PRECISION BIOSCIENCES

Virtual Gene Editing R&D Event

September 9, 2021

Forward Looking Statements

This presentation (together with any other statements or information that we may make in connection herewith) may contain forward-looking statements. All statements other than statements of present and historical facts contained in this prospectus, including without limitation, statements regarding our future results of operations and financial position, business strategy and approach, including related results, prospective products, planned preclinical or greenhouse studies and clinical or field trials, including expected release of data and dosage exploration, capabilities, including expected production levels and manufacturing timeframes, of our manufacturing facility, management's expectations regarding pipelines and milestones for product candidates and our food editing platform, and timing and likelihood of success, as well as plans and objectives of management for future operations, may be forward-looking statements. Without limiting the foregoing, the words "aim", "anticipate," "believe," "could," "expect," "should," "plan," "intend," "estimate," "target," "may," "will," "would," "potential," the negative thereof and similar words and expressions are intended to identify forward-looking statements. These forward-looking statements reflect various assumptions of Precision's management that may or may not prove to be correct. No forward-looking statement is a guarantee of future results, performance, or achievements, and one should avoid placing undue reliance on such statements.

Forward-looking statements are based on management's current expectations, beliefs and assumptions and on information currently available to us. Such statements are subject to a 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 and requirements under our current debt instruments; 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 dependence on our ARCUS technology; the initiation, cost, timing, progress, achievement of milestones and results of research and development activities, preclinical or greenhouse studies and clinical or field trials; public perception about genome editing technology and its applications; competition in the genome editing, biopharmaceutical, biotechnology and agricultural biotechnology fields; our or our collaborators' ability to identify, develop and commercialize product candidates; pending and potential 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' ability to obtain and maintain regulatory approval of our product candidates, and any related restrictions, limitations and/or warnings in the label of an approved product candidate; our or our collaborators' 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; our ability to achieve our anticipated operating efficiencies at our manufacturing facility; delays or difficulties in our and our collaborators' ability to enroll patients; if our product candidates do not work as intended or cause undesirable side effects; risks associated with applicable healthcare, data 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 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 scientific and management personnel; market and economic conditions; effects of natural and manmade disasters, public health emergencies and other natural catastrophic events effects of the outbreak of COVID-19, or any pandemic, epidemic or outbreak of an infectious disease; insurance expenses and exposure to uninsured liabilities; effects of tax rules; risks related to ownership of our common stock and other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2021, as any such factors may be updated from time to time in our other filings with the SEC, and accessible on the SEC's website at www.sec.gov and the Investors & Media page of our website 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 do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

This presentation may also contain estimates, projections, and/or other information regarding our industry, our business and the markets for certain of our product candidates, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, clinical trials, studies and similar data prepared by market research firms and other third parties, from industry, medical and general publications, and from government data and similar sources. Information that is based on estimates, forecasts, projections, market research, or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information.

1

PRECISION & VERSATILITY

ARCUS has the potential to address a broader spectrum of genetic diseases

2

3 INDs/CTAs in **3** YEARS

Program	Indication	Delivery	Research	Candidate Selection	IND-Enabling	Expected IND/CTA
PBGENE-PCSK9	Familial Hypercholesterolemia	AAV				2022
PBGENE-PH1	Primary Hyperoxaluria Type 1	LNP				2023
PBGENE-HBV	Chronic Hepatitis B	LNP				2024

3

ECURE

NEW Collaboration focused on gene insertion & accelerating clinical validation of ARCUS

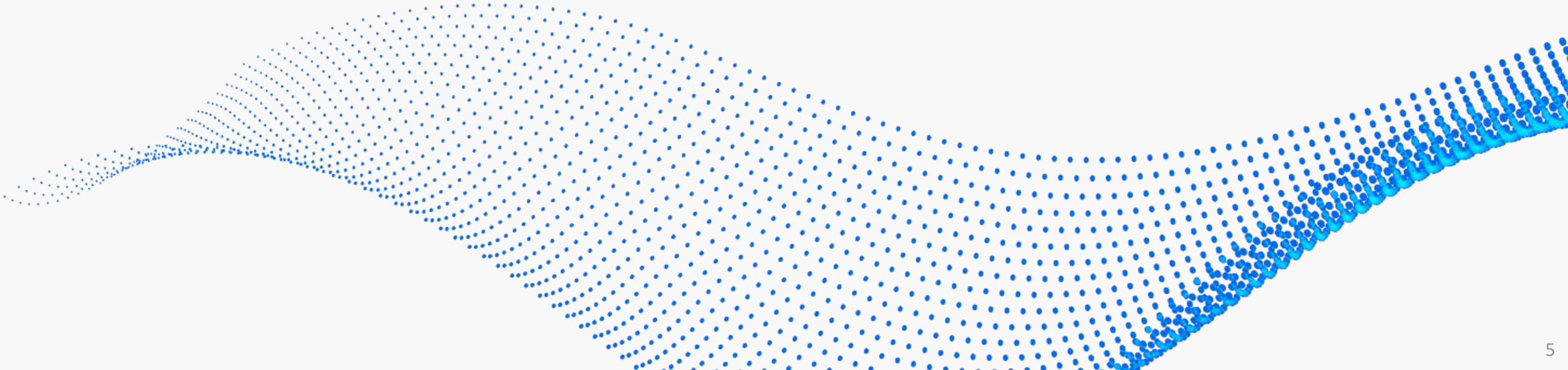
AGENDA:

Intro to ARCUS
for *in vivo* Gene Editing

Gene Editing Pipeline
& Strategy

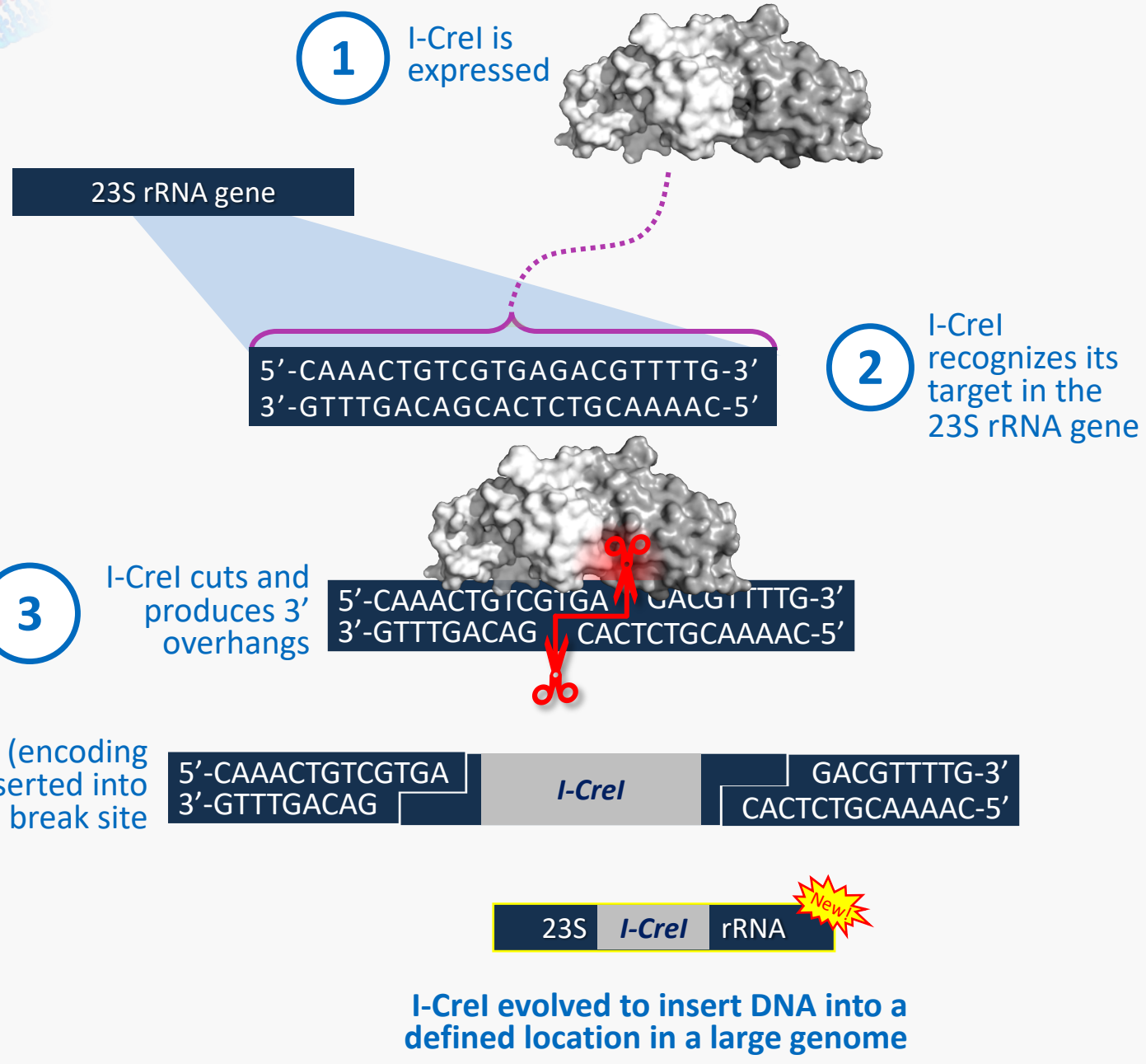
The Next Frontier

INTRO TO ARCUS
FOR *in vivo* GENE EDITING




Chlamydomonas reinhardtii

ARCUS is derived from **I-CreI**, a homing endonuclease from algae evolved for precise genome editing.



I-CreI evolved to insert DNA into a defined location in a large genome

ARCUS: Custom Engineered from I-CreI

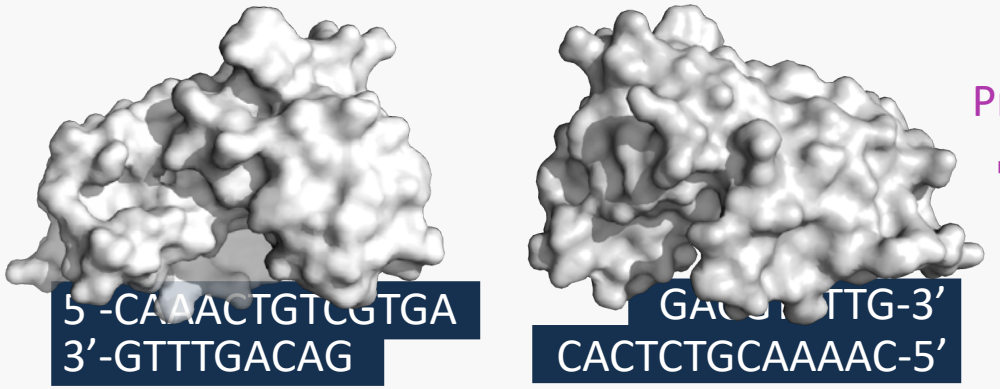
I-CreI can be redesigned to edit new DNA sequences

I-CreI

(Homodimer)

monomer 1

monomer 2



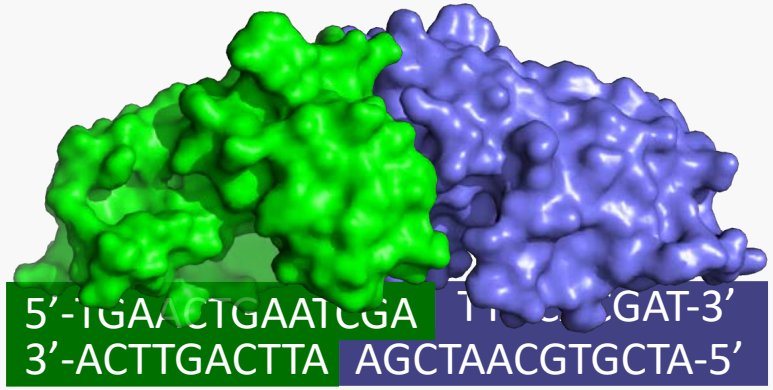
“Left” half of natural target

“Right” half of natural target

Protein Engineering

ARCUS

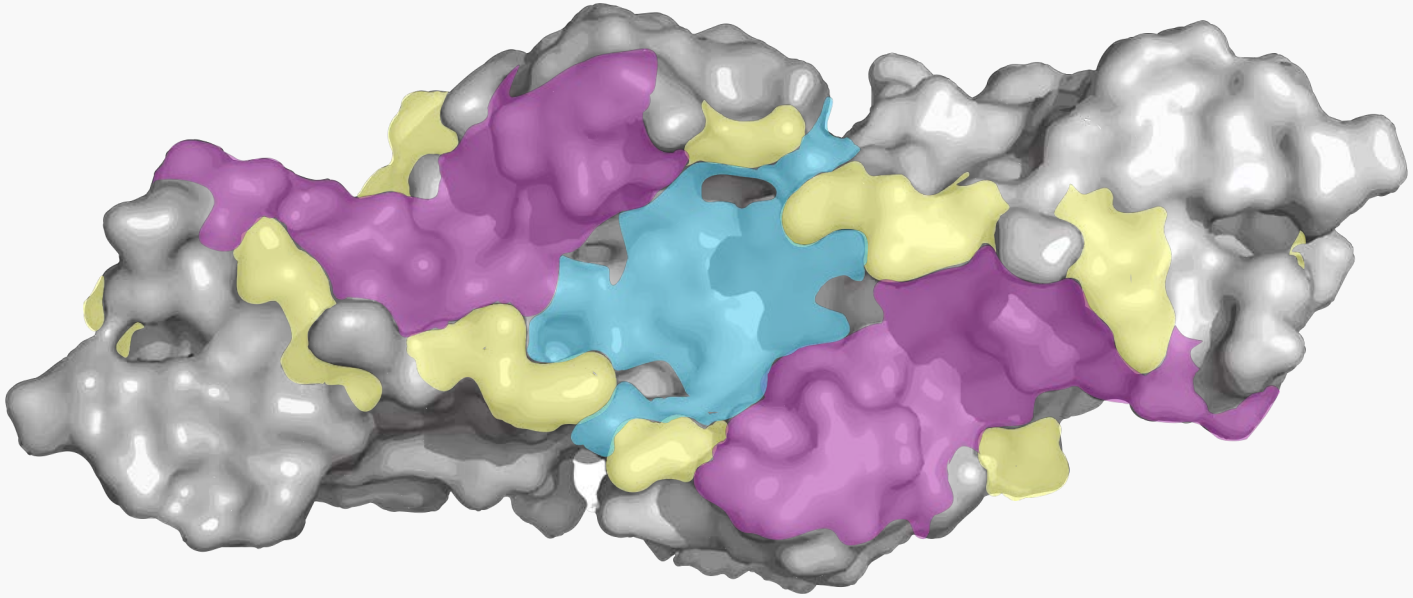
(Single Chain)



“Left” half of new target “Right” half of new target

Creating and Optimizing ARCUS Nucleases

The DNA-binding surface of I-CreI can be extensively re-engineered to produce each new ARCUS nuclease



Controls Efficiency

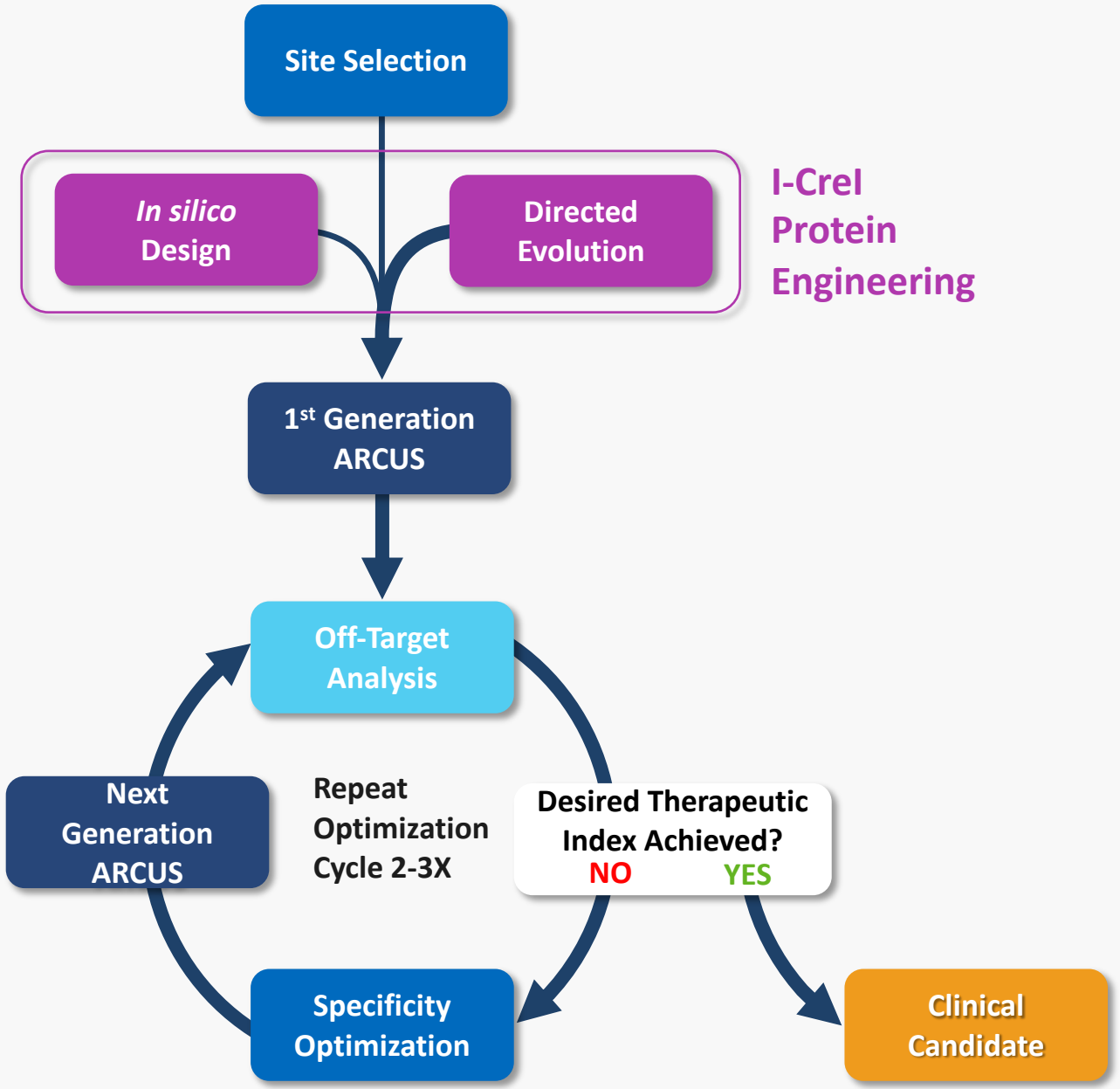
Controls Specificity

Controls Affinity

Creating and Optimizing ARCUS Nucleases

Lead Generation

Lead Optimization



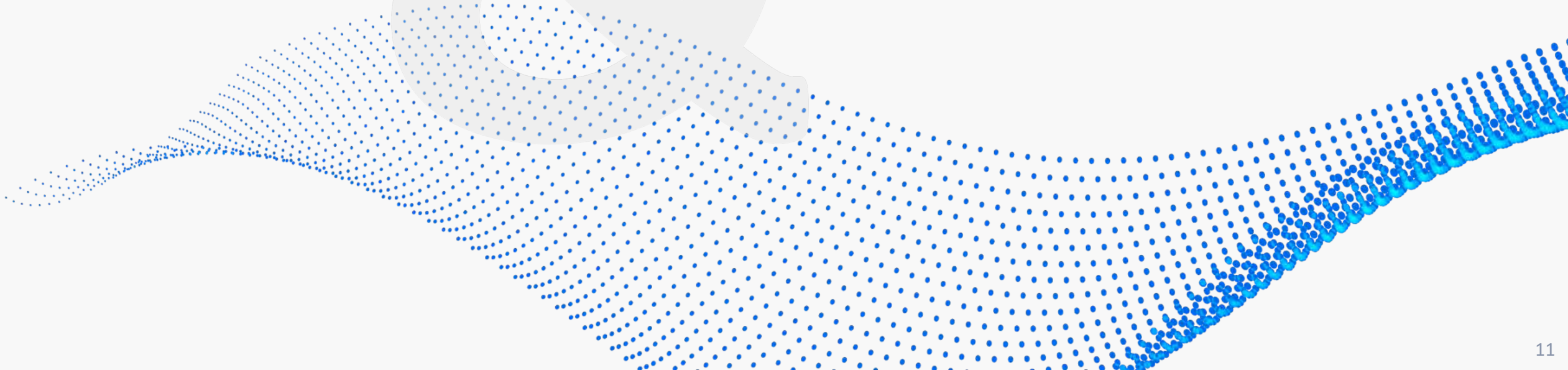
PRECISION

- Safety
- Specificity

&

VERSATILITY

- ARCUS is Easy to Deliver
- ARCUS Performs Complex Edits
  (Gene Insertion & Gene Repair)

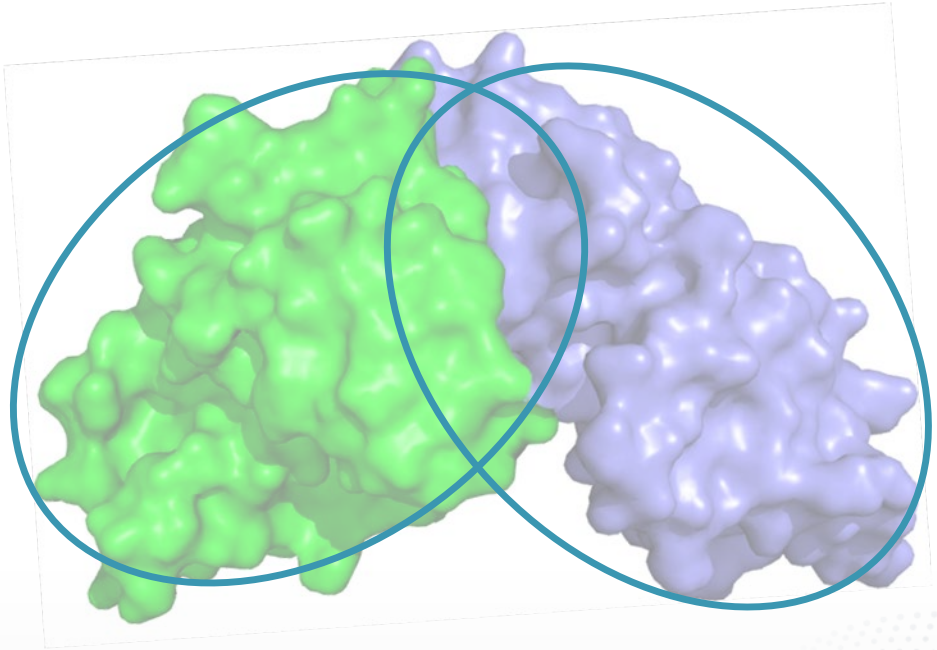


Safety and Specificity

ARCUS is inactive until it binds to its target DNA site

This allows ARCUS to be expressed for extended periods of time without accumulating off-target gene edits.

Inactive Form of ARCUS
closed configuration buries the active site inside the protein

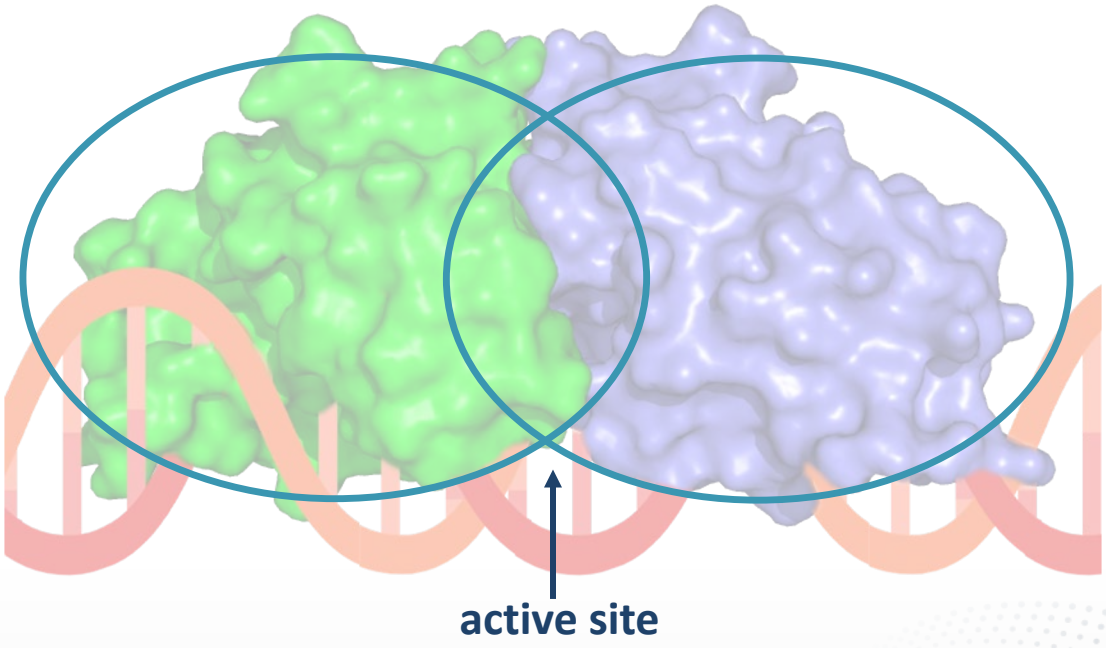


Safety and Specificity

ARCUS is inactive until it binds to its target DNA site

This allows ARCUS to be expressed for extended periods of time without accumulating off-target gene edits.

