PRECISION
BIOSCIENCES

Corporate Deck

January 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, 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 September 30, 2023, 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
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Corporate & Technology Overview

Focusing on Our Foundation—In Vivo Gene Editing

Precision—from dual to a single platform gene editing company

Ex Vivo CAR T
Accretive Event

In Vivo
Gene Editing

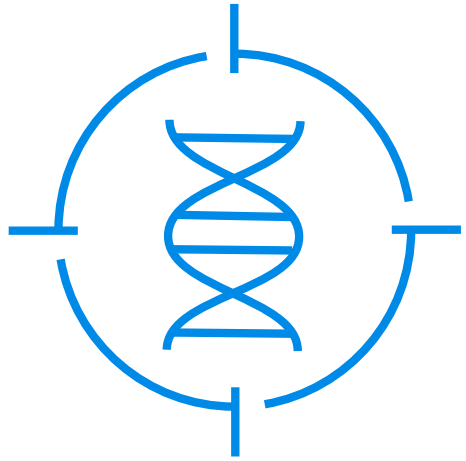
Go-Forward Singular Focus

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 (12/31/2023) = $116 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 first half of 2026.

Focused Execution 2023-2025



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

Single Gene Editing Platform Funding Through Allogeneic CAR T Platform Deals

Unlocking $47 million in upfront and potential near-term payments

Announced January 2024

- **TG Therapeutics: Azer-cel for Autoimmune diseases; extends cash runway into first half of 2026**

- Exclusive license to azer-cel for non-cancer indications

Upfront and Near-Term Payments: $17.5M

- Upfront: $10M
  - $5.25M cash plus TGTX purchase of 2.9 million Precision stock at $0.77/share, a 100% premium to the 30-day VWAP
  - $2.5M to be paid within 1st anniversary of signing[1]
- Near-Term clinical milestone payment: $7.5M
- $288M[2] potential additional milestone payments
- Royalties: Mid-single digit to low-double digit

Announced August 2023

- **Imugene Limited: Azer-cel for cancer; reduced OpEx and extended cash runway**

- Exclusive global license to azer-cel for cancer indications
- Assumed Precision's CAR-T infrastructure

Upfront and Near-Term Payments: $29M

- Upfront $21M
  - $8M paid upon close
  - $13M convertible note matures on 1-year anniversary
- Near-Term Payment: $8M

- $198M in potential milestones for azer-cel
- $145M in potential milestones each for up to 3 additional research programs

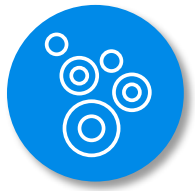
- Royalties: Double digit

1 *DTIL equity @ 100% premium to 30-day VWAP prior to payment*
2 *Additional milestone payments do not include the $7.5M Phase 1 Near term milestone*

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

Celgene · Kite, A GILEAD Company · Abeona THERAPEUTICS

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

JOHNS HOPKINS UNIVERSITY & MEDICINE · Duke UNIVERSITY · Sangamo

Alex Kelly
Since Oct 2020
Chief Financial Officer

Allergan · MERCK · PHARMACIA

Cindy Atwell
Since Apr 2019
Chief Business Officer

Halozyme · abbvie · AMYLIN

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

MOFFITT CANCER CENTER

Juli Blanche
Since May 2022
Chief People Officer

Celgene · Bristol Myers Squibb · MERCK

Dario Scimeca
Since June 2019
General Counsel

Genentech · élan

Neil Leatherbury
Since March 2017
Senior VP, CMC

mirna THERAPEUTICS · AZAYA THERAPEUTICS

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

VWR · UNIVERSITY OF NOTRE DAME

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

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Stanley Frankel, M.D.
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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 Where Defined Outcomes Are Essential

PROGRAM	INDICATION	TISSUE	TARGET	EDIT TYPE / DELIVERY	RESEARCH	CANDIDATE SELECTION	IND-ENABLING	PARTNER
★ PBGENE-HBV	Chronic hepatitis B	Liver	HBV	Elimination/LNP				
★ PBGENE-PMM	m3243 primary mitochondrial myopathy	Muscle	PMM	Elimination/AAV				
PBGENE-NVS	Sickle cell disease/ beta thalassemia	HSCs	—	Insertion/—				NOVARTIS
PBGENE-DMD	Duchenne muscular dystrophy	Muscle	DMD	Excision/AAV				Prevail THERAPEUTICS A Wholly Owned Subsidiary of Eli Lilly and Company
PBGENE-LLY2	Undisclosed	Liver	—	Insertion/—				
PBGENE-LLY3	Undisclosed	CNS	—	—				
★ iECURE-OTC	Ornithine transcarbamylase deficiency	Liver	OTC	Insertion/AAV				ECURE

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 Therapeutic Goods Administration for the initiation of a first-in-human Phase 1/2 trial evaluating ECUR-506, incorporating an ARCUS nuclease for the treatment of OTC deficiency in pediatric (or neonatal) patients.
- Additional approvals expected in 2024. iECURE is preparing sites and **anticipates initiating the global clinical trial in first half of 2024**.

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

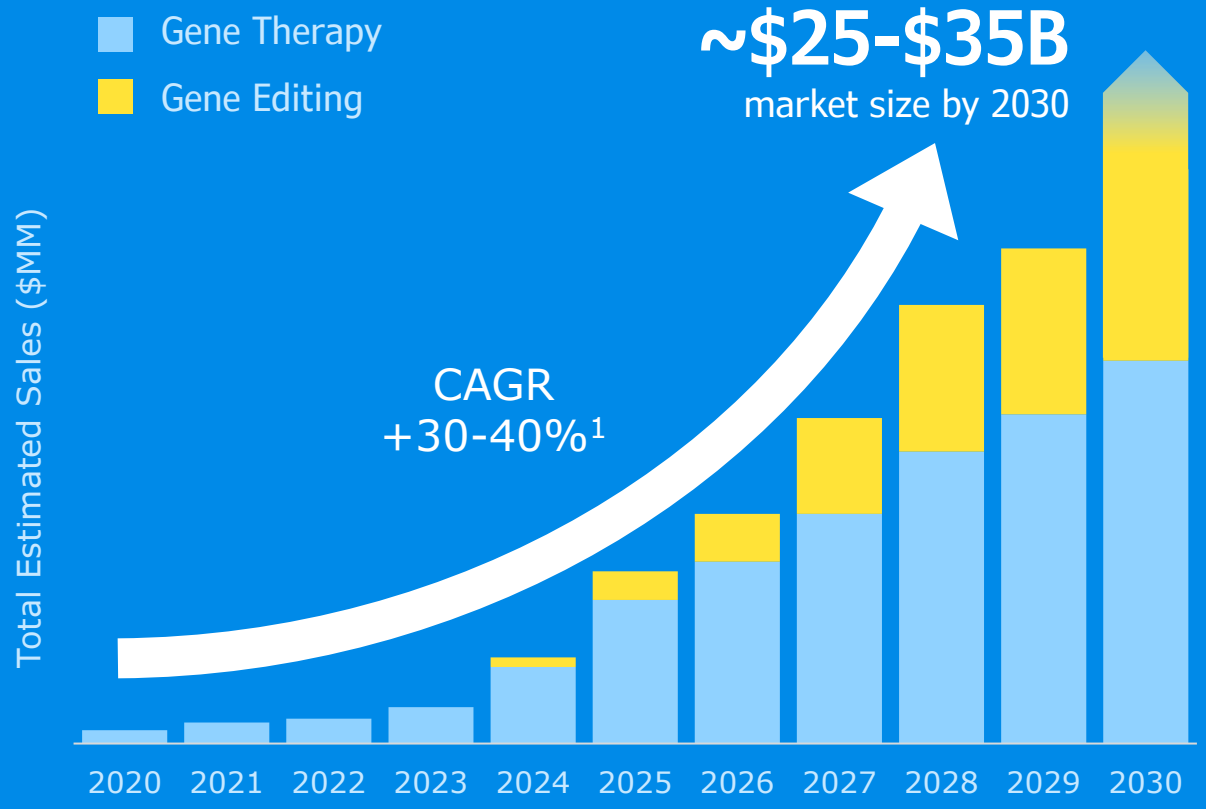
People WW with OTCD

- 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



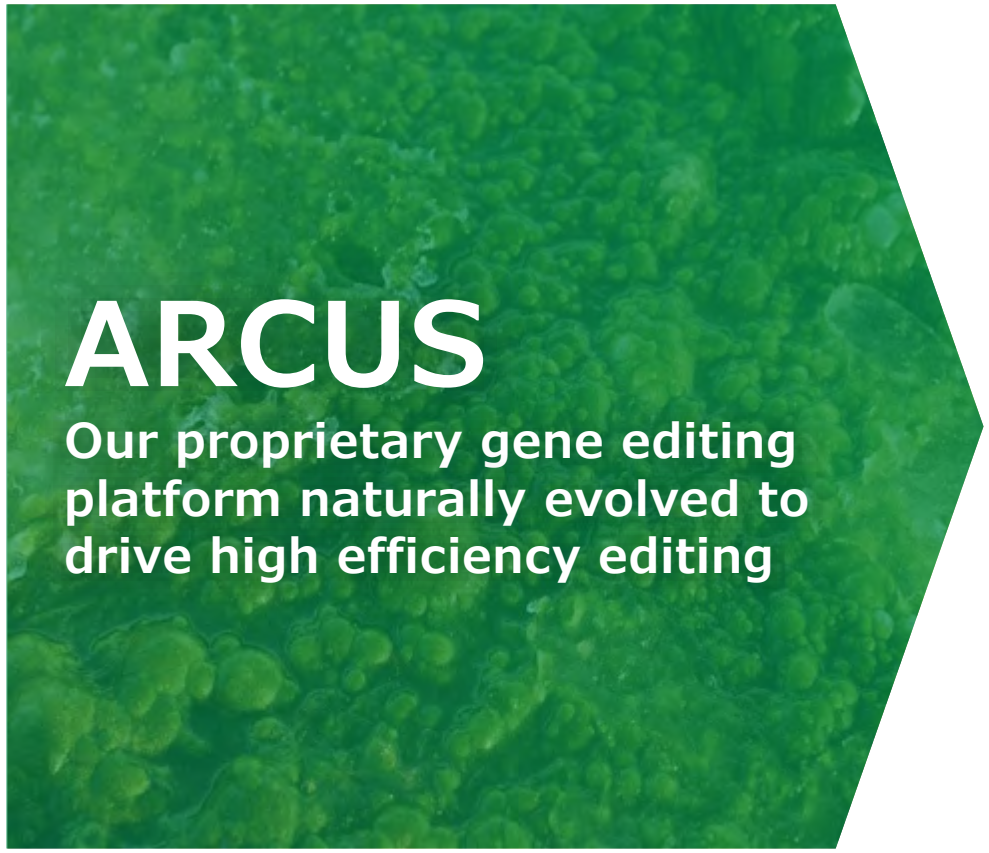
Gene Editing Expected to Disrupt and Continue to Grow the Genetic Medicines Market

Precision's programs represent a US market opportunity to 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

Bringing the Dream to Reality with Creation of ARCUS



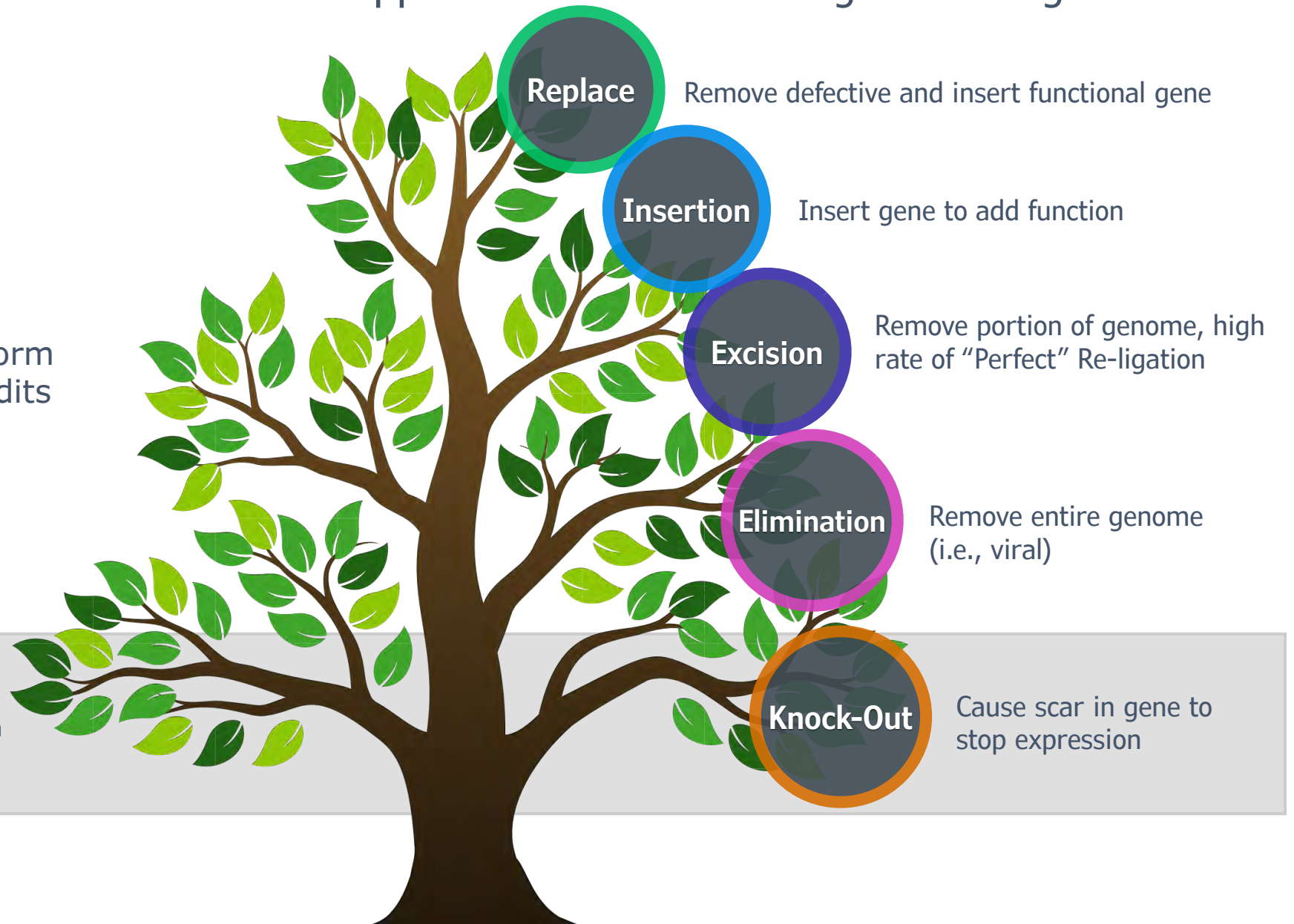
- ARCUS is derived from the **homing endonuclease I-CreI** found in green algae
- **Evolved to safely edit by inserting in genome, adding function**
  - CRISPR-based editing tools engineered from enzymes evolved to knockout DNA only
- Extremely efficient at generating **Defined Outcomes* due** to predominant 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 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

Defined Outcomes
Accomplished Through
ARCUS Advantages

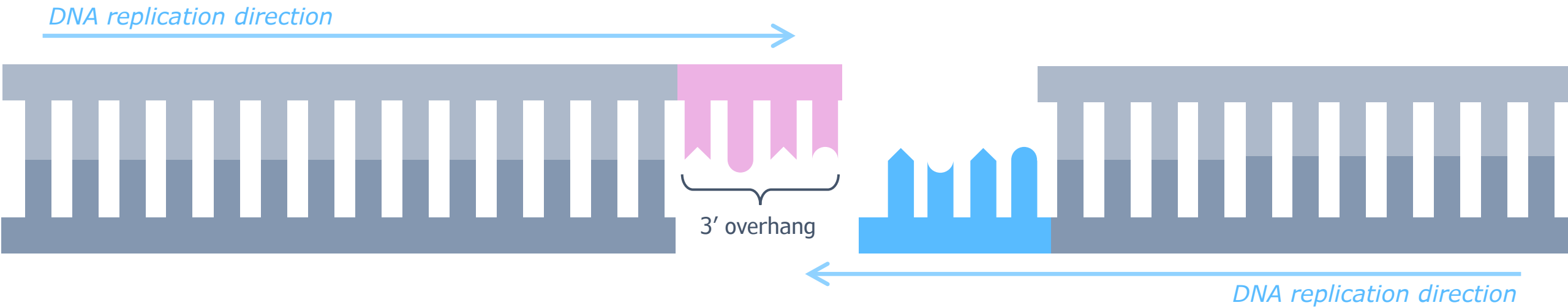
The Cut

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

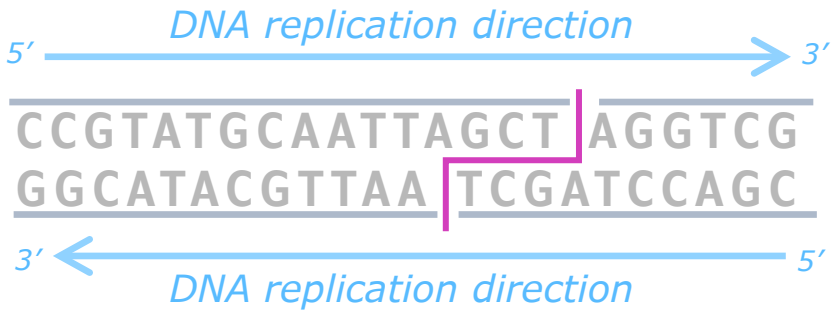
- Due to ARCUS unique 3' overhang cut, "sticky-end" breaks at off-target sites, are detected with higher sensitivity than blunt cuts generated by CRISPR…allows Precision to engineer and optimize for high specificity and off-target edits below limit of detection

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

CCGTATGCAATTA | GCTAGGTCG
GGCATACGTTAAT | CGATCCAGC

Blunt cut induces NHEJ

TALEN/ZFN

CCGTATGCA | ATTAGCTAGGTCG
GGCATACGTTAAT | CGATCCAGC

Cas12a

CCGTATGCAATTAGCTA | GGCAT
GGCATACGTTAATCGATCCGT | A

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

Base Editors

CCGTAGCAATTAGCTA | GGATG
GGCATCGTTAATCGATCCGTAC

Prime Editors

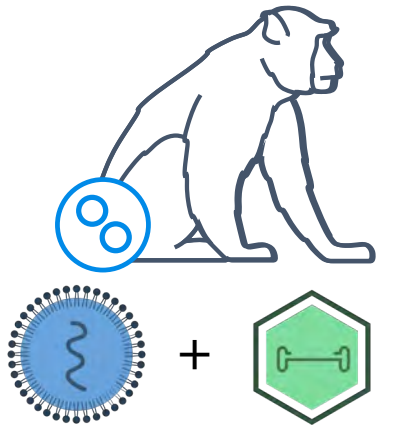
CCGTATGCAATTAGCTA | GGCAT
GGCA | TACGTTAATCGATCCGTA

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

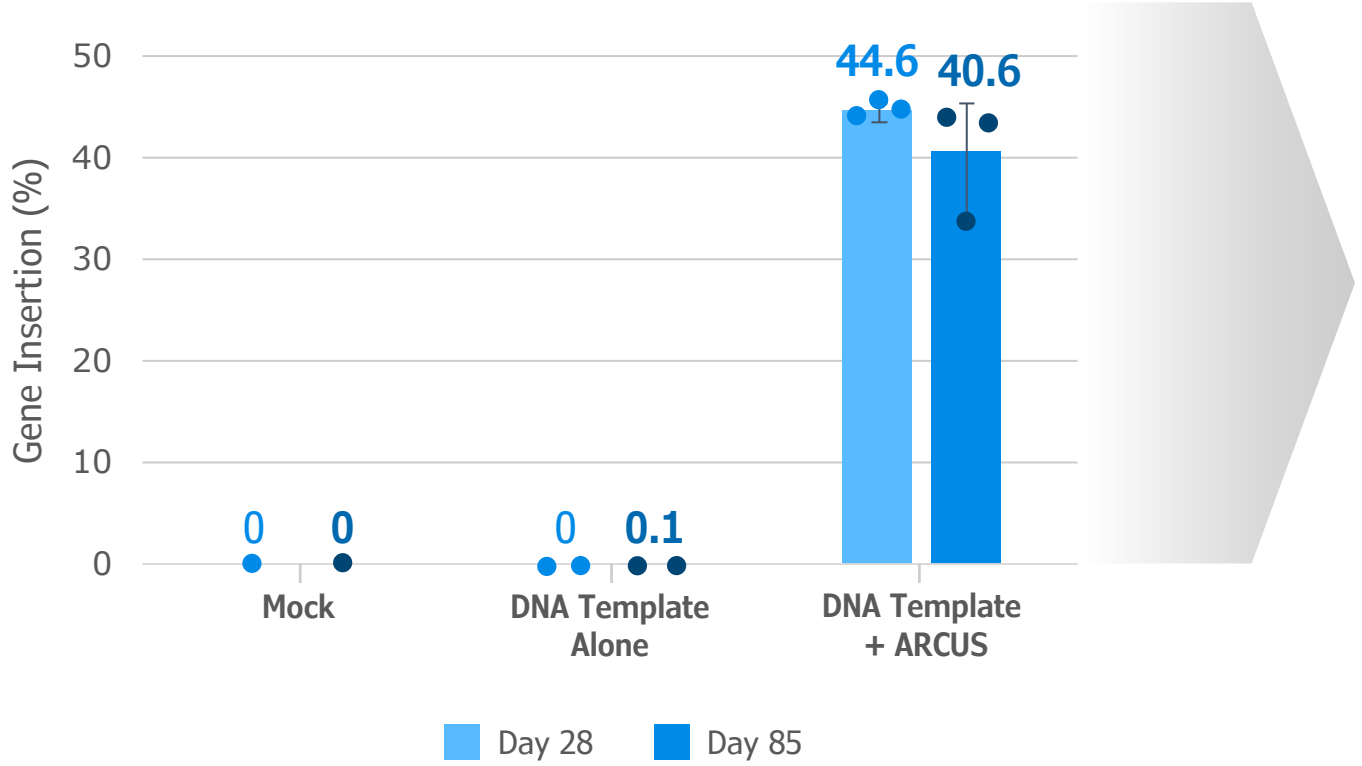
Nondividing cells in vivo



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
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ARCUS Advantages

