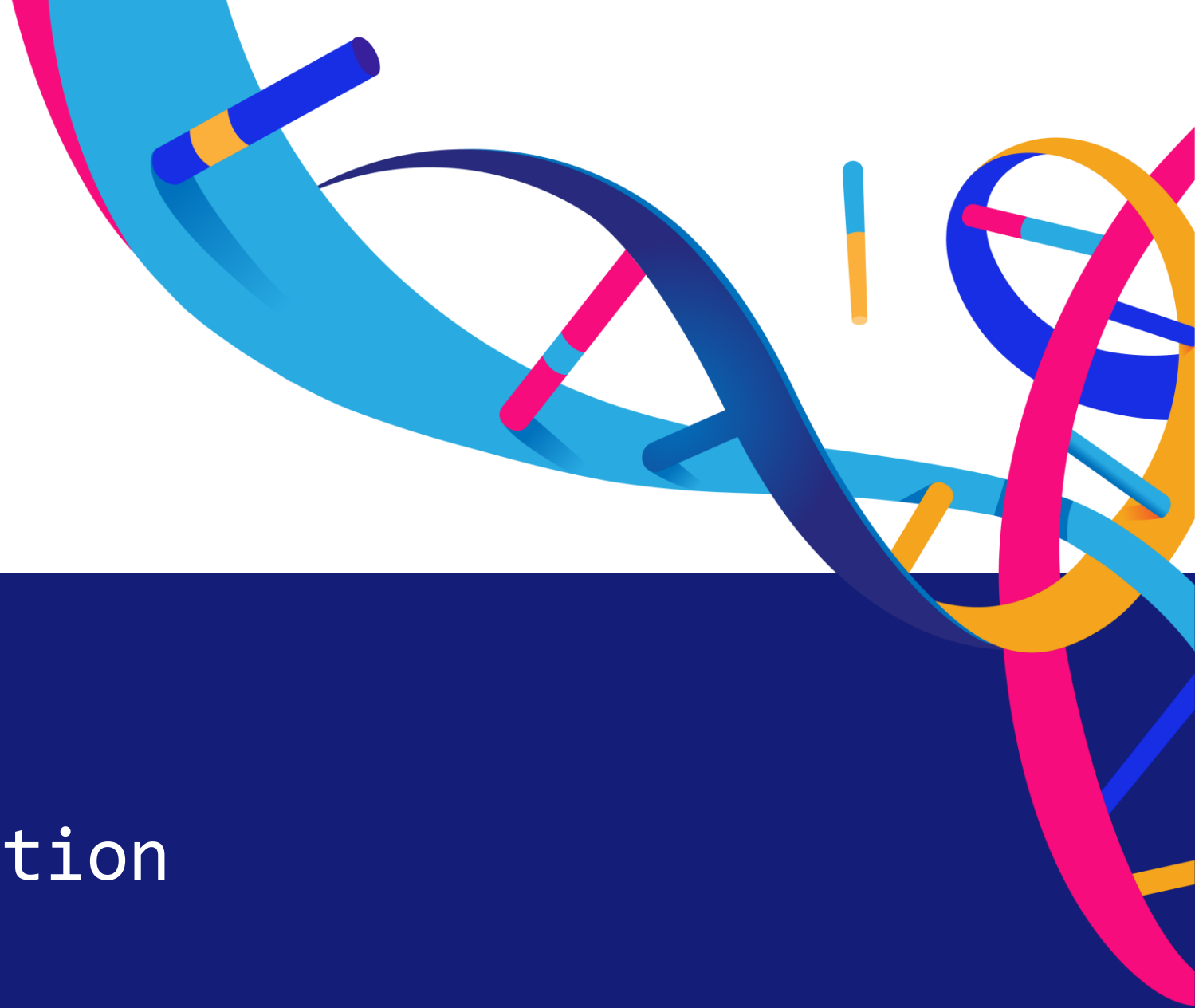




Delivering on the promise  
of Prime Editing

# Corporate Presentation

February 2024

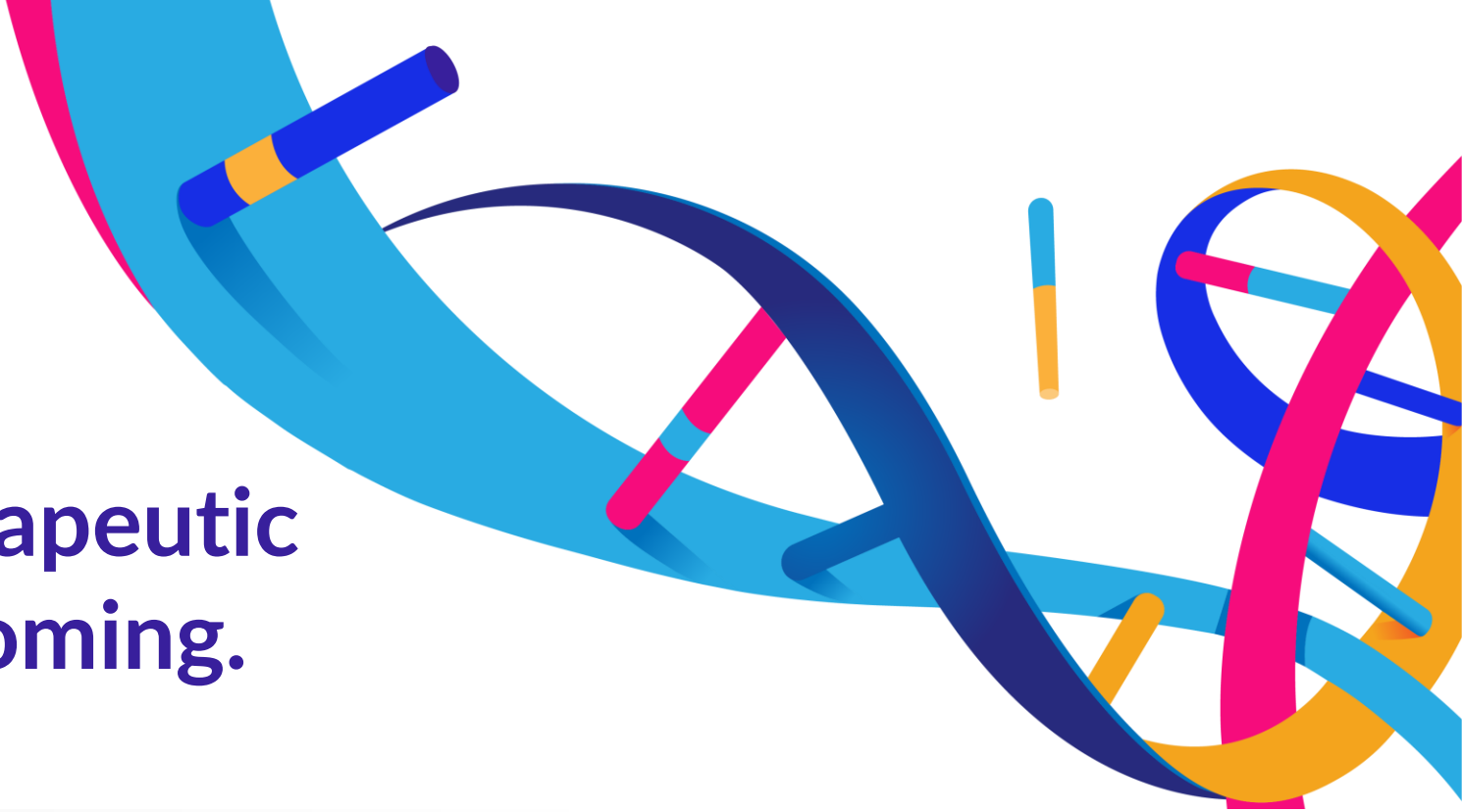


# Forward Looking Statements

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 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 our anticipated initial IND submission for CGD as early as 2024 with additional 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; 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 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 December 31, 2023 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 Intellia Therapeutics to run a Phase 1 trial of its gene editing therapy for transthyretin (ATTR) amyloidosis with c... for the first pivotal study of an *in vivo* gene editing tr...

## *New Gene Editing Treatment Cuts Dangerous Cholesterol in Small Study*

The trial involved only 10 patients, but it suggests cholesterol can be permanently reduced with a single... risk of heart disease.

## *Panel Says That Innovative Gene Editing Cure Is Safe Enough for Patients*

The decision by an advisory committee may lead to Food and Drug Administration approval of the first treatment for humans that uses the CRISPR gene-editing system.

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

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

\* 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

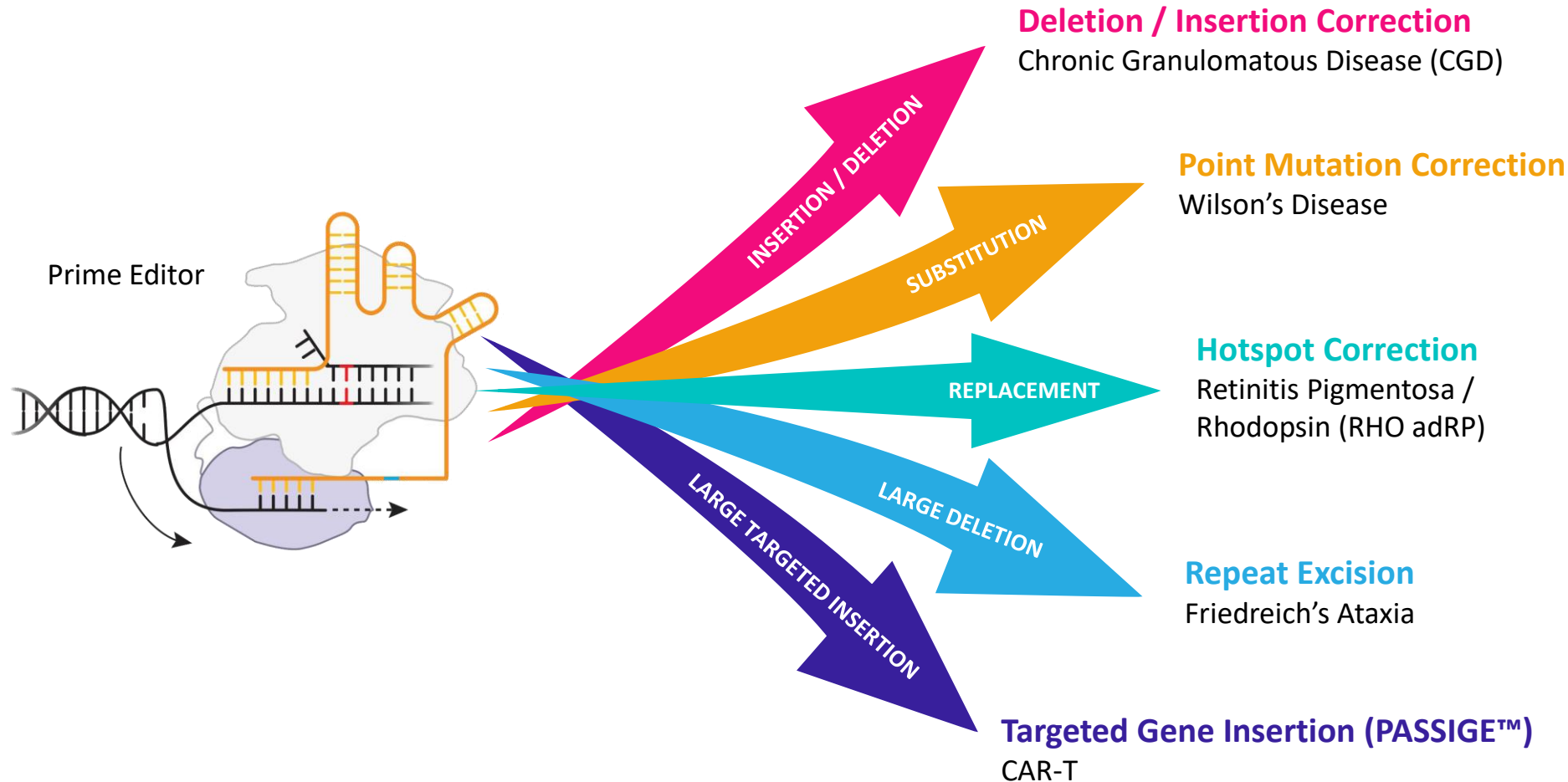
In 2024, Prime Medicine expects to bring the first-ever Prime Editing-based therapeutic candidate to patients and build value through strategic investments in pipeline and platform advancements

