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Delivering on the promise
of Prime Editing

Corporate Presentation

May 2024

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, as amended. These forward-looking statements contain information about our current and future prospects and our operations, which are based on currently available information. All statements other than statements of historical facts contained in this presentation, including statements regarding our strategy, projects and plans 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," "hope," "intend," "may," "might," "objective," "opportunity," "plan," "predict," "positioned," "possible," "potential," "project," "seek," "should," "strategy," "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 potential of PM359 to correct the causative mutation of CGD; the anticipated maturation into a clinical-stage company by bringing PM359 into clinical development in 2024 with initial clinical data expected in 2025; the initiation, timing, progress and results of our research and development programs, preclinical studies and future clinical trials, and the release of data related thereto; our ability to demonstrate, and the timing of, preclinical proof-of-concept in vivo for multiple programs; our ability to pursue our areas of focus and any additional programs we may advance; our ability to quickly leverage programs within our initial target indications and to progress additional programs to further develop our pipeline; the potential of Prime Editors to reproducibly correct disease-causing genetic mutations across different tissues, organs and cell types, and the capacity of our PASSIGE technology to edit CAR-T cells for the treatment of certain cancers and immune diseases; the timing of our regulatory filings, including filings anticipated in 2025; our ability to demonstrate superior off-target profiles for Prime Editing programs; the further advancement of Prime Editors to maximize their versatility, precision and efficiency; the continued development and optimization of various non-viral and viral delivery systems, including our universal liver-targeted LNP delivery approach; the expansion of Prime Editing's therapeutic potential to extend the reach and impact of Prime Editing to areas beyond our current areas of focus; the potential of Prime Editing to offer curative genetic therapies for a wide spectrum of diseases; the scope of protection we are able to establish and maintain for intellectual property rights covering our Prime Editing technology; 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 current and future product candidates; the research collaboration with Cimeio to combine our and Cimeio's respective technologies, including our Prime Editing platform and Cimeio's SCIP platform, and the goals of such collaboration, the potential benefits of such collaboration and technology thereunder, including the ability to cure various diseases and replace existing treatments such as transplantation; 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; 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; and our expectations regarding the anticipated timeline of our cash runway and future financial performance. 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 Annual Report on Form 10-K, 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 subject to any obligations under applicable law. 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.

Information regarding our estimated cash, restricted cash, cash equivalents, and investments as of March 31, 2024 is based on preliminary unaudited estimates prepared by and is the responsibility of management. Our independent registered public accounting firm has not audited, reviewed or performed any procedures with respect to such preliminary estimates and accordingly does not express an opinion or any other form of assurance with respect thereto. During our financial closing process our estimates can differ materially from our initial estimates presented herein based on our receipt of updated information.

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.

“The age of human therapeutic gene editing isn’t just coming. It’s already here.”*

FDA allows first pivotal trial of an in vivo gene editing treatment from Intellia

Lei Lei Wu
News Reporter

The FDA cleared In
therapy for transthy
for the first pivotal

F.D.A. Approves Sickle Cell Treatments, Including One That CRISPR

People with the genetic disease have new opportunities
eliminate their symptoms, but the treatments come with
obstacles that limit their reach.

New Gene Editing Treatment Cuts Dangerous Cholesterol in Small Study

The trial involved only 10 patients,
be permanently reduced with a sin
risk of heart disease.

Prime Medicine receives FDA clearance to run first prime editing clinical trial

Lei Lei Wu
News Reporter

* David Liu, Ph.D., Co-Founder of Prime Medicine

Now is *our* moment:

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

we are building on decades of progress to deliver the promise of one-time, curative genetic therapies to address the widest spectrum of diseases

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BROAD OPPORTUNITY TO ADDRESS LARGE MARKETS

PLATFORM MODULARITY

EFFICIENT DELIVERY

DIFFERENTIATED SAFETY PROFILE

PIPELINE ALIGNED TO CORE AREAS OF FOCUS

Prime Medicine is Developing One-Time, Curative Genetic Therapies

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In 2024, Prime Medicine expects to bring the first-ever Prime Editing-based therapeutic candidate to patients and build value through strategic investments in pipeline and platform advancements

Strategic priorities:

- Mature into **clinical-stage** company
- Advance next wave of programs across **range of target tissues**
- Strengthen **modular Prime Editing platform**
- Leverage **business development** to accelerate pipeline, extend reach

We Believe Prime Editing is the Only Gene Editing Technology That Can Edit, Correct, Insert and Delete DNA Sequences in Any Target Tissue

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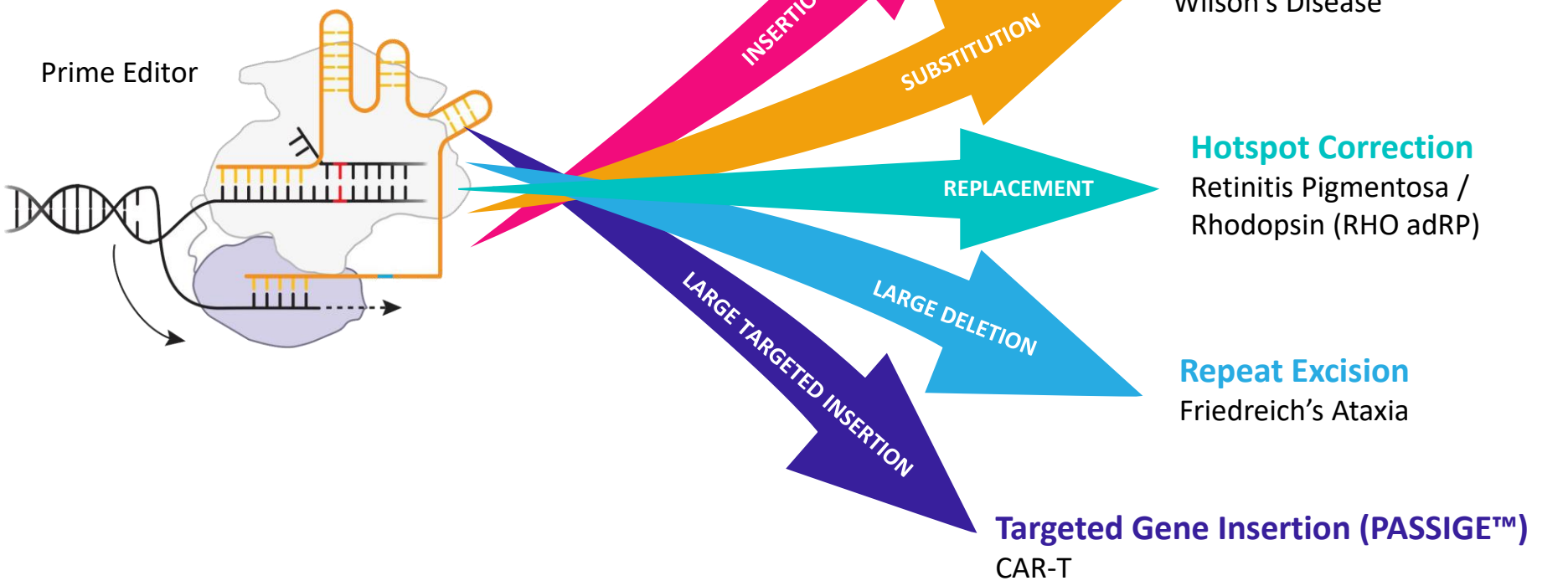
Corrects mutations across many organisms, organs and cell types, in dividing and non-dividing human cells



Deletion / Insertion Correction
Chronic Granulomatous Disease (CGD)

Point Mutation Correction
Wilson's Disease

Hotspot Correction
Retinitis Pigmentosa / Rhodopsin (RHO adRP)

Repeat Excision
Friedreich's Ataxia

Targeted Gene Insertion (PASSIGE™)
CAR-T

Broad and versatile editing capabilities unlock opportunities across **thousands of indications,** including genetic diseases, infectious diseases, cancers and immunological diseases

CAR-T = chimeric antigen receptor (CAR)-T cell therapy

Prime Editing is Designed with a Wide Range of Genome Editing Capabilities

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Flexibility to select right approach for each indication based on editing need

Prime Editing Approach	Small edits (e.g., all 12 bp swaps, 1-bp to 20-bp ins or del, combinations thereof)	Mid-sized edits (e.g., hotspot corrections, del up to 1-kb, ins up to 250 bp)	Large deletions (e.g., multi-kb repeat excision, exon del)	Large insertions or inversions (e.g., targeted multi-kb gene integration)
Short Flap Prime Editing	✓ +++			
Dual Flap Prime Editing	✓ ++	✓ +++	✓ +++	
Long Flap Prime Editing	✓ ++	✓ +++	✓ ++	
PASSIGE™		✓ +	✓ +	✓ +++

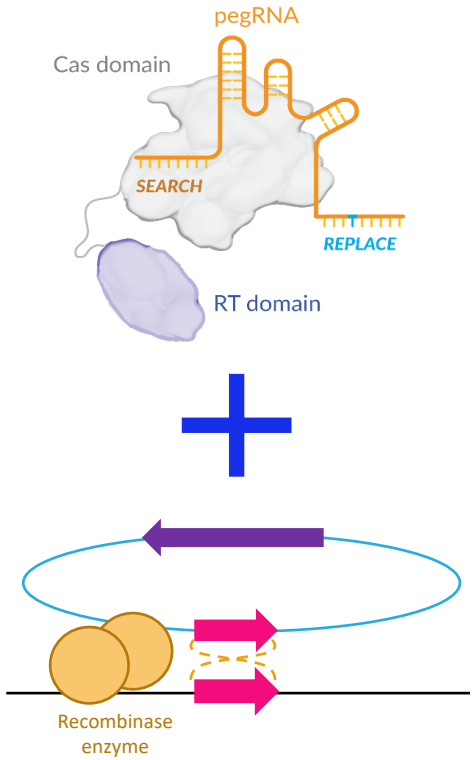
✓ = capable of the edit

+/++/+++ = how fit Prime Medicine believes the technology is for making the edit, based on Prime Medicine's internal assessment

BP = base pair; KB = kilobase

PASSIGE™ Technology Enables Prime Editing to Insert Gene Sized Sequences Precisely, Potentially Addressing Large Markets

PASSIGE: Prime-Assisted Site-Specific Integrase Gene Editing:
One step non-viral multi-kilobase-size gene editing approach with no double-stranded breaks



Where we are working today:

- **Non-viral, multiplex-edited CAR-T therapies**
- **Cystic Fibrosis**

Areas of opportunity:*

- **Targeted whole gene replacement for bone marrow diseases**
  (e.g., Hereditary anemias, such as Fanconi Anemia)
- **Correct inversion mutations**
  (e.g., Hemophilia A*)
- **Targeted whole gene replacement for rare liver diseases**
  (e.g., Phenylketonuria,* Tyrosinemia*)
- ***In vivo* protein factory**
  (e.g., GLA enzyme for Fabry's disease*)

*Not part of Prime Medicine's current pipeline

Prime Editing Platform Modularity Accelerates and De-Risks Ongoing Efforts, Enables Rapid Generation of New Product Candidates

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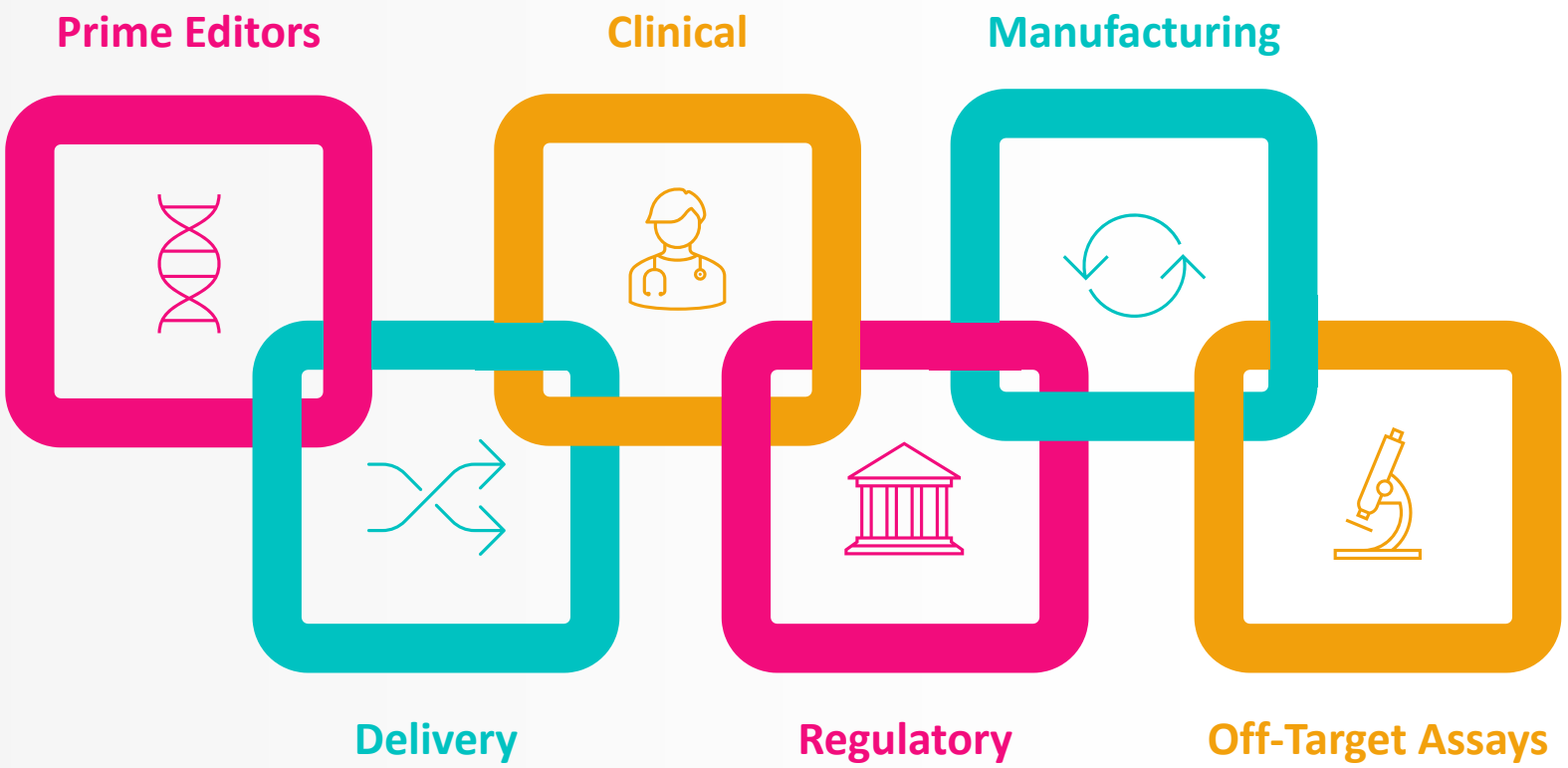
Core components can be readily leveraged to accelerate pipeline growth, efficiency and execution



Prime Editing Can Be Delivered with High Efficiency, Correcting Pathogenic Mutations at Levels Expected to Reverse Disease

