UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

August 7, 2023
Date of Report (Date of earliest event reported)

Prime Medicine, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**001-41536**	**84-3097762**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**
21 Erie Street		
Cambridge, MA		**02139**
(Address of principal executive offices)		**(Zip Code)**

(617) 564-0013
(Registrant's telephone number, including area code)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common stock, par value $.00001 per share	PRME	The Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule12b-2 of the Securities Exchange Act of 1934 (§250.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02 Results of Operations and Financial Condition.

On August 7, 2023, Prime Medicine, Inc. (the "Company") issued a press release announcing its financial results and business highlights for the quarter ended June 30, 2023. A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

Item 7.01 Regulation FD Disclosure.

A copy of the Company's August 2023 corporate presentation is furnished as Exhibit 99.2 to this Current Report on Form 8-K, which is incorporated herein by reference.

The information contained in Item 2.02 and Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.1 and Exhibit 99.2 attached hereto, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press Release, dated August 7, 2023, furnished herewith.
99.2	Presentation, dated August 2023, furnished herewith.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: August 7, 2023

Prime Medicine, Inc.

By: /s/ Keith Gottesdiener

Name: Keith Gottesdiener, M.D.

Title: President and Chief Executive Officer

Prime Medicine Reports Second Quarter 2023 Financial Results and Provides Business Updates

-- Presented new preclinical data demonstrating ability of Prime Editing to correct causative mutation of CGD and highlighting ability of PASSIGE™ platform to multiplex edit CAR-T cells at ASGCT Annual Meeting --

-- Entered strategic collaboration with Cimeio Therapeutics; multiplexing Cimeio's shielded variants with therapeutic edits may meaningfully expand reach of Prime Editing --

-- Cash, cash equivalents, investments and restricted cash balance of $221.1 million as of June 30, 2023 --

Cambridge, Mass., August 7, 2023 – Prime Medicine, Inc. (Nasdaq: PRME), a biotechnology company committed to delivering a new class of differentiated one-time curative genetic therapies, today reported financial results and provided business updates for the second quarter ended June 30, 2023.

"In recent months, we continued to advance our diversified portfolio of Prime Editing programs while also executing against a strategic partnering strategy aimed at further expanding the broad therapeutic potential of Prime Editing," said Keith Gottesdiener, M.D., President and Chief Executive Officer of Prime Medicine. "PM359, our product candidate for the treatment of CGD, is progressing well, and at the ASGCT Annual Meeting in May, we presented new preclinical data demonstrating its ability to reproducibly correct the CGD disease-causing mutation in $CD34^+$ cells *ex vivo* with no detectable off-target editing. These findings further support our belief in the potential of this program to change the trajectory of this recurrent debilitating condition, and we look forward to sharing additional *in vitro* and *in vivo* data on this program and others later this year."

Dr. Gottesdiener continued, "Also in the second quarter, we entered into a research collaboration with Cimeio Therapeutics, gaining access to Cimeio's powerful CD117 immunotherapy technology for genetic diseases. We are pleased to be working together to evaluate combining Prime Editing enabled protective shielding with multiplexed therapeutic edits to potentially reduce the toxicity and increase the efficiency of existing HSC transplant regimens. These combined technologies may enable us to more gently and effectively treat a wider range of genetic diseases than currently possible, and future applications may include selection of *in vivo* edited HSCs, which could allow for the treatment of genetic diseases without transplantation. This partnership reflects the tremendous breadth of our Prime Editing technology, as well as our commitment to leveraging its versatility, precision and efficiency to improve the care and treatment of patients worldwide."

Recent Business Updates

Pipeline

- Prime Medicine continued to advance its strategic pipeline of eighteen programs and remained on track to initiate investigational new drug (IND)-enabling studies of PM359, its development candidate for chronic granulomatous disease (CGD), in 2023.
- In May 2023, Prime Medicine presented new preclinical data at the American Society of Gene and Cell Therapy (ASGCT) 26^{th} Annual Meeting. These data further demonstrated the potential for Prime Editing to correct the causative mutation of CGD and showcased the potential application of the **P**rime **A**ssisted **S**ite-**S**pecific **I**ntegrase **G**ene **E**diting (PASSIGE™) platform to generate multiplex-edited CAR-T cells for the treatment of certain cancers and immune diseases. Read the full data here.

Corporate

- In June 2023, Prime Medicine announced a research collaboration with Cimeio Therapeutics to develop Prime Edited Shielded Cell and Immunotherapy Pairs™ (SCIP) for genetic diseases, acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The goal of the research is to reduce the toxicity of

conditioning regimens and introduce new therapeutic options to meaningfully expand the utility of hematopoietic stem cell (HSC) transplant and enable the *in vivo* selection of edited HSCs to potentially remove the need for transplantation entirely. Under the terms of the agreement, Prime Medicine will develop a Prime Editor for Cimeio's CD117 shielding variant that will then be evaluated by both companies; if the research collaboration is successful, the companies will grant exclusive license options to each other for their technologies. If the companies exercise their exclusive license options, they will each be eligible to receive economics on net sales of licensed products.

Anticipated Upcoming Milestones

Prime Medicine expects the following activities and next steps to drive the Prime Editing platform forward:

Pipeline

- Initiate investigational new drug (IND)-enabling studies for PM359 in CGD in 2023.
- Expand preclinical proof-of-concept *in vivo* data, with plans to share data from *in vivo* rodent studies and large animal studies from several programs in the second half of 2023.
- Share in vitro preclinical data in additional liver, eye and neuromuscular programs.
- Complete first IND filing as early as 2024 and additional IND filings anticipated in 2025.

Platform

- Continue to develop and optimize non-viral and viral delivery systems and share additional proof-of-concept data from *in vivo* rodent and large animal studies in the second half of 2023.
- Further demonstrate superior off-target profiles for Prime Editing programs.
- Expand Prime Editing using proprietary recombinase technologies for new and existing programs.
- Maximize Prime Editing's broad therapeutic potential and create value through strategic business development that extends the reach and impact of Prime Editing to areas beyond Prime Medicine's current areas of focus.