## 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

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



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

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

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

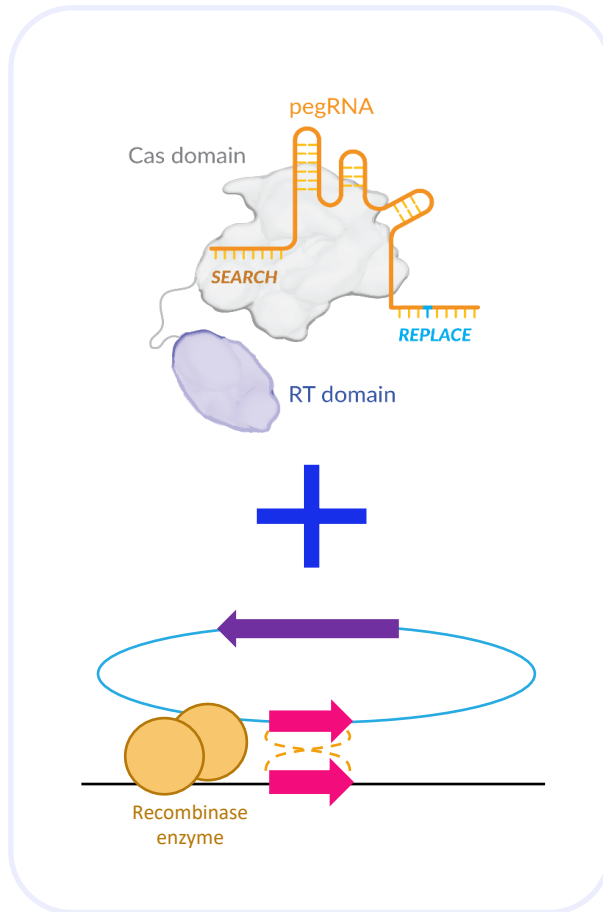
+ / ++ / +++ = how fit Prime Medicine believes the technology is for making the edit, based on Prime Medicine's internal assessment



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

PASSIGE: Prime-Assisted Site-Specific Integrase Gene Eding:

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\*)



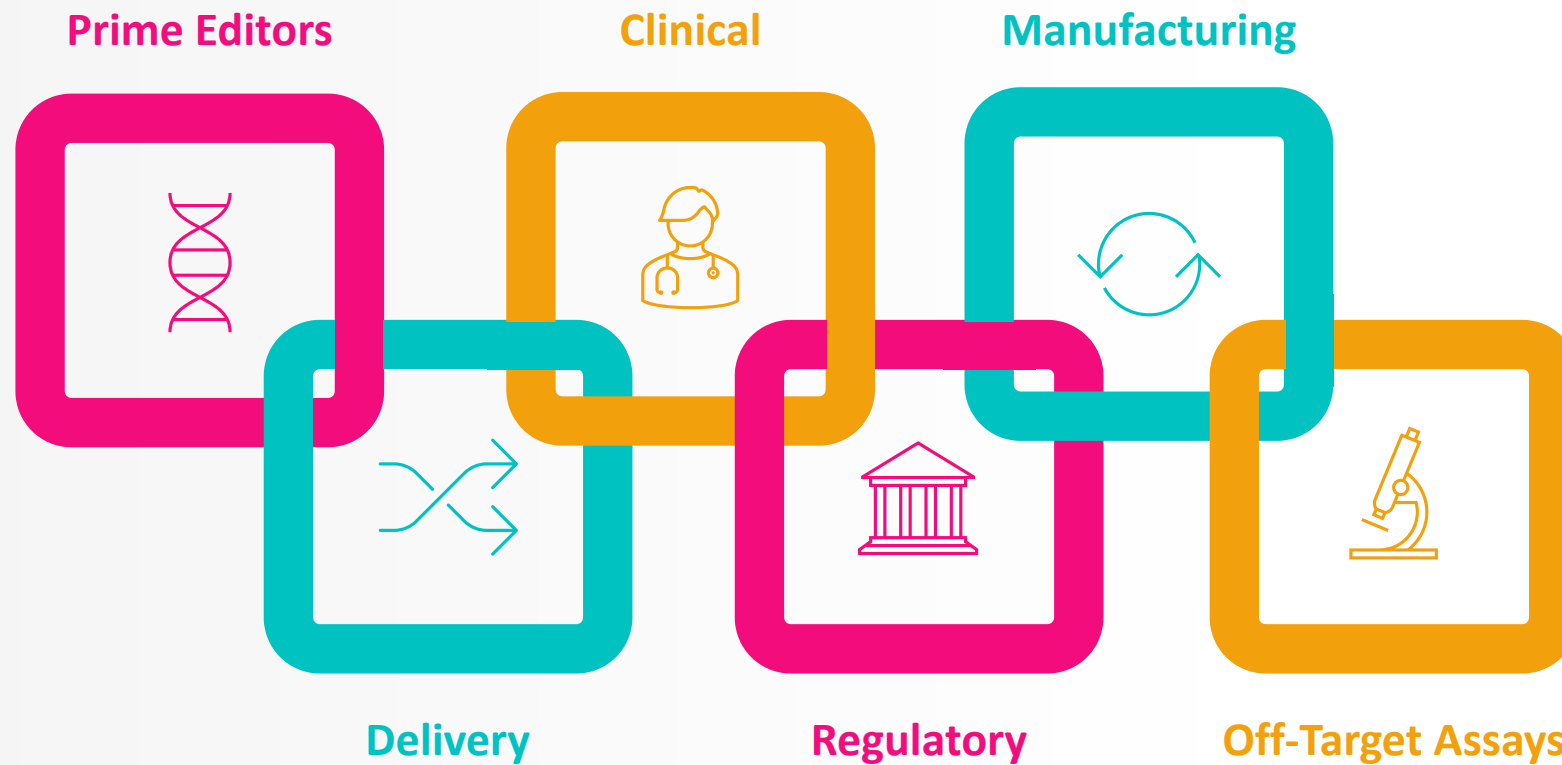
**In vivo protein factory**

(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

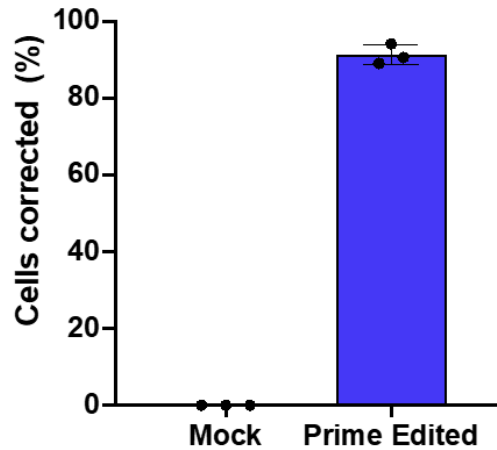
Core components can be readily leveraged to accelerate pipeline growth, efficiency and execution



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

1

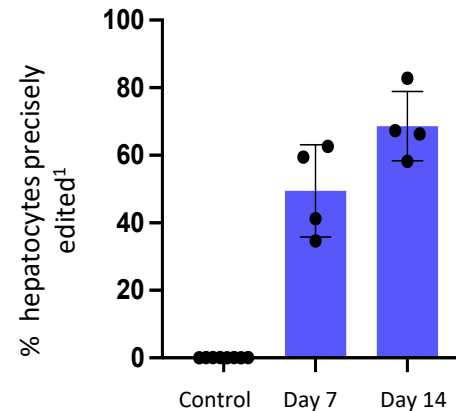
## Ex Vivo (Human CD34+ Cells)



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

2

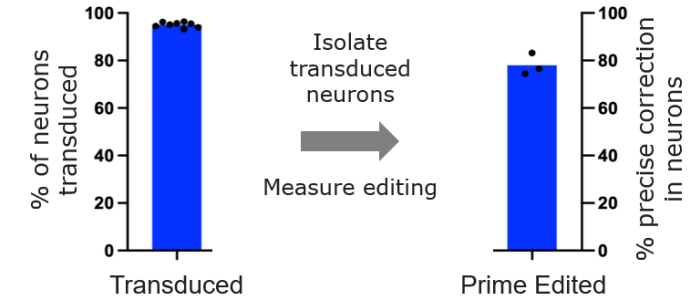
## In Vivo – LNP (NHP Liver)



Up to ~83% of hepatocytes precisely edited in NHPs<sup>1</sup>

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

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

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

✓ No detectable double strand breakage

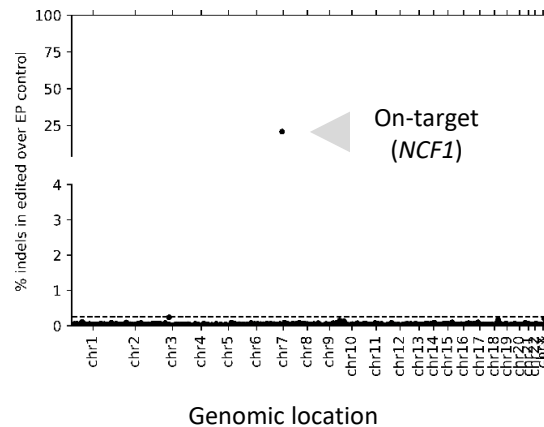
✓ No detectable off-target edits

✓ No detectable bystander edits

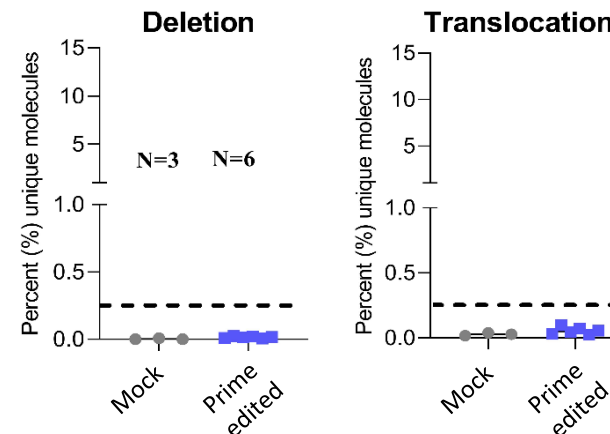
✓ No detectable large deletions, chromosomal translocations or rearrangements

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

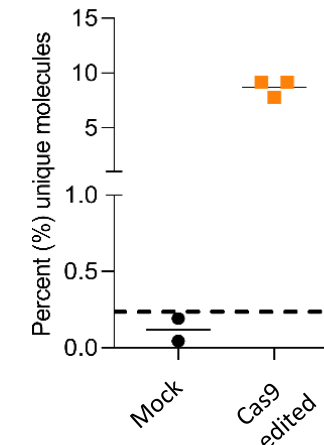
No off-target editing detected in healthy human donor CD34+ cells<sup>1</sup>



No large deletions or translocations observed in bone marrow engrafted Prime-Edited LT-HSCs<sup>2</sup>