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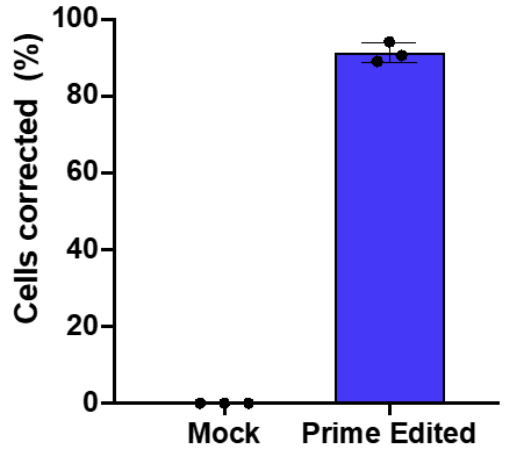
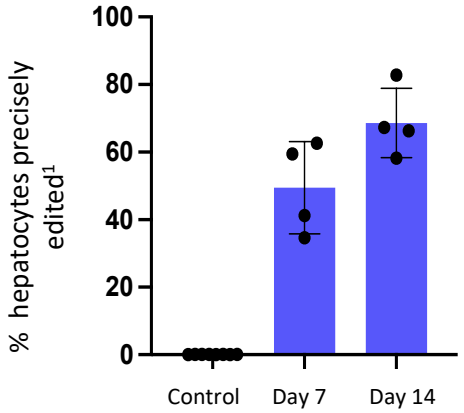
1 Ex Vivo (Human CD34+ Cells)



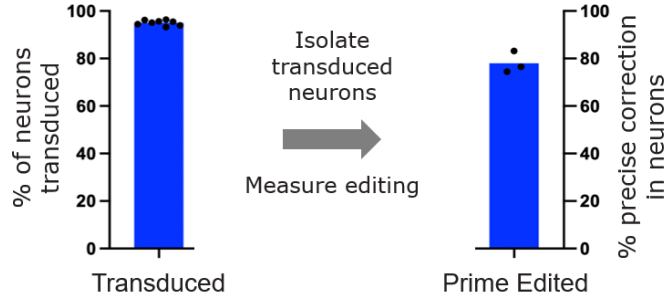
>90% editing of CD34+ cells *ex vivo* via electroporation

2 In Vivo – LNP (NHP Liver)



Up to ~83% of hepatocytes precisely edited in NHPs[1]

3 In Vivo – AAV (Mouse Brain and Eye)



>80% precise editing in mouse CNS

>70% precise editing in mouse photoreceptors

Proof-of-concept in initial indications may accelerate development of subsequent programs within each area of focus

NHP = non-human primate; CNS = central nervous system; [1]% Hepatocytes precisely edited is calculated from NGS of whole liver biopsy, factored for 60% of cells in liver are hepatocytes (Based on PK/PD relationships and qualifications of cell types in liver: Wang et al Sci. Rep. (2021) 11:19396; MacParland et al Nat Commun. (2018) 9:4383; Hansel et al, Curr Protoc Toxicol (2014) 62:14.12.1; Kmiec, Adv Anat Embryol Cell Biol. (2001) 161:III–XIII. 1–151).

Prime Editing Has Highly Differentiated Safety Profile: No Off-Target Activity Detected in Any Lead Program

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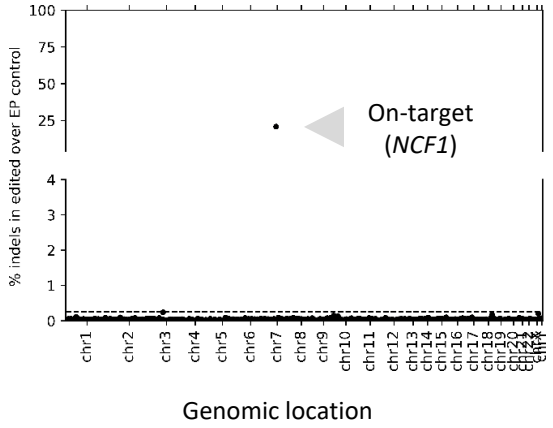
Prime Editing has been evaluated across comprehensive suite of robust, IND-ready assays for off-target discovery

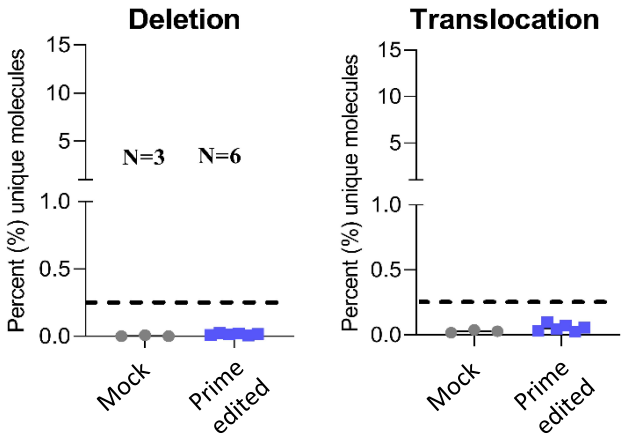
- **No** detectable double strand breakage
- **No** detectable off-target edits
- **No** detectable bystander edits
- **No** detectable large deletions, chromosomal translocations or rearrangements

Examples from CGD Program that are being used to support IND/CTA filings:

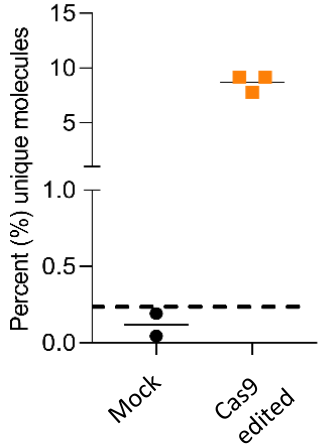
No off-target editing detected in healthy human donor CD34+ cells[1]



No large deletions or translocations observed in bone marrow engrafted **Prime-Edited** LT-HSCs[2]



Translocation positive control: **Cas9 nuclease-edited** cells[3]



[1]Analysis of edited CD34+ cells from CGD program: Targeted *in vitro* Analysis of 550 potential off-target sites of off-target editing. [2]Data from *in vivo* analysis from mouse bone marrow harvested 16 weeks after engraftment was complete. [3]Positive control generated by transfecting HEK293T with sgRNA targeting *NCF1* and SpCas9 mRNA. HSC = hematopoietic stem cell; IND = investigational new drug; CTA = clinical trial application

Direct Comparisons of Prime Editors to CRISPR Showed Substantially Fewer Off-Target Edits Detected with Prime Editing

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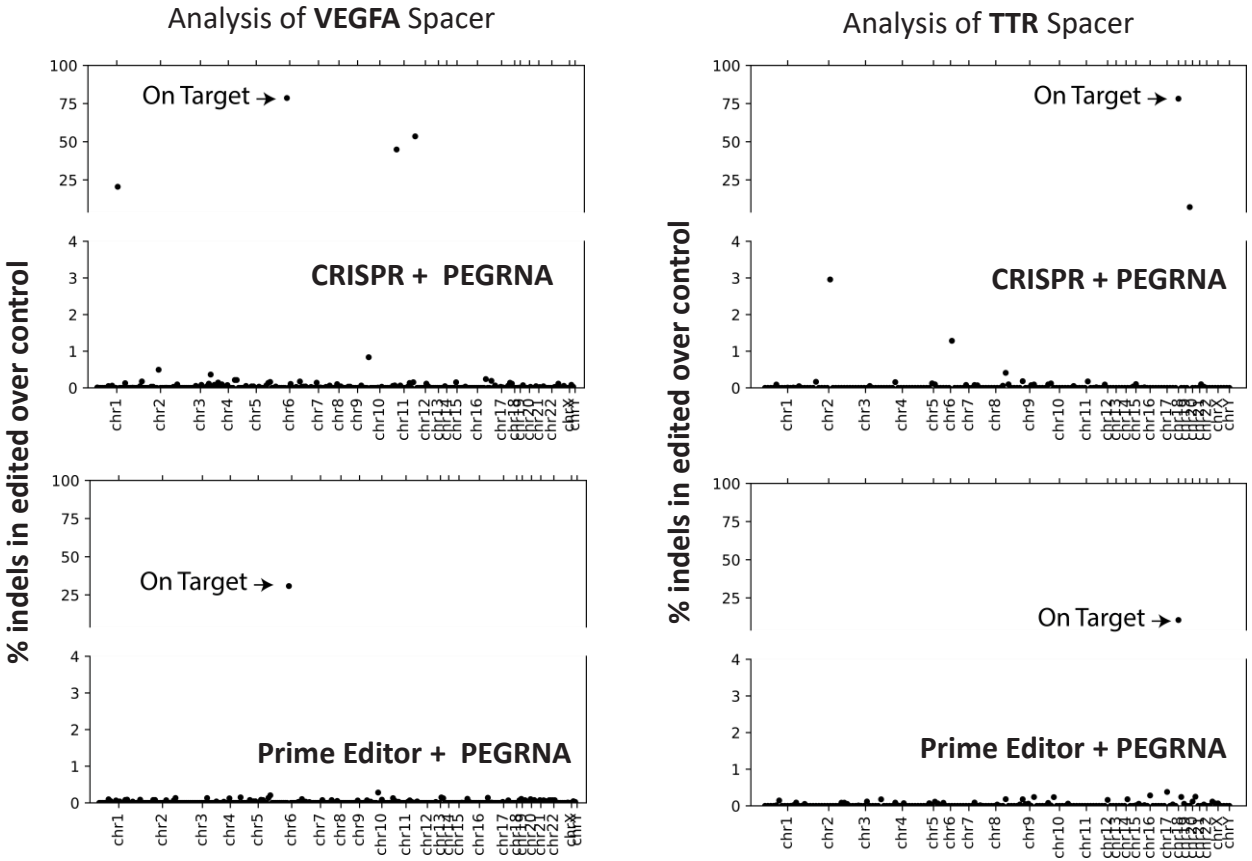
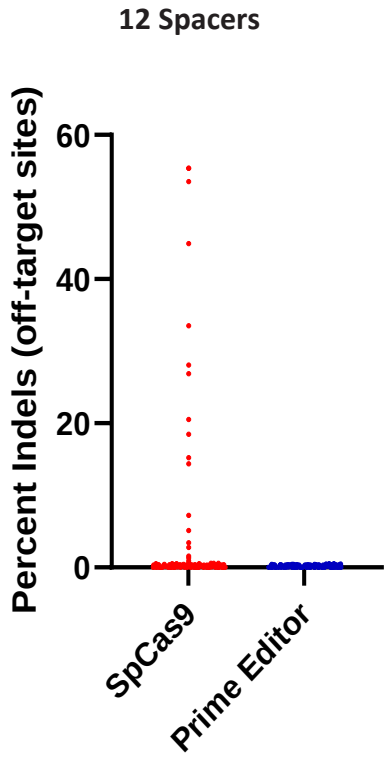
Examples from evaluation of potential off-target sites in Prime Edited or CRISPR-edited cells by deep sequencing





In silico and biochemical tools can be used to define potential off-target sites for Prime Editors

Our Pipeline: Aligned to Core Modular Platforms, With Additional Programs Advancing as Potential Partnership Opportunities

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Modular platform	Indication	Delivery	Discovery	Lead optimization	IND-enabling	Phase 1/2
HEMATOLOGY & IMMUNOLOGY	Chronic Granulomatous Disease	*ex vivo*				
	Other programs in discovery: Fanconi Anemia, Cell Shielding					
LIVER	Wilson's Disease	LNP				
	Glycogen Storage Disease 1b	LNP				
	Undisclosed	LNP				
LUNG	Cystic Fibrosis*	LNP/AAV				
OCULAR	Retinitis Pigmentosa/Rhodopsin	AAV				
	Other programs in discovery: Retinitis Pigmentosa/Usher Syndrome, Fuchs' Endothelial Corneal Dystrophy					
NEURO	Friedreich's Ataxia	AAV				
	Other programs in discovery: Amyotrophic Lateral Sclerosis, Huntington's Disease, Fragile X Syndrome					
MUSCULAR	Myotonic Dystrophy Type 1	viral/non-viral				
	Other programs in discovery: Oculopharyngeal Muscular Dystrophy, Duchenne Muscular Dystrophy					
ADDITIONAL PROGRAMS *Advancing as potential partnership opportunities*	CAR-T (oncology/autoimmune)	*ex vivo*				
	Other programs in discovery: Usher Syndrome (Type 3) (ear); Non-Syndromic Hearing Loss – GJB2 (ear)					

LNP = lipid nanoparticle; AAV = adeno-associated virus; *Initial research funding provided by the Cystic Fibrosis Foundation

Hematology and Immunology

Advancing PM359 to the Clinic for Chronic Granulomatous Disease (CGD), A Disease of Significant Unmet Need

Rare genetic disease, characterized by defective neutrophil function

- Serious life-threatening disease presents in childhood; life expectancy at least 40 years
- Caused by mutation in the p47^{phox} protein[1]
  - Found globally; 100's of patients in U.S. alone[2]
- Results in recurrent, life-threatening infections
  - Difficult to eradicate
  - Frequent hospitalizations, IV antibiotics
  - Potentially deadly infections from normal exposures (gardening, swimming)
- Causes ongoing autoimmunity and inflammation
  - Deteriorating lung function
  - Inflammatory bowel-like syndromes
  - Urinary and gastrointestinal obstruction
- Current treatment options
  - Lifelong anti-microbial therapy: ultimately fails due to evolution of antimicrobial resistance
  - Allogeneic HSCT, only curative option: complicated by GvHD, graft failure, limited availability

We believe Prime Editing is uniquely well-suited to address this form of CGD

NCF1 gene encodes the p47^{phox} protein; HSCT = hematopoietic stem cell transplant; GvHD = graft vs. host disease; [1]P47^{phox} mutation in 25% of patients [2]Prevalence 1:100K-200K

Preclinical Data Support Advancement of PM359 for the Treatment of Chronic Granulomatous Disease

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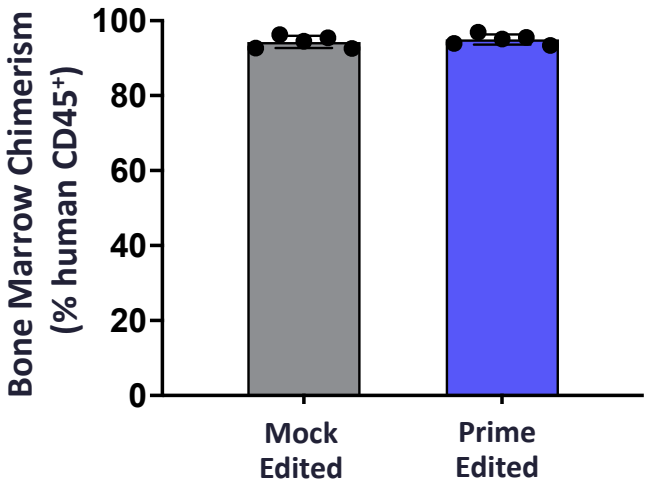
Maintenance of >85% of corrected patient long-term HSCs with complete restoration of NADPH oxidase in neutrophils observed

