Unlocking the therapeutic power of suppressor tRNAs for DMD

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Parent Project Muscular Dystrophy

Tevard's approach to genetic medicine seeks to revolutionize therapy

A single tRNA medicine to treat patients across multiple indications

- 35 million genetic disease cases globally are estimated to be caused by nonsense mutations
- Using therapeutic tRNAs harnesses the power of translation to overcome the effects of nonsense mutations
- This is a scalable, gene agnostic approach capable of restoring full-length protein in any disease caused by a nonsense mutation
- Strong partnerships with patient organizations

The Central Dogma

DNA (genes/instructions)

4 letters
(nucleotides)

Transcription

mRNA

4 letters
(ribonucleotides)

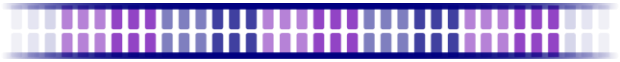
Translation

protein (function)

20 words
(amino acids)

The challenge of developing a genetic therapy for DMD

DMD gene



2.4 million nucleotides (0.1% of the human genome)

Transcription

DMD mRNA

14,000 ribonucleotides

Translation

Dystrophin protein

427,000 M_r

3rd largest protein

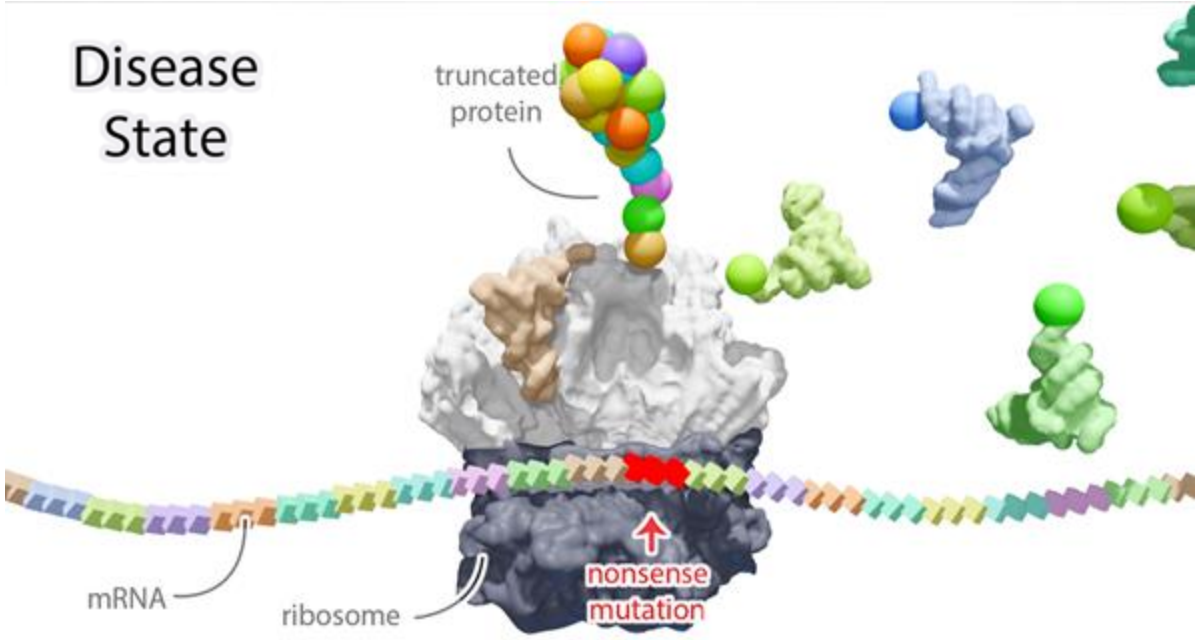
Protein synthesis depends on tRNAs decoding information stored in DNA

The genetic code: 61 sense + 3 stop codons

Second Position

First Position	U				C				A				G				Third Position
	code	Amino Acid			code	Amino Acid			code	Amino Acid			code	Amino Acid			
U	UUU	phe			UCU	ser			UAU	tyr			UGU	cys			U
	UUC				UCC				UAC				UGC				C
	UUA	leu			UCA				UAA	?			UGA	?			A
	UUG				UCG				UAG	?			UGG	trp			G
C	CUU	leu			CCU	pro			CAU	his			CGU	arg			U
	CUC				CCC				CAC				CGC				C
	CUA				CCA				CAA	gln			CGA				A
	CUG				CCG				CAG				CGG				G
A	AUU	ile			ACU	thr			AAU	asn			AGU	ser			U
	AUC				ACC				AAC				AGC				C
	AUA				ACA				AAA	lys			AGA	arg			A
	AUG	met			ACG				AAG				AGG				G
G	GUU	val			GCU	ala			GAU	asp			GGU	gly			U
	GUC				GCC				GAC				GGC				C
	GUA				GCA				GAA	glu			GGA				A
	GUG				GCG				GAG				GGG				G

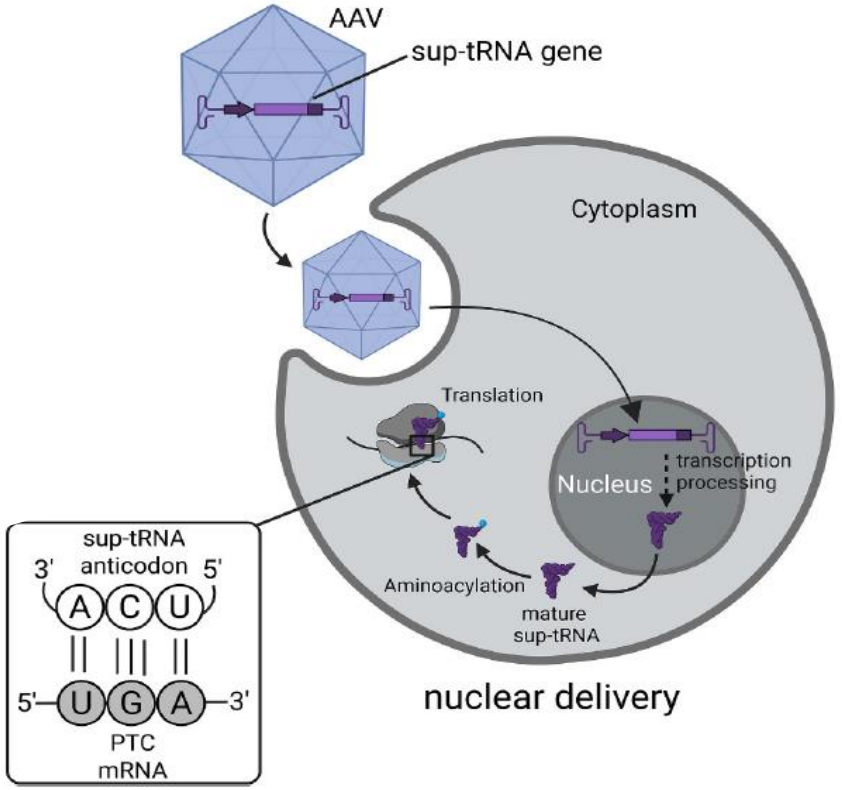
Nonsense mutations prevent full-length protein production



A nonsense mutation is a misplaced stop codon

Tevard's approach has unique advantages over traditional gene