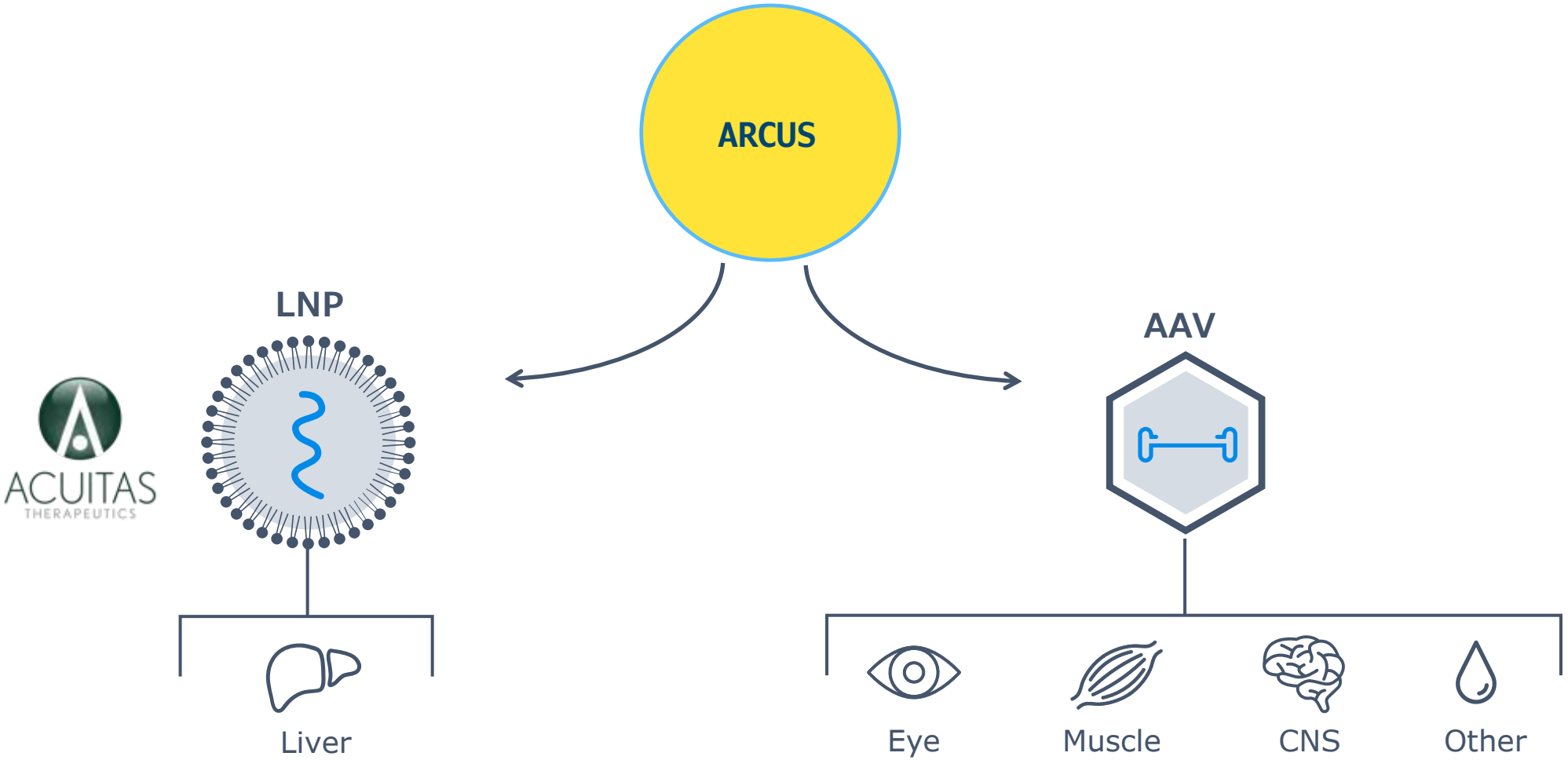
The Cut

The Size

The Simplicity

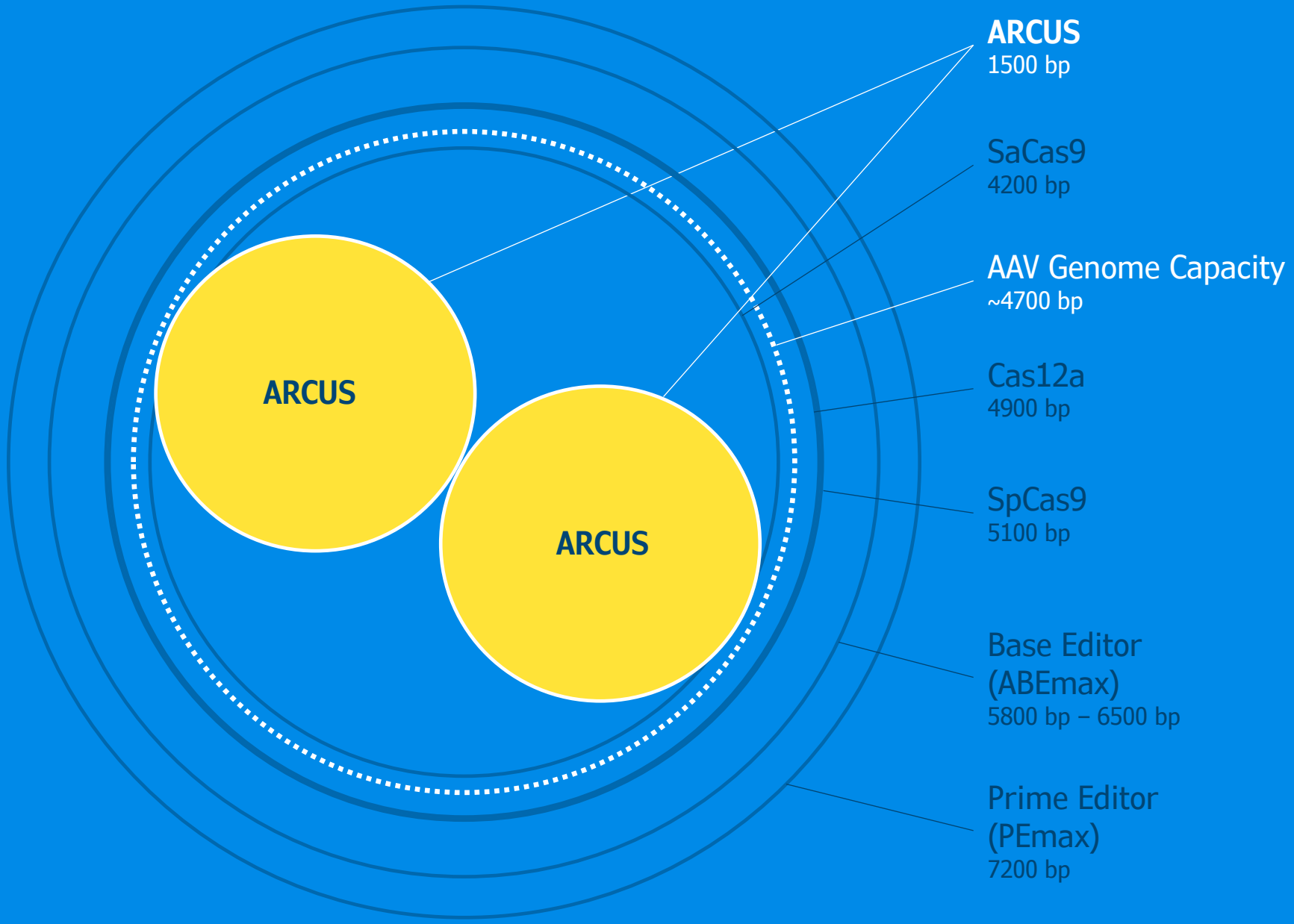
Size Matters for Where You Can Deliver

ARCUS can use different delivery vehicles to target diverse tissue types



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

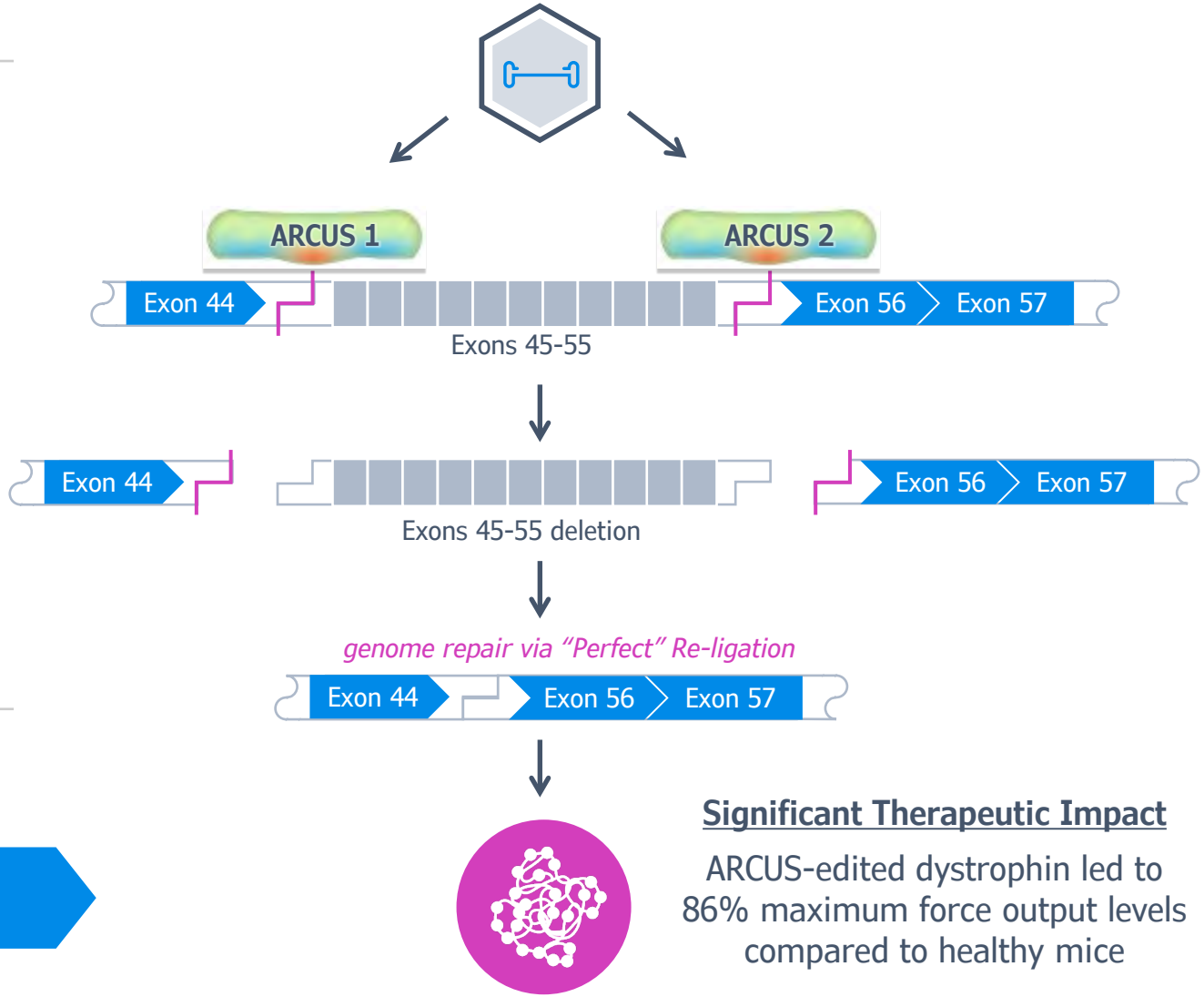
Small ARCUS Size Allows Two Nucleases in One AAV for **Gene Excision** in DMD



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

ARCUS Nucleases Excise Mutations and Restore Function in DMD

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



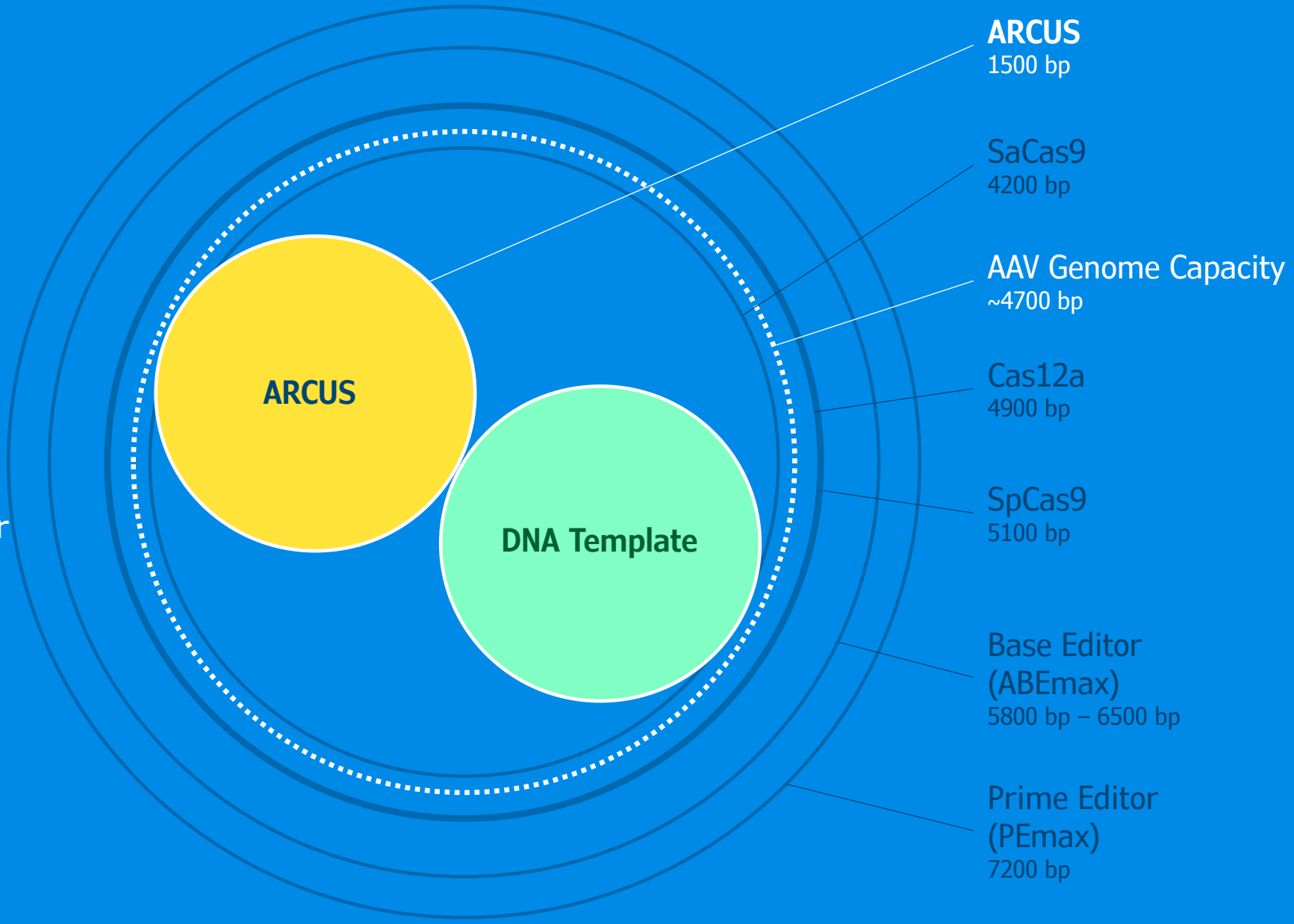
GOAL: Restore dystrophin expression

Significant Therapeutic Impact

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

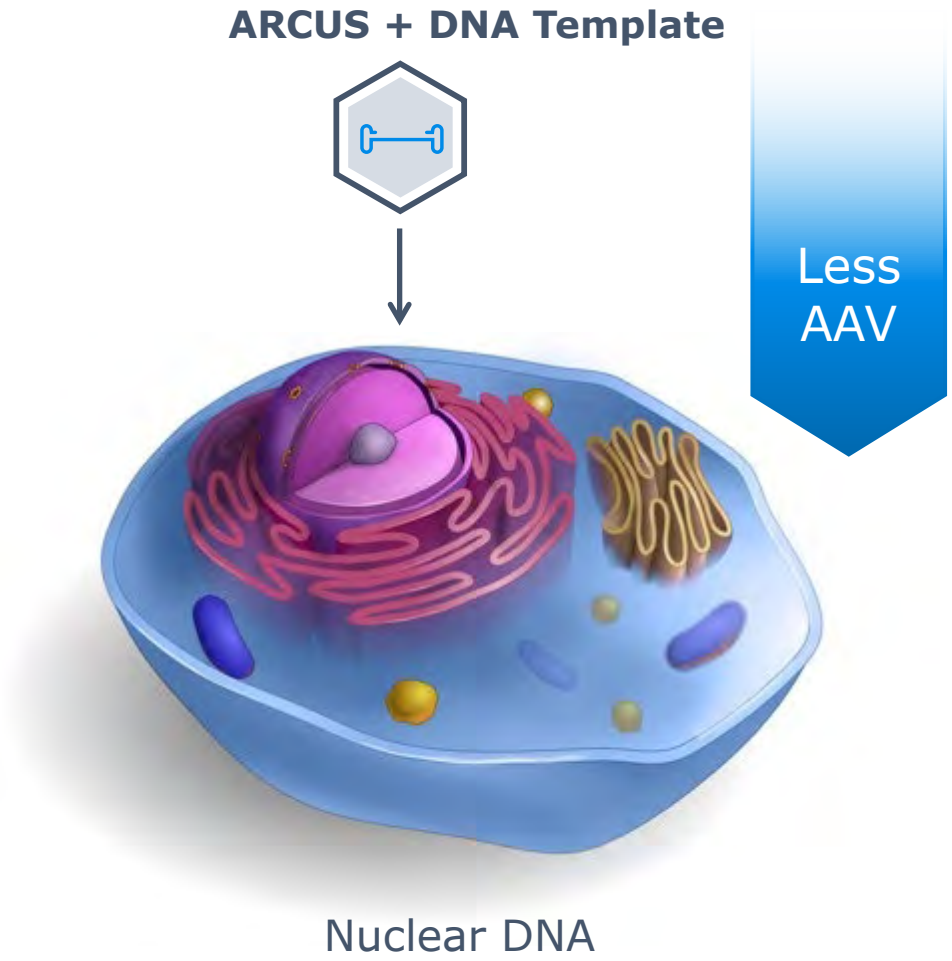
Size Matters for **What** You Can Deliver:

