PRECISION BIOSCIENCES

Corporate Deck

June 2024

Forward-Looking Statements

This presentation contains forward-looking statements, as may any related presentations, within the meaning of the Private Securities Litigation Reform Act of 1995. The Company intends such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements contained herein and in any related presentation that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding the pre-clinical and clinical development, research advancement and expected safety, efficacy and benefit of our product candidates and gene editing approaches, including editing efficiency, defined outcomes, therapeutic edits, safety and differentiating aspects; the suitability of azer-cel for oncology indications and non-oncology indications including immunological diseases; the suitability of ARCUS nucleases for gene insertion, large gene deletion, mitochondrial gene editing, and other complex gene editing approaches; the expected timing of regulatory processes; expectations about our operational initiatives and business strategy; expectations about achievement of key milestones; expectations about market trends and opportunity; expectations regarding partnership opportunities; our expected cash runway; expectations about achievement of key milestones and receipt of any milestone, royalty, or other payments; expectations regarding our liquidity and capital resources; and anticipated timing of initial clinical data. In some cases, you can identify forward-looking statements by terms such as "aim," "anticipate," "approach," "believe," "contemplate," "could," "designed to", "estimate," "expect," "goal," "intend," "look," "may," "mission," "plan," "possible," "potential," "predict," "project," "promise," "pursue," "should," "target," "will," "would," and other similar words or expressions, or the negative of these words or similar words or expressions, are intended to identify forward-looking statements, though not all forward-looking statements use these words or expressions.

Forward-looking statements are based on management's current expectations, beliefs and assumptions and on information currently available to us. These statements are neither promises nor guarantees, but involve number of known and unknown risks, uncertainties and assumptions, and actual results may differ materially from those expressed or implied in the forward-looking statements due to various important factors, including, but not limited to: our ability to become profitable; our ability to procure sufficient funding to advance our programs; risks associated with raising additional capital and requirements under our current debt instruments and effects of restrictions thereunder; our operating expenses and our ability to predict what those expenses will be; our limited operating history; the success of our programs and product candidates in which we expend our resources; our limited ability or inability to assess the safety and efficacy of our product candidates; our dependence on our ARCUS technology; the risk that other genome-editing technologies may provide significant advantages over our ARCUS technology; the initiation, cost, timing, progress, achievement of milestones and results of research and development activities, preclinical studies and clinical trials; public perception about genome editing technology and its applications; competition in the genome editing, biopharmaceutical, and biotechnology fields; our or our collaborators' ability to identify, develop and commercialize product candidates; potential product liability lawsuits and penalties against us or our collaborators related to our technology and our product candidates; the U.S. and foreign regulatory landscape applicable to our and our collaborators' development of product candidates; our or our collaborators' or other licensees' ability to advance product candidates into, and successfully design, implement and complete, clinical or field trials; our or our collaborators' other licensees' ability to advance product candidates into, and successfully design, implement and complete, clinical or field trials; potential manufacturing problems associated with the development or commercialization of any of our product candidates; delays or difficulties in our and our collaborators' ability to enroll patients; changes in interim "top-line" and initial data that we announce or publish; if our product candidates do not work as intended or cause undesirable side effects; risks associated with applicable healthcare, data protection, privacy and security regulations and our compliance therewith; the rate and degree of market acceptance of any of our product candidates; the success of our existing collaboration agreements, and our ability to enter into new collaboration arrangements; our current and future relationships with and reliance on third parties including suppliers and manufacturers; our ability to obtain and maintain intellectual property protection for our technology and any of our product candidates; potential litigation relating to infringement or misappropriation of intellectual property rights; our ability to effectively manage the growth of our operations; our ability to attract, retain, and motivate key executives and personnel; market and economic conditions; effects of system failures and security breaches; effects of natural and manmade disasters, public health emergencies and other natural catastrophic events; effects of sustained inflation, supply chain disruptions and major central bank policy actions; insurance expenses and exposure to uninsured liabilities; effects of tax rules; risks related to ownership of our common stock; our ability to meet the requirements of and maintain listing of our common stock on NASDAQ or other public stock exchanges and other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2024, as any such factors may be updated from time to time in our other filings with the SEC, which are accessible on the SEC's website at www.sec.gov and the Investors page of our website under SEC Filings at investor.precisionbiosciences.com.

All forward-looking statements speak only as of the date of this presentation and, except as required by applicable law, we have no obligation to update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Precision consults with various presentation speakers and compensates them for their time and expertise.

Today’s Agenda

- Corporate Overview
- Technology Overview
- Chapter 1 – PBGENE-HBV
- Chapter 2 – PBGENE-PMM
- Chapter 3 – HDR Insertion and Replacement

PRECISION BIOSCIENCES

Corporate Overview

Focusing on Our Foundation—*In Vivo* Gene Editing

Through our gene editing platform ARCUS

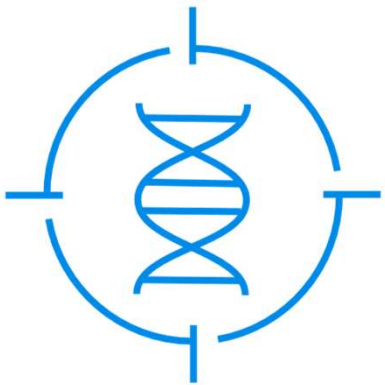
Go-Forward Singular Focus

In Vivo Gene Editing

Pivoting to Our Foundational Strength

- ARCUS - wholly owned genome editing platform
- Optimized for gene insertion, excision, and elimination
- Over 25 years of gene editing expertise and protein engineering
- Cash & cash equivalents (3/31/2024) = $137 million
- Expect existing cash and cash equivalents, expected operational receipts, operational efficiencies, availability of the ATM facility, and available credit to fund OpEx and CapEx into **second half of 2026**

Focused Execution 2024-2026



Expected cash runway now enables funding *In Vivo* programs through Phase 1 data

Precision BioSciences End-to-End Research & Development Capabilities

1 | Nuclease Generation & Characterization

- Protein Engineering
- Bioinformatics
- Specificity and Off-target Analysis
- Nuclease Optimization

2 | Gene Delivery & In Vivo/In Vitro PoC

- Gene Discovery
- In-House and Partnered PoC Animal Studies
- Novel Delivery

3 | CMC Material Generation and Toxicology

- Analytical and Process Development
- IND-Enabling / GLP Toxicology Studies
- Quality
- External Manufacturing

4 | Regulatory and Clinical Development

- FDA Pre-IND and Global Early Scientific Advise
- US and Ex US Regulatory Filings
- Clinical Operations
- Translational Analysis

Developing Wholly Owned Gene Editing Programs

Developing Partnered Gene Editing Programs

Precision BioSciences Leadership Team

Michael Amoroso
Since Oct 2021
President &
Chief Executive Officer

Jeff Smith, Ph.D.
Since March 2006
Chief Research Officer,
Co-Founder

Alex Kelly
Since Oct 2020
Chief Financial Officer

Cindy Atwell
Since Apr 2019
Chief Business Officer

Alan List, M.D.
Since Apr 2021
Chief Medical Officer

Juli Blanche
Since May 2022
Chief People Officer

Dario Scimeca
Since June 2019
General Counsel

Neil Leatherbury
Since March 2017
Senior VP, CMC

Cassie Gorsuch, Ph.D.
Since June 2016
Head, Gene Discovery

Precision BioSciences Board of Directors

Kevin Buehler
Since July 2019
Board Chair

Alcon · NOVARTIS

Michael Amoroso
Since Sep 2021
President &
Chief Executive Officer

Celgene · Kite (A GILEAD Company) · Abeona THERAPEUTICS

Melinda Brown
Since May 2022
Audit Chair

tapestry · PEPSICO

Stanley Frankel, M.D.
Since Apr 2021
Science & Technology Chair

AMGEN · Celgene · Bristol Myers Squibb · MERCK

Geno Germano
Since March 2020
Compensation Chair

Pfizer · Wyeth · Elucida Oncology

Shari Lisa Pire, J.D.
Since Nov 2021

PLUME PHARMA · COGNATE BIOSERVICES · COBRA BIOLOGICS

Sam Wadsworth, Ph.D.
Since Nov 2021

ultragenyx · sanofi · genzyme

ARCUS Focused on Sophisticated Edits Leveraging Unique Advantages

PROGRAM	INDICATION	TISSUE	TARGET	EDIT TYPE / DELIVERY	RESEARCH	IND-ENABLING	CLINICAL	PARTNER
PBGENE-HBV	Chronic hepatitis B	Liver	HBV	Elimination/LNP				
PBGENE-PMM	m3243 primary mitochondrial myopathy	Muscle	PMM	Elimination/AAV				
PBGENE-DMD	Duchenne muscular dystrophy	Muscle	DMD	Excision/AAV				
PBGENE-LIVER	Undisclosed	Liver	—	Insertion/—				
PBGENE-CNS	Undisclosed	CNS	—	—				
iECURE-OTC*	Ornithine transcarbamylase deficiency	Liver	OTC	Insertion/AAV				ECURE
PBGENE-NVS	Sickle cell disease/ beta thalassemia	HSCs	—	Insertion/—				NOVARTIS

Returning to Precision Under Assessment

*iECURE-OTC also named ECUR-506 under investigation in the OTC-HOPE study

Ornithine Transcarbamylase (OTC) Program is First ARCUS *In Vivo* Gene Editing Program to Progress into the Clinic

ARCUS *in vivo* gene editing now clinical stage following December 2023 approval:

- iECURE received approval from the Australian TGA, U.K. MHRA and U.S. FDA regulatory bodies for the initiation of OTC-HOPE, a first-in-human Phase 1/2 trial evaluating ECUR-506, incorporating an ARCUS nuclease for the treatment of OTC deficiency in neonatal male patients.
- **FDA Fast Track** Designation Received
- iECURE is now enrolling patients **for its global clinical trial.**

CTA acceptance is important milestone for ARCUS

"The acceptance of iECURE's CTA marks an important milestone for patients with OTC deficiency. This is the first ARCUS in vivo gene editing program to progress into the clinic. We look forward to supporting iECURE's continued progress with this program." – *Michael Amoroso*

28% Of liver cells in NHPs demonstrated durable expression of the human OTC gene at the 1-year time point **following administration of ECUR-506**

***Note: therapeutic benefit expected at 5%+ editing[3]**

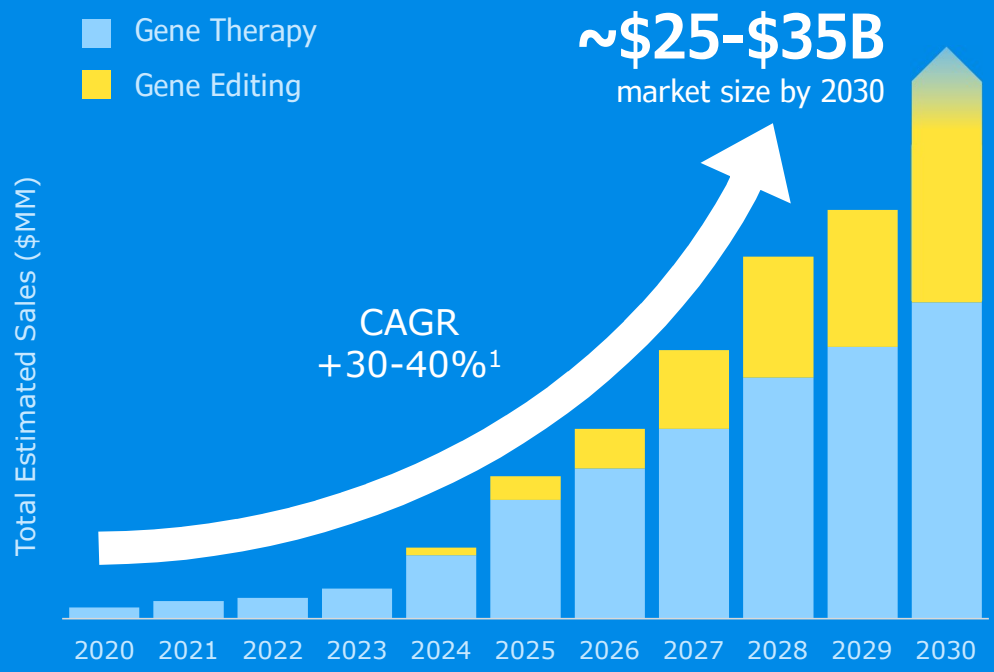
~10,000 People WW with OTCD

- Disease prevalence is between 1 in 60,000 and 1 in 72,000
- **Neonatal onset has been associated with mortality rates as high as 74%**

[1] Complete removal of OTC activity results in severe neonatal disease, while decreased OTC results in late-onset.
[2] Onset may occur at any age though is more common in infancy. HAC: Hyperammonemic Crisis, defined as plasma ammonia levels ≥ 150 µmol/L together with clinical symptoms probably related to hyperammonemia. OTC: Ornithine Transcarbamylase. Source: UpToDate; Orphanet; Hasegawa et. Al. J Pediatr Surg. 1995. Ah et. Al. GeneReviews. 2017. NORD; Lamb et. Al. BJM. 2016. Brassier et. Al. Orphanet Journal of Rare Disease 2015.; Unsinn et. Al. Orphanet Journal of Rare Diseases. 2016; Summar et al. NIH. 2008; Buerger et. Al. J. Inherit. Metab. Dis. 2013; ClearView Analysis.
[3] 5-10% or greater editing or periportal hepatocytes expected to yield therapeutic benefit per KOL feedback; 5% threshold supported by Annals of Clinical and Translational Neurology

