Shifting Heteroplasmy with PBGENE-PMM: Gene Editing Therapy for m.3243A>G Associated Mitochondrial Myopathy

Wendy Shoop, PhD

June 27, 2024

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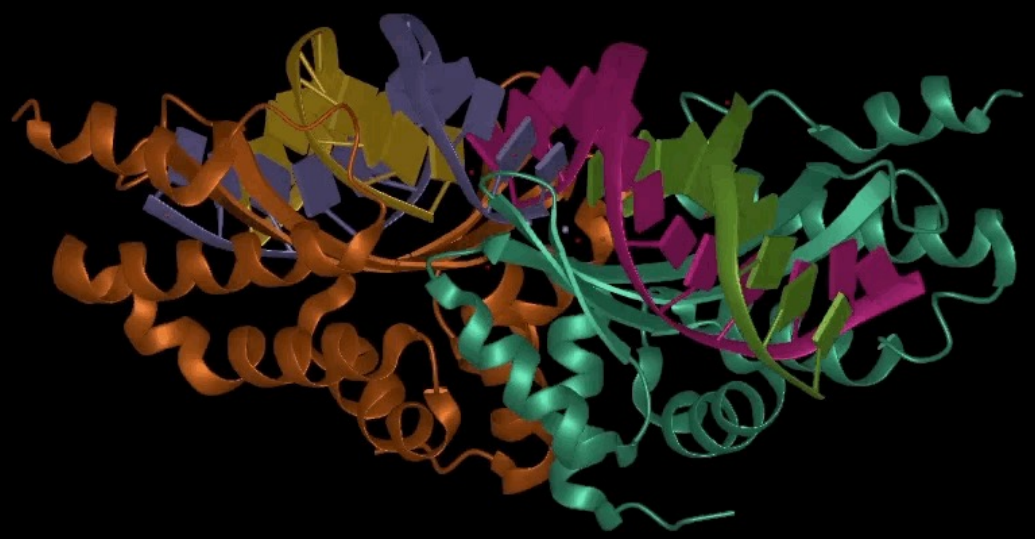
Disclosures

- I am an employee of Precision BioSciences.

Outline

- Precision BioSciences and ARCUS gene editing
- Applications for ARCUS gene editing of mitochondrial DNA
  - Common deletion (del_mtDNA^{4977})
  - m.3243A>G
  - Mouse m.5024C>T
- PBGENE-PMM

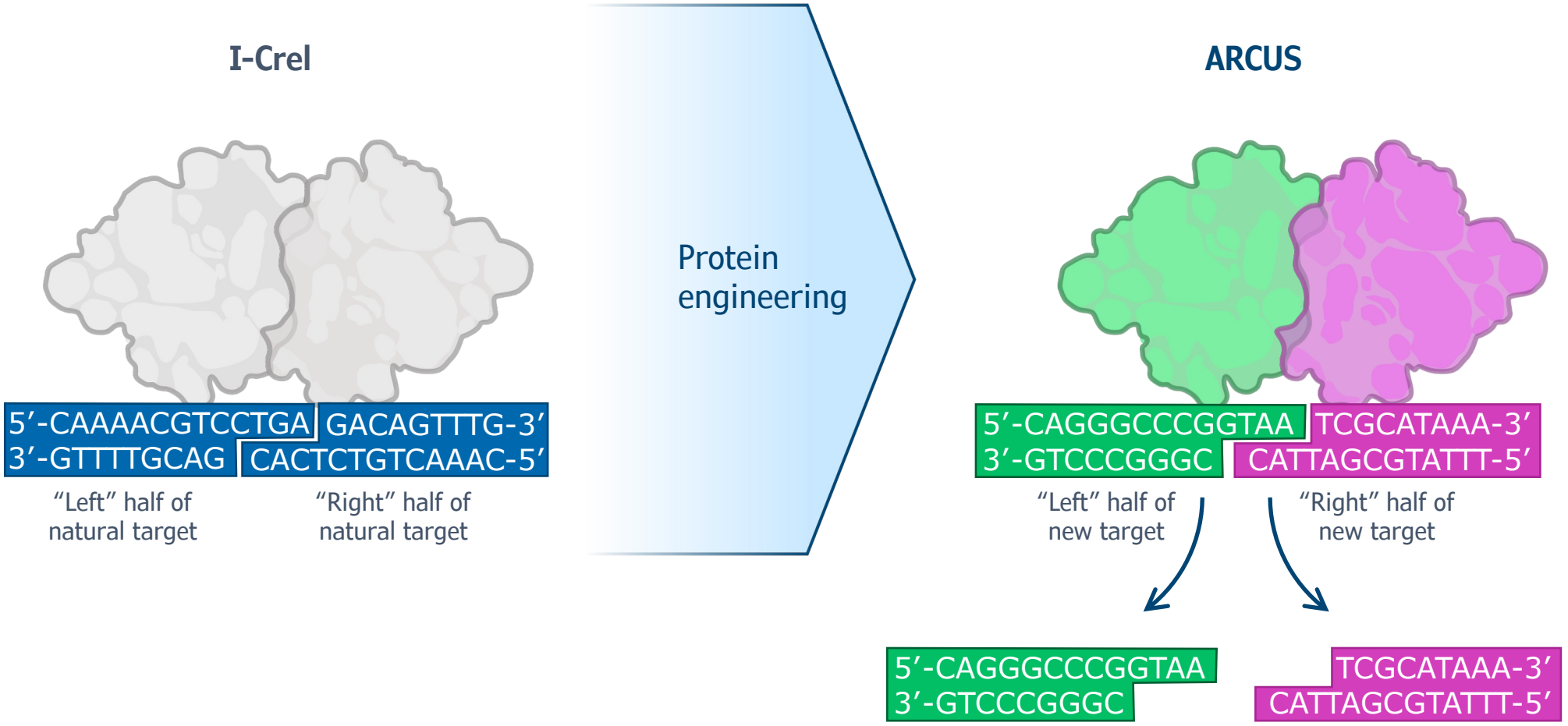
ARCUS: Engineering nature's gene editing system



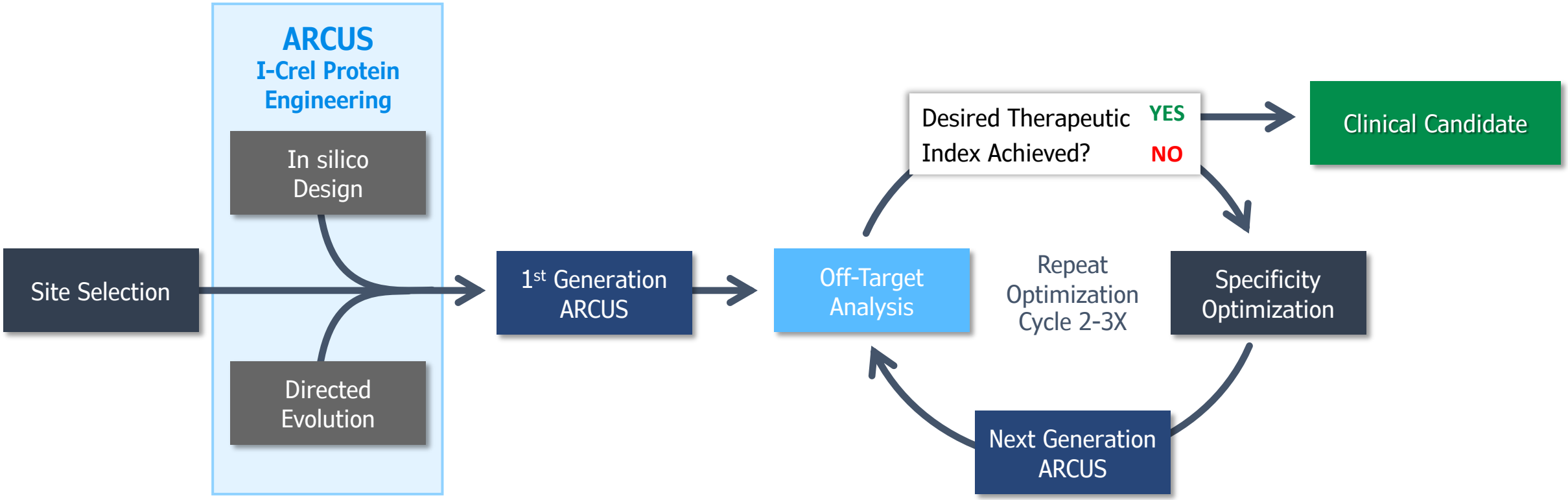
I-CreI bound to target DNA sequence

- ARCUS is derived from **I-*Cre*I**, a homing endonuclease from algae
- Recognizes 22bp target sequence through extensive **protein-DNA** interactions
- Does not require guide RNA
- DNA recognition and cleavage activity are fully integrated into **one protein** for tight regulation

ARCUS generates targeted DNA double-strand breaks



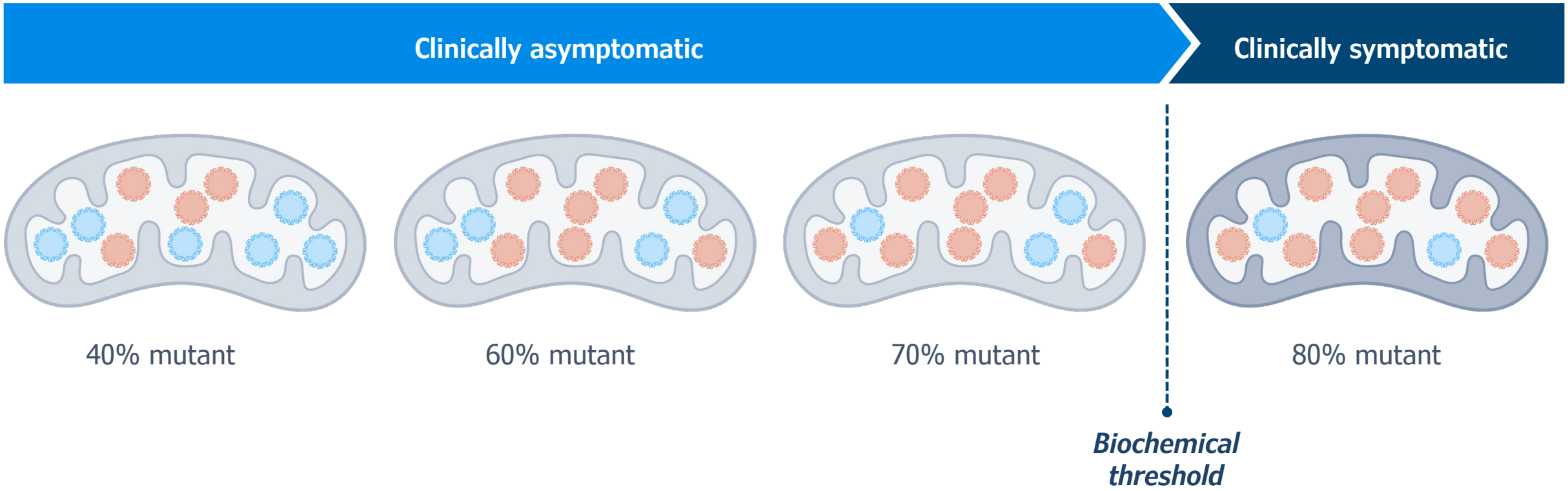
ARCUS protein engineering is an iterative process