Second Quarter 2023 Financial Results:

- **R&D Expenses:** Research and development (R&D) expenses were $34.6 million for the three months ended June 30, 2023, as compared to $18.9 million for the three months ended June 30, 2022. This increase was primarily due to increases in lab supplies, personnel, and facilities costs as the company continues to expand and build out its R&D activities and function.
- **G&A Expenses:** General and administrative (G&A) expenses were $10.7 million for the three months ended June 30, 2023, as compared to $7.4 million for the three months ended June 30, 2022. This increase was primarily due to an increase in professional and consultant costs and personnel costs primarily attributable to the build-out of the company's G&A team to support our R&D function.
- **Net Loss:** Net loss was $42.4 million for the three months ended June 30, 2023, as compared to $29.3 million for the three months ended June 30, 2022.
- **Cash Position:** As of June 30, 2023, cash, cash equivalents, investments and restricted cash were $221.1 million, as compared to $263.0 million as of March 31, 2023.

Financial Guidance

Based on its current operating plans, Prime Medicine expects that its cash, cash equivalents and investments as of June 30, 2023, will be sufficient to fund its anticipated operating expenses and capital expenditure requirements into 2025.

About Prime Medicine

Prime Medicine is a leading biotechnology company dedicated to creating and delivering the next generation of gene editing therapies to patients. The Company is leveraging its proprietary Prime Editing platform, a versatile, precise and efficient gene editing technology, to develop a new class of differentiated, one-time, potentially curative genetic therapies. Designed to make only the right edit at the right position within a gene while minimizing unwanted DNA modifications, Prime Editors have the potential to repair almost all types of genetic mutations and work in many different tissues, organs and cell types.

Prime Medicine is currently progressing a diversified portfolio of eighteen programs initially focused on genetic diseases with a fast, direct path to treating patients or with a high unmet need because they cannot be treated using other gene-editing approaches. Over time, the Company intends to maximize Prime Editing's therapeutic potential and advance potentially curative therapeutic options to patients for a broad spectrum of diseases. For more information, please visit www.primemedicine.com.

Cautionary Note Regarding Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements about Prime Medicine's beliefs and expectations regarding: the initiation, timing, progress, and results of its research and development programs, preclinical studies and future clinical trials, and the release of data related thereto, including the initiation of IND-enabling studies for PM359 in 2023, its ability to expand preclinical proof-of-concept *in vivo* data and plans to share data from several programs in the second half of 2023, the timing of its regulatory filings, including its anticipated initial IND application submission as early as 2024 with additional filings anticipated in 2025, and plans to share preclinical *in vitro* data in additional programs; the potential of PM359 to reproducibly correct the causative mutation of CGD, and the capacity of its PASSIGE technology to edit CAR-T cells for the treatment of certain cancers and immune diseases; its development and optimization of various non-viral and viral delivery systems; its ability to demonstrate superior off-target profiles for Prime Editing programs; its expansion of Prime Editing using proprietary recombinase and/or retrotransposon and other proprietary technologies; the expansion of Prime Editing's therapeutic potential and the creation of value through strategic business development to extend the reach and impact of Prime Editing to areas beyond Prime Medicine's current areas of focus; its expectations regarding the breadth of Prime Editing technology; the research collaboration to combine Prime Medicine and Cimeio's respective technologies, including Prime Medicine's 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; and the exercise of the exclusive options and payment of economics; the implementation of its strategic plans for its business, programs, and technology; and its estimates of expenses, capital requirements, and needs for additional financing and its expectations regarding the ability to fund its anticipated operating expenses and capital expenditure requirements into 2025. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: uncertainties related to the authorization, initiation, and conduct of preclinical and IND-enabling studies and other development requirements for potential product candidates, including uncertainties related to opening INDs and obtaining regulatory approvals; risks related to the development and optimization of new technologies, the results of preclinical studies, or clinical studies not being predictive of future results in connection with future studies; the scope of protection Prime Medicine is able to establish and maintain for intellectual property rights covering its Prime Editing technology; Prime Medicine's ability to identify and enter into future license agreements and collaborations; and general economic, industry and market conditions, including rising interest rates, inflation, and adverse developments affecting the financial

services industry. These and other risks and uncertainties are described in greater detail in the section entitled “Risk Factors” in Prime Medicine’s most recent Quarterly Report on Form 10-Q, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Prime Medicine’s views only as of today and should not be relied upon as representing its views as of any subsequent date. Prime Medicine explicitly disclaims any obligation to update any forward-looking statements subject to any obligations under applicable law. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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Condensed Consolidated Balance Sheet Data
(unaudited)

(in thousands)	June 30, 2023	December 31, 2022
Cash, cash equivalents, and investments	$ 207,618	$ 293,921
Total assets	280,865	360,314
Total liabilities	40,763	44,044
Total stockholders' equity	240,102	316,270

Condensed Consolidated Statement of Operations
(unaudited)

	Three Months Ended June 30,	
(in thousands, except share and per share amounts)	2023	2022
Operating expenses:		
Research and development	$ 34,599	$ 18,940
General and administrative	10,658	7,365
Total operating expenses	45,257	26,305
Loss from operations	(45,257)	(26,305)
Other income (expense):		
Change in fair value of short-term investment — related party	263	(3,723)
Other income, net	2,640	238
Total other income (expense), net	2,903	(3,485)
Net loss before income taxes	(42,354)	(29,790)
(Provision for) benefit from income taxes	(31)	442
Net loss	$ (42,385)	$ (29,348)
Cumulative dividend on preferred stock	—	(6,293)
Net loss attributable to common stockholders	$ (42,385)	$ (35,641)
Net loss per share attributable to common stockholders, basic and diluted	$ (0.47)	$ (1.76)
Weighted-average common shares outstanding, basic and diluted	90,467,298	20,227,343

Prime Medicine

August 2023

Forward-Looking Statements

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

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

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

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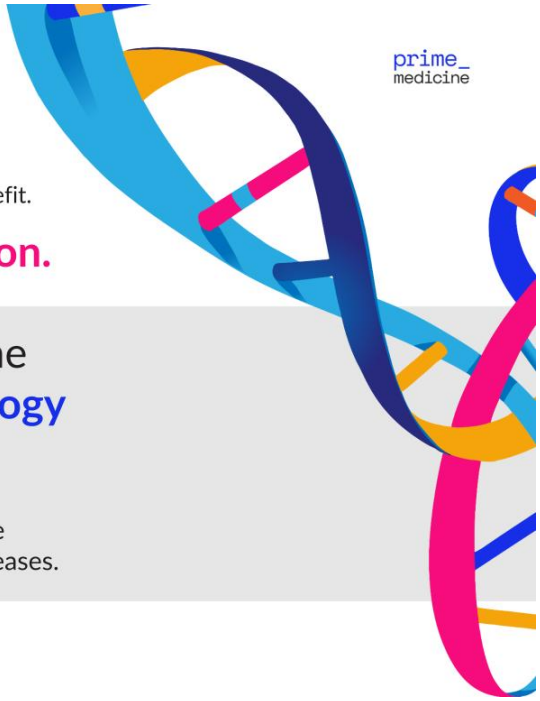
30 years after the first patient was treated with gene therapy, gene editing is only just beginning to demonstrate clinical benefit.