ARCUS Potential to Capture a Significant Portion of the Genetic Medicines Market Versus Other Liver-focused Editors

The Genetic Medicines Market Opportunity is Substantial



Gene Editing Expected to Disrupt and Continue to Grow the Genetic Medicines Market

Precision's programs represent a US market opportunity to potentially treat

400-500k patients*

Note: 1. Based on analysis from Cowen 2023, Grandview 2023, Allied 2023 and BCC 2023 research reports; * Total addressable market (TAM) assumed at 100% share

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ARCUS Technology Overview

Bringing the Dream to Reality with Creation of ARCUS

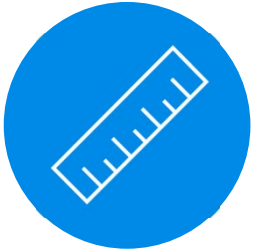
- ARCUS is derived from the **homing endonuclease I-CreI** found in green algae
- **Evolved to safely edit by inserting in genome, adding function**
  - CRISPR-based editing tools engineered from enzymes evolved to knockout DNA only
- Extremely efficient at generating **Defined Outcomes* due** to predominant repair using **Homology Directed Repair (HDR)** or **"Perfect Religation"** versus Non-Homologous End Joining (NHEJ)
- DNA recognition and cutting **fully integrated** into a single protein component for high specificity and efficiency – no guide RNA
- **Iterative protein engineering** to optimize for safety
- **> 65 patents issued** covering ARCUS and in vivo gene editing

***Defined Outcome** = desired therapeutic edit and effect

ARCUS is a Sophisticated Editing Tool With Clear Differentiation Versus Other Gene Editing Modalities

All About The Cut

- 3 Prime Overhang Cut
- Drives Homology-Directed Repair (HDR)
- Complementary overhangs drive "Perfect" Re-ligation



Size Matters

- Smallest gene editor (~1500 bp)
- Small size enables delivery of MORE payload allowing sophisticated edits
- Enables delivery both non-viral and viral, to diverse tissues in the body

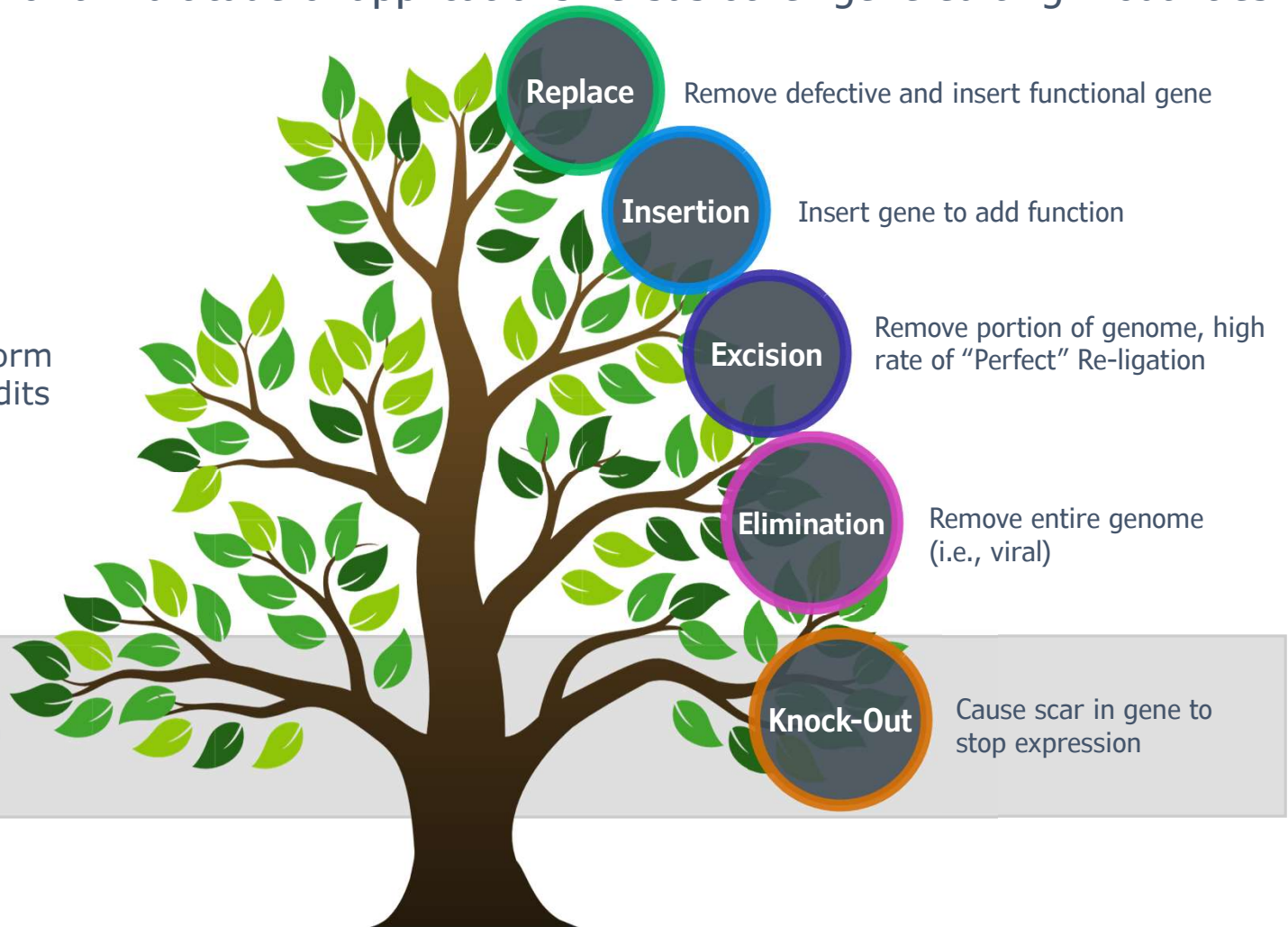
Keep It Simple

- Only single component editor that recognizes and cuts DNA
- Single component streamlines delivery and results in highest efficiency
- Single component editor requires lower dose of delivery vehicle

ARCUS for the More Sophisticated Gene Edit

Designed by nature for a multitude of applications versus other gene editing modalities

ARCUS
Capability To Perform
"Sophisticated" Edits



"Low Hanging Fruit"
Commoditized application for all gene editors

Degree of Difficulty

Defined Outcomes
Accomplished Through
ARCUS Advantages

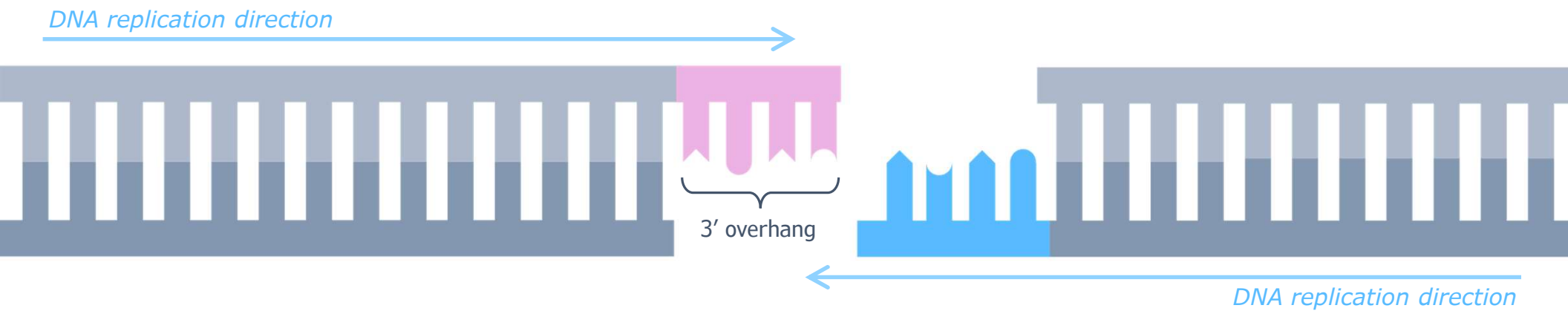
The Cut

The Size

The Simplicity

It's All About The Cut

ARCUS's 3 prime, 4 base pair cut drives efficacy and safety



This unique cut drives high efficiency repair by HDR OR "Perfect" Re-ligation leading to Defined Outcomes

- Due to ARCUS unique 3' overhang cut, "sticky-end" breaks at off-target sites, are detected with higher sensitivity than blunt cuts generated by CRISPR…allows Precision to engineer and optimize for high specificity and off-target edits below limit of detection

The ARCUS Cut is Uniquely Designed to Drive Defined Outcomes

ARCUS cut leads to HDR or “Perfect” Re-ligation

Generates a 3′ overhang required for Defined Outcomes by HDR or Perfect Re-ligation

The ARCUS Cut

Cas9

Blunt cut induces NHEJ

TALEN/ZFN

Cas12a

Staggered cut in wrong 5′ direction for HDR, therefore NHEJ repair

Base Editors

Prime Editors

Single, double, or unintended DNA breaks results in interrupted repair state*, HDR not attainable

**Genotoxic effects of base and prime editing in human hematopoietic stem cells*; Nature Biotechnology, 2023, Fiumara, M.

ARCUS Can Drive Efficient HDR in Both Dividing and Non-Dividing Cells…
…Previously Thought to be Nearly Impossible for Gene Editing

"By the late 1980's, dogma in the field of DNA repair held that end joining, rather than HDR, is the dominant DSB pathway in mitotically dividing mammalian cells in culture."

–Fyodor D. Urnov,
The CRISPR Journal, V1. N1. 2018

"However, traditional HDR has very low efficiency in most human cell types, particularly in non-dividing cells, and competing non-homologous end joining (NHEJ) leads predominantly to insertion-deletion (indel) byproducts"

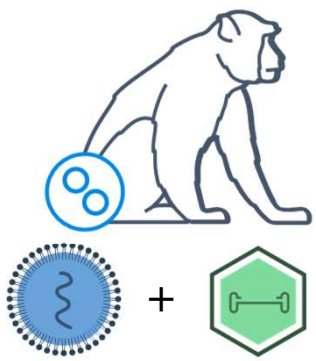
–Broad Institute Patent Filing
USPTO 11643652

"Inability to correct genes in non-dividing cells since currently, HDR DNA repair machinery is only expressed in dividing cells."

–Prime Medicine 10K, 2023

ARCUS Inserts with High Efficiency in Adult Nonhuman Primates, Example Previously Thought to be Unachievable

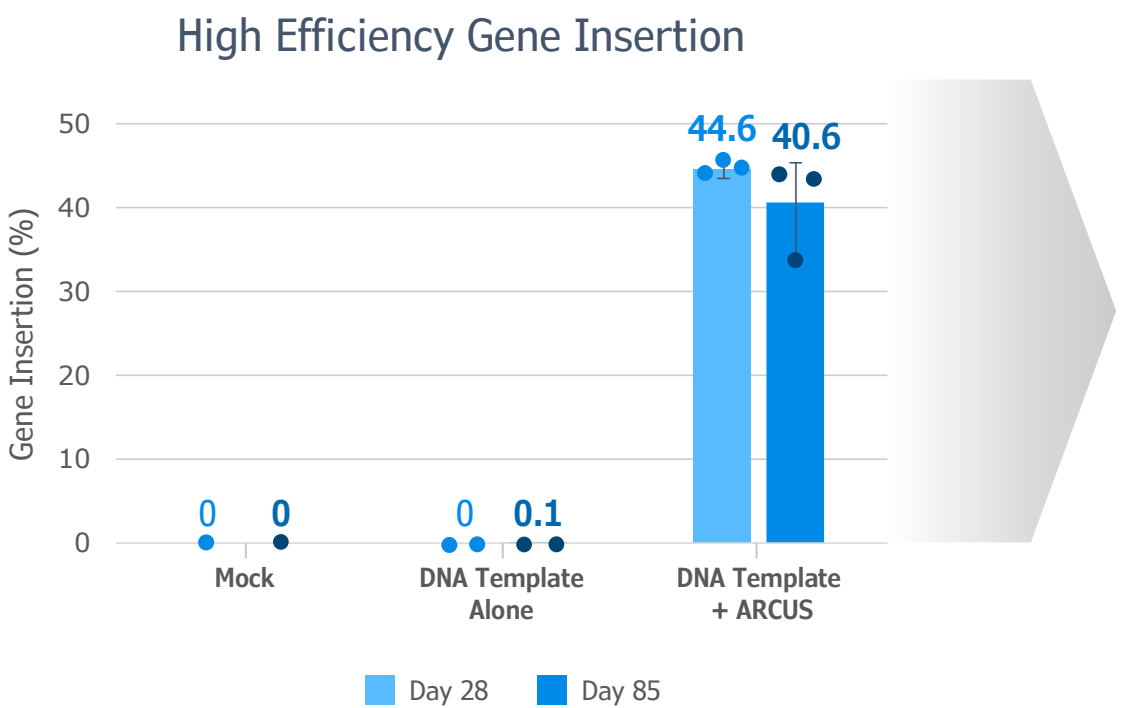
Nondividing cells in vivo



ARCUS LNP
1.75 mg/kg

+

DNA Template AAV
3e13 vg/kg



>3x
insertion efficiency of CRISPR-based approach*

*45% gene insertion calculated for total liver tissue, much higher if only calculating insertion into hepatocytes
*ASGCT 2023, poster 926, Regeneron/Intellia, "Targeted Gene Insertion of *Factor 9* as a Potential Durable Treatment for Hemophilia B"