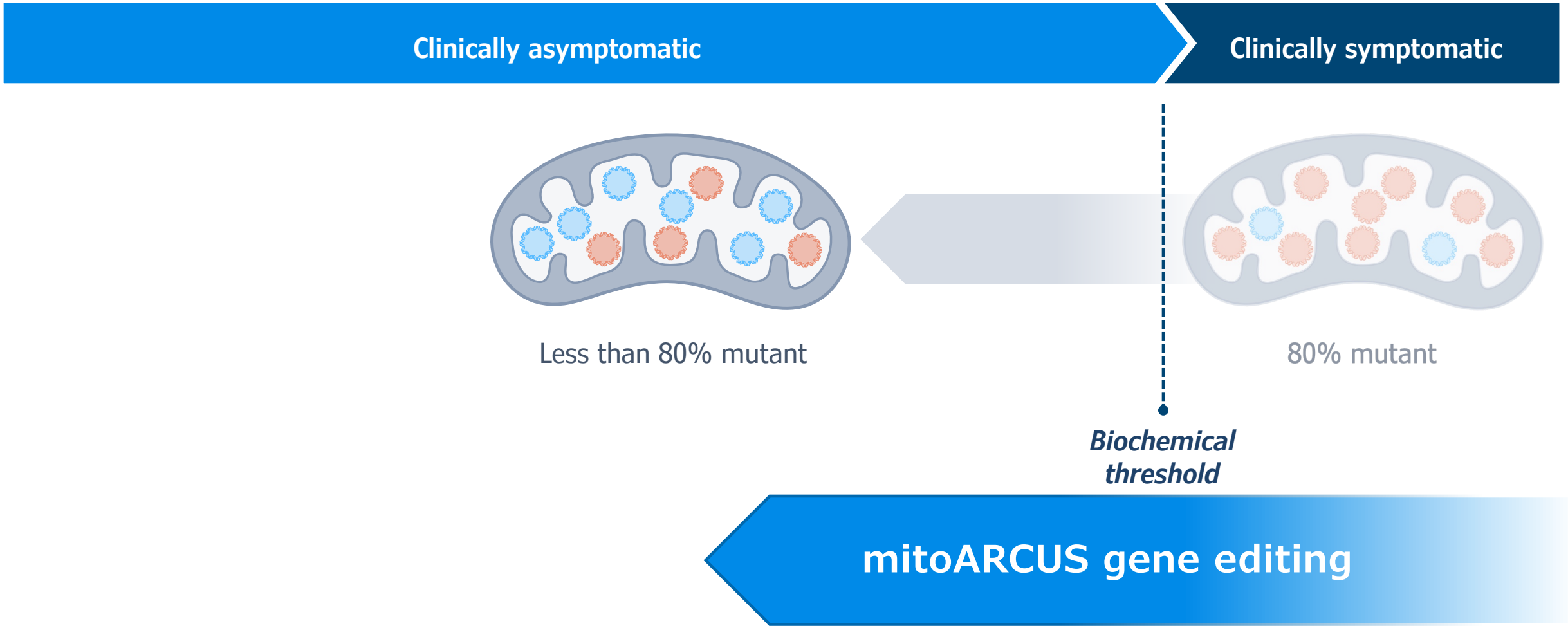
Applications for ARCUS

- **Nuclear gene editing**
  - Targeted gene insertion
    - *ECUR-506 IND and CTA approved*
  - Elimination of viral DNA
    - *PBGENE-HBV IND/CTA expected 2024*
  - Gene knockout
  - Excision of precise regions of genome
- **Mitochondrial gene editing (mitoARCUS)**

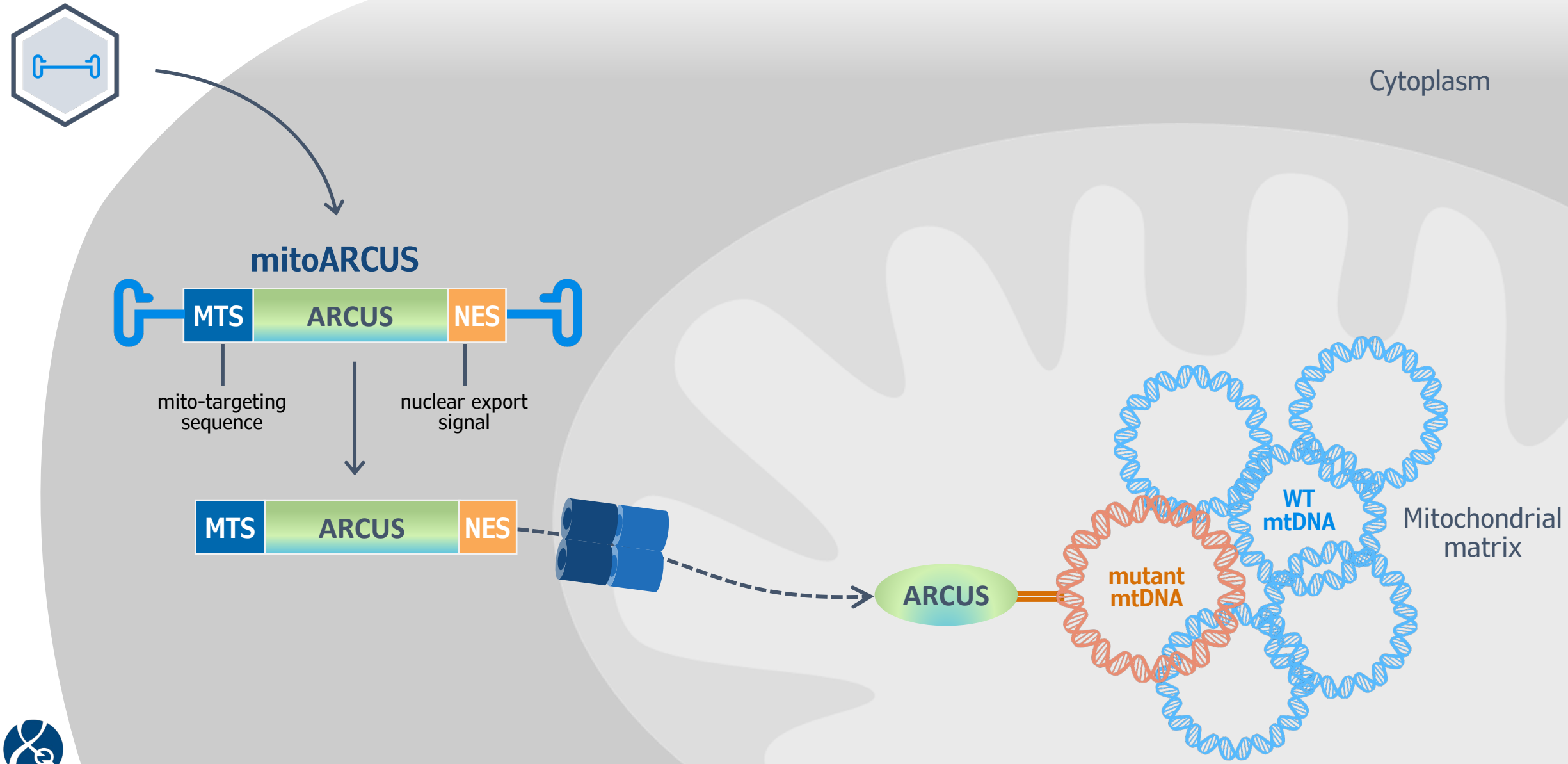
Heteroplasmic mtDNA mutations exhibit a threshold at which symptoms manifest



Heteroplasmic mtDNA mutations exhibit a threshold at which symptoms manifest



mitoARCUS therapeutic approach to shift heteroplasmy



mitoARCUS gene editing seeks to eliminate mutant heteroplasmic mtDNA

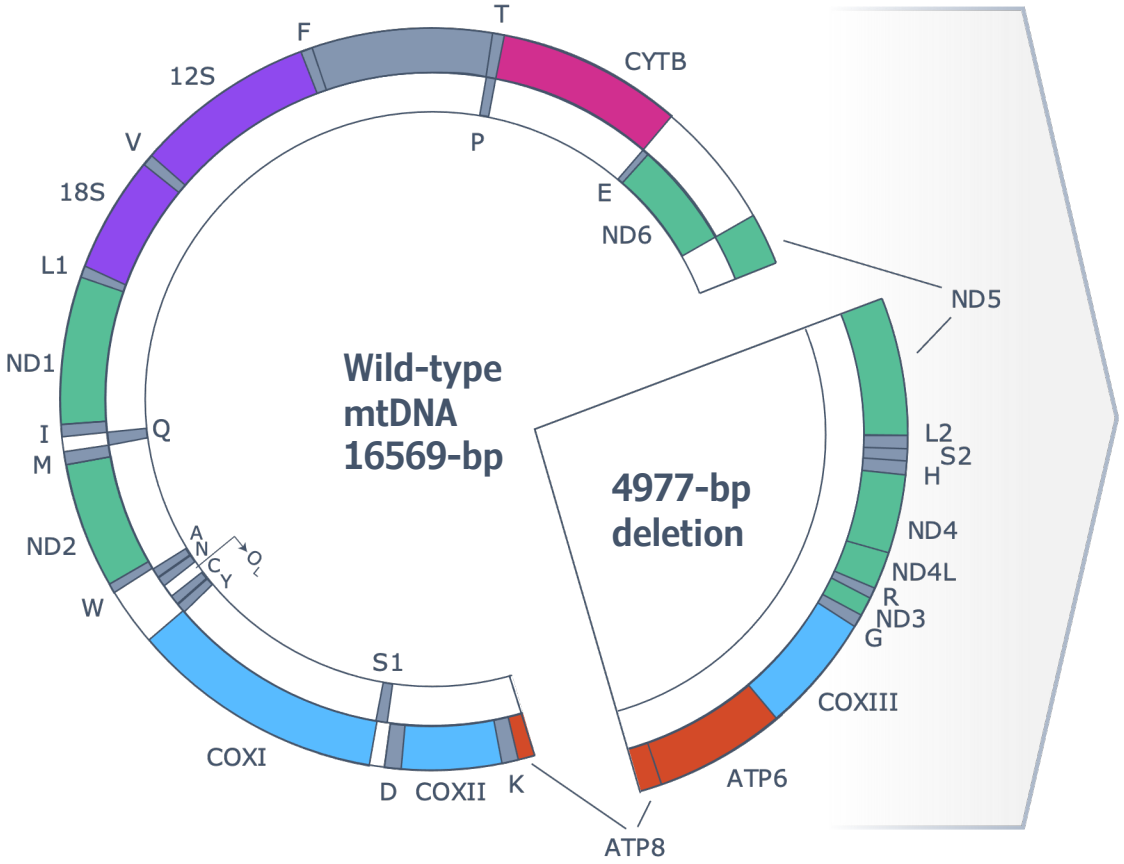
Applications

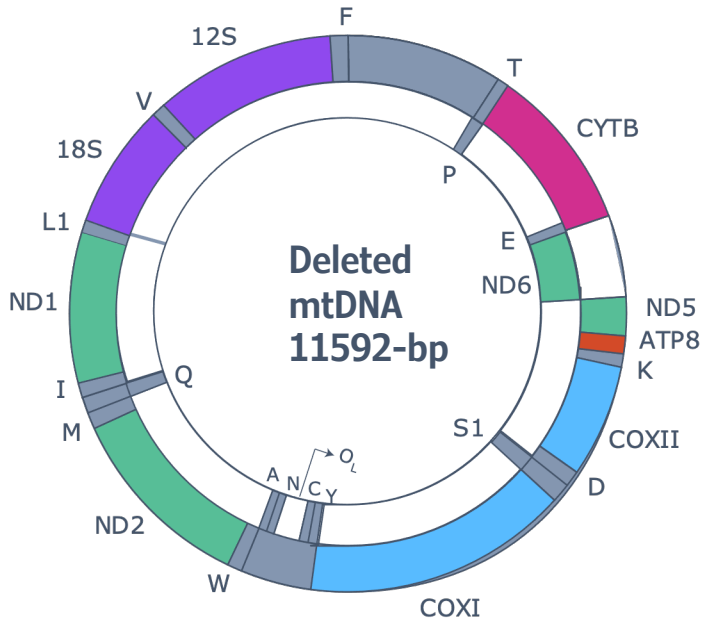
- Heteroplasmic deletions
- Heteroplasmic point mutations

Discovery stage	**Lead mitochondrial editing therapeutic program**	Research investigation
Common deletion (del_mtDNA^{4977})	**m.3243A>G**	**Mouse m.5024C>T**

Common deletion (del_mtDNA^{4977})