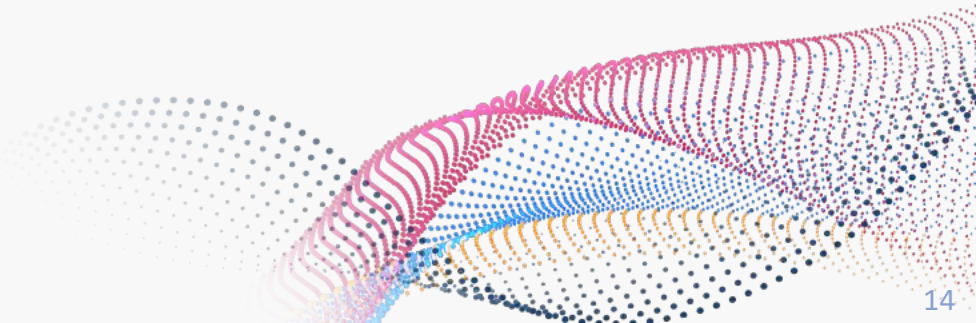
Active Form of ARCUS
open configuration allows the active site to access DNA



Safety and Specificity

Off-target editing: Detection is the challenge

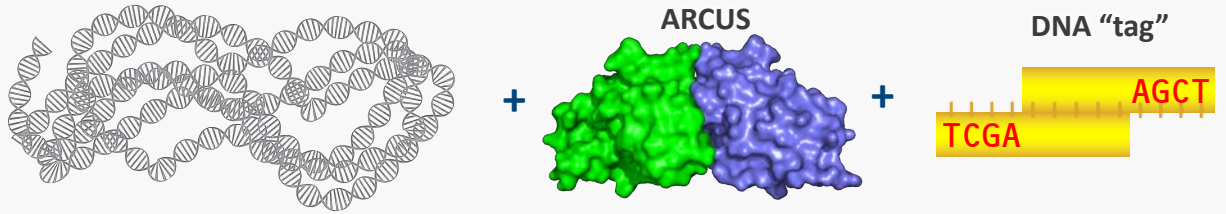
- The number of off-target sites identified is a function of how well they can be detected.
- Off-target sites are very difficult to detect for most editing platforms.
- If you can detect better, you can engineer a better editing enzyme.



Safety and Specificity

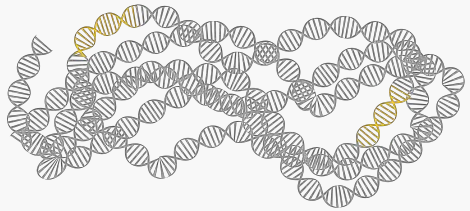
Oligo Capture: a genome-wide assay for ARCUS off-target editing

Step 1: Transfect cells with ARCUS and a DNA “tag”



Step 2: The “tag” is captured at DNA breaks resulting from ARCUS cleavage

Step 3: Genomic DNA is isolated from cells and evaluated on a next-gen sequencer to identify all sites where the “tag” was captured



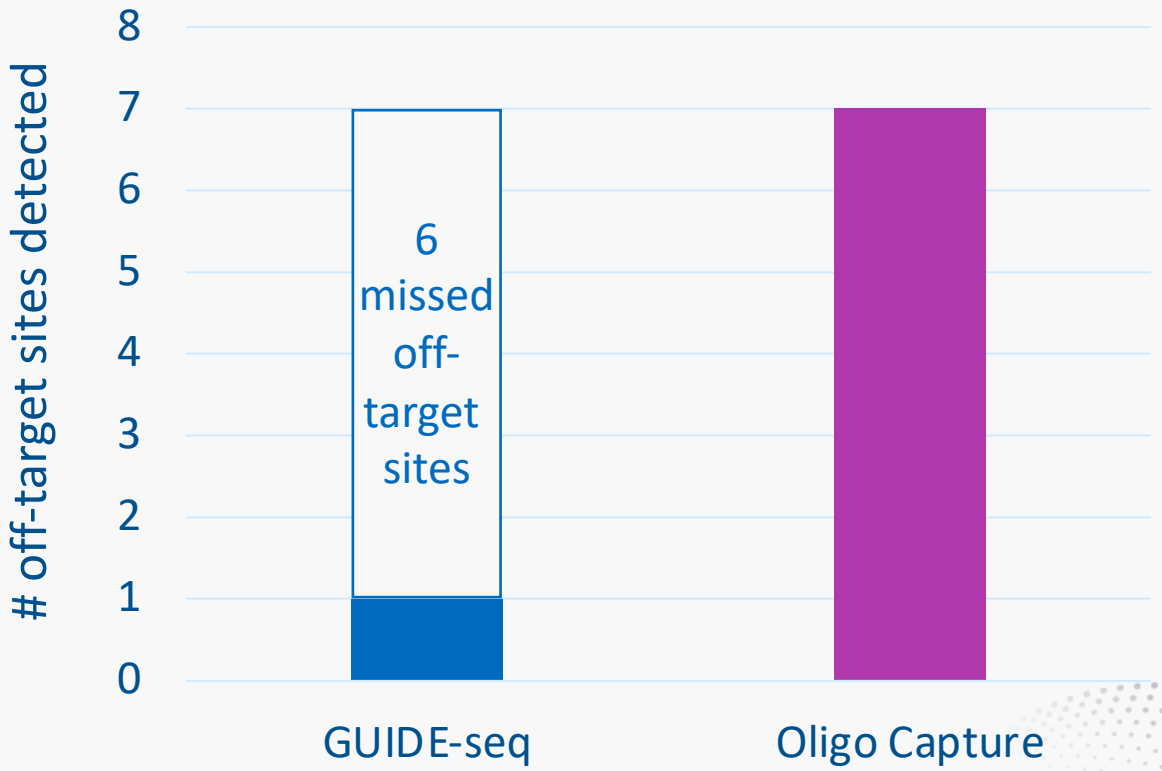
Step 4: Sites of on- and off-target capture of the DNA “tag” are identified and deep sequenced to confirm editing

ATGCTAGCTAGCTAGCTGATCGATGCTAGCTAGCTAGCTA
GTAGCTAGTAAGCTGATCGTAGCTGCCGCTGCTAGCTGA
TGCGCTAGTAGCTGCTAGTCGCTAGTCGGCAGTCGATGC
TGCTAGCTAGTAGCTGCATGCTAGCTAGTGTGTCGATGT

Safety and Specificity

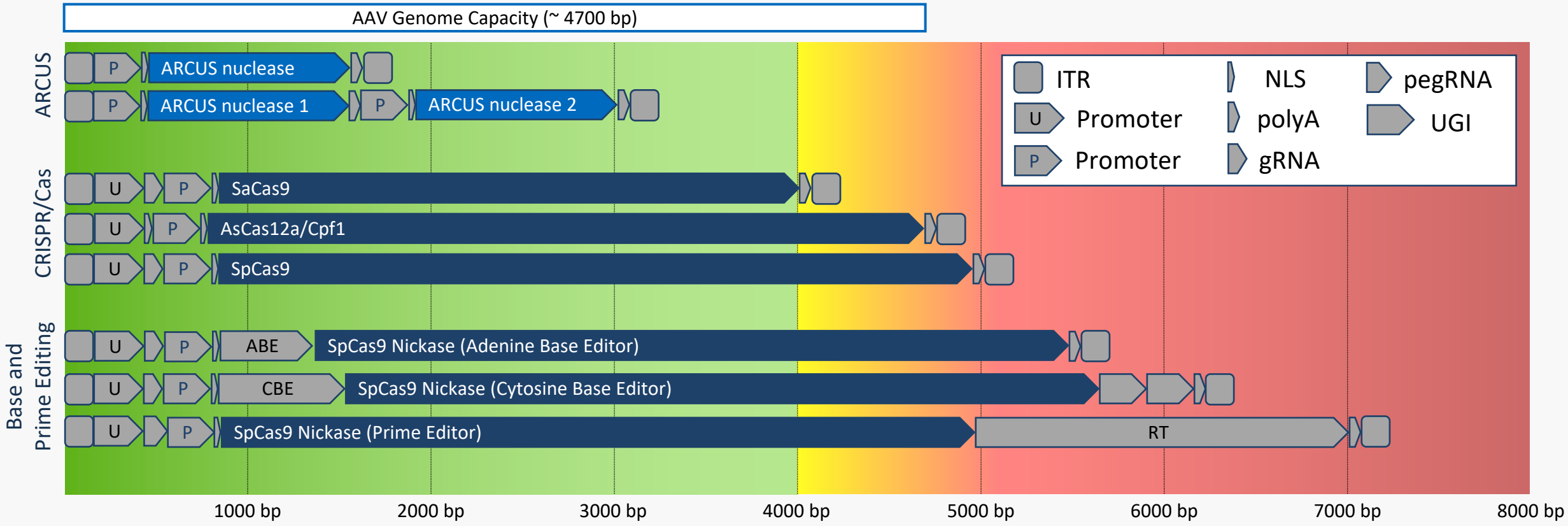
Oligo Capture has been shown to be far more sensitive than assays developed for CRISPR

Wang, *et al.* (2018 *Nat. Biotechnol.* **36**(8):717-725) used both Oligo Capture and GUIDE-seq (the "gold standard" method for CRISPR) to locate sites of off-target editing in non-human primates treated with a PCSK9-targeting ARCUS. **GUIDE-seq correctly identified one off-target site. Oligo Capture correctly identified seven off-target sites.**



ARCUS Is Easy to Deliver

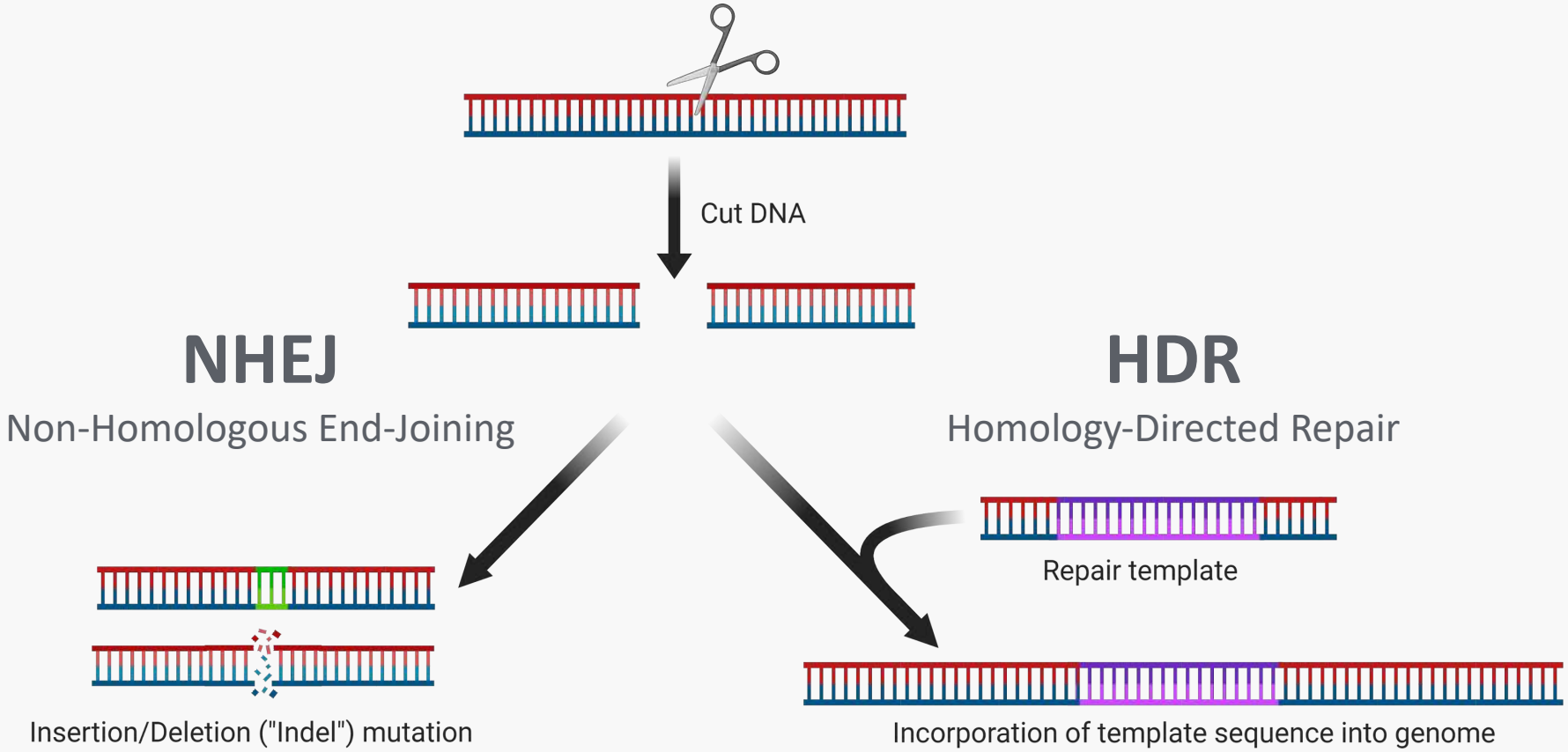
The small size of ARCUS makes it compatible with single AAV delivery



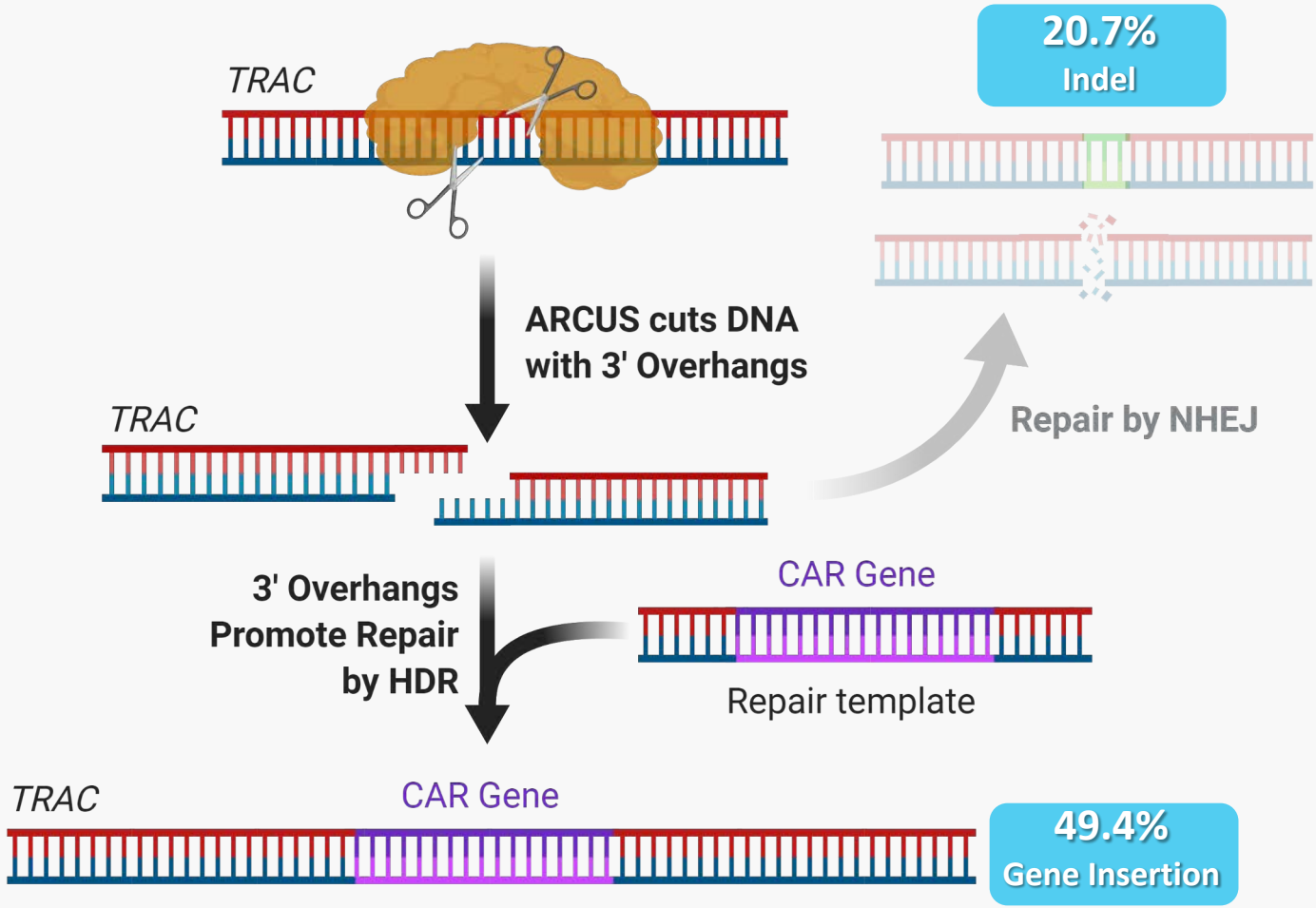
Sizes obtained from: WO 2020/236982 – SpCas9, SpCas9 Nickase, SaCas9, UGI; WO 2018/195545 – AsCas12a; WO 2020/160514 – CBE; US 2021/0130805 – ABE; WO 2020/191242 – RT, pegRNA; WO 2015/138510 – U6

DNA Cuts Can Be Repaired by Either NHEJ or HDR.

Complex gene insertion or gene repair edits require HDR.



ARCUS Performs Complex Edits



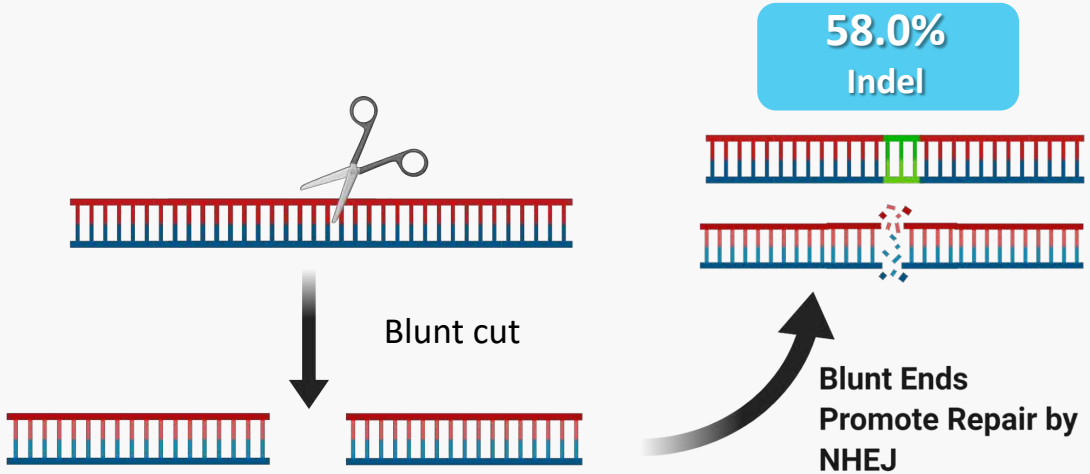
Precision BioSciences' CAR T Engineering Process

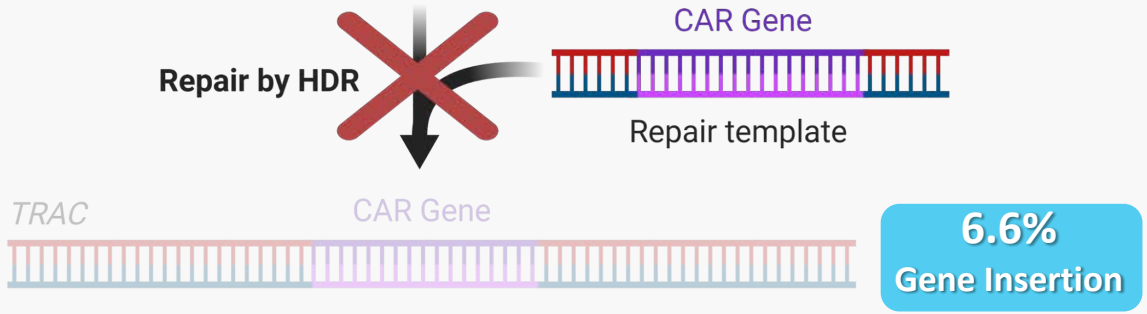
ARCUS Promotes HDR

Cuts made by ARCUS have 3' overhangs and are repaired primarily via HDR

This enables complex edits like gene insertion

Blunt Cuts are Repaired Primarily via NHEJ





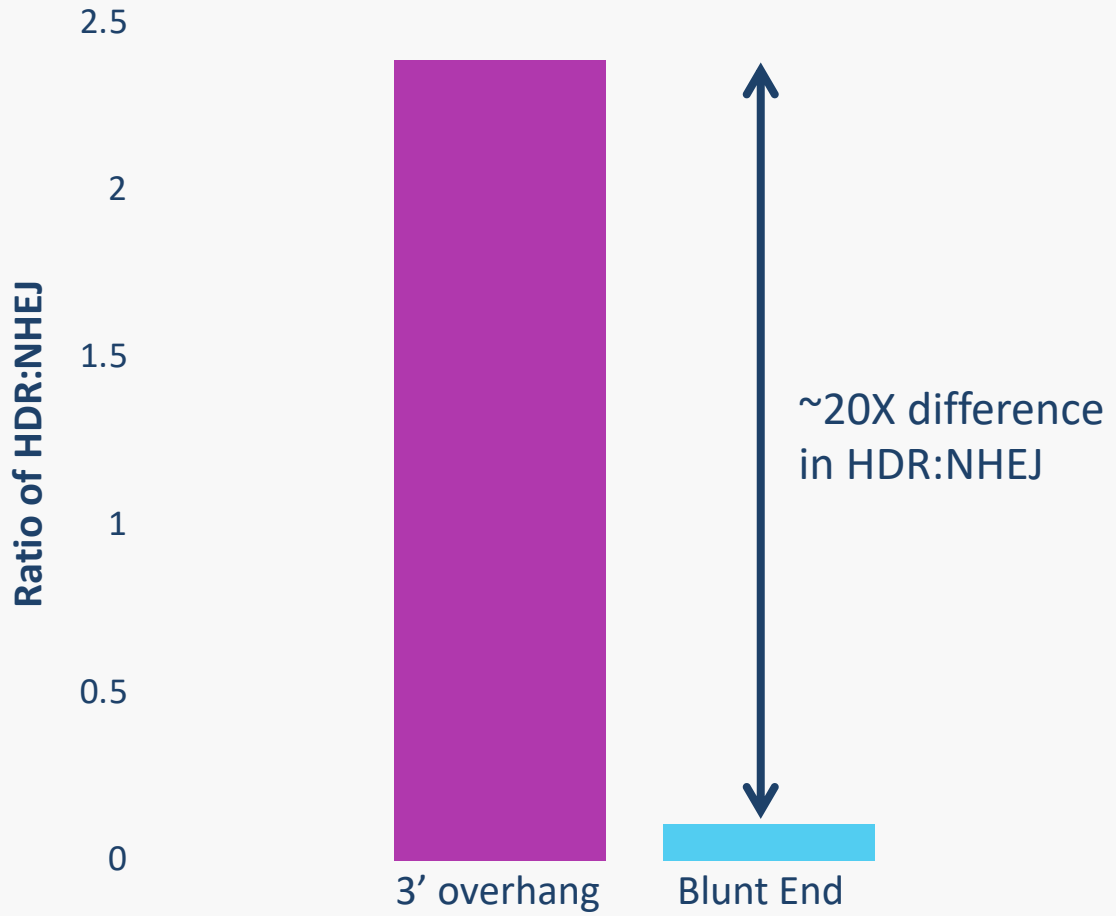
3’ overhangs are necessary for efficient HDR

ARCUS Performs Complex Edits

HDR:NHEJ Ratio

The 3’ overhangs created by ARCUS very significantly shift the ratio of HDR:NHEJ to favor HDR

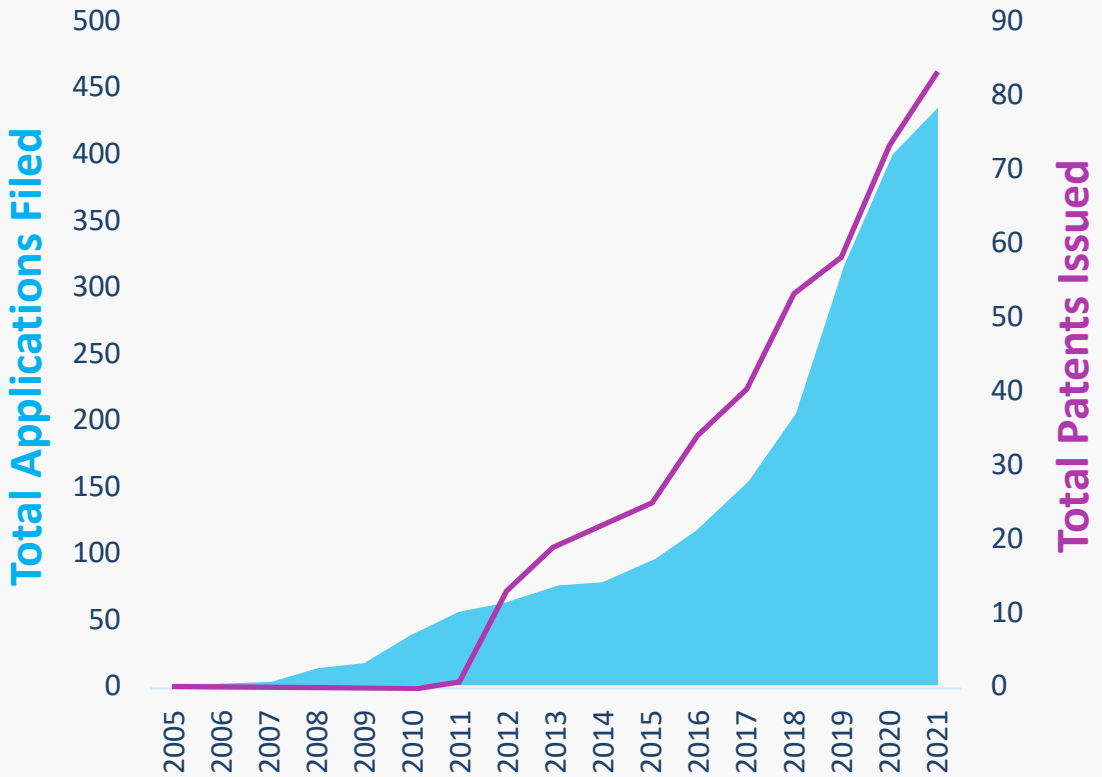
We believe ARCUS is the ideal tool for gene insertion and repair.