Defined Outcomes
Accomplished Through
ARCUS Advantages

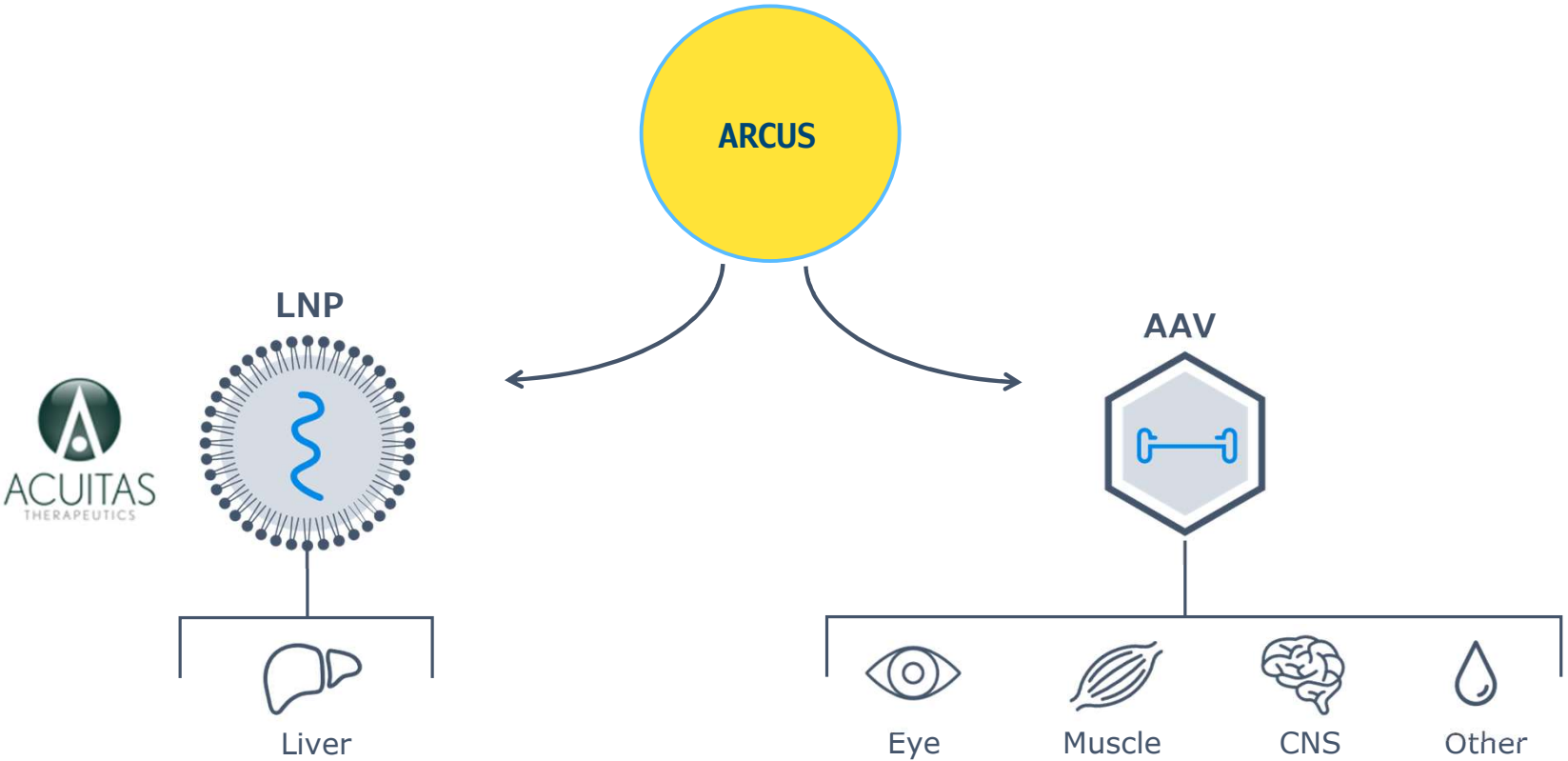
The Cut

The Size

The Simplicity

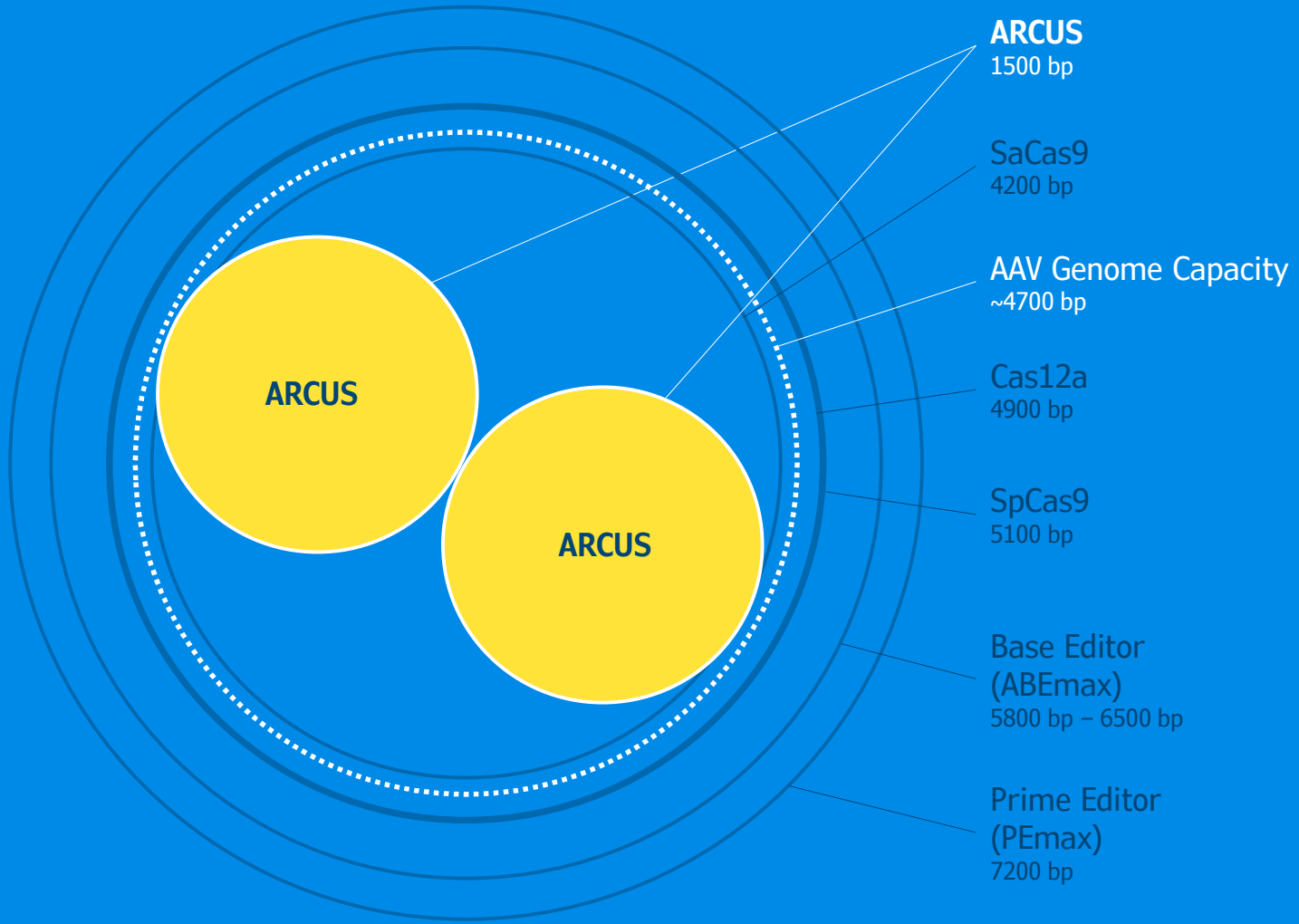
Size Matters for Where You Can Deliver

ARCUS can use different delivery vehicles to target diverse tissue types



Size Matters for **What** You Can Deliver:

Small ARCUS Size Allows Two Nucleases in One AAV for **Gene Excision** in DMD

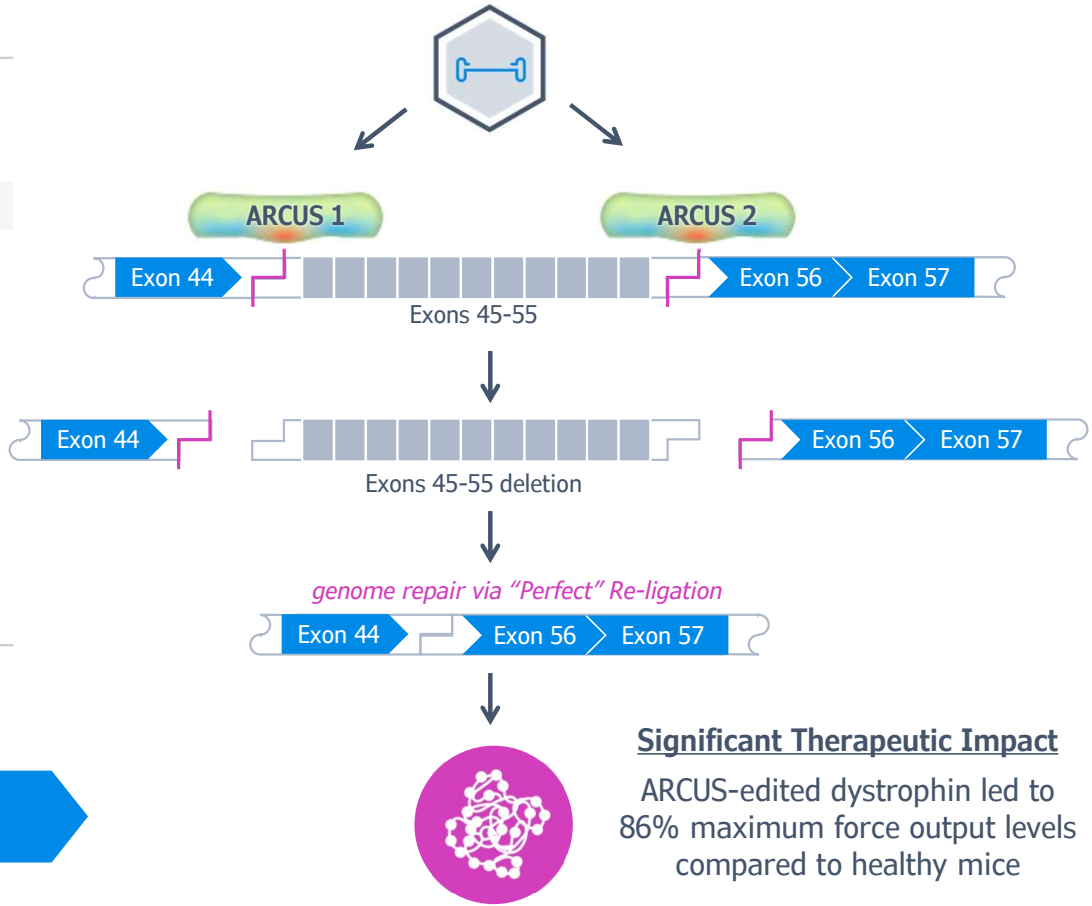


Sizes include editor and expression machinery; ARCUS nuclease is 1062 bp

ARCUS Nucleases Excise Mutations and Restore Function in DMD

PBGENE-DMD Program

Two complementary ARCUS nucleases delivered in a single AAV are used to excise a mutation **"hot spot"** in Exons 45-55 responsible for ~50% of DMD cases



GOAL: Restore dystrophin expression

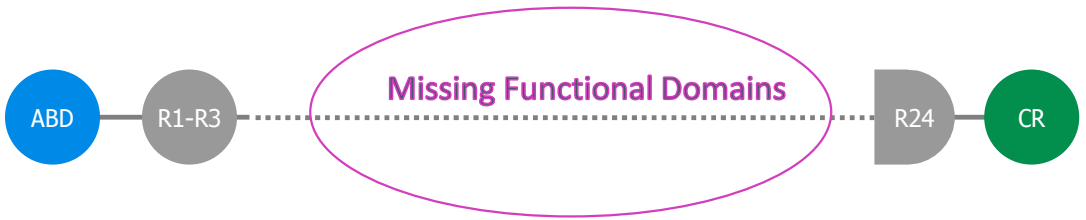
Significant Therapeutic Impact

ARCUS-edited dystrophin led to 86% maximum force output levels compared to healthy mice

The Size: ARCUS-Edited Dystrophin Preserves Majority of Protein Domains With the Goal of Improving Function