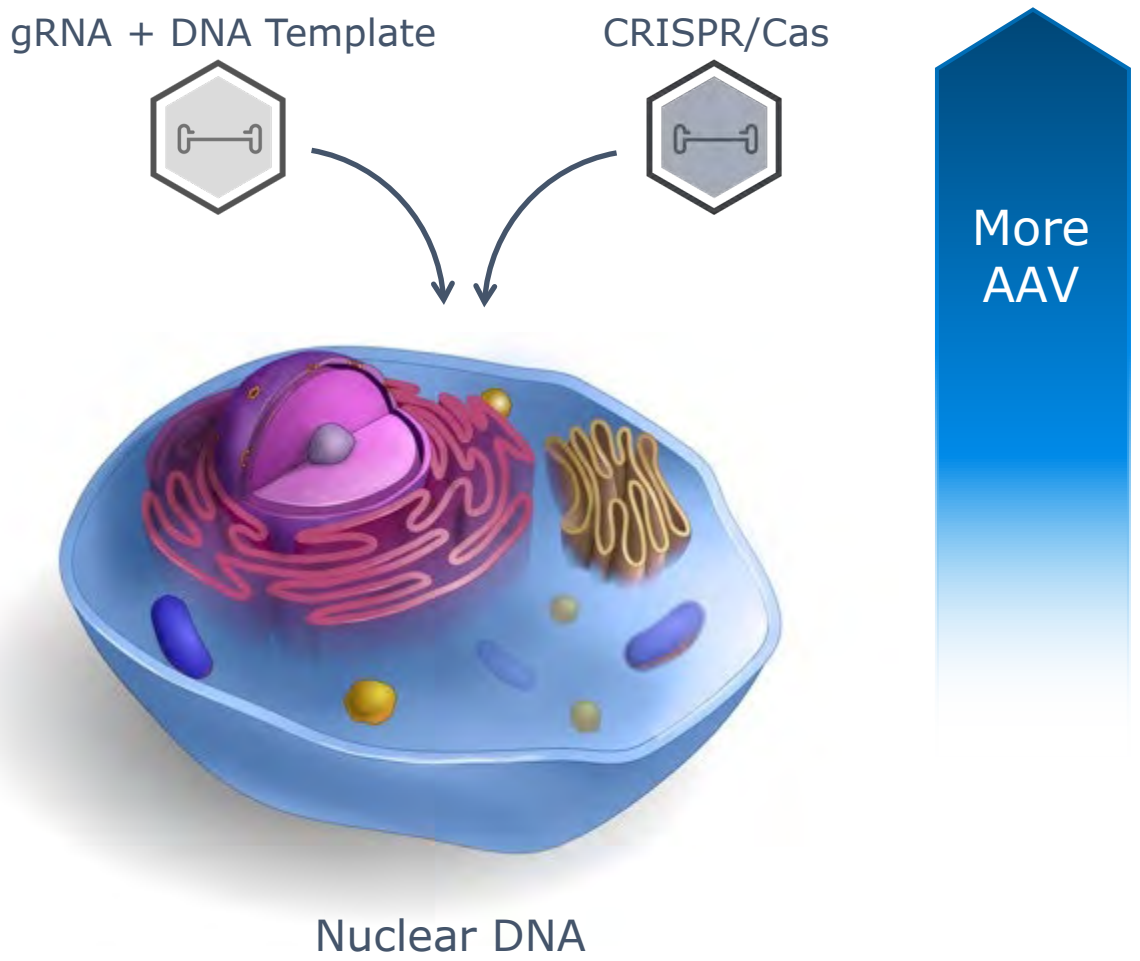
Allowing Delivery with a DNA Template in a Single AAV for **Gene Insertion**



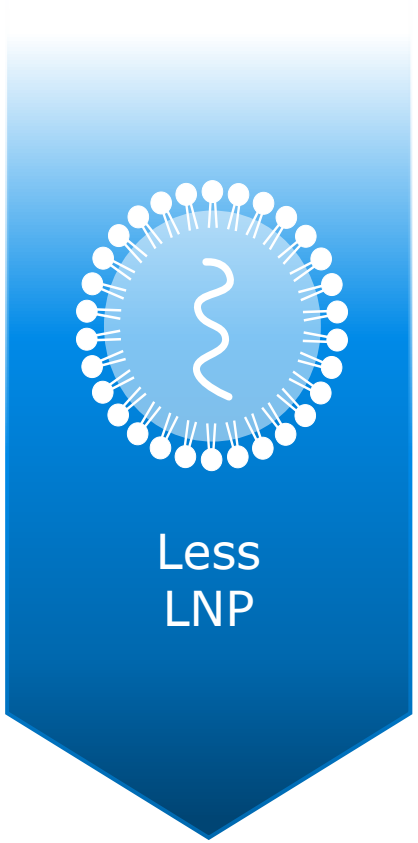
Sizes include editor and expression machinery; ARCUS nuclease is 1062 bp

Why does Size Matter for Safety?
Potential for Lower AAV Dose





Why does Size Matter for Safety?
Potential for Lower Total LNP Dose



mRNA quality is a driver of tolerability for LNP-based products

- High purity mRNA is essential to prevent immunotoxicity.
- Longer mRNAs are often associated with increased presence of “abortive transcripts,” which compromise purity.
- Shorter mRNAs are easier to produce with high purity and therefore favorable for tolerability.

LNPs are restricted to <100nm in size for efficient liver uptake

- Due to this size restriction, the number of mRNA molecules that fit into an LNP is directly related to the size of the mRNA.
- ARCUS-encoding mRNA is ~4x smaller than Cas9-encoding mRNA.
- Ability to package more mRNA molecules per particle may increase potency of drug product and yield a more favorable safety profile.

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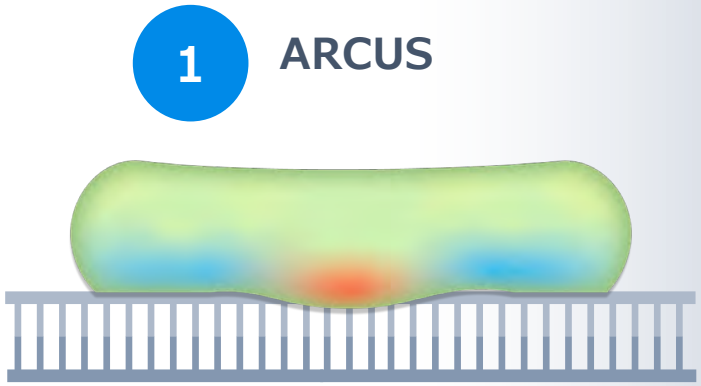
Simplicity: ARCUS is the Only Single Protein Component Editor



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**

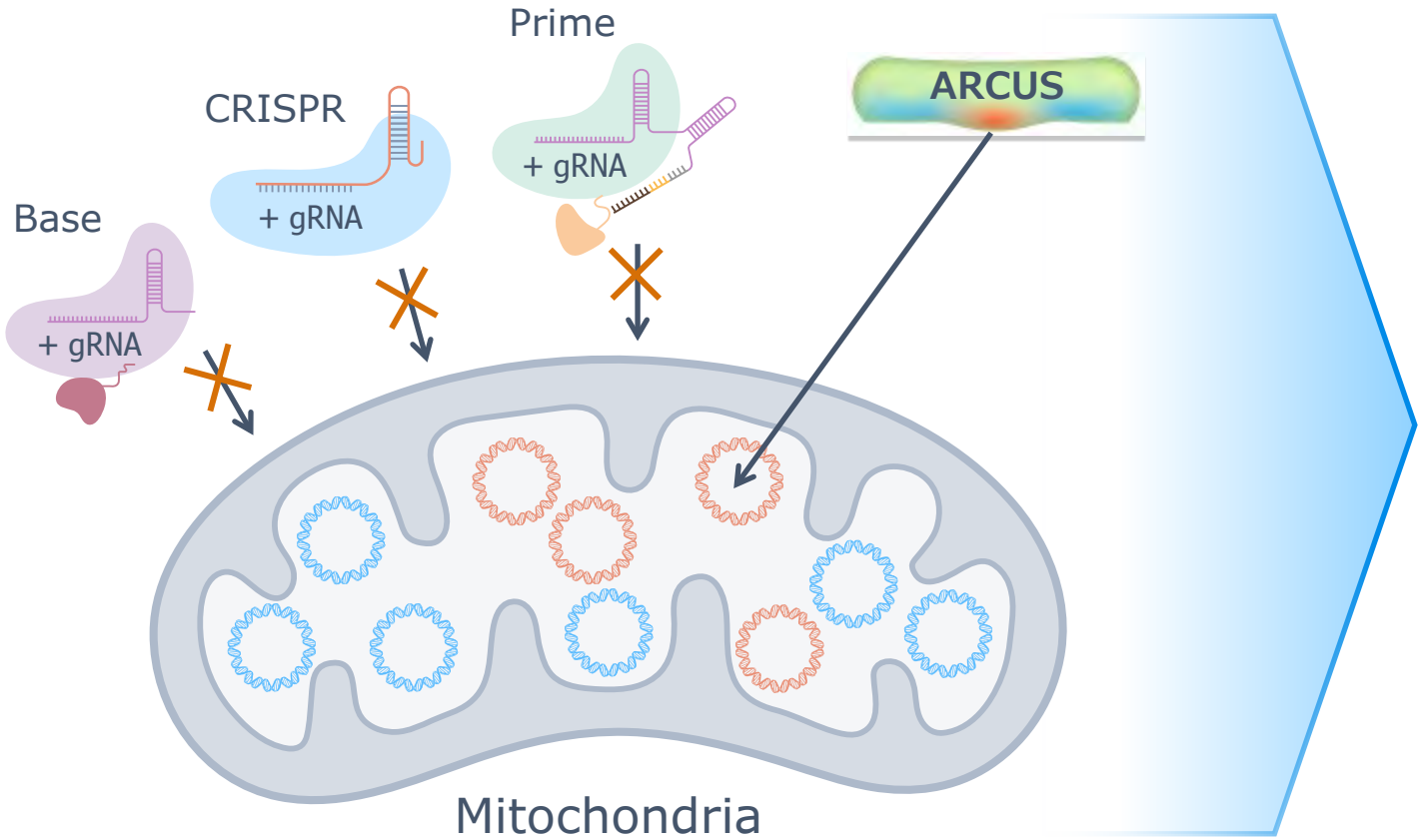
Single component **requires less** AAV and potentially less LNP

〉 **Easy to deliver**

〉 **High efficiency**

〉 **Low dose improves safety**

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

Received: 18 May 2023

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Wendy K. Shoop[1,2], Janel Lape[1], Megan Trum[1], Alea Powell[1], Emma Sevigny[1], Adam Mischler[1], Sandra R. Bacman[3], Flavia Fontanesi[3], Jeff Smith[1], Derek Jantz[1], Cassandra L. Gorsuch[1] & Carlos T. Moraes[3]

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

Safety Outcomes
Accomplished Through
ARCUS Advantages

The Cut

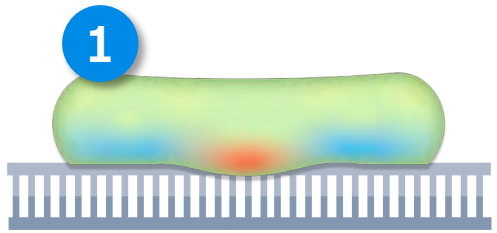
The Size

The Simplicity

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

Targeted Editing

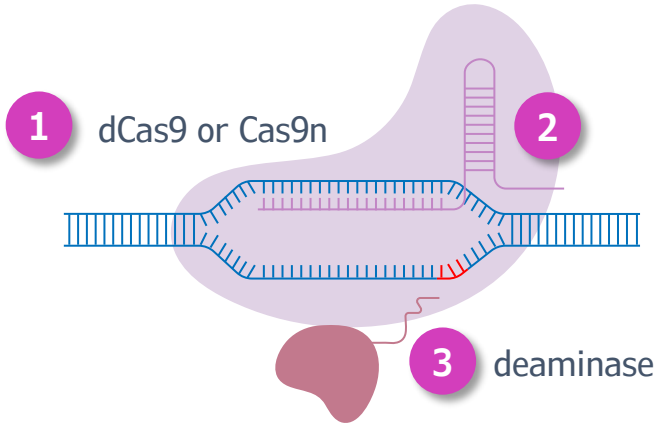
ARCUS



Single Component

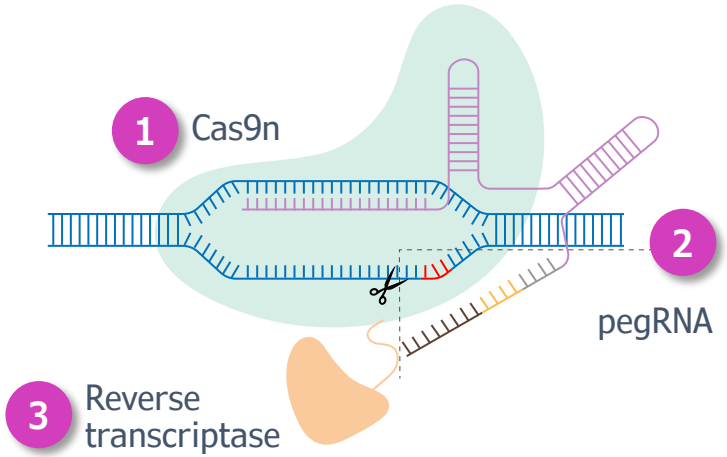
Potential for guide independent effector off-target activity

Base Editor



Promiscuous Deamination

Prime Editor



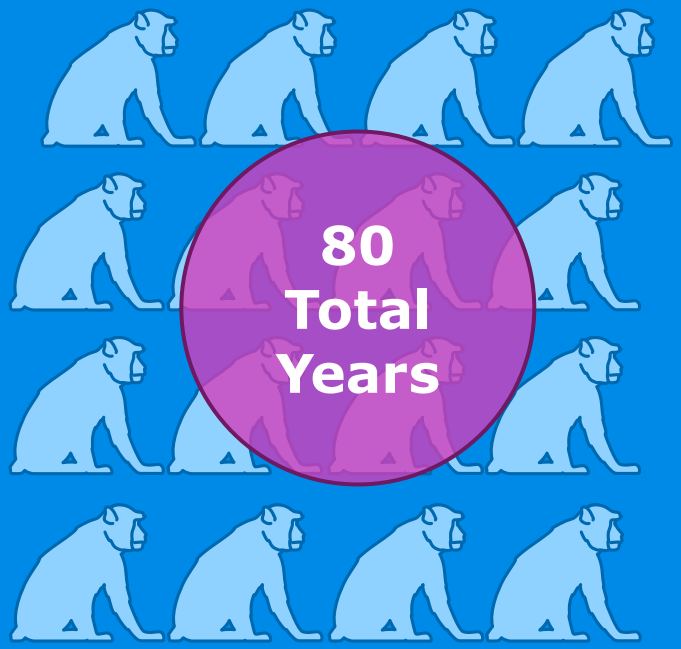
Documented Structural Rearrangements

〉 **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

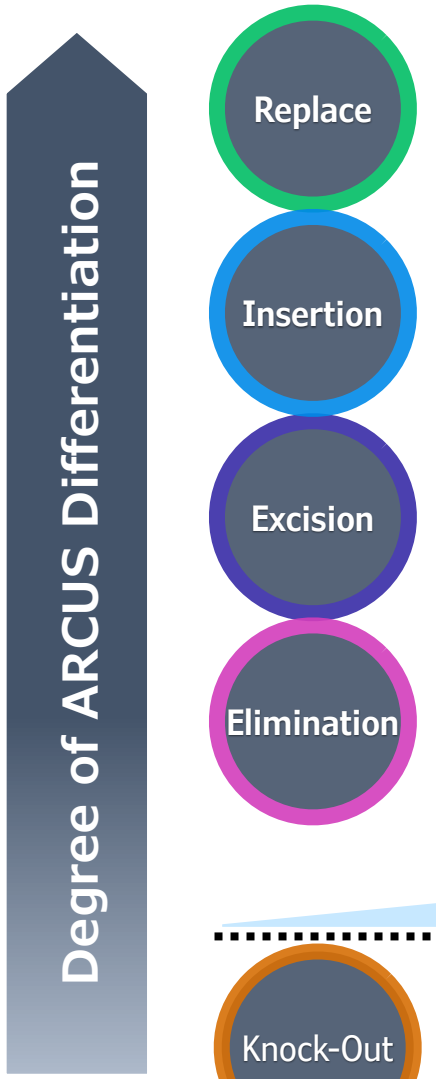
6 NHPs on study for
>3.5 years

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

Precision Only Focused On ARCUS Differentiation By Edit Type



Replace

Insertion

Excision

Elimination

Knock-Out

Wholly-Owned

Future Precision Programs

PBGENE-HBV

PBGENE-PMM

Partnered Programs

PBGENE-NVS NOVARTIS

PBGENE-LLY2 Lilly

iECURE-OTC ECURE

PBGENE-DMD Lilly

PBGENE-LLY3 (CNS) Lilly

Edit Type and Delivery Undisclosed

ARCUS for edit types beyond gene knockouts/deletions

All Gene Editors Are Capable of Gene Knockout/deletion, especially at the Liver

Chapter 1 PBGENE-HBV | Chapter 2 PBGENE-PMM | Chapter 3 Future HDR Programs | HDR Program List

PRECISION
BIOSCIENCES

ARCUS Differentiation By Edit Type

Strategic Overview of Precision Programs

PRECISION
BIOSCIENCES

Chapter 1:
PBGENE-HBV
Viral Elimination

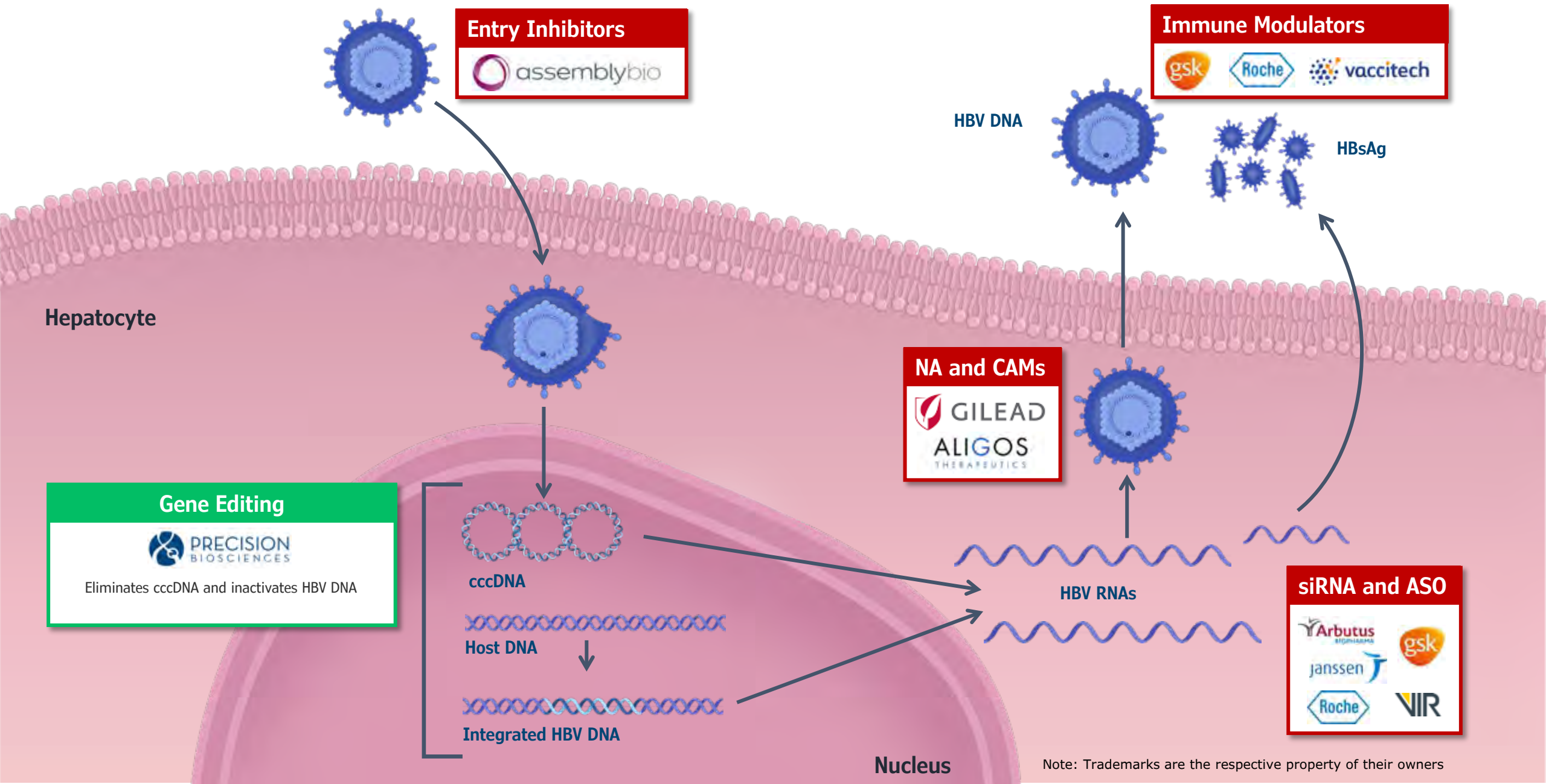
Back to Menu

Executive Summary on PBGENE-HBV Program

ARCUS Potential Curative Strategy for HBV Elimination Ready For Clinic in 2024

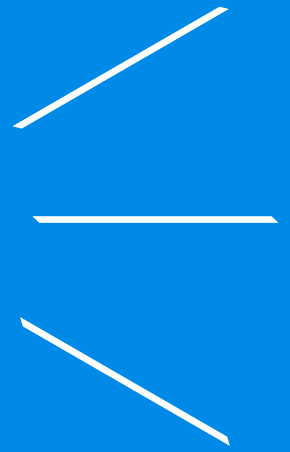
- ARCUS only modality currently designed to eliminate cccDNA and inactivate integrated HBV DNA
  -> essential for functional cure (undetectable HBV DNA and HBsAg after a finite treatment course)
- PBGENE-HBV AASLD 2023 data demonstrated strong proof of concept for efficacy and safety
- **Precision Advancing Next Steps:**
  - Final PBGENE-HBV clinical candidate ready
  - On-going discussions with global regulatory authorities to determine first wave markets
  - FIH site-selection and feasibility in process
  - Final step: pre-CTA/IND toxicology
  - 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