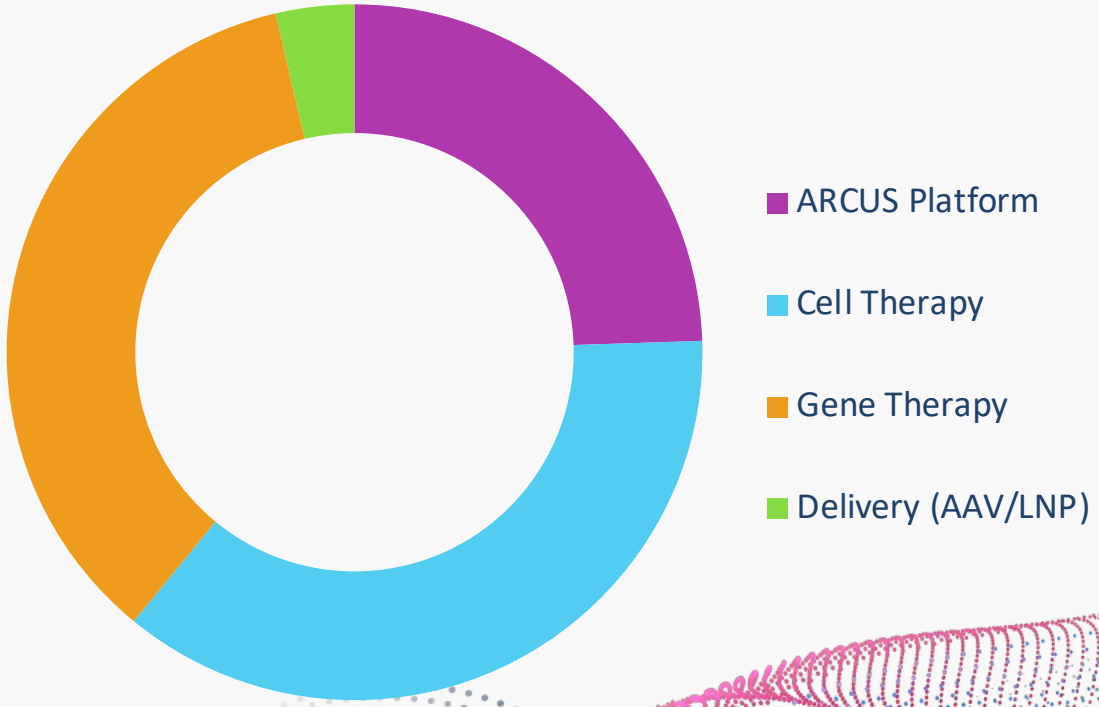
Intellectual Property

- Precision BioSciences controls over 80 issued patents related to ARCUS and its applications
- ARCUS platform and nucleases are unencumbered by third-party IP

Applications and Issued Patents by Year

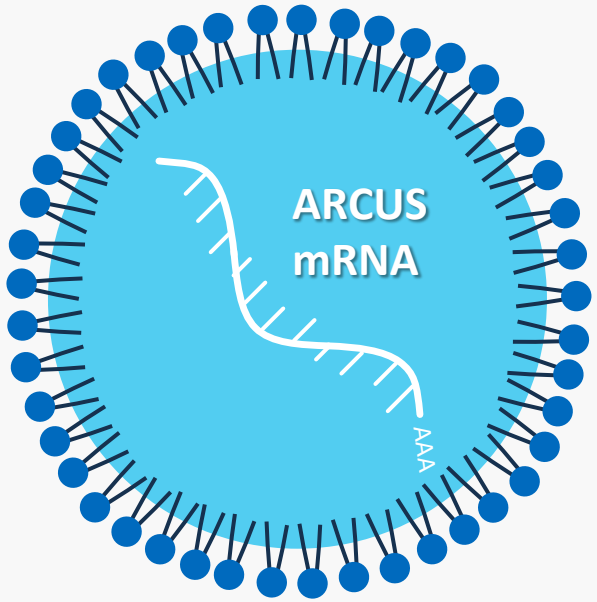


Intellectual Property Distribution



Two In-House Delivery Platforms:
LNP & AAV

LNP
Lipid Nanoparticle:



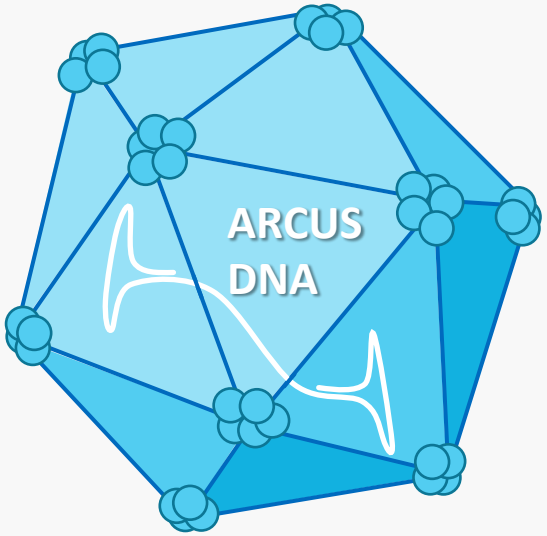
- Efficient delivery to liver
- Short half-life
- No neutralizing antibodies
- Potential to repeat-dose
- Good translation from NHP

ACUITAS * THERAPEUTICS

*Precision has non-exclusive rights to evaluate Acuitas Therapeutics, Inc.'s LNP technology for delivery of ARCUS and the option to develop and commercialize LNP-delivered ARCUS products

Two In-House Delivery Platforms:
LNP & AAV

AAV
Adeno-Associated Virus:



Delivery to other tissues

Deliver HDR donor for knock-in

Established manufacturing

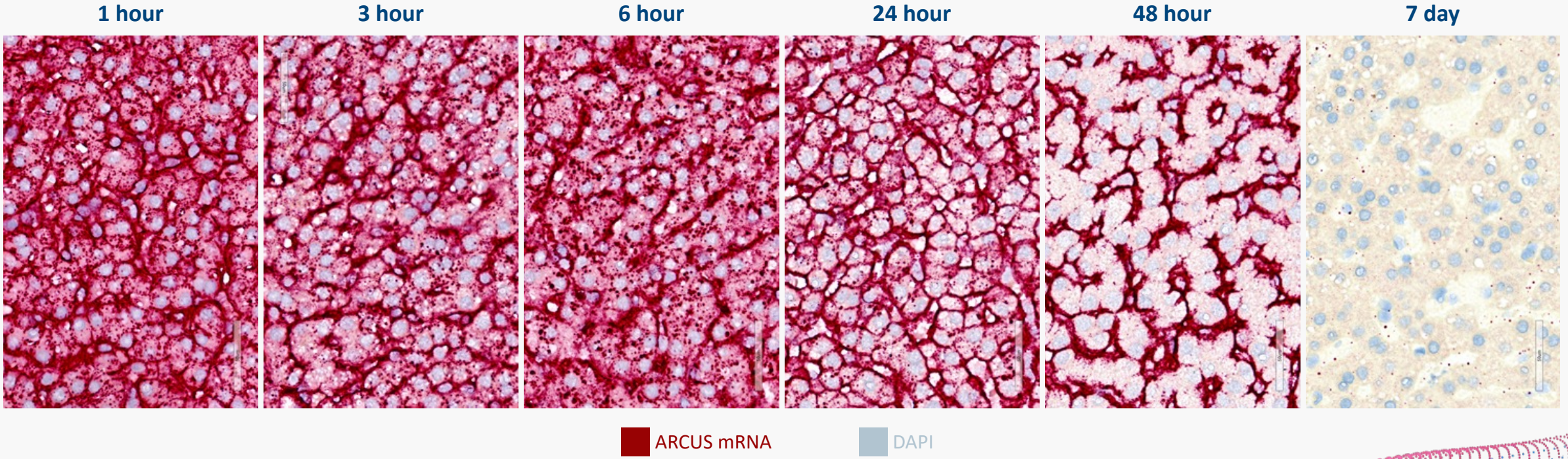
Established regulatory pathway

Promoters localize expression

LNP Biodistribution and Pharmacokinetics

LNP Delivers ARCUS Efficiently to NHP Liver and Dissipates in Days

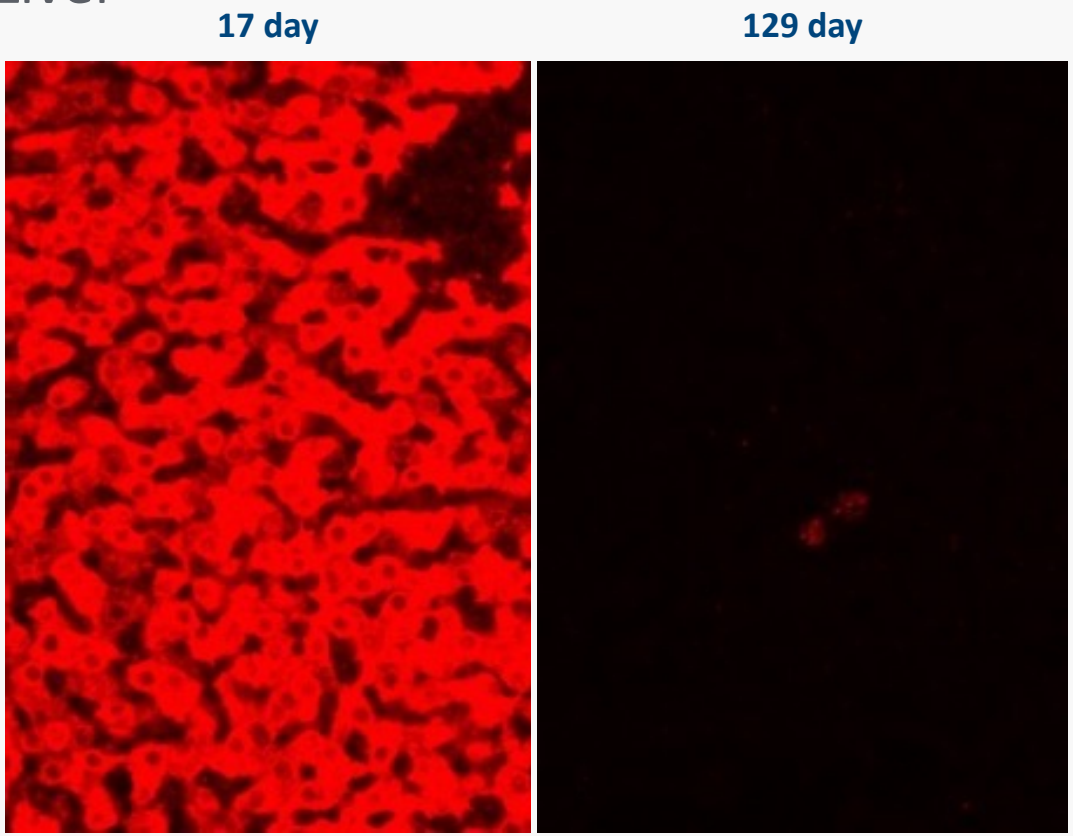
Lipid Nanoparticle (LNP)
2 mg/kg IV



AAV Biodistribution and Pharmacokinetics

AAV Delivers ARCUS Efficiently to NHP Liver and Persists Longer than LNP

Adeno-Associated Virus (AAV)
3e13 vg/kg AAV8 IV



Wang, *et al.* (2018) *Nat. Biotechnol.* **36**(8):717-725

ARCUS mRNA

MCAT: Manufacturing Center for Advanced Therapeutics

17,300 sq. ft. facility in Durham, NC

Fully **cGMP** compliant

CAR T, mRNA, and **AAV platforms**

Currently producing clinical trial material for **CAR T programs**

Directions for Q&A:

To ask a question, please use dial-in conference call numbers

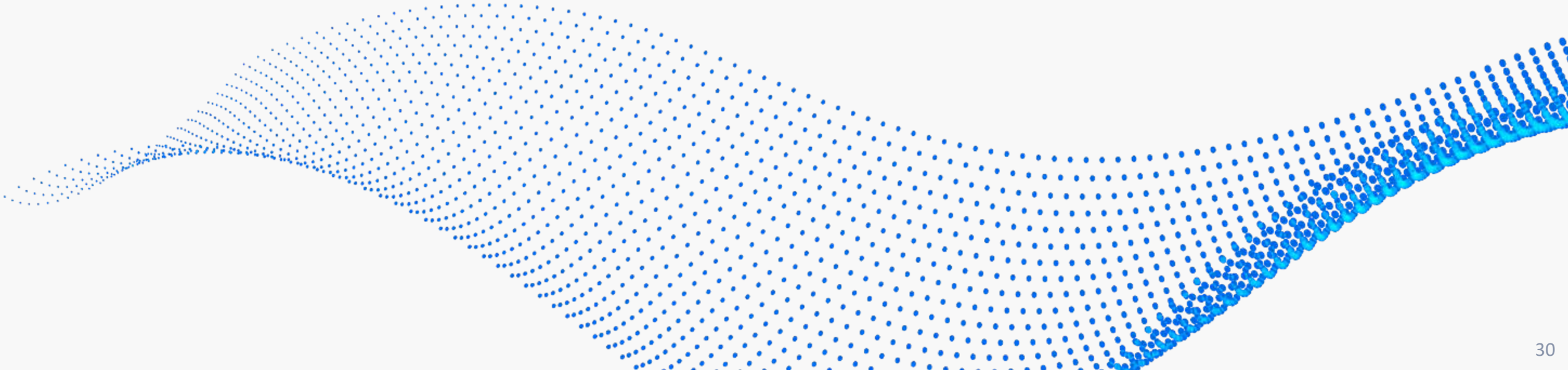
- **(866) 970-2058** DOMESTIC
- **(873) 415-0216** INTERNATIONAL

The conference ID number for the call is **6376435**

When asking a question, **please mute your webcast video.**

ARCUS Q&A

GENE EDITING PIPELINE & STRATEGY



Gene Editing Pipeline

Program	Indication	Tissue	Target	Delivery	Research	Candidate Selection	IND-Enabling	Expected IND/CTA	Partner
PBGENE-PCSK9*	Familial Hypercholesterolemia	Liver	*PCSK9*	AAV				2022	
PBGENE-PH1	Primary Hyperoxaluria Type 1	Liver	*HAO1*	LNP				2023	
PBGENE-HBV	Chronic Hepatitis B	Liver	*HBV*	LNP				2024	
PBGENE-DMD	Duchenne Muscular Dystrophy	Muscle	*DMD*	AAV				--	Lilly
PBGENE-LLY2	Undisclosed – Liver	Liver	Undisclosed	Undisclosed				--	Lilly
PBGENE-LLY3	Undisclosed - CNS	CNS	Undisclosed	Undisclosed				--	Lilly

*iECURE plans to develop PBGENE-PCSK9 through Phase 1 clinical trial.
Precision retains rights to future development and commercialization of PBGENE-PCSK9

Gene Editing Pipeline **Validation & Expansion** Creates Value

1

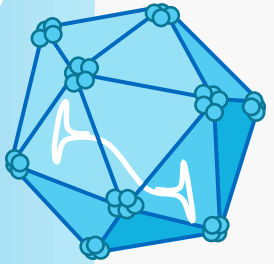
Clinical Validation

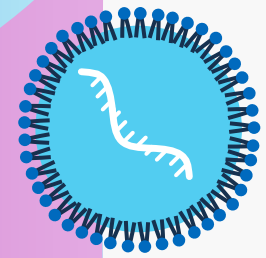
Knock-out Genes in Liver

2

Pipeline Expansion

Complex Edits & Multiple Tissues





PBGENE-DMD
PBGENE-LLY2*
PBGENE-LLY3*

	2022	2023	2024
AAV	PBGENE-PCSK9		
LNP		PBGENE-PH1	PBGENE-HBV
IND/CTA Submission			

*Precision has not disclosed the method of delivery or target for PBGENE-LLY2 & PBGENE-LLY3.

In Vivo Gene Editing Partnering Strategy

Precision Biosciences Programs

Leverage extensive NHP data to achieve clinical validation of liver knock-out programs

Where Precision Biosciences can be 1st gene editing program into clinic

Pursue novel gene insertion targets requiring complex edits as we build scale

Partnering Strategy to Build Precision Scale

Speed

Economics

Capabilities

Capacity

Market

Transformative Gene Editing Partnership for Precision

Research collaboration and license agreement aimed at treating challenging genetic diseases

3 Initial collaboration for 3 programs, including DMD

3 + 3 Lilly retains right to select up to 3 additional gene targets

Precision - Pre-IND R&D; **Lilly** - IND to commercial

Upfront payment of $135 million including $35 million equity stake

Up to $420M per target in development and commercialization milestones

Mid-single digit to low-teens tiered royalties

iECURE Collaboration Provides Potential Rapid Path to Clinical Validation

Collaboration leverages extensive ARCUS knock-out data in NHPs, rapidly advances first ARCUS nuclease into the clinic, and validates ARCUS for gene insertion

PRECISION BIOSCIENCES

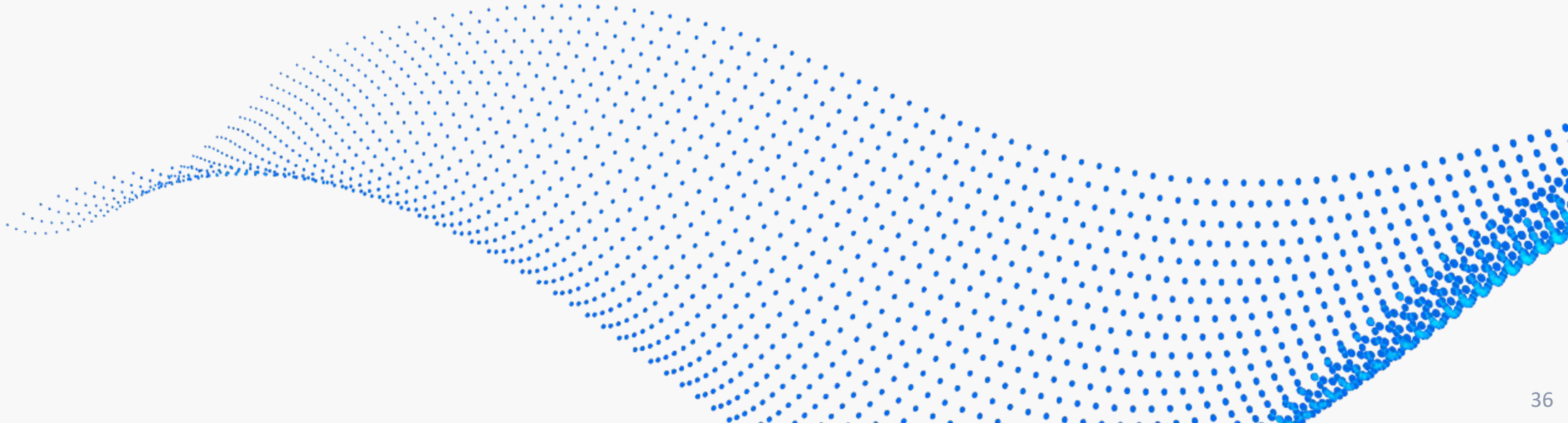
- Rapid path for PBGENE-PCSK9 through clinical POC; no cost to Precision
- Maintains commercial rights to PBGENE-PCSK9 for CV disease[1]
- Equity stake in iECURE, milestones & royalties on four gene insertion programs

ECURE

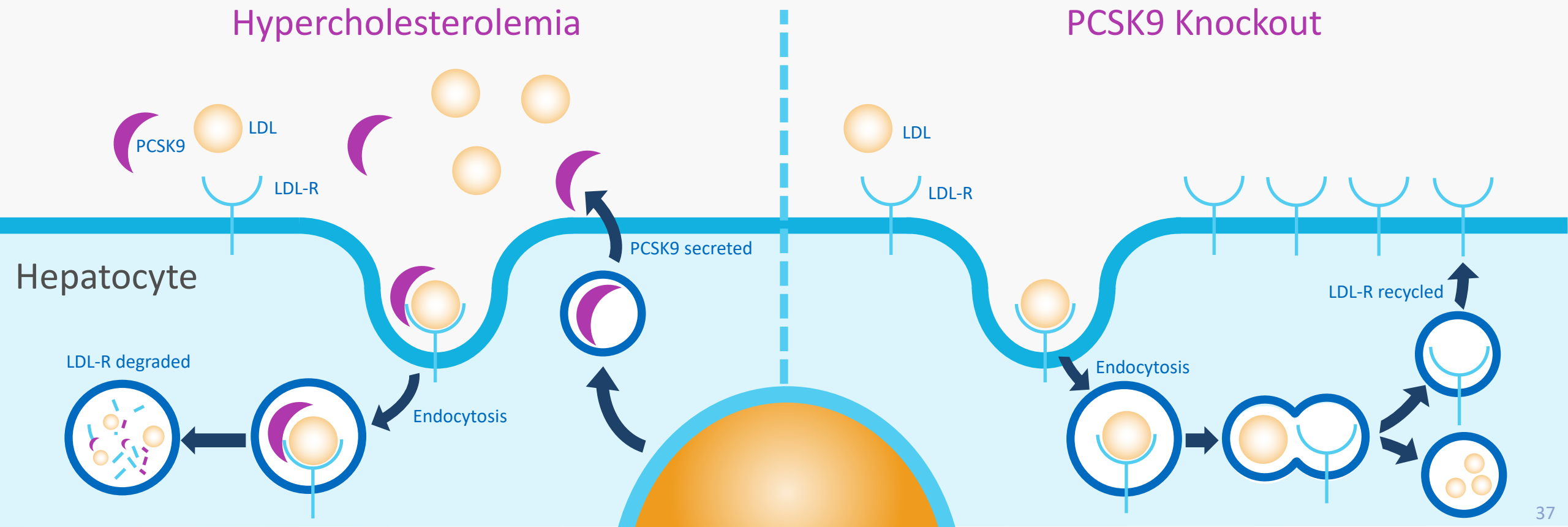
- Partnered with the Penn University of Pennsylvania Gene Therapy Program
- Plan to advance PBGENE-PCSK9 to Phase 1 clinical study and submit CTA in 2022 for FH on Precision's behalf
- Rights to develop PCSK9 nuclease for gene insertion in 4 rare indications, including PKU and OTC

[1] Precision retains rights to PBGENE-PCSK9 except for the gene insertion applications for treatment of the 4 rare indications licensed to iECURE

DEVELOPMENT PROGRAMS:
PCSK9 FAMILIAL HYPERCHOLESTEROLEMIA (FH)

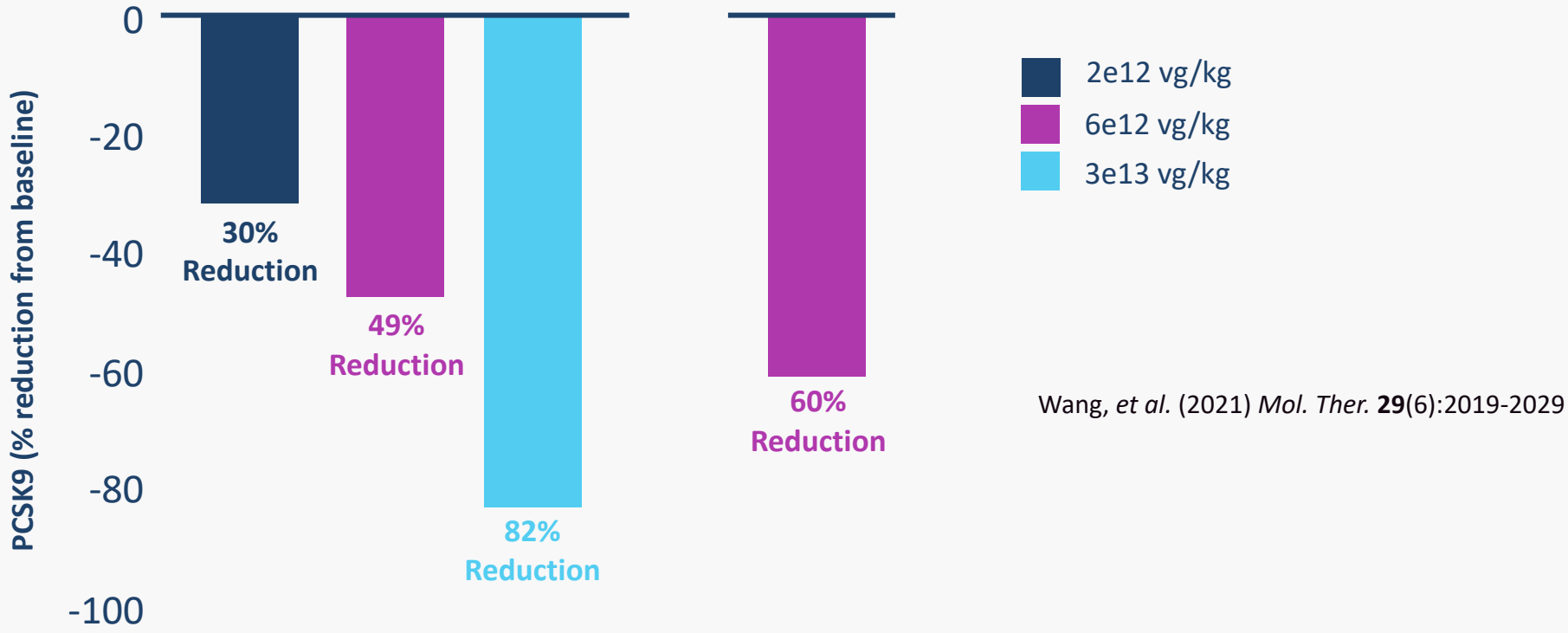


Familial Hypercholesterolemia



PBGENE-PCSK9: Stable Knockout of PCSK9 Observed in NHPs

A single dose of AAV8-ARCUS reduced serum PCSK9 levels by up to 82% in non-human primates



Wang, *et al.* (2021) *Mol. Ther.* **29**(6):2019-2029

M1PCSK9

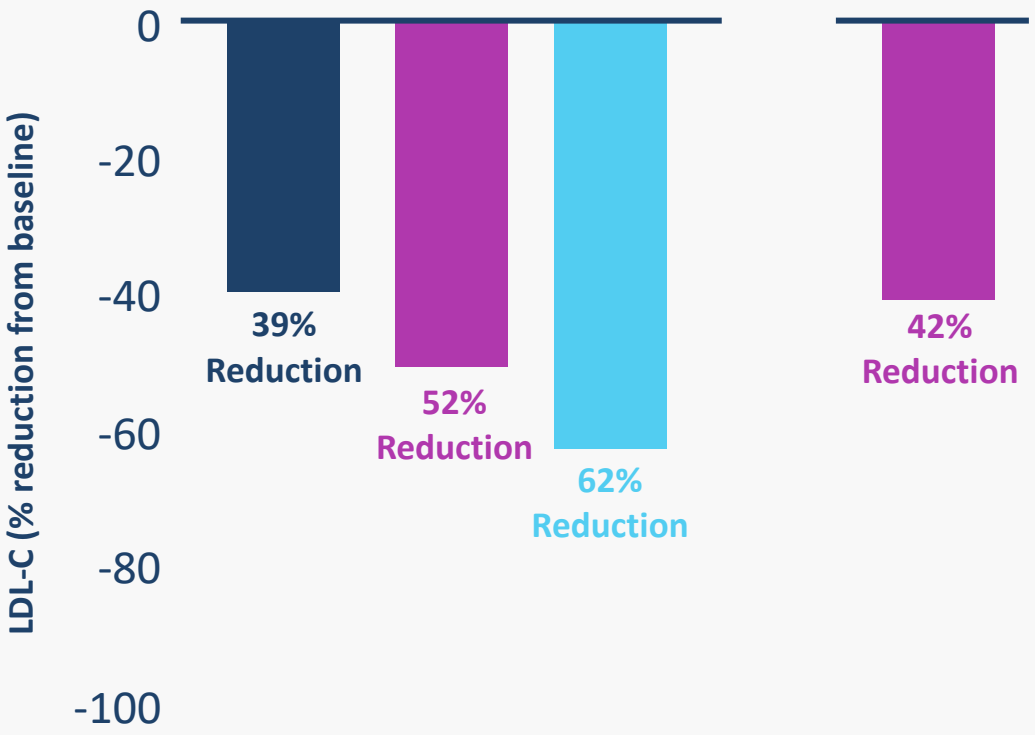
Generation 1 ARCUS
Average Reduction Over
728 Days Post-Treatment

M2PCSK9

Generation 2 ARCUS
Average Reduction Over
771 Days Post-Treatment

PBGENE-PCSK9: Stable Reduction in LDL-c Observed in NHPs

A single dose of AAV8-ARCUS reduced LDL-c levels by up to 62% in non-human primates



Wang, *et al.* (2021) *Mol. Ther.* **29**(6):2019-2029

M1PCSK9

Generation 1 ARCUS

Average Reduction Over 728 Days Post-Treatment

M2PCSK9

Generation 2 ARCUS

Average Reduction Over 771 Days Post-Treatment

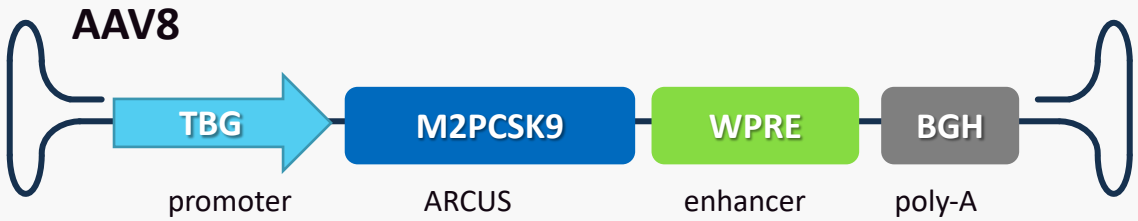
PBGENE-PCSK9 Vector

AAV was selected as the delivery technology for PBGENE-PCSK9

- The underlying genetic causes of FH result in reduced lipid uptake by liver.
- FH is expected to impairLNP uptake by hepatocytes.