Normal Dystrophin

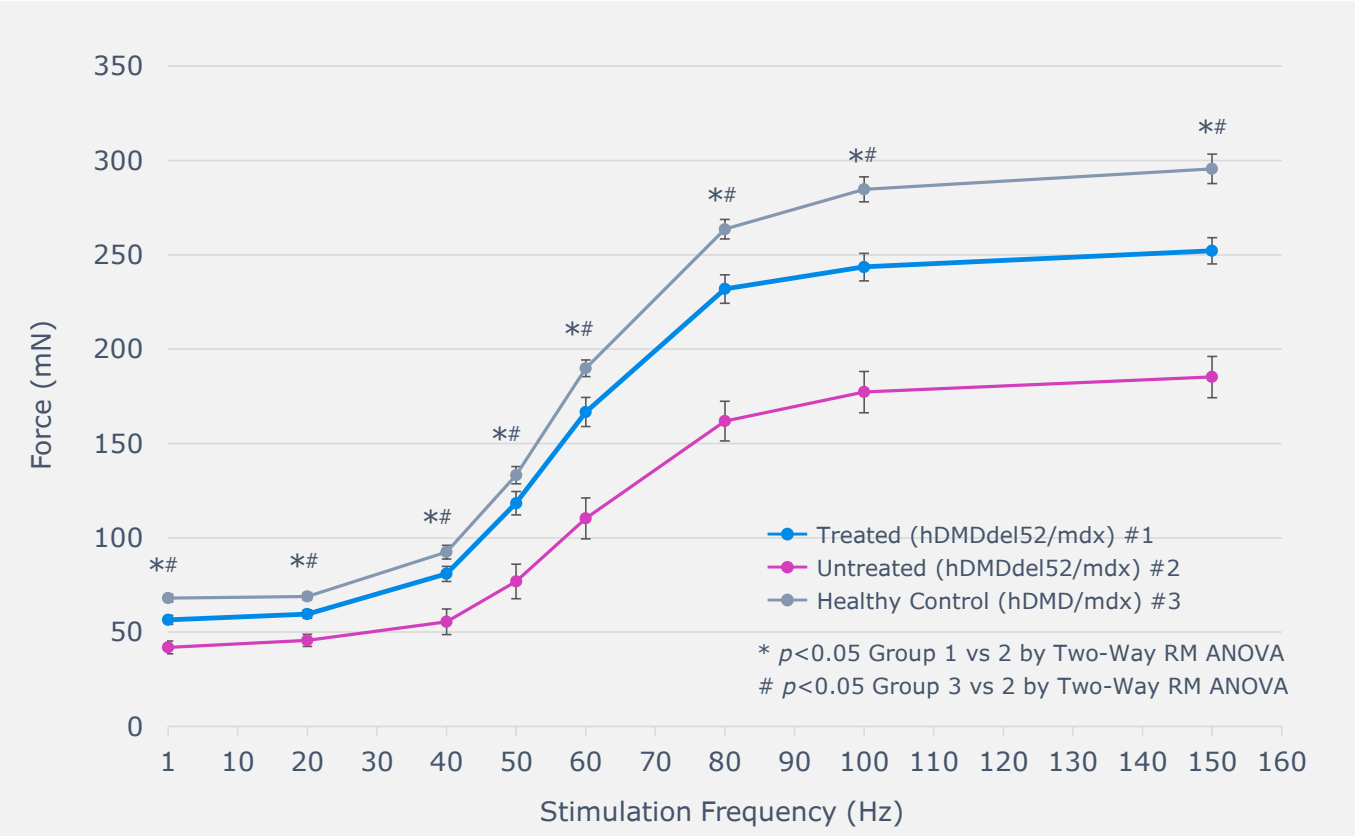
ELEVIDYS (Sarepta)
Received accelerated approval in US



ARCUS Edited Dystrophin

ABD: actin binding domain, R: rod domain, CR: cysteine-rich domain, CT: carboxyl-terminus domain

Maximum Force Output in ARCUS-Treated Mice was Significantly Improved



ARCUS-treated mice achieved:

Editing in **heart, diaphragm, and skeletal muscle**

Evidence of edited dystrophin in **muscle satellite cells**

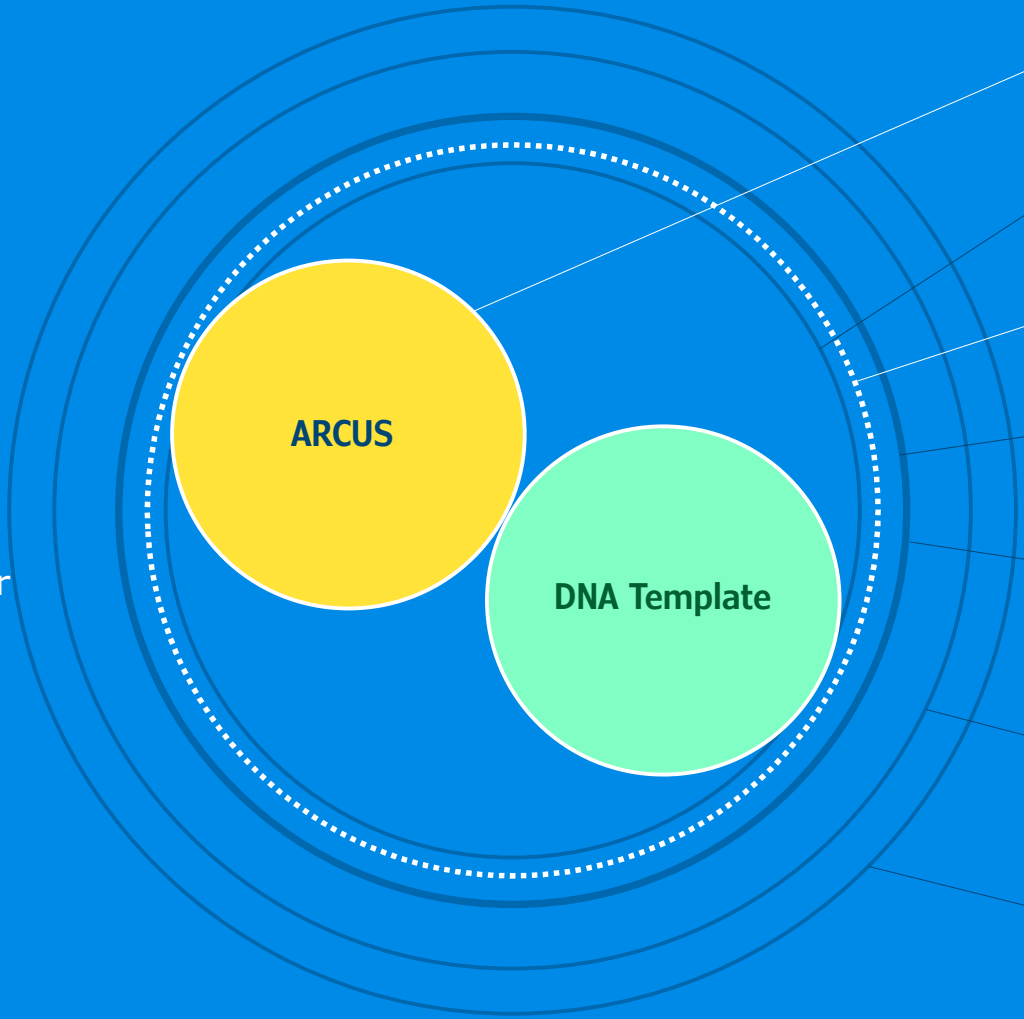
Leading to:

86% Maximum Force Output Levels

compared to non-diseased, control mice in the calf

Size Matters for **What** You Can Deliver:

Allowing Delivery with a DNA Template in a Single AAV for **Gene Insertion**



ARCUS
1500 bp

SaCas9
4200 bp

AAV Genome Capacity
~4700 bp

Cas12a
4900 bp

SpCas9
5100 bp

Base Editor
(ABEmax)
5800 bp – 6500 bp

Prime Editor
(PEmax)
7200 bp

Sizes include editor and expression machinery; ARCUS nuclease is 1062 bp

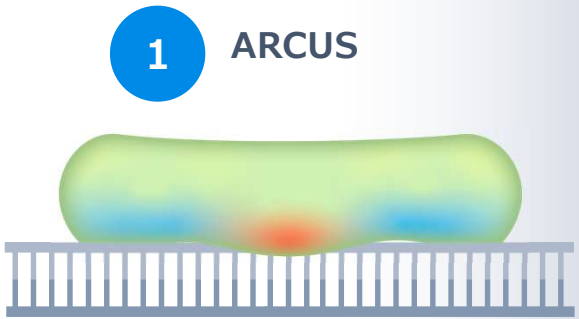
Defined Outcomes
Accomplished Through
ARCUS Advantages

The Cut

The Size

The Simplicity

Simplicity: ARCUS is the Only Single Protein Component Editor



Single protein with a DNA recognition motif and catalytic activity all in one; **no guide RNA required**

Editing outcome not dependent on simultaneous delivery of multiple components leading to **higher efficiency**

Single component **requires less** AAV and potentially less LNP

〉 Easy to deliver

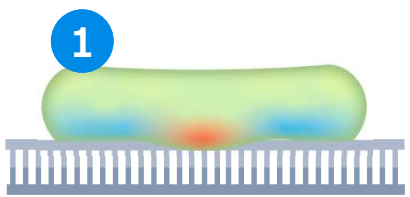
〉 High efficiency

〉 Low dose improves safety

Why does Simplicity Matter for Safety?
ARCUS Integrated Cleavage and Binding Activity Allows for Precise Targeting

Targeted Editing

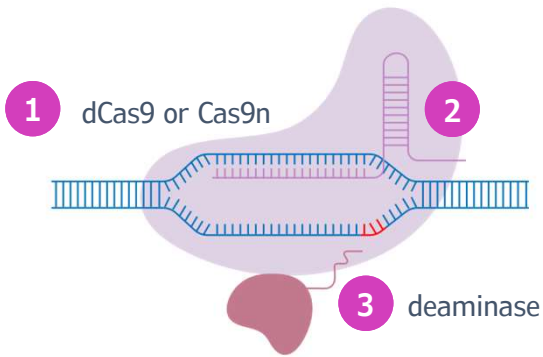
ARCUS



Single Component

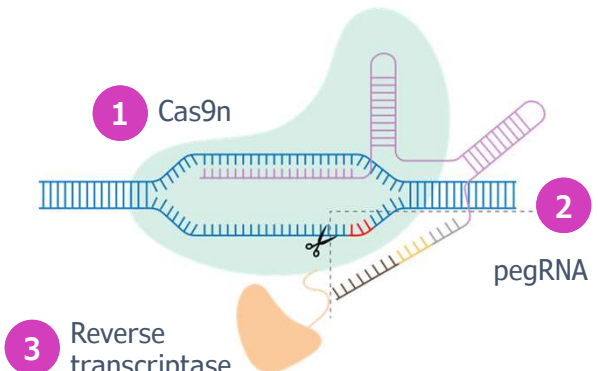
Potential for guide independent effector off-target activity

Base Editor



Promiscuous Deamination

Prime Editor



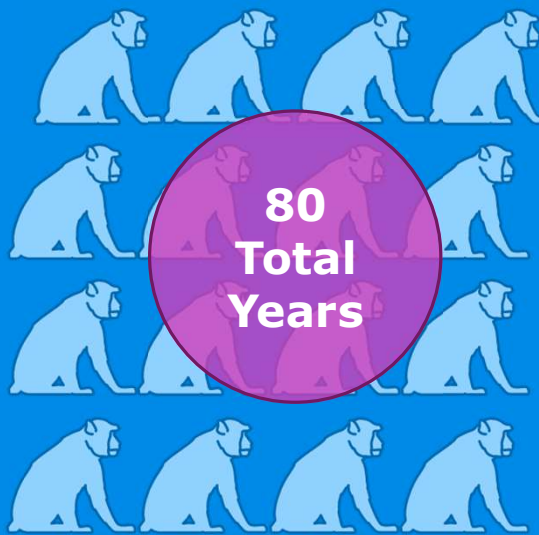
Documented Structural Rearrangements

〉 **CRISPR CAS-based editors with two components share similar safety concerns**

Source: Fiumara, et al. Genotoxic effects of base and prime editing in human hematopoietic stem cells Nature 2023

ARCUS Safety and Durability Supported By Longest Ongoing Gene Editing NHP Study

NHPs have been on study
without any serious adverse events



10 NHPs on study for
>6 years

6 NHPs on study for
>3.5 years

16 NHPs treated with the ARCUS nuclease
and followed for long term safety

Stable & Durable Reductions in PCSK9 & LDL-C maintained throughout study

Note: NHP Study conducted using PBGENE-PCSK9 nuclease designed to knockout PCSK9 gene