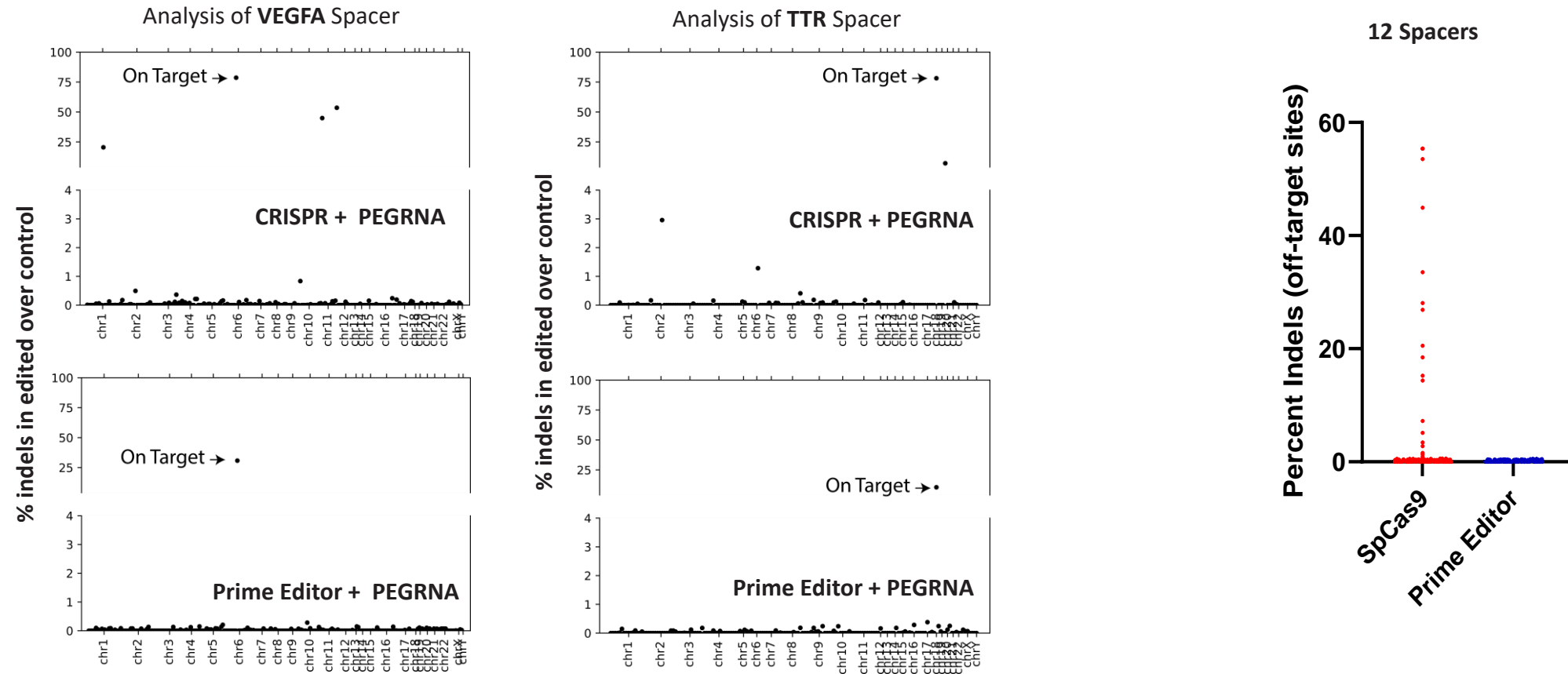
Translocation positive control: Cas9 nuclease-edited cells<sup>3</sup>



<sup>1</sup>Analysis of edited CD34+ cells from CGD program: Targeted *in vitro* Analysis of 550 potential off-target sites of off-target editing. <sup>2</sup>Data from *in vivo* analysis from mouse bone marrow harvested 16 weeks after engraftment was complete. <sup>3</sup>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

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



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

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	CAR-T (oncology/autoimmune)	ex vivo				
	Other programs in discovery: Usher Syndrome (Type 3) (ear); Non-Syndromic Hearing Loss – GJB2 (ear)					
Advancing as potential partnership opportunities						



# 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<sup>phox</sup> protein<sup>1</sup>
  - Found globally; 100's of patients in U.S. alone<sup>2</sup>
- 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

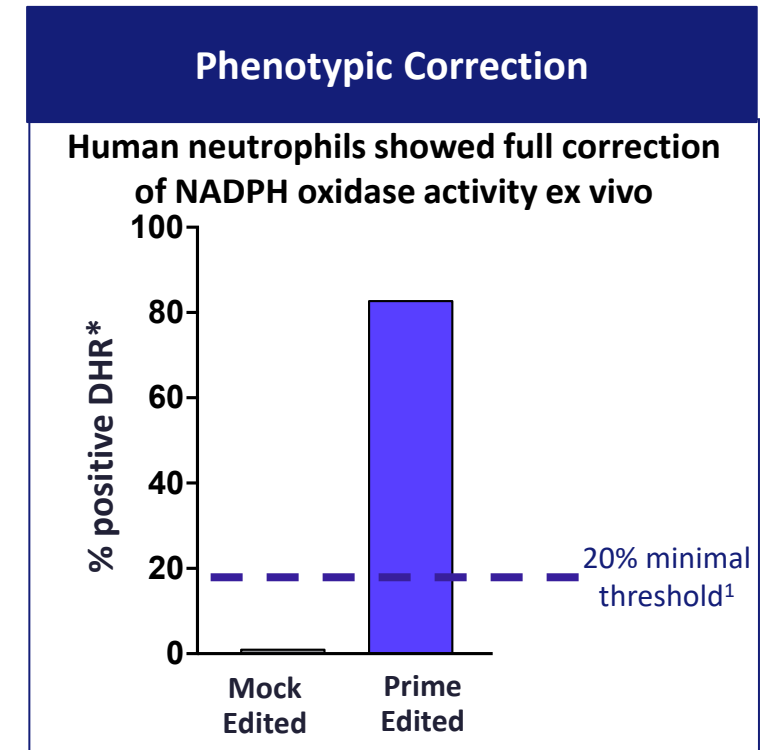
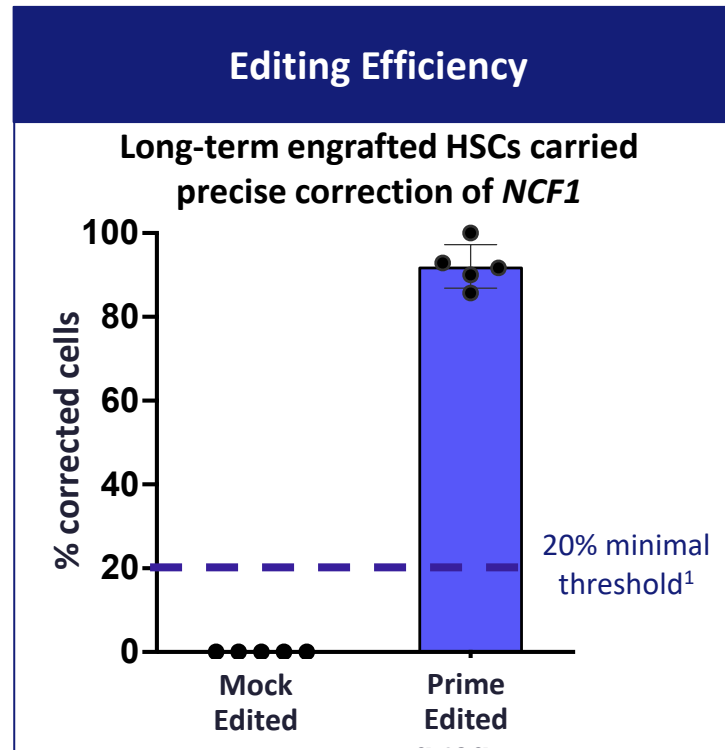
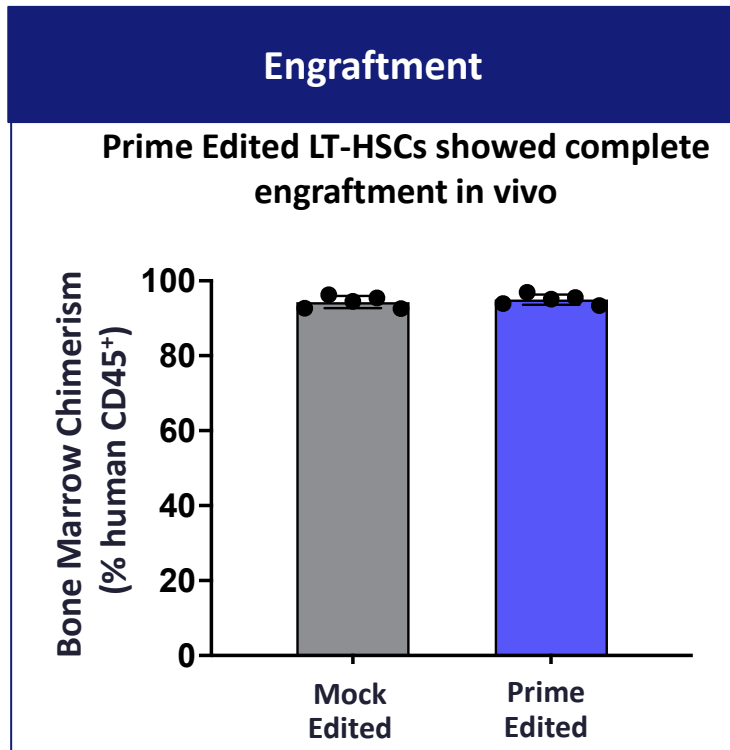


We believe Prime Editing is uniquely well-suited to address this form of CGD



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

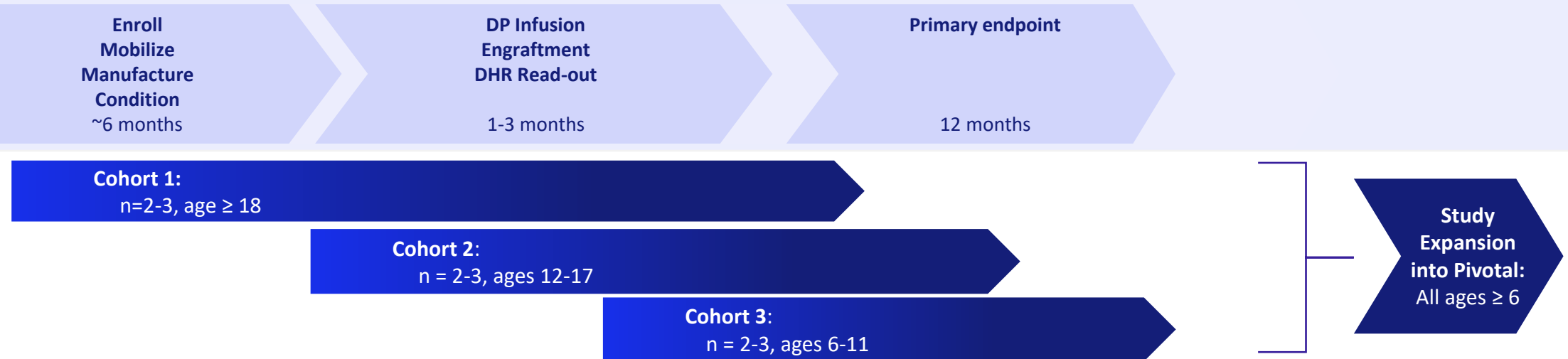
Maintenance of >85% of corrected patient long-term HSCs with complete restoration of NADPH oxidase in neutrophils observed



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

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

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/CTA 1H 2024**  
**First clinical data expected in 2025**

# Regulatory Interactions in U.S. and Globally

## Further Support Near-Term Clinic Entry with PM359

### 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

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

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:

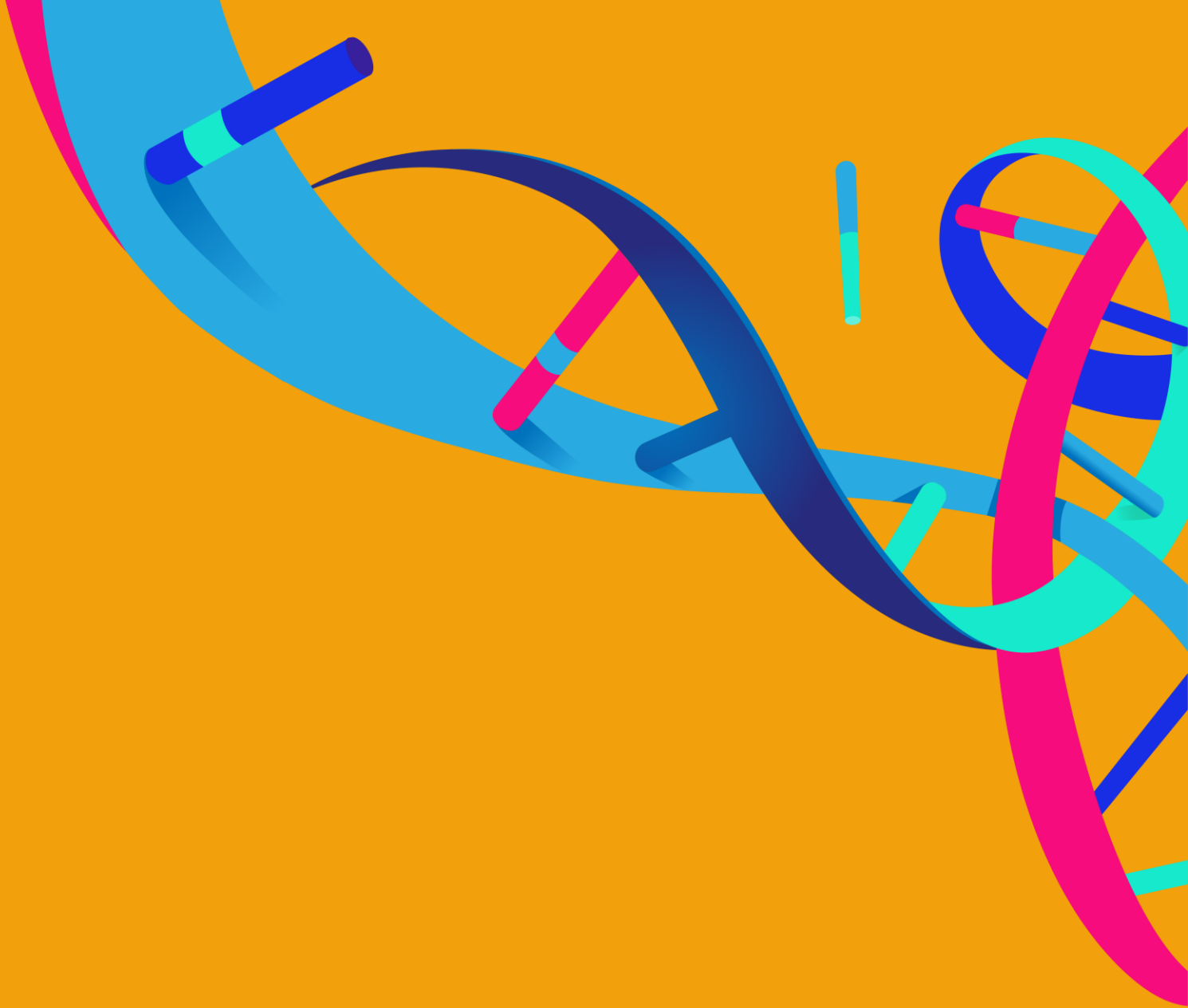
- Extend utility of HSC transplant
- Enable selection of *in vivo* edited HSCs, allowing for treatment of genetic diseases without transplant

## Efforts could significantly broaden addressable market

Current Focus:	Potential Platform Expansion:		
<i>Autologous HSC Transplant with Corrective Edit</i>	<i>Low Intensity Autologous HSC Transplant</i>	<i>Low Intensity Allogeneic HSC Transplant</i>	<i>In Vivo HSC Gene Editing Therapies</i>

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

# 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:

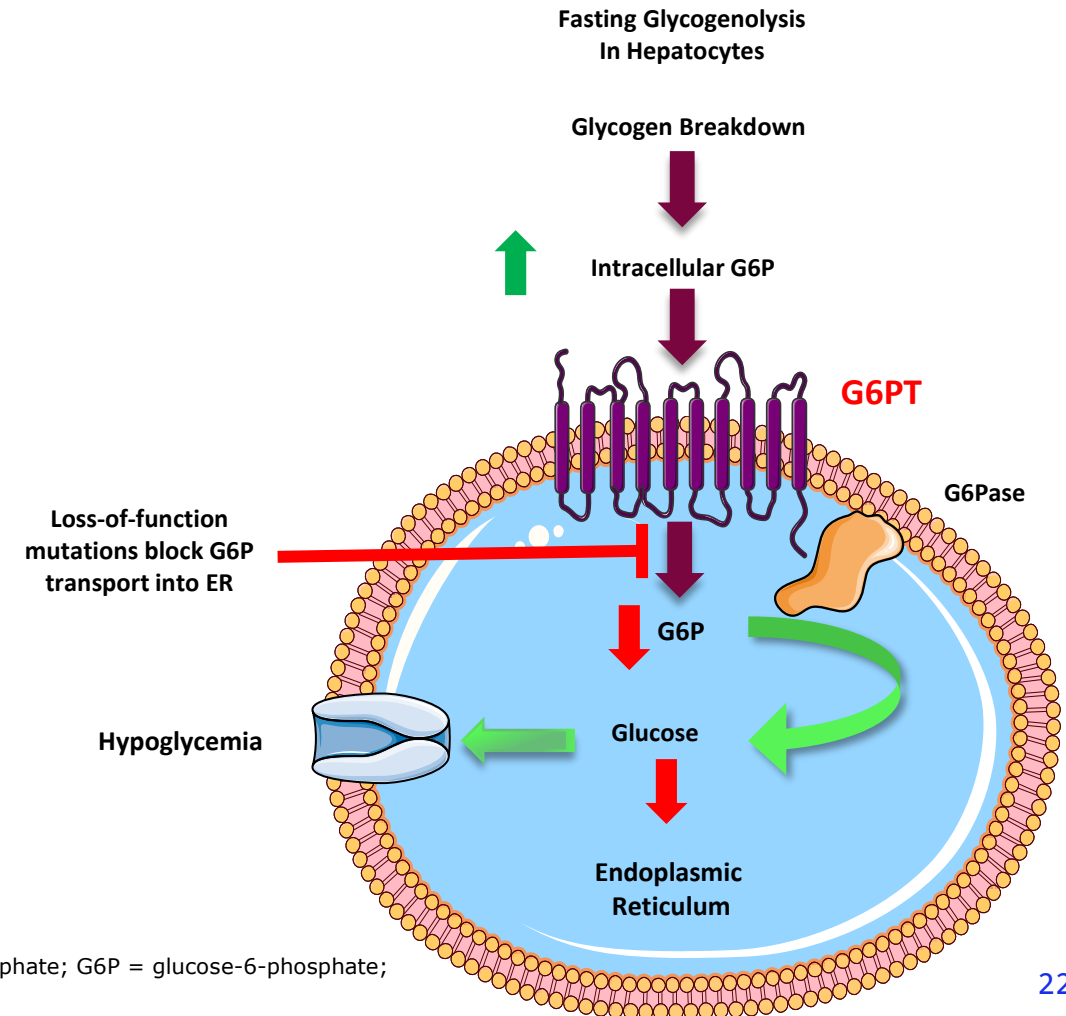
- Autosomal recessive, caused by mutations in the *SLC37A4* gene that encodes G6PT, a glucose-6-phosphate transporter
- **p.L348fs** and **p.G339C** mutations found in ~50% of GSD1b patient population

### 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:

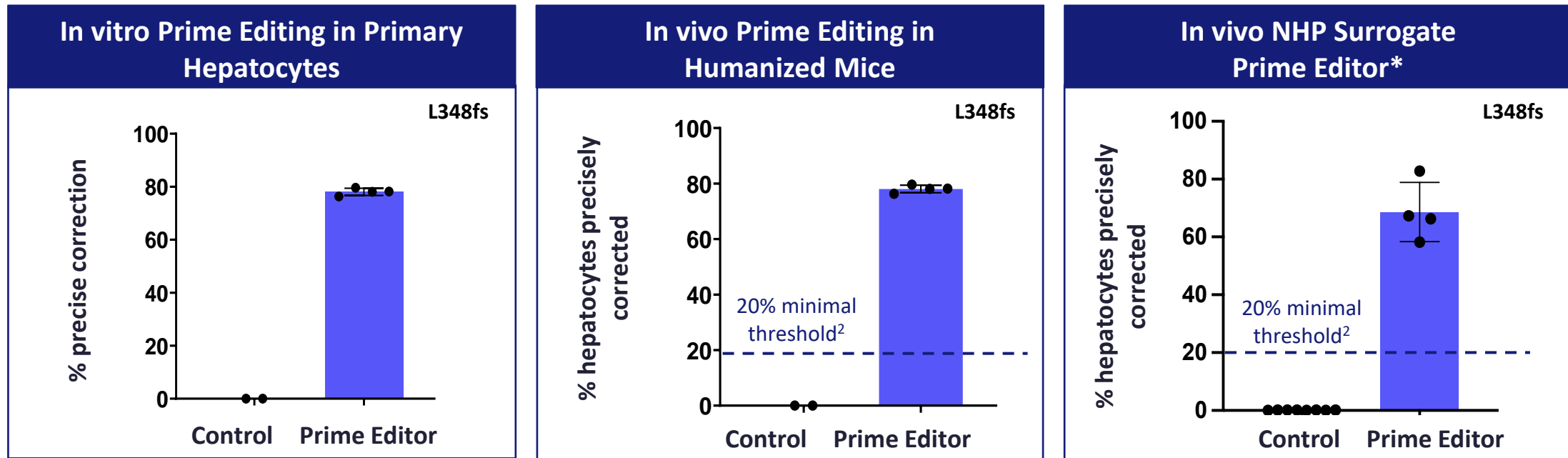
- IV administration of liver targeted LNP Prime Editors to correct either p.L348fs mutation or the p.G339C mutation to restore glucose homeostasis in patients with GSD1b



# Advancing Prime Editors for Two Prevalent Glycogen Storage Disease 1b Mutations<sup>1</sup>



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



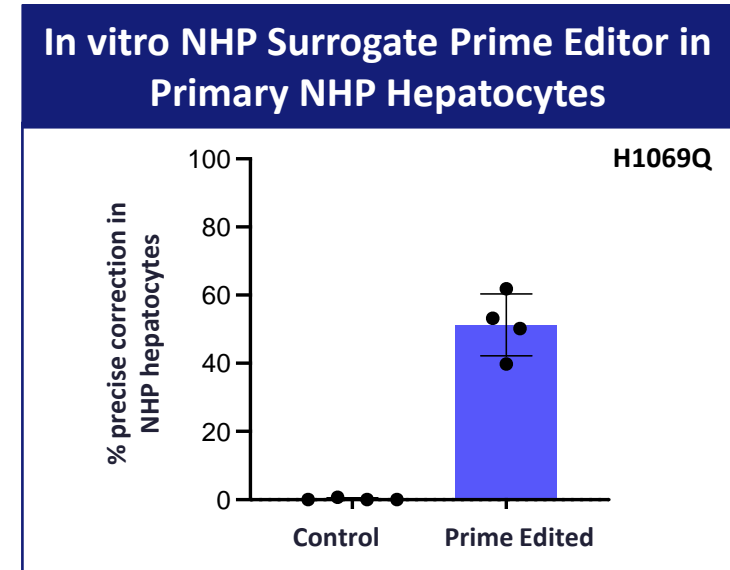
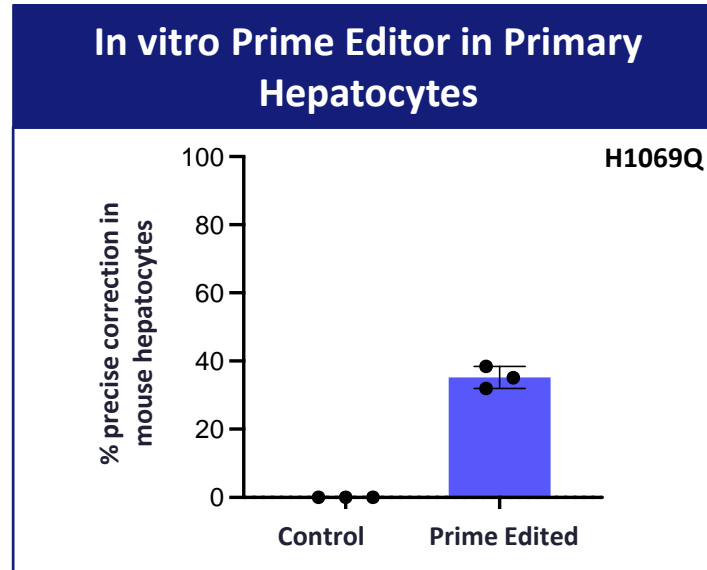
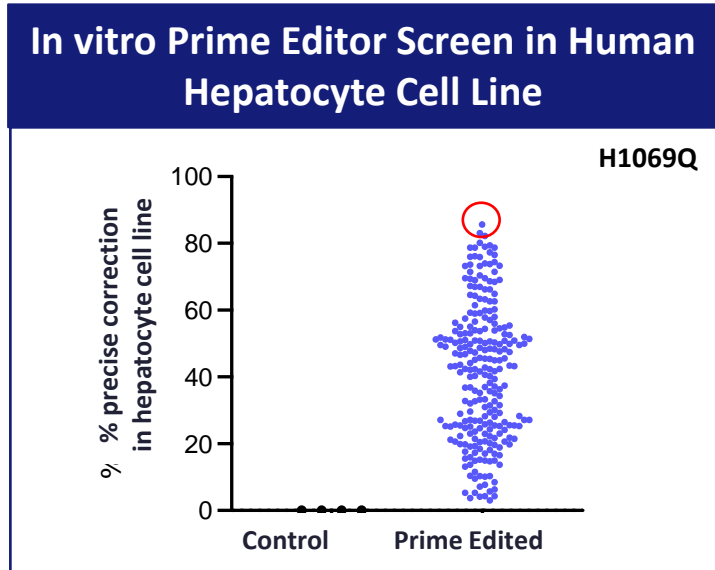
- Prime Editors to correct key mutations are making good progress through lead optimization
- Comprehensive suite of assays developed to enable selection of development candidate and advance to IND enabling studies
- Prime's Universal LNP and modular platform is being applied to accelerate Glycogen Storage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