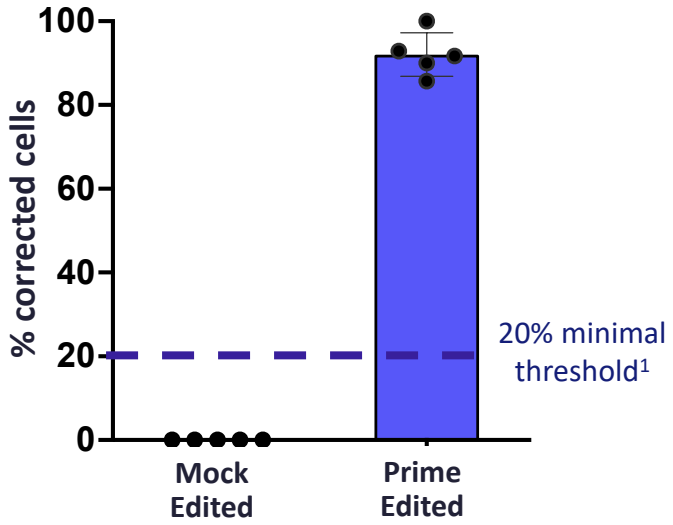
Engraftment

Prime Edited LT-HSCs showed complete engraftment in vivo



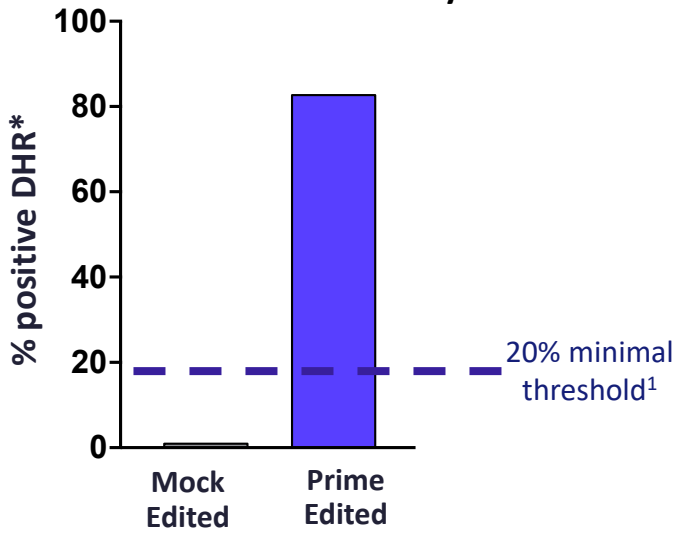
Editing Efficiency

Long-term engrafted HSCs carried precise correction of *NCF1*



Phenotypic Correction

Human neutrophils showed full correction of NADPH oxidase activity ex vivo



- Full immune system reconstitution by Prime Edited LT-HSCs
- Edited LT-HSC derived neutrophils had normal enzymatic activity (NADPH oxidase)

HSC = hematopoietic stem cell; LT-HSC = long term HSC; DHR = dihydrorhodamine; * normalized to healthy donor control. [1]Minimal threshold for patient benefit per Marciano BE, Zerbe CS, Falcone EL, et al. X-linked carriers of chronic granulomatous disease: Illness, lyonization, and stability. *J Allergy Clin Immunol*. 2018;141(1):365-371. doi:10.1016/j.jaci.2017.04.035.
Data presented at ASGCT and ESGCT 2023

With PM359, Prime Medicine is Set to Become a Clinical Stage Company Poised to Deliver Data in Near-Term

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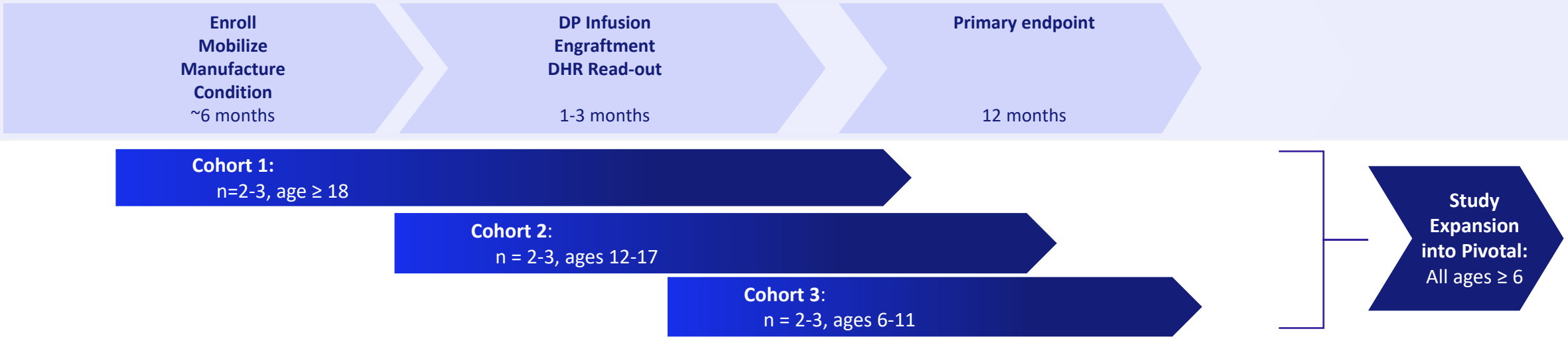
PM359 is comprised of autologous hematopoietic stem cells modified *ex vivo* using Prime Editing



Key eligibility criteria

- delGT mutation in *NCF1* gene
- Dihydrorhodamine (DHR) combined with CGD
- Recent or on-going infectious/inflammatory CGD complications

Key outcome measures

- DHR > 20% normal neutrophil function
- Resolution pre-existing infectious/inflammatory CGD complications
- Frequency new infectious/inflammatory CGD complications

- ✓ DP manufacturing site GMP ready
- ✓ Prime Editing components GMP manufactured, QC tested and ready-for-use to make PM359
- ✓ Global trial sites selected to maximize access to patients, expedite enrollment

IND cleared April 2024
First clinical data expected in 2025

DP = drug product; GMP = good manufacturing practice; QC = quality control; IND = investigational new drug

Regulatory Interactions in U.S. and Globally Further Support Near-Term Clinic Entry with PM359

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In 2023, Prime Medicine:

- ☑ Engaged in **multiple formal and informal interactions** with global regulatory agencies on PM359 program and Prime Editing platform
  - INTERACT and pre-IND meetings with the FDA
  - Interactions with one ex-U.S. agency to-date; two additional pending for early 2024
- ☑ **Prime Medicine has aligned with FDA recommendations** regarding:
  - Preclinical data
  - Toxicology
  - CMC
  - Off-target
  - Clinical development plans
- ☑ Received **Orphan Drug** and **Rare Pediatric Disease Designations** from FDA

INTERACT = INitial Targeted Engagement for Regulatory Advice on CBER producTs; FDA = U.S. Food and Drug Administration; CMC = chemical, manufacturing, and controls

Expanding HSC Platform: Cell Shielding and *In Vivo* Delivery or Targeting

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Current efforts in cell shielding lay foundation for expanding to additional rare and non-rare HSC diseases

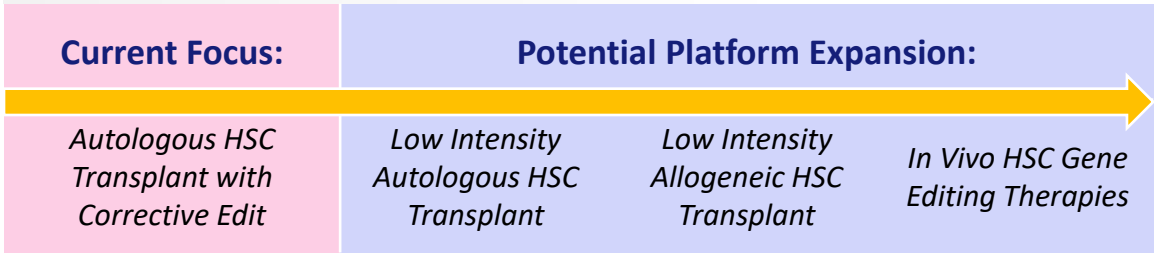
- HSCT market is large and growing
  - Approximately 20K transplants in U.S. annually
- However, myeloablative conditioning regimens are major deterrent
- Cell shielding can gradually and selectively deplete diseased HSCs, reducing toxicity and increasing safety of conditioning process
  - Potential to improve accessibility, eligibility and outcomes, and significantly expand HSC market
- We believe Prime Editing is the most effective way to edit cell shielding epitopes
  - Potential to make any edit, including multiplex with other corrective edits

Continuing to expand HSC platform:

In combination with cell shielding, Prime Editing may:

- Extend utility of HSC transplant
- Enable selection of *in vivo* edited HSCs, allowing for treatment of genetic diseases without transplant

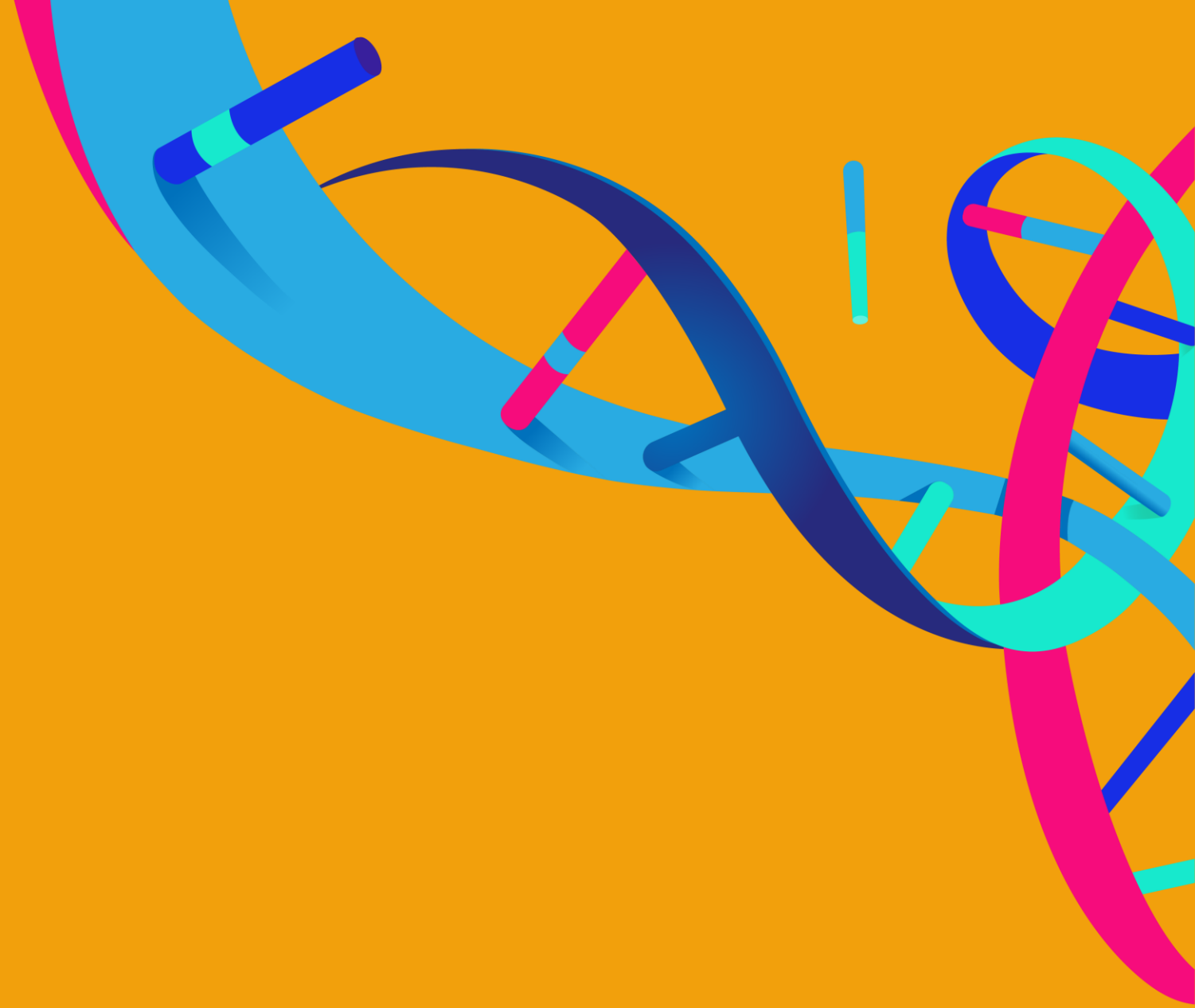
Efforts could significantly broaden addressable market



In June 2023, Prime Medicine entered a research collaboration with Cimeio Therapeutics to develop Prime Editors for Cimeio's CD117 shielding variant

CD117 = cluster of differentiation 117

Liver Disease



Prime Editing to Potentially Correct Pathogenic Mutations Causing Glycogen Storage Disease Type 1b (GSD1b)

Initially aiming to correct the two most prevalent mutations that cause GSD1b, carried by ~ 50% of patients

Glycogen Storage Disease Type 1b

Description:

- Rare disease preventing production of glucose during fasting state, causing hypoglycemic episodes and associated seizures

Human genetics and biology:

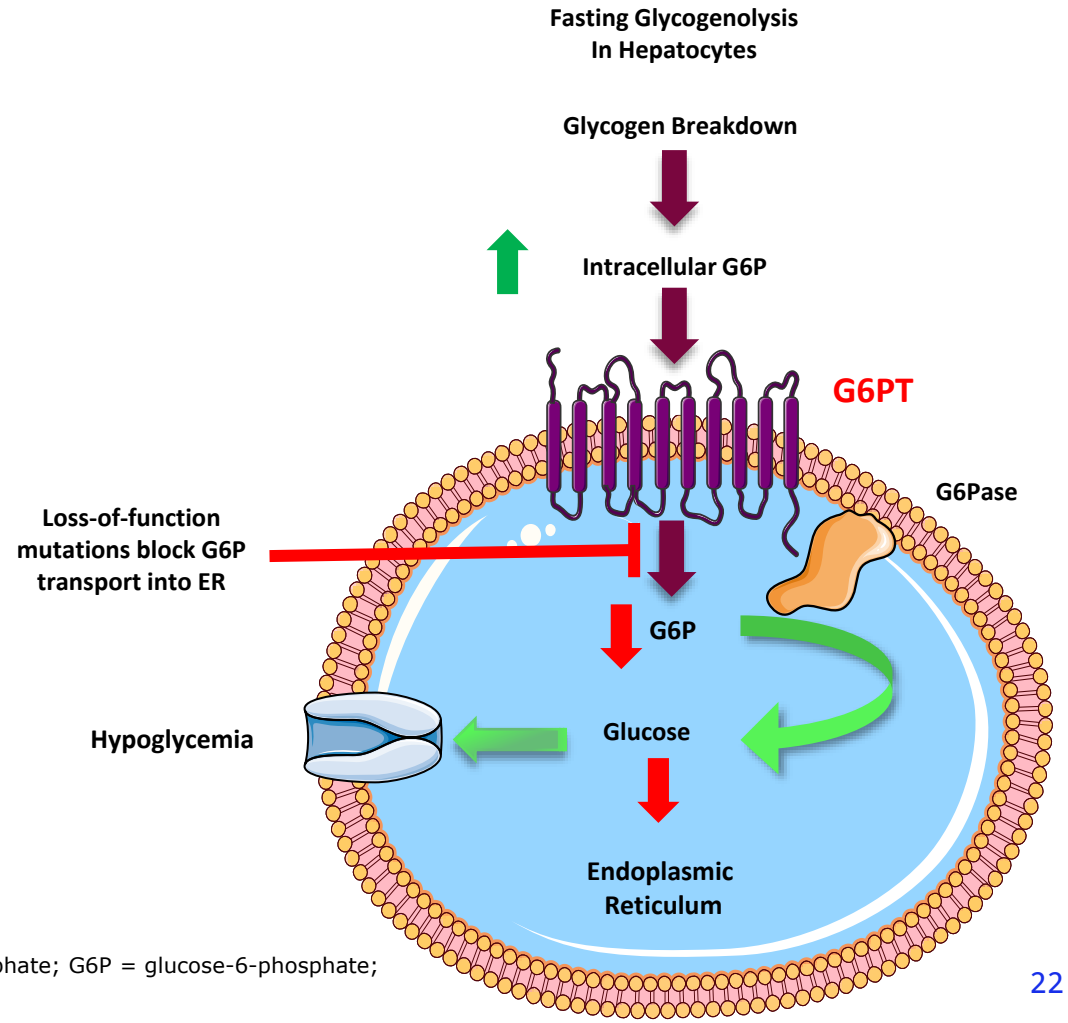
- Autosomal recessive, caused by mutations in the *SLC37A4* gene that encodes G6PT, a glucose-6-phosphate transporter
- **p.L348fs and p.G339C mutations** found in ~50% of GSD1b patient population