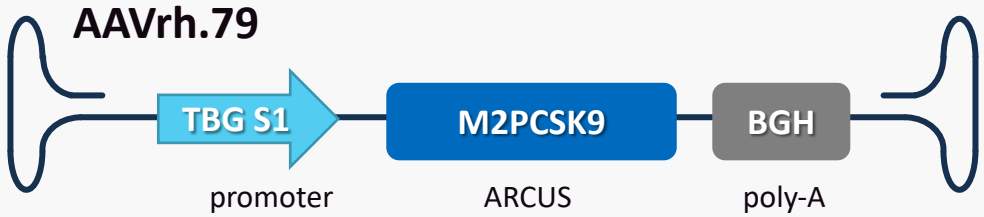
Research Vector

- Wang, *et al.* (2018) *Nat. Biotechnol.* **36**(8):717-725
- Wang, *et al.* (2021) *Mol. Ther.* **29**(6):2019-2029



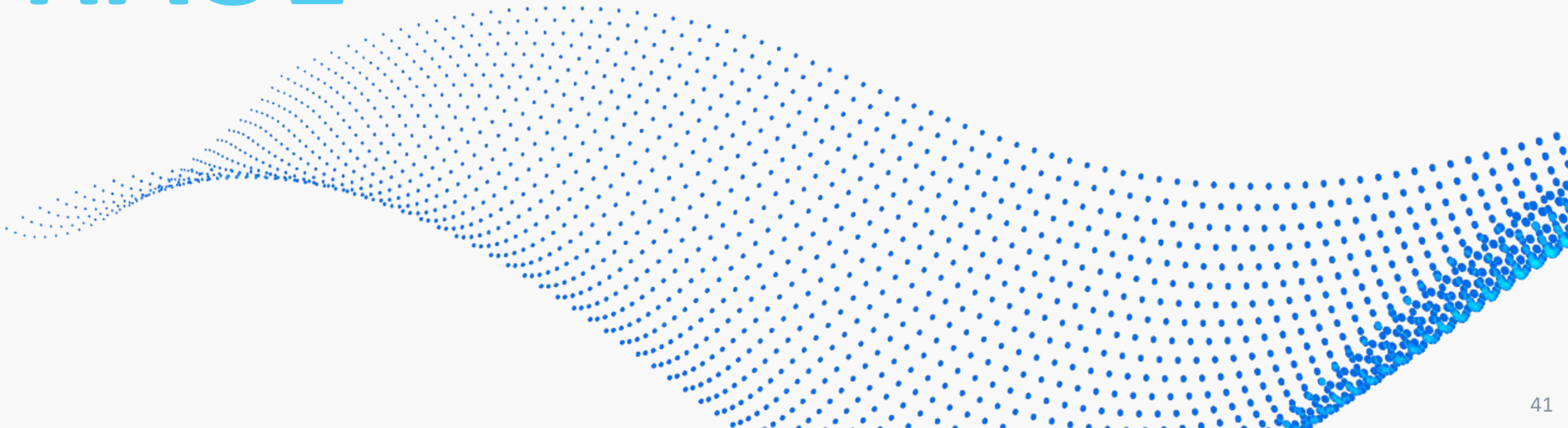
Anticipated Clinical Vector

- Promoter reduced and enhancer removed to reduce off-target editing
- Capsid changed to rh.79 to reduce frequency of NAbs



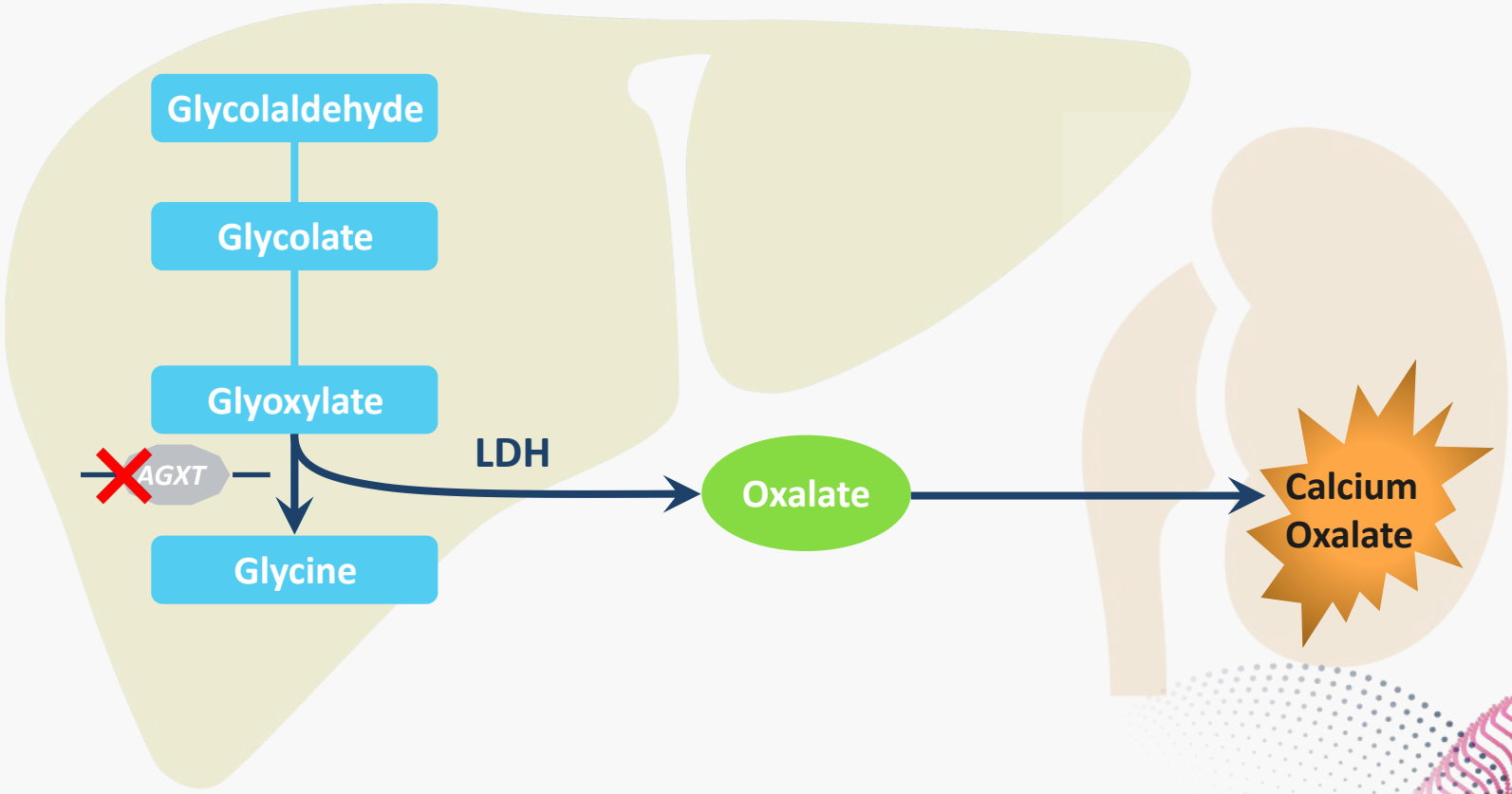
DEVELOPMENT PROGRAMS:

HAO1 PRIMARY HYPEROXALURIA TYPE 1



PBGENE-PH1

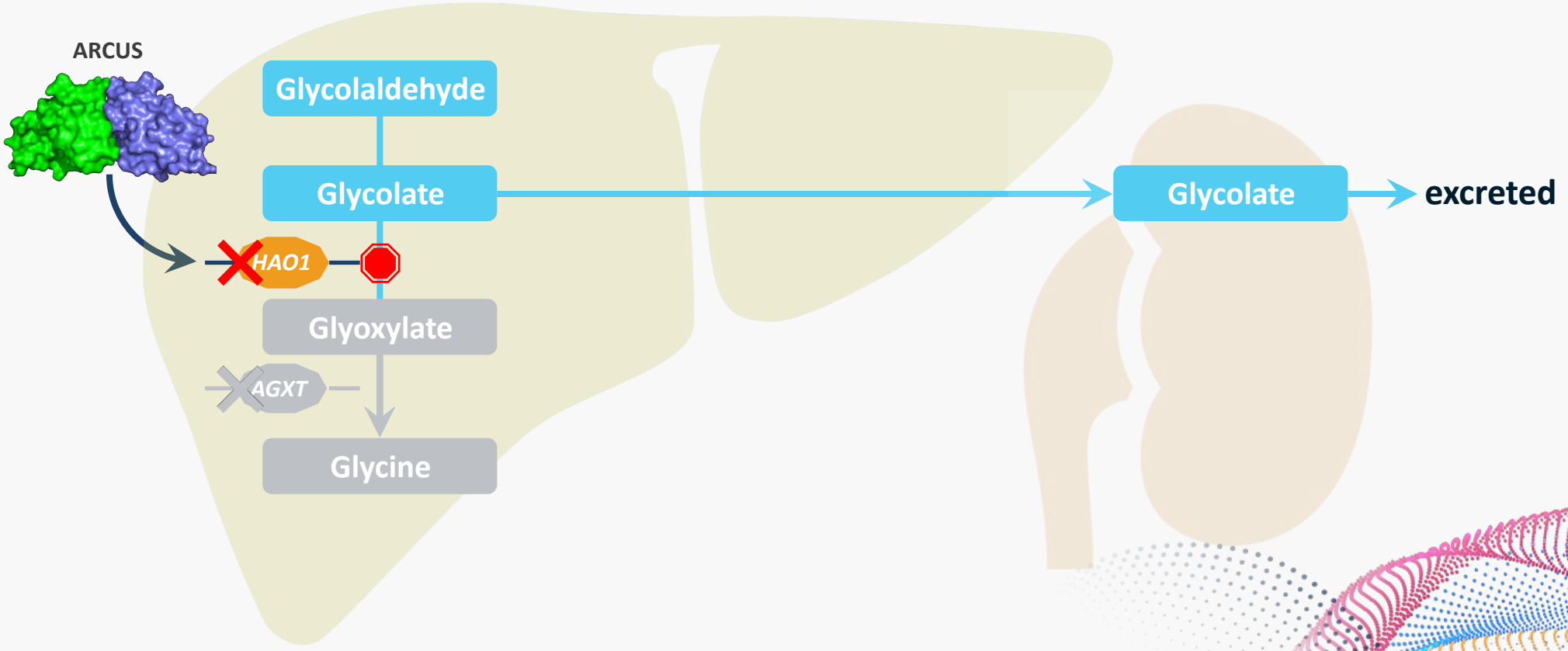
Primary Hyperoxaluria Type 1 is a potentially fatal genetic disease caused by a gene mutation that leads to the accumulation of calcium oxalate crystals in the kidneys.



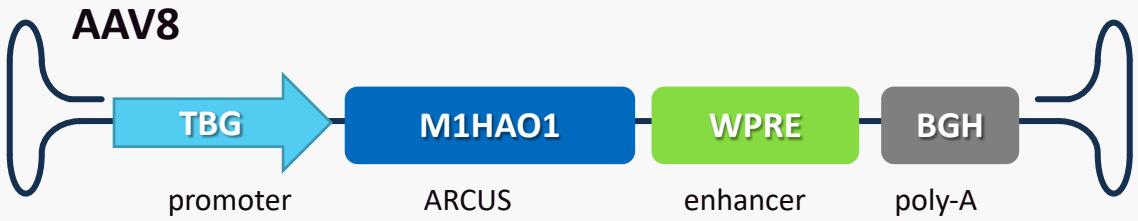
PBGENE-PH1

Primary Hyperoxaluria Type 1 is a potentially fatal genetic disease caused by a gene mutation that leads to the accumulation of calcium oxalate crystals in the kidneys.

Suppressing expression of the ***HAO1* gene** is a proven method for treating the disease by reducing the formation of calcium oxalate.



Research Vector

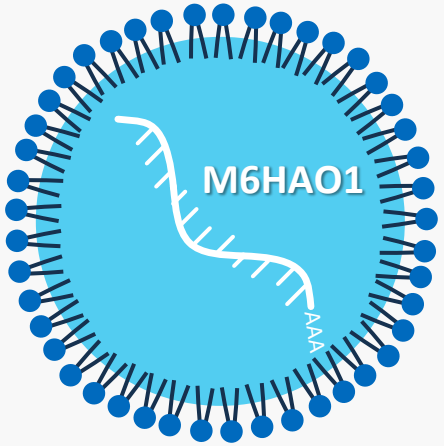


PBGENE-PH1 Formulation

LNP was selected as the delivery technology for PBGENE-PH1

Anticipated Clinical Formulation

- Generation 6 ARCUS nuclease for *HAO1*
- Lipid nanoparticle formulation with optimized mRNA sequence

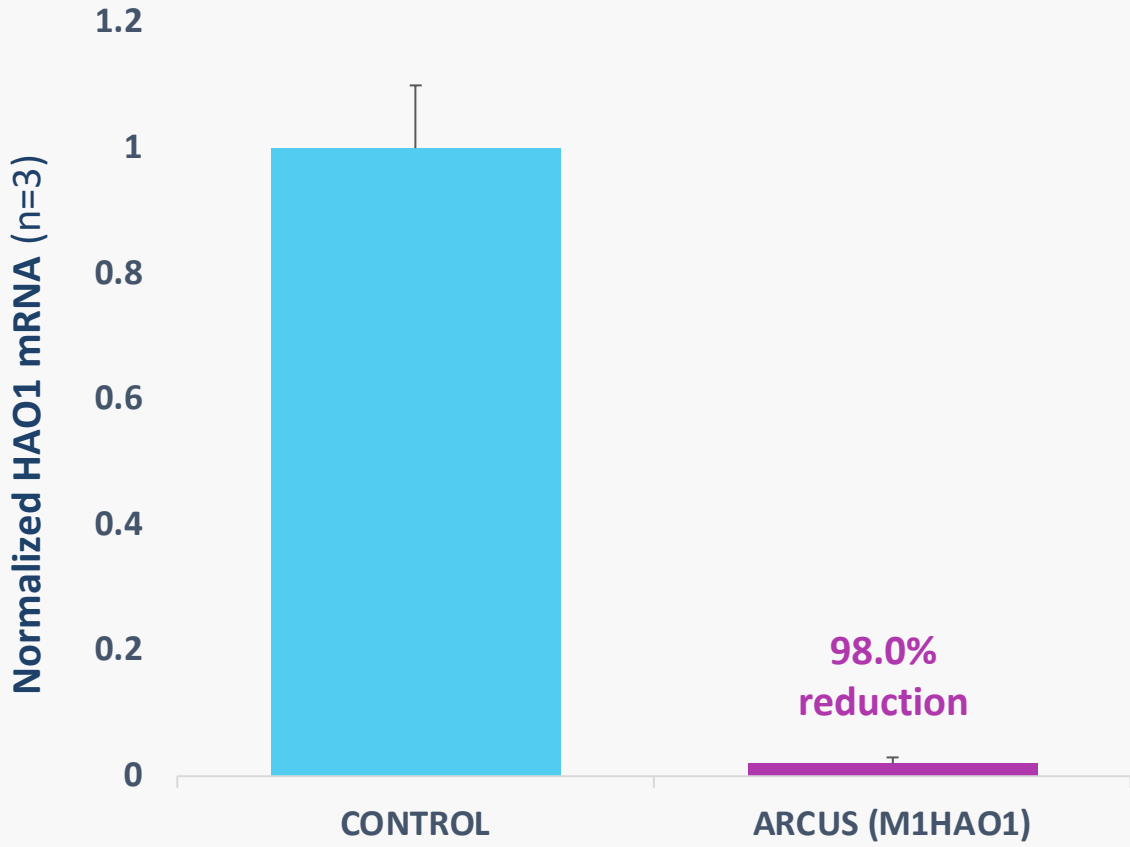


PBGENE-PH1 Proof of Concept in Non-Human Primates

ARCUS treatment decreased ***HAO1* mRNA** by 98% in NHPs

AAV Dose 3e13 vg/kg (n=3)

ARCUS Reduced *HAO1* mRNA levels



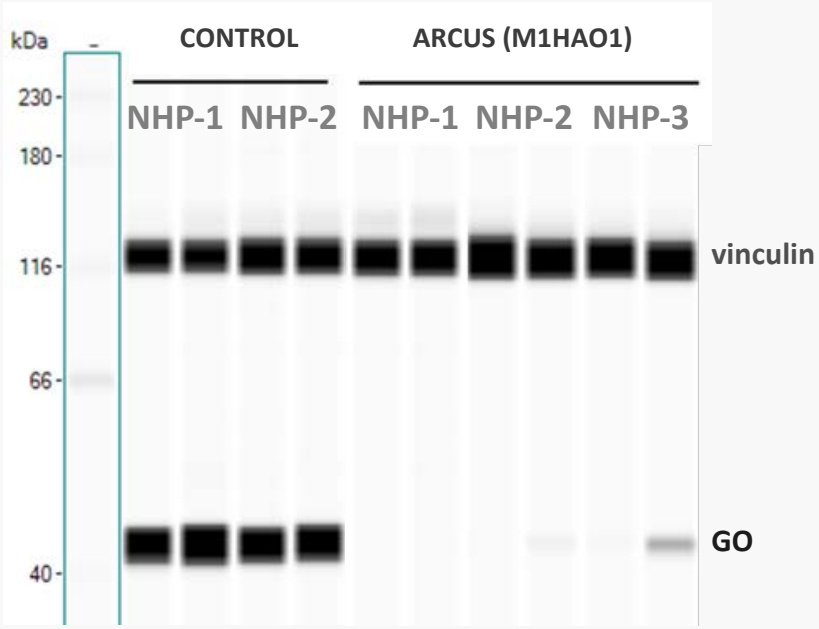
ARCUS Reduced GO Protein Levels

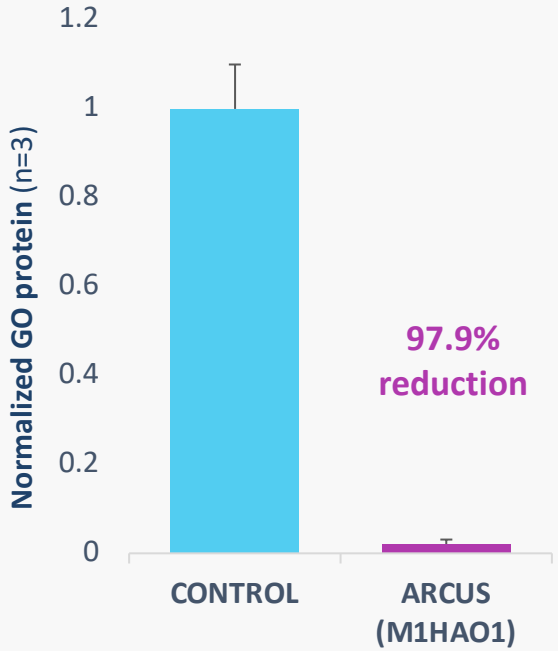
PBGENE-PH1 Proof of Concept in Non-Human Primates

ARCUS treatment decreased **GO protein**[1] by 97.9% in NHPs

AAV Dose 3e13 vg/kg (n=3)

[1]GO (Glycolate Oxidase) is the protein encoded by *HAO1*



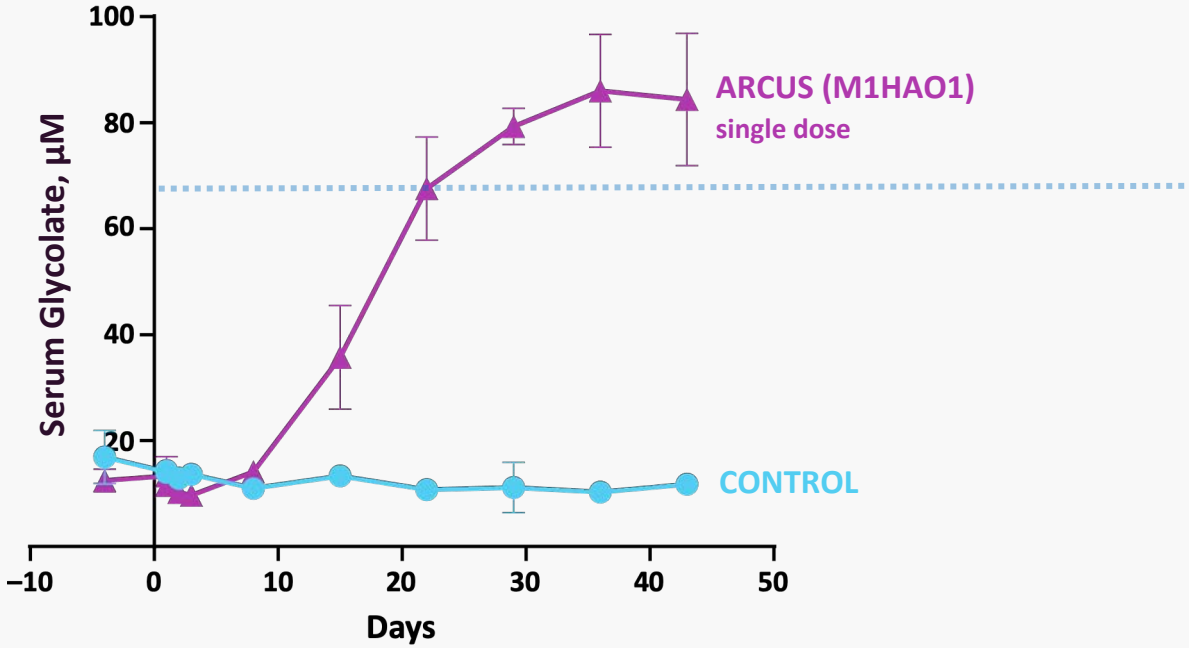


PBGENE-PH1 Proof of Concept in Non-Human Primates

PH1

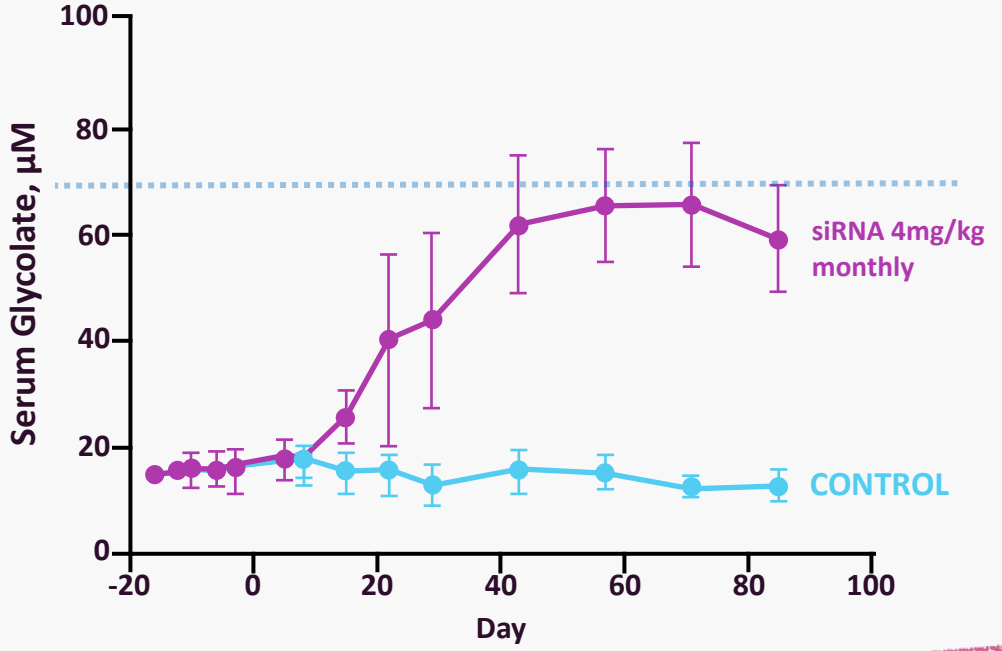
Serum glycolate

ARCUS treatment significantly increased serum glycolate levels in non-human primates