<sup>1</sup> Majority of GSD1b patients have L348fs and G339C mutations in U.S. and Europe; <sup>2</sup> Rutten, M. G. S., Derks, T. G. J., Huijckman, 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<sup>1</sup> Mutations



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



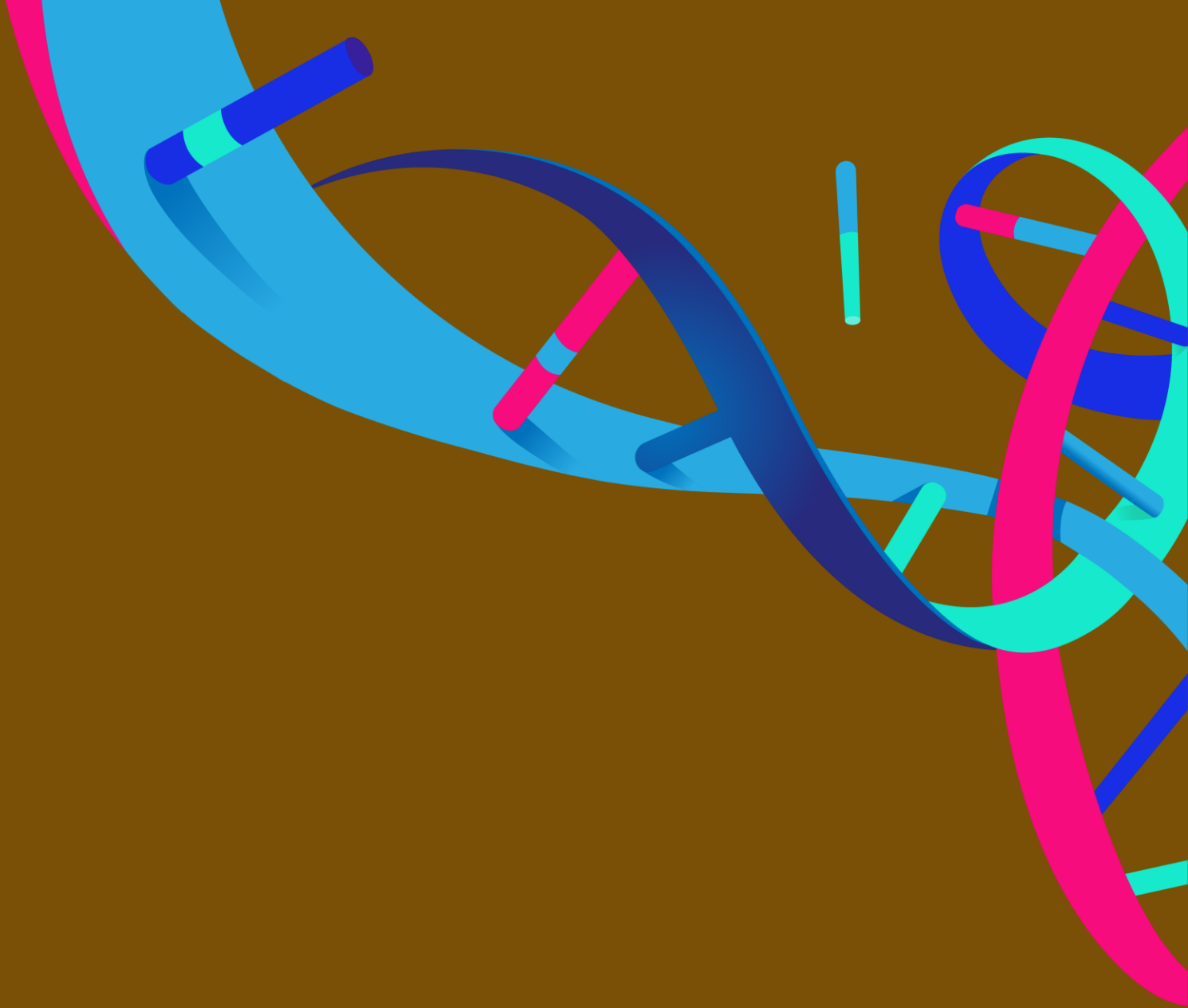
In vivo delivery to NHPs and humanized mice using Prime's Universal Targeted LNP ongoing

- 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

<sup>1</sup> 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

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.

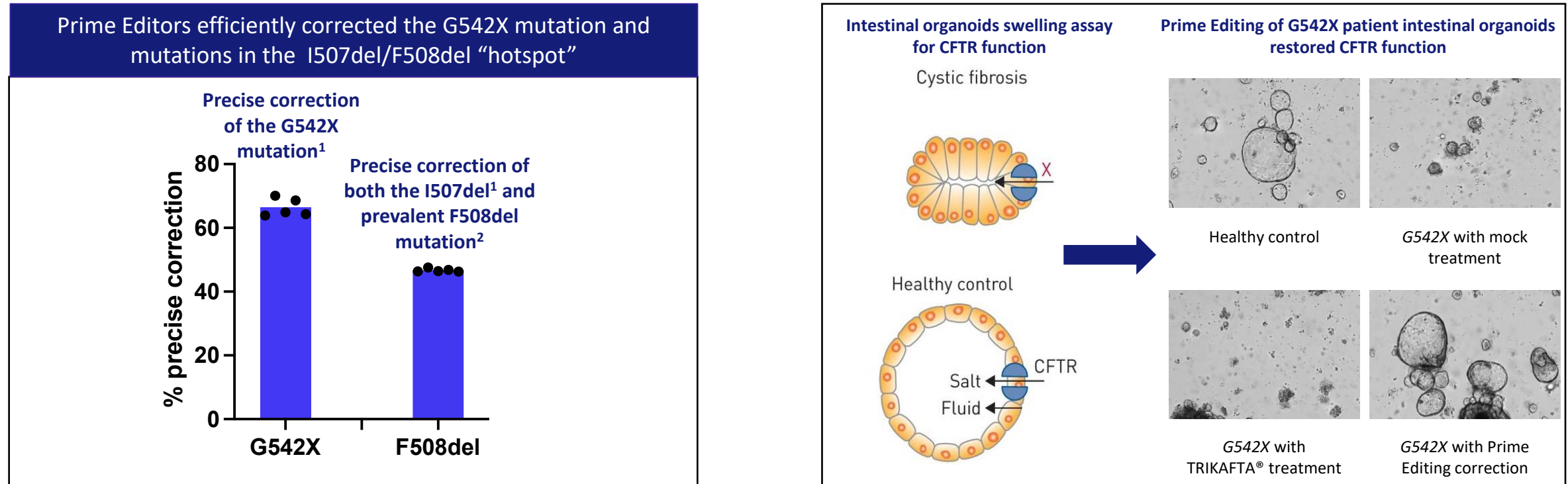
There is no cure and existing treatments are ineffective for, or not tolerated by, approximately **15%** of patients.

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

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

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



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

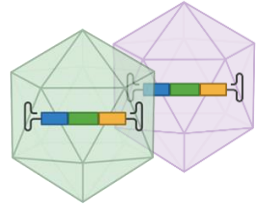
- LNP delivered Prime Editors efficiently corrected patient Human Bronchial Epithelial (HBE) progenitors *in vitro*
- Identified early LNP formulations to deliver Prime Editors to lung basal cells *in vivo*

# Ocular Diseases



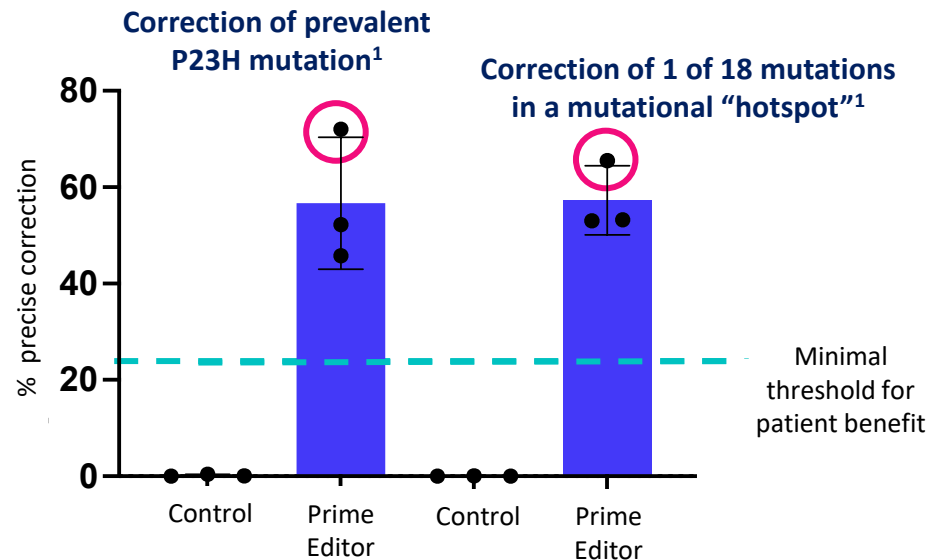
# Early Data with Proprietary Dual-AAV System: Key Step Toward Unlocking Opportunities in Retinal Diseases and Larger Indications