Unmet need:

- Standard of care focuses on reducing symptom severity rather than treating the underlying cause of the disease
- No disease modifying therapies approved

Prime Medicine's approach:

- IV administration of liver targeted LNP Prime Editors to correct either p.L348fs mutation or the p.G339C mutation to restore glucose homeostasis in patients with GSD1b



G6PT = glucose-6-phosphate transporter (SLC37A4); G6Pase = glucose-6-phosphate phosphatase; Pi inorganic phosphate; G6P = glucose-6-phosphate; IV = intravenous

Advancing Prime Editors for Two Prevalent Glycogen Storage Disease 1b Mutations[1]

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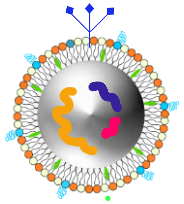
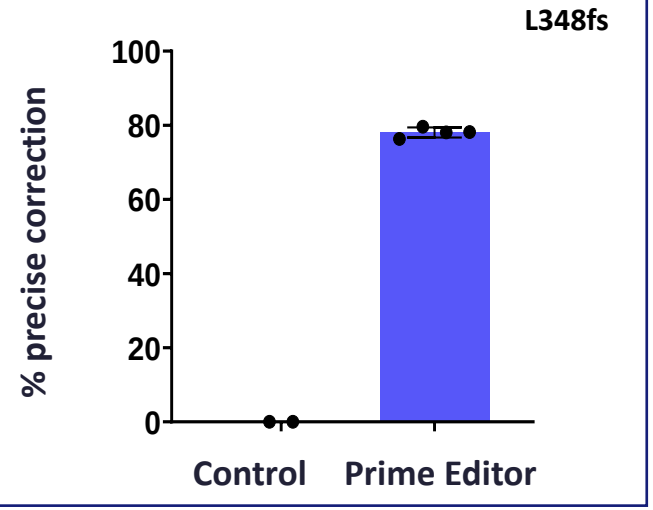


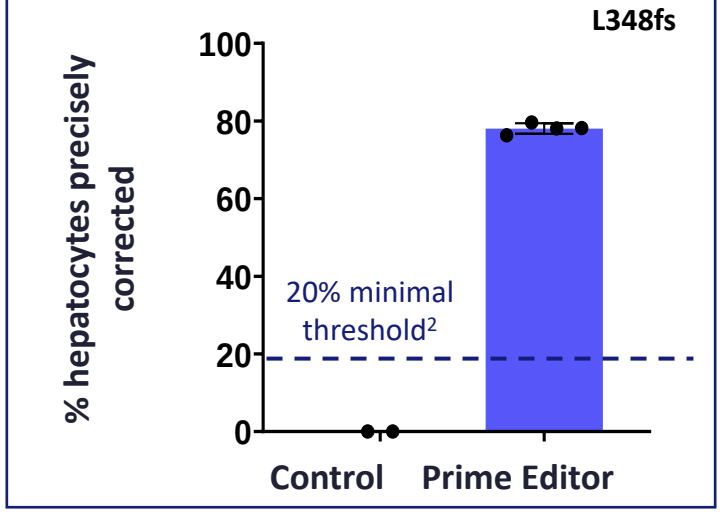
Universal targeted LNP

Prime Editors showed good activity in vivo in humanized mice and in NHP

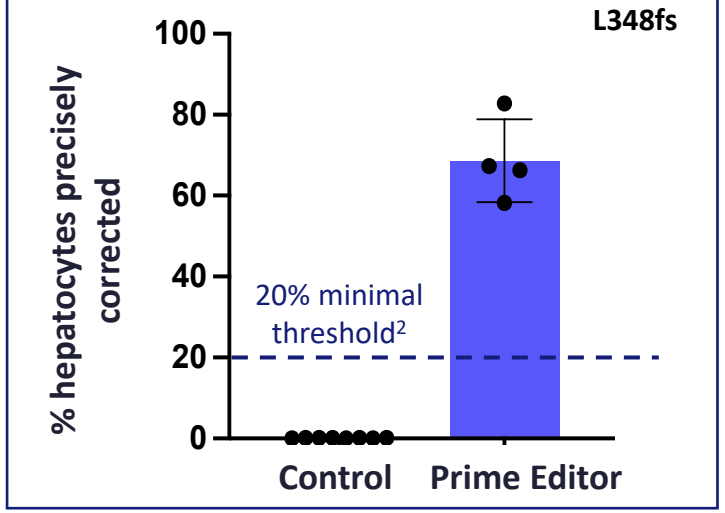
In vitro Prime Editing in Primary Hepatocytes



In vivo Prime Editing in Humanized Mice



In vivo NHP Surrogate Prime Editor*

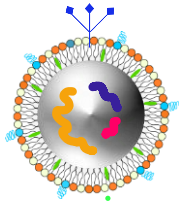


- Prime Editors to correct key mutations are making good progress through lead optimization
- Comprehensive suite of assays developed to enable selection of development candidate and advance to IND enabling studies
- Prime's Universal LNP and modular platform is being applied to accelerate Glycogen Storage Disease 1b
- In safety studies, Prime's Universal LNP generally well tolerated at 2.0mg/kg in NHPs and 3.0mg/kg in rat

[1] Majority of GSD1b patients have L348fs and G339C mutations in U.S. and Europe; [2] Rutten, M. G. S., Derks, T. G. J., Huijkman, N. C. A., Bos, T., Kloosterhuis, N. J., van de Kolk, K. C. W. A., Wolters, J. C., Koster, M. H., Bongiovanni, L., Thomas, R. E., de Bruin, A., van de Sluis, B., & Oosterveer, M. H. (2021). Modeling Phenotypic Heterogeneity of Glycogen Storage Disease Type 1a Liver Disease in Mice by Somatic CRISPR/CRISPR-associated protein 9-Mediated Gene Editing. Hepatology (Baltimore, Md.), 74(5), 2491–2507. https://doi.org/10.1002/hep.32022. * Surrogate Prime Editor is highly similar to human guide

Wilson's Disease Program Continues to Make Progress Against Prevalent[1] Mutations

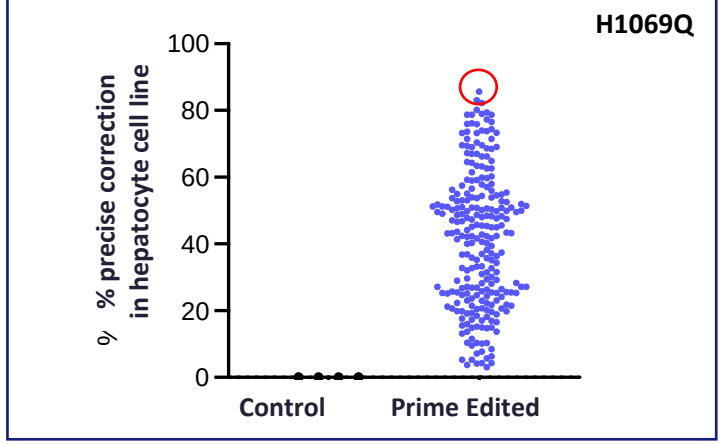
prime_ medicine



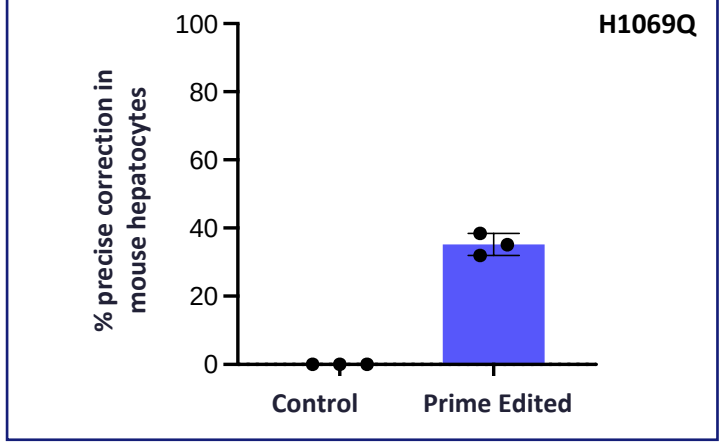
Universal targeted LNP

Highly active Prime Editors for Wilson's Disease undergoing in vivo optimization

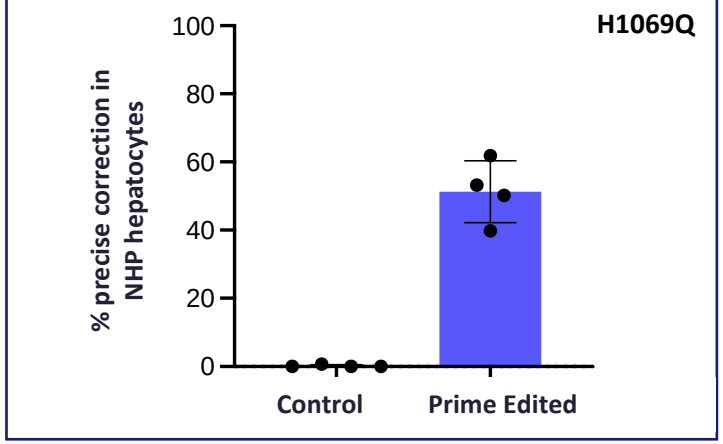
In vitro Prime Editor Screen in Human Hepatocyte Cell Line



In vitro Prime Editor in Primary Hepatocytes



In vitro NHP Surrogate Prime Editor in Primary NHP Hepatocytes

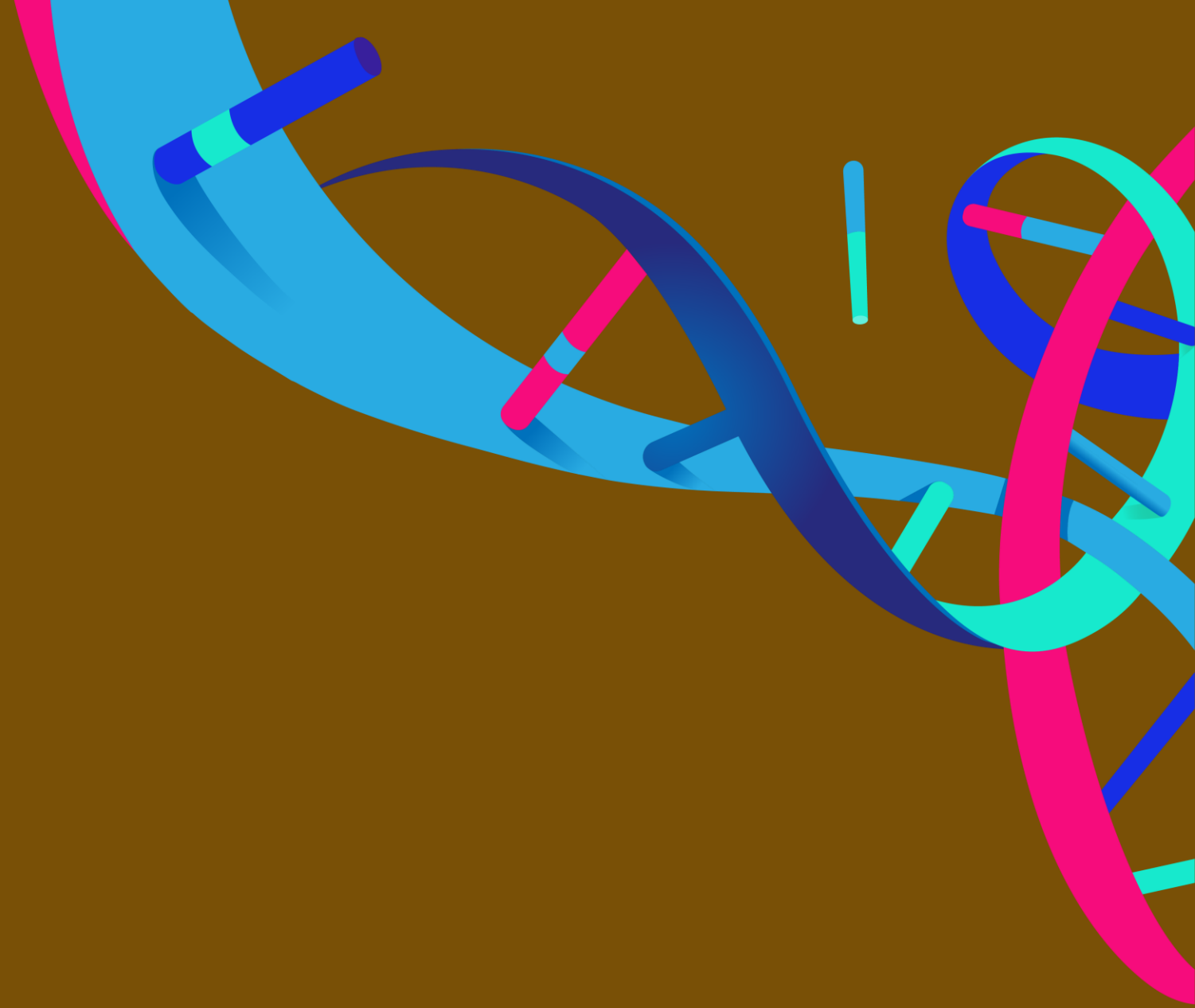


In vivo delivery to NHPs and humanized mice using Prime's Universal Targeted LNP ongoing

- We believe primary hepatocyte data most predictive of in vivo efficacy
- Comprehensive suite of assays developed to enable selection of development candidate and advance to IND enabling studies
- Humanized mouse colonies and NHP colony established for in vivo optimization
- Prime's Universal LNP and modular platform is being applied to accelerate Wilson's Disease

[1] More than 50% of all Wilson's Disease patients have the H1069Q mutation in USA and Europe. Additional Hotspot editor addressing R778L in development.

Lung Disease



In January, Entered into Agreement with CF Foundation for Up to $15 Million to Support Development of Prime Editors for CF

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Funding accelerates development of potentially curative therapies for cystic fibrosis (CF)

Progressing two distinct strategies:

- **Hotspot editing:** potential to address numerous mutations at mutational hotspots with a small number of Prime Editors
- **PASSIGE:** potential to address nearly all CF patients with a single superexon insertion strategy
- **Funding will also accelerate ongoing LNP delivery efforts to the lung**

With infrastructure support and foundational guidance, CF Foundation brings a world-class research lab with established assays, animal models, reagents, patient samples, as well as deep clinical experience and important patient and advocacy efforts

CF impacts close to **40,000** people in the United States.

There is no cure and existing treatments are ineffective for, or not tolerated by, approximately **15%** of patients.