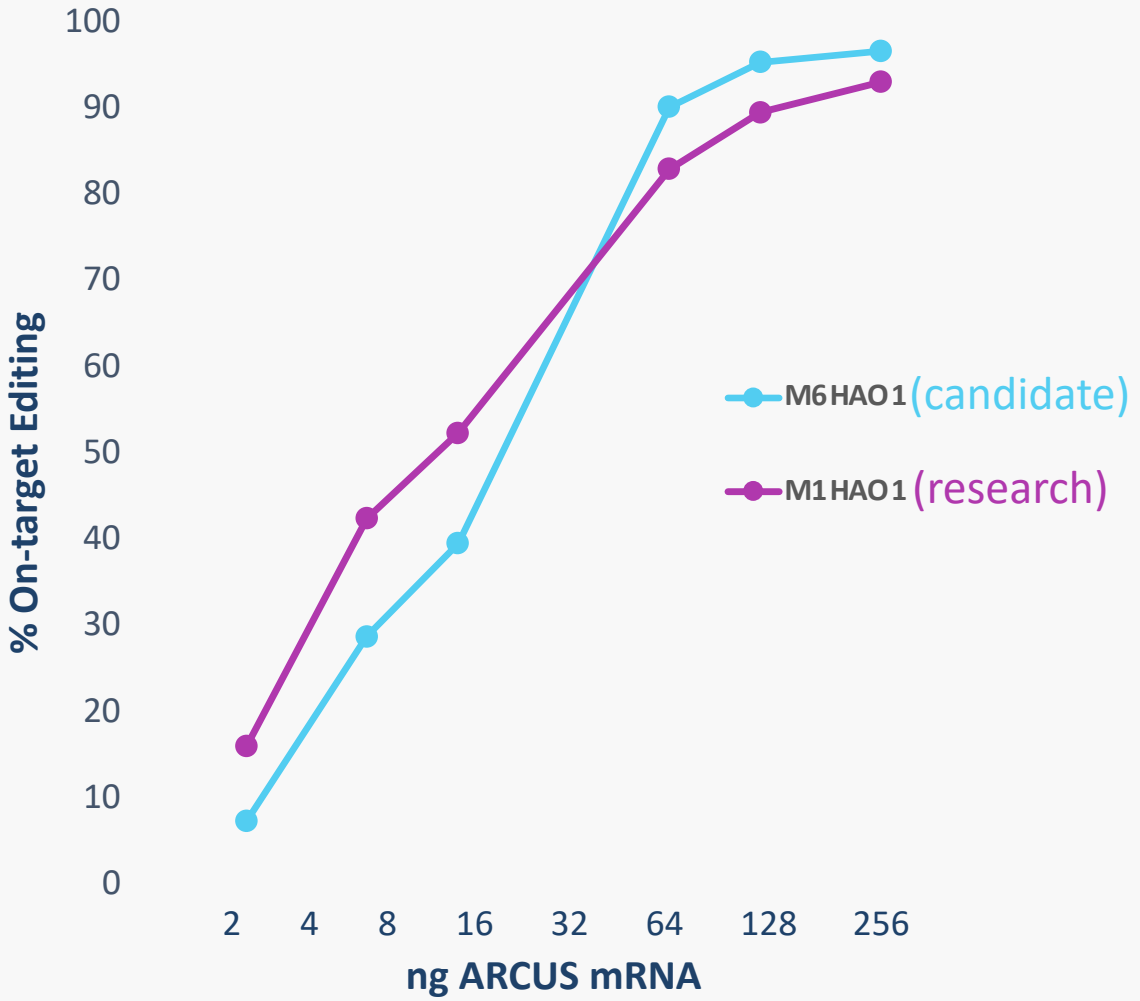
siRNA

Published serum glycolate levels in NHPs treated with an siRNA against *HAO1* (Alnylam, PCT/US2015/054881)



PBGENE-PH1: Development Candidate

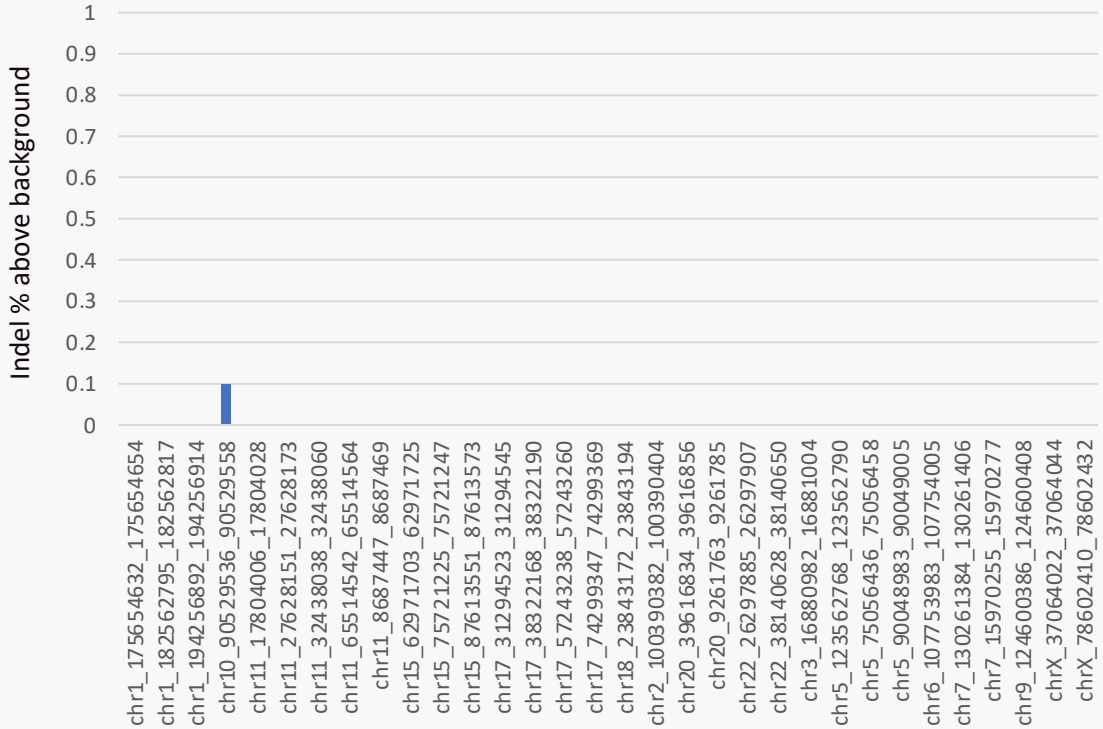
On-Target Editing: The optimized ARCUS candidate (**M6HAO1**) had comparable on-target editing efficiency to the research nuclease in transfected cells in vitro.



PBGENE-PH1: Development Candidate

Off-Target Editing: One potential off-target site was identified in human cells transfected with 100ng of M6HAO1 mRNA.

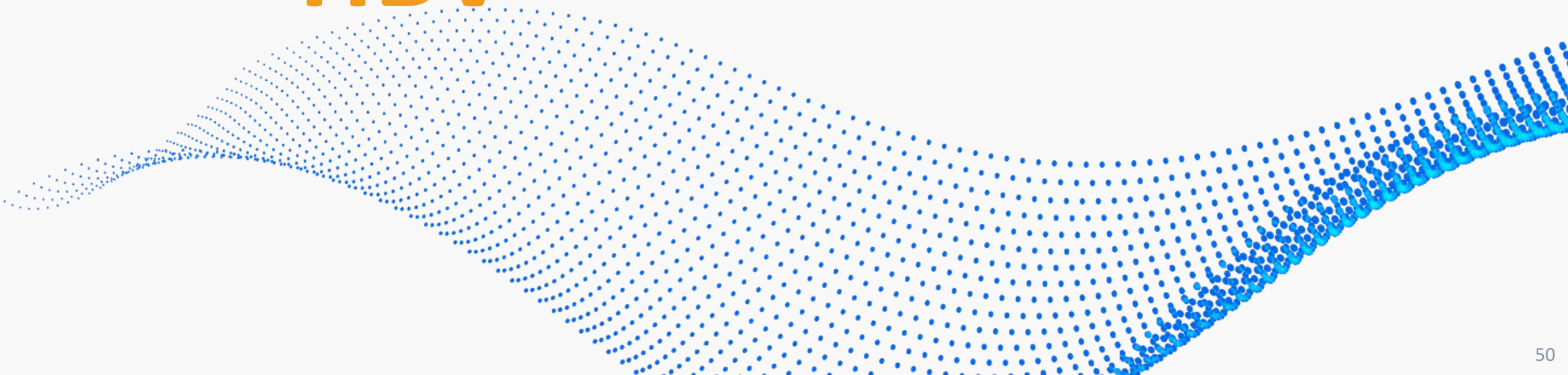
Frequency of off-target editing by Oligo Capture



The top 32 sites identified by the Oligo Capture assay were deep sequenced in gDNA isolated from primary human hepatocytes transfected with 100ng of mRNA encoding the M6HAO1 nuclease. One site in a non-coding region of the genome was found to have a very low frequency of editing (0.1%) at levels above a mock transfected control.

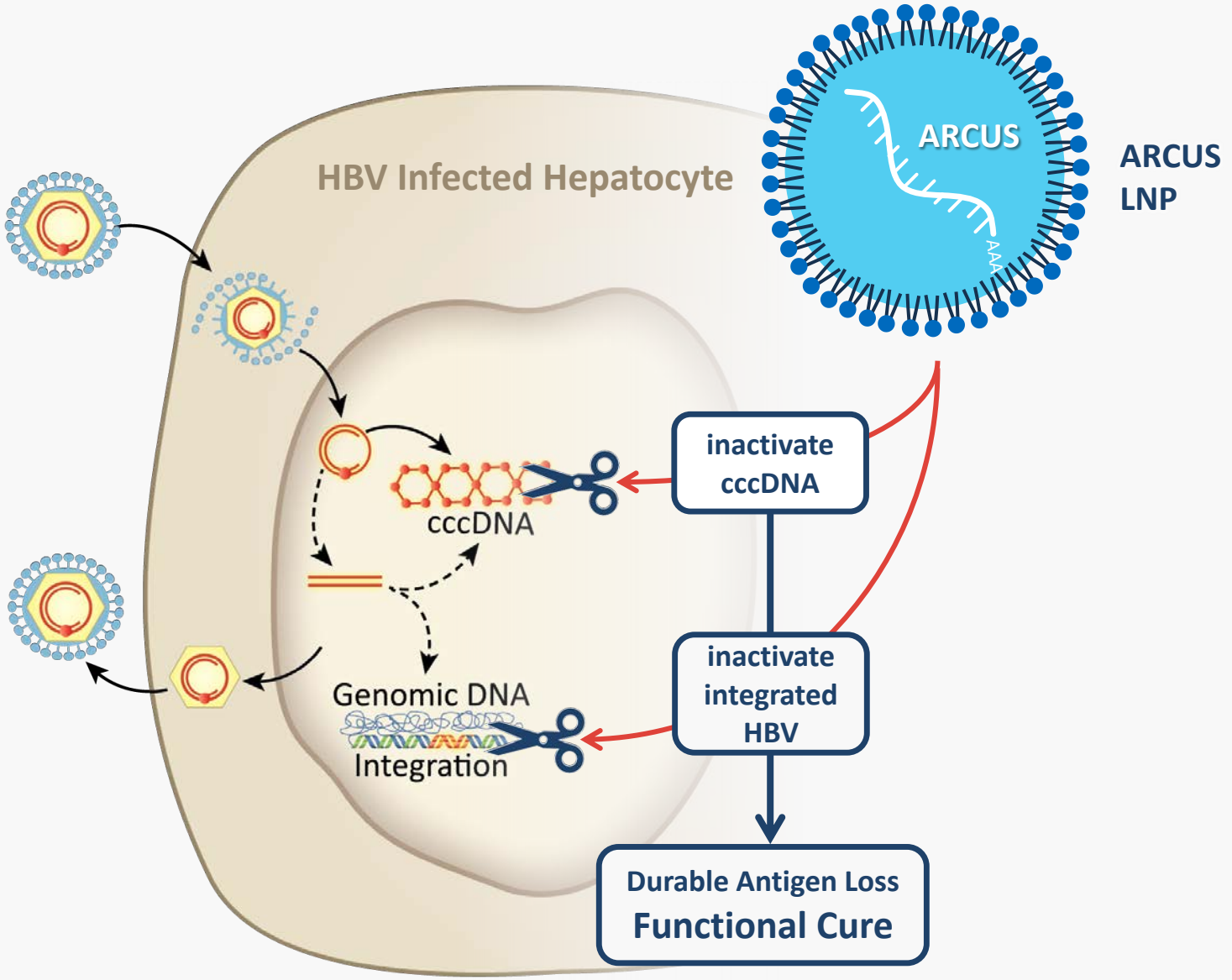
DEVELOPMENT PROGRAMS:

HBV CHRONIC HEPATITIS B



PBGENE-HBV Therapeutic Strategy

ARCUS-mediated inactivation of cccDNA and integrated HBV could result in a functional cure

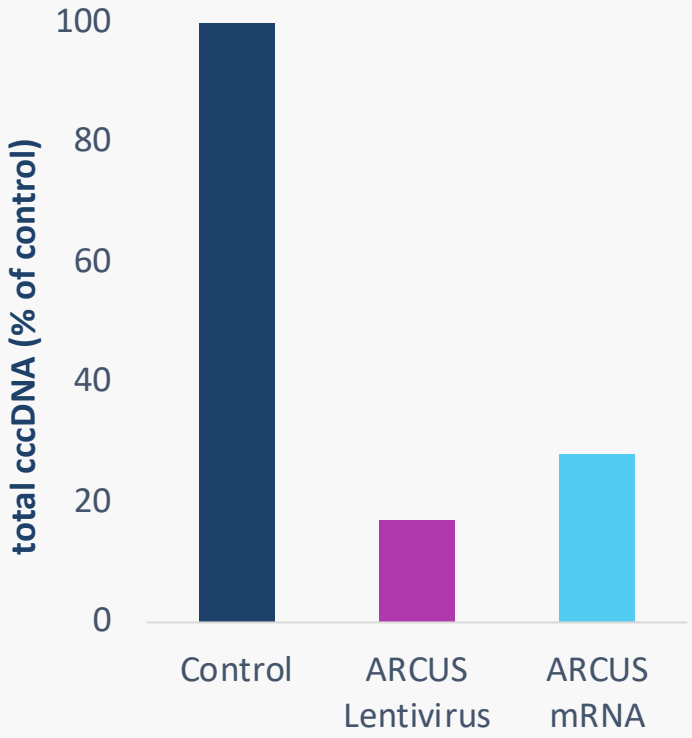


Antiviral Activity in HBV-Infected Human Hepatocytes

HBV

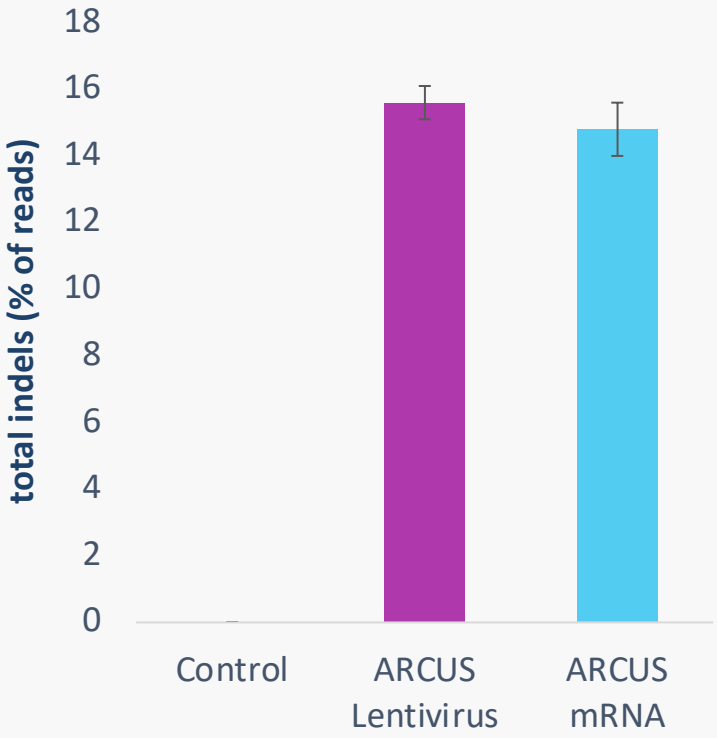
cccDNA

ARCUS treatment resulted in significant reductions in total HBV cccDNA



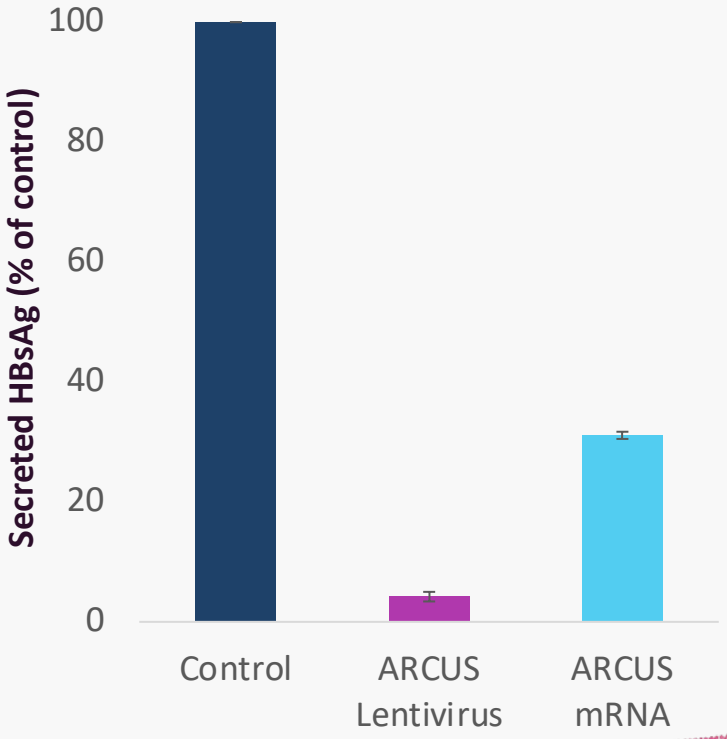
Indels

Indel mutations were detected in the remaining HBV genomes following ARCUS treatment

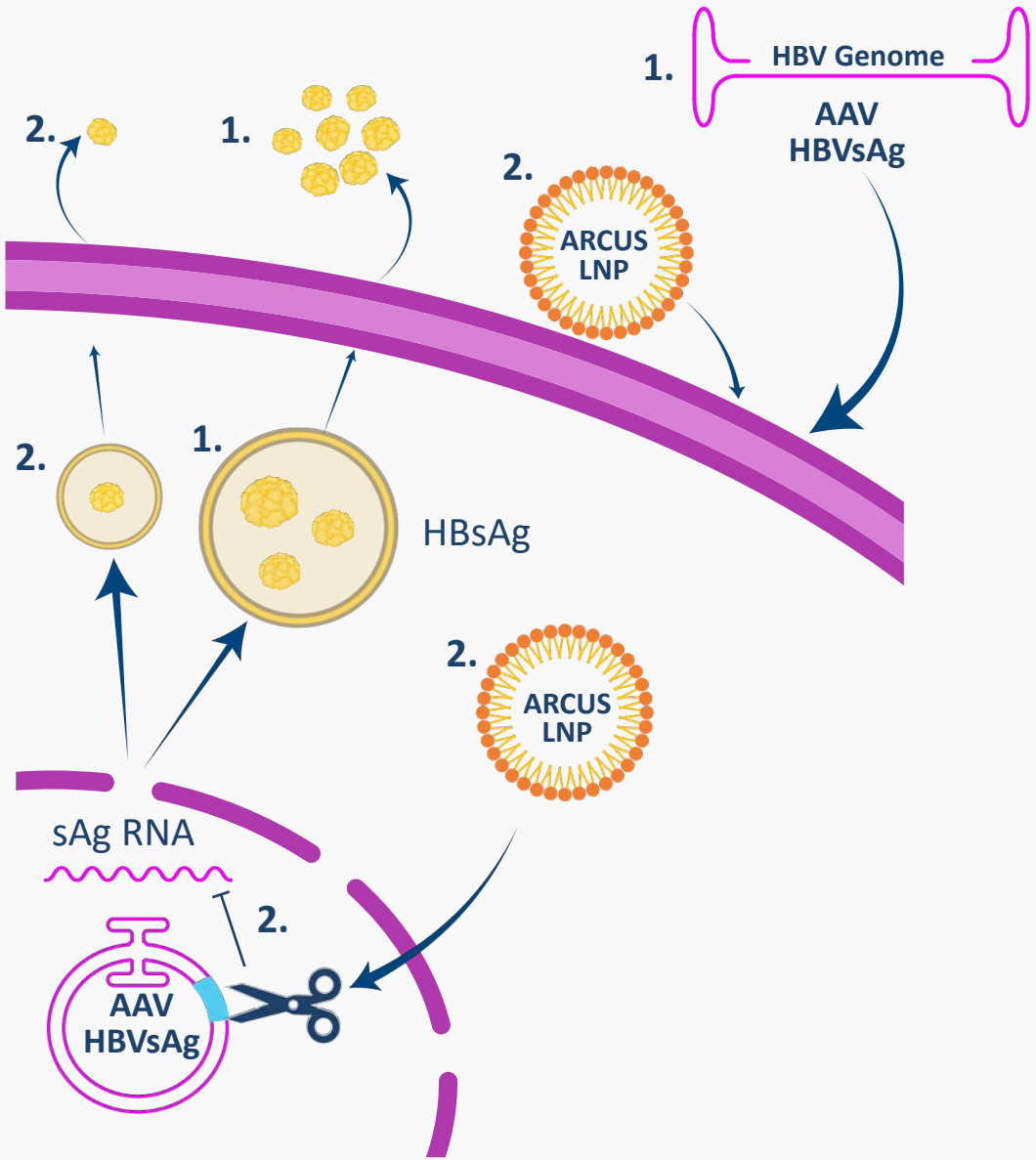


HBsAg

ARCUS treatment resulted in significant reductions in secreted S-antigen



Challenge: There is No *in vivo* Model of Human HBV Infection



We developed a novel *in vivo* model for HBV editing

HBV genome sequences are delivered on an AAV vector.

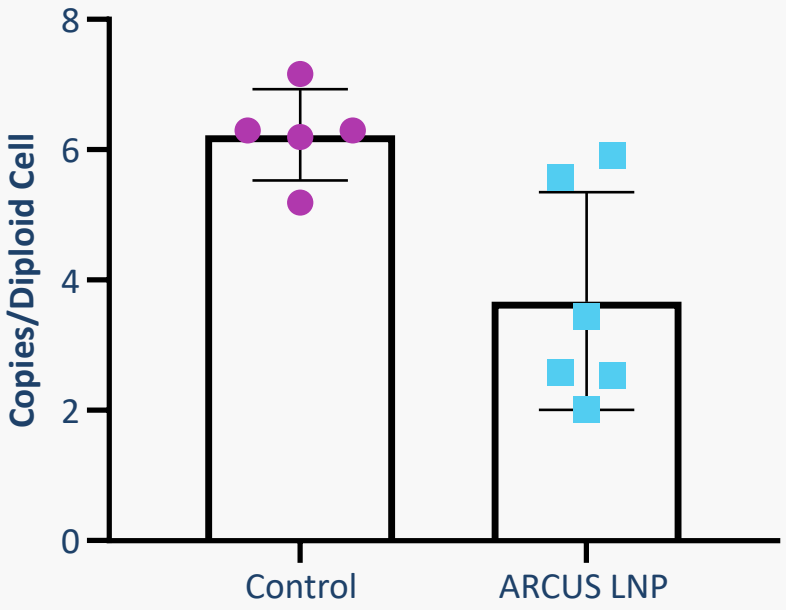
HBV sequences are then deleted by ARCUS delivered by LNP.