Now is the moment for a revolution.

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

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



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

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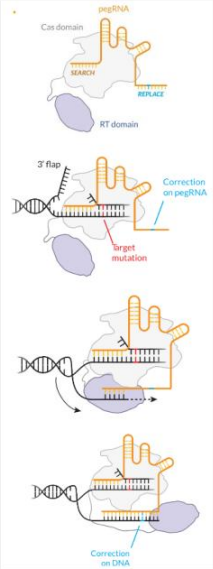

Prime Editing (PE) stands out as a best-in-class genetic medicine approach

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

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

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

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

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

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

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

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

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

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In ~2.5 years since company inception:

Built and advanced a strategic portfolio

Identified and progressed initial pipeline of 18 programs

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

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

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

Advanced CMC and delivery capabilities

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

Optimized and expanded Prime Editing platform, capabilities and IP

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

Established strong corporate position

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

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

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

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

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

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To be discussed in detail today

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

Initially focused on our first two strategic indication categories in diseases where Prime Editing could offer compelling advantages over current standard-of-care and novel therapeutic modalities in development

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

Prime Edited CGD **patient** CD34⁺ cells generate myeloid cells that produce p47^{phox} protein and NADPH oxidase activity

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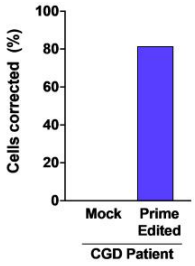
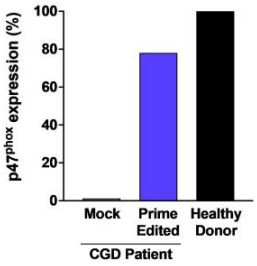
Myeloid progeny of Prime-Edited CD34⁺ cells from patient donor show functional p47^{phox} expression

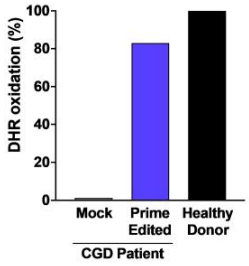
Post-editing patient CD34⁺ cell clonal analysis[1]



p47^{phox} expression[2] restored in CGD myeloid cells[3]



PE restores NADPH oxidase activity in myeloid cell progeny[4]



Gene corrected → p47^{phox} expression restored → Function recovered

Prime Editing results in ~80% of the p47^{phox} levels in healthy donor myeloid cells, and restores oxidase activity in myeloid cells

[1]234 clones analyzed; [2]Normalized to healthy donor controls; [3]Myeloid cells produced from CD34+ cells were analyzed by flow cytometry for detection of myeloid markers including CD13 (percentage of cells expressing CD13 is depicted); [4] Oxidization of dihydrorhodamine (DHR) to fluorescent rhodamine by functional myeloid cells. Performed in collaboration with Dr. Suk See DeRavin (National Institute of Health (NIH) – National Institute of Allergy and Infectious Diseases (NIAID) and Dr. Harry Malech (NIH - NIAID). Data presented at ASGCT 26th Annual Meeting, May 2023.

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

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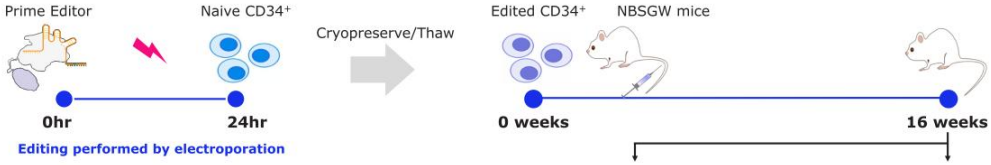
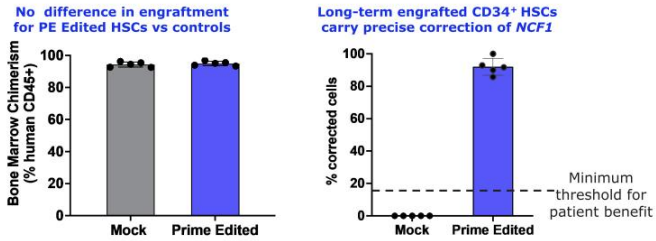
Maintenance of >92% corrected long-term HSCs following 16-week engraftment



Conclusions

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



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

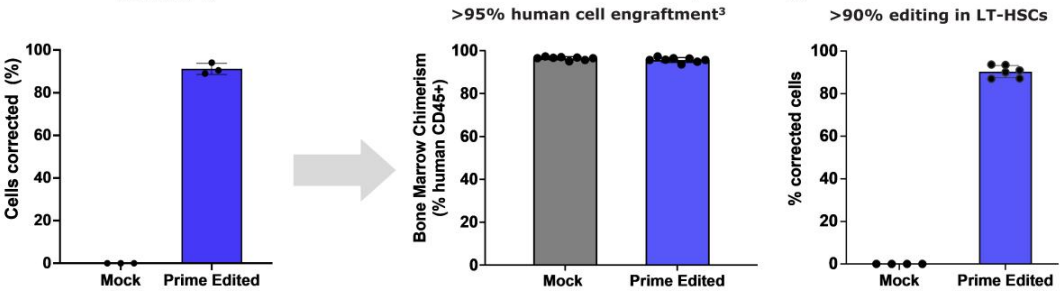
Successful Prime Editing in long-term HSC population: Prime Editing is highly reproducible

prime_ medicine

Long-term study with cells from single donor (Donor 2) shows ~90% LT-HSC correction (similar to Donor 1 results on previous slide)[1]

***ex vivo* >90% cells corrected**
(Donors 2-4)

in vivo analysis shows:
(Donor 2 only)[2]



Similar editing efficiency, engraftment and preservation of long-term HSCs observed across all four donors