4977bp of mtDNA are missing in genomes with the common deletion

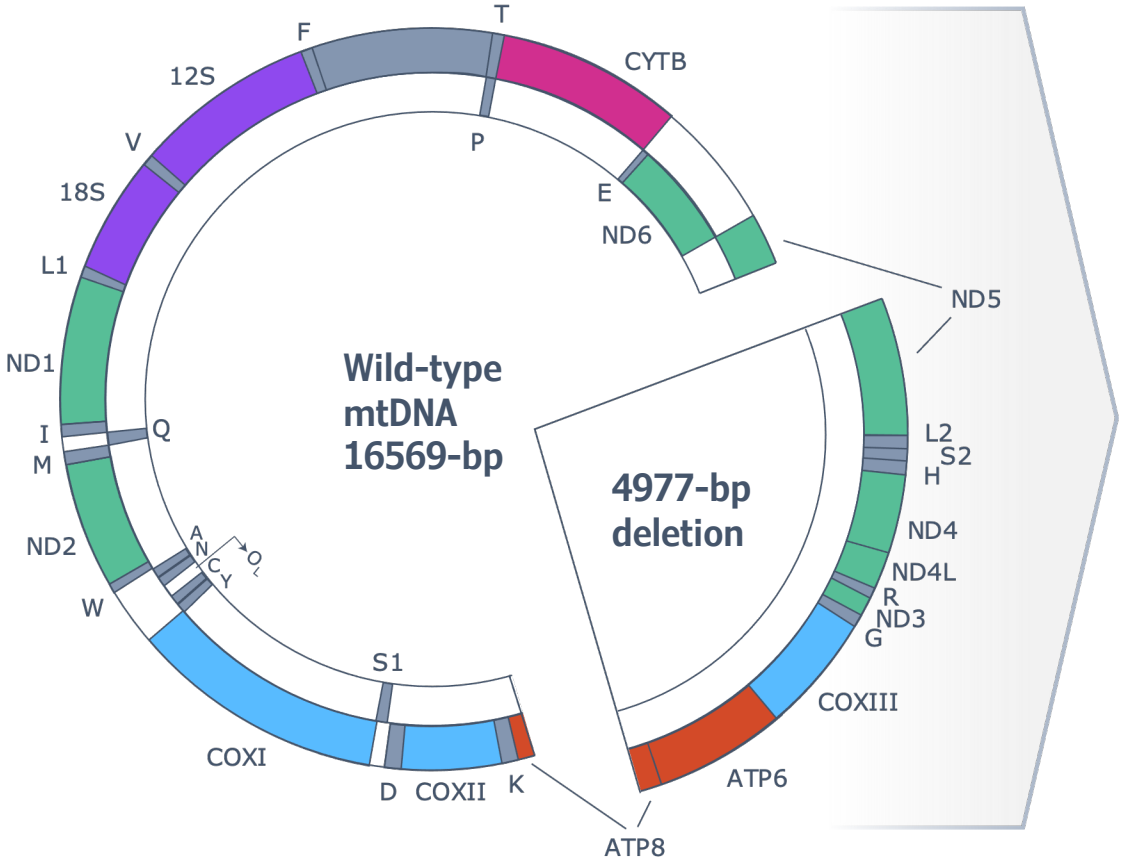


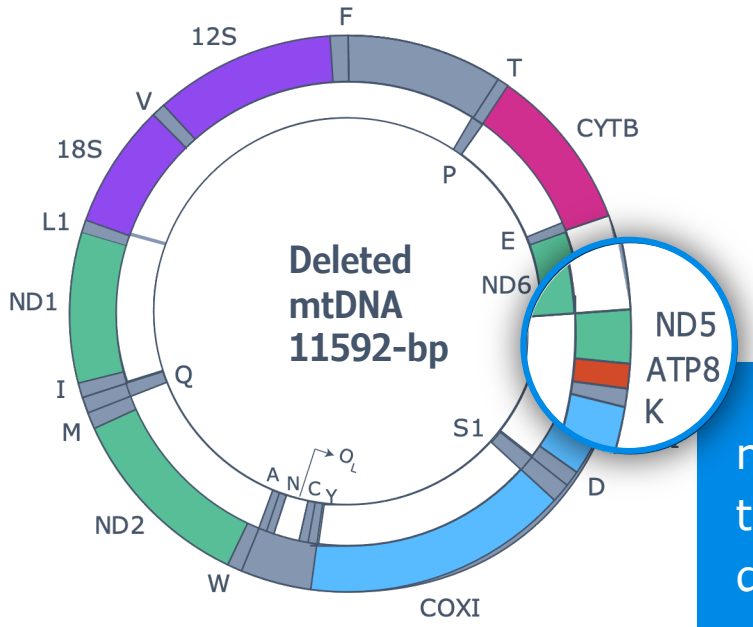


Implicated in:

- Myopathies
- Kearns-Sayre syndrome
- Alzheimer's disease
- Chronic progressive external ophthalmoplegia
- Pearson syndrome

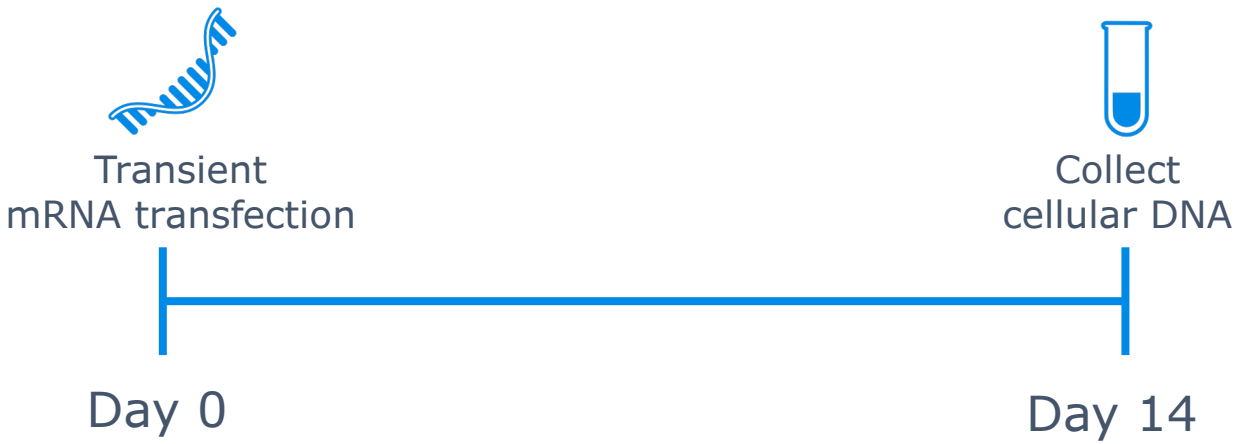
4977bp of mtDNA are missing in genomes with the common deletion

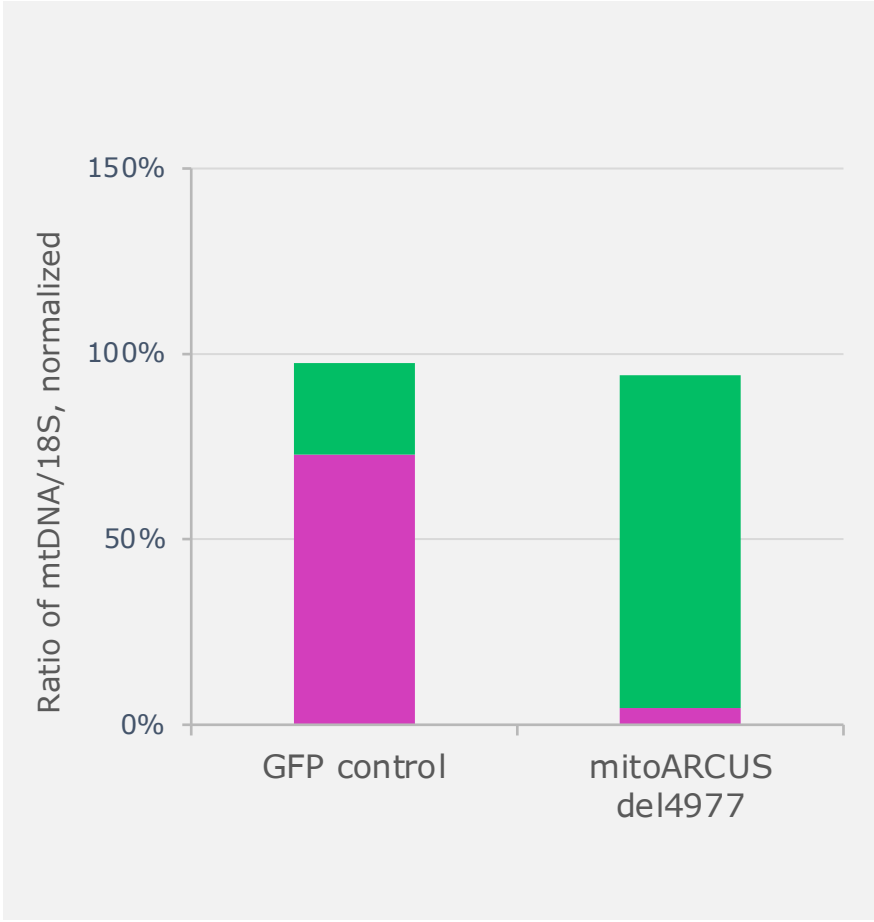




mitoARCUS nuclease that recognizes deletion breakpoint = **mitoARCUS_del4977**

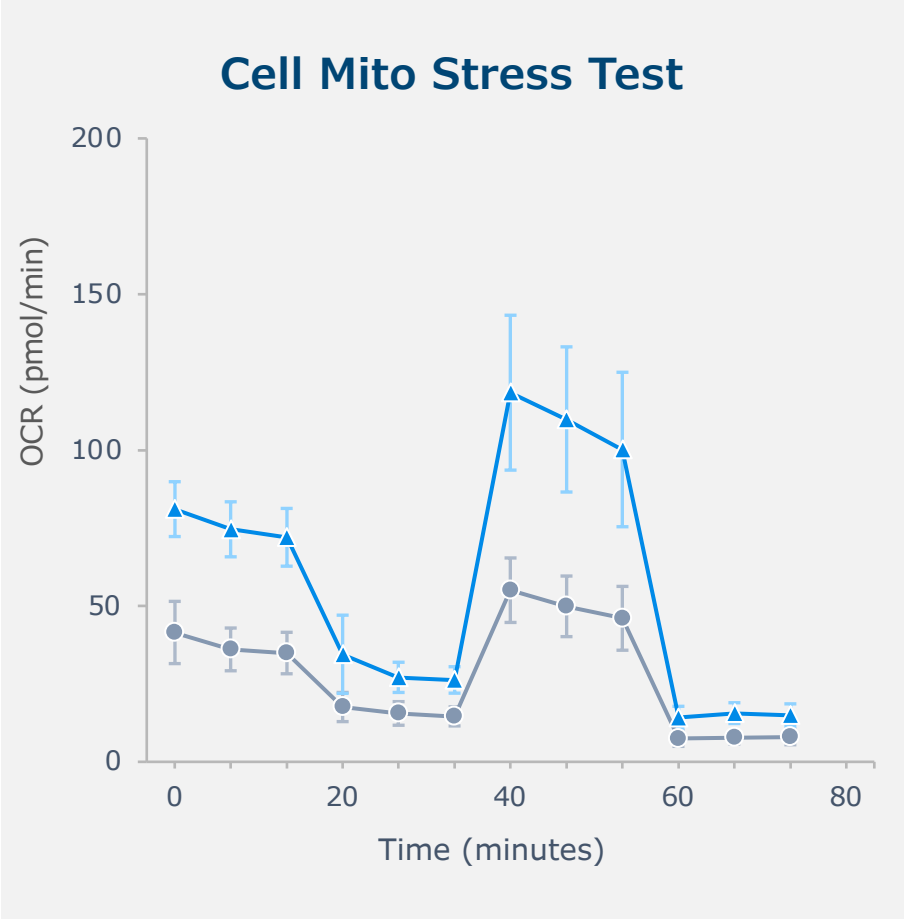
mitoARCUS_del4977 effectively eliminates mtDNA molecules containing common deletion *in vitro*