Mouse Episomal Model Results

LNP-ARCUS efficiently edited HBV sequences **in an immunodeficient mouse model**

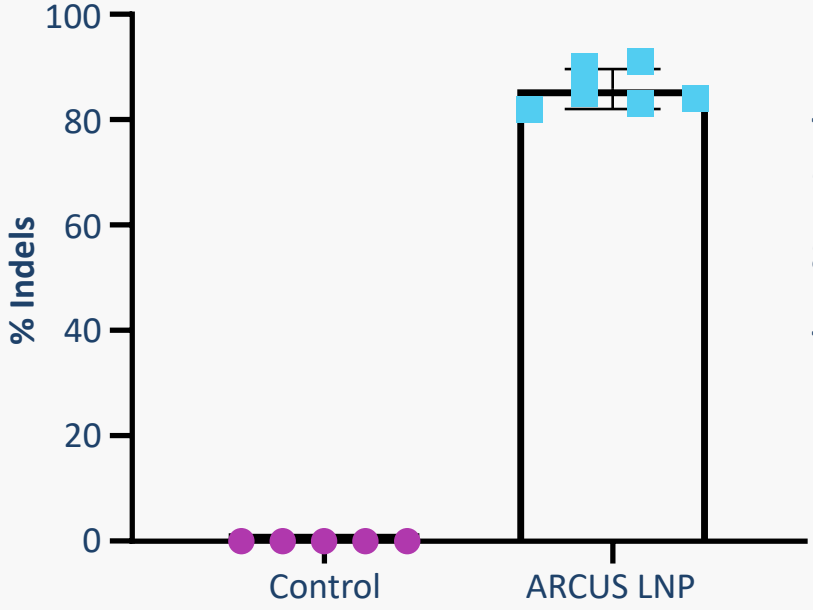
AAV Copy Number

ARCUS treatment resulted in significant reductions in total AAV genome copies



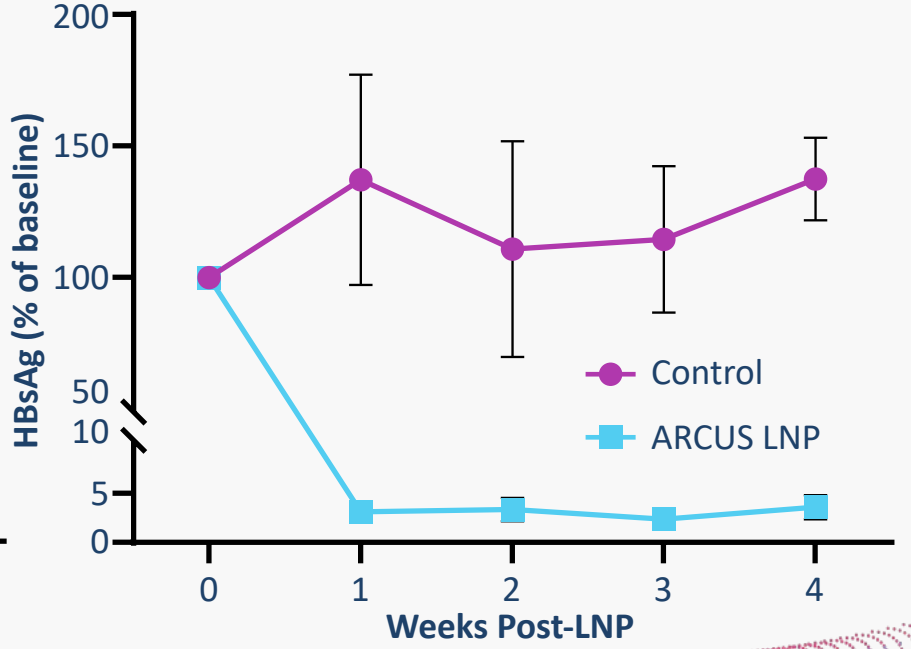
Indels

ARCUS treatment introduced a high frequency of indel mutations into the remaining AAV genomes



HBsAg

ARCUS treatment resulted in a significant reduction in serum S-antigen

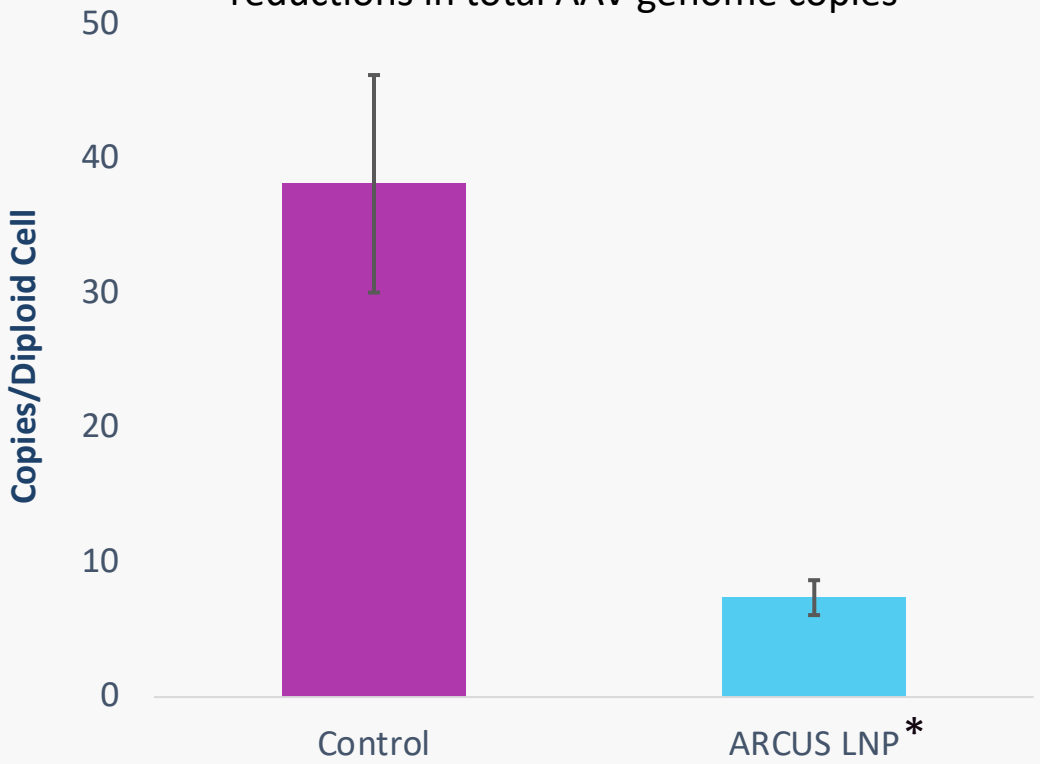


NHP Episomal Model Results

LNP-ARCUS efficiently edited HBV sequences **in a NHP model**

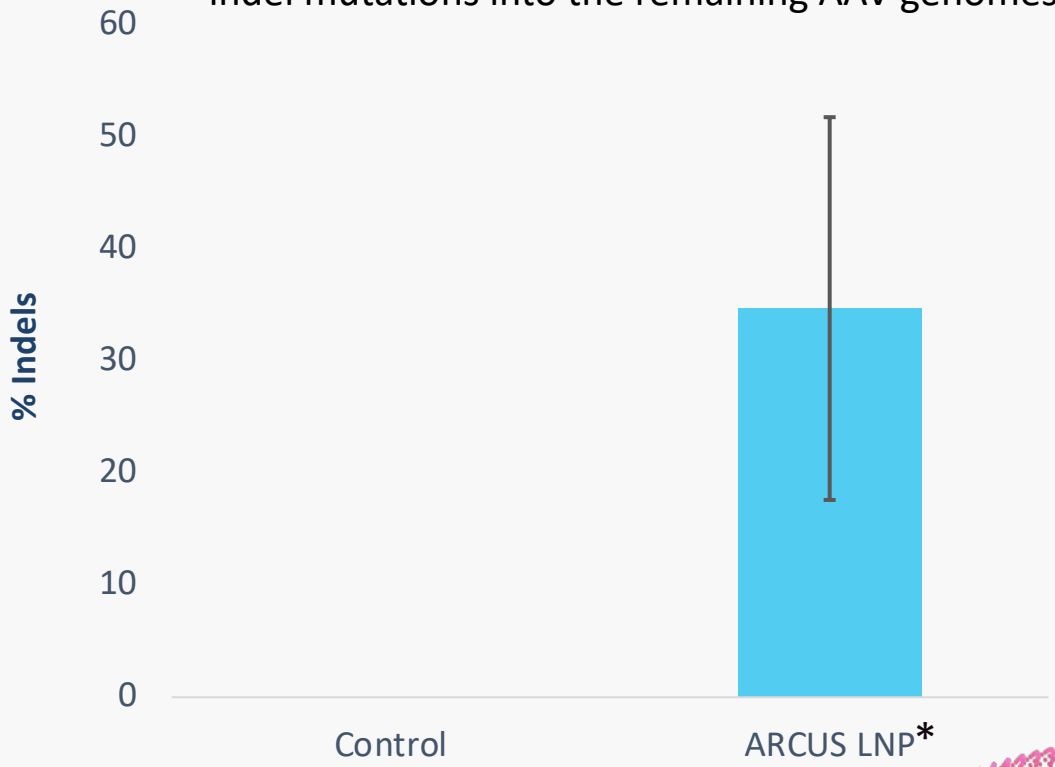
AAV Copy Number

ARCUS treatment resulted in significant reductions in total AAV genome copies



Indels

ARCUS treatment introduced a high frequency of indel mutations into the remaining AAV genomes

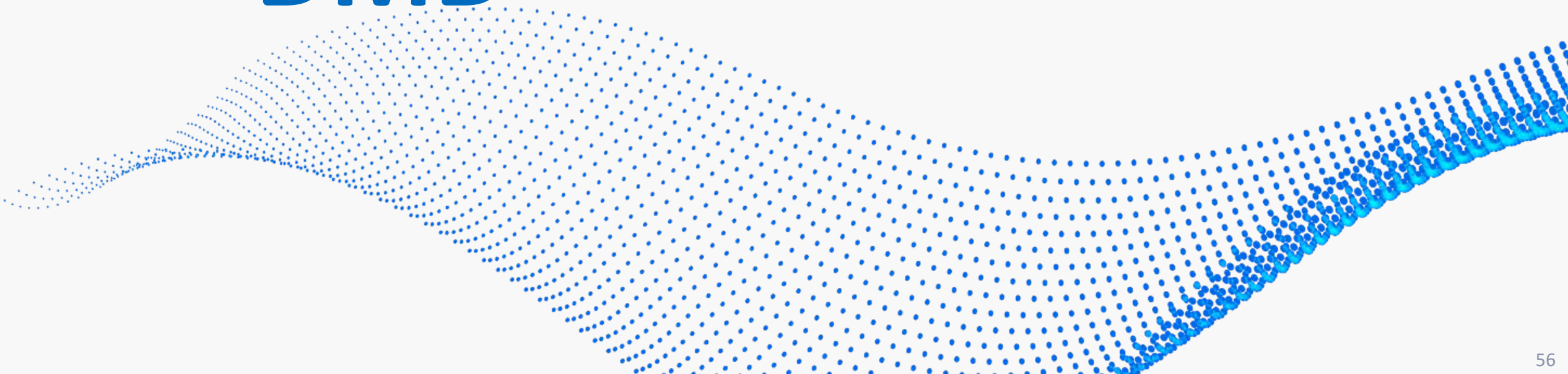


Note: HBsAg is quickly neutralized in immunocompetent NHPs and is not useful as a biomarker in these animals

*LNP provided by Acuitas Therapeutics

DEVELOPMENT PROGRAMS:

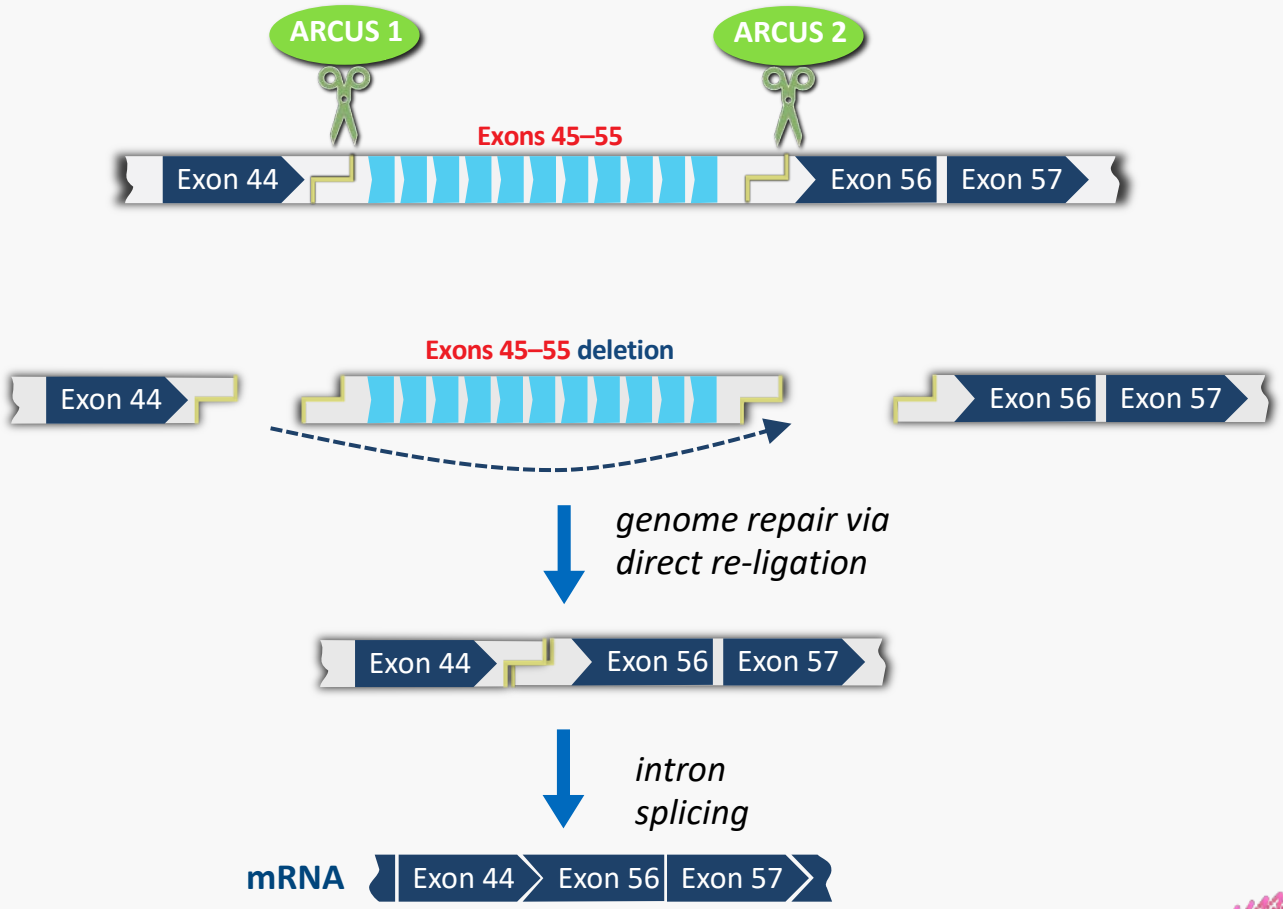
DMD Duchenne Muscular Dystrophy



ARCUS for Therapeutic Treatment of DMD

DMD

Goal: Restore dystrophin expression by deleting exons 45-55 using a pair of ARCUS nucleases intended to remove a mutation hotspot responsible for >50% of DMD

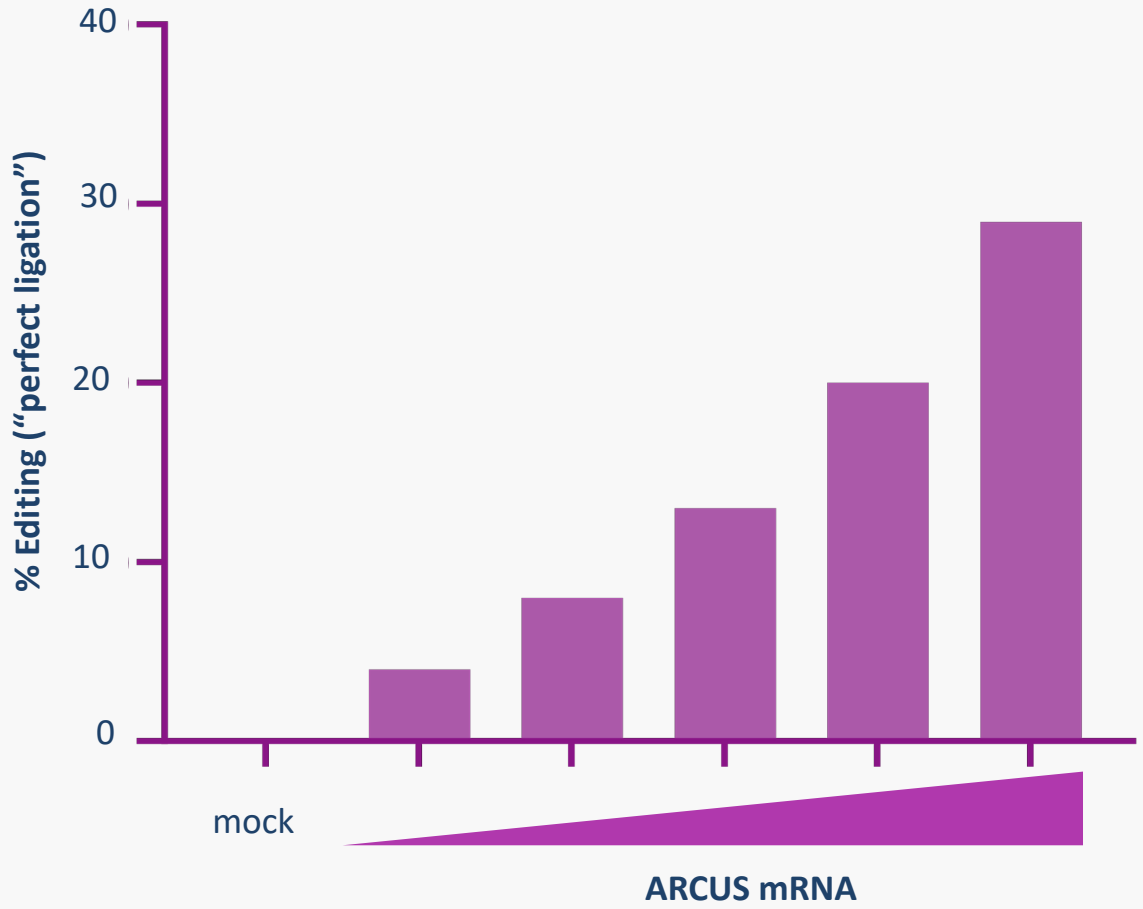


DMD

Dystrophin Gene Correction Observed in DMD Patient Myoblasts

Corrected DNA

Exons 45-55 deleted

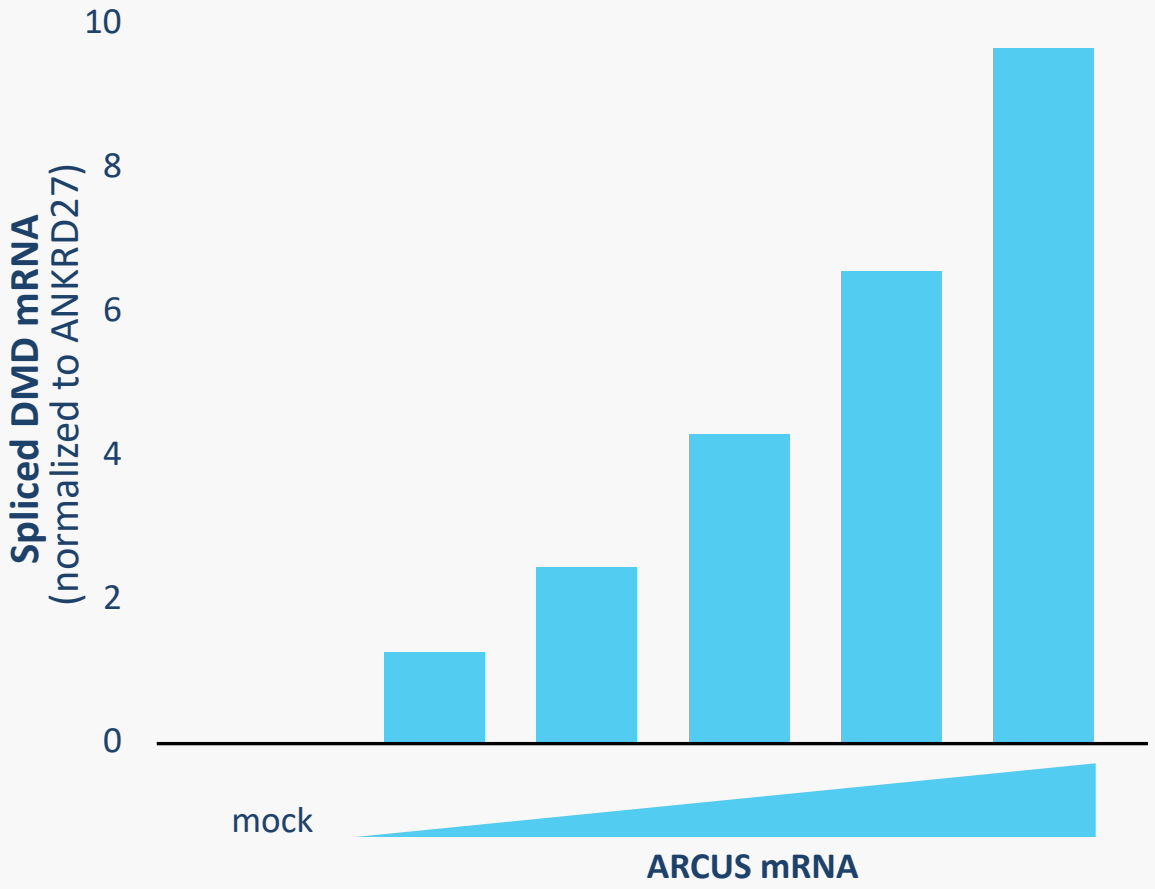


DMD

Dystrophin Gene Correction Observed in DMD Patient Myoblasts

Corrected mRNA

Exon 44 spliced to Exon 56

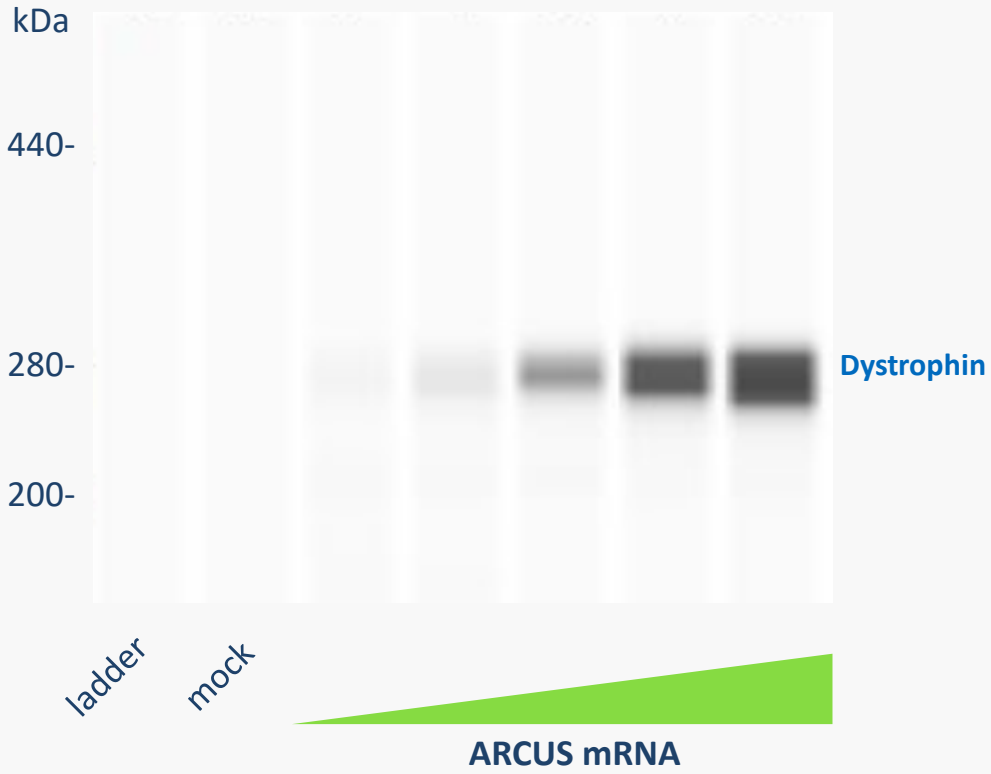


Dystrophin Gene Correction Observed in DMD Patient Myoblasts

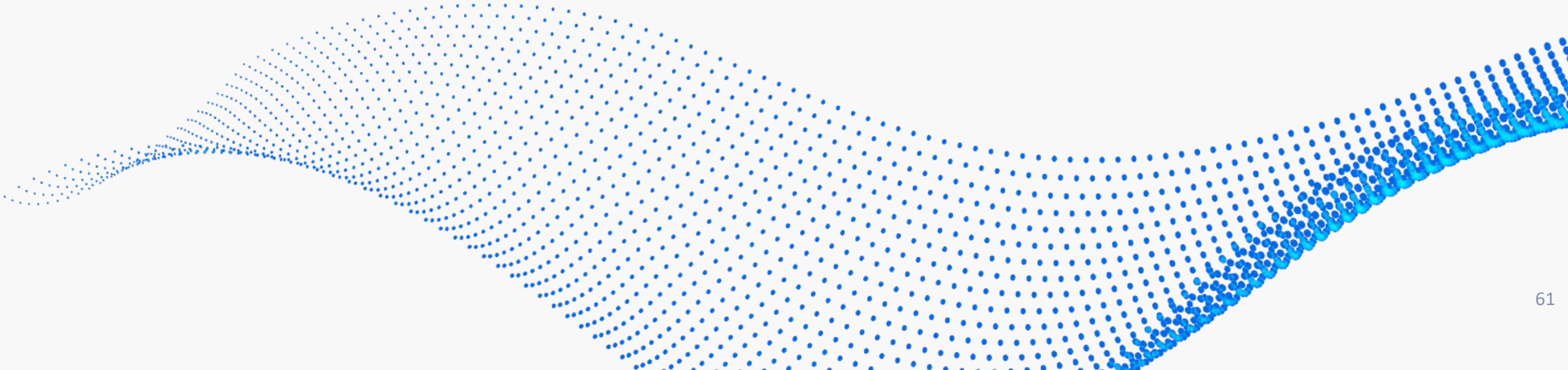
DMD

Corrected Protein

Dystrophin protein expressed



The Next Frontier



Mitochondrial Diseases

- Mitochondria are the powerhouse of the cell
- Pathogenic mutations in mitochondrial genome reduce the ability to generate energy resulting in cell injury or death
- Affects 1 in 5,000 individuals
- Often affects multiple organ systems, especially the brain, heart and muscles