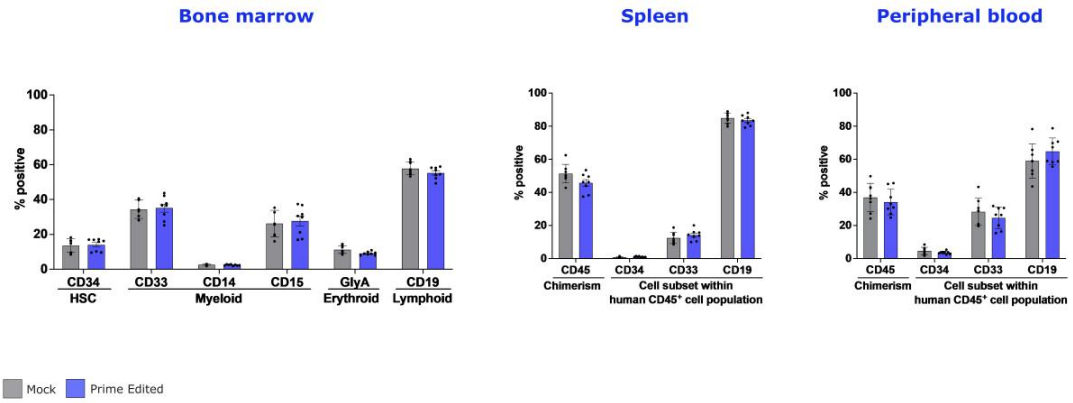
[1]Long-term engraftment is 16-weeks after CD34+ cell infusion.
[2]Data for donors 1,3,4 is highly similar
[3]No significant difference in engraftment between Mock and PE groups. Statistical analyses by two-way ANOVA.

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

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

prime_ medicine

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

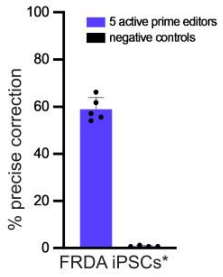


No significant difference between Mock and PE groups. Statistical analyses by two-way ANOVA.
Data presented at ASGCT 26th Annual Meeting, May 2023.

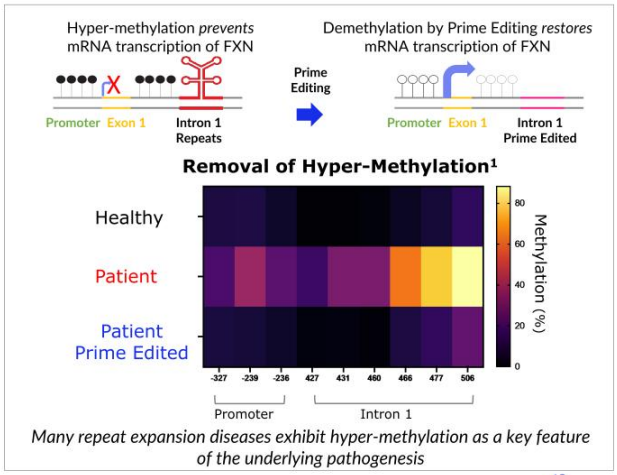
Successful Prime Editing removal of pathogenic repeats: Friedreich's ataxia

prime_ medicine

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



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



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

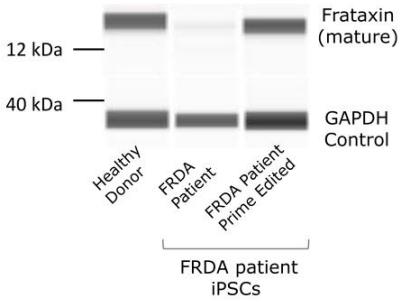
FXN: frataxin gene: FRDA: Friedreich's ataxia; iPSCs: induced pluripotent stem cells. 1 Methylation quantified by bisulfite sequencing

prime_ medicine

Successful Prime Editing removal of pathogenic repeats

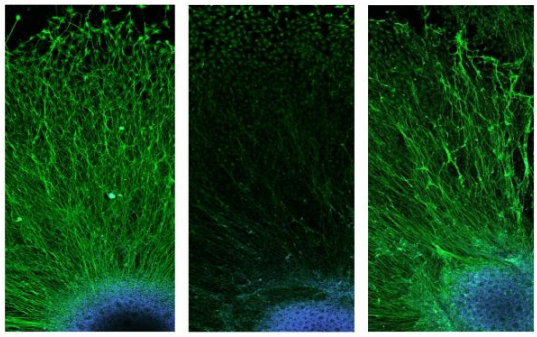
High efficiency Prime Editing restores FXN protein expression and sensory neuron function in Friedreich's Ataxia patients' dorsal root ganglia

Restoration of Frataxin protein expression after Prime Editing



Restoration of axonal projections after Prime Editing

βIII-TUB
DAPI



Healthy Donor | FRDA Patient | FRDA Patient Prime-Edited

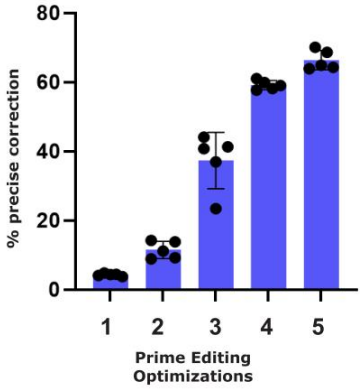
FXN: Frataxin; FRDA: Friedreich's Ataxia; iDRG: iPSC-derived dorsal root ganglia. DAPI: nuclear staining; βIII-TUB: axonal projection staining

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

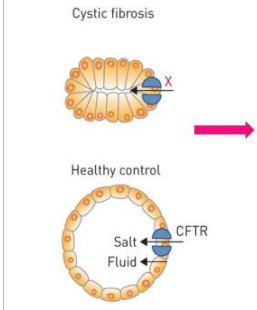
prime_ medicine

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

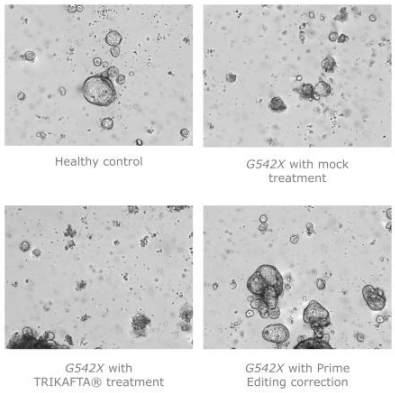
Optimization results in high efficiency Prime Editors that precisely correct G542X mutation



