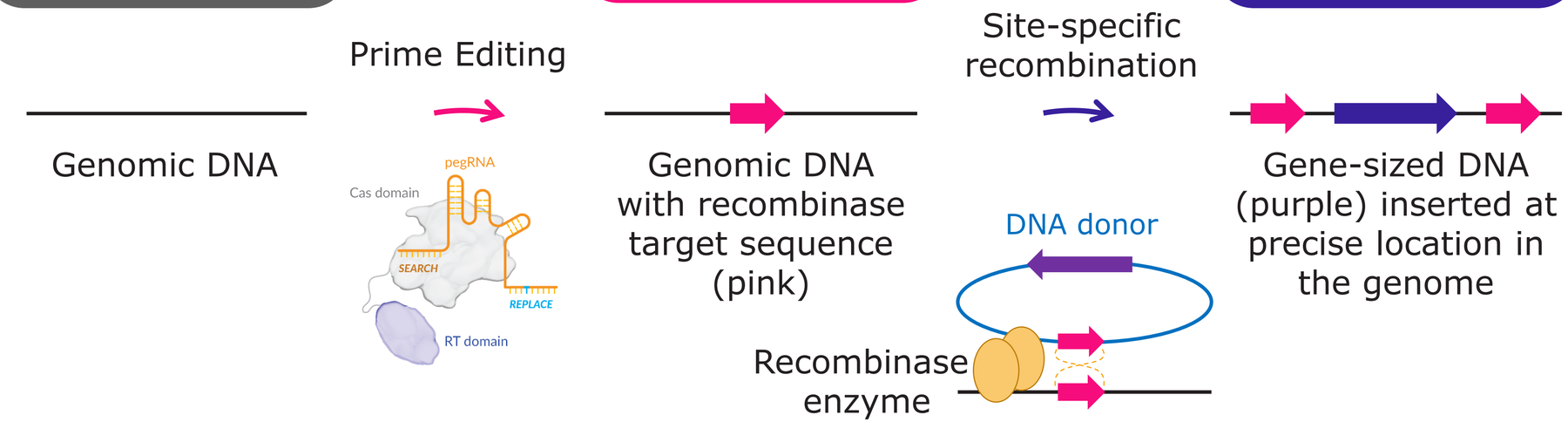
Prime Assisted Site-Specific Integrase Gene Editing

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

Precise target location in genomic DNA

Programmed insertion of recombinase DNA target sequence

Integration of DNA at precise location



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

PASSIGE: Efficient insertion of gene-sized sequence into a *single targeted* genomic site in human primary T cells

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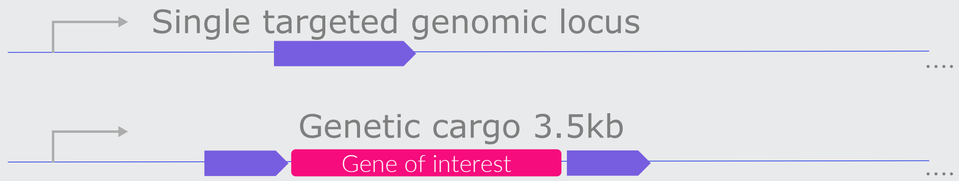
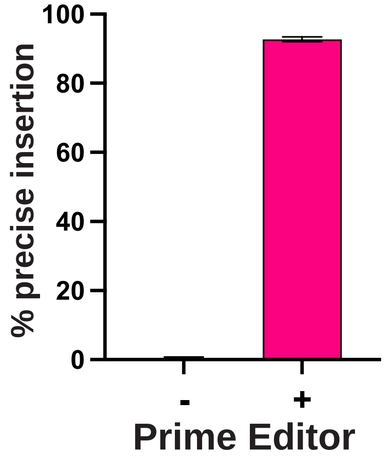
PASSIGE **one-step non-viral** approach for precise introduction of gene sized cargo into the genome