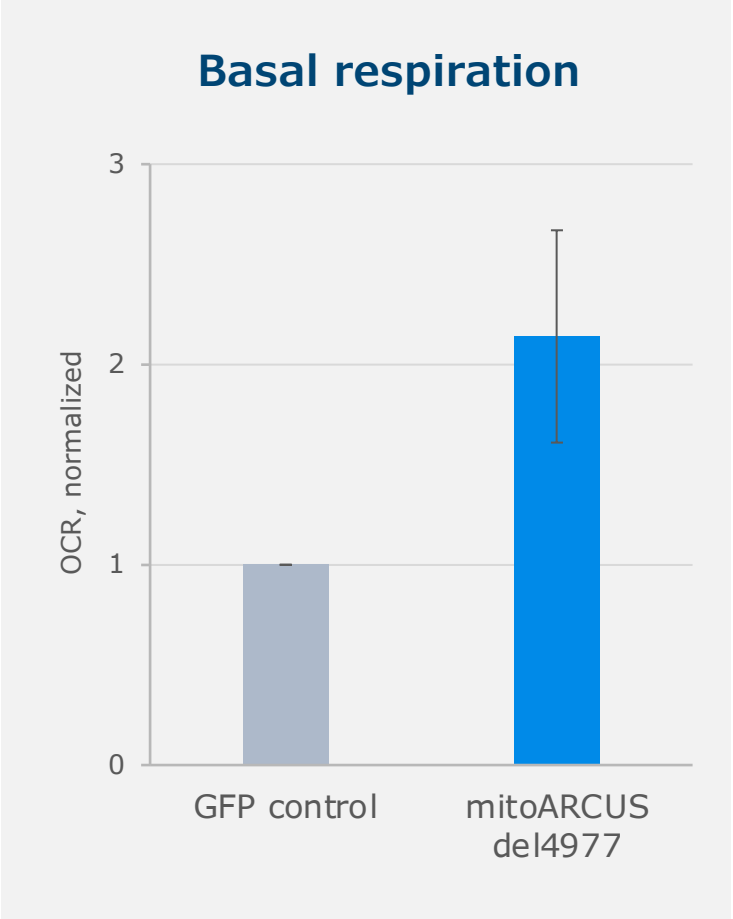


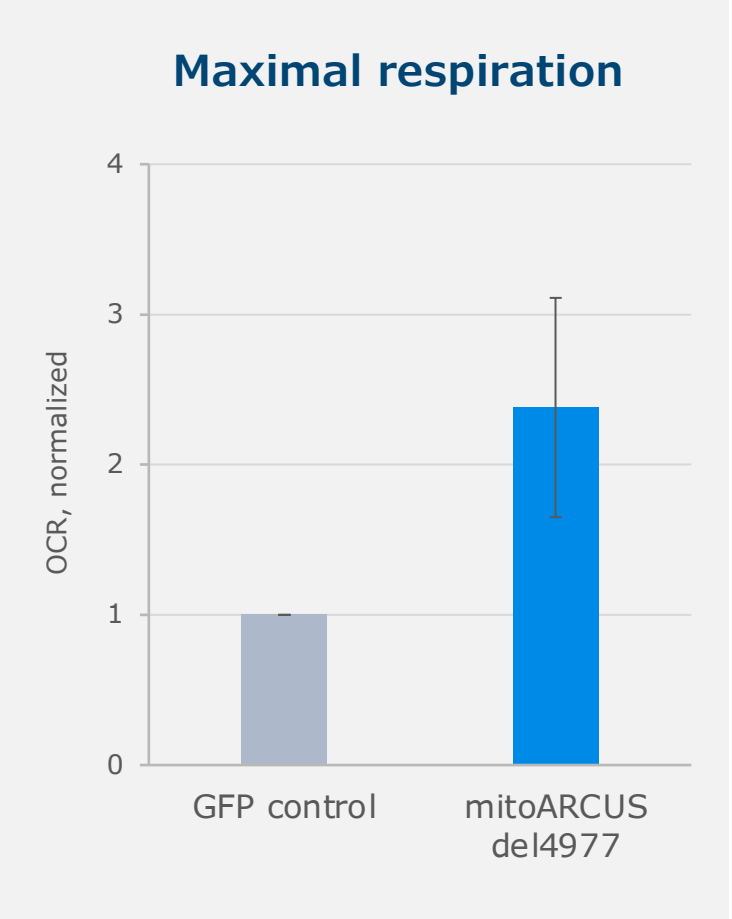


Unpublished data

mitoARCUS_del4977-edited cells demonstrates improved mitochondrial function



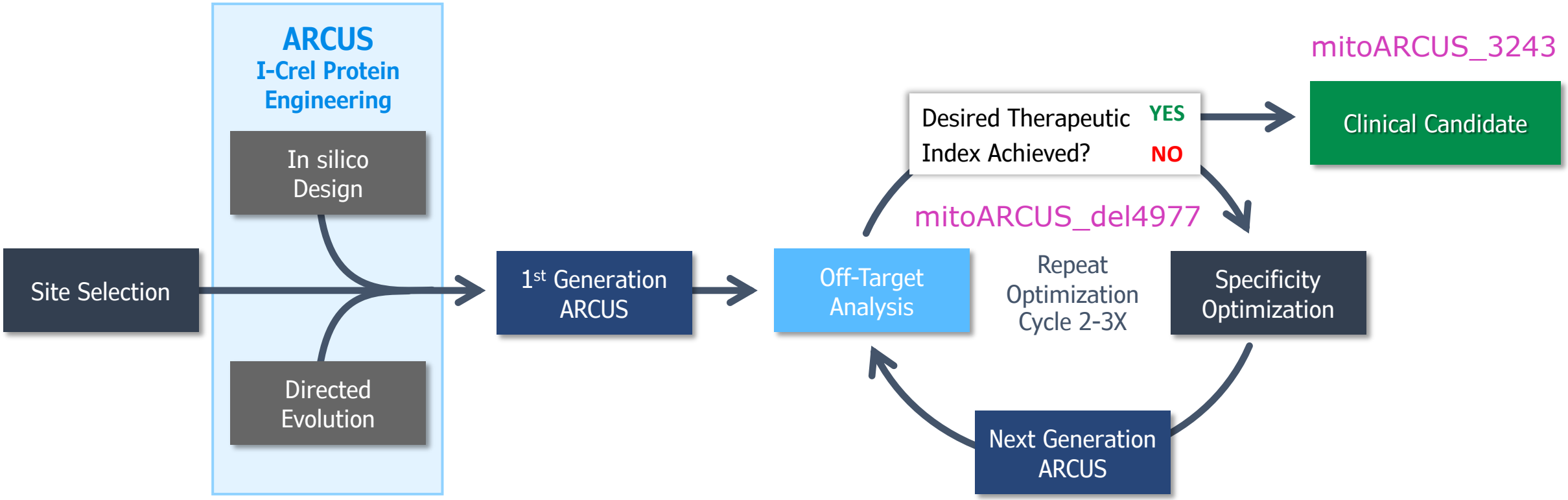




GFP control mitoARCUS_del4977

Unpublished data

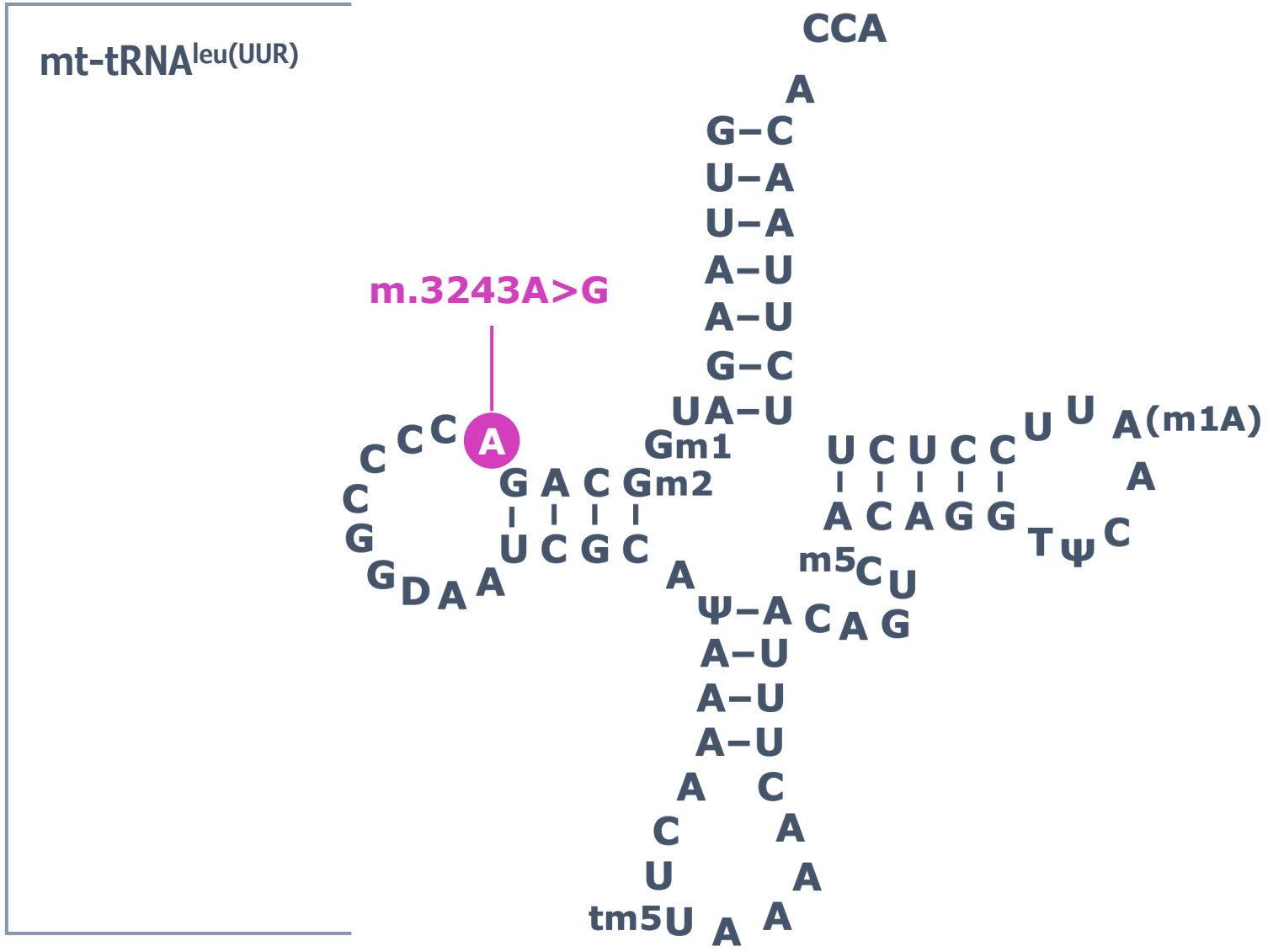
Nuclease optimization for mitoARCUS_del4977 is ongoing



m.3243A>G


A
G–C
U–A
U–A
A–U
A–U
G–C
UA–U
C C C A
C
C
G
G D A A
G A C Gm2
I I I I
U C G C
Gm1
A
U C U C C
I I I I I
A C A G G
U U A(m1A)
A
T ψ C
m5C U
Ψ–A C A G
A–U
A–U
A–U
A C
C A
U A
tm5U A A

m.3243A>G is the most common pathogenic mtDNA point mutation



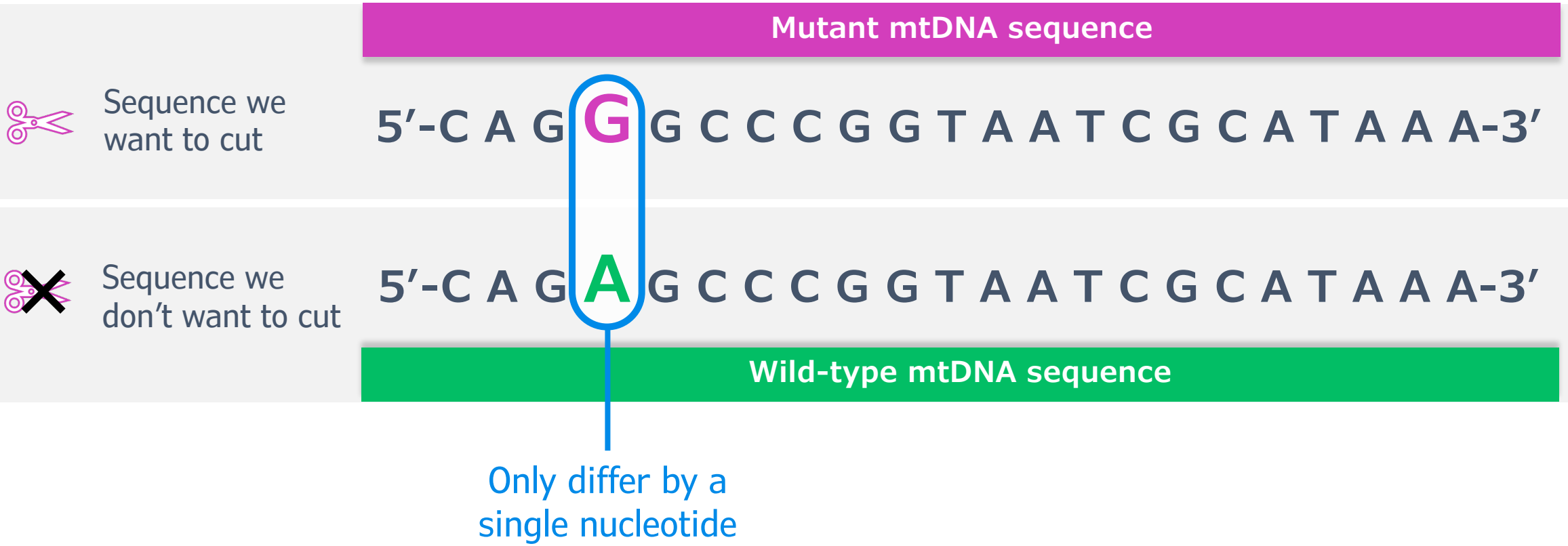
m.3243A>G

- Estimated population prevalence of ~1 in 500 individuals[1]
- Impacts tRNA stability/modification and disrupts mitochondrial protein production
- Implicated in many disorders