Intestinal organoids swelling assay for CFTR function



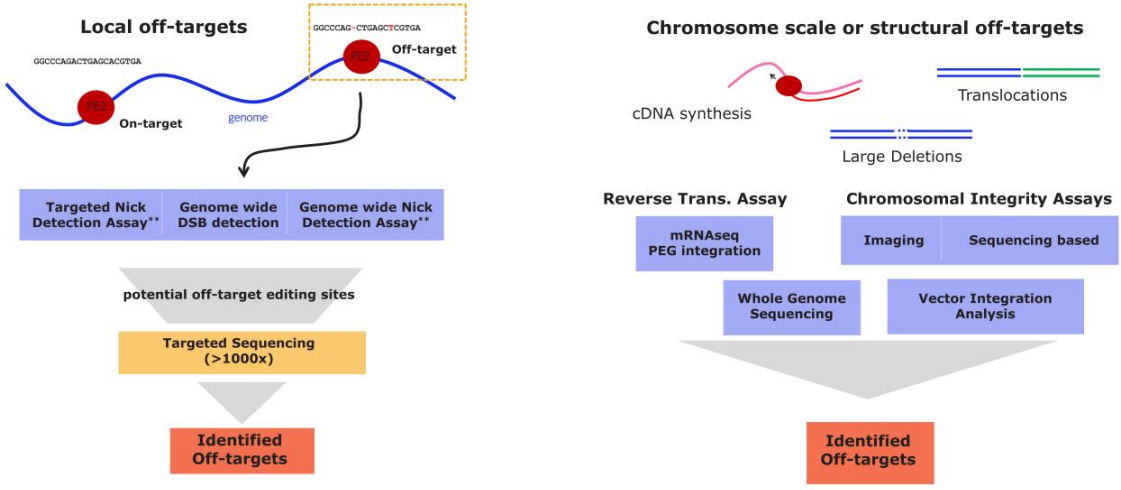
Prime Editing of patient intestinal organoids restores swelling and CFTR function



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

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

prime_ medicine

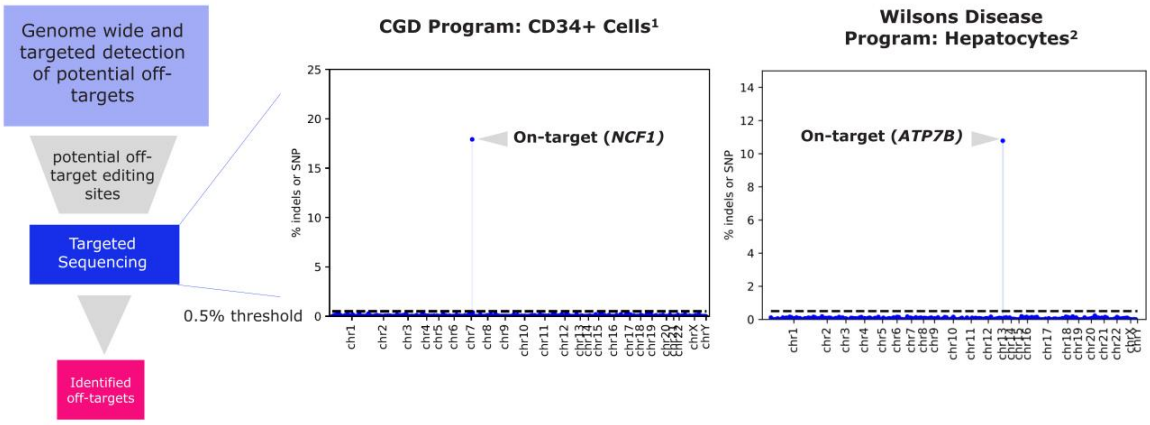


*Preliminary plans pending discussions with regulatory agencies; **Proprietary assay developed by Prime

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

prime_ medicine

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

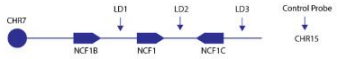


¹Analysis of edited CD34+ cells from CGD program: Targeted Analysis of 550 potential off-target sites of off-target editing. ²Analysis of edited iHEP (iPSG hepatocyte) cells from the Wilsons Disease program: Targeted Analysis of 170 potential off-target sites. SNP: Single nucleotide polymorphisms

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

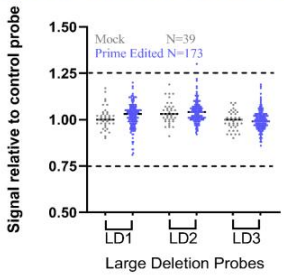
prime_ medicine

Digital PCR Large Deletion Assay

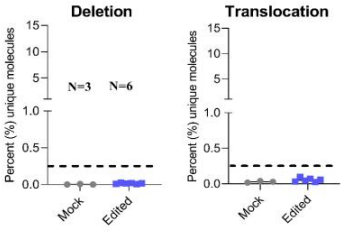


One-sided PCR Chromosomal alterations assay

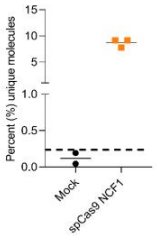
No large deletions in pre-infusion CD34⁺ cell clones



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



Translocation Positive Control: Cas9 nuclease edited cells



Data from analysis of total human material from mouse bone marrow harvested 16 weeks after engraftment
dPCR: CD34⁺ population was sorted and expanded in colony forming media, individual colonies were picked and presence of the indicated chromosomal segments measured, N=number of colonies measured
One-Sided PCR: total material was amplified using a one-sided pcr protocol to identify genomic sequence changes adjacent to the edit site. Positive control sample was generated by transfecting HEK293T with sgRNA against NCF1 and SpCAS9 mRNA.
Data presented at ASGCT 26th Annual Meeting, May 2023.