PBGENE-HBV Leverages the ARCUS Advantages of **Size & Simplicity**



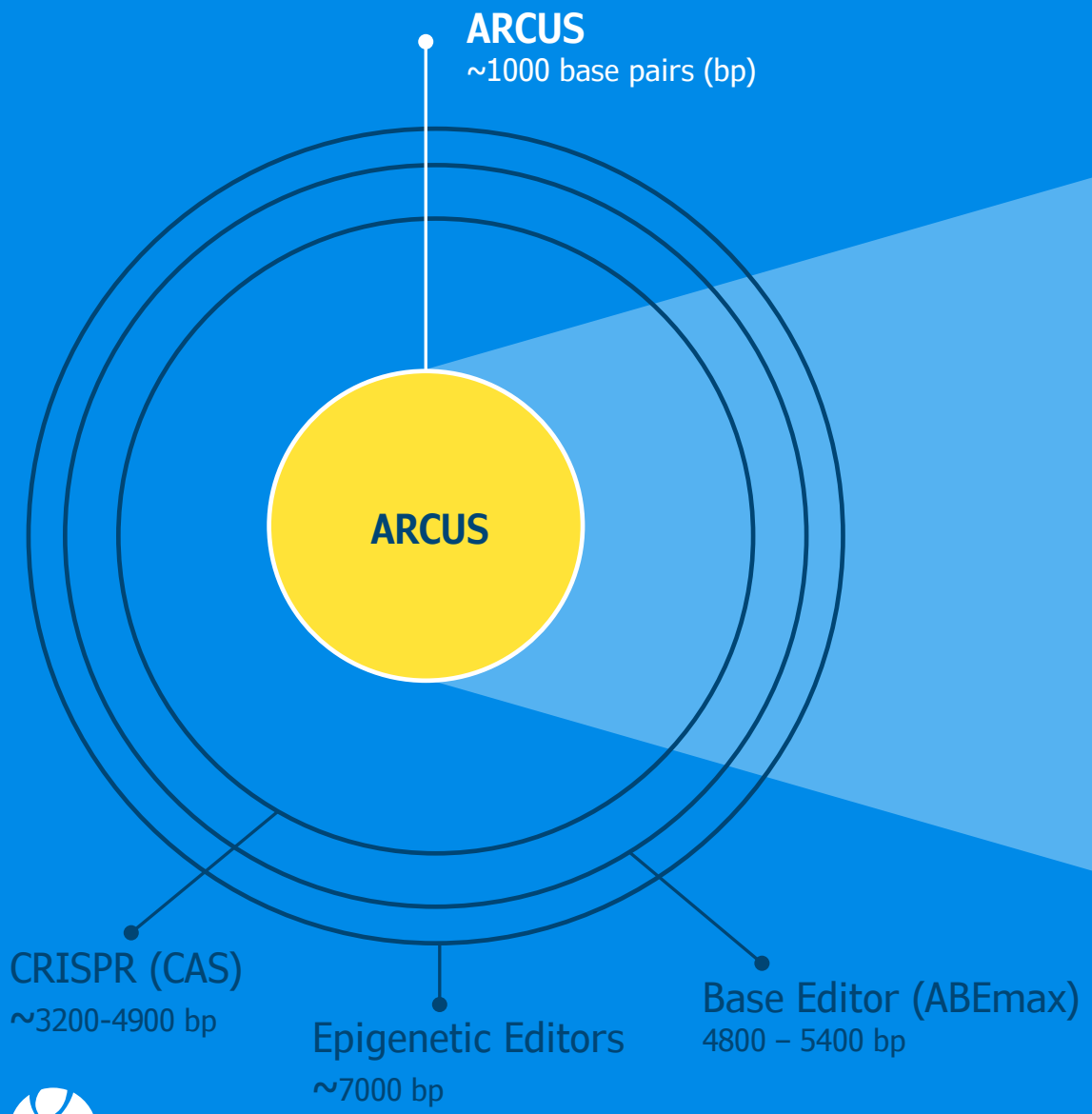
The Cut

The Size

PBGENE-HBV Program

The Simplicity

Size Optimal to Target cccDNA and Integrated HBV DNA



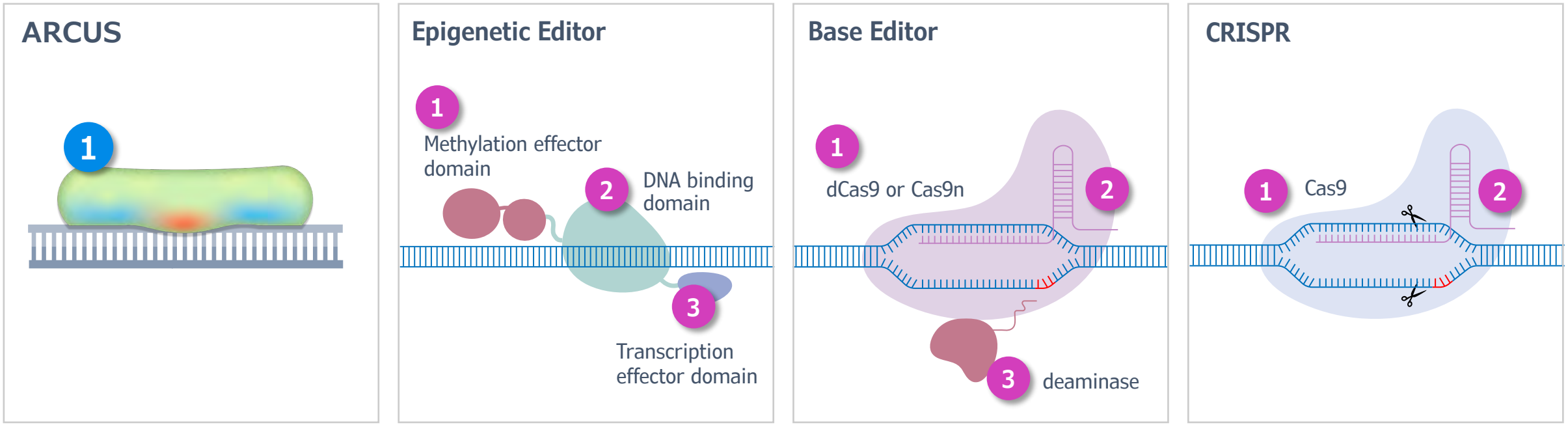
Small size may allow easier access to DNA for target site editing

—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

Targeting cccDNA:
ARCUS Gene Editing Versus Other Genetic Modalities in Development

		ARCUS	Epigenetic Editor[1]	Base Editor (Development Paused[2])	CRISPR Editor[3]
cccDNA Engagement	Edit Result	**Designed to eliminate cccDNA** directly at high efficiency	Silences cccDNA via methylation	Mutates and Inactivates cccDNA	Creates cccDNA indels vs. elimination of cccDNA
	Cut type	3' overhang cut resulting in double stranded break	Methylation (No Cut)	Single Stranded Nick	Blunt cut resulting in double stranded break
	Impact	**Permanent and Durable elimination of cccDNA**	Unproven durability cccDNA still persists and can become reactivated	Mutated cccDNA still persists	Potential permanent elimination of cccDNA (data unknown)
Size and Simplicity	Kilobases (kb)	~1 kilobases **Small**	~7 kilobases Very Large	4.8-5.4 kilobases Large	3.2-4.1 kilobases Large
	# of Components	1 component / **Simple**	>3 components / Very Complex	3 components / Very Complex	2 components / Complex
Therapeutic Scope and Evidence	Scope of Genotypes	**Target site conserved** across >92% of isolates across genotypes	Target Site Undisclosed	Undisclosed Variable depending on gRNA	Target Site Undisclosed
	In Vitro	**cccDNA elimination** leads to ↓HbeAg, HbsAg (PHH), HBV DNA/RNA ↓HbsAg (Int. HBV DNA)	↓HbeAg & HbsAg (cccDNA) ↓HbsAg (Int. HBV DNA)	↓HbsAg, HbeAg, HBV DNA, HBV RNA (PHH), HbsAg (Int. HBV DNA)	↓HbsAg & HbeAg (at lower efficiency)
	In Vivo Models	↓HBV DNA & HbsAg (NHP & Transgenic Mice)	↓HBV DNA & HbsAg (Transgenic Mice)	↓HBV DNA & HbsAg (Transgenic & Humanized Mice)	↓HBV DNA & HbsAg (Transgenic Mice)
	Potential Risk	Final clinical candidate shows **enhanced specificity with no detectable off-target editing at maximal on-target editing dose**	Potential unintended off target effects by released/cleaved effector domain	Potential unintended off-target effects; high affinity towards integrated HBV DNA and off-targeting by guide independent base editing	Potential unintended off-target effects; high affinity towards integrated HBV DNA

No head-to-head studies of these approaches have been conducted and therefore no conclusions concerning safety or efficacy can be drawn

[1]Epigenetic Editor data to date presented by Chroma Medicine

[2]. Beam Tx announced portfolio prioritization and pausing development of HBV program; 10/19/23 Press Release

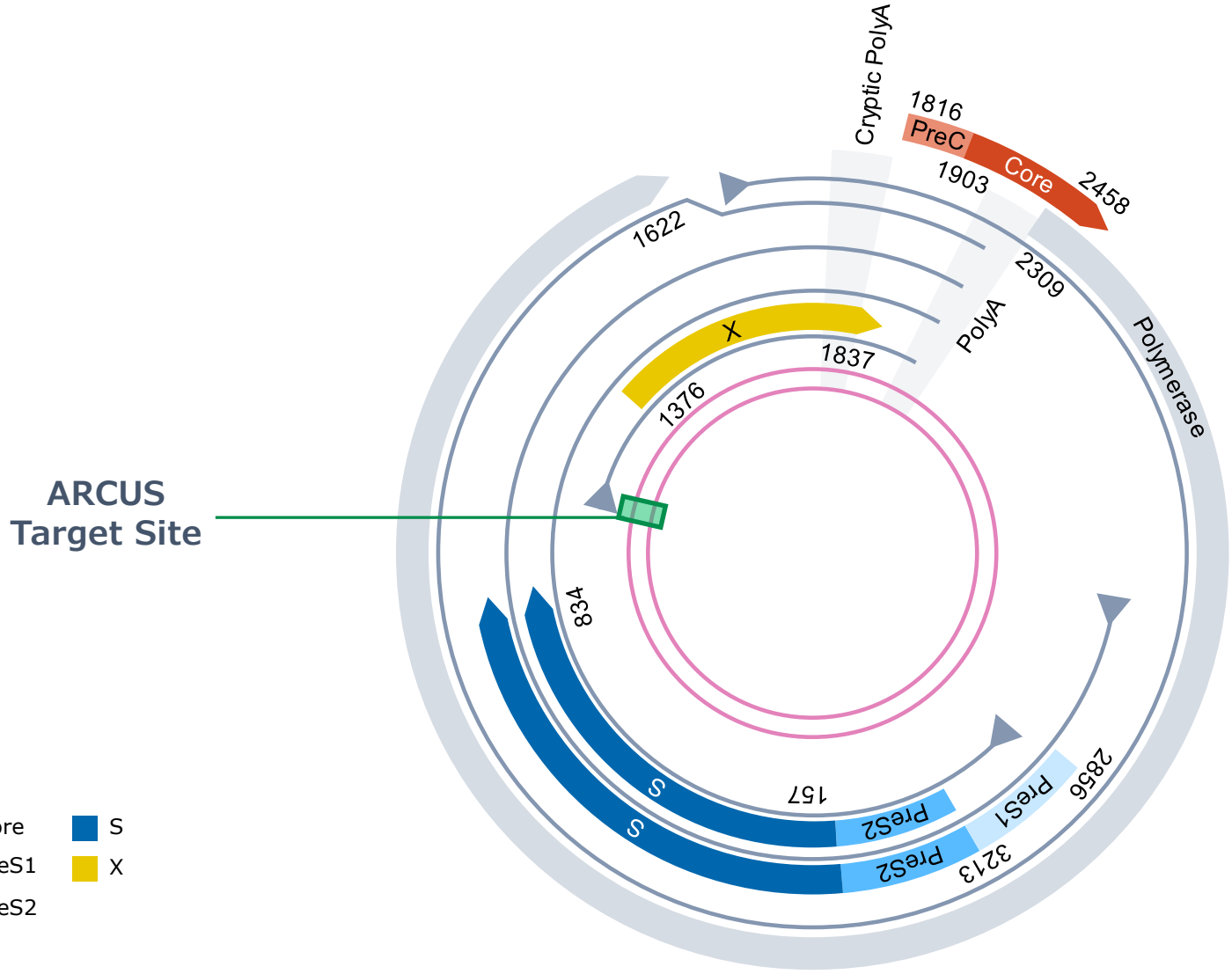
[3]. Seeger, et al. 2014, 2016; https://pubmed.ncbi.nlm.nih.gov/25514649/; https://pubmed.ncbi.nlm.nih.gov/27203444/

> 300 million
cHBV infections globally

> 1,000,000
cHBV infections in the US

PBGENE-HBV Designed For Broad Patient Applicability

Broad Patient Applicability:
ARCUS Recognizes a Highly Conserved Sequence in cccDNA

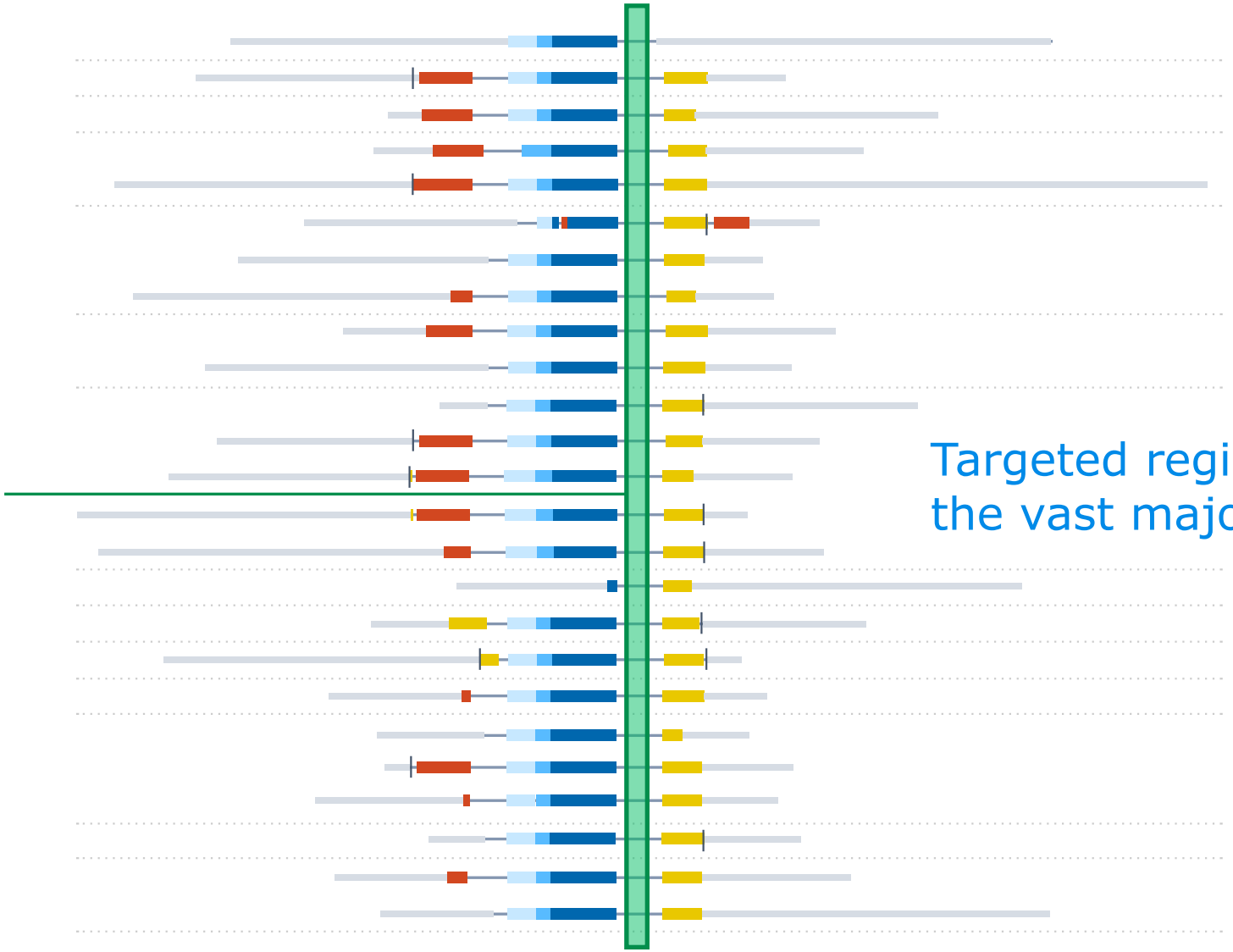


Target site conserved in

>92% of isolates across genotypes[1,2]

1. Gorsuch CL, et al. Mol Ther. 2022;30(suppl 9):2909-2922. 2. Image source adapted from: Tu T, et al. *Viruses.* 2021;13(2):180.

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

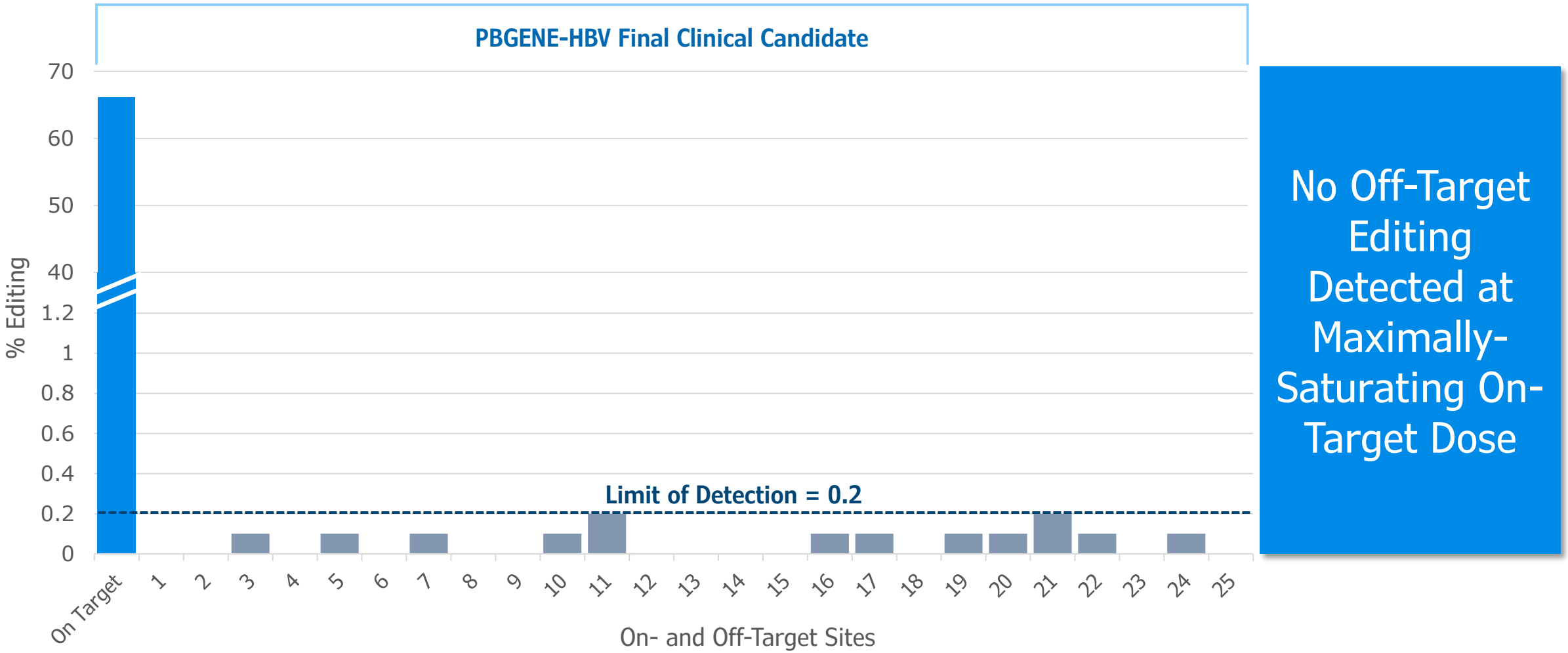
AASLD 2023 Data Update

Summary of New PBGENE-HBV Data Presented

- Enhanced Specificity With No Detectable Off-Target Editing at Maximal On-target Editing Dose
- NHP Study Demonstrated Up to 99% Viral Engagement
- Eliminated cccDNA and Inhibited Viral Markers in PHH
- ~95% Durable HBsAg Reduction Across Doses in Mouse Study
- Significant HBV DNA Reduction in Transgenic Mouse Supports Potential for Stopping NUC and Functional Cures in Future FIH Study