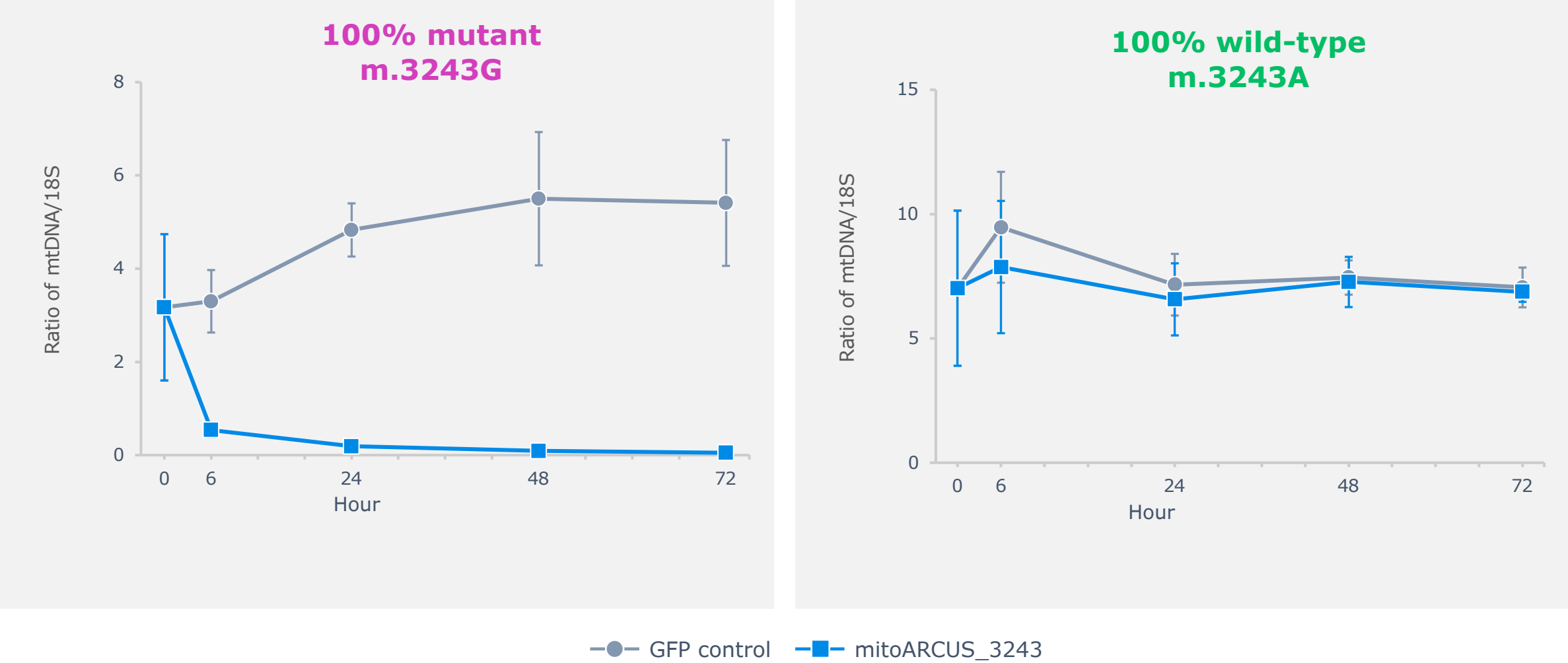
Sources:
1. Manwaring et al 2007. Population prevalence of the MELAS A3243G mutation. Mitochondrion

Nuclease specificity is crucial to discriminate single nucleotide change

mitoARCUS nuclease specific to mutant m.3243G = **mitoARCUS_3243**

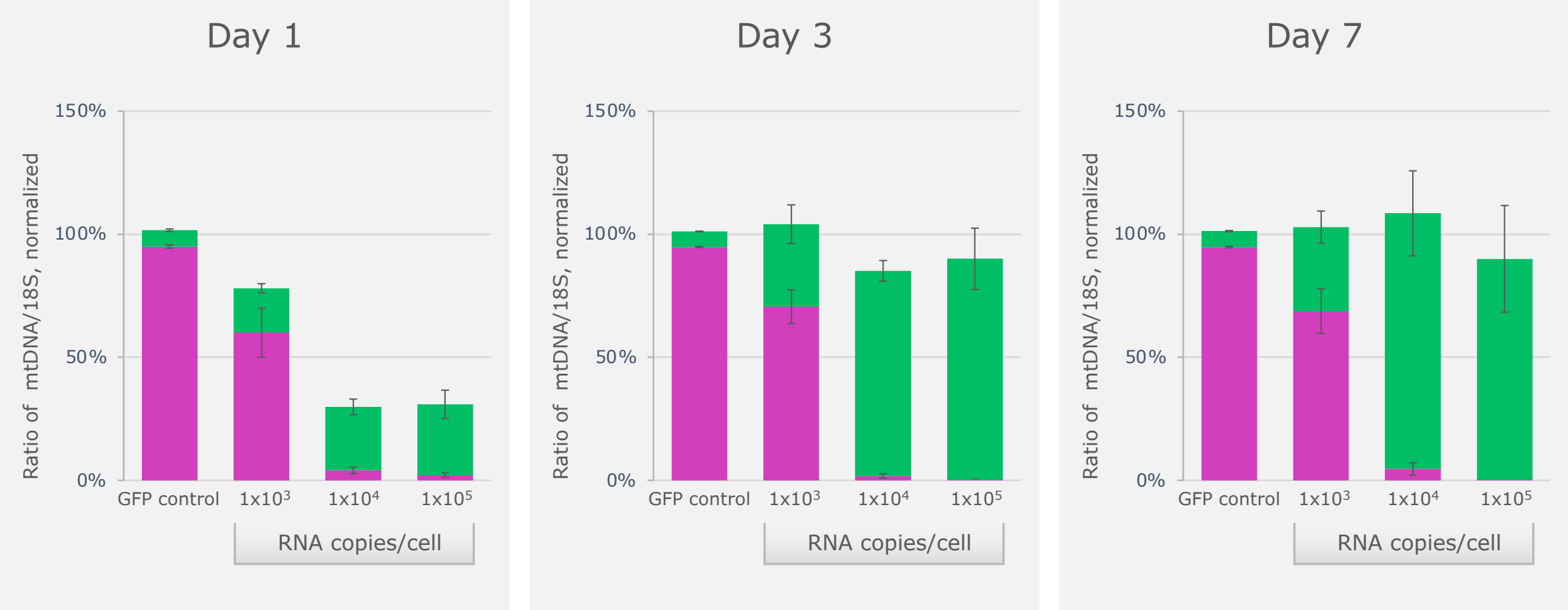


mitoARCUS_3243 efficiently eliminates mutant m.3243G, but does not cut wild-type m.3243A



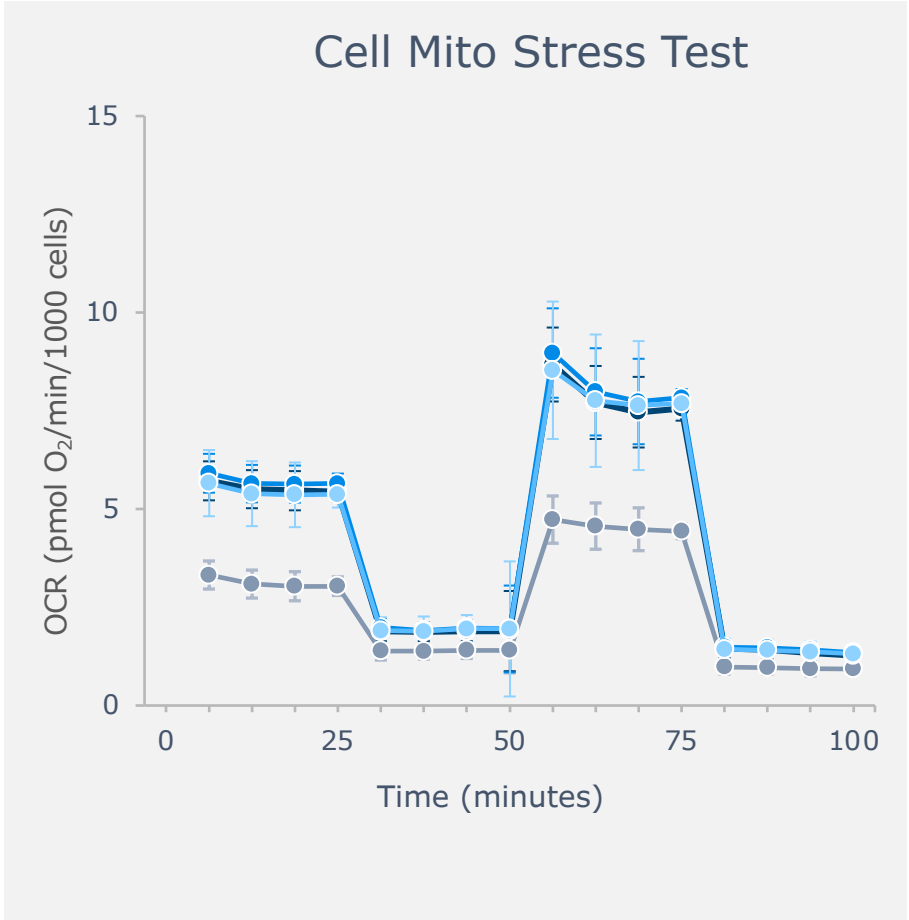
Shoop et al 2023 – Nature Metabolism

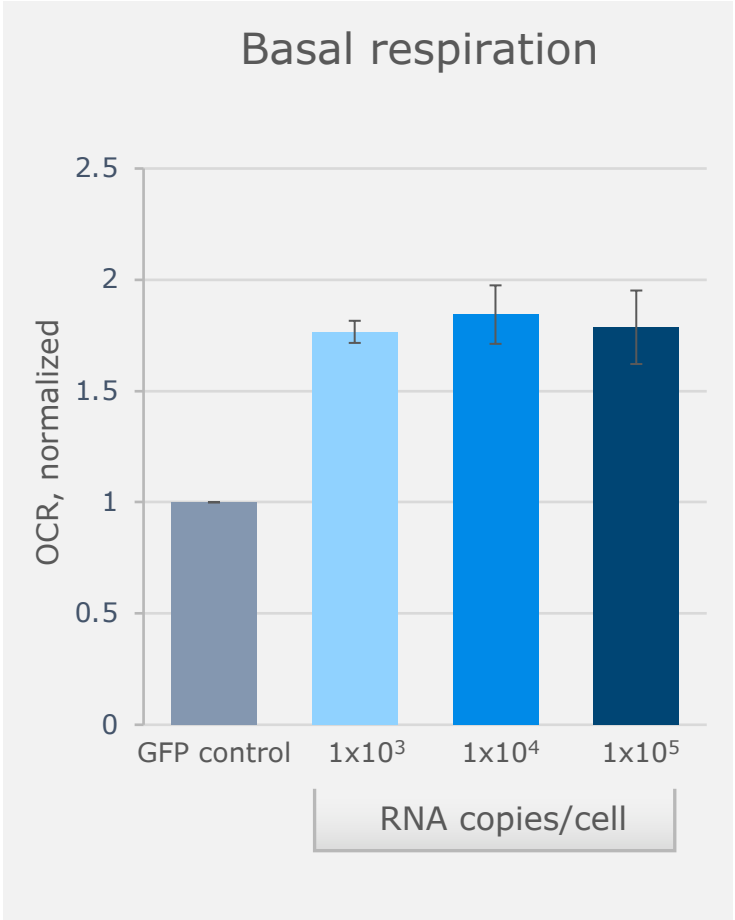
mitoARCUS_3243 shifts heteroplasmy in 95% mutant cybrid cells