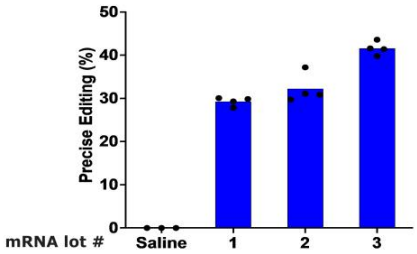
LNP Delivery: Optimization of mRNA increases Prime Editing efficiency and leads to reduction of PCSK9 protein in serum

prime_ medicine

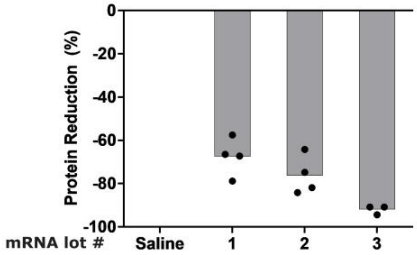
Prime Editor LNP delivered to the liver a **precisely introduced stop codon** in PCSK9 gene in mice

Prime Editor LNP delivered systemically
- Prime Editor mRNA
- Prime Eeditor guide RNA

Optimized mRNA increases Prime Editing in whole liver



Optimized mRNA decreases PCSK9 protein in blood



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

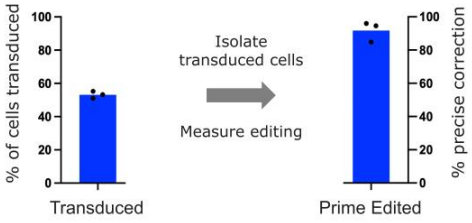
Prime Editing Delivery: CSF and Local Administration to CNS via dual AAV achieves high efficiency in mouse brain

prime_ medicine

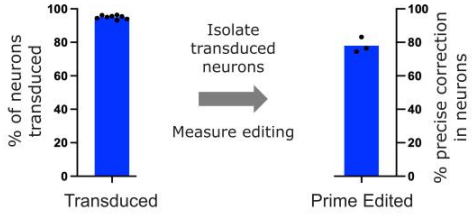
Dual AAV[2] effectively delivers to ~ 95%, and precisely edits ~80%, of neurons in adult mice

Prime Editor dual AAV
- Prime Editor
- Prime Eeditor dual guide RNA

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



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



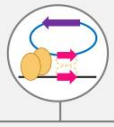
[1]Three weeks in neonatal mice via intra-cerebral infusion (ICV); 5 weeks in adult mice via local administration into cerebellum or cortex. [2]Prime Editor cassette with neuron-specific promoter. All experiments shown are Proof of Concept delivery experiments using a control Prime Editor site.

Prime Medicine has rapidly advanced and substantially improved Prime Editing

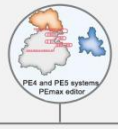
prime_ medicine

Seminal Prime Editing Publication[1]
- All base pair edits, insertions of 40+ bp, deletions of 80+ bp
- Efficiencies ranging from ~10%-60%
- Targeted introduction of recombinase site

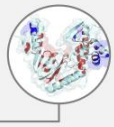
PASSIGE System
- Advanced PE+ recombinase approach
- Targeted whole gene insertions with up to 60% efficiency

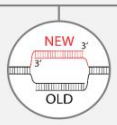


PE4, PE5, and PEmax[3]
- Up to 7-fold increase in editing
- Up to 2-fold decrease in byproducts



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





Dual Flap Prime Editing[2]
- Efficiencies ≥80%
- Hotspot editing and larger insertions
- Synergies with recombinase enzymes (>5-kb targeted DNA integration)

Engineered pegRNAs[4]
- Improved pegRNA stability
- Up to 4-fold increase in editing

pegRNA Enhancements
- New classes of efficiency-increasing pegRNAs enhancements

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

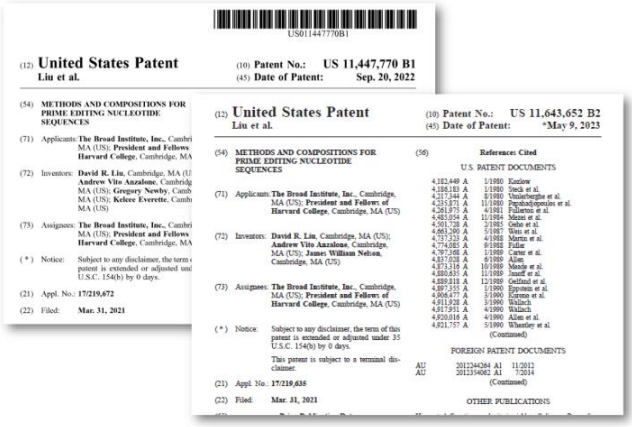
Prime Medicine holds foundational IP for Prime Editing

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

Patent portfolio includes:

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

Prime Medicine has filed for additional IP protection for technological advancements



US011447770B1

(12) **United States Patent**
Liu et al.

(10) **Patent No.: US 11,447,770 B1**
(45) **Date of Patent: Sep. 20, 2022**

(54) **METHODS AND COMPOSITIONS FOR PRIME EDITING NUCLEOTIDE SEQUENCES**

(71) Applicants: **The Broad Institute, Inc.**, Cambri MA (US); **President and Fellows Harvard College**, Cambridge, MA

(72) Inventors: **David R. Liu**, Cambridge, MA (U **Andrew Vito Anzalone**, Cambridg MA (US); **Gregory Newby**, Camb MA (US); **Kelcee Everette**, Camb MA (US)

(73) Assignees: **The Broad Institute, Inc.**, Cambri MA (US); **President and Fellows Harvard College**, Cambridge, MA

(*) Notice: Subject to any disclaimer, the term patent is extended or adjusted und U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/219,672**

(22) Filed: **Mar. 31, 2021**

(12) **United States Patent**
Liu et al.

(10) **Patent No.: US 11,643,652 B2**
(45) **Date of Patent: *May 9, 2023**

(54) **METHODS AND COMPOSITIONS FOR PRIME EDITING NUCLEOTIDE SEQUENCES**

(71) Applicants: **The Broad Institute, Inc.**, Cambridge, MA (US); **President and Fellows of Harvard College**, Cambridge, MA (US)

(72) Inventors: **David R. Liu**, Cambridge, MA (US); **Andrew Vito Anzalone**, Cambridge, MA (US); **James William Nelson**, Cambridge, MA (US)

(73) Assignees: **The Broad Institute, Inc.**, Cambridge, MA (US); **President and Fellows of Harvard College**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/219,635**

