Prime Medicine

September 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 Friedrich'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, 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.
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.

Now is the moment for a revolution.

30 years after the first patient was treated with gene therapy, gene editing is only just beginning to demonstrate clinical benefit.
Delivering the full promise of gene editing requires an extremely powerful technology

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

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

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

Efficiency: Durable and high-efficiency editing demonstrated across Prime Medicine portfolio
✓ Permanent edits that are passed along to daughter cells
✓ Corrects genes in situ, maintaining native gene control
✓ Single-dose, potentially curative correction to wild-type sequence

Breadth: Able to address ~90% of disease-causing mutations in multiple tissue types and cells
✓ Corrects mutations in dividing and non-dividing human cells
✓ 100’s of potential indications already available in Prime Editing’s toolbox
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**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

In ~2.5 years since company inception:

- 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

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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<tr>
<th>STRATEGIC CATEGORY</th>
<th>TARGET TISSUE</th>
<th>INDICATION</th>
<th>DELIVERY</th>
<th>DISCOVERY</th>
<th>LEAD OPTIMIZATION</th>
<th>IND-ENABLING</th>
<th>Phase 1/2</th>
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Initially focused on our first two strategic indication categories in diseases where Prime Editing could offer compelling advantages over current standard-of-care and novel therapeutic modalities in development.

*Pipeline reflects the current development stage and will be updated quarterly.
Prime Edited CGD patient CD34⁺ cells generate myeloid cells that produce p47^{phox} protein and NADPH oxidase activity.

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

1. Post-editing patient CD34⁺ cell clonal analysis
2. p47^{phox} expression restoration in CGD myeloid cells
3. PE restores NADPH oxidase activity in myeloid cell progeny

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.

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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

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-PrkdcscidIl2rgtm1Wjl/TomJ 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

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)\(^2\)

\(>95\%\) human cell engraftment\(^3\)

\(>90\%\) editing in LT-HSCs

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

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\(^1\) 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.

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

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.

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

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

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

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
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

FRDA patient iPSCs

Healthy Donor

FRDA Patient

FRDA Patient Prime-Edited

FRDA patient iPSCs

12 kDa

40 kDa

GAPDH

Control

Frataxin (mature)

13

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

**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*

Local off-targets

Off-target

On-target

Genome

Targeted Nick Detection Assay**

Genome wide DSB detection

Genome wide Nick Detection Assay**

Targeted Sequencing (>1000x)

potential off-target editing sites

Identified Off-targets

Chromosome scale or structural off-targets

cDNA synthesis

Translocations

Large Deletions

Reverse Trans. Assay

Chromosomal Integrity Assays

mRNAseq

PEG integration

Whole Genome Sequencing

Vector Integration Analysis

Identified Off-targets

*Preliminary plans pending discussions with regulatory agencies; **Proprietary assay developed by Prime
Safety: Preliminary off-target analyses demonstrate minimal or no off-target editing

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

1 Analysis of edited CD34+ cells from CGD program: Targeted Analysis of 550 potential off-target sites of off-target editing.
2 Analysis of edited iHEP (iPSG hepatocyte) cells from the Wilsons Disease program: Targeted Analysis of 170 potential off-target sites. SNP: Single nucleotide polymorphisms
Safety: No large deletions or translocations detected in Prime Edited LT-HSCs

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.

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

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

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

**Optimized mRNA increases**
Prime Editing 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

Dual AAV\(^2\) effectively delivers to \(\sim 95\%\), and precisely edits \(\sim 80\%\), of neurons in adult mice

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

0 weeks \(\rightarrow\) 3-5 weeks

Neonatal mice \(\to\) ICV infusion\(^1\)
transduced cortex (left) and precisely edited cortical cells (right)

Adult mice \(\to\) local administration\(^1\)
transduced neurons (left) and precisely edited neurons\(^2\) (right)

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<th>% of cells transduced</th>
<th>% of neurons transduced</th>
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Isolate transduced cells

Measure editing

\(^1\)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

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

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 PEG RNA, Prime Editor protein and, optionally, recombinase (expected to issue Q3 2023)

Prime Medicine has filed for additional IP protection for technological advancements
Prime Assisted Site-Specific Integrase Gene Editing

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

Precise target location in genomic DNA

Programmed insertion of recombinase DNA target sequence

Integration of DNA at precise location

Genomic DNA

Prime Editing

Genomic DNA with recombinase target sequence (pink)

Site-specific recombination

Gene-sized DNA (purple) inserted at precise location 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

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

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

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

Prime Editing to insert recombinase site
Recombinase to integrate anti-CD19 CAR

Insertion of 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: Knockout of B2M can be achieved in 95% of Prime-Edited T cells and PASSIGE CAR-T cells reduce tumor burden \textit{in vivo}.

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

\(\beta_2\) microglobulin is knocked out by introducing a stop codon precisely in the B2M gene.

Anti-CD19 CAR-T cells generated with PASSIGE show reduced tumor burden \textit{in vivo}.

Knockout with Prime Editing is efficient in T cells and can be done in multiplex.
Business Development and Partnering: A major focus for 2023

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<tr>
<td>Independently developing and commercializing in <strong>appropriate disease areas</strong> (our pipeline)</td>
<td>Entering strategic collaborations to <strong>extend the reach and impact of PE, provide funding</strong>, and create value in areas we may not enter ourselves in the near-term but may enter later</td>
<td>Partnering and licensing to access <strong>enabling technologies</strong>, including delivery, manufacturing and technologies synergistic with Prime Medicine products</td>
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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.
Prime Medicine and Cimeio: Research collaboration to enable best-in-class HSC medicines

**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
Prime can multiplex to combine shielding with therapeutic edits

Multiplex Editing in Single Electroporation Step

Patient HSCs Carrying Pathogenic Mutation

Electroporate

Edit #1 Genetic Correction

Prime Editing to make a precise genetic correction of a pathogenic mutation

Edited HSCs Carrying Corrected Gene and CD117 Shielding Edit

Edit #2 Shielding Edit

Prime Editing to make a single amino acid substitution at epitope required for antibody binding

*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

- September 2019: $115M Series A
- October 2019: Prime Editing seminal Nature paper
- July 2020: Commenced Corporate Operations
- April 2021: $200M Series B
- Oct 2022: ~$200M IPO

Successful Growth of Talent

- July 2020: 4
- July 2021: 43
- Dec 2021: 90
- 2023 YTD: 184+
Key upcoming events will continue to drive the Prime Medicine platform forward

Summary of select ongoing activities and next steps for Prime Medicine

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

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

Strong cash position: Cash, cash equivalents and investments as of 6/30/2023 sufficient to fund anticipated operating expenses and capital expenditure requirements into 2025.
Backup
Unmet needs in Cystic Fibrosis: Potential to restore CFTR function in patients with G542X mutation

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

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

**Intestinal organoids swelling assay for CFTR function**

- Healthy control
- G542X with mock treatment
- G542X with TRIKAFTA® treatment
- G542X with Prime Editing correction

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

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