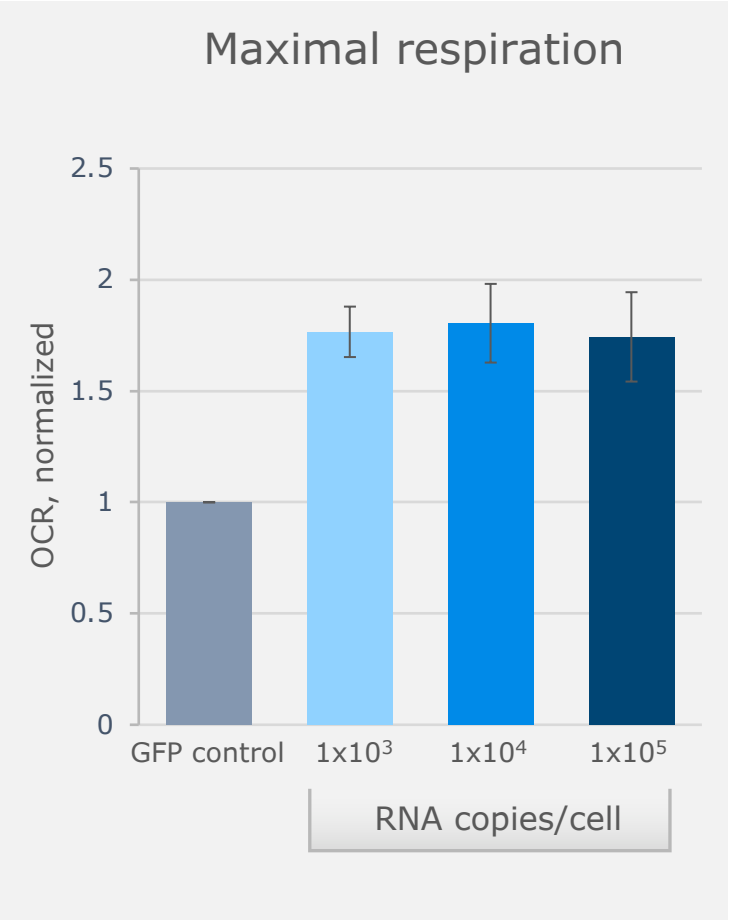


Shoop et al 2023 – Nature Metabolism

Specific elimination of mutant m.3243G leads to improvements in mitochondrial function



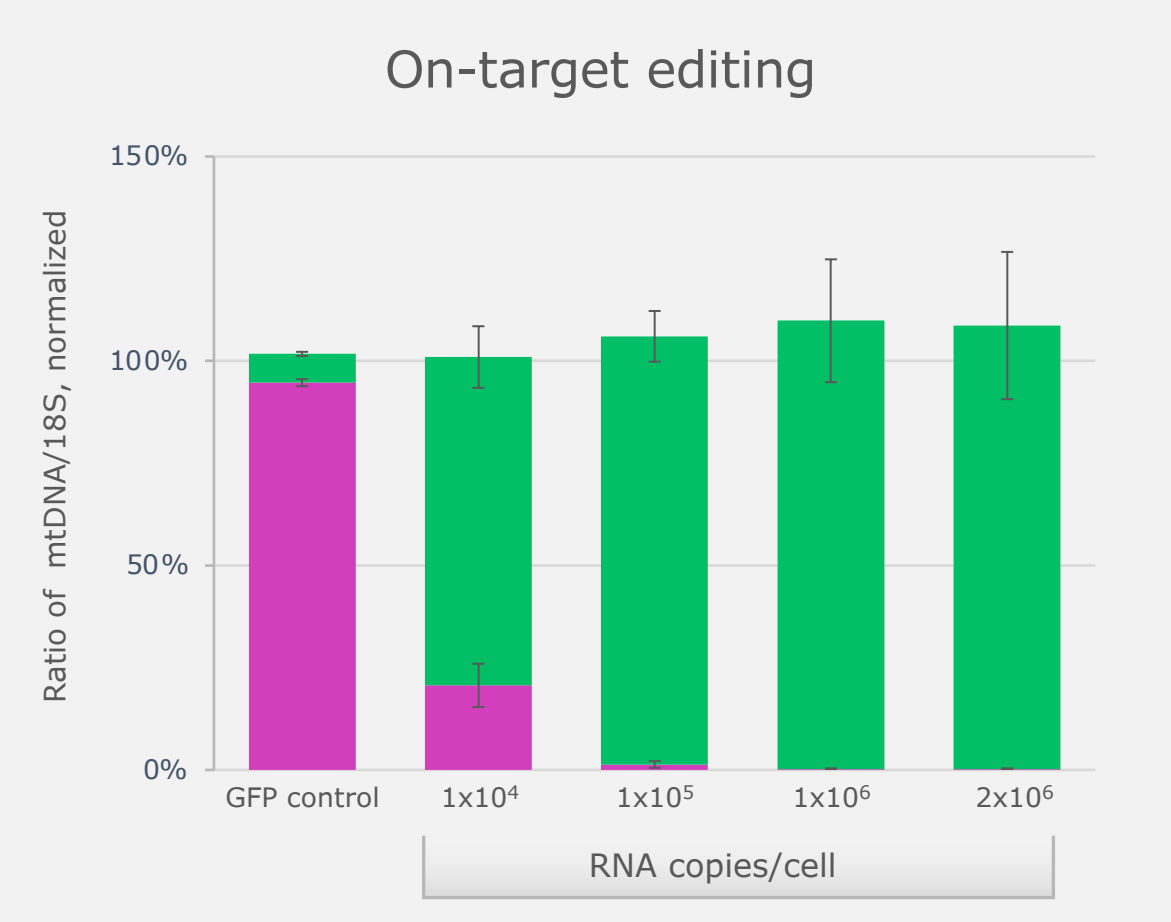


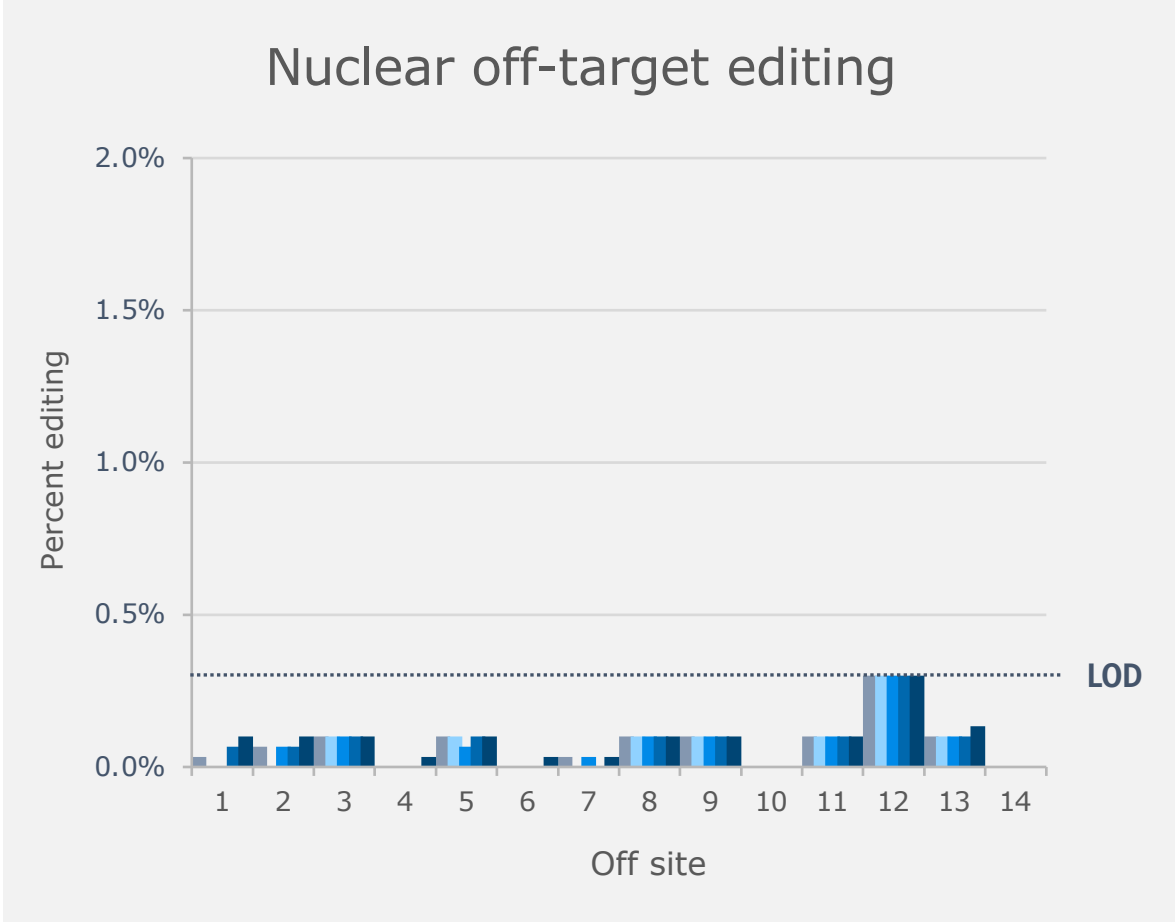


GFP control — 1x10³ RNA copies/cell — 1x10⁴ RNA copies/cell — 1x10⁵ RNA copies/cell

Shoop et al 2023 – Nature Metabolism

Nuclear off-target editing is eliminated with MTS and NES



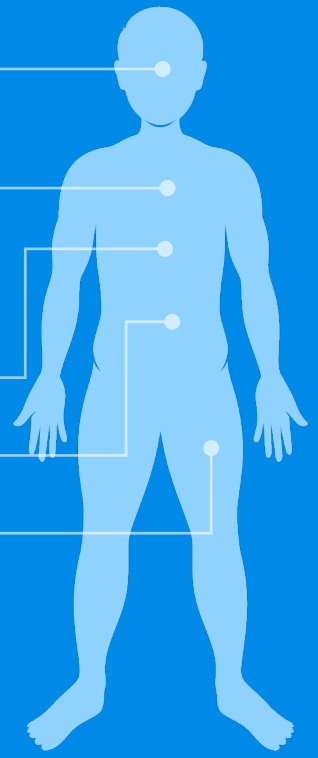


Shoop et al 2023 – Nature Metabolism

Developing mitoARCUS_3243 for patients with m.3243 mitochondrial disease

m.3243-associated mitochondrial diseases often lead to defects in energy production affecting high energy-demand tissues (e.g. skeletal muscle)