Target CTA/IND
2024

PRECISION
BIOSCIENCES

PBGENE-HBV

Viral Elimination

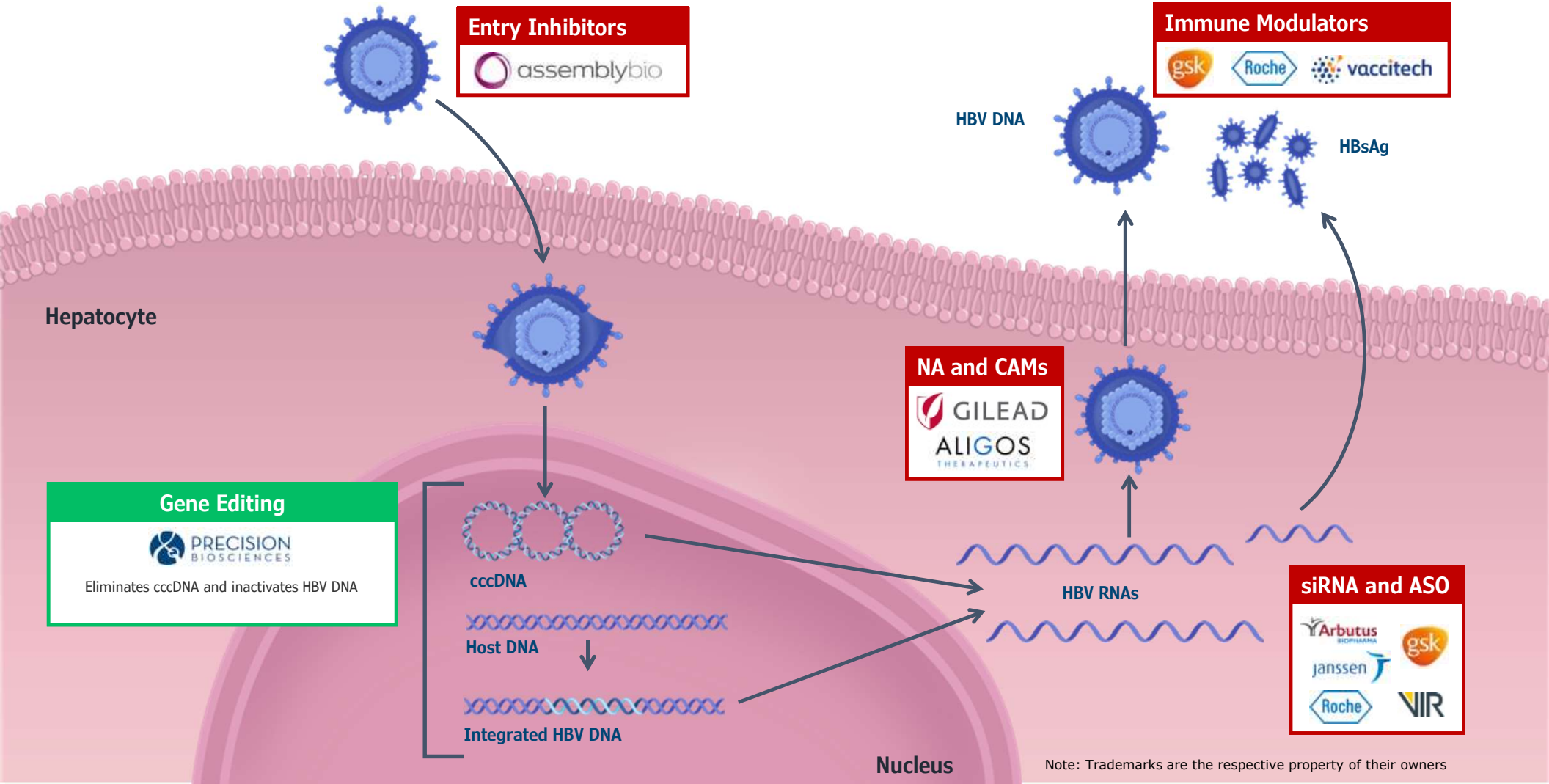
> 300 million
cHBV infections globally

> 1,000,000
cHBV infections in the US

PBGENE-HBV Designed For Broad Patient Applicability

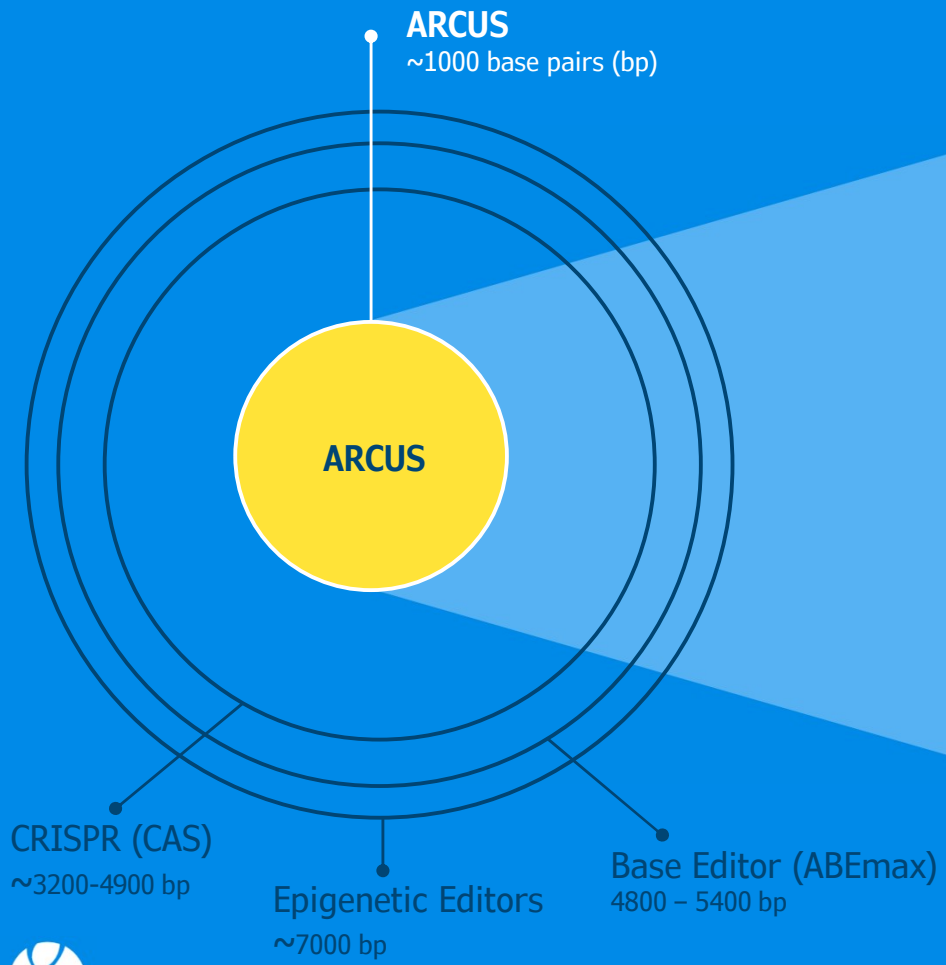
- Only modality designed to eliminate cccDNA and inactivate integrated HBV DNA -> essential for functional cure (undetectable HBV DNA and HBsAg)
- **Precision Advancing Next Steps:**
  - Final PBGENE-HBV clinical candidate ready
  - On-going discussions with global regulatory authorities in first wave markets
  - Final step: pre-CTA/IND toxicology studies on-going
  - FIH study site-selection and feasibility in process
  - **CTA/IND expected filing in 2024**

Only ARCUS designed to eliminate cccDNA and inactivate HBV DNA



Note: Trademarks are the respective property of their owners

Size & Simplicity Optimal to Target cccDNA and Integrated HBV DNA



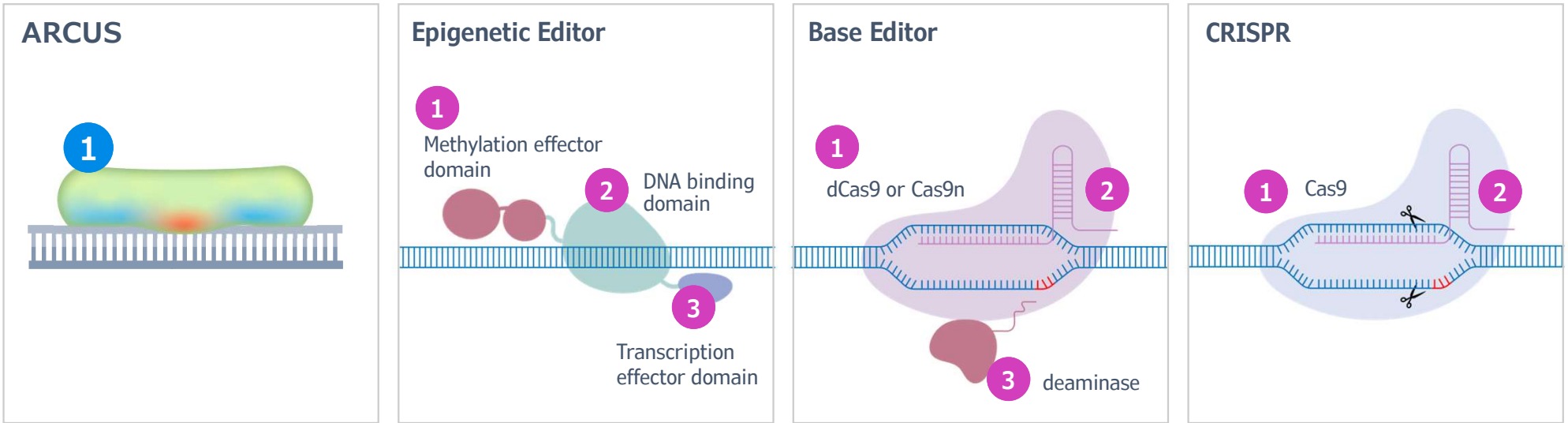
Small size and single component may allow easier access to DNA for target site editing

—impact of DNA methylation and chromatin structure is less relevant for ARCUS due to small protein size

ARCUS is efficient at targeting **cccDNA + integrated HBV DNA[1]**

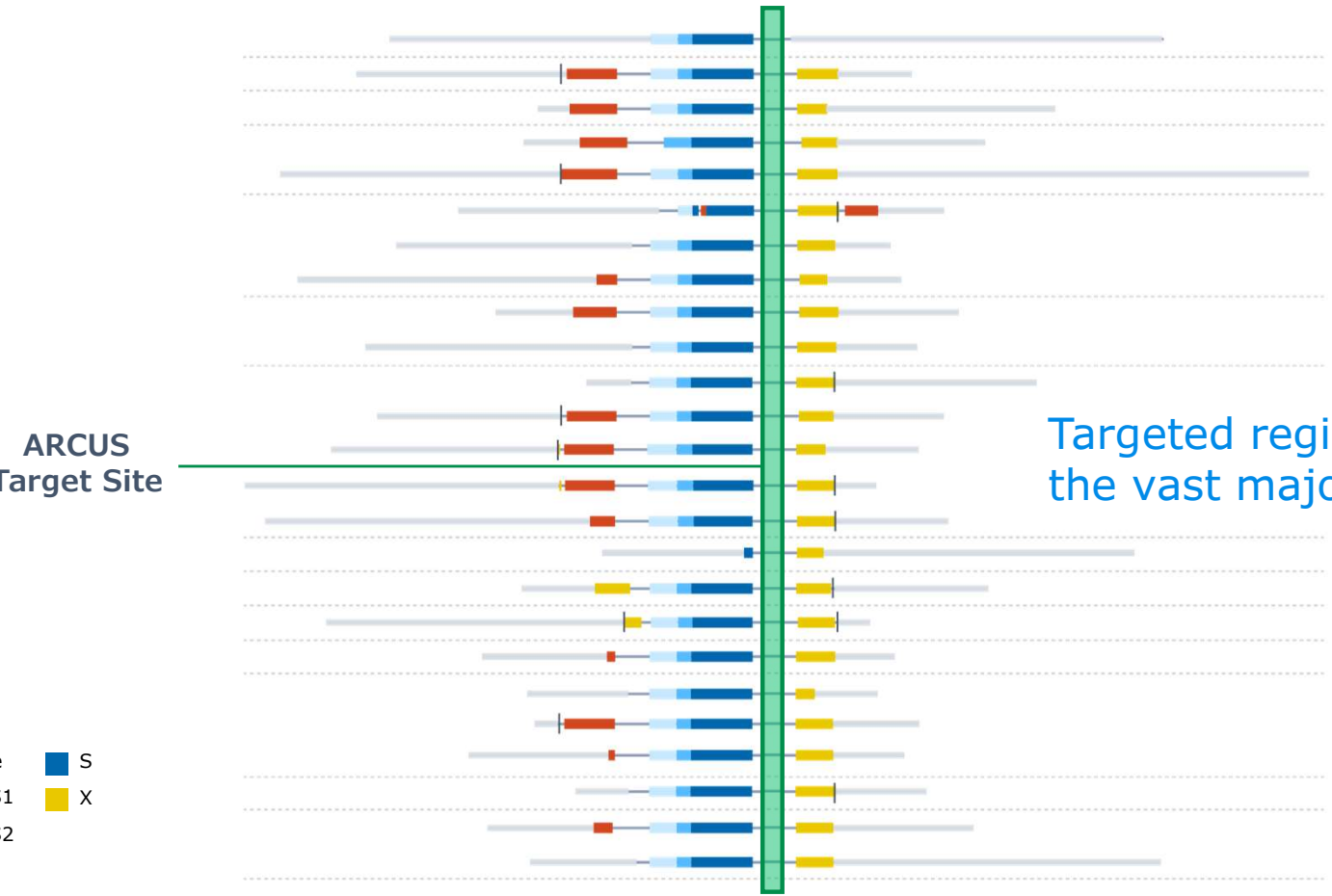
1. Data on file, Precision R&D Day Presentation

Simplicity: ARCUS is the only single component editor



Efficacy	Single component of ARCUS means more efficient packaging and delivery than multicomponent editors
Safety	Cleavage of linkers in multicomponent fusion protein editors releases effector domains with safety risk of uncontrolled, off-target editing

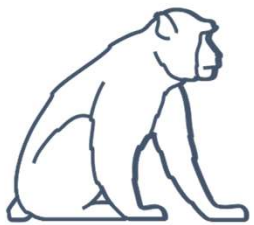
Broad Patient Applicability:
ARCUS Recognizes a Highly Conserved Sequence in Integrated HBV DNA