Prime Medicine believes Prime Editing-based approaches could eventually benefit **more than 93%** of all people with CF.

With CF Foundation's support, Prime Medicine has the potential to deliver a one-time, non-viral therapy that offers first cure to all patients living with CF

CF = Cystic Fibrosis

With Hotspot Editing, Prime Editors Corrected "High Unmet Need" CF Mutations, Including the Prevalent G542X (null) Mutation

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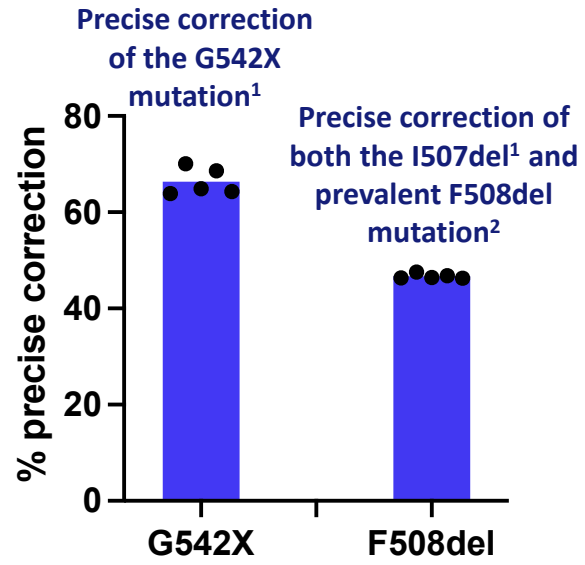
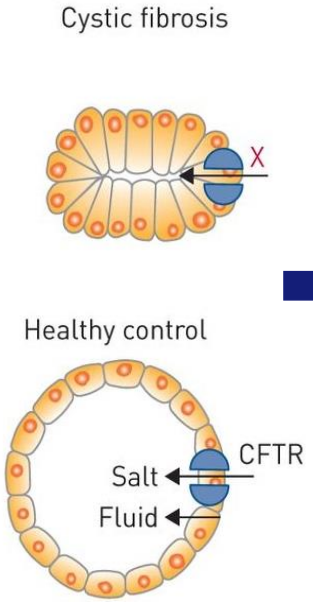
Eight hotspot Prime Editors could address the "high unmet need" mutations; These **same** eight hotspot Prime Editors could address >93% of **all** CF patients

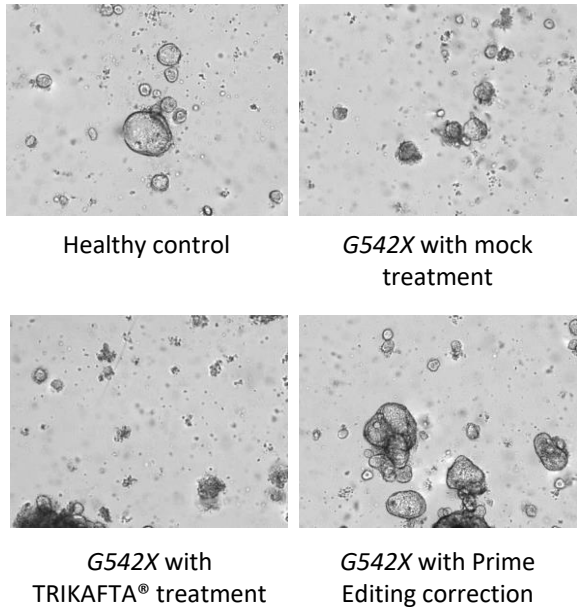
Prime Editors efficiently corrected the G542X mutation and mutations in the I507del/F508del "hotspot"



Intestinal organoids swelling assay for CFTR function



Prime Editing of G542X patient intestinal organoids restored CFTR function



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

- LNP delivered Prime Editors efficiently corrected patient Human Bronchial Epithelial (HBE) progenitors *in vitro*
- Identified early LNP formulations to deliver Prime Editors to lung basal cells *in vivo*

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

[1]G542X and I507del are "high unmet need" mutations; F508del is one of the most prevalent CF mutations; [2]data show correction in patient induced pluripotent stem cells. Each dot shows a different Prime Editor

Ocular Diseases

Early Data with Proprietary Dual-AAV System: Key Step Toward Unlocking Opportunities in Retinal Diseases and Larger Indications

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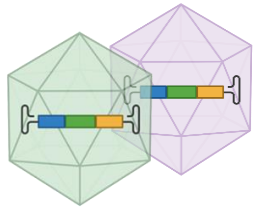
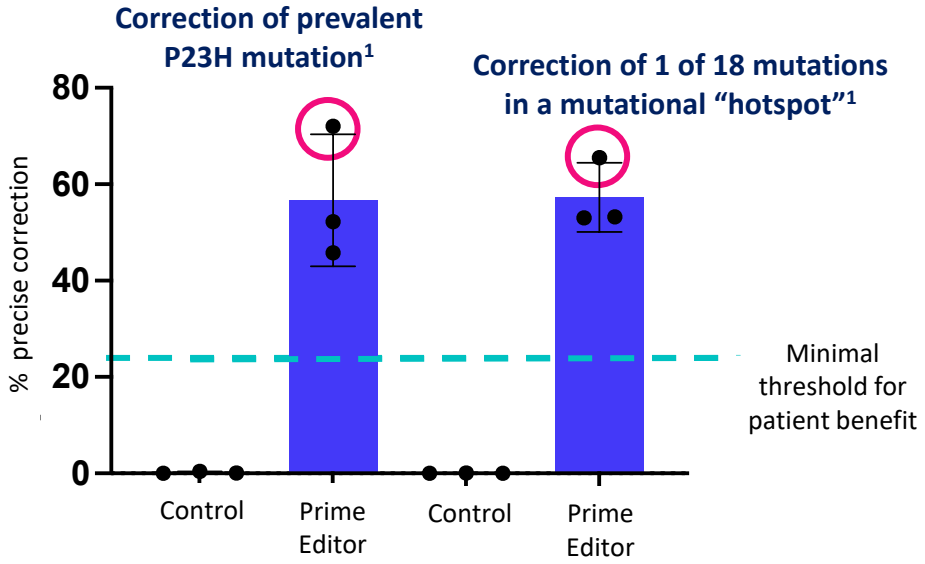
Proof-of-concept achieved: demonstrated ability to correct pathogenic mutations in eye cells with high efficiency and no off-target edits detected



Proprietary dual AAV

In RHO adRP, Prime Editors efficiently corrected a prevalent RHO mutation and all mutations in a mutational "hotspot"



- Precise and efficient correction of prevalent *RHO* mutations: up to ~65-70% precise correction in photoreceptors *in vivo*
- Prime Editors prevented degeneration of retina *in vivo*
- Generally well-tolerated, with no detectable immune response
- No off-target editing detected in human photoreceptors
- No detectable evidence of viral vector integration into retina cells

Proof-of-concept in RHO adRP potentially accelerates development of all retina programs, including Retinitis Pigmentosa/Usher Syndrome program, as well as other ophthalmological diseases

[1]Editing within transduced area of mouse retina; 25% is predicted to be therapeutically beneficial based on Cideciyan et al., 1998. PNAS 95, 7103-7108. Mutations in RHO p.P23H and the two hotspot mutations p.V345L/p.P347L affect approximately 60% of patients with RHO adRP. Single Prime Editor corrects 18 different pathogenic mutations within single hotspot. Data presented at RD2023, October 2023.

Prime Editing to Potentially Correct Pathogenic Mutations Causing Rhodopsin Associated Autosomal Dominant Retinitis Pigmentosa

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Correct prevalent pathogenic mutations in rods to stabilize vision

Disease severity and unmet need

- Rare inherited retinal disease that leads to vision loss and blindness
- No disease modifying approved therapies
- Progressive loss of vision frequently leading to legal blindness by age 40-50

Human biology:

- RHO adRP is caused by mutations in RHO gene encodes opsin which is localized to the outer segments of rod photoreceptors
- Isomerization of 11-cis retinal associated with opsin (Rhodopsin) to all-trans retinal is required for vision
- Rhodopsin and is necessary for structural integrity of rod photoreceptors (and subsequently cones)

Prime Medicine's therapeutic approach:

- Dual AAV based prime editing approach to correct mutations in Rod Photoreceptors

OPPORTUNITY

Prevalence

RHO adRP affects 1 in 50,000 in the US

- P23H transversion accounts for ~30% of US patients
- P347L is the most common mutation in Europe and accounts for ~21% of patients
- 3 other mutations T58R, R135L, V345L account for ~14% of patients

Current Treatment

No Treatment currently available

Neuromuscular Disease

Repeat Expansion Diseases:
A Set of Targets Tailored for Prime Editing Approaches

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Our initial approach is to establish the utility and breadth of Prime Editing technology by precisely removing repeat sequences in the pathological target tissues

Mutation within EXON

Huntington's Disease

Caused by CAG repeat in exon 1 of *HTT*

Prevalence
1 in 15,000 – 20,000 in Western Population

Oculopharyngeal Muscular Dystrophy

Caused by GCG repeat in exon 1 of *PABPN1*

Prevalence
1 in 100,000 in Western Population

Mutation within INTRON

Fuchs' Endothelial Corneal Dystrophy

Caused by CTG repeat in intron 3 of *TCF4*

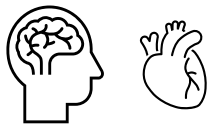
Prevalence
4% of adults >40 years old

Amyotrophic Lateral Sclerosis

Caused by GGGGCC repeat in intron 1 of *C9ORF72*

Incidence
650-1,700 in US and EU5

Friedreich's Ataxia



Caused by GAA repeat in intron 1 of *FXN*

Prevalence
1 in 50,000

Mutation within UTR

Myotonic Dystrophy Type 1

Caused by CTG repeat in 3'UTR of *DMPK*

Prevalence
1 in 2,300

Fragile X Syndrome

Caused by CGG repeat in 5'UTR of *FMR1*

Prevalence
1 in 4,000 male
1 in 8,000 female

short to medium repeat length (typically <200)

medium to very long repeat length (>200, can be several thousands)

Note: The above figure exemplifies our initial approach to repeat expansion diseases, showing disease names, primary organs affected by disease, approximate estimates of prevalence or incidence, type of expansion mutation, gene where expansion mutation occurs, location and approximate length of expansion mutation within the gene

Early *In Vitro* and *In Vivo* Data Suggest Potential for Prime Editing To Address Many Neuromuscular Repeat Expansion Diseases

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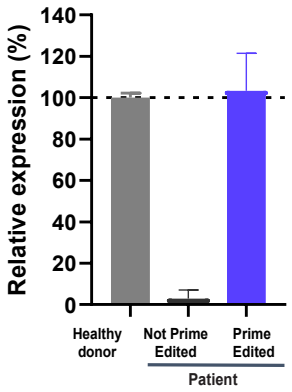
Prime Editors offer potential for genetic correction in patient-derived neurons and muscle

Fragile X Syndrome

PE restored FMRP expression

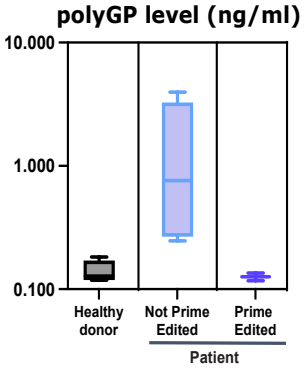
- FMR1 methylation resolved
- FMR1 transcripts normalized
- FMRP protein normalized



Amyotrophic Lateral Sclerosis

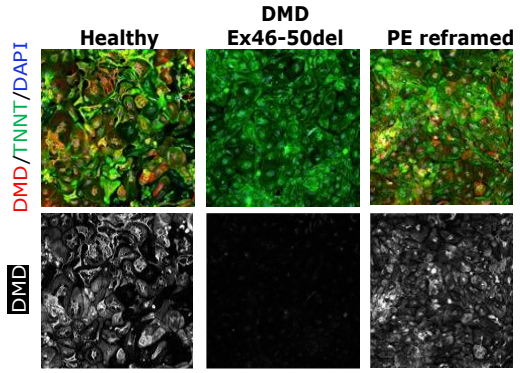
PE restored motor neuron function

- toxic RNA foci resolved
- RAN peptides resolved
- C9ORF72 level restored



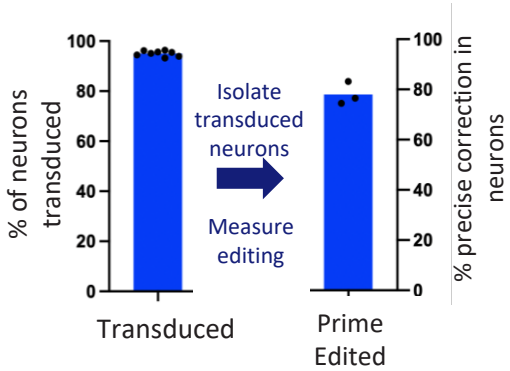
Duchenne Muscular Dystrophy

PE restored dystrophin and cardiomyocyte function



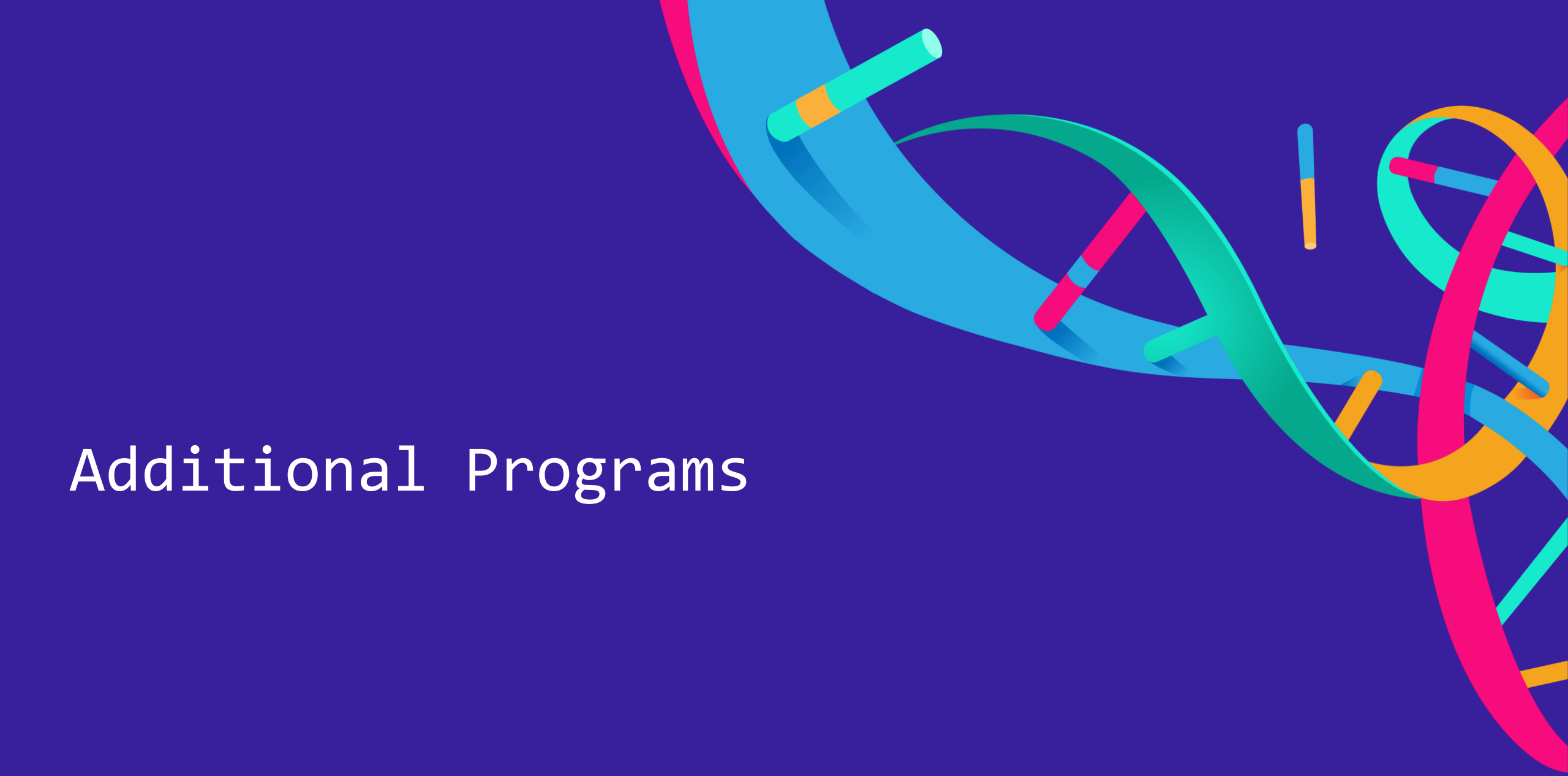
Delivery

PE efficiently edited rodent neurons *in vivo* delivered by dual AAV



- Prime Editors offer a potential curative therapeutic approach for repeat expansion diseases and other neuromuscular diseases
- Prime Medicine is leading with Friedreich's ataxia and amyotrophic lateral sclerosis
- Efficient Prime Editing of neurons by local delivery to the CNS observed in mice
- Current focus on modular AAV delivery system to CNS in large animal studies