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

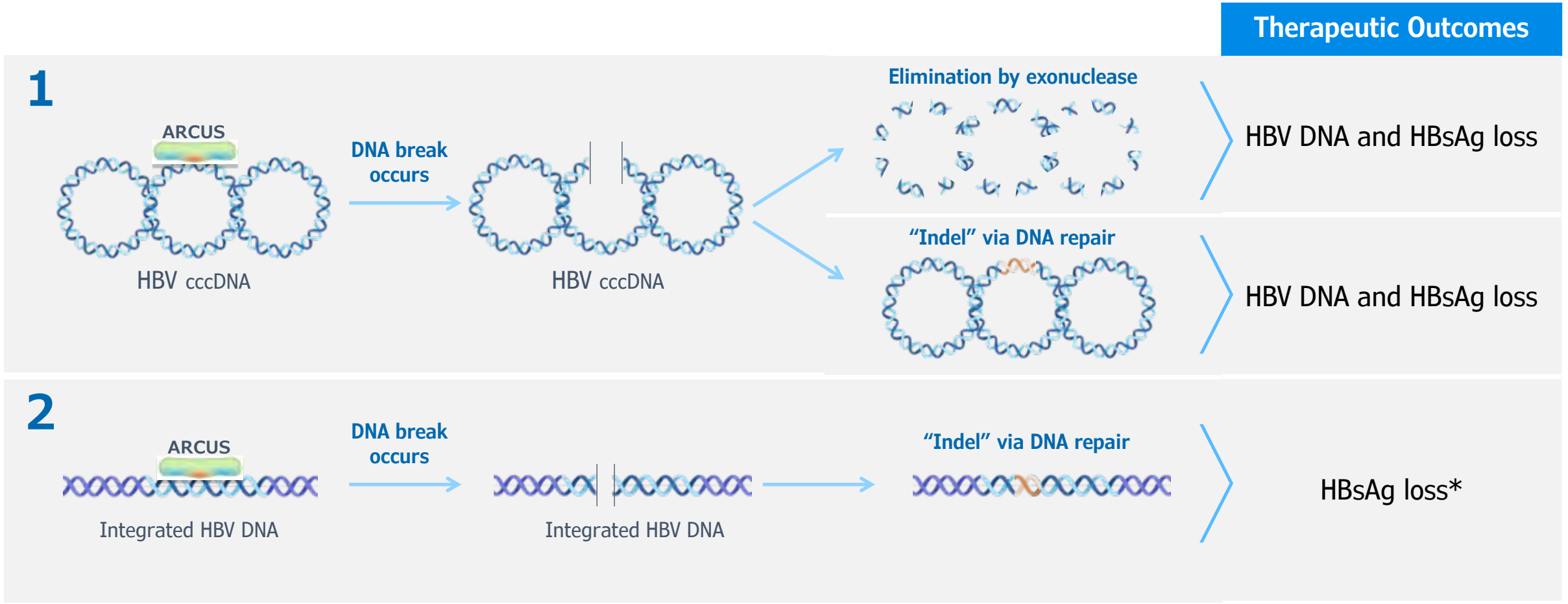
NEW DATA



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

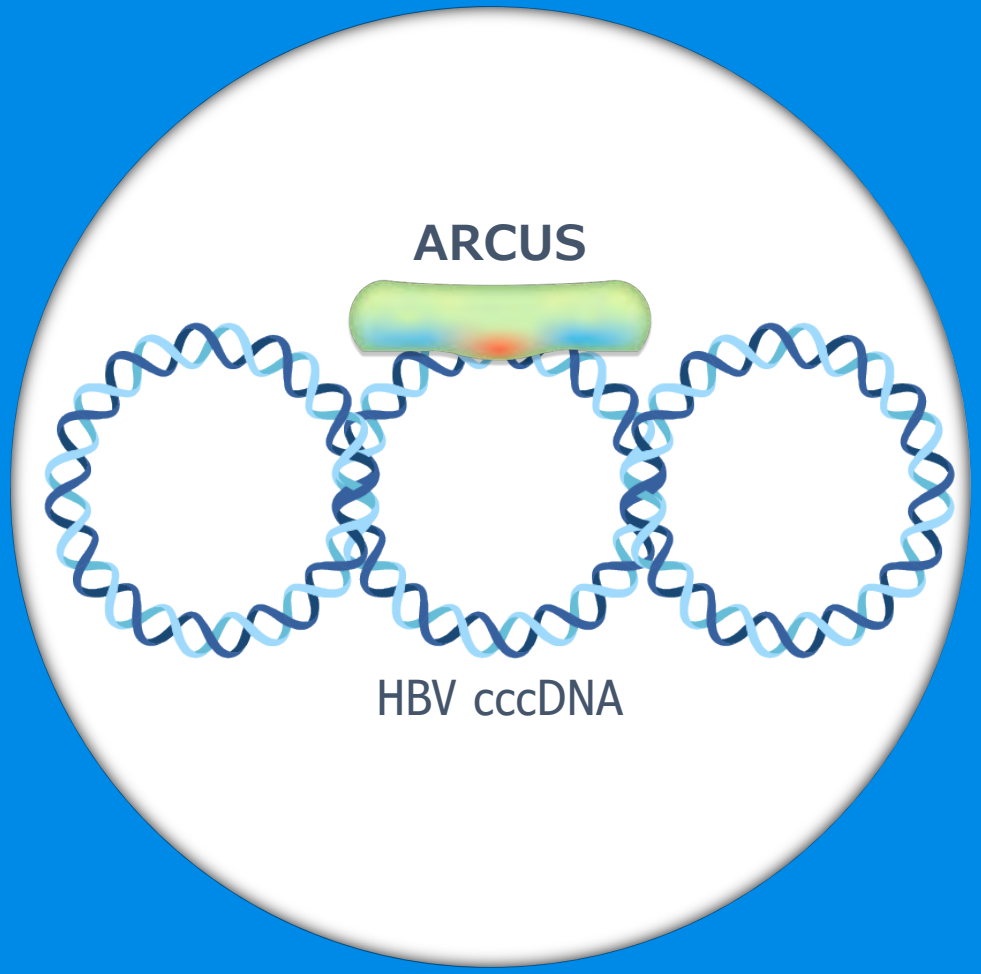
Notes:
1. The final optimized clinical candidate nuclease shows enhanced specificity from prior versions by eliminating off-target editing above LOD when examining 384 potential off-target sites

ARCUS Approach to Eliminate cccDNA and Inactivate Integrated HBV DNA to Drive Durable Antigen Loss with Goal of Functional Cure



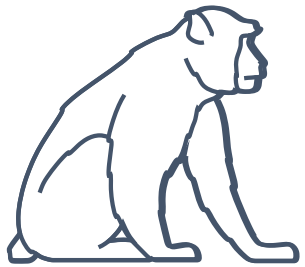
*Note: Integrated DNA does not produce HBV DNA

Eliminate cccDNA

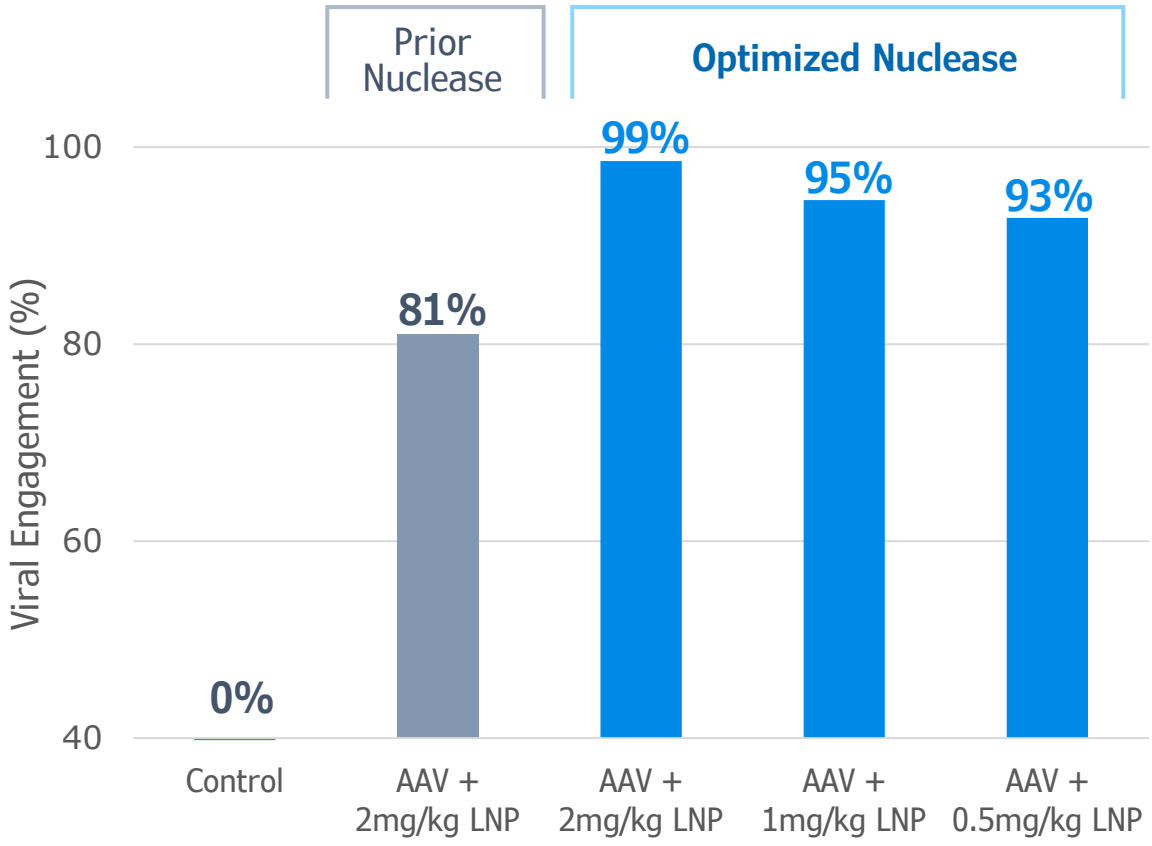


Efficacy: Non-Human Primate (NHP) Study Demonstrates Up to 99% Viral Engagement, Suggestive of Strong Potential Efficacy Profile of PBGENE-HBV

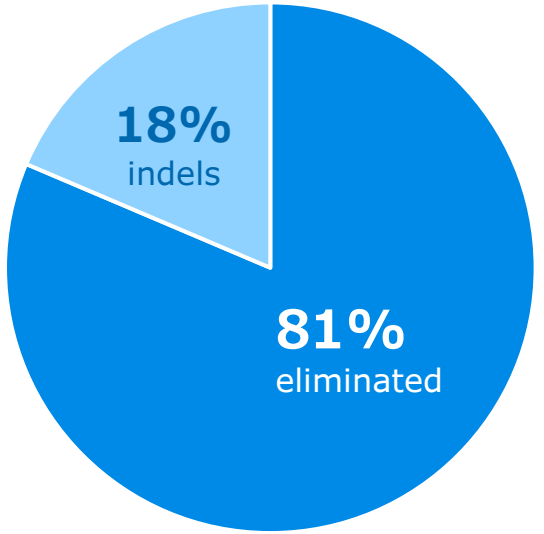
NEW DATA



ARCUS LNP



99% viral engagement
at highest dose in NHP study

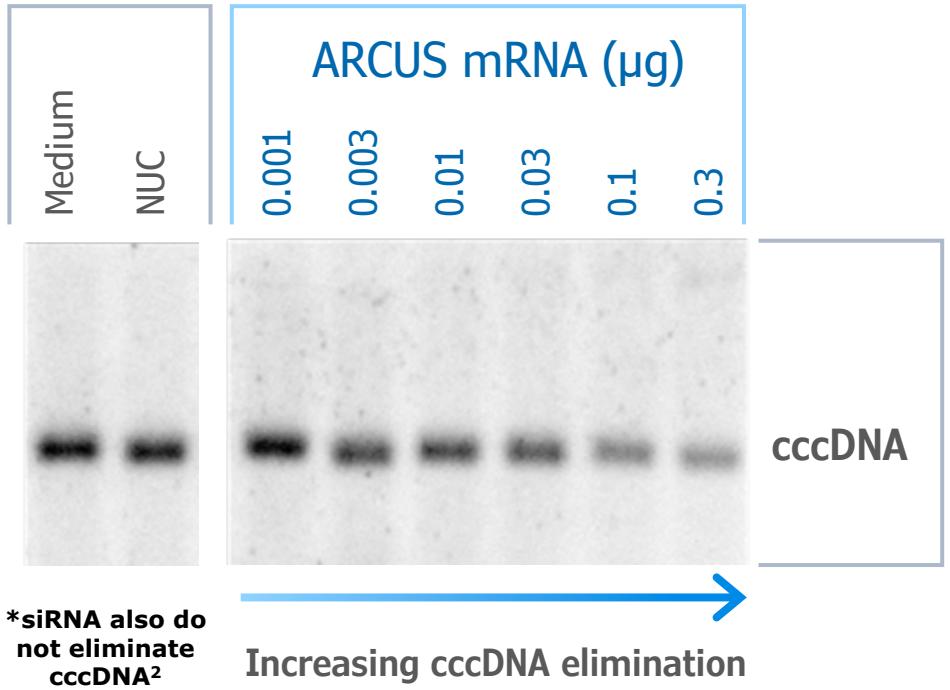


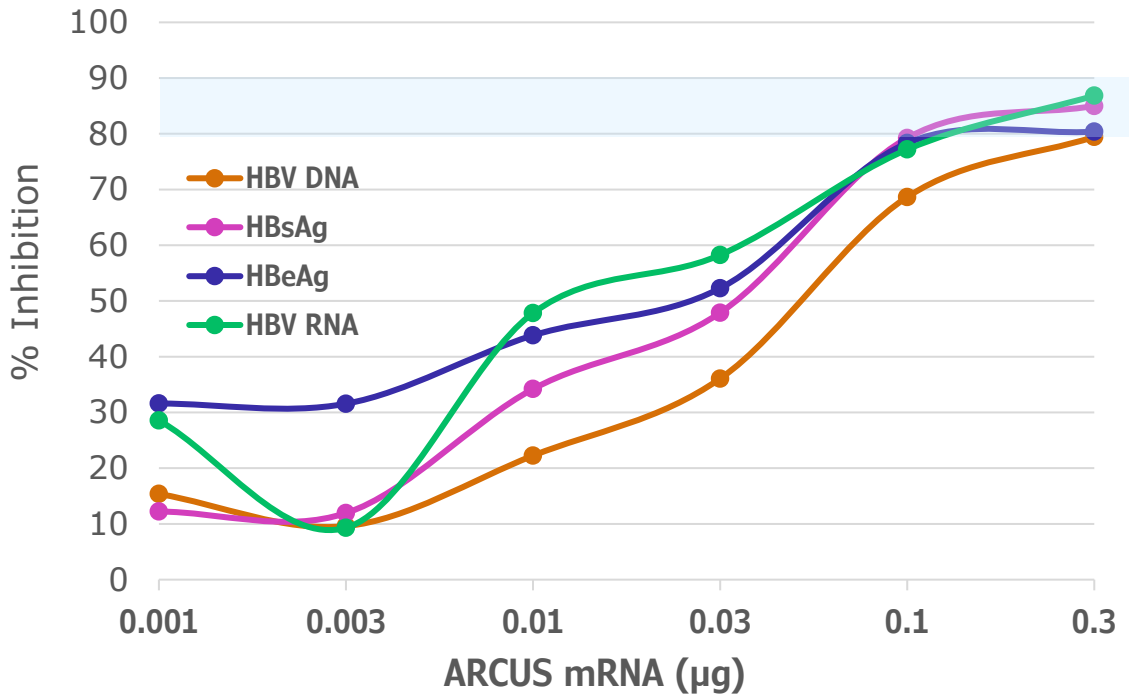
Final clinical candidate expected to eliminate majority of cccDNA, this unique mechanism of action is critical to drive durable functional cures

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 Eliminates cccDNA and Inhibits Viral Markers in HBV-Infected Primary Human Hepatocytes (PHH)

NEW DATA





Proof of principle: Final clinical candidate nuclease demonstrates a dose-dependent elimination of cccDNA

Final clinical candidate reduces HBsAg, HBeAg, HBV DNA, and HBV RNA by 80-90%

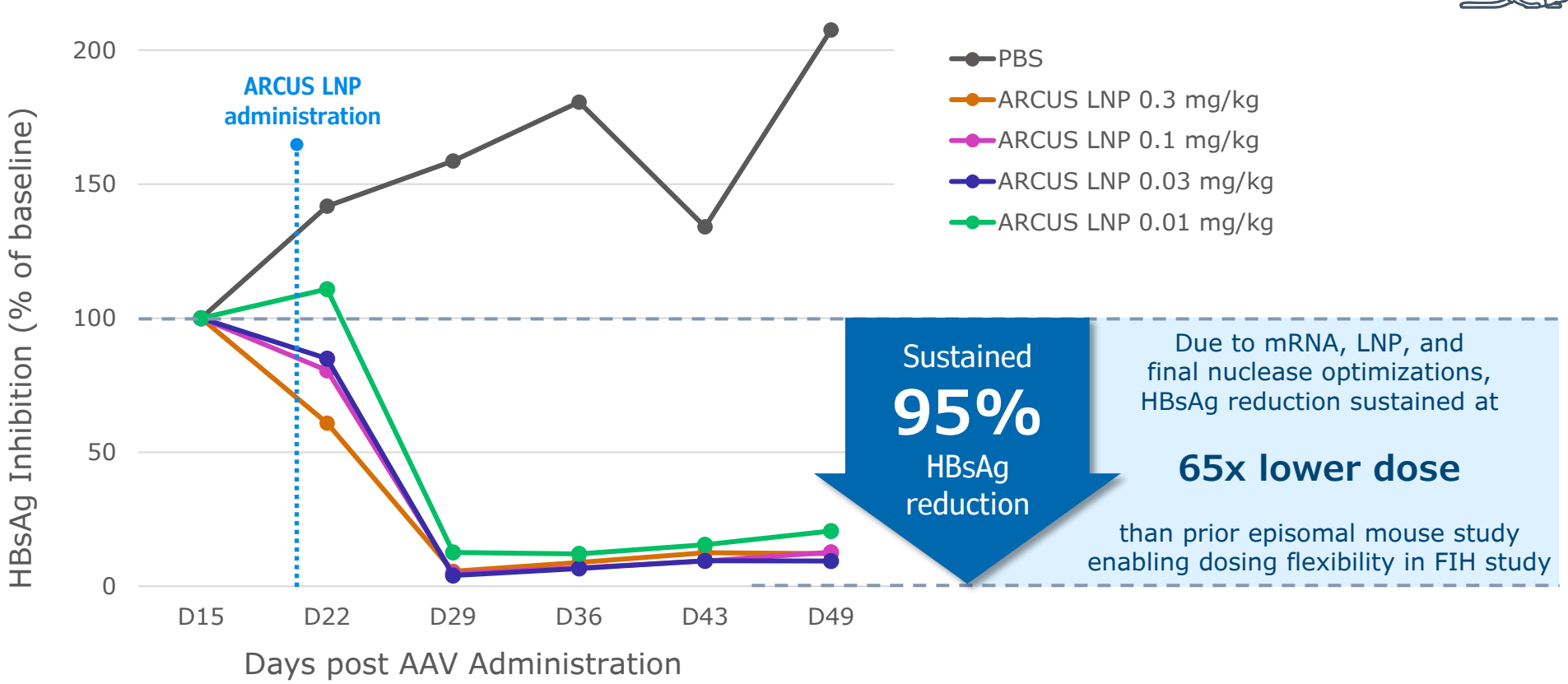
(vs. 77% HBsAg and 80% HBV DNA reduction in prior nuclease)

Notes:
1. NUC is nucleos(t)ide analog and in this experiment, lamivudine (LAM) was used
2. *Therapeutic shutdown of HBV transcripts promotes reappearance of the SMC5/6 complex and silencing of the viral genome in vivo;* Allweiss L., et al. 2022

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

NEW DATA

Prior Nuclease	Final Clinical Candidate
90% viral engagement	95% viral engagement