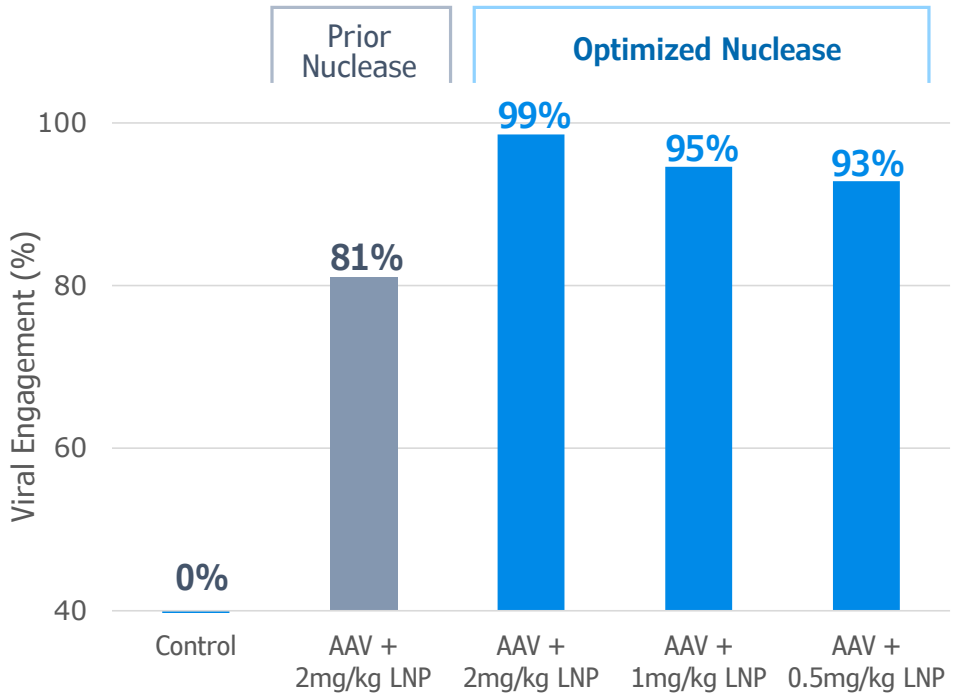
Targeted region is present in the vast majority of integrations[1]

1. van Buuren, N, et al. *JHEP* Rep. 4.4 (2022): 100449. Published 2022 Feb 12. doi:10.1016/j.jhepr.2022.100449

Efficacy: Non-Human Primate (NHP) Study Demonstrates Up to 99% Viral Engagement, Suggestive of Strong Potential Efficacy Profile of PBGENE-HBV



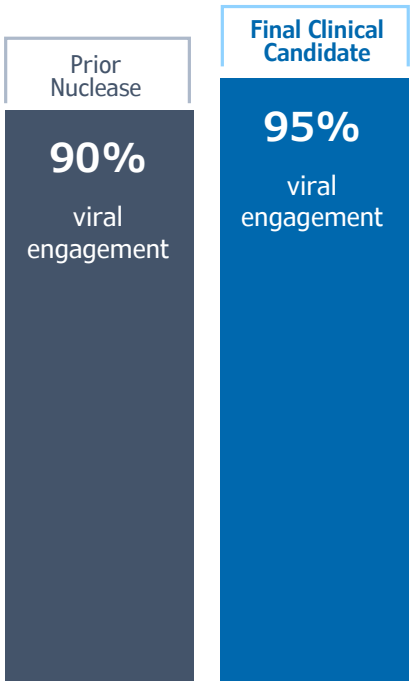
ARCUS LNP

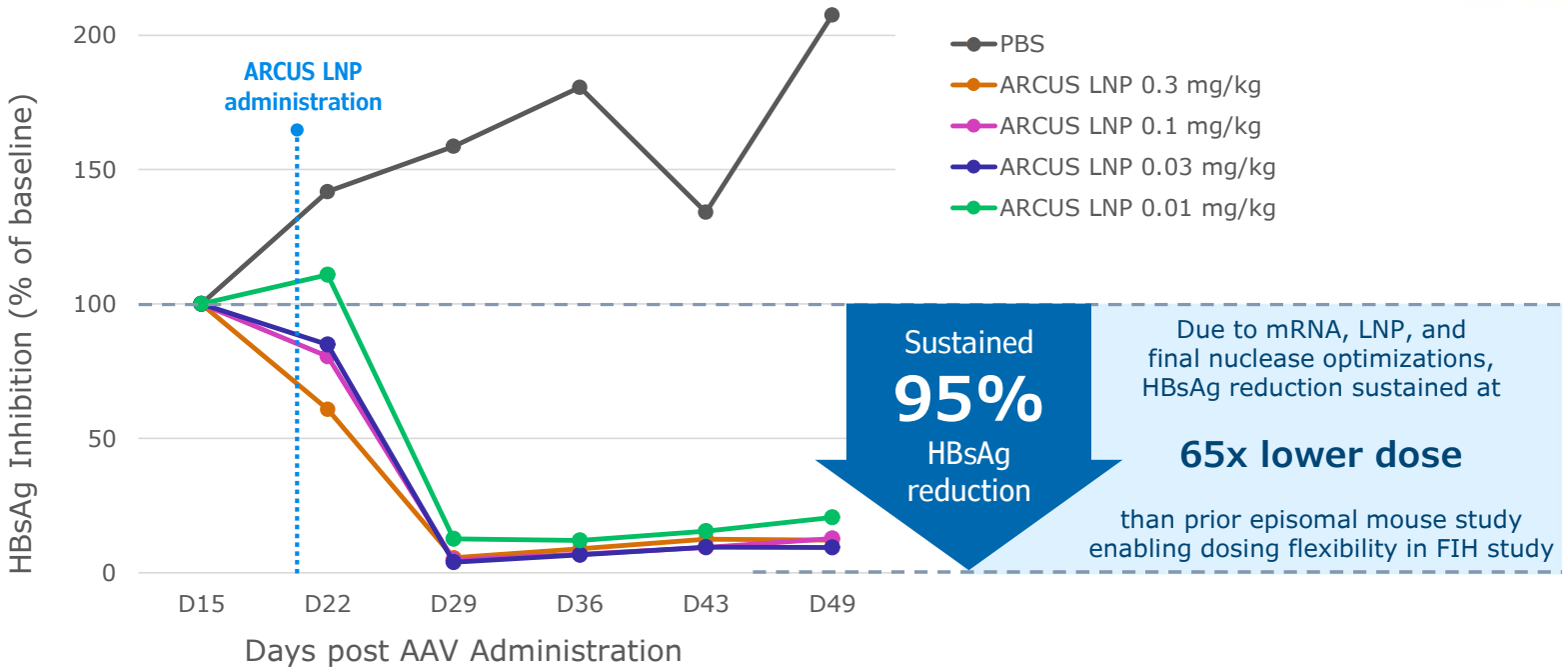


Final clinical candidate expected to eliminate majority of cccDNA, this unique mechanism of action is critical to drive durable functional cures

Notes:
1.Final optimized candidate nuclease derived from prior optimized nuclease - only one amino acid difference with similar efficacy
2.NHP study- 2 doses of PBGENE-HBV 42 days apart; viral engagement (elimination + inactivation through indels) measured at D90
3.Prior nuclease data presented at R&D Day in Sep ’23 - substantial improvement from prior NHP study showing 66% elimination and 15% indels

Efficacy: PBGENE-HBV Demonstrates Up to 95% Durable HBsAg Reduction Across Dose Levels in Episomal Mouse Study

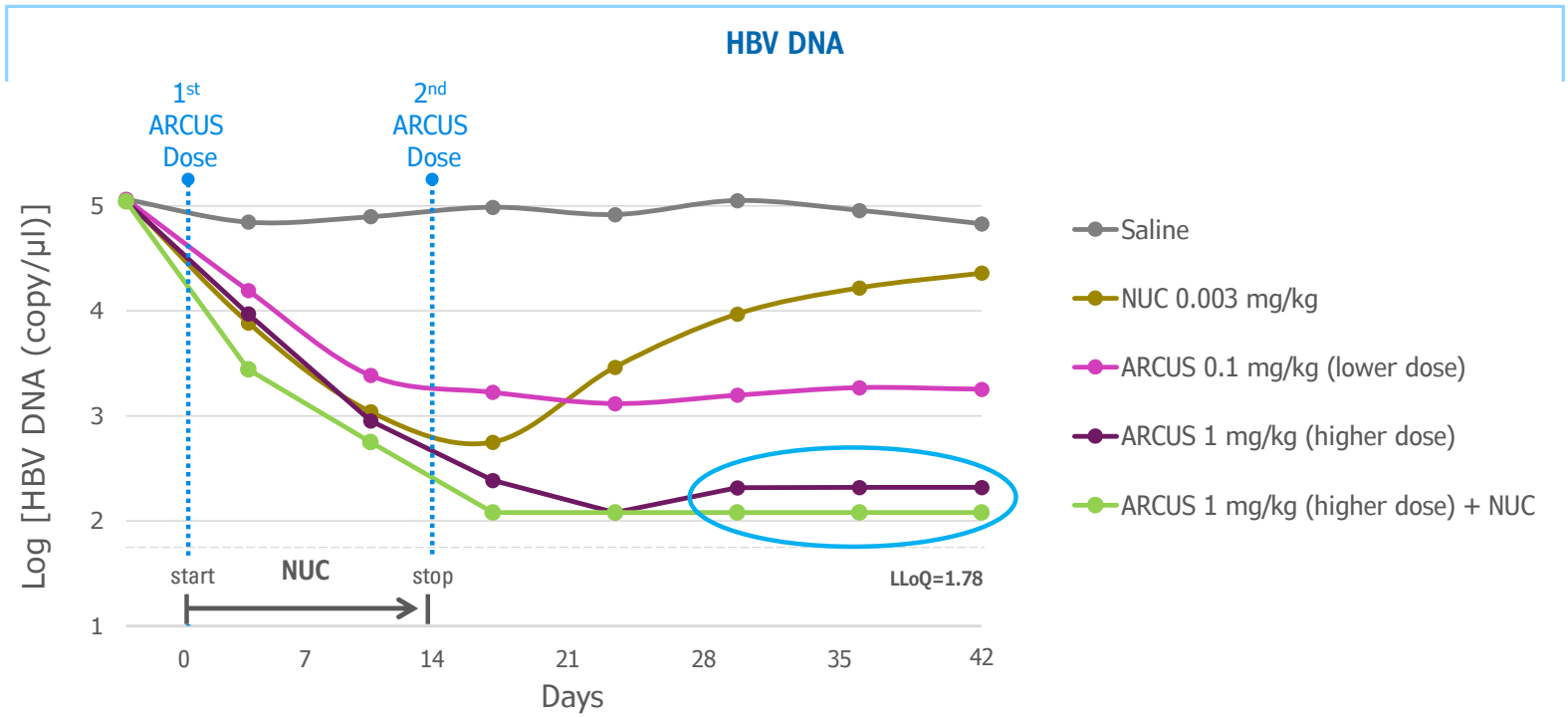




Final clinical candidate nuclease offers dosing flexibility while continuing to demonstrate high viral engagement resulting in significant and durable HBsAg reduction necessary to drive functional cures

Notes:
1. Prior nuclease data shared at R&D Day in September ’23, and prior nuclease tested at a higher 2mg/kg dose
2. Viral engagement (elimination +/- inactivation through indels); ARCUS LNP administration at D21

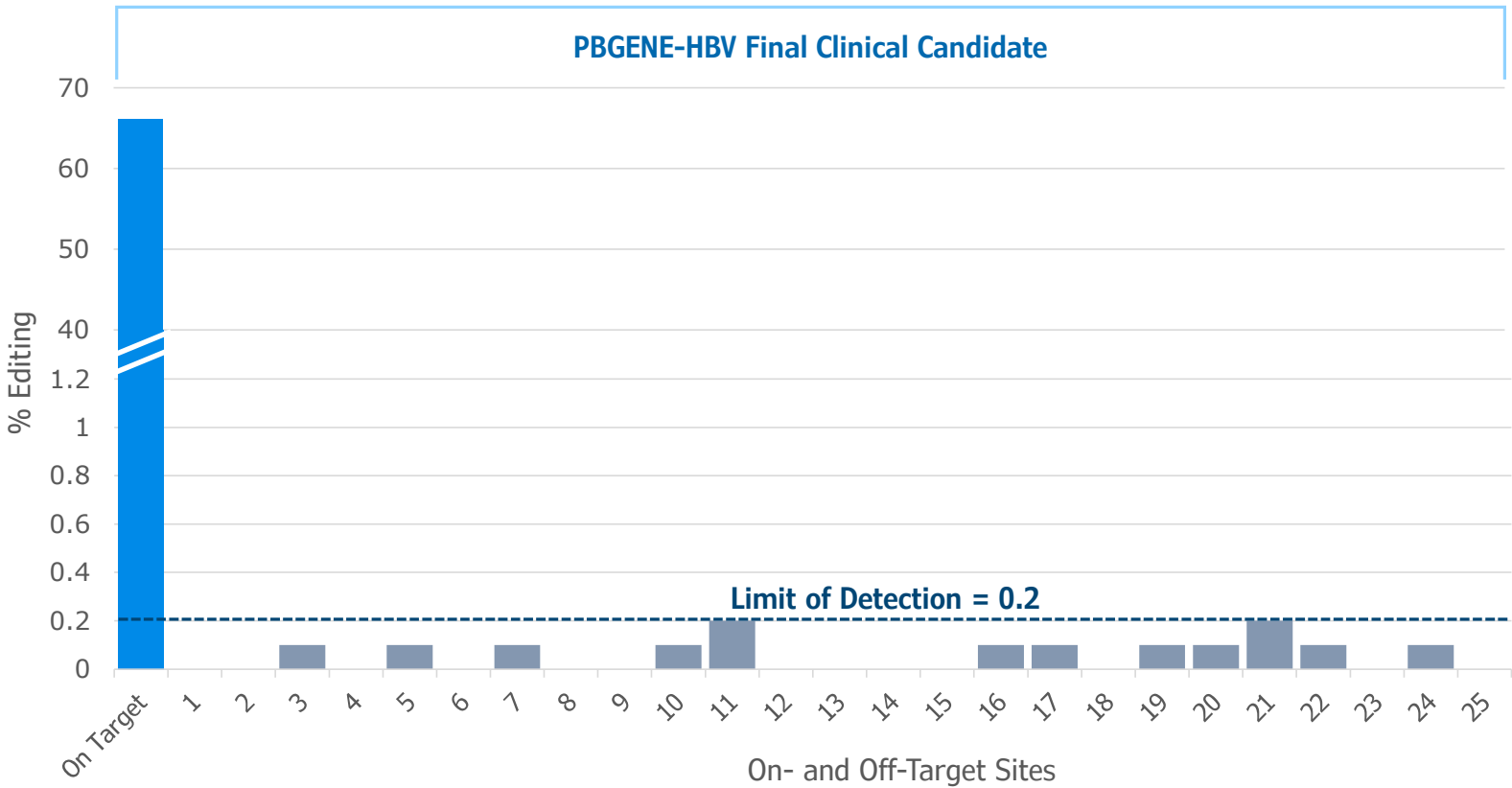
Efficacy–New Model: PBGENE-HBV Significantly and Sustainably Reduces HBV DNA as a Monotherapy in New Transgenic Mouse Model