Fragile X is caused by mutations in FMR1 gene; RAN peptides = Repeat Associated Non-AUG translation of peptides; DMD = Duchenne Muscular Dystrophy; PE = Prime Editing; TNNT = Troponin T; DAPI = 4',6-diamidino-2-phenylindole



Additional Programs

Delivering on the promise
of Prime Editing

PASSIGE™ and Multiplex Prime Editing Create Potentially Best-in-Class Allogenic CAR-T Cell Product

prime_ medicine

Modularity of platform has potential to accelerate development of additional CAR-T programs

	Existing Limitations	Prime Editing Solution
Multiplex Engineering	✗ Low payload integration efficiency ✗ Constrained to limited number of knock-outs and limited single base pair changes	✓ **>80% integration** efficiency to date, aimed at TRAC locus to maintain **endogenous control** ✓ Capable of **multiple edits done safely**, each with a **full suite of functional modifications**
Safety	✗ Random or semi-random integration ✗ High rate of translocations / chromosomal abnormalities	✓ **Precise on-target** transgene integration ✓ Based on our extensive off-target evaluations in other settings, **there is the potential for no detectable off-target edits, translocations, or unintended structural abnormalities** in Prime-Edited CAR-T's
Manufacturing / Cost of Goods	✗ Dependence on viral components ✗ Complicated by multi-step engineering	✓ **Entirely non-viral** manufacturing process ✓ **Single-step** editing and integration

TRAC = T-cell receptor alpha constant; Data presented at ASH, December 2022, ASGCT, May 2023 and ASH, December 2023

Non-Viral PASSIGE Delivery Supports Integration of CD19 CAR Under Endogenous Control of *TRAC* Locus in up to 80% of T Cells

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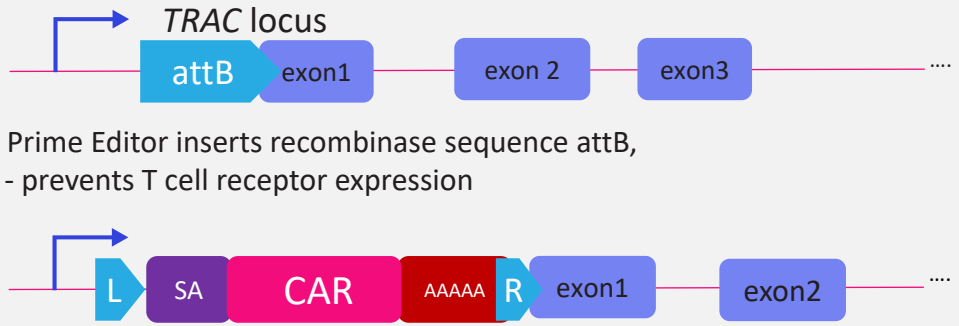
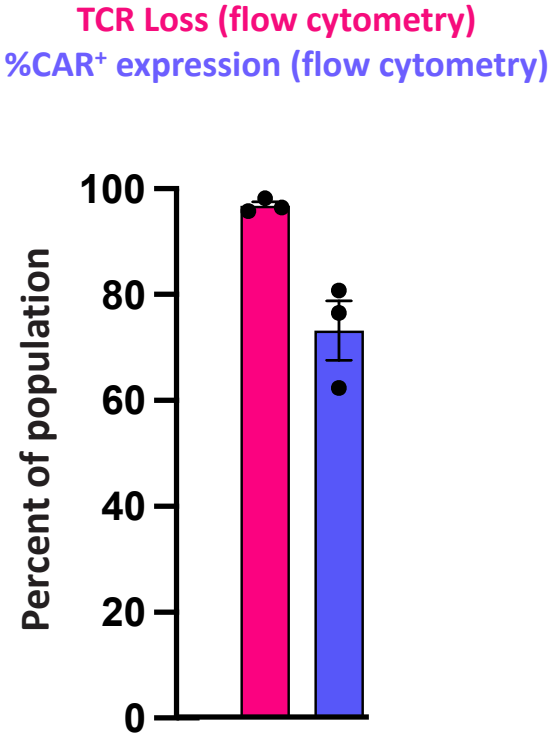
Prime Editing at *TRAC* locus can lead to >95% loss of T cell receptor expression

Schematic for PASSIGE mediated CAR integration





- ✓ Loss of endogenous TCR with attB insertion in *TRAC* exon 1
- ✓ Use of endogenous *TRAC* promoter allows for tuned regulation of CAR expression[1]
- ✓ Promoter-less cargo will not express if integrated elsewhere in genome
- ✓ Pilot studies – no integration elsewhere in genome
- ✓ Up to 8.9kB insertion with high efficiency may enable bi-cistronic CAR

[1]Eyquem et al. (Sadelain) 2017. attB = recombinase attachment site; PASSIGE = prime assisted site-specific integrase gene editing; TCR = T cell receptor; CD19 = cluster of differentiation 19; CAR = chimeric antigen receptor; SA = splice acceptor; AAAAAA = polyA signal

Beyond Precisely Inserting a Chimeric Antigen Receptor, We Can Simultaneously Multiplex Edit to Create a CAR-T Product

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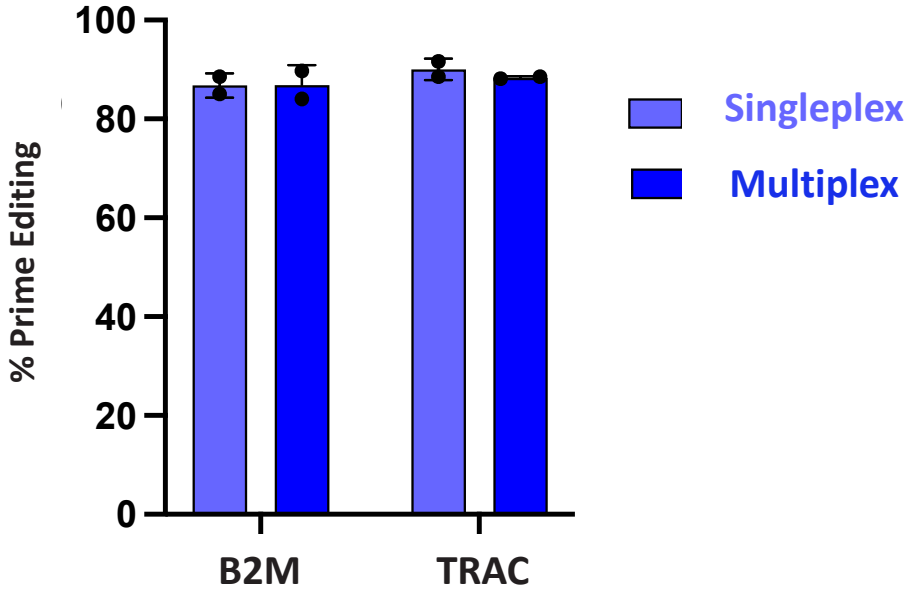
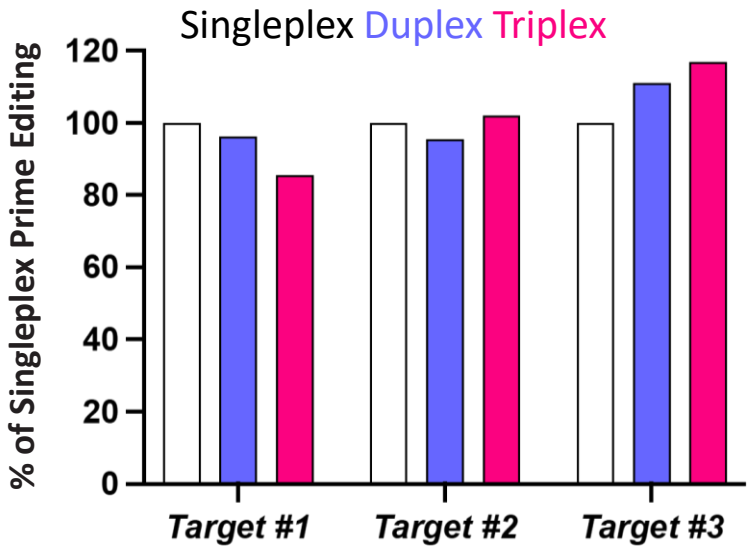
Prime Editors can be multiplexed to introduce multiple genomic modifications in CAR-T cells

β2 microglobulin (B2M) was knocked out by introducing a stop codon precisely in the B2M gene



- Knockout with Prime Editing was efficient in T cells and could be done in multiplex B2M knockout leading to immune evasion

Prime Editing efficiency was maintained in multiplex at three target sites



- PASSIGE and multiplex Prime Editing efficiency were maintained in multiplex
- Up to 6 multiplex edits in T cells with high efficiency

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

Prime Medicine's Multiplexed CD19 CAR-T Cells are Functional *In Vitro* and *In Vivo*

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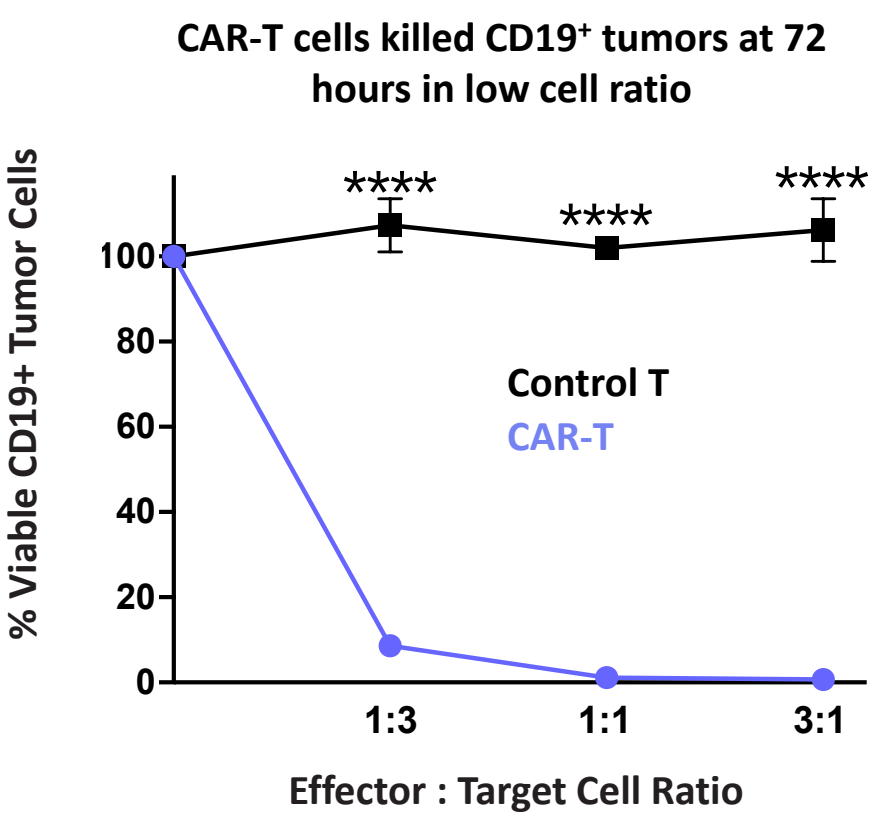
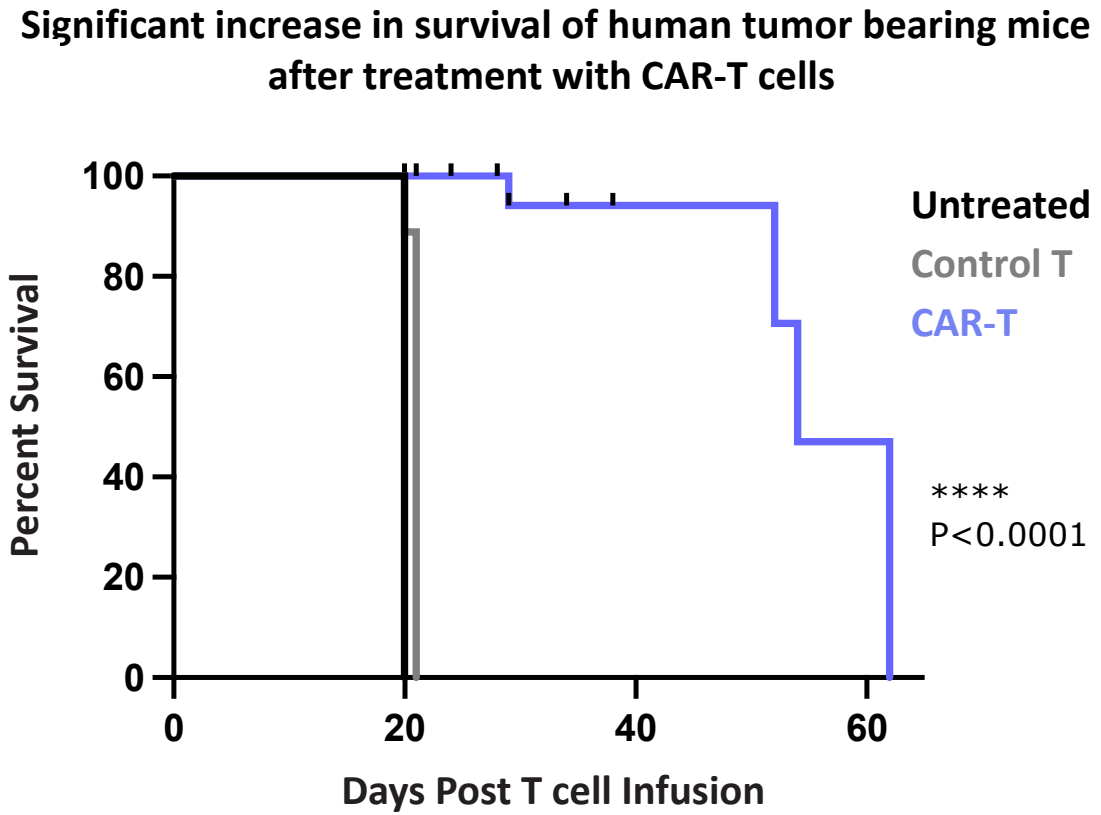
In vitro and in vivo assays showed CD19 CAR-T functionality and specificity for target cell antigen