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

<sup>1</sup>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

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

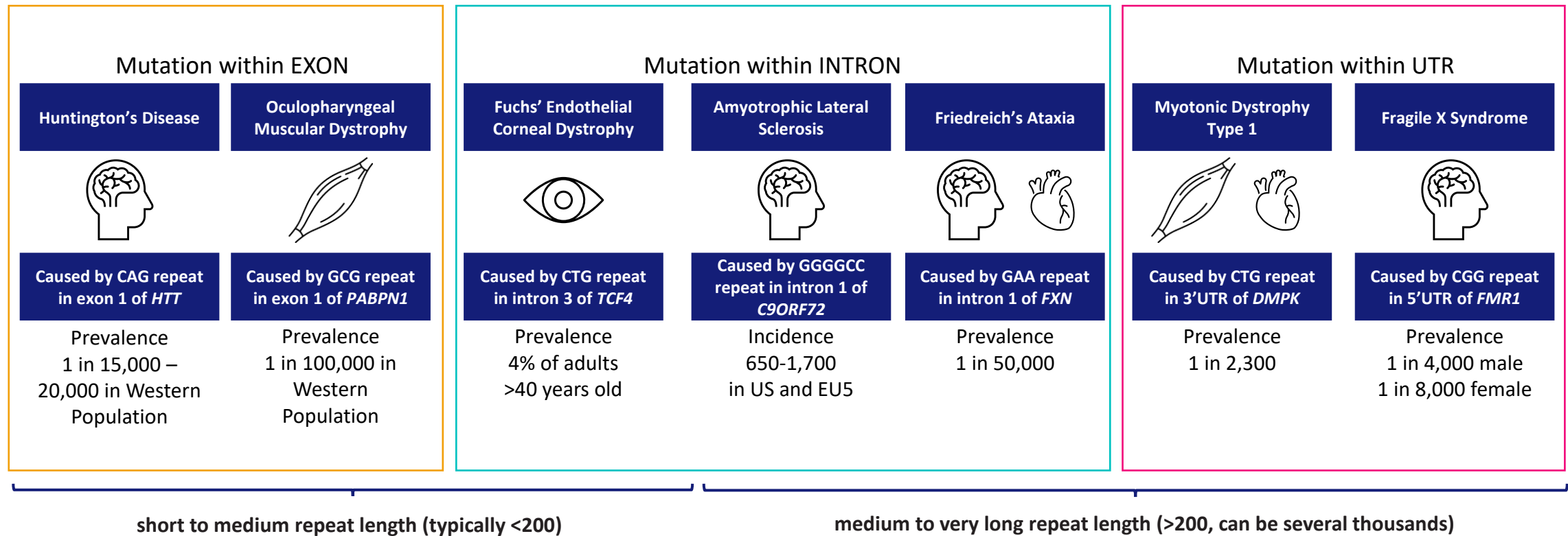
No Treatment currently available



# Neuromuscular Disease

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

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

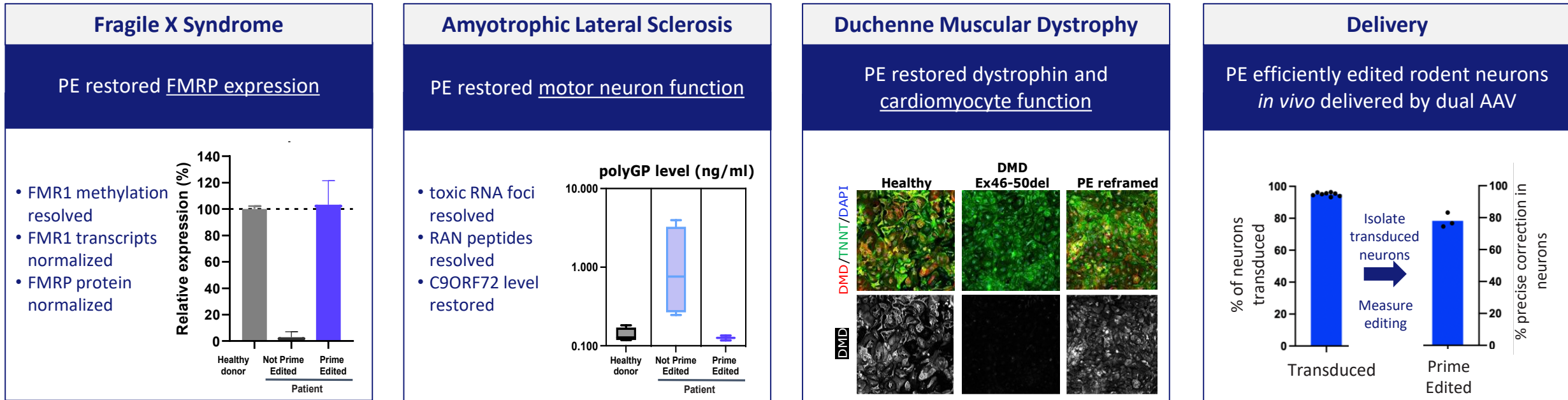


Note: The above figure exemplifies our initial approach to repeat expansion diseases, showing disease names, primary organs affected by disease, approximate estimates of prevalence or incidence, type of expansion mutation, gene where expansion mutation occurs, location and approximate length of expansion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



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

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



- 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

# Additional Programs

Delivering on the promise  
of Prime Editing



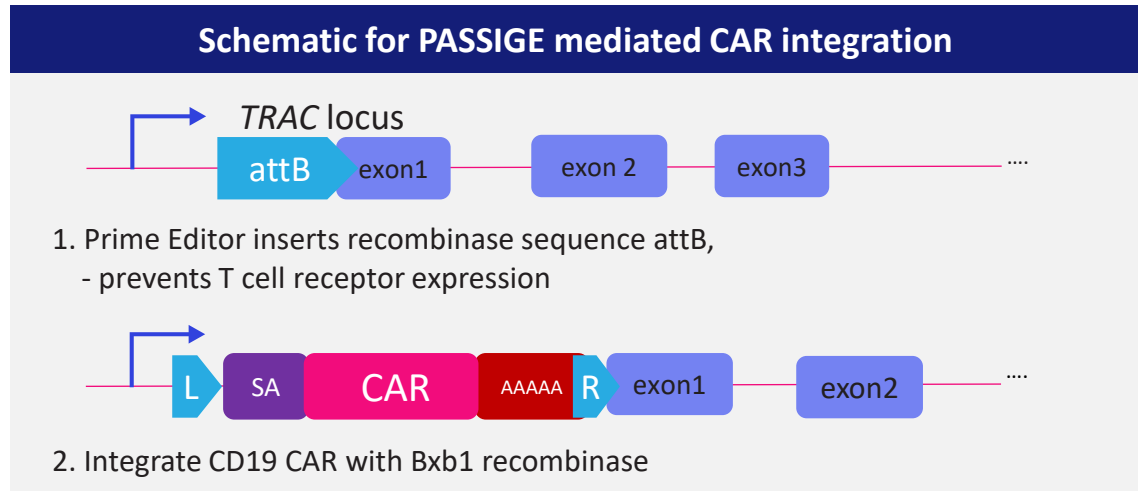
# PASSIGE™ and Multiplex Prime Editing Create Potentially Best-in-Class Allogenic CAR-T Cell Product

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

	Existing Limitations	Prime Editing Solution
Multiplex Engineering	<ul style="list-style-type: none"> <li>✗ Low payload integration efficiency</li> <li>✗ Constrained to limited number of knock-outs and limited single base pair changes</li> </ul>	<ul style="list-style-type: none"> <li>✓ <b>&gt;80% integration</b> efficiency to date, aimed at TRAC locus to maintain <b>endogenous control</b></li> <li>✓ Capable of <b>multiple edits done safely</b>, each with a <b>full suite of functional modifications</b></li> </ul>
Safety	<ul style="list-style-type: none"> <li>✗ Random or semi-random integration</li> <li>✗ High rate of translocations / chromosomal abnormalities</li> </ul>	<ul style="list-style-type: none"> <li>✓ <b>Precise on-target</b> transgene integration</li> <li>✓ Based on our extensive off-target evaluations in other settings, <b>there is the potential for no detectable off-target edits, translocations, or unintended structural abnormalities</b> in Prime-Edited CAR-T's</li> </ul>
Manufacturing / Cost of Goods	<ul style="list-style-type: none"> <li>✗ Dependence on viral components</li> <li>✗ Complicated by multi-step engineering</li> </ul>	<ul style="list-style-type: none"> <li>✓ <b>Entirely non-viral</b> manufacturing process</li> <li>✓ <b>Single-step</b> editing and integration</li> </ul>

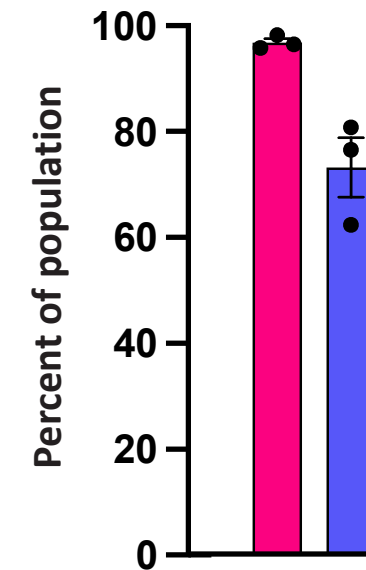
# Non-Viral PASSIGE Delivery Supports Integration of CD19 CAR Under Endogenous Control of *TRAC* Locus in up to 80% of T Cells

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



- ✓ Loss of endogenous TCR with attB insertion in *TRAC* exon 1
- ✓ Use of endogenous *TRAC* promoter allows for tuned regulation of CAR expression<sup>1</sup>
- ✓ 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

TCR Loss (flow cytometry)  
%CAR<sup>+</sup> expression (flow cytometry)

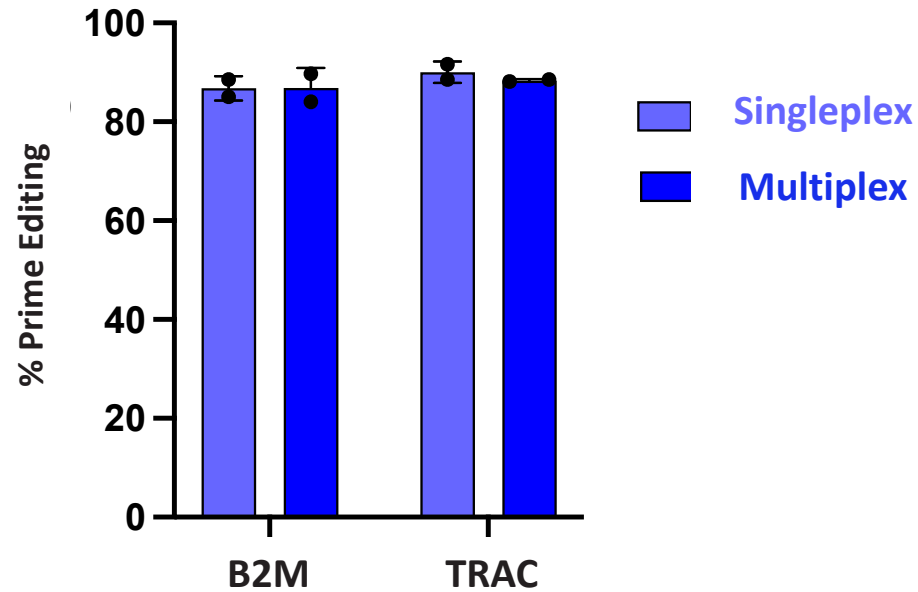


<sup>1</sup>Eyquem et al. (Sadelain) 2017. attB = recombinase attachment site; PASSIGE = prime assisted site-specific integrase gene editing; TCR = T cell receptor; CD19 = cluster of differentiation 19; CAR = chimeric antigen receptor; SA = splice acceptor; AAAAAA = polyA signal

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

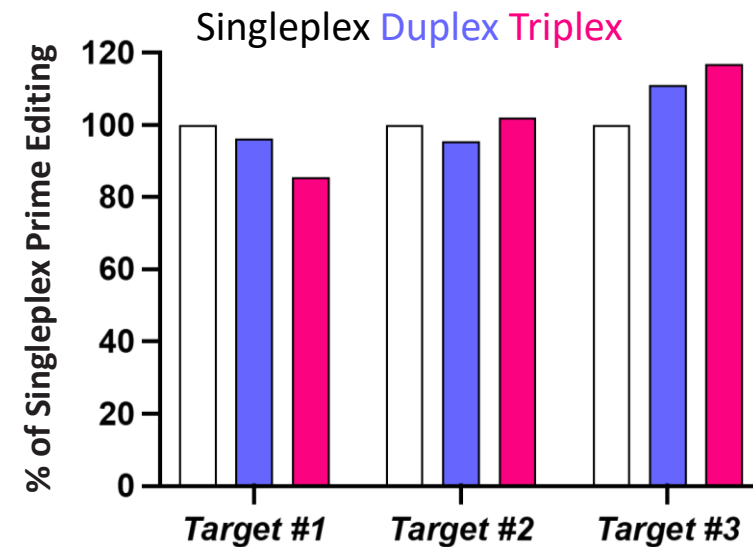
Prime Editors can be multiplexed to introduce multiple genomic modifications in CAR-T cells