Even after stopping NUC, PBGENE-HBV durably reduces HBV DNA as seen in combination cohort. Supports potential for stopping NUC and functional cures in future FIH study

Notes:
1. NUC = nucleos(t)ide analog, entecavir used in this study
2. HBV DNA levels measured in plasma

Safety: PBGENE-HBV Final Clinical Candidate Shows Enhanced Specificity With No Detectable Off-Target Editing



No Off-Target Editing Detected at Saturating On-Target Dose

Notes:
1. The final optimized clinical candidate nuclease shows enhanced specificity from prior versions by eliminating off-target editing above LOD when examining 384 potential off-target sites

PBGENE-HBV Program Accomplishments

- [x] Finalized mRNA optimization of payload and LNP formulation leading to 8x improvement in protein expression
- [x] FDA INTERACT Meeting in July 2023
- [x] Final Clinical Candidate Nominated
- [x] FDA Pre-IND Meeting in January 2024
- [ ] Submit IND/CTA in 2024 — *on-track*
- [ ] Initiate First-in-Human (FIH) Clinical Studies — *site-selection underway*

PBGENE-HBV Phase 1 Clinical Considerations

Phase 1 Clinical Study Design Considerations

- **Global clinical trial across all genotypes**
- **Adult patients currently treated with SoC**
  - Nucleos(t)ide analogs
- **Exclude patients with decompensated liver disease**
  - Measured by Fibroscan scores
- **Finite treatment duration with option for repeat dosing**
  - ≤3 doses of PBGENE-HBV
- **Dose escalation followed by dose expansion trial design endorsed by multiple global regulatory bodies**

Phase 1 Clinical Parameters To Be Considered

- **Safety Considerations:**
  - Tolerability (DLTs, AEs and ALT flares)
  - PK
  - Pharmacodynamics
- **Efficacy Considerations:**
  - HBsAg reduction and negativity
  - HBV DNA monitoring
  - HBV RNA (surrogate marker for cccDNA)
  - HBcrAg (surrogate marker for cccDNA)
  - cccDNA target engagement
  - Functional Cure rate

1 *Proposed clinical trial considerations; final protocol will establish specific inclusion/exclusion criteria along with primary, secondary and exploratory endpoints*
2 *HBcrAg is emerging surrogate biomarker for core related antigen which is a proxy for cccDNA*

Target CTA/IND
2025

PRECISION
BIOSCIENCES

PBGENE-PMM

Mutant Mitochondrial DNA Elimination

Primary Mitochondrial Myopathy (PMM) Currently Lacks a Curative Treatment

15-25K m.3243 PMM patients in the US alone

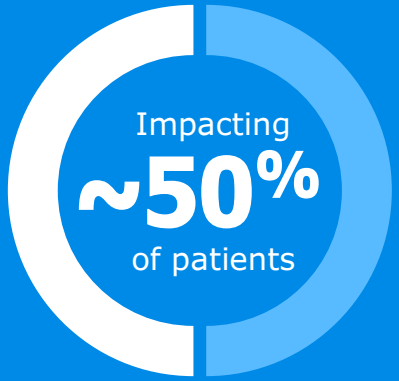
Mitochondrial diseases (MDs)

are the most common hereditary metabolic disorders and have an overall frequency[2]

1 in 4,300

A key manifestation of mitochondrial disease is[3]

PMM

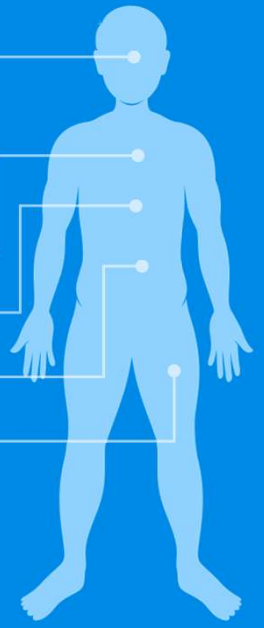


Primary mitochondrial myopathies (PMM)

are genetically defined disorders leading to defects in energy production predominantly affecting skeletal muscle

PMM is debilitating[1]:

- Chronic progressive external ophthalmoplegia
- Respiratory failure
- Exercise Intolerance
- Multi organ dysfunction
- Impaired Mobility
- Generalized weakness

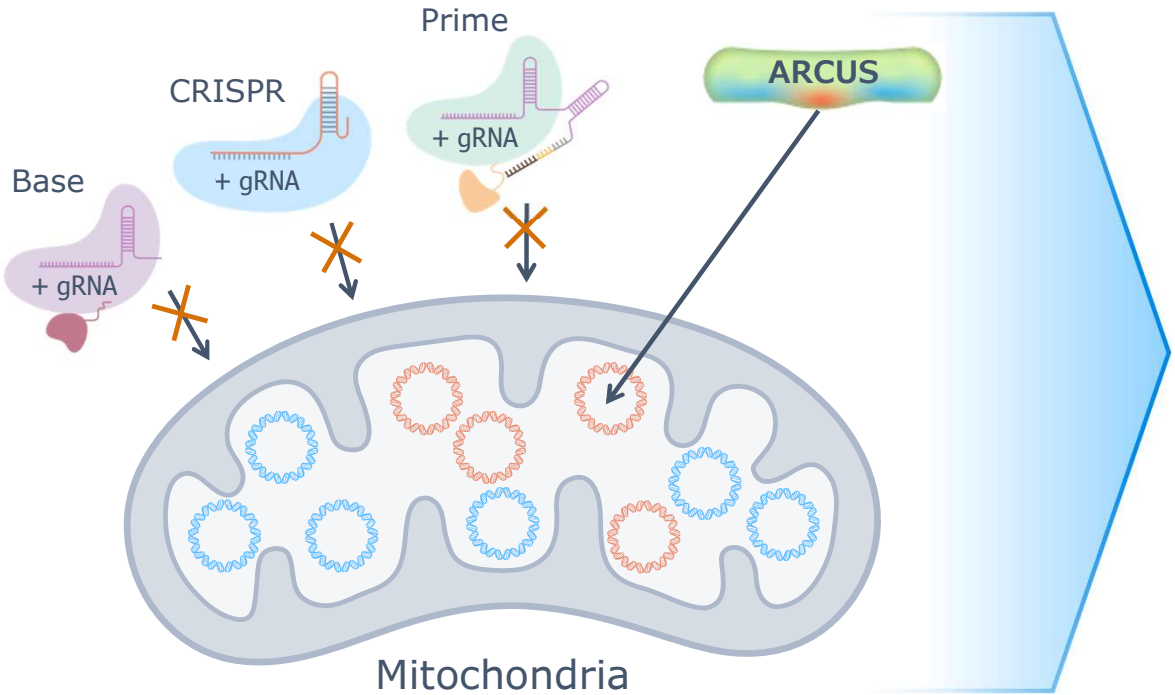


Patients today lack curative treatments and receive supportive care only through "mito cocktails"[1]

Sources:

1. https://www.ninds.nih.gov/health-information/disorders/mitochondrial-myopathies; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6938233/
2. https://ng.neurology.org/content/6/6/e519
3. Chinnery et al., Molecular Pathology …1997 Brain 120, 1713-1721; myopathy can reach up to 80% of patients depending on driver mutation (e.g., m.3243)
4. https://pubmed.ncbi.nlm.nih.gov/25652200/

Simplicity: ARCUS Can Go Where Few Other Gene Editors Can Follow



nature metabolism

Article

https://doi.org/10.1038/s42255-023-00932-6

Efficient elimination of MELAS-associated m.3243G mutant mitochondrial DNA by an engineered mitoARCUS nuclease

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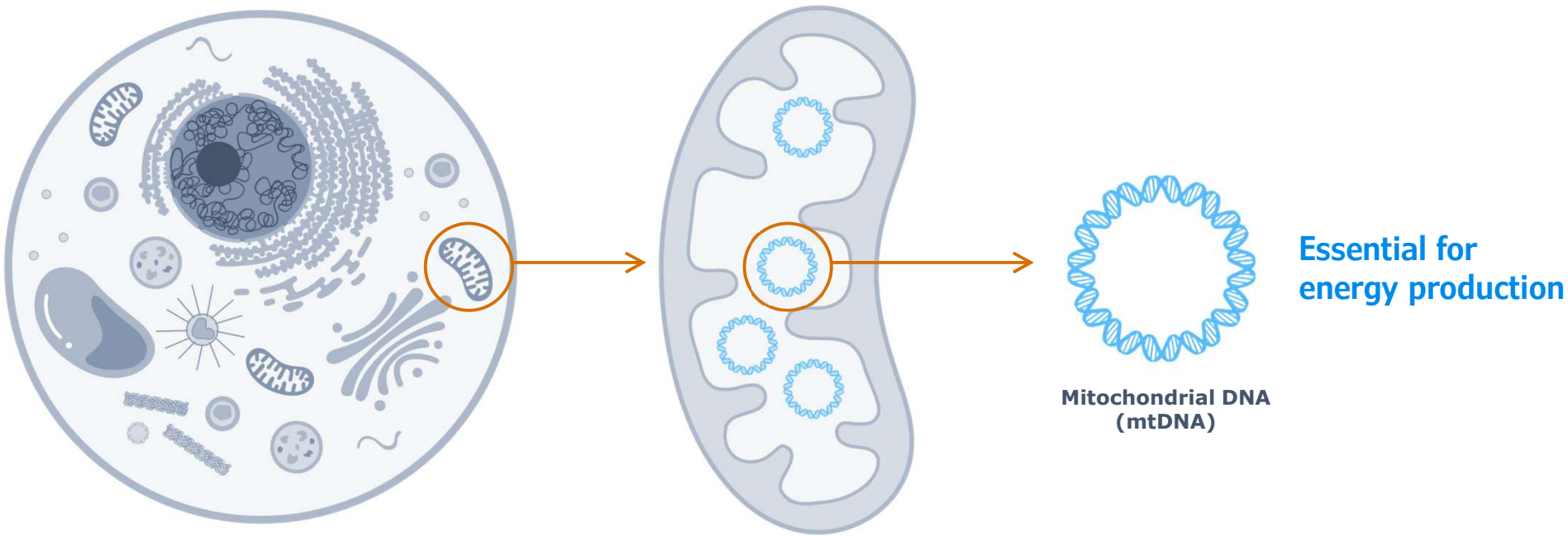
Wendy K. Shoop, Janel Lape, Megan Trum, Alea Powell, Emma Sevigny, Adam Mischler, Sandra R. Bacman, Flavia Fontanesi, Jeff Smith, Derek Jantz, Cassandra L. Gorsuch & Carlos T. Moraes

PBGENE-PMM Program Highlights

- Single component nature of ARCUS allows specific editing of mutant mtDNA with no off-target editing
- ARCUS-induced heteroplasmy shift resulting in improved mitochondrial and respiratory function in edited cells
- No evidence of mitoARCUS editing nuclear DNA

Multi-Copy Mitochondrial DNA (mtDNA) is Critical for Mitochondrial Function



PBGENE-PMM Distinguishes a Single Base Difference at m.3243

m.3243A>G

- **Mutation Prevalence of 1/500**[1]
- **~36% of Mitochondrial Diseases are driven by m.3243A>G**[2]

m.3243 associated PMM estimated at **~15-25k patients in the US alone**[3]

Mutant mtDNA sequence

5′-C A G **G** G C C C G G T A A T C G C A T A A A-3′

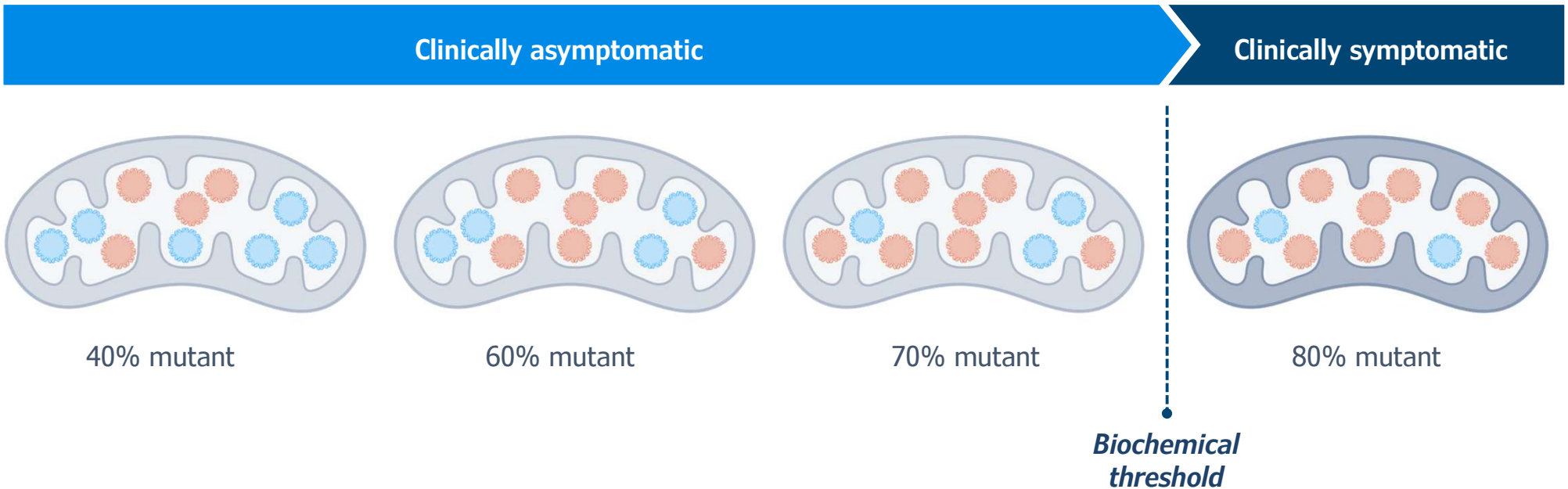
5′-C A G **A** G C C C G G T A A T C G C A T A A A-3′