(22) Filed: **Mar. 31, 2021**

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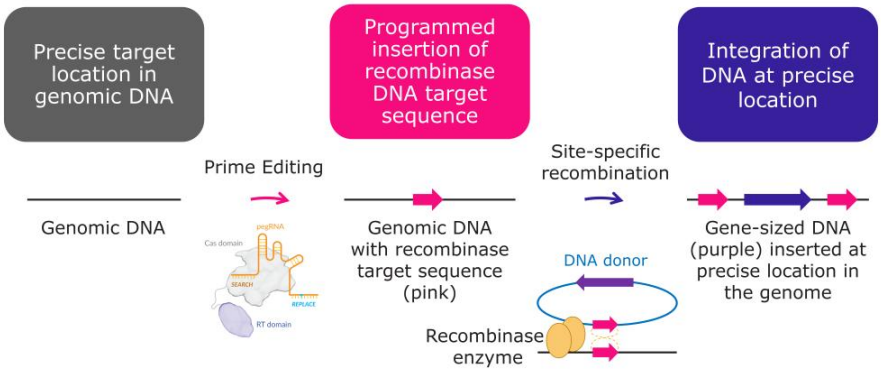
(Continued)

OTHER PUBLICATIONS

prime_ medicine

Prime Assisted Site-Specific Integrase Gene Editing

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



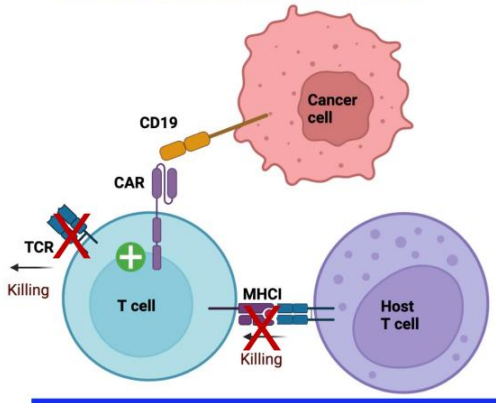
One step non-viral kilobase-size gene editing approach – without double stranded breaks

PASSIGE and multiplex Prime Editing approach for allogeneic off-the-shelf CAR-T cell product

prime_ medicine

Supports potential for Prime Editing to be applied to develop a best-in-class allogeneic CAR-T cell product

Model of Multiplex Edited CAR-T



PASSIGE to integrate CAR at T cell receptor (*TRAC*) locus

- ✓ Make T cells tumor-specific
- ✓ T cell receptor KO prevents GvHD

Multiplex with Prime Editing to KO *B2M*, remove MHC Class I

- ✓ Evade patient immune system
- ✓ Allows for repeat administration if needed

Components for all Edits delivered together without the use of viruses

CAR: chimeric antigen receptor; TRAC: T-cell receptor alpha constant; PASSIGE: Prime-Assisted Site-Specific Integrase Gene Editing

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

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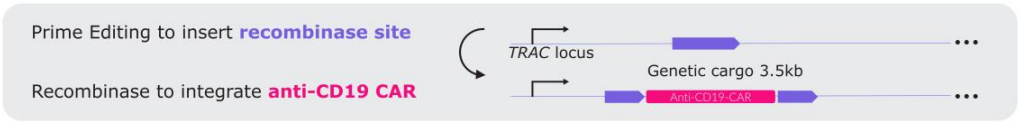
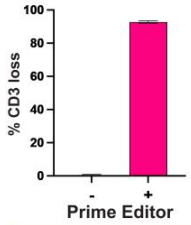
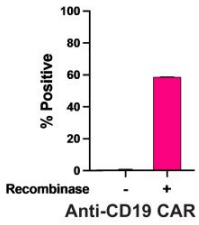
PASSIGE **one-step non-viral** approach for precise introduction of genetic cargo into the genome



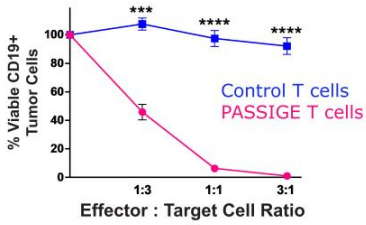
Insertion of recombinase site - over 90% efficiency



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



Tumor cell killing at 72 hours



Targeted integration of the anti-CD19 CAR has been observed to provide potent tumor killing function in preclinical studies

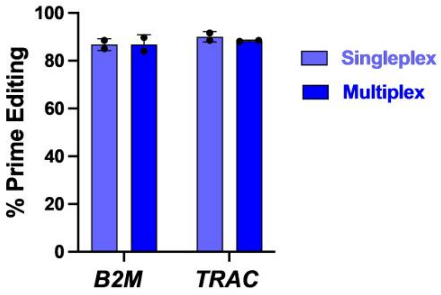
PASSIGE: Prime-Assisted Site-Specific Integrase Gene Editing;
n = 2 technical replicates ; Far right panel: n = 4 technical replicates; Two-way ANOVA with Bonferroni post-test *** P = 0.0002; **** P < 0.0001
Data presented at ASGCT 26th Annual Meeting, May 2023.

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

prime_ medicine

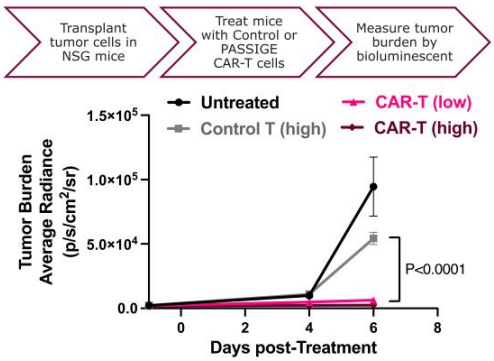
Prime Editing technologies can be used to introduce multiple genomic modifications in cell therapies

β2 microglobulin is knocked out by introducing a stop codon precisely in the B2M gene



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

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



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

prime_ medicine

Business Development and Partnering: A major focus for 2023

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

1

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

2

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

3

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

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

PE = Prime Editing

Prime Medicine and Cimeio: Research collaboration to enable best-in-class HSC medicines

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Goal: Reduce toxicity of conditioning regimens and introduce new therapeutic options to expand utility of HSC transplant and in vivo genetic therapies

Broad Opportunity

HSCT market is large and growing, but conditioning toxicity is major bottleneck

- HSC transplant is curative for many diseases, but utility is limited by need for myeloablative conditioning regimens
- Less toxic regimen could expand addressable market by multiples of current size

Combining Prime Editing with Cimeio's SCIP platform may:

- Improve safety and effectiveness of HSC transplant, significantly improving accessibility, eligibility and outcomes
- Enable selection of *in vivo* edited HSCs, allowing for treatment of genetic diseases without transplant