CAR = chimeric antigen receptor; PASSIGE = prime assisted site-specific integrase gene editing; CD19 = cluster of differentiation 19; Control T has GFP inserted in T cells instead of CD19 CAR; *TRAC* = T cell receptor alpha constant; in vitro data: statistical significance determine by one-way analysis of variance (ANOVA) with Bonferroni post-test; in vivo data: survival curve difference determined by log-rank test

Corporate

Business Development Will Play Critical Role in Building Prime Medicine

Prime Medicine plans to remain active in both sell-side and buy-side business development, with the goal of accelerating our pipeline, bolstering our financial resources, and maximizing the potential of Prime Editing

Recent accomplishments have built a strong foundation to facilitate execution of a multi-pronged business development strategy in 2024 and beyond

- ✓ NHP proof-of-concept achieved
- ✓ Murine proof-of-concept achieved across several programs and delivery modalities
- ✓ Received FDA clearance of first IND application following positive regulatory discussions
- ✓ Industrialization of Prime Editing platform, enabling the exploitation of modularity to rapidly develop product candidates
- ✓ Foundational patents issued

Within Our Core

Partner at the right time with goal to accelerate and globalize

Outside Our Core

Collaborate/license now (e.g., CAR-T, ear, cardiovascular/cardiometabolic)

Access Enabling Innovation

Advance delivery and manufacturing capabilities

NHP = non-human primate; IND = investigational new drug; FDA = U.S. Food and Drug Administration

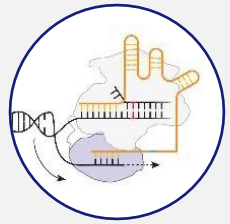
Prime Medicine Holds Extensive Intellectual Property for Prime Editing Technologies

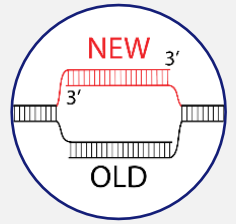
Prime Medicine's IP includes:

- ***Multiple configurations*** of RNA-templated gene editing
  - Prime Editor protein configurations: fusion, separate and split configurations
  - pegRNA configurations: fusion, split, separate and engineered configurations
  - Dual flap and dual guide RNA editing systems
- ***Broad diversity*** of RNA-templated gene editing systems
  - Large variety of nucleic acid programmable DNA binding proteins
  - Extensive range of RNA-dependent DNA polymerases (reverse transcriptases)
- ***PASSIGE™***: System using Prime Editing and recombinase to insert gene-sized DNA at chosen target location in genome
  - PASSIGE systems include various gene editing configurations and recombinases
- ***Additional gene editing technology*** including DNA-dependent DNA polymerase editing
- ***Program-specific patent filings*** for pipeline programs

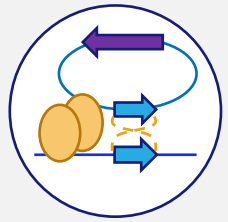
Prime Medicine has 4 in-licensed issued US patents and 1 allowed in-licensed US application

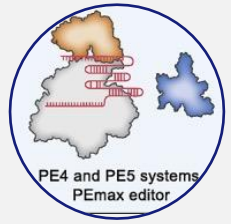
- Numerous pending applications worldwide with broad coverage
- Aggressive filing strategy covering technological advances


Seminal Prime Editing Publication



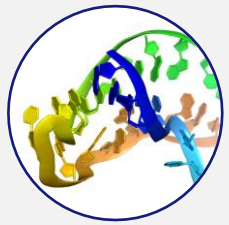
Dual Flap Prime Editing

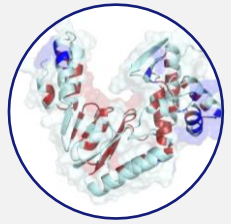

PASSIGE System

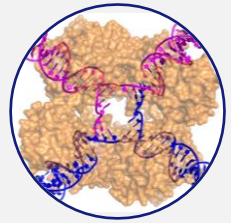


PE4, PE5, and PEmax

Engineered pegRNAs


pegRNA Enhancements


Novel PE Proteins


Improved recombinases

Key Upcoming Events will Drive Prime Medicine Forward, Support Our Maturation into a Clinical-Stage Company

Summary of key ongoing activities and planned next steps for Prime Medicine in 2024-2025

Pipeline

Hematology & Immunology

- ✓ Secure FDA clearance of IND application for PM359 for Chronic Granulomatous Disease (CGD)
- Announce initial clinical data from Phase 1/2 clinical trial of PM359 in CGD in 2025
- Advance Shielded HSC and Immunotherapy Pairs (SCIP) technology, establish preclinical proof-of-concept in HSC and immunotherapy, and identify first clinical program(s) with this approach in 2024
- Advance Prime Medicine's differentiated CAR-T program (using PASSIGE™) into lead optimization

Liver

- Continue to advance preclinical studies for three liver programs; initiate IND-enabling activities for at least one program in 2024, leading to an IND/CTA in 2H 2025/1H 2026

Ocular

- Nominate development candidate for Retinitis Pigmentosa / Rhodopsin (RHO) and initiate IND-enabling activities in 2024

Neuromuscular

- Continue to advance Friedreich's Ataxia program; advance one other program into lead optimization in 2024

Platform

Delivery

- Nominate first development candidate using Prime Medicine's liver-targeted universal LNP platform in 2024
- In large animal studies, establish AAV delivery platform and a route of administration for neuromuscular programs in 2024

Regulatory

- Advance discussions with regulatory agencies on platform strategy for streamlined development

As of March 31, 2024, Prime Medicine had estimated cash, restricted cash, cash equivalents and investments of $224.2 million*

IND = investigational new drug; CTA = clinical trial application; HSC = hematopoietic stem cell. *As of March 31, 2024, Prime Medicine had estimated restricted cash of $13.5 million.

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Delivering on the promise of Prime Editing

Appendix

primemedicine.com

Team with Significant Scientific and Drug Development Experience

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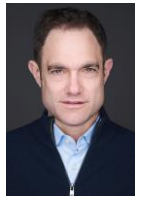
Team

Keith Gottesdiener, M.D.
President and CEO
Rhythm Pharmaceuticals · MERCK



Allan Reine, M.D.
Chief Financial Officer
FOGHORN THERAPEUTICS · pieris

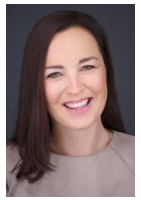
Jeremy Duffield, M.D., Ph.D.
Chief Scientific Officer
VERTEX · Biogen · MGH 1811

Ann L. Lee, Ph.D.
Chief Technical Officer
Bristol Myers Squibb · MERCK · Juno Therapeutics · Celgene

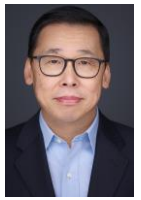
Andrew Anzalone, M.D., Ph.D.
Co-Founder and Head of Prime Editing Platform
BROAD INSTITUTE

Meredith Goldwasser, Sc.D.
SVP, Head of Strategy and Corporate Ops
agios · Genentech · NOVARTIS

Richard Brudnick
Chief Business Officer
CODIAK · Bioverativ · Biogen

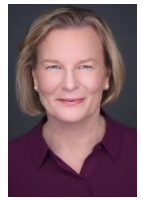


Niamh Alix
Chief Human Resources Officer
Orchard therapeutics · Lonza · NOVARTIS



Fubao Wang, Ph.D
SVP, Head of Regulatory
SAREPTA THERAPEUTICS · MERCK · SANOFI

Mohammed Asmal, M.D., Ph.D.
SVP, Head of Clinical
bluebirdbio · VERTEX



Karen Brown, Ph.D., JD
SVP, Intellectual Property and Legal Affairs
OBSIDIAN THERAPEUTICS · Ironwood · VERTEX

Carman Alenson, CPA
Chief Accounting Officer and SVP Finance
agios · amag

Board of Directors

Keith Gottesdiener, M.D.
President and CEO, Prime Medicine

David Schenkein, M.D.
General Partner, GV

Robert Nelsen
Managing Director, Arch Ventures

Jeff Marrazzo
Former CEO, Spark Therapeutics

Michael A. Kelly
Founder & President of Sentry Hill Partners, LLC

Wendy Chung, M.D., Ph.D.
Chair of Pediatrics, Boston Children's Hospital

Thomas Cahill, M.D., Ph.D.
Managing Partner, Newpath Partners

Kaye Foster
Senior Advisor, Boston Consulting Group

Scientific Advisory Board

David Liu, Ph.D.
(SAB Chair and Co-Founder)

Yvonne Chen, Ph.D.

Agnieszka Czechowicz, M.D., Ph.D.

Guangping Gao, Ph.D.

Jim Haber, Ph.D.

Anastasia Khvorova, Ph.D.

Ben Kleinstiver, Ph.D.

Muthiah (Mano) Manoharan, Ph.D.

Eric Olson, Ph.D.

Gerald Schwank, Ph.D.

Jay Shendure, MD, Ph.D.

Samuel Sternberg, Ph.D.

Shengdar Tsai, Ph.D.

Building the Company

Currently

- ~230 employees; approximately 85% across R&D and Clinical Development organizations
- C-Suite and key functional leadership and employees in place organization wide
- Strengthened core capabilities across the company including automated high throughput screening, comprehensive end-to-end guide RNA chemistry production, extensive internal CMC capabilities through GLP, LNP discovery through GLP production for Prime Editor delivery
- Established clinical development and regulatory affairs expertise and capabilities

Critical Milestones Achieved

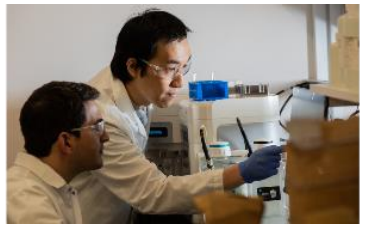
September 2019 $115M Series A

October 2019 Prime Editing seminal Nature[1] paper

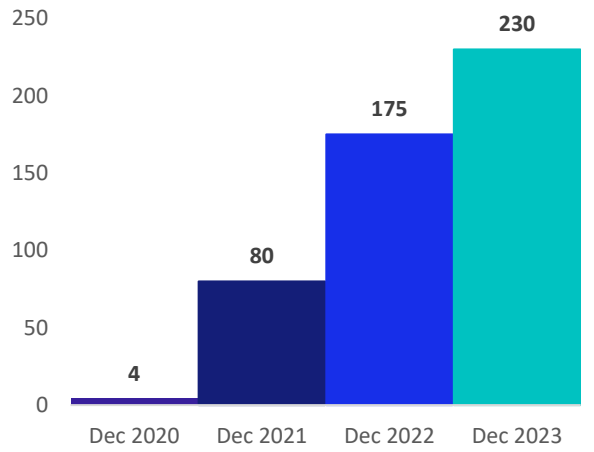
July 2020 Commenced Corporate Operations

April 2021 $200M Series B

Oct 2022 ~$200M IPO



Successful Growth of Talent



CMC = chemistry, manufacturing and controls; GLP = good laboratory practice; LNP = lipid nanoparticle

Friedreich's Ataxia (FRDA) is an Autosomal Recessive Repeat Expansion Neuromuscular Disease

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Clinical Manifestations

- Multisystem disorder affecting the nervous system, heart, pancreas, retina
- Gait and limb ataxia due to sensory neuropathy, cerebellar pathology
- Age of onset 5 – 16 years. Mean age of death: 39 years

Human biology:

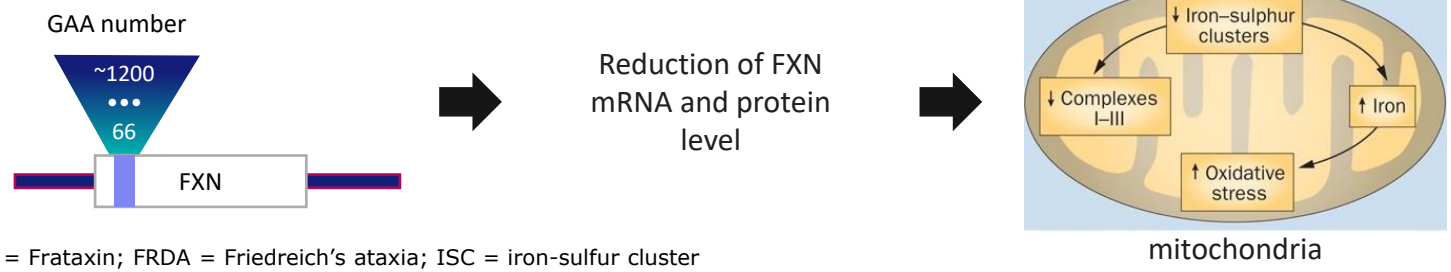
- Autosomal recessive: GAA repeat expansion in intron 1 of Frataxin (FXN) gene
- Full-penetrance allele carries 66 to 1,200 GAA repeats
- GAA repeat expansion causes decreased FXN mRNA and frataxin protein
- Defective iron metabolism causes reduced activity of ISC-containing enzymes in mitochondria, impairing energy generation in sensory neurons and cardiac cells

Prime Medicine's therapeutic approach:

- AAV-delivery of Prime Editor to remove pathological GAA repeats from FXN and restore frataxin protein expression.