***Alpers Disease**: Progressive Infantile Poliodystrophy*

***Barth Syndrome:** Lethal Infantile Cardiomyopathy*

Complex (I-V) Deficiency

Co-Enzyme Q10 Deficiency

Kearns-Sayre Syndrome

***LBSL:** Leukodystrophy*

***LCAD:** Long-Chain Acyl-CoA Dehydrogenase Deficiency*

***MELAS:** Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like Episodes*

***MERRF:** Myoclonic Epilepsy & Ragged-Red Fiber Disease*

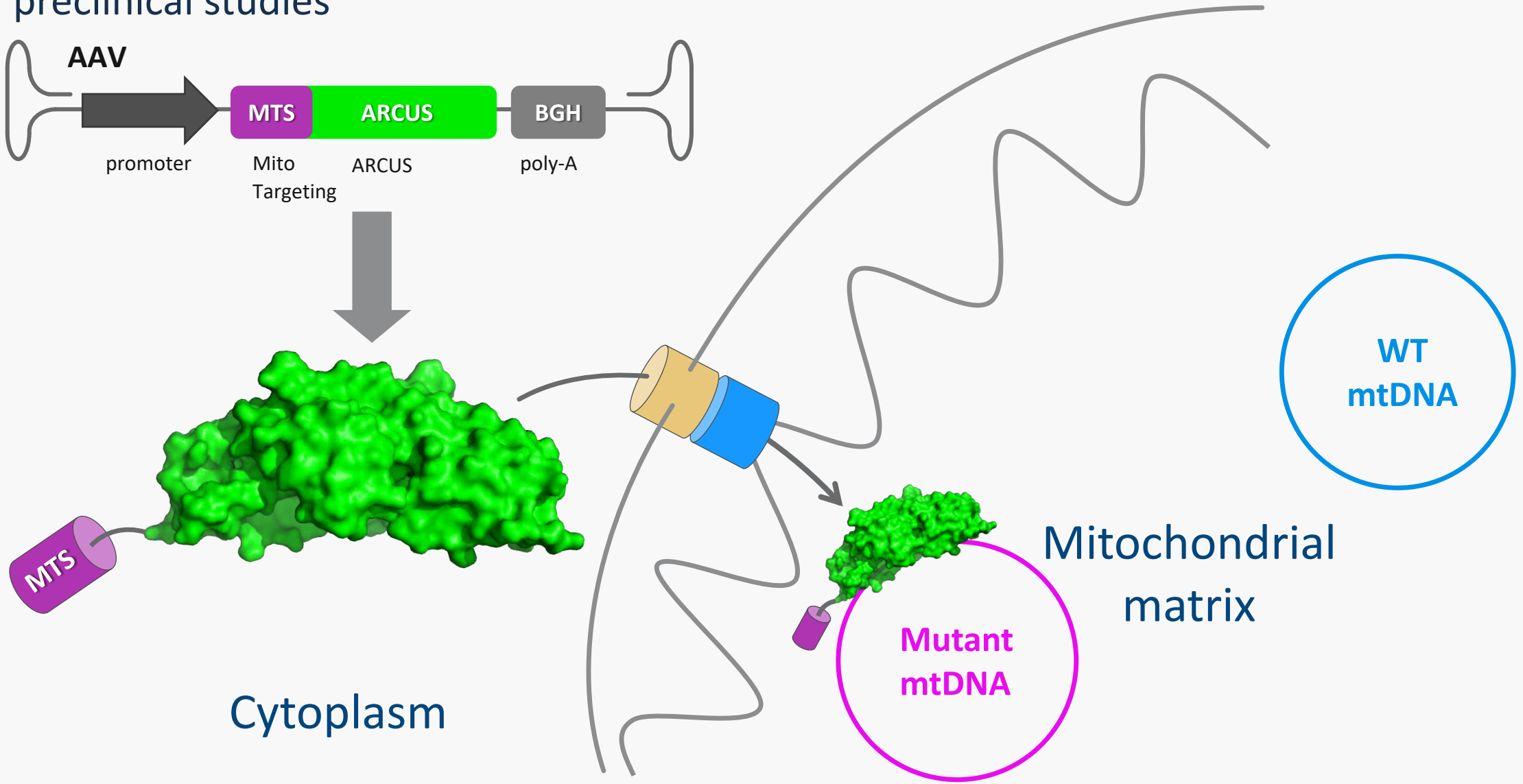
***NARP:** Neuropathy, Ataxia and Retinitis Pigmentosa*

Pearson Syndrome

***SCAD:** Short-Chain Acyl-CoA Dehydrogenase Deficiency*

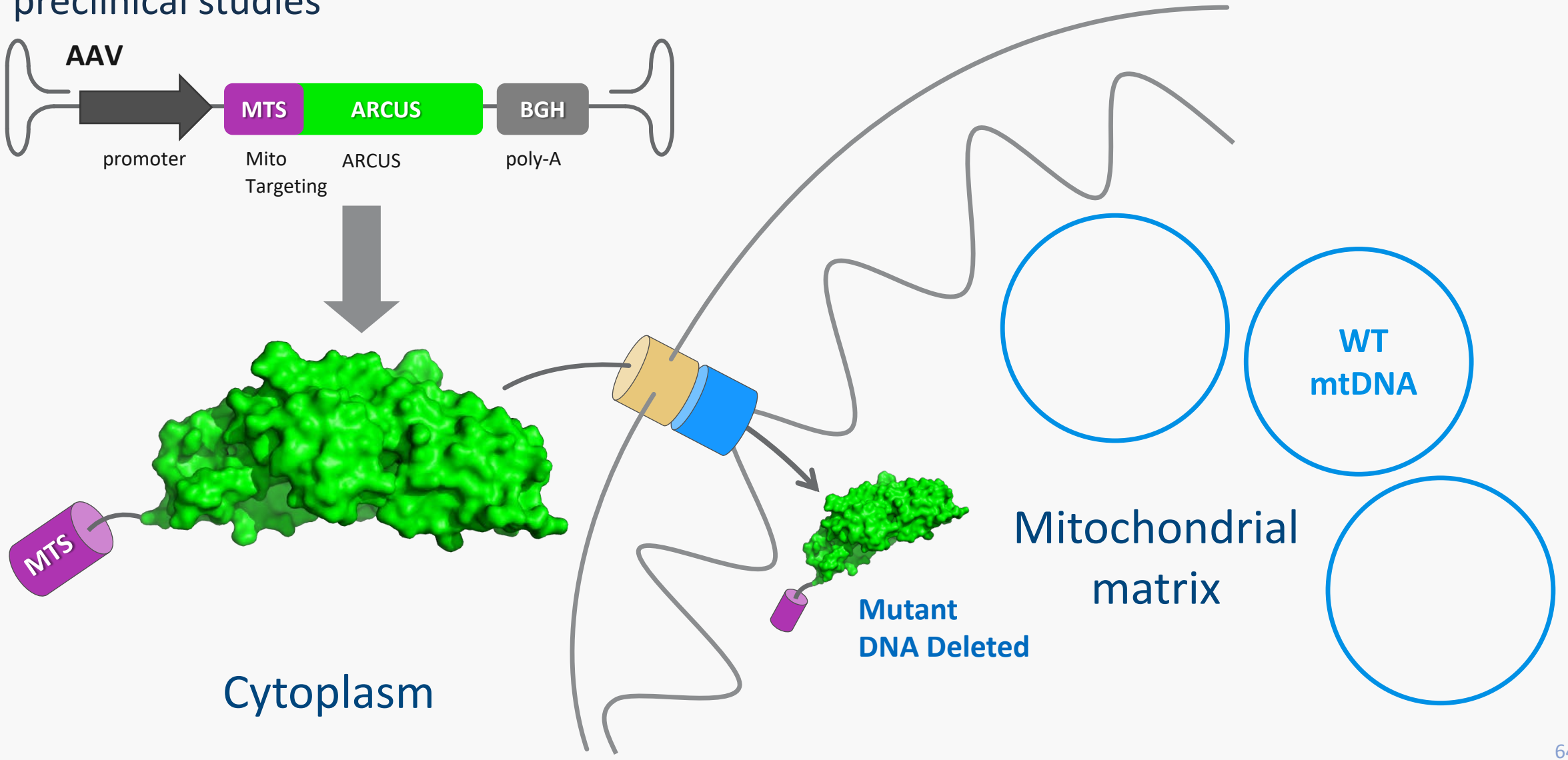
Mitochondrial Genome Editing

ARCUS has selectively eliminated mutant mitochondrial genomes that cause disease in preclinical studies



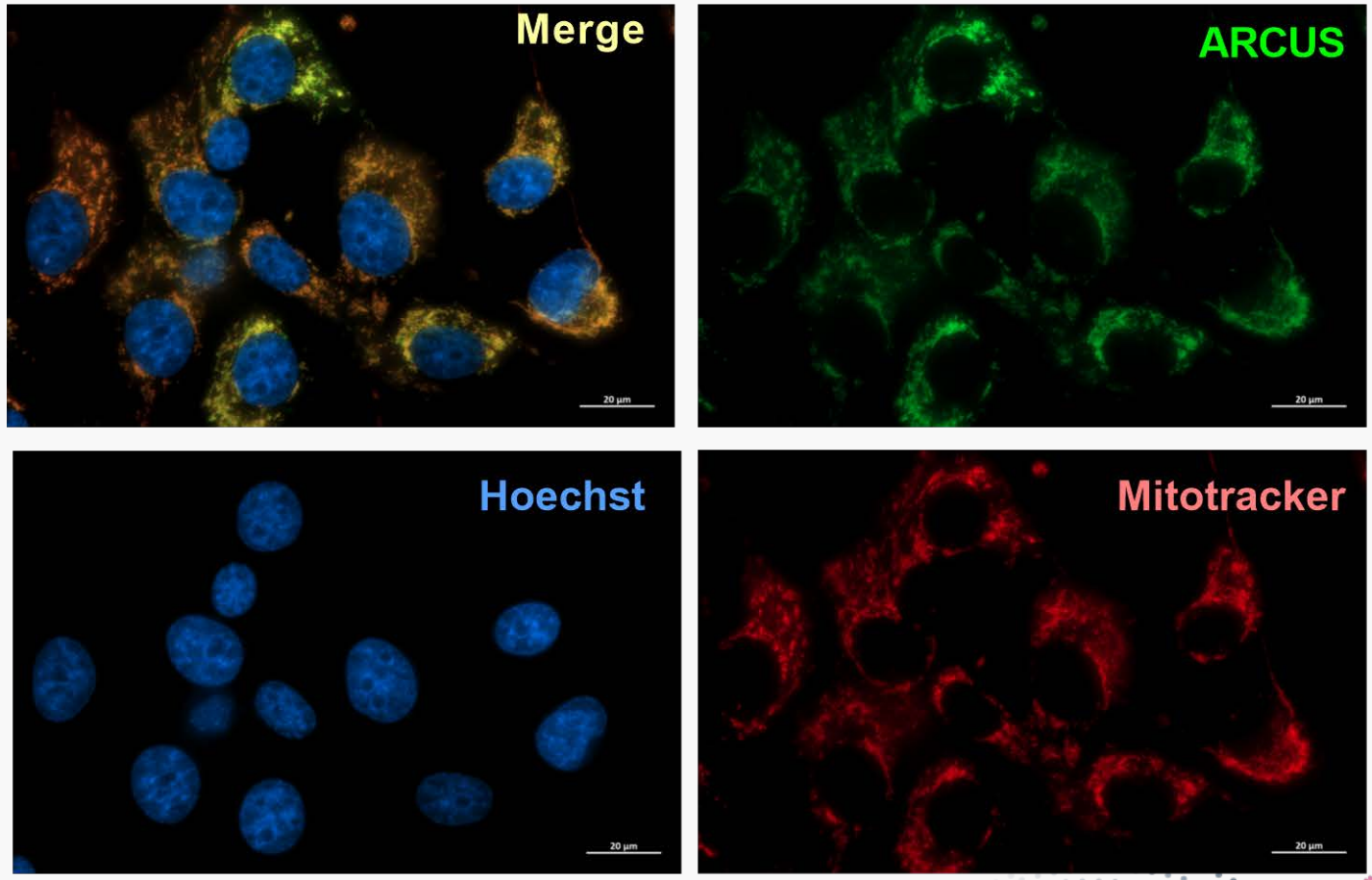
Mitochondrial Genome Editing

ARCUS has selectively eliminated mutant mitochondrial genomes that cause disease in preclinical studies



Mitochondrial Genome Editing

ARCUS fused to a Mitochondrial Targeting Sequence (MTS) localized to mitochondria in vitro



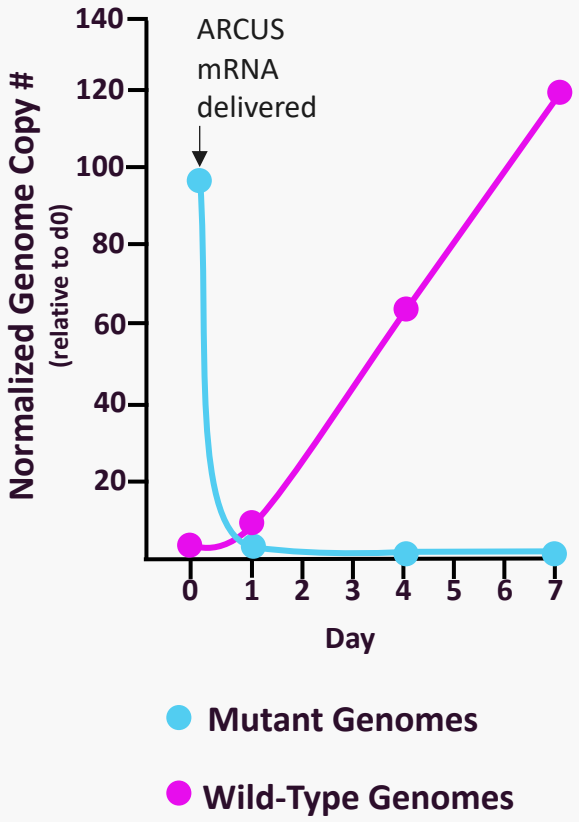
Zekonyte, *et al* (2021) *Nat Commun* 12(1):3210

Mitochondrial Genome Editing

ARCUS restored markers of mitochondrial function in a cell model of mitochondrial disease

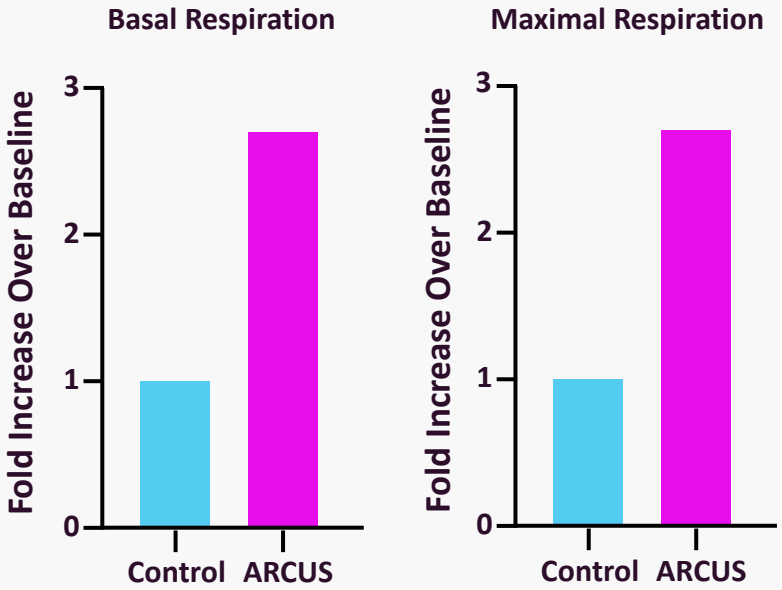
ARCUS Deleted Mutant Genomes

Hybrid cells were converted to >99% WT genomes in one week



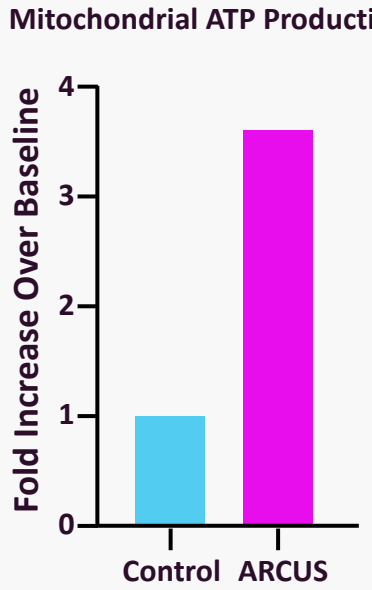
ARCUS Improved Respiration

Elimination of defective genomes improved basal and maximal respiration



ARCUS Increased ATP Production

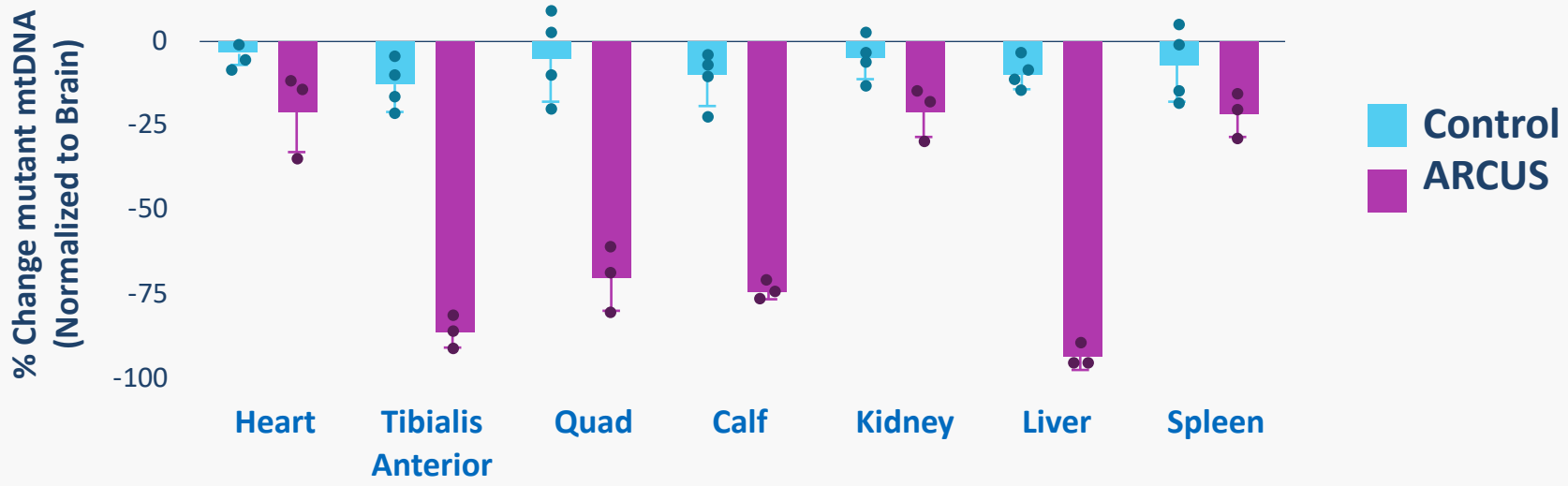
Restoration of mitochondria function increased ATP production by oxidative phosphorylation



Mitochondrial Genome Editing

AAV-delivered ARCUS eliminated mutant mitochondrial genomes in a mouse model

Reduction in mutant genomes following systemic AAV9-ARCUS delivery (4e9 vg/kg)

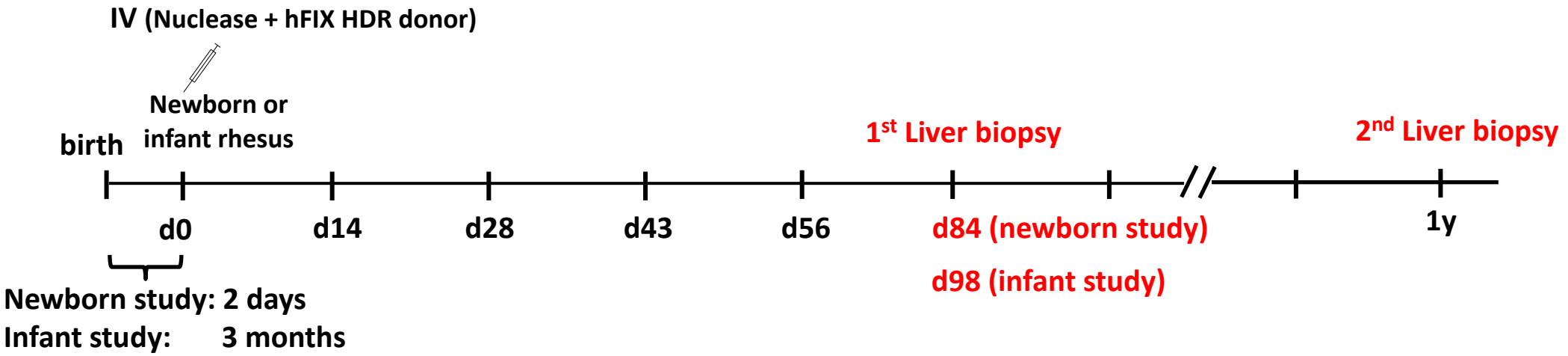


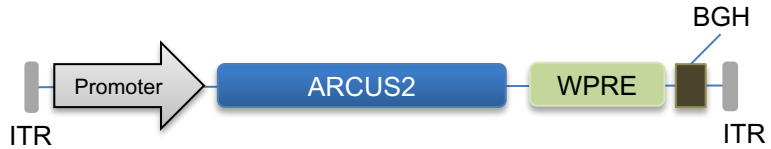
Zekonyte, *et al* (2021) *Nat Commun* 12(1):3210

Gene Insertion into the *PCSK9* locus in Newborn and Infant NHPs

In collaboration with the University of Pennsylvania Gene Therapy Program

ARCUS-mediated hFIX Gene Targeting in Newborn or Infant NHPs





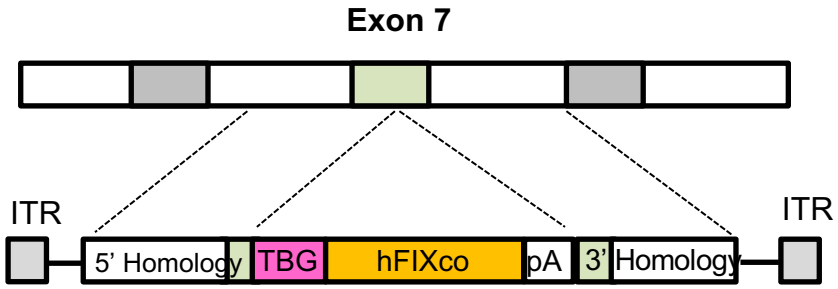
AAV.ARCUS2.WPRE

($1x10^{13}$ GC/kg)

AAV.hFIXco-HDR

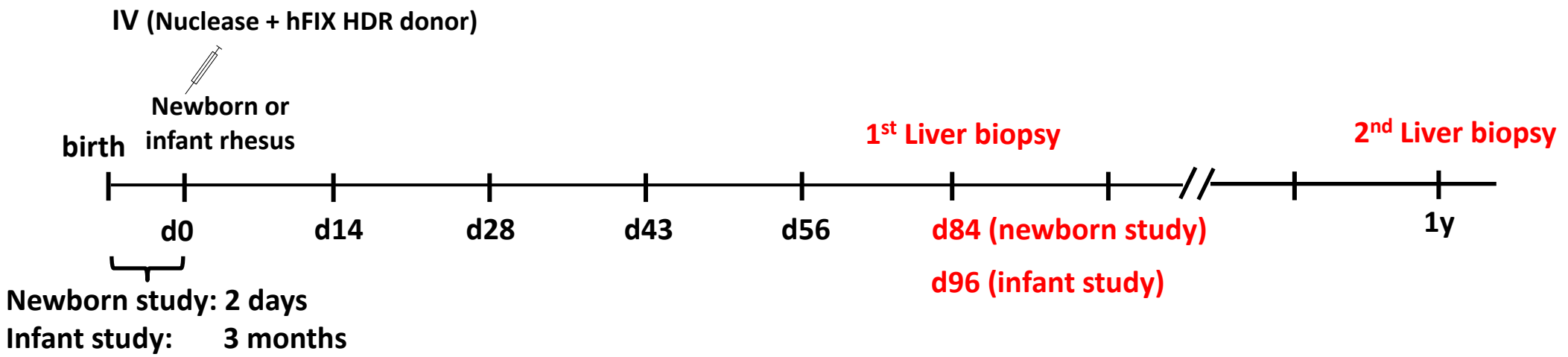
($3x10^{13}$ GC/kg)