Due to mRNA, LNP, and final nuclease optimizations, HBsAg reduction sustained at

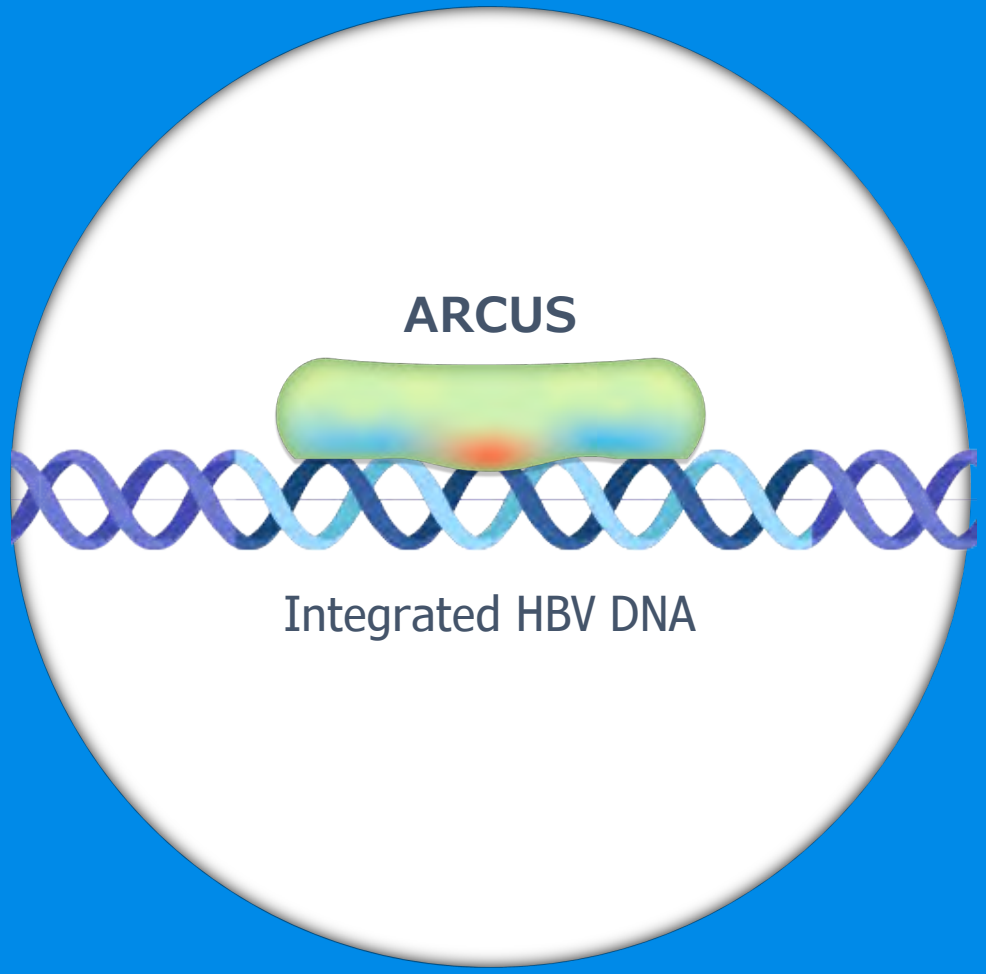
65x lower dose

than prior episomal mouse study enabling dosing flexibility in FIH 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

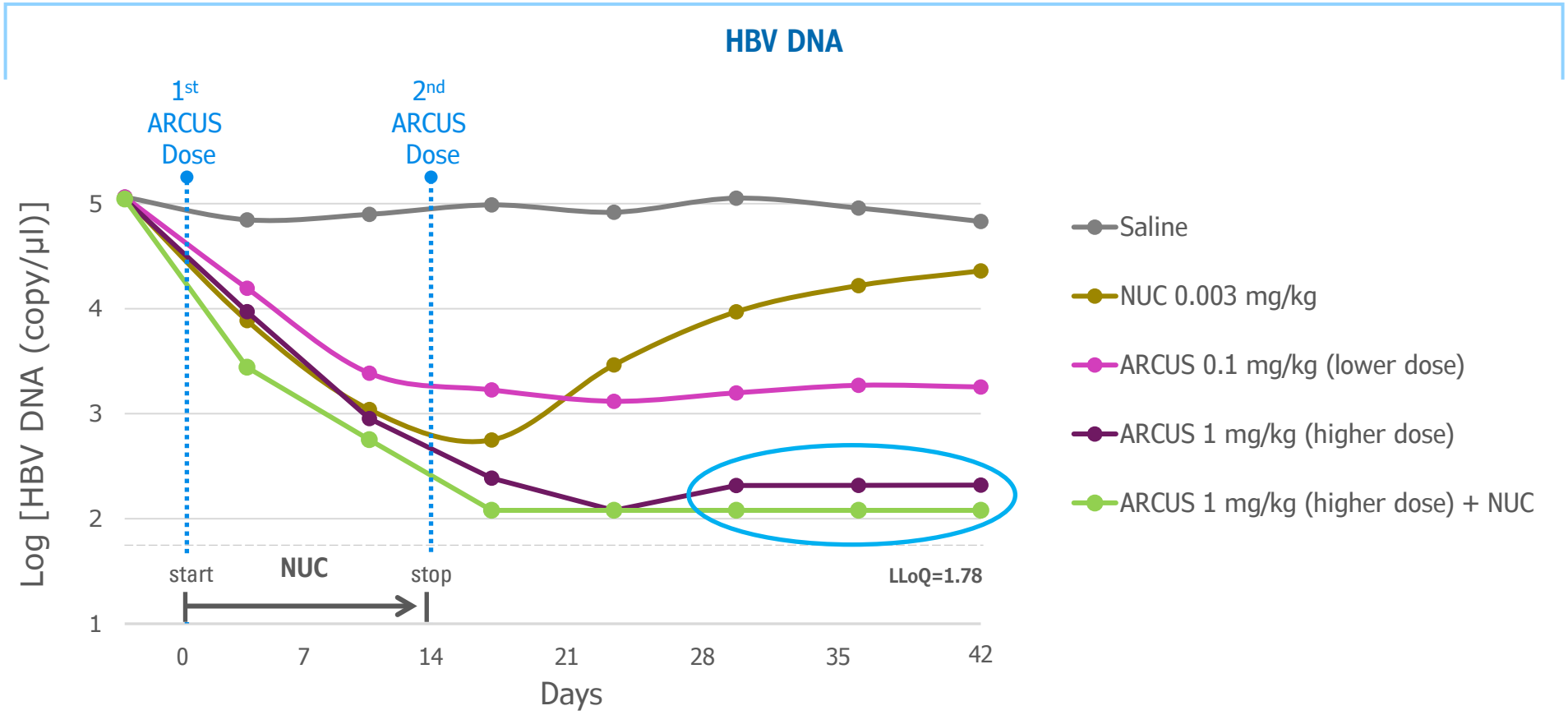
Notes:
1. Prior nuclease data shared at R&D Day in September '23, and prior nuclease tested at a higher 2mg/kg dose
2. Viral engagement (elimination +/- inactivation through indels); ARCUS LNP administration at D21

Inactivate Integrated HBV DNA



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

NEW DATA



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

ARCUS Potential Curative Strategy for HBV

〉 Eliminate cccDNA

〉 Inactivate HBV DNA

- **Size Optimal:** Target cccDNA and Integrated HBV DNA
- **Simplicity of ARCUS:** single component editor offers advantages when applied to HBV elimination
- **mRNA Sequence Optimization**: 8x improvement in protein expression permitting dosing flexibility
- **ARCUS Dual Mechanism:** eliminates cccDNA and inactivates integrated HBV DNA across models in robust preclinical package
- **First Gene Editor in HBV:** ARCUS is engineered to benefit wide-range of patients by targeting >92% of isolates across genotypes

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
- [x] Final Clinical Candidate Nominated
- [ ] Submit IND/CTA in 2024 — *on-track*
- [ ] Initiate First-in-Human (FIH) Clinical Studies — *site-selection underway*

PRECISION
BIOSCIENCES

Chapter 2:

PBGENE-PMM

Mutant Mitochondrial DNA Elimination

Back to Menu

Primary Mitochondrial Myopathy (PMM) Currently Lacks a Curative Treatment

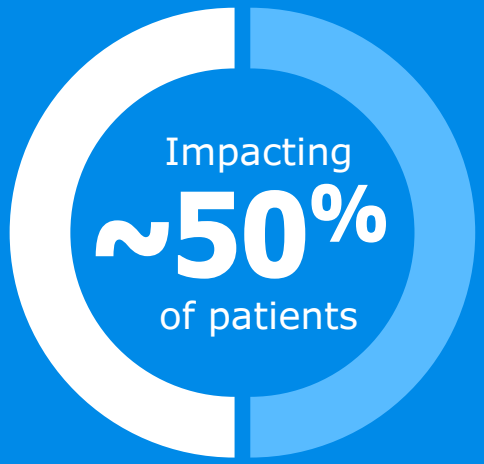
Mitochondrial diseases (MDs)

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

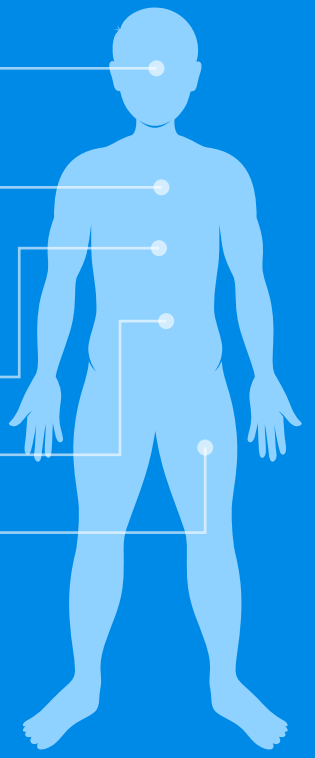


Primary mitochondrial myopathies (PMM)

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

PMM is debilitating[1]:

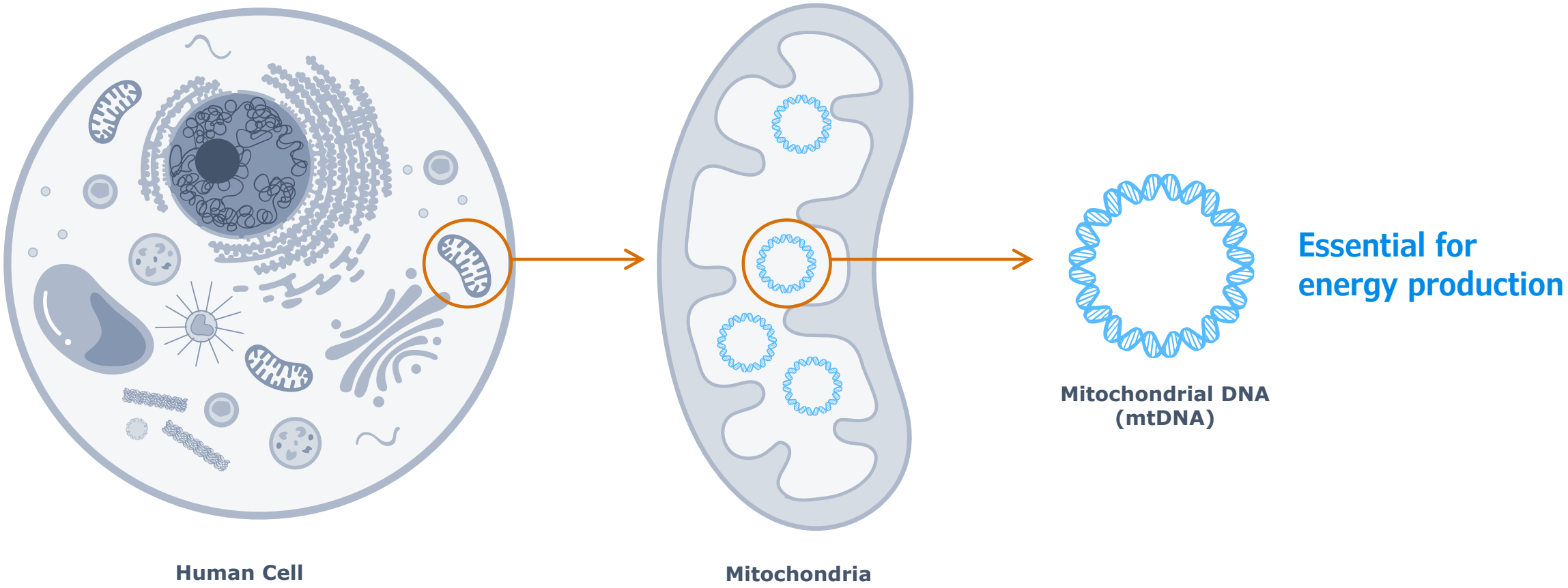
- Chronic progressive external ophthalmoplegia
- Respiratory failure
- Exercise Intolerance
- Multi organ dysfunction
- Impaired Mobility
- Generalized weakness



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/

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 **~14k 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′

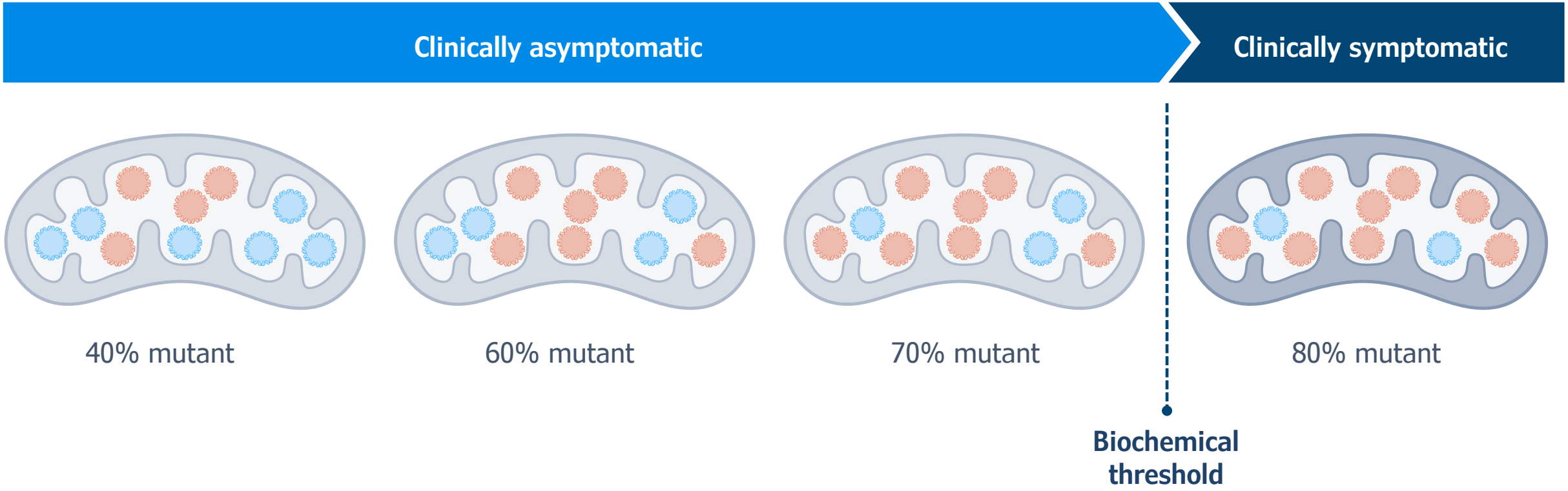
5′-C A G **A** G C C C G G T A A T C G C A T A A A-3′

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

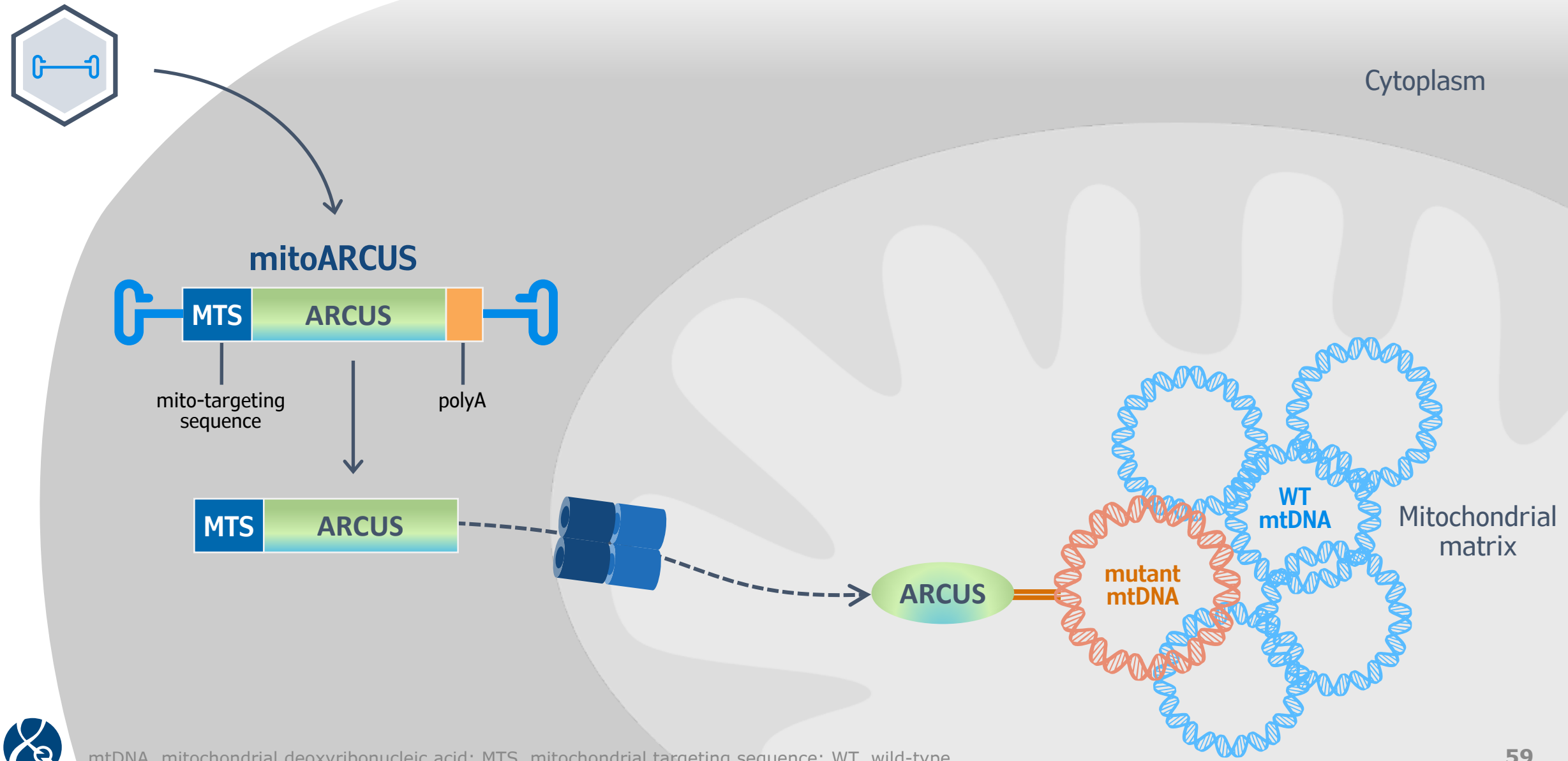
mtDNA Mutations Are Commonly Heteroplasmic

Situation where two or more mtDNA variants exist in same mitochondria



mtDNA, mitochondrial DNA.

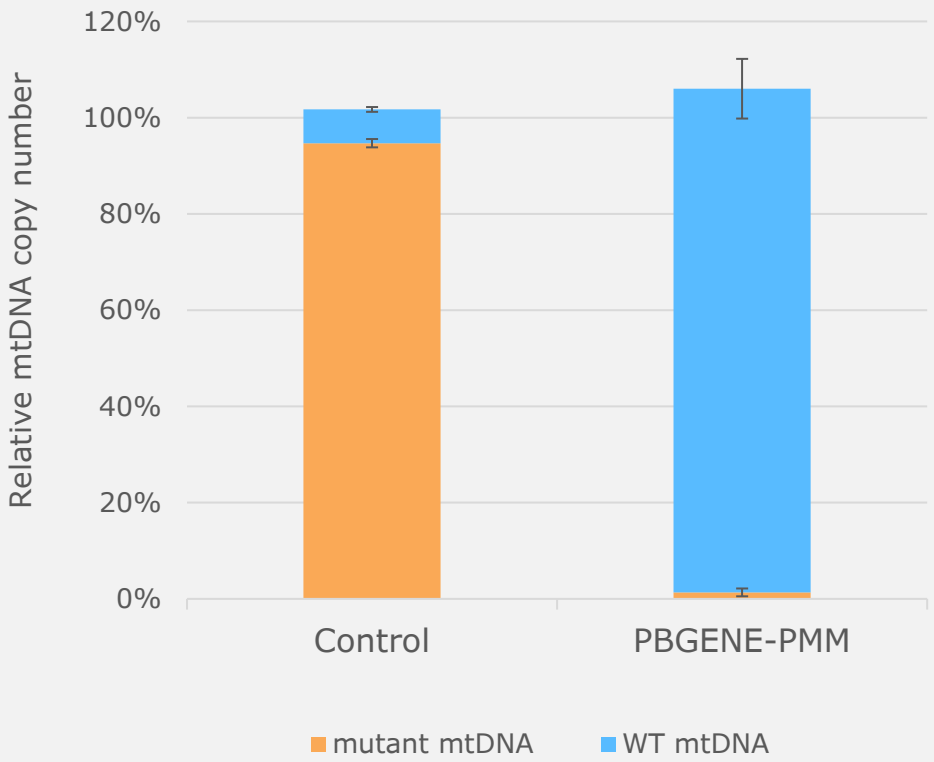
mitoARCUS Therapeutic Approach to Shift Heteroplasmy



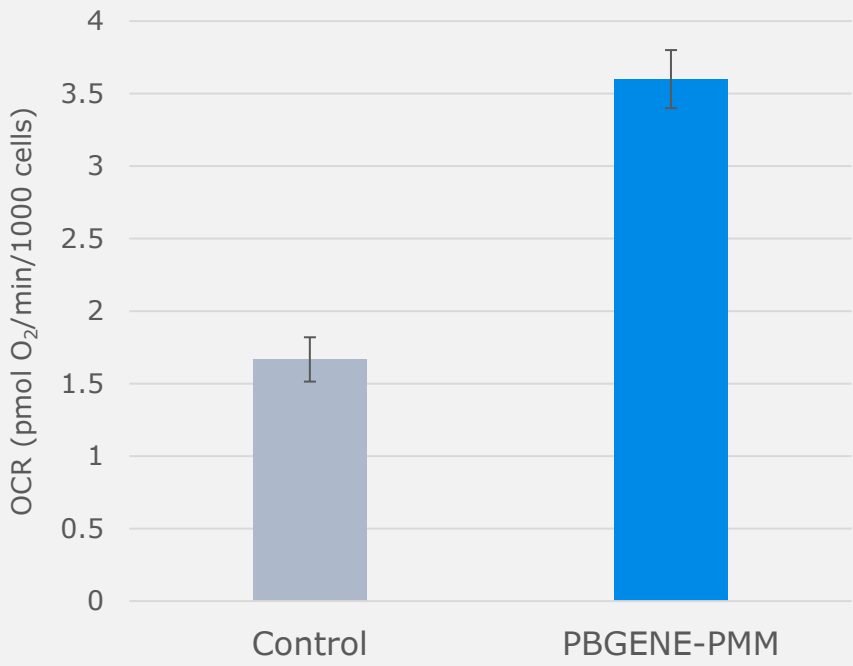
mtDNA, mitochondrial deoxyribonucleic acid; MTS, mitochondrial targeting sequence; WT, wild-type.