Strategic Rationale

Developing Prime Editor for Cimeio's CD117 shielding variant

- CD117 is a cell-surface receptor that plays a critical role in survival, proliferation and differentiation of HSCs; blocking or ablating CD117 signaling results in death of the HSC
- CD117 epitopes can be edited to ablate antibody binding while retaining receptor function. This enables clearance of wild type CD117 expressing cells, while protecting cells with the edited epitope
- Prime Editing appears to be an effective way to edit Cimeio's anti-CD117 binding epitopes

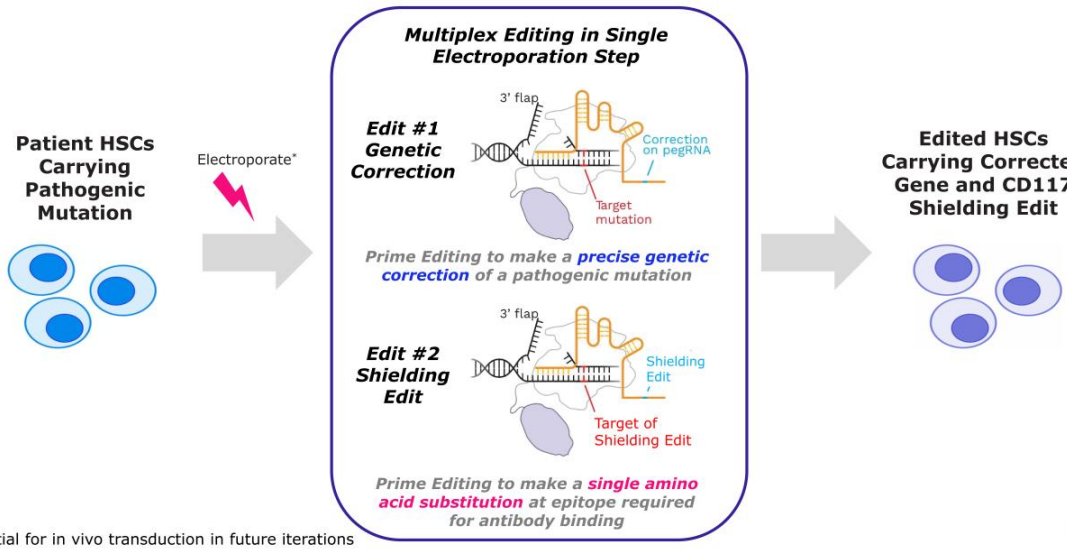
Collaboration Details

If successful, companies will grant exclusive license options to each other:

- Prime will receive exclusive option to license SCIP technology for CD117-shielded HSC transplant, as well as *in vivo* editing of CD117-shielded HSCs for genetic diseases
- Cimeio will receive exclusive option to license Prime Editing for CD117-shielded allogeneic HSC product for AML/MDS and, potentially, a second shielding protein for use in AML/MDS
- If options are exercised, both companies are eligible to receive economics on net sales of licensed products

HSC = Hematopoietic Stem Cell; AML/MDS = Acute Myeloid Leukemia/Myelodysplastic Syndrome; SCIP = Shielded Cell and Immunotherapy Pairs

Prime can multiplex to combine shielding with therapeutic edits



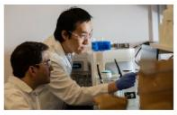
*Potential for in vivo transduction in future iterations

Building the Company

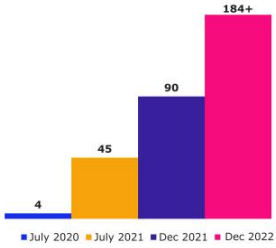
Currently

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

Critical Milestones Achieved



Successful Growth of Talent



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

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Summary of select ongoing activities and next steps for Prime Medicine

Pipeline

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

Platform

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

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

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Backup

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

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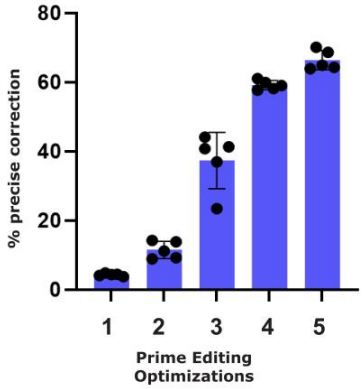
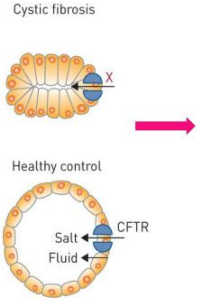
One-time, non-viral delivery to patient intestinal organoids restores CFTR function

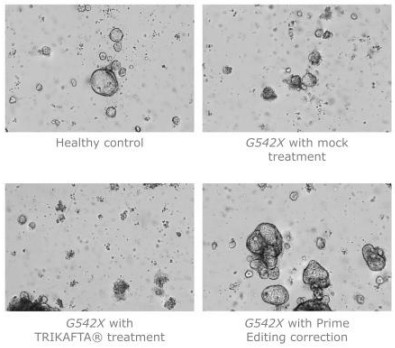
Optimization results in high efficiency Prime Editors that precisely correct G542X mutation



Intestinal organoids swelling assay for CFTR function



Prime Editing of patient intestinal organoids restores swelling and CFTR function



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

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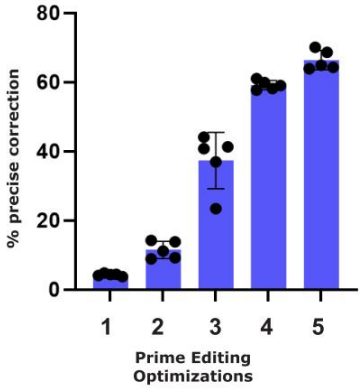

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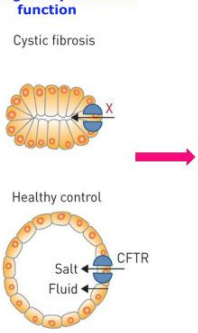

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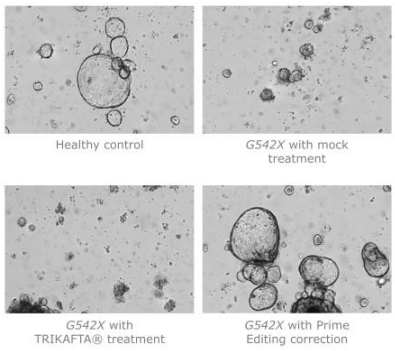

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