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



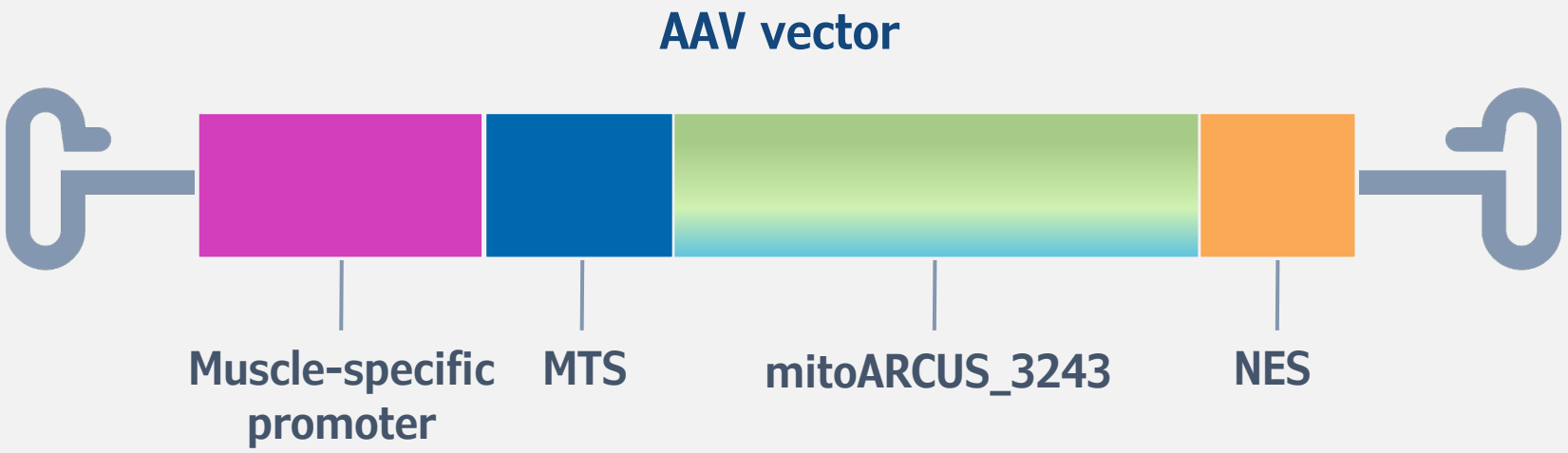
Patients today lack curative treatments and receive supportive care only through "mito cocktails"[1]

m.3243A>G

m.3243-associated mitochondrial disease estimated at

Sources:
1. https://www.ninds.nih.gov/health-information/disorders/mitochondrial-myopathies; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6938233/
2. Calculated based disease epidemiology studies and secondary literature

PBGENE-PMM is the first therapeutic designed to eliminate mutant m.3243G mtDNA



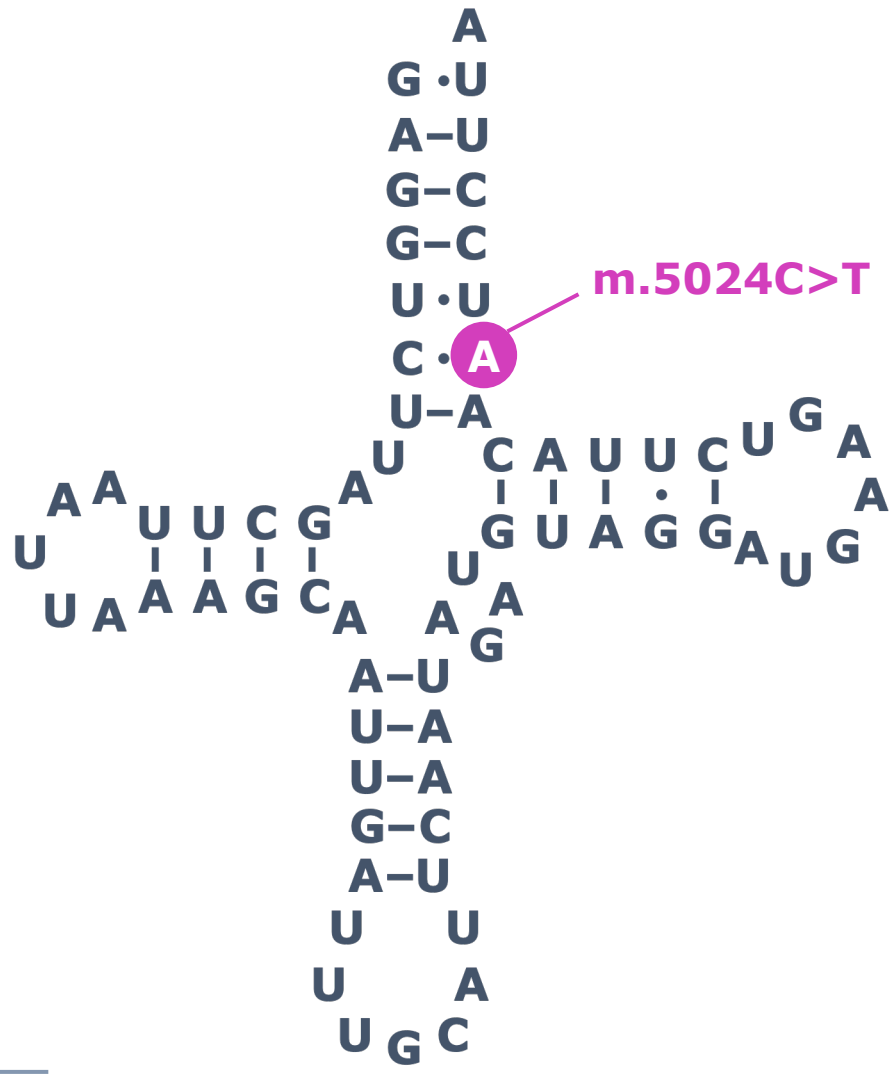
Objective | Systemically administer PBGENE-PMM to patients with m.3243-associated mitochondrial disease to elicit a shift in heteroplasmy in skeletal muscle

Use m.5024C>T mouse model with surrogate nuclease to translate preclinical data

Mouse m.5024C>T

Leveraging the m.5024C>T heteroplasmic mouse model to determine clinical dosing

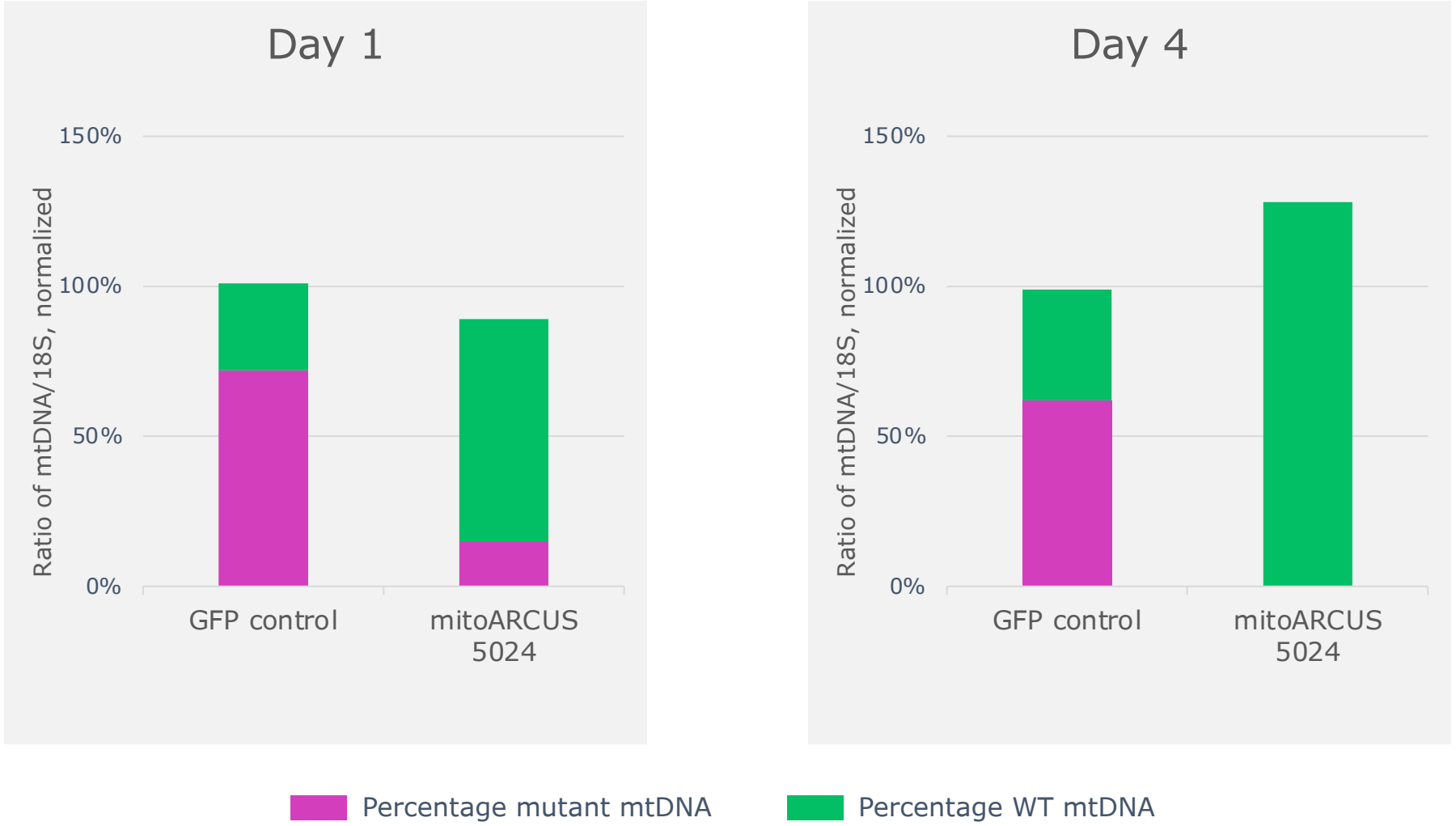
mt-tRNA^{Ala}



m.5024C>T

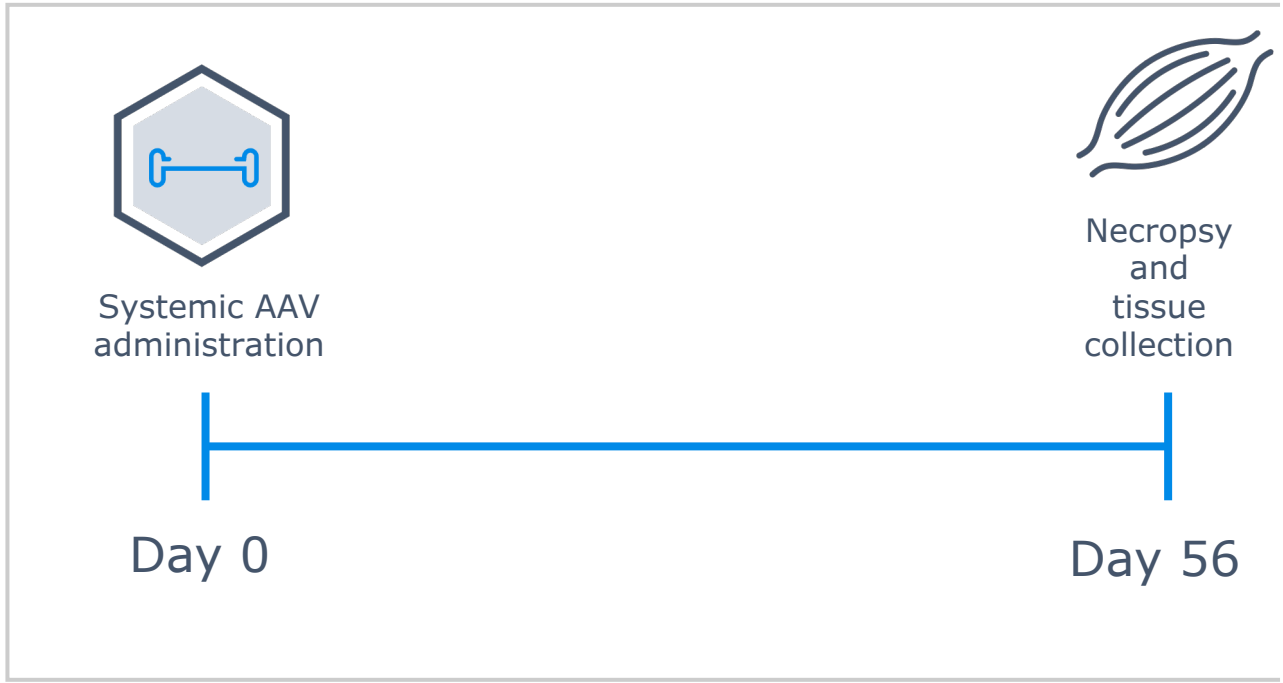
- No overt clinical phenotype
- Model provides POC for therapeutic approach
- Surrogate mitoARCUS nuclease developed that is specific for mutant m.5024T mtDNA = **mitoARCUS_5024**