Prevalence

Approximately 4,000 patients in the US, ~15-19k globally



Source: bicycling.com, Bryan Kirkwood

FXN = Frataxin; FRDA = Friedreich's ataxia; ISC = iron-sulfur cluster

Efficient Removal of Pathogenic Repeats in Friedreich's Ataxia Patient Cells by Prime Editors

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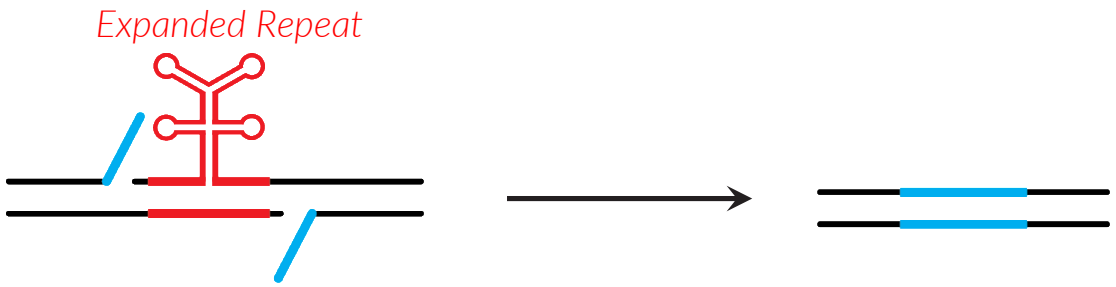
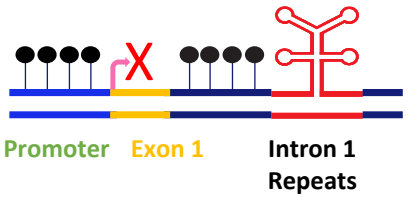
Removal of pathological GAA repeats and hypermethylation at the Frataxin (*FXN*) gene in Friedreich's Ataxia patient cells

Dual-flap Prime Editing loops out expanded repeat

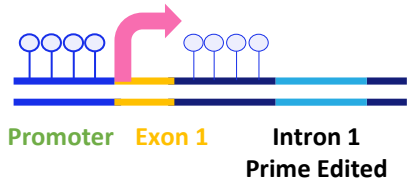


Hypermethylation prevents mRNA transcription of *FXN*



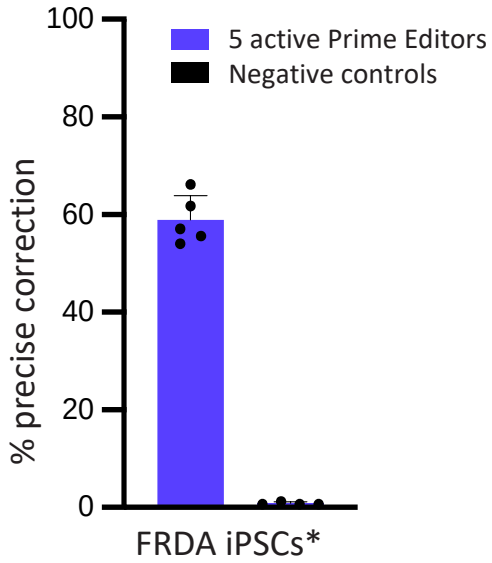
Prime Editing

Demethylation by Prime Editing restores mRNA transcription of *FXN*

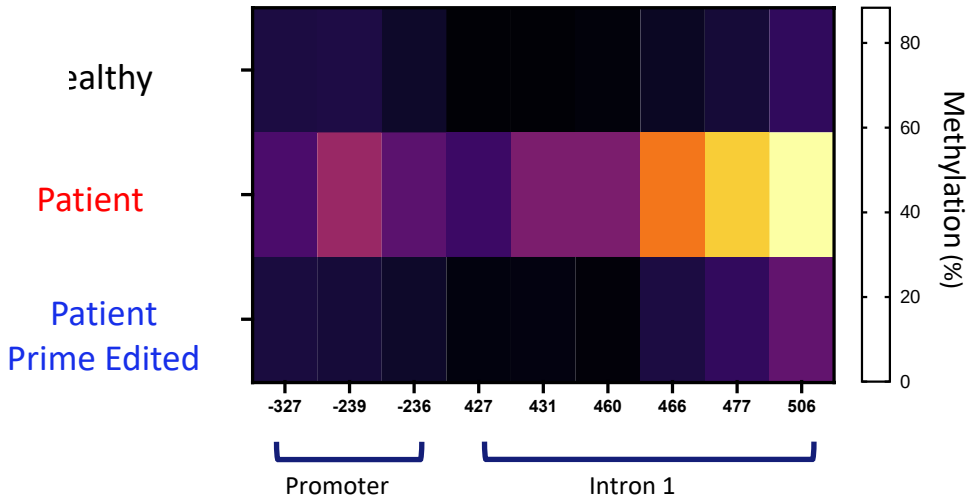


Conclusions

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



Removal of Hypermethylation[1]



Many repeat expansion diseases exhibit hypermethylation 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

Prime Editors Efficiently Remove Pathogenic Repeats in Friedreich's Ataxia Patient Cells and Restore Frataxin Function

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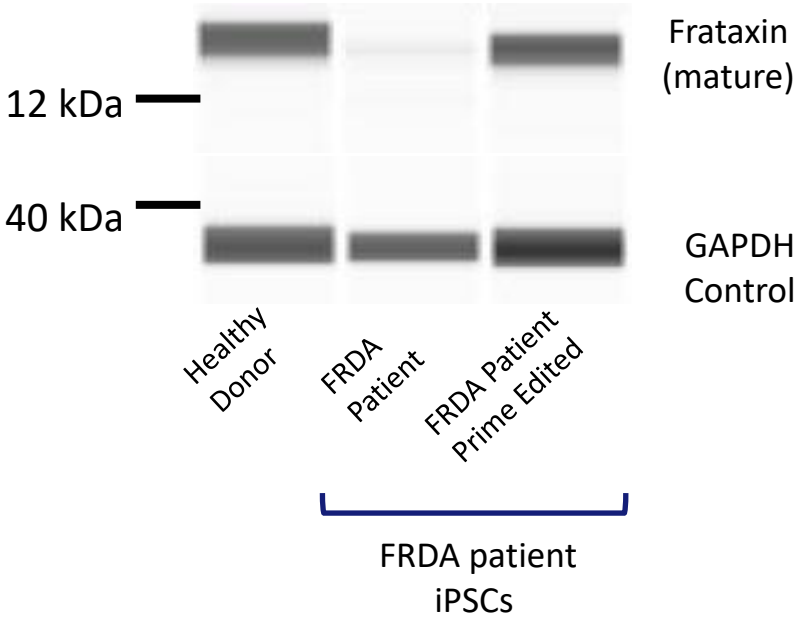
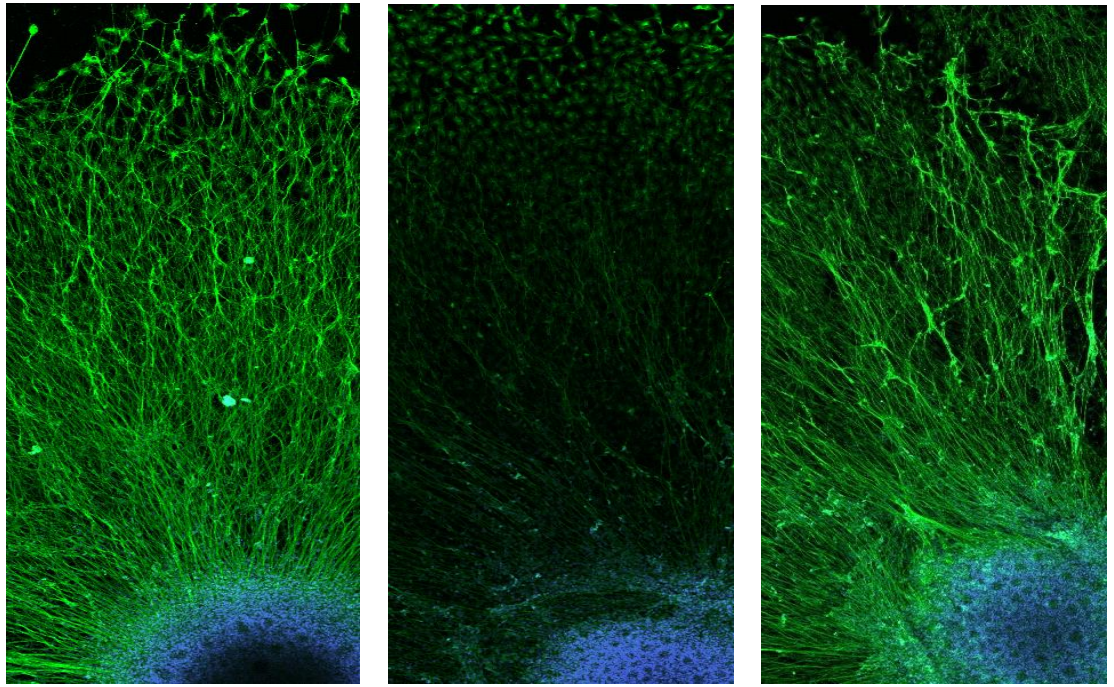
High-efficiency Prime Editing restores FXN protein expression and sensory neuron phenotype in Friedreich's Ataxia patients' dorsal root ganglia organoids

Restoration of Frataxin protein expression after delivery of Prime Editor



Restoration of axonal projections after Prime Editor correction

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

With Hotspot Editing, Prime Editors Corrected "High Unmet Need" CF Mutations, Including the Prevalent G542X (null) Mutation

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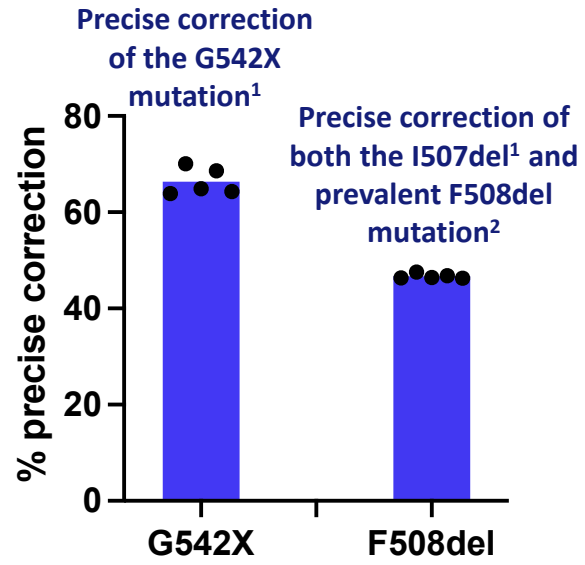
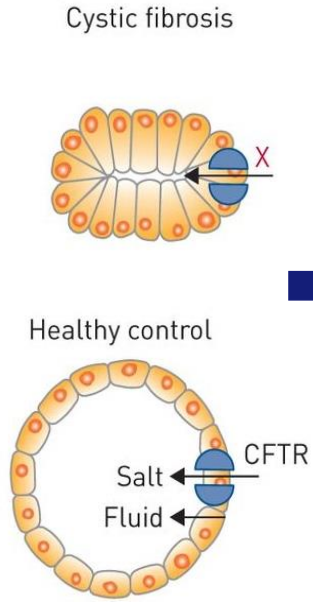
Eight hotspot Prime Editors could address the "high unmet need" mutations; These **same** eight hotspot Prime Editors could address >93% of **all** CF patients

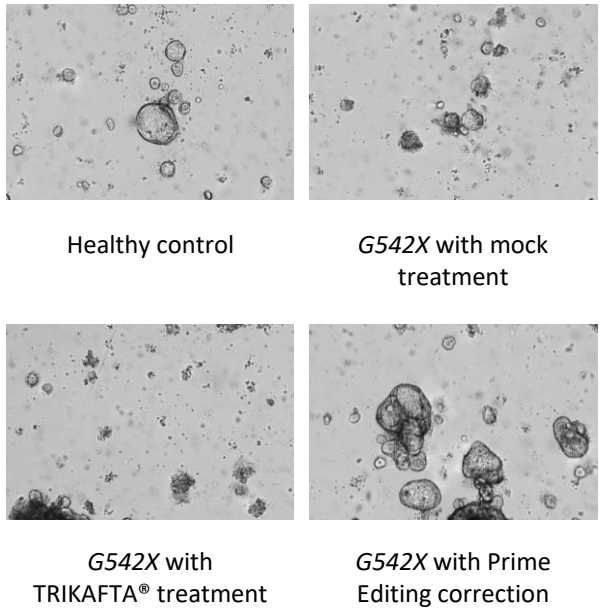
Prime Editors efficiently corrected the G542X mutation and mutations in the I507del/F508del "hotspot"



Intestinal organoids swelling assay for CFTR function



Prime Editing of G542X patient intestinal organoids restored CFTR function



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

- LNP delivered Prime Editors efficiently corrected patient Human Bronchial Epithelial (HBE) progenitors *in vitro*
- Identified early LNP formulations to deliver Prime Editors to lung basal cells *in vivo*

Van Mourik et al., 2019. Actual time course: 24 hours. TRIKAFTA® is a registered trademark of Vertex Pharmaceuticals, Incorporated.
[1]G542X and I507del are "high unmet need" mutations; F508del is one of the most prevalent CF mutations; [2]data show correction in patient induced pluripotent stem cells. Each dot shows a different Prime Editor

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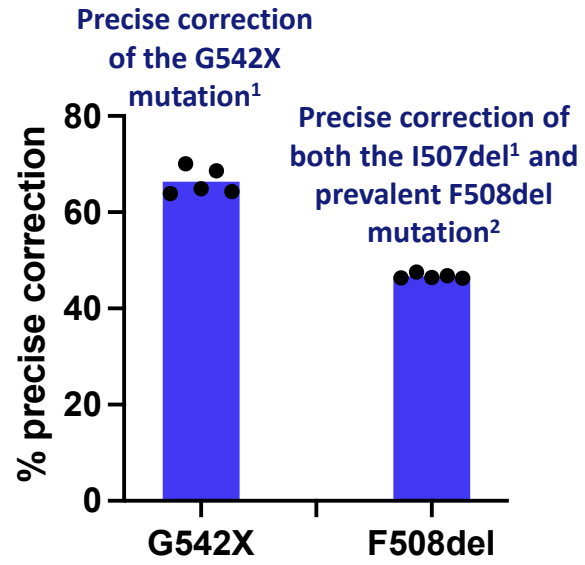

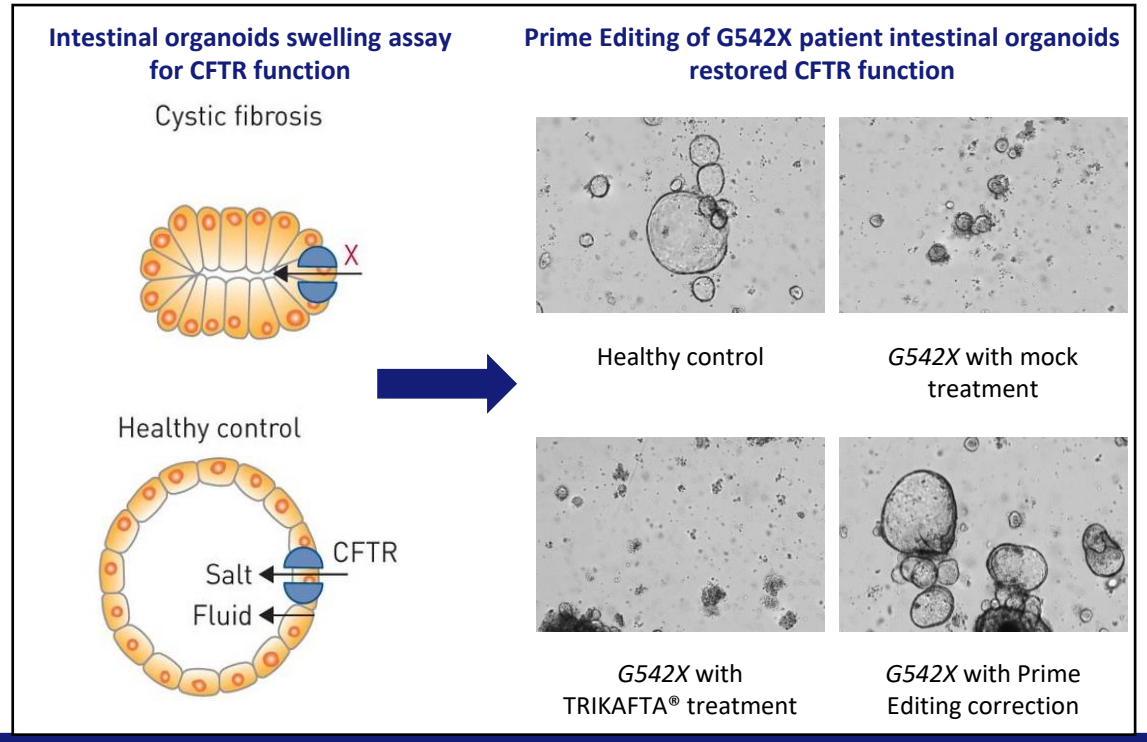

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