PBGENE-PMM Improved Mitochondrial Function

On target efficacy

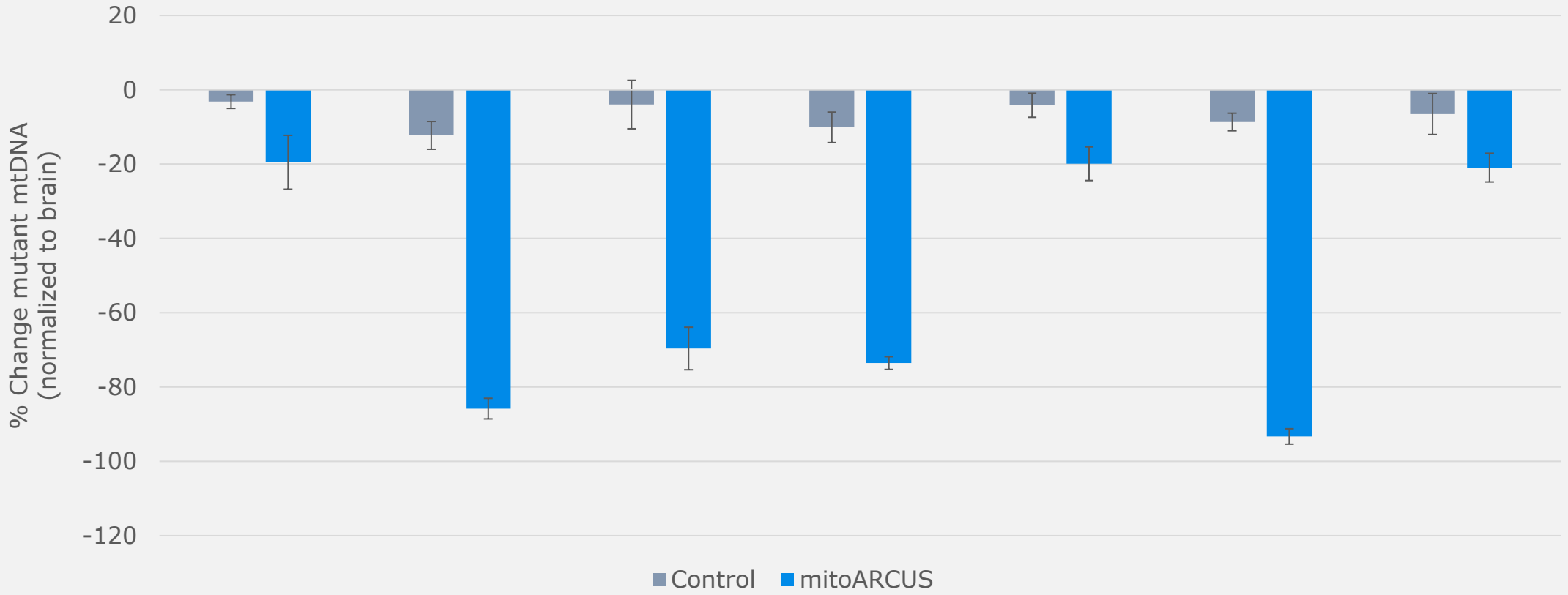


Impact on energy production



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.

Reasons to Believe in Precision's Approach to Treat PMM

Target CTA/IND
2025

- Simplicity of ARCUS **single component editor** enables targeting mutant mitochondrial DNA whereas other **guide RNA-based editors cannot**
- Opportunity for a **one-time, potentially curative treatment** for adult patients who today are only treated with supportive care "mito-cocktails"
- Current ARCUS nuclease can accurately discriminate a single nucleotide change **shifting heteroplasmy in favor of wild type** and improving mitochondrial function; **no evidence of mitoARCUS editing nuclear DNA**
- **Potentially first-in-class opportunity for m.3243** associated PMM targeting CTA and/or IND in 2025; ARCUS can be further developed to target other mitochondrial mutations

PRECISION
BIOSCIENCES

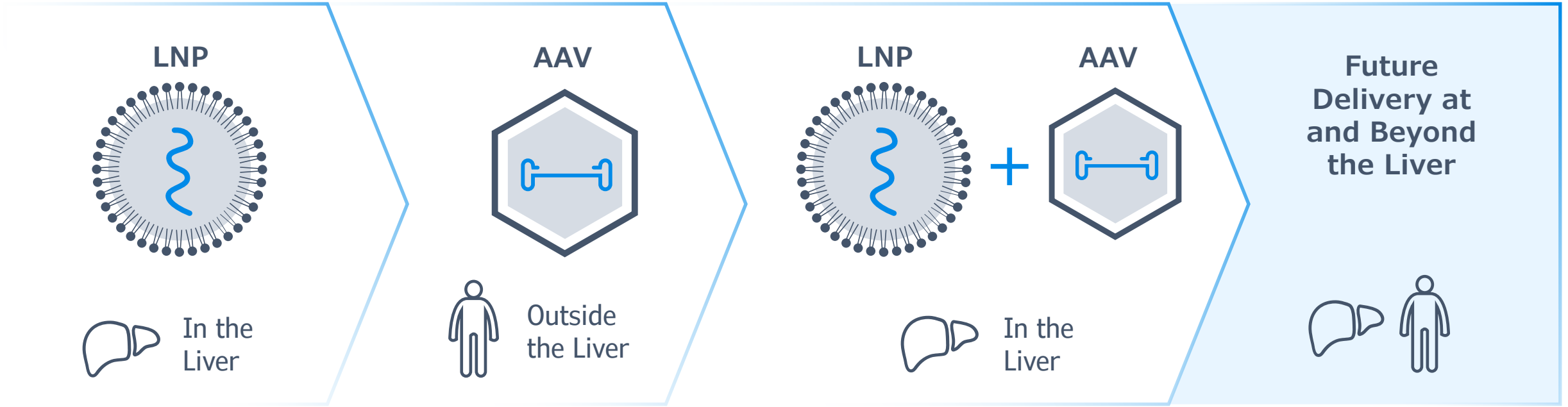
Chapter 3: Road To HDR Gene Insertion & Replacement

Back to Menu

Derisking Through Internal Program Development, Delivery, and Select Partners

Current Program Development

Future HDR Gene Insertion/Replace Program



Leveraging PBGENE-HBV and partnered program learnings utilizing optimized LNP

Leveraging PBGENE-PMM and partnered AAV-based programs to derisk ongoing and future insertion programs

Demonstrated POC:
- Gene Insertion (in vivo ✓)
- Gene Replace (in vitro ✓)

★ **Novel Delivery vehicles under exploration to enable HDR-insert & replace to all tissues of body**

ARCUS HDR Gene Insertion Validated by Big Pharma and Biotech Partners

2020

Prevail THERAPEUTICS
A Wholly Owned Subsidiary of Eli Lilly and Company

Key Accomplishments

- AAV + LNP delivery for gene insertion in liver
  - Achieved 45% gene insertion[1]; 3x higher than CRISPR[2]

2021

ECURE

Key Accomplishments

- Robust in vivo liver insertion data with ~20% insertion across all ages
- Stable gene insertion > 1 year
- CTA (Australia) for OTC program accepted in Dec 2023

2022

NOVARTIS

Key Accomplishments

- Novel approach to bring sophisticated edits beyond the liver
  - Gene insertion in hematopoietic stem cells in vivo

1. 45% gene insertion calculated for total liver tissue, much higher if only calculating insertion into hepatocytes
2. ASGCT 2023, poster 926, Regeneron/Intellia, "Targeted Gene Insertion of *Factor 9* as a Potential Durable Treatment for Hemophilia B"

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"

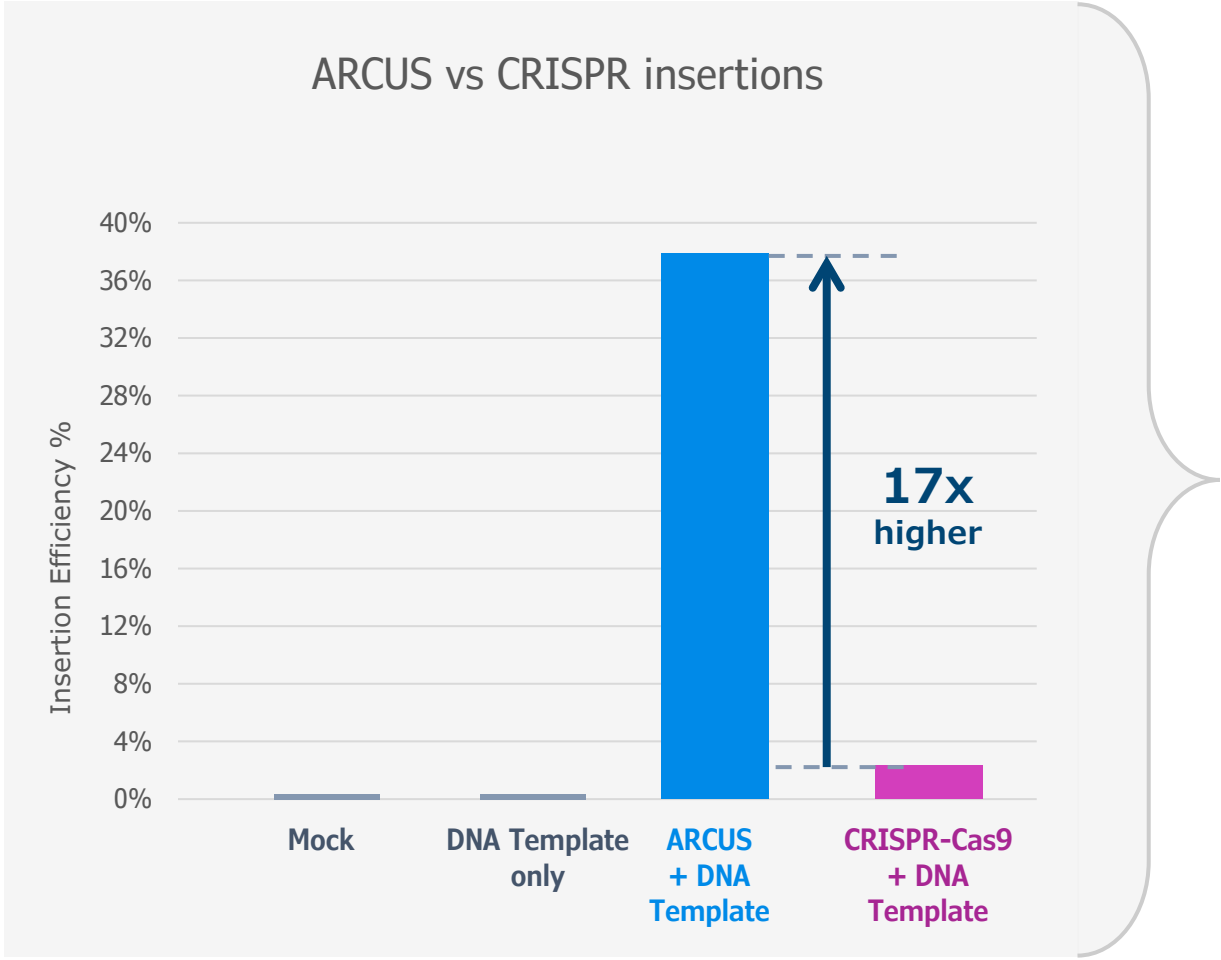
–Broad Institute Patent Filing
USPTO 11643652

"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 Inserted with 17x Higher Efficiency than CRISPR

A true head-to-head comparison



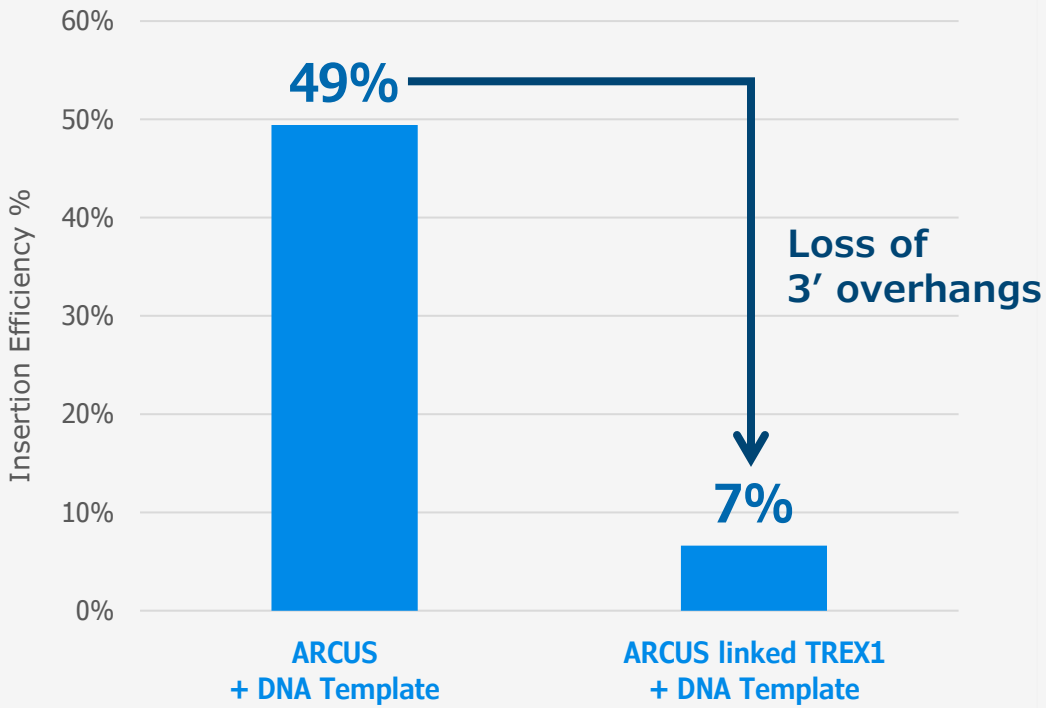
Head-to-head comparison at **same site, same dose,** with **same DNA template.**

ARCUS was More Efficient

Data on file, *in vitro* experiment conducted in primary cells

3’ Overhangs Promoted Insertion Through HDR

Chewing off the 3' overhangs impacts insertion efficiency



- TREX1 removes 3’ overhangs of ARCUS
- TREX1 generates CRISPR-like blunt cuts
- Blunt cut ablates insertion efficiency

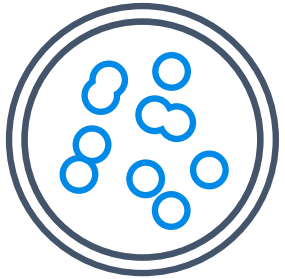
The CUT Matters

Data on file, experiment conducted in HEK293 cells

Gene Insertion Efficiency and Outcomes are Context-Dependent

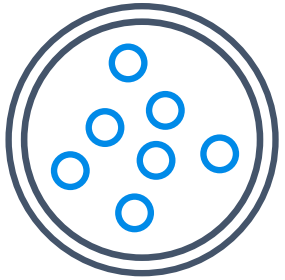
1

Dividing cells in culture



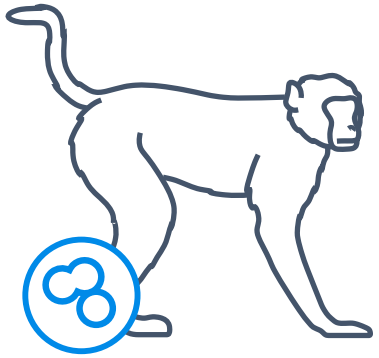
2

Non-dividing, primary cells in culture



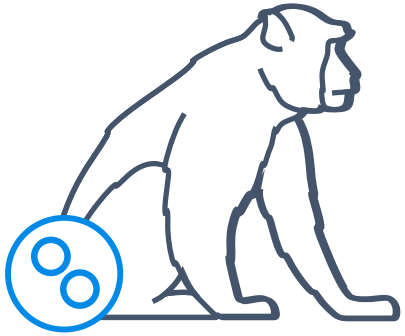
3

Dividing cells in vivo (infant/child)



4

Non-dividing cells in vivo (adults)*

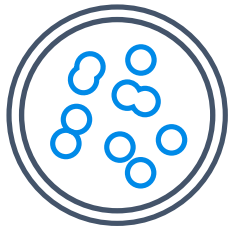


Increasing Level of Evidence & Difficulty

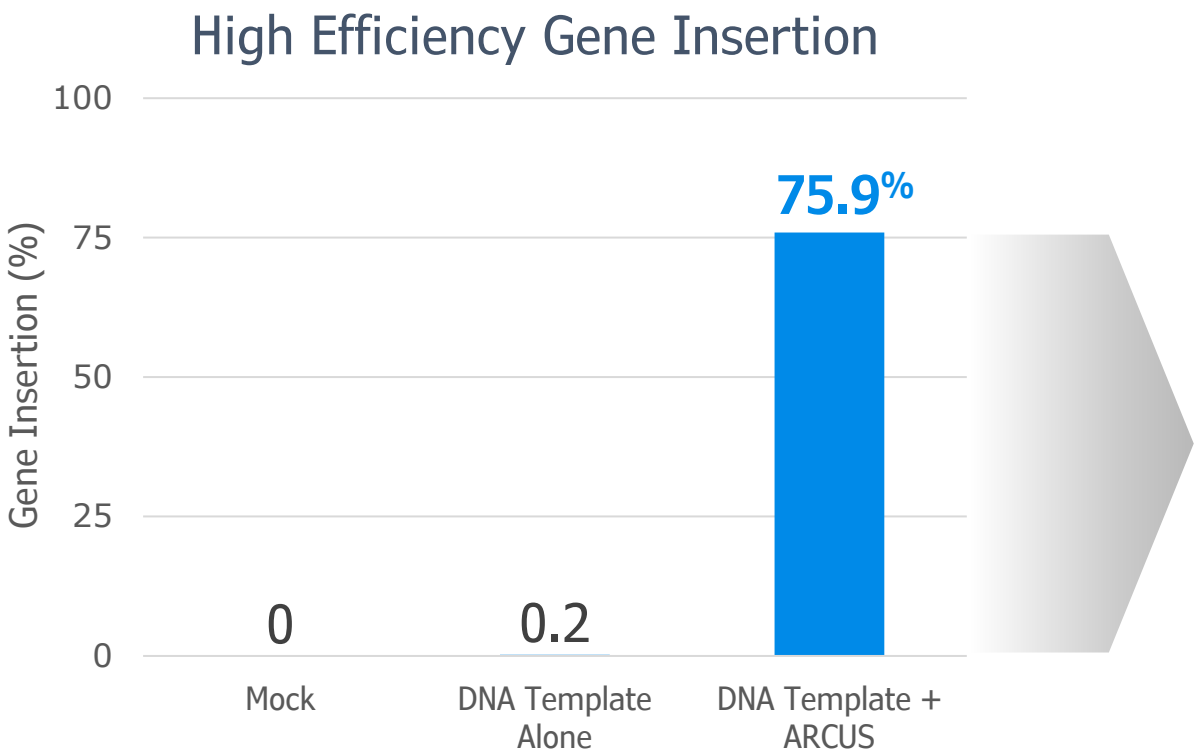
*Note: Data in adult non-dividing NHPs already shared in Cut section of opening slides – on slide 13