mitoARCUS_5024 effectively eliminates mutant m.5024T mtDNA in vitro



Unpublished data

mitoARCUS_5024 in vivo study design

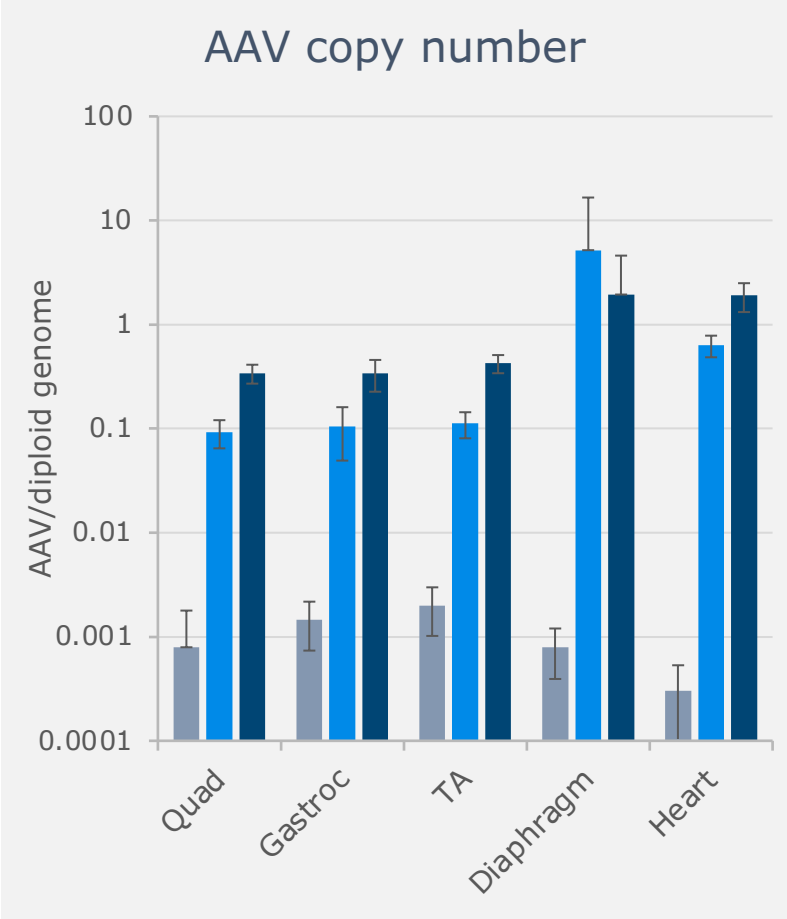


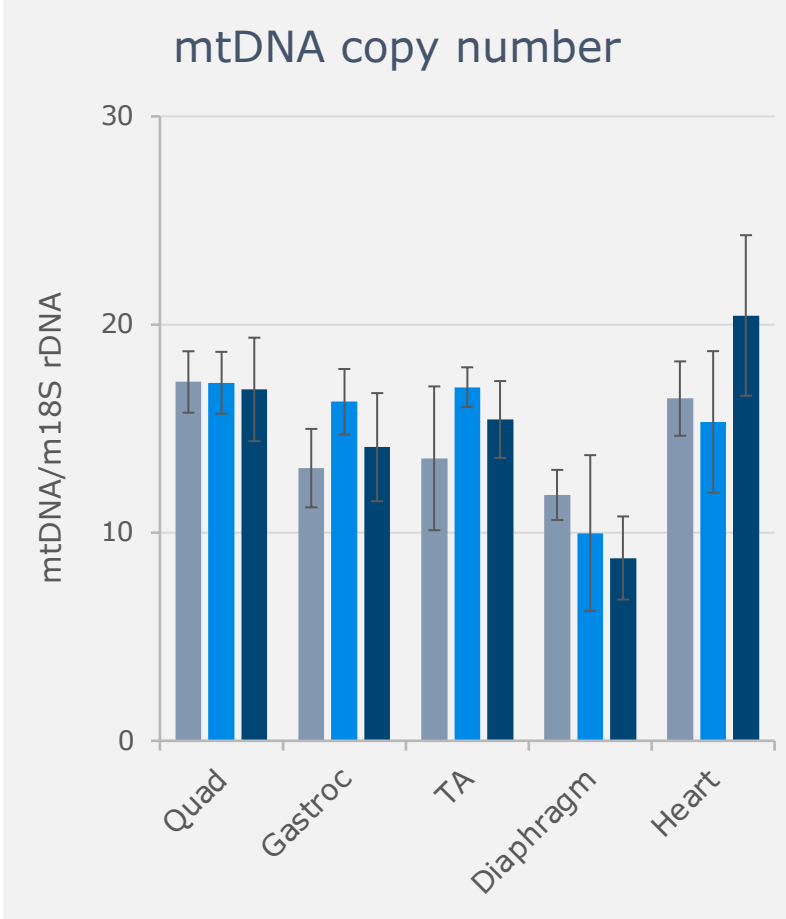
Group	Treatment	Dose	N
1	PBS	N/A	5
2	mitoARCUS_5024	$2.5x10^{13}$ vg/kg	7
3	mitoARCUS_5024	$1x10^{14}$ vg/kg	7

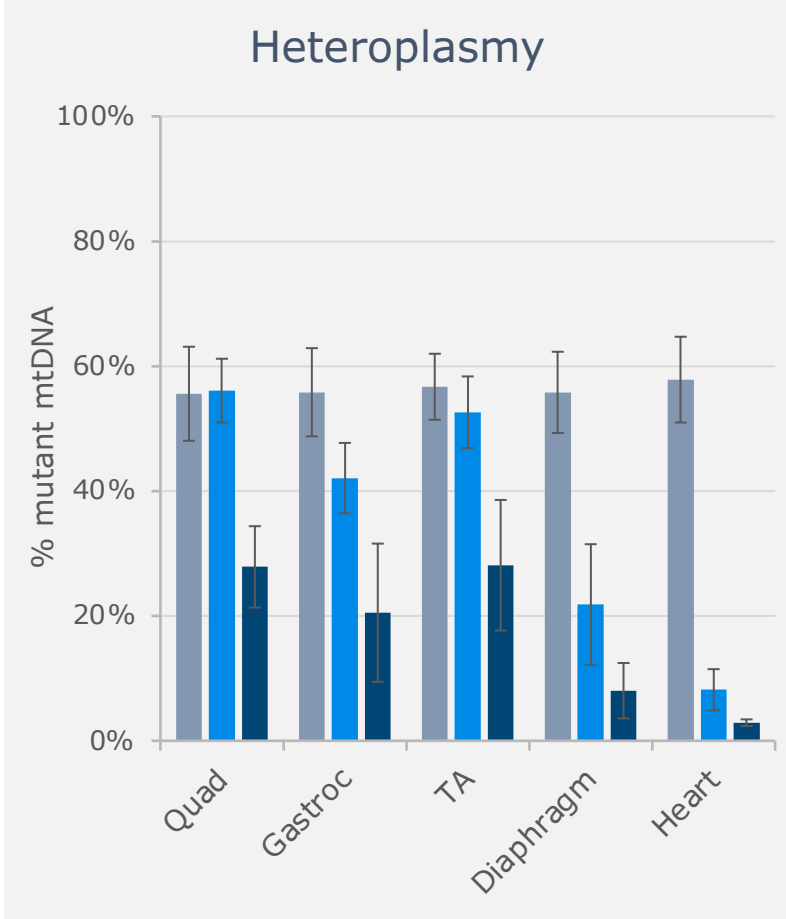
PURPOSE:

To evaluate ability of mitoARCUS_5024 to shift heteroplasmy in target tissues following systemic AAV administration in m.5024C>T heteroplasmic mice

mitoARCUS_5024 effectively transduces target tissues and eliminates mutant mtDNA without inducing mtDNA depletion



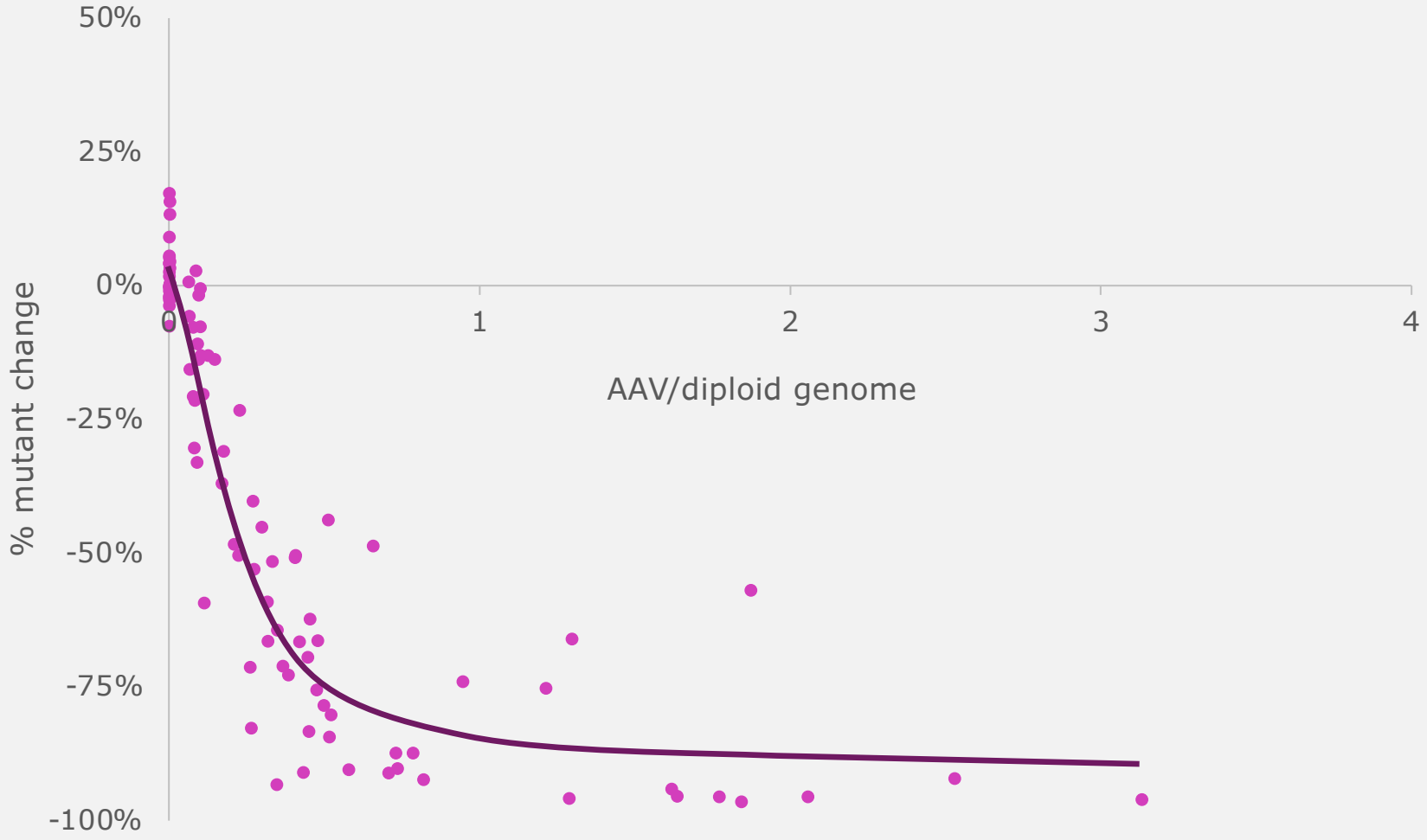




PBS control mitoARCUS_5024 2.5x10^{13} vg/kg mitoARCUS_5024 1x10^{14} vg/kg

Unpublished data

AAV biodistribution drives mutant mtDNA elimination in target tissues



Minimal amounts of AAV are needed to drive heteroplasmy shift in target tissues

Unpublished data

PBGENE-PMM

PBGENE-PMM program overview

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

Conclusions

ARCUS platform generates highly specific nucleases capable of discriminating a single nucleotide

ARCUS can be trafficked to mitochondria to selectively eliminate mutant mtDNA, both deletions and point mutations

ARCUS-mediated rescue of mtDNA heteroplasmy improves mitochondrial respiration

ARCUS can be systemically delivered using AAV to reach high energy-demand tissues

Preclinical data suggests low levels of AAV presence in target tissues is sufficient to shift heteroplasmy in m.5024C>T mouse model and gives reason to believe in PBGENE-PMM

Acknowledgements

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