Wild-type (healthy) mtDNA sequence

1.Manwaring et al 2006 Population prevalence of the MELAS A3243G mutation. Mitochondrion
2.Schon et al., 2023, National Mitochondrial Disease Registry in England... Euromit2023 Conference, Bologna, Italy, June 13, 2023;
3. Calculated based disease epidemiology studies and secondary literature; estimated 14k patients with NMDAS scores 2-4 in US alone

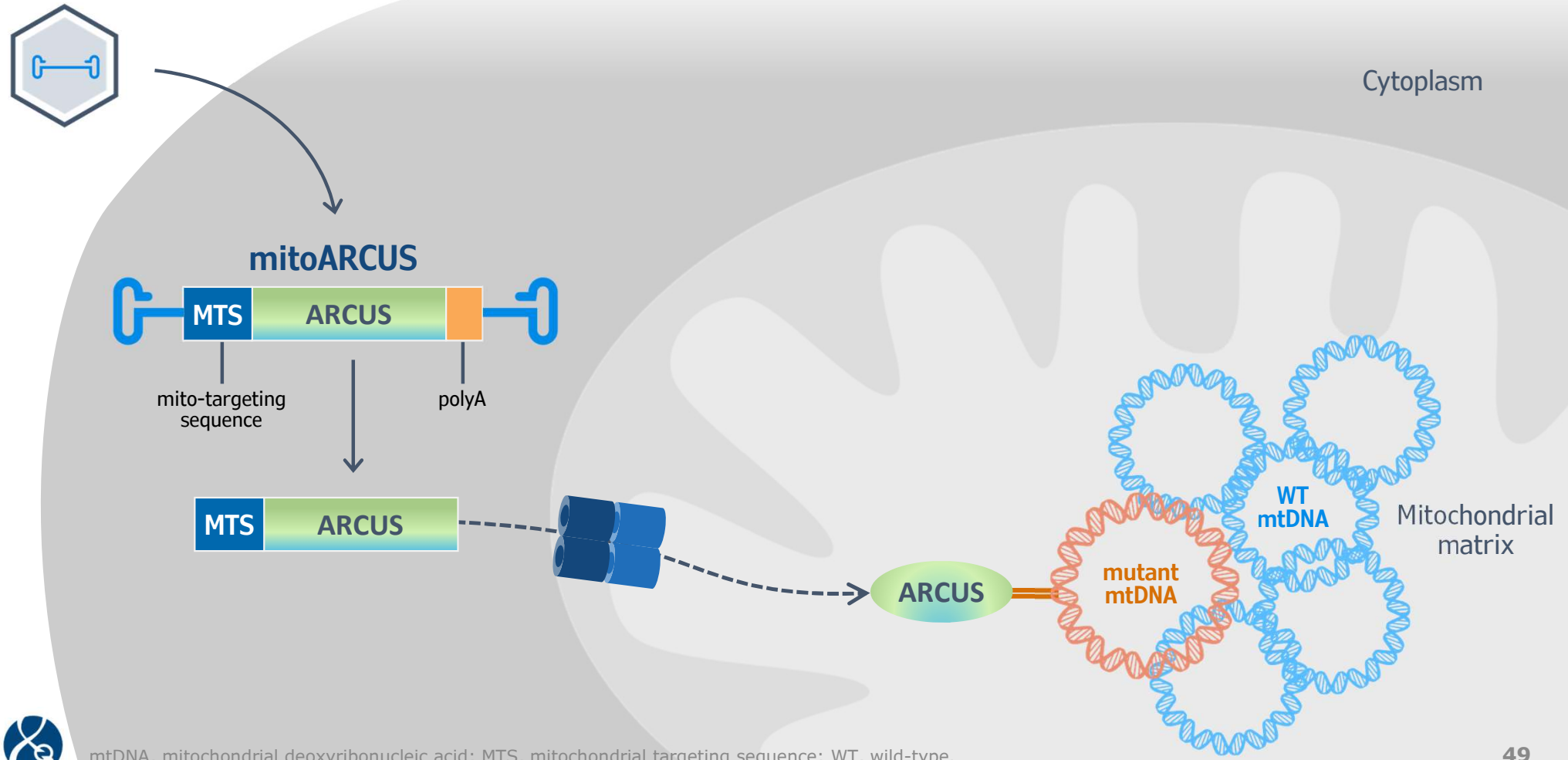
mtDNA Mutations Are Commonly Heteroplasmic

Situation where two or more mtDNA variants exist in same mitochondria



mtDNA, mitochondrial DNA.

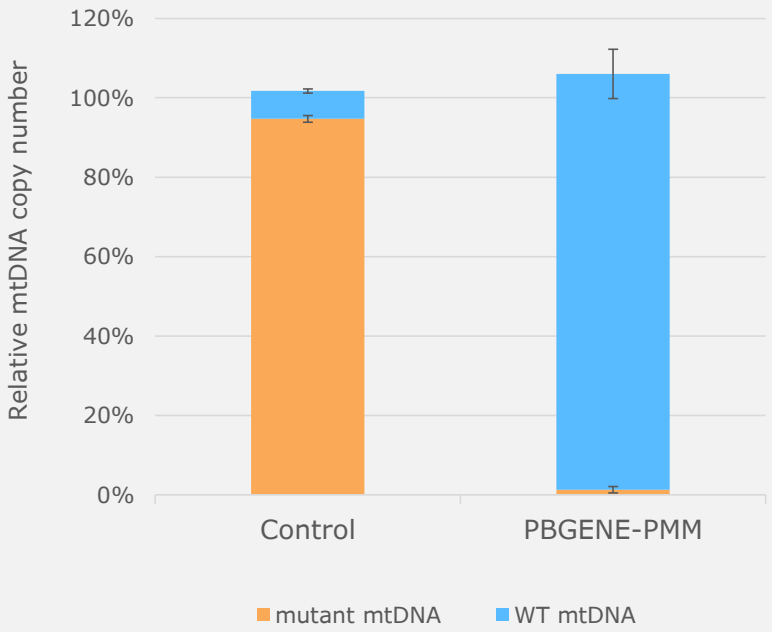
mitoARCUS Therapeutic Approach to Shift Heteroplasmy



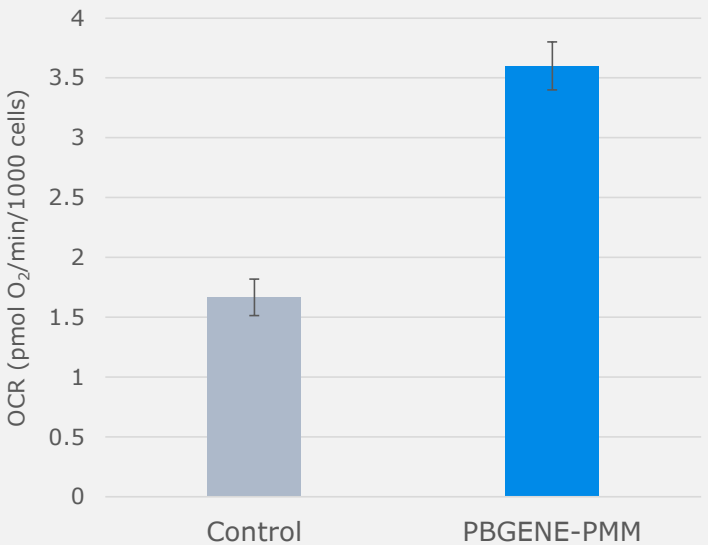
mtDNA, mitochondrial deoxyribonucleic acid; MTS, mitochondrial targeting sequence; WT, wild-type.

PBGENE-PMM Improved Mitochondrial Function

On target efficacy

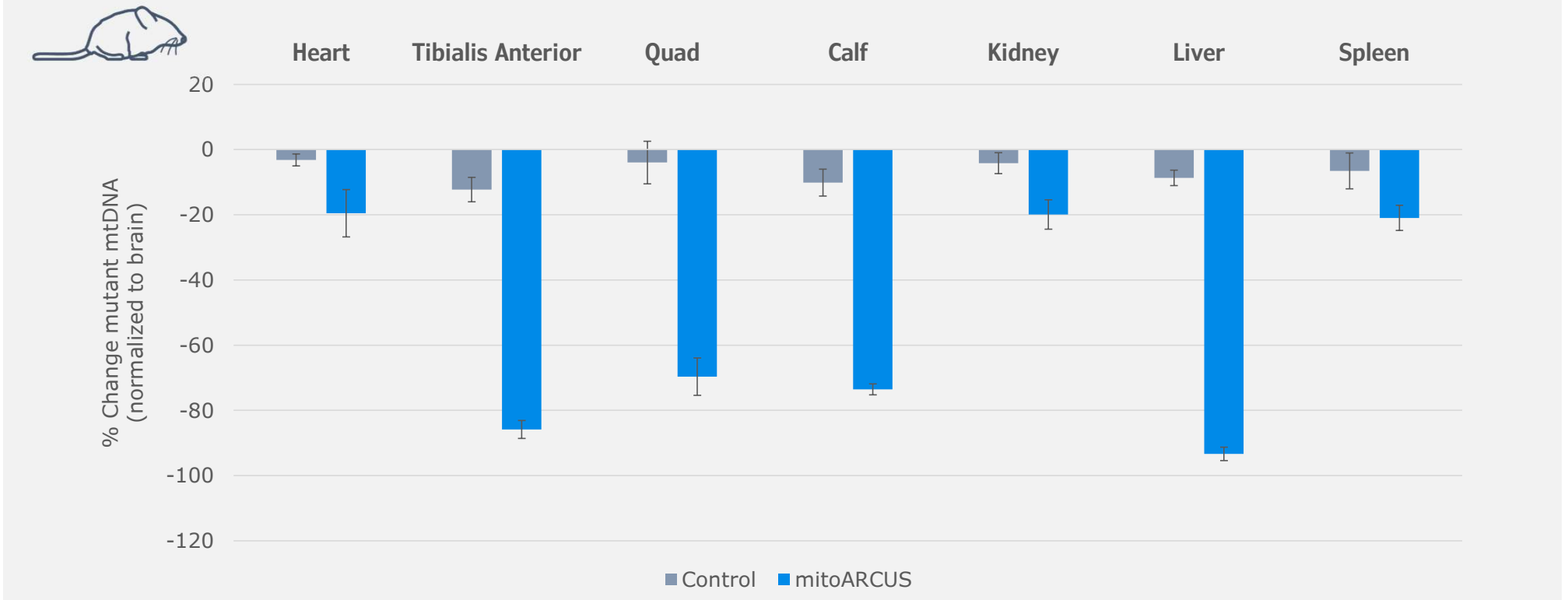


Impact on energy production



mtDNA, mitochondrial DNA; WT, wild-type; experiments in cybrid cells.

mitoARCUS Shifted Heteroplasmy in *In Vivo* Mouse Model



mtDNA, mitochondrial DNA.

Zekonyte U, et al. *Nat Commun*. 2021. 2021;12(1):3210.

PBGENE-PMM Program Accomplishments

	☑	Final Clinical Candidate
	☑	PoC and Dose Finding Studies underway
on-track	☐	Initiate GLP Tox
In-process	☐	Identify First-in-Human Study Sites
on-track	☐	CTA/IND in 2025

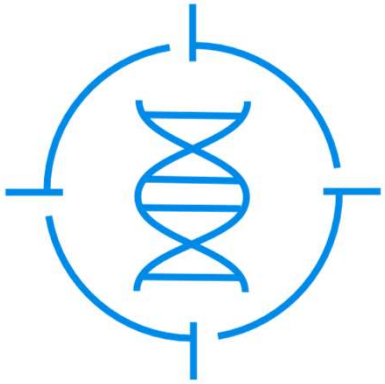
Focusing on Our Foundation—*In Vivo* Gene Editing

Through our gene editing platform ARCUS

Focused Execution 2024-2026

Go-Forward Singular Focus

In Vivo Gene Editing



Expected cash runway now enables funding *In Vivo* programs through Phase 1 data

Pivoting to Our Foundational Strength

- ARCUS - wholly owned genome editing platform
- Optimized for gene insertion, excision, and elimination
- Over 25 years of gene editing expertise and protein engineering
- Cash & cash equivalents (3/31/2024) = $137 million
- Expect existing cash and cash equivalents, expected operational receipts, operational efficiencies, availability of the ATM facility, and available credit to fund OpEx and CapEx into **second half of 2026**