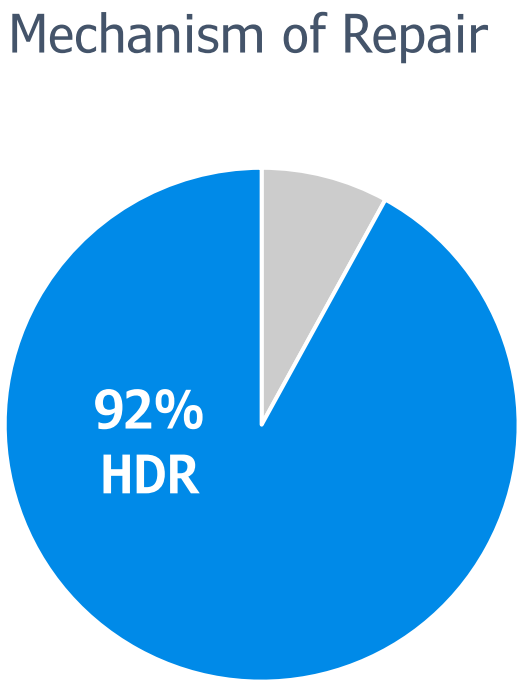
ARCUS Inserted with High Efficiency in Dividing Cells in Culture

1



Dividing cells in culture

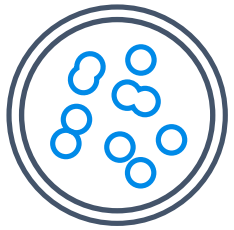




Data on file

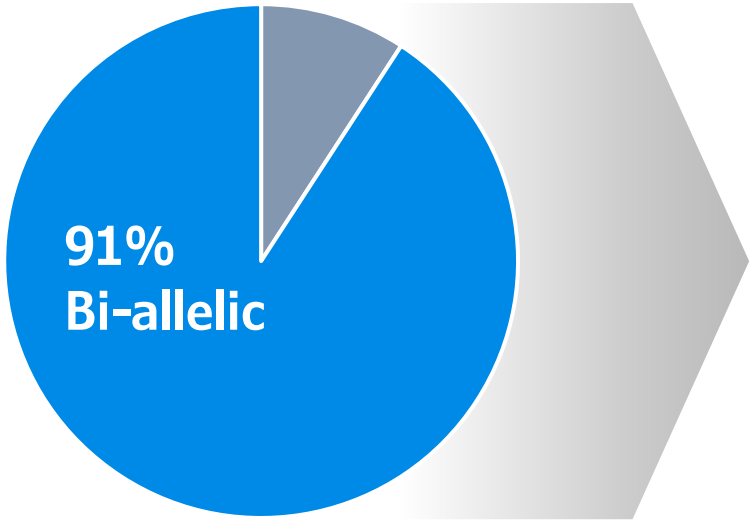
ARCUS Inserts Efficiently in Both Copies of Target Gene Resulting in High Functional Impact - Dividing Cells in Culture

1

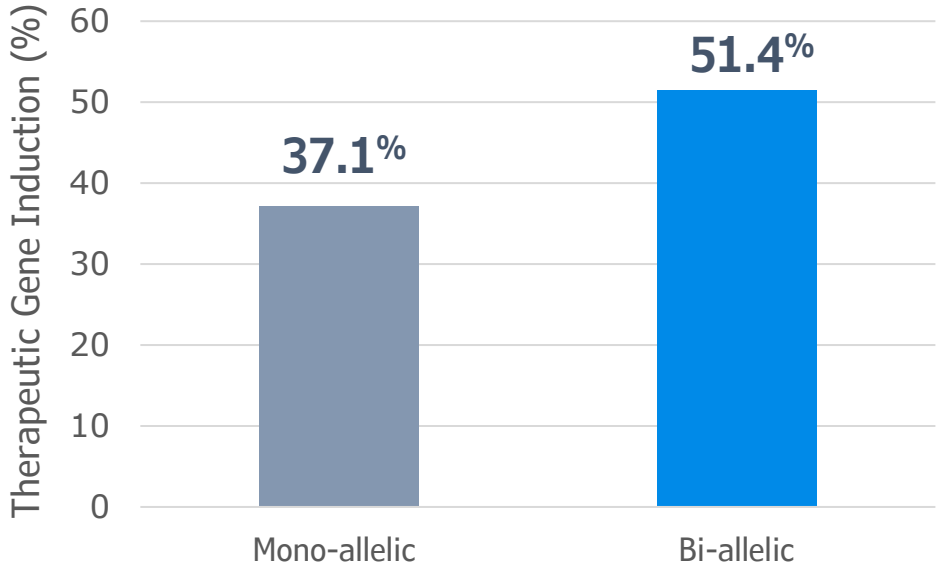


Dividing cells in culture

ARCUS inserts in both alleles*



Bi-allelic editing results in high functional impact

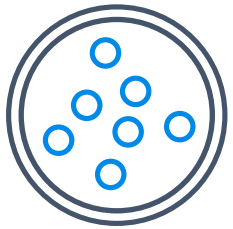


ARCUS Bi-Allelic Insertion Results in Robust Therapeutic Effect

Data on file; *Initial results based on PCR genotyping of single clones, sequencing confirmation in progress; based on cells with insertions.

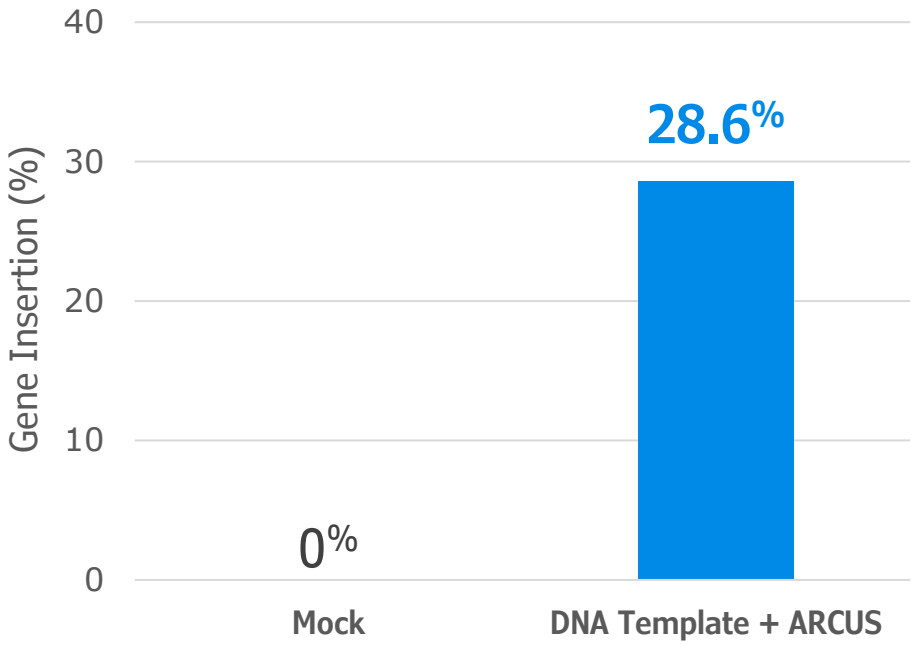
ARCUS Inserts Efficiently in Non-Dividing Cells - in Culture

2

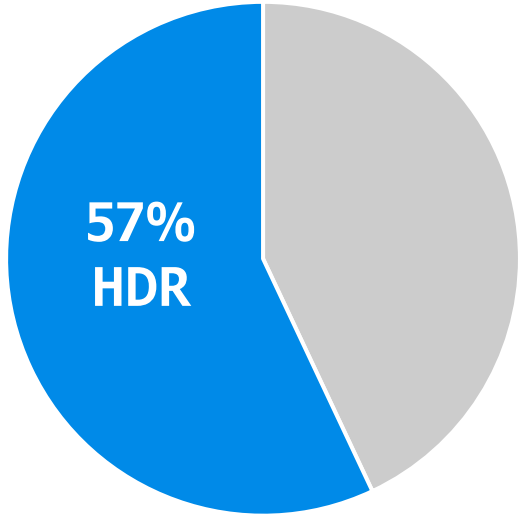


Nondividing primary cells in culture

High Efficiency Gene Insertion



Mechanism of Repair



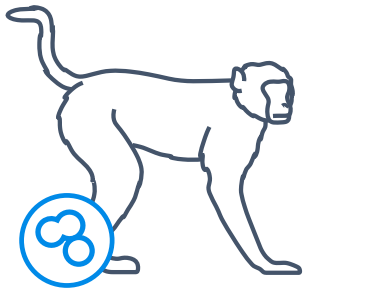
ARCUS Ability to Insert by HDR in Non-Dividing Cells is Attributable to the Unique 3' Overhang Cut

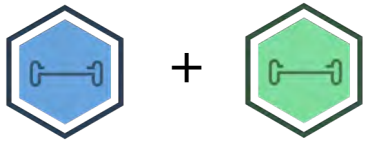
Data on file, experiment conducted in primary human hepatocytes

ARCUS Inserts with High Efficiency in Infant Nonhuman Primates; Sustained Effect Demonstrated at 12 months

3

Dividing cells in vivo

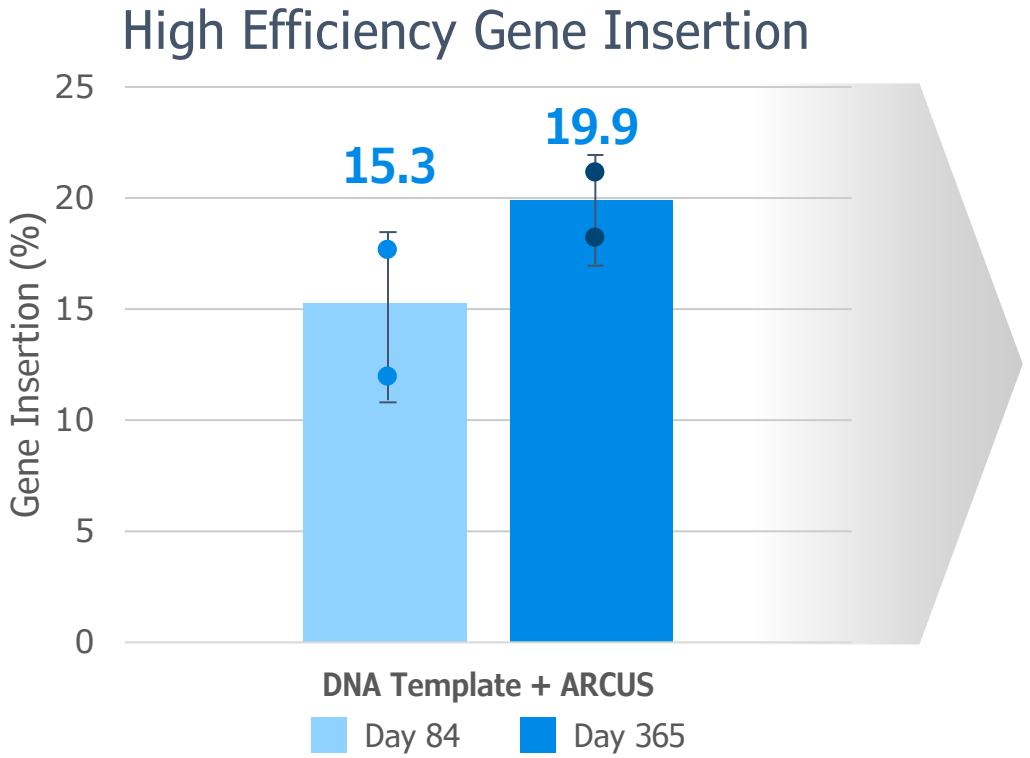


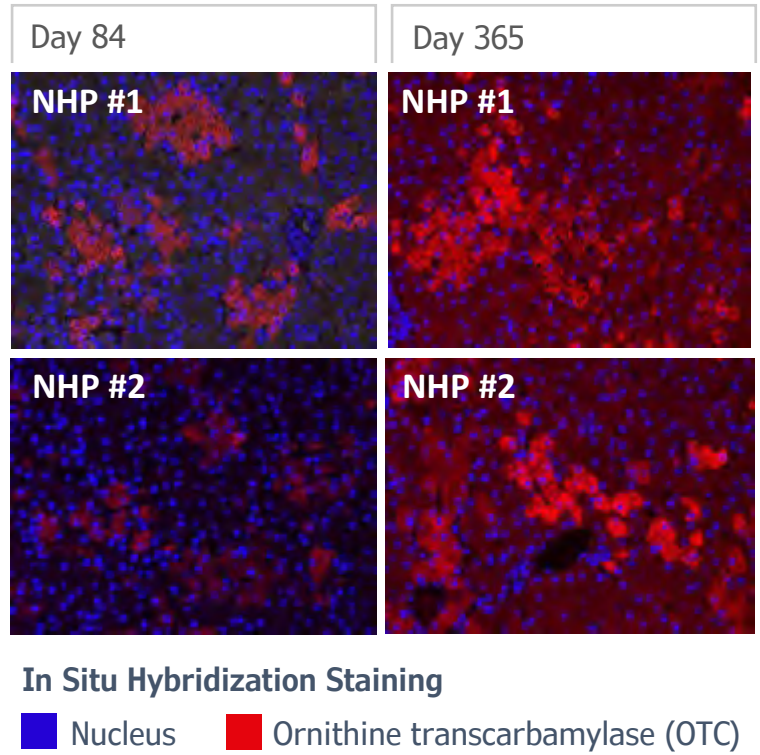


ARCUS AAV
1e13 vg/kg

\+

DNA Template AAV
3e13 vg/kg





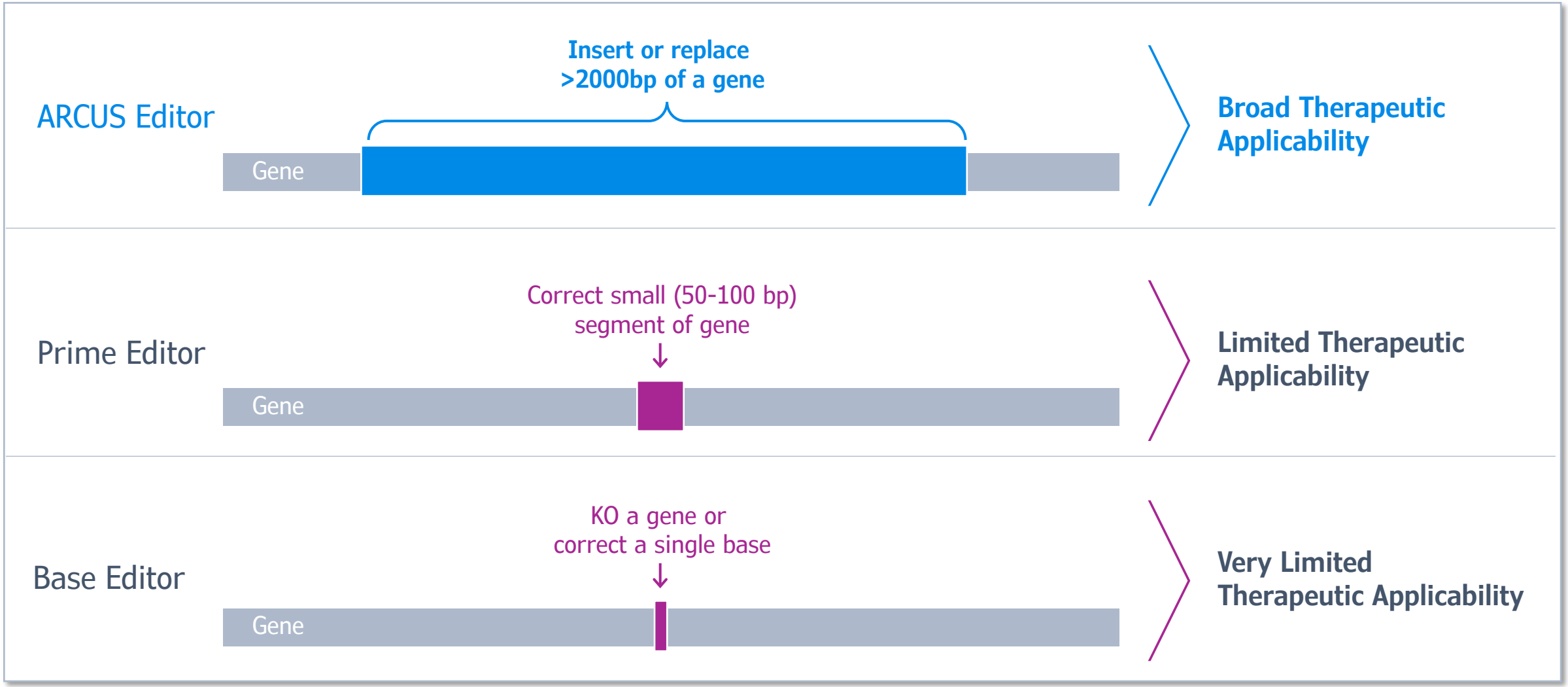
ARCUS is Ideal for Therapeutic Gene Insertion

- ✓ High efficiency insertion rates
- ✓ High HDR observed
- ✓ Biallelic editing demonstrated

Designed to Increase Therapeutic Effect

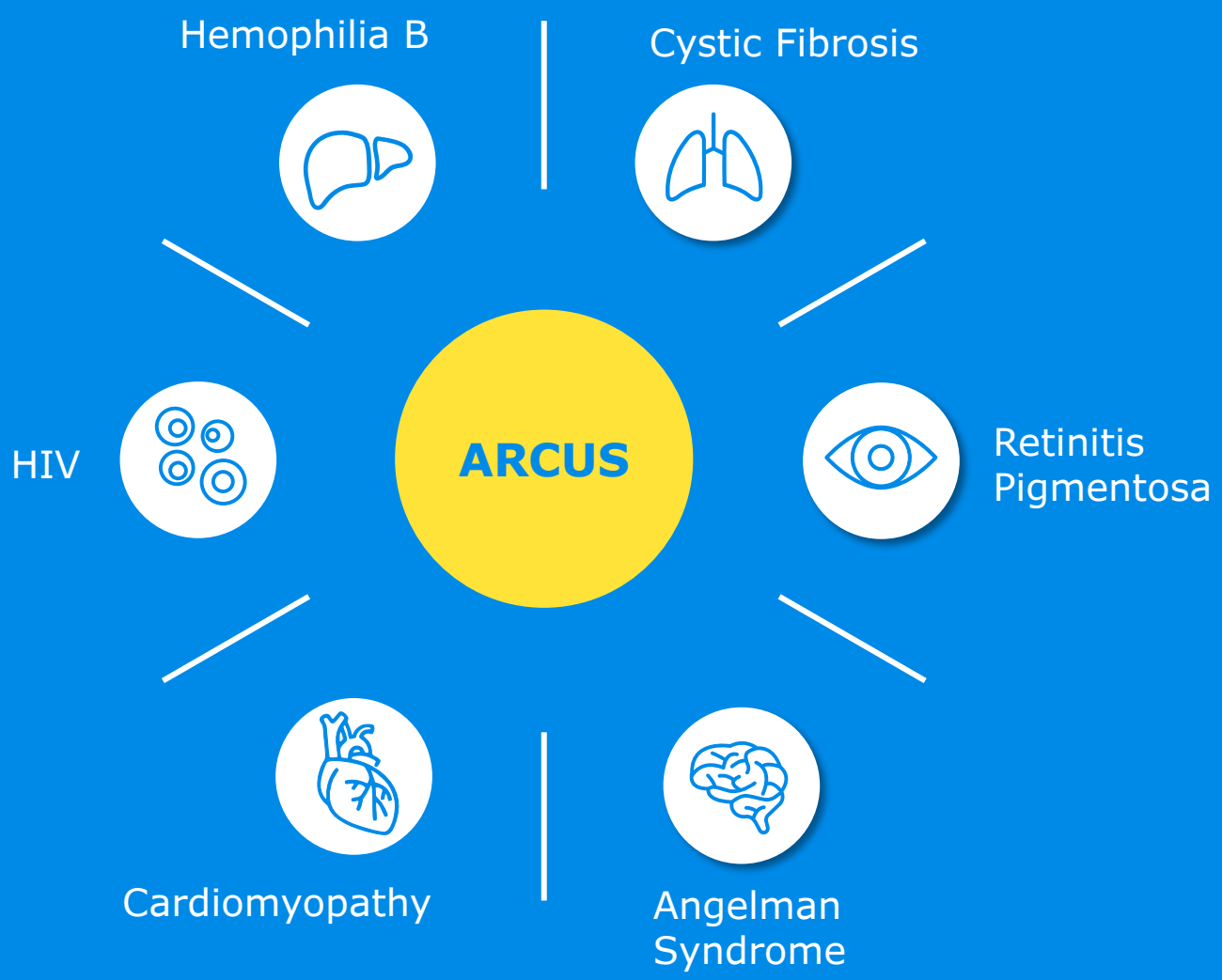
★ **Breadth in Level of Evidence Demonstrating Insertion in Dividing and Non-Dividing Cells In Vitro and In vivo**

Therapeutic Breadth: ARCUS is Best Suited to Insert or Replace Genes



Note: Prime is investigating approaches utilizing recombinases to insert up to 5kb, however delivery challenges expected given large nuclease size as well as low editing efficiency utilizing recombinases

Back to Cut | Back to Safety

Examples of Opportunities for Gene Insertion & Replacement Through HDR

ARCUS can unlock Gene Insertion & Replacement through HDR across a broad range of tissue types at the Liver and beyond