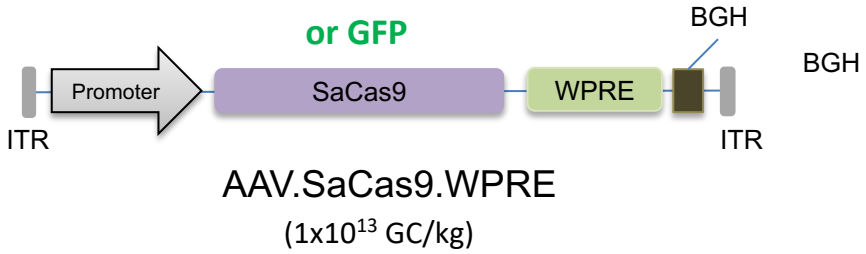
hPCSK9 locus

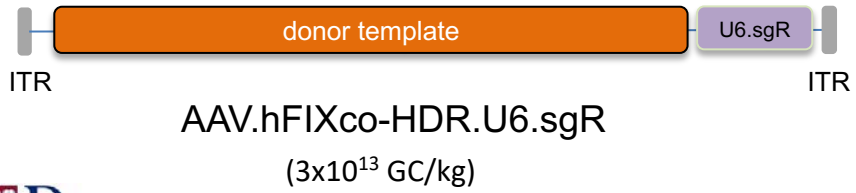


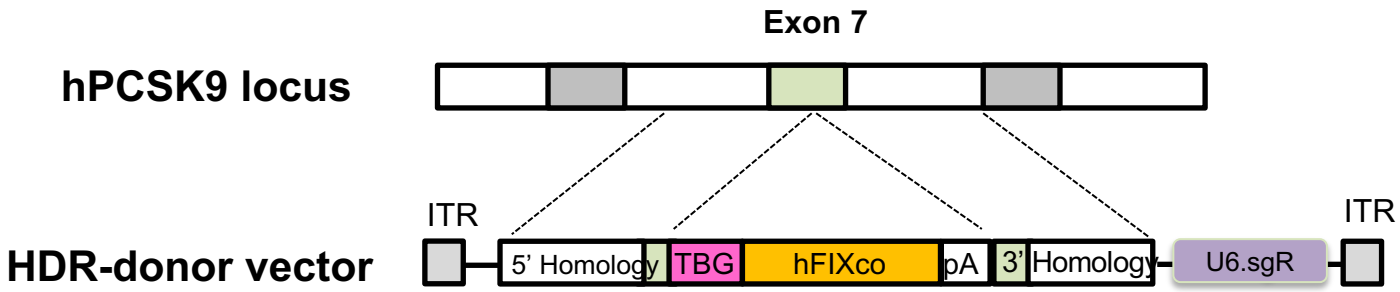
HDR-donor vector

CRISPR/Cas9-mediated hFIX Gene Targeting in Newborn or Infant NHPs

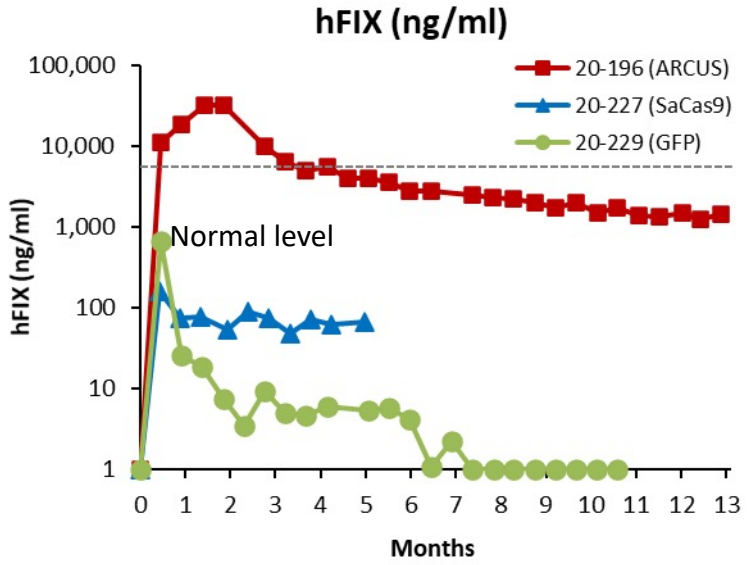


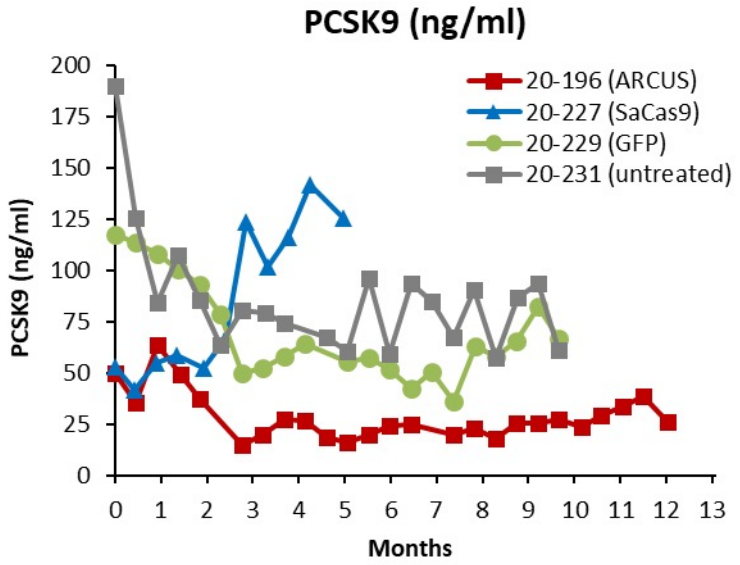


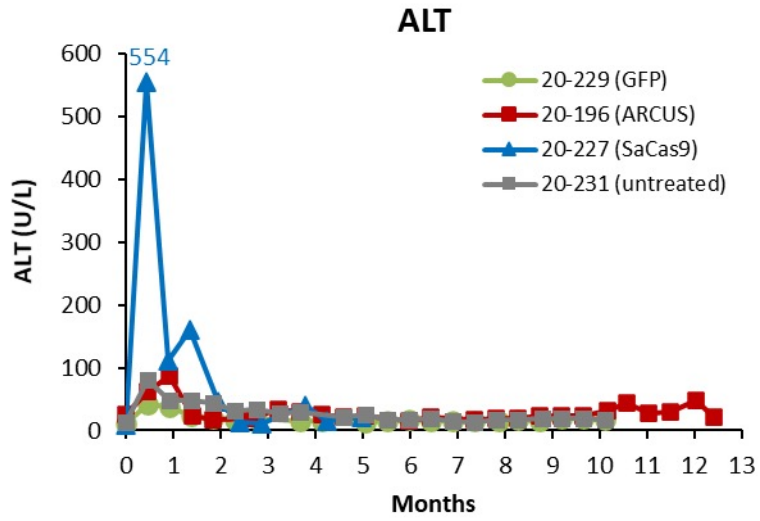


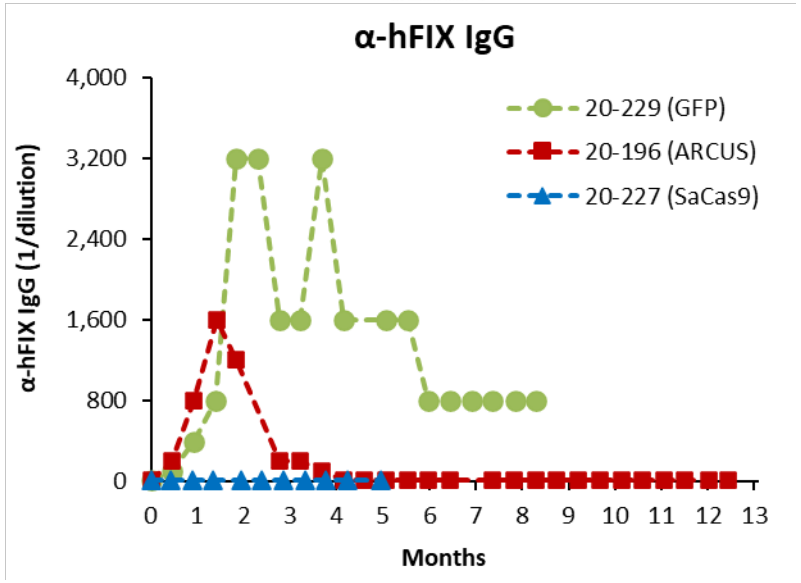


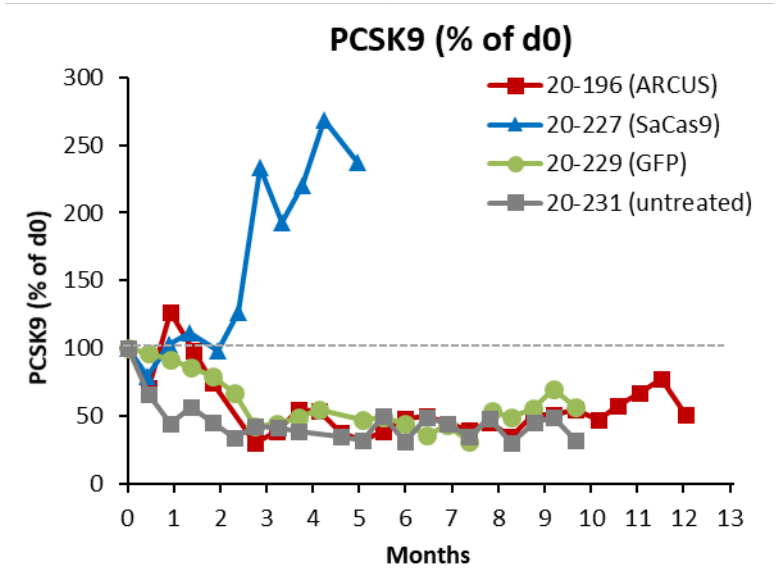
Nuclease-mediated hFIX Gene Targeting in *Newborn* NHPs

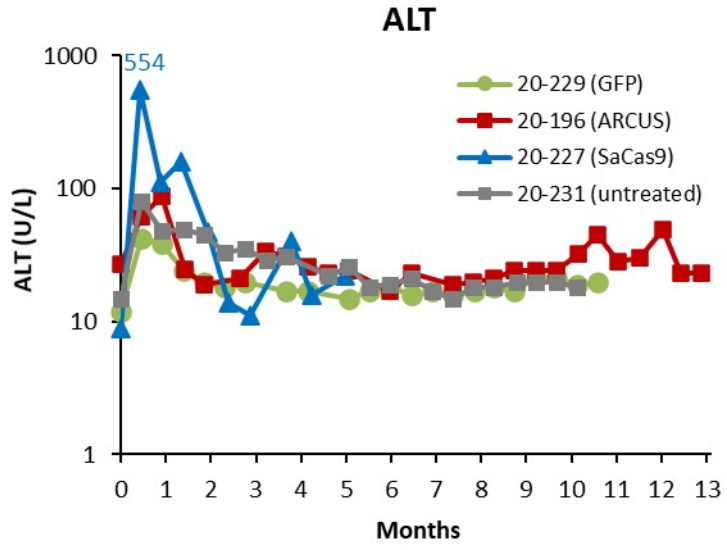




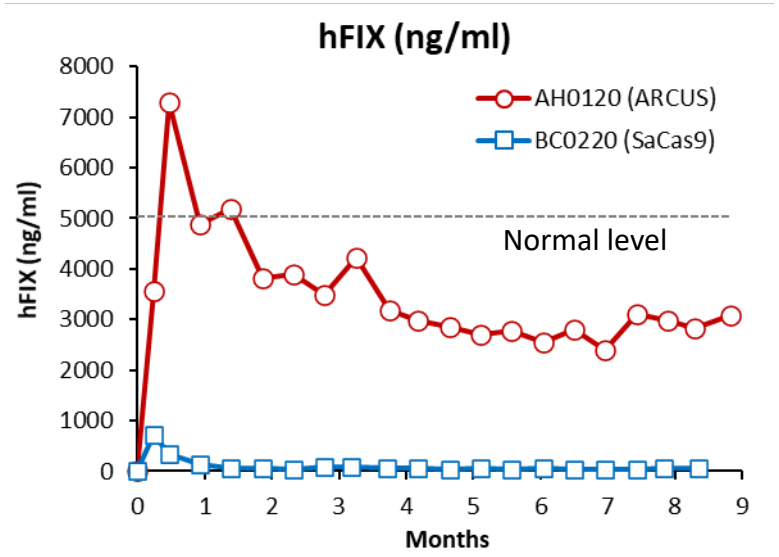


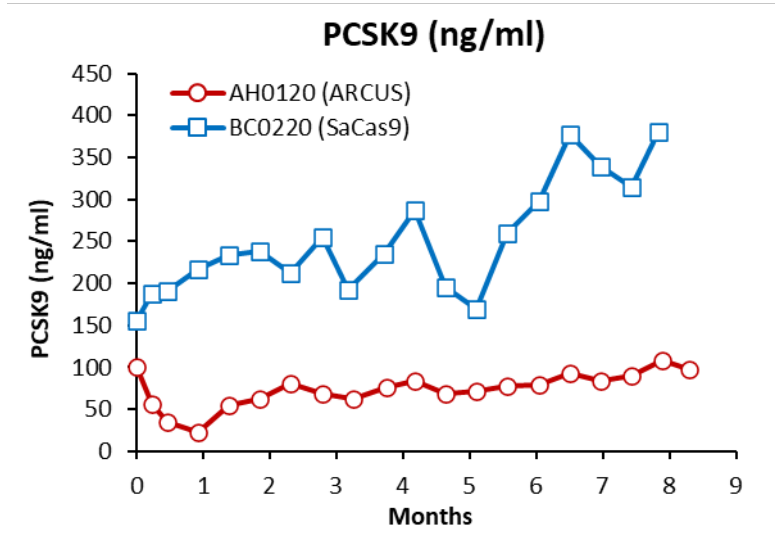


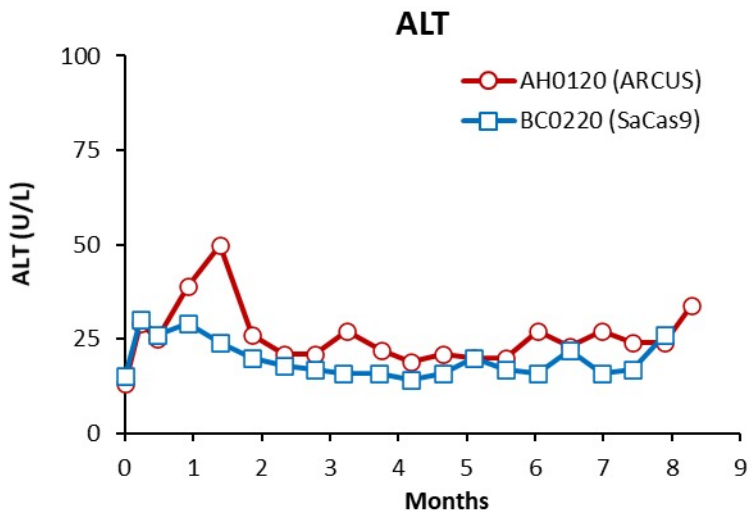


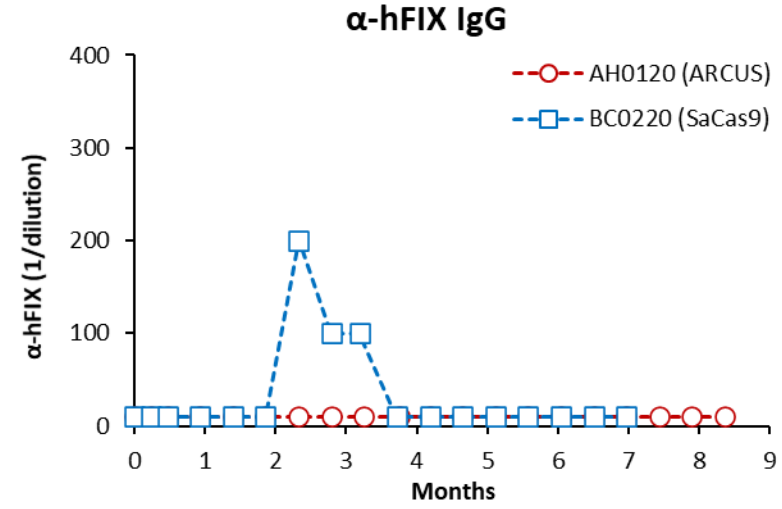


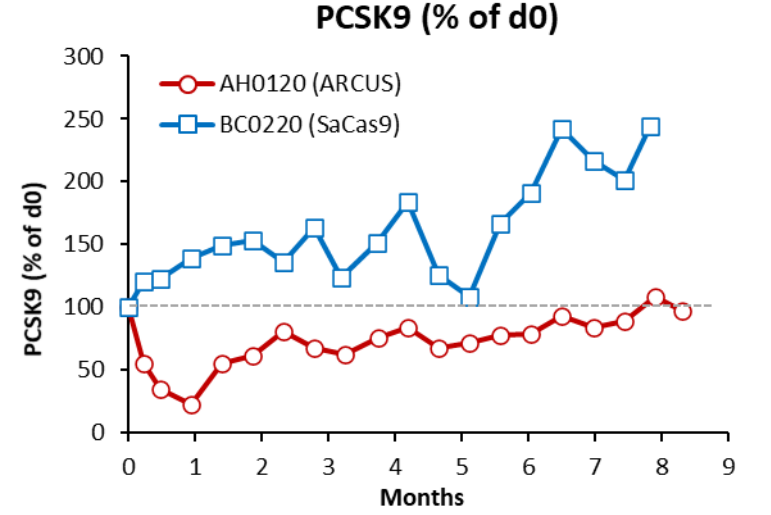
Nuclease-mediated hFIX Gene Targeting in *Infant* NHPs

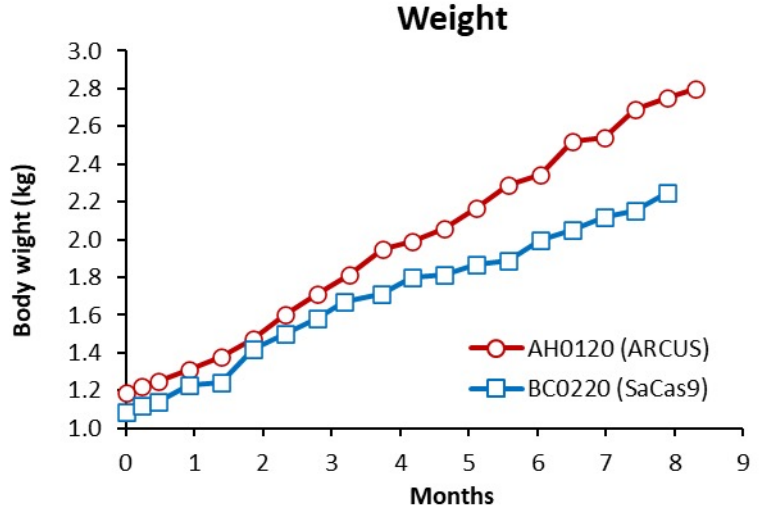






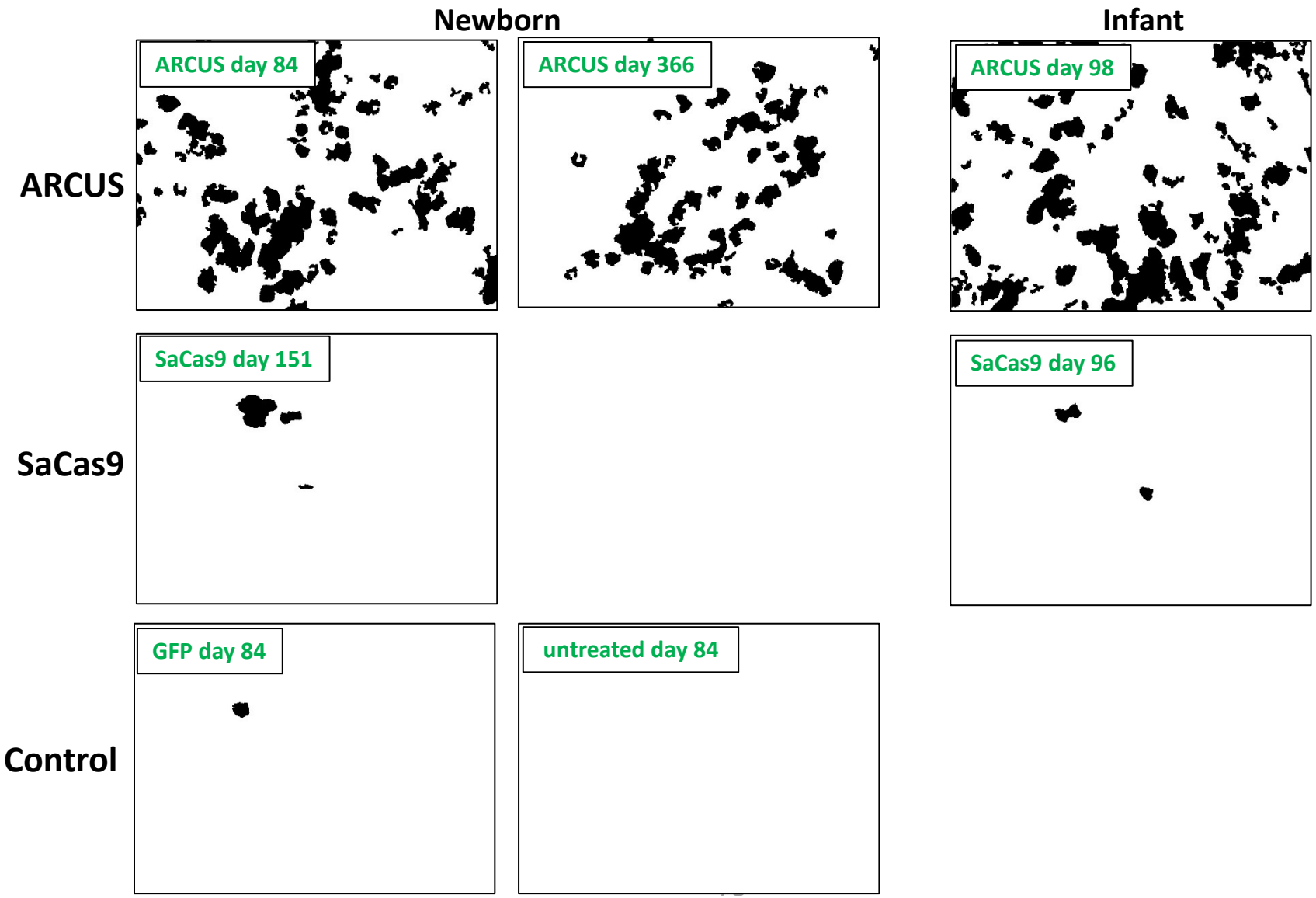






Nuclease-mediated Gene Targeting in *Newborn* and Infant NHPs

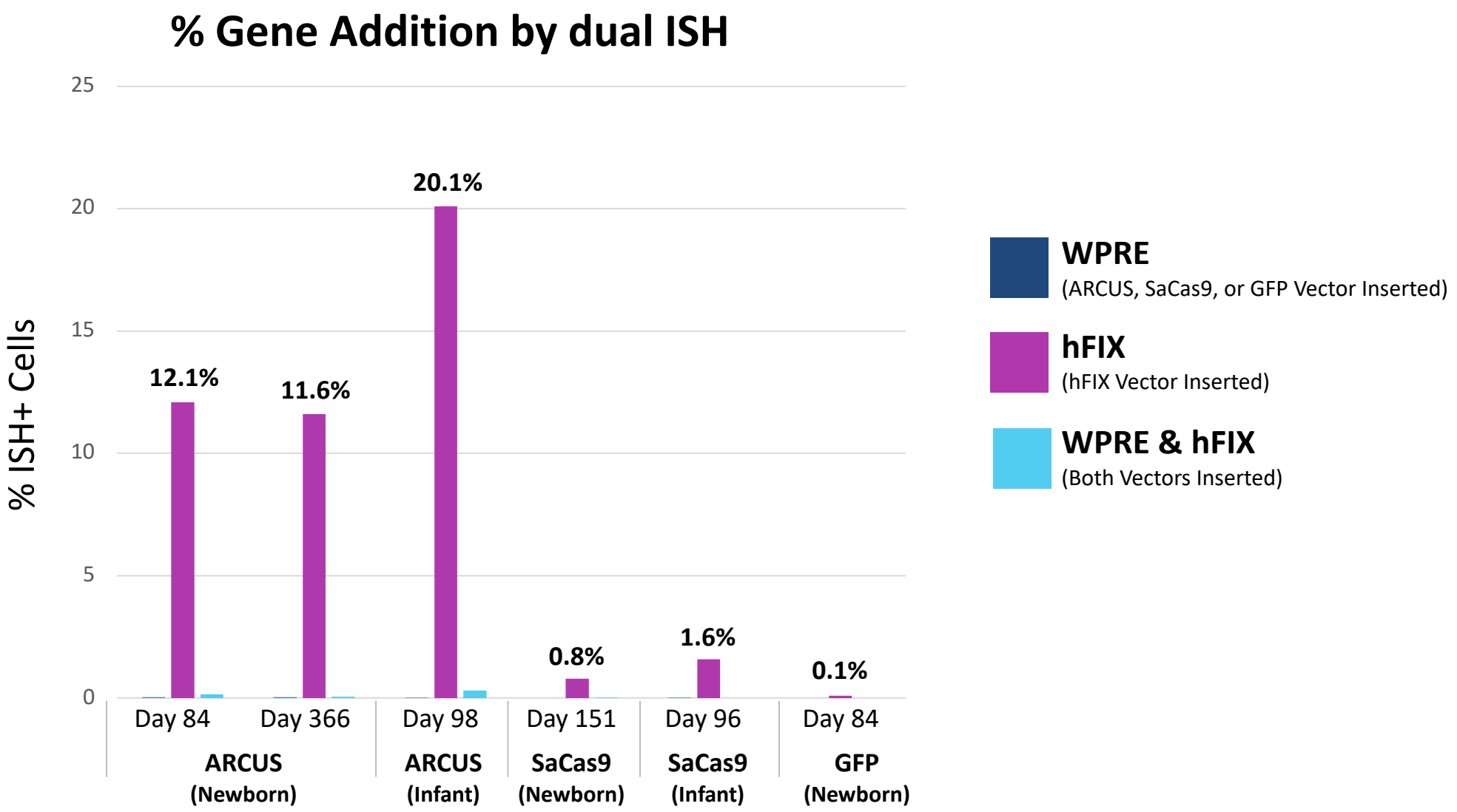
hFIXco ISH – Digitalized images for quantification of transduction %



Penn
University of Pennsylvania

GENE THERAPY PROGRAM

Nuclease-mediated Gene Targeting in Newborn and Infant NHPs



Conclusions

- Transgenes were targeted efficiently to the *PCSK9* locus using ARCUS in newborn and infant NHPs
- Gene addition appeared to be stable over time
- This may represent a “universal” approach to treating rare genetic diseases caused by loss-of-function mutations in liver

1

PRECISION & VERSATILITY

ARCUS has the potential to address a broader spectrum of genetic diseases

2

3 INDs/CTAs in **3** YEARS

Program	Indication	Delivery	Research	Candidate Selection	IND-Enabling	Expected IND/CTA
PBGENE-PCSK9	Familial Hypercholesterolemia	AAV				2022
PBGENE-PH1	Primary Hyperoxaluria Type 1	LNP				2023
PBGENE-HBV	Chronic Hepatitis B	LNP				2024

3

ECURE

NEW Collaboration focused on gene insertion & accelerating clinical validation of ARCUS