$\beta$ 2 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

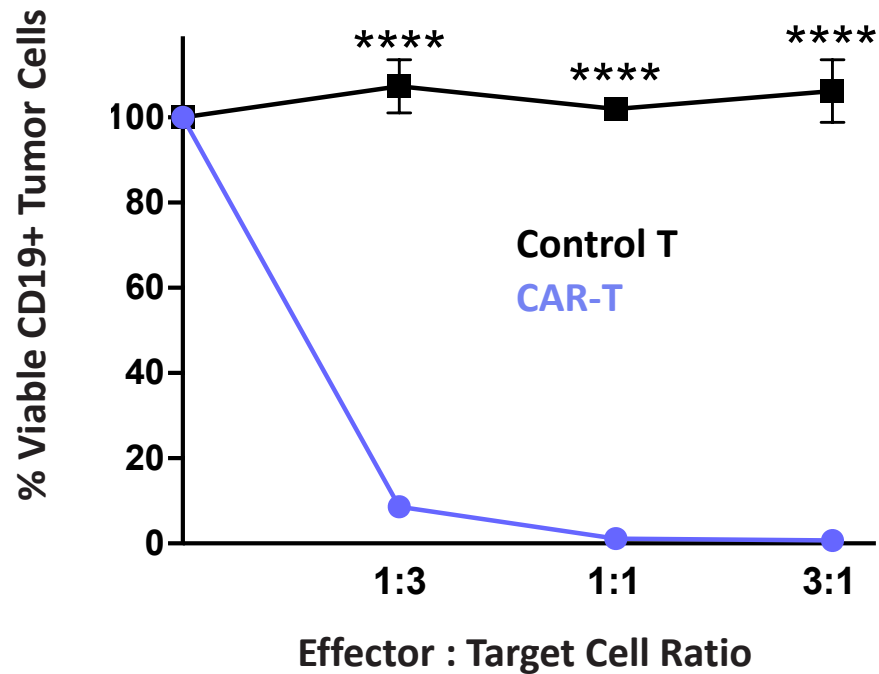


- PASSIGE and multiplex Prime Editing efficiency were maintained in multiplex
- Up to 6 multiplex edits in T cells with high efficiency

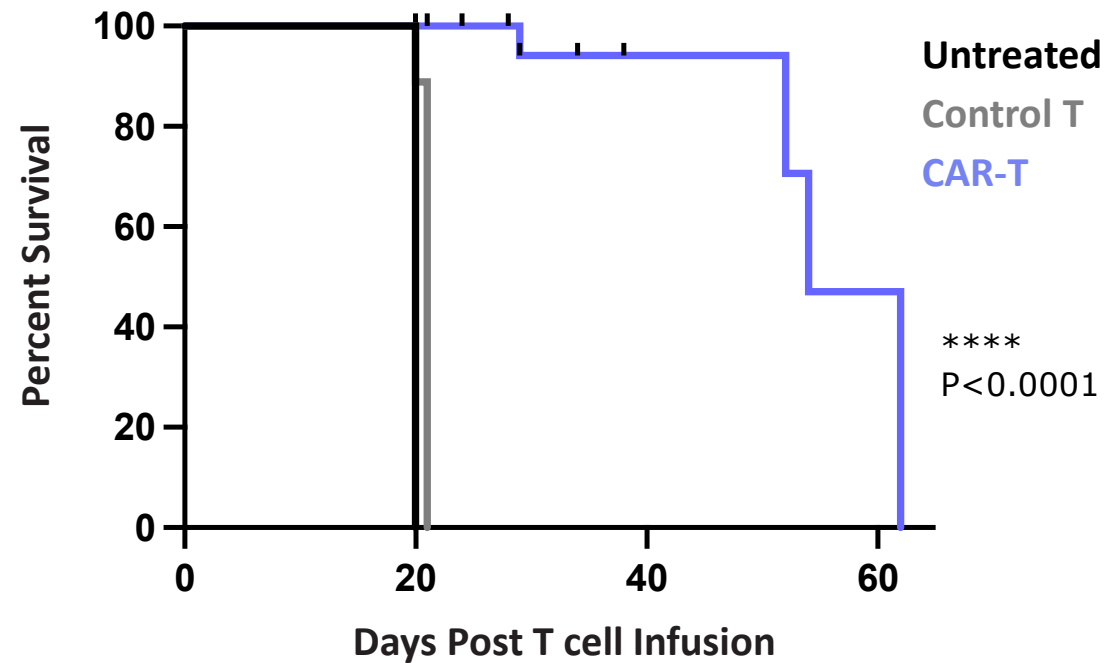
# Prime Medicine's Multiplexed CD19 CAR-T Cells are Functional In Vitro and *In Vivo*

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

CAR-T cells killed CD19<sup>+</sup> tumors at 72 hours in low cell ratio



Significant increase in survival of human tumor bearing mice after treatment with CAR-T cells



# 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
- ✓ Expected first IND/CTA 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



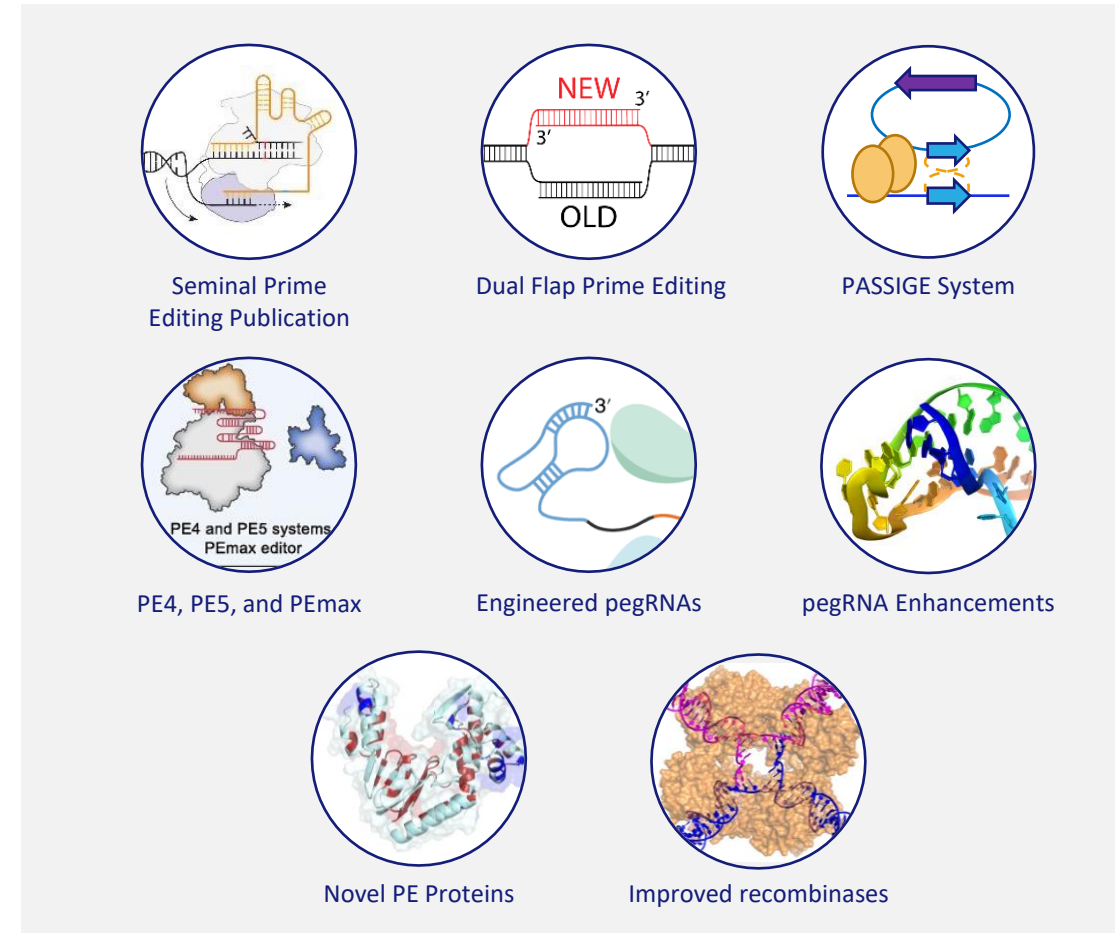
# Prime Medicine Holds Extensive Intellectual Property for Prime Editing Technologies

## 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 3 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



# 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	<b>Hematology &amp; Immunology</b>	<ul style="list-style-type: none"> <li>- Open IND and/or CTA for planned Phase 1/2 study in Chronic Granulomatous Disease in 1H 2024, with anticipated initial clinical data in 2025</li> <li>- 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</li> <li>- Advance Prime Medicine's differentiated CAR-T program (using PASSIGE™) into lead optimization</li> </ul>
	<b>Liver</b>	<ul style="list-style-type: none"> <li>- 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</li> </ul>
	<b>Ocular</b>	<ul style="list-style-type: none"> <li>- Nominate development candidate for Retinitis Pigmentosa / Rhodopsin (RHO) and initiate IND-enabling activities in 2024</li> </ul>
	<b>Neuromuscular</b>	<ul style="list-style-type: none"> <li>- Continue to advance Friedreich's Ataxia program; advance one other program into lead optimization in 2024</li> </ul>
Platform	<b>Delivery</b>	<ul style="list-style-type: none"> <li>- Nominate first development candidate using Prime Medicine's liver-targeted universal LNP platform in 2024</li> <li>- In large animal studies, establish AAV delivery platform and a route of administration for neuromuscular programs in 2024</li> </ul>
	<b>Regulatory</b>	<ul style="list-style-type: none"> <li>- Advance discussions with regulatory agencies on platform strategy for streamlined development</li> </ul>

As of December 31, 2023, Prime Medicine had estimated cash, restricted cash, cash equivalents and investments of \$135.2 million\*



Delivering on the promise  
of Prime Editing

# Thank You!

[primemedicine.com](https://primemedicine.com)





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# Appendix

[primemedicine.com](https://primemedicine.com)



# Team with Significant Scientific and Drug Development Experience

## Team



**Keith Gottesdiener, M.D.**  
President and CEO



**Allan Reine, M.D.**  
Chief Financial Officer



**Jeremy Duffield, M.D., Ph.D.**  
Chief Scientific Officer



**Ann L. Lee, Ph.D.**  
Chief Technical Officer



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



**Meredith Goldwasser, Sc.D.**  
SVP, Head of Strategy and Corporate Ops



**Richard Brudnick**  
Chief Business Officer



**Niamh Alix**  
Chief Human Resources Officer



**Fubao Wang, Ph.D.**  
SVP, Head of Regulatory



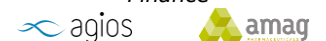
**Mohammed Asmal, M.D., Ph.D.**  
SVP, Head of Clinical



**Karen Brown, Ph.D., JD**  
SVP, Intellectual Property and Legal Affairs



**Carman Alenson, CPA**  
Chief Accounting Officer and SVP Finance



## 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**  
Former Acting CFO, Amgen  
**Wendy Chung, M.D., Ph.D.**  
Professor of Genetics, Columbia University  
**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.**

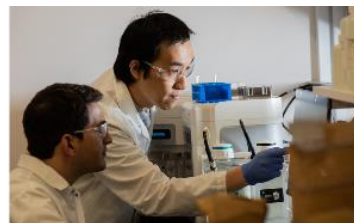
**Shengdar Tsai, Ph.D.**

# Building the Company

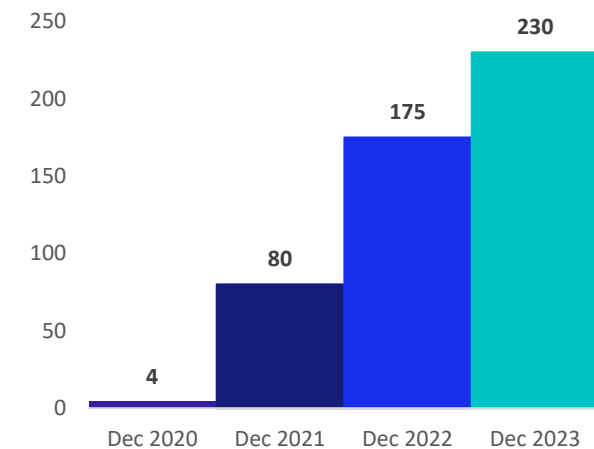
## Currently

- ~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
- Locations in Cambridge, MA and a chemistry facility in Watertown, MA, with buildout of 150,000 square feet permanent space in a Cambridge facility, target for move in 1H 2024