Prime Editing to insert **recombinase attachment site**

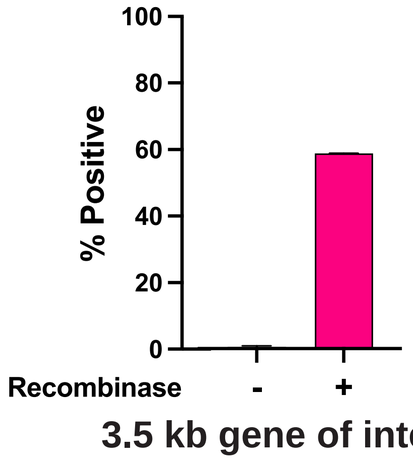
Recombinase to integrate **genetic cargo**



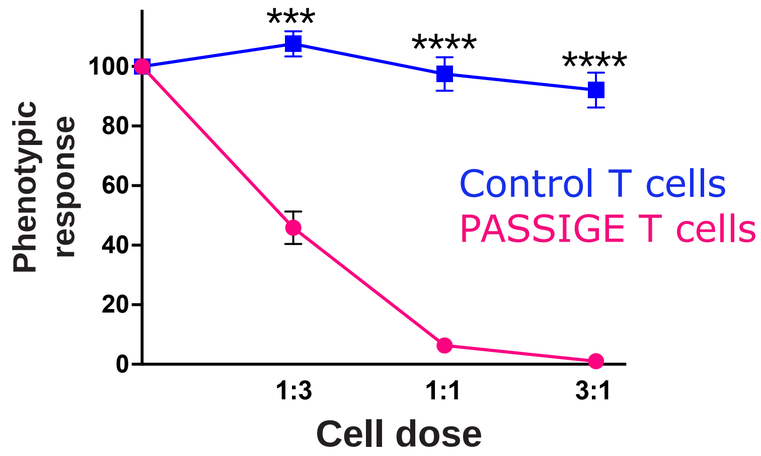
Insertion of recombinase site - over 90% efficiency



Integration of genetic cargo at single *targeted site in* 60% of T cells



Phenotypic impact from newly inserted gene of interest



The targeted inserted gene of interest provides a potent new cell function

PASSIGE: Prime-Assisted Site-Specific Integrase Gene Editing;
n = 2 technical replicates ; Far right panel: n = 4 technical replicates; Two-way ANOVA with Bonferroni post-test *** P = 0.0002; **** P < 0.0001

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.

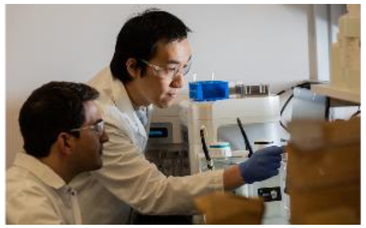
PE = Prime Editing

Building the Company

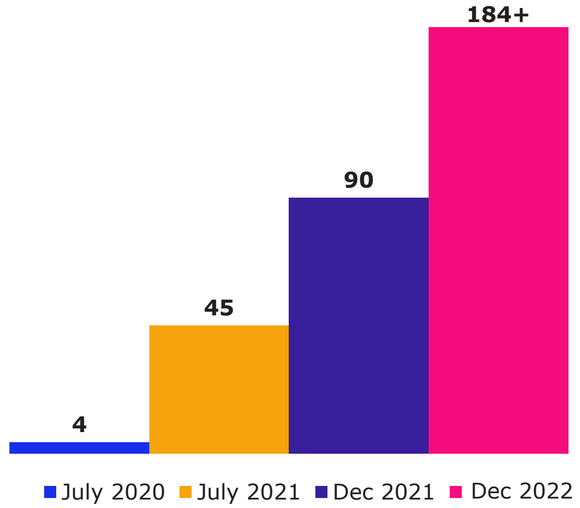
Currently

- 184+ 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 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

- Nominate 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 short-term investments as of 9/30/2022, together with approximately gross $200M raised in October IPO, sufficient to fund anticipated operating expenses and capital expenditure requirements into 2025.

Prime Medicine

January 2023