## Critical Milestones Achieved



## Successful Growth of Talent





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

## 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.

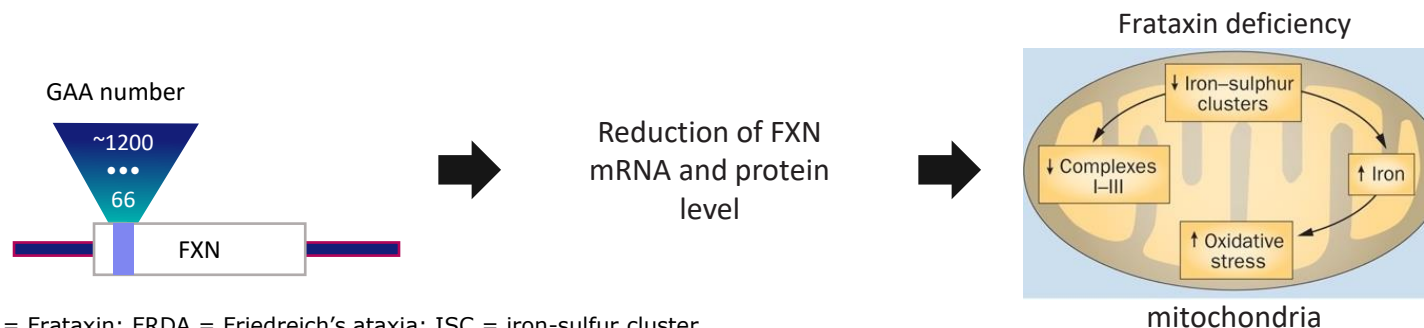


## Prevalence

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



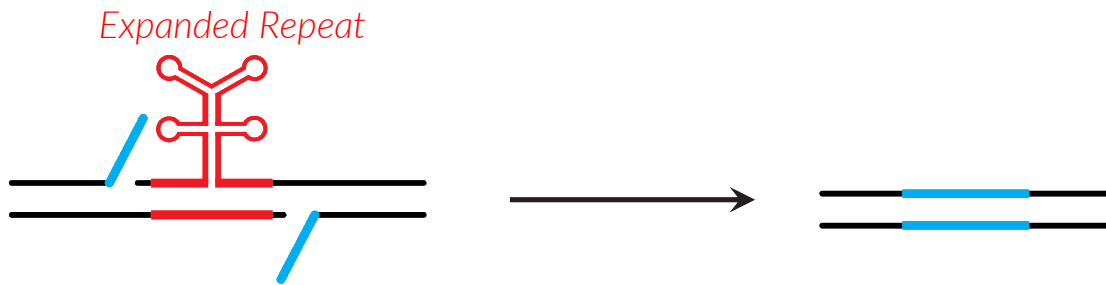
Source: bicycling.com, Bryan Kirkwood



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

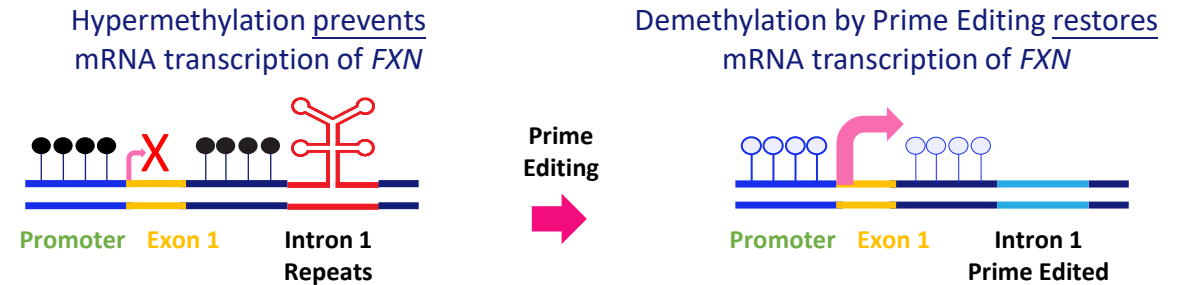
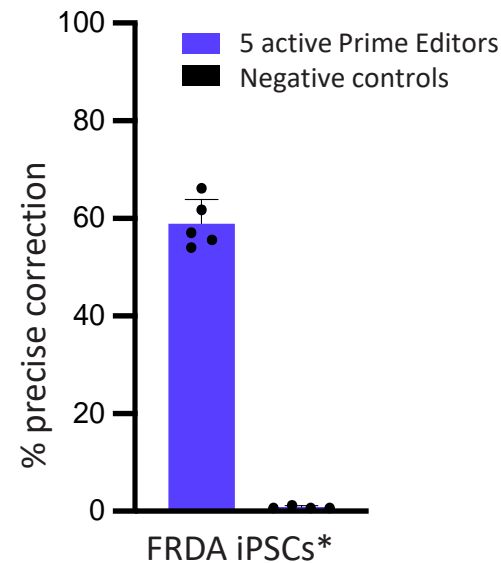
Removal of pathological GAA repeats and hypermethylation at the Frataxin (FXN) gene in Friedreich's Ataxia patient cells

Dual-flap Prime Editing loops out expanded repeat

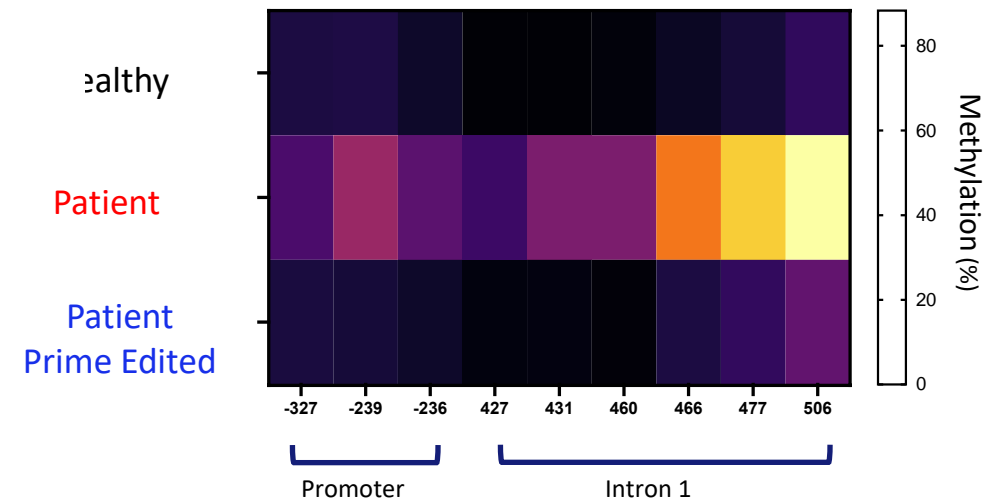


## Conclusions

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



Removal of Hypermethylation<sup>1</sup>



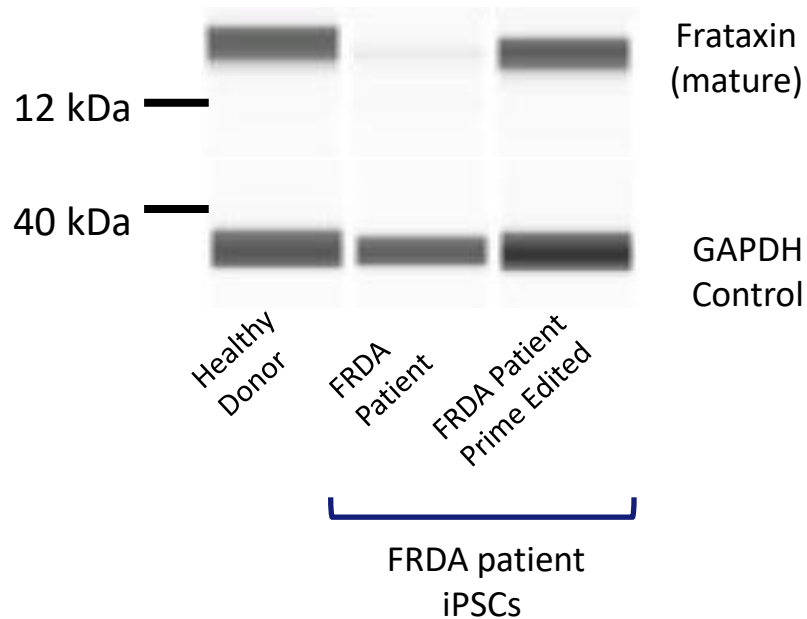
Many repeat expansion diseases exhibit hypermethylation as a key feature of the underlying pathogenesis



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

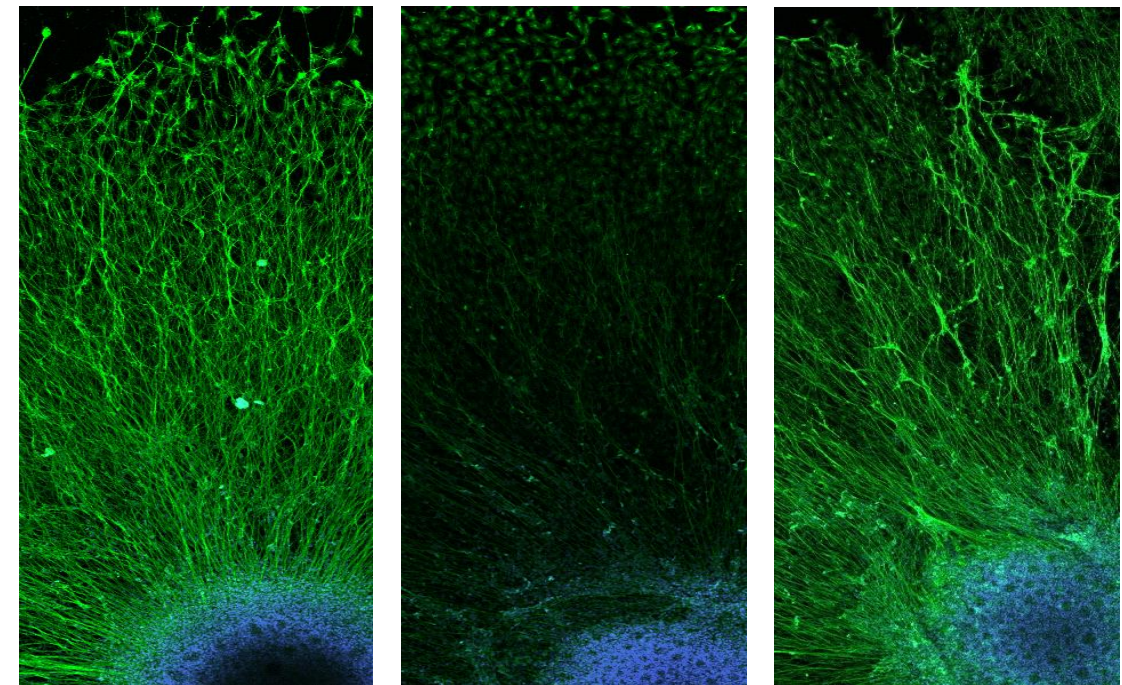
High-efficiency Prime Editing restores FXN protein expression and sensory neuron phenotype in Friedreich's Ataxia patients' dorsal root ganglia organoids

Restoration of Frataxin protein expression after delivery of Prime Editor



Restoration of axonal projections after Prime Editor correction

$\beta$ III-TUB  
DAPI



Healthy Donor

FRDA Patient

FRDA Patient  
Prime-Edited



Delivering on the promise  
of Prime Editing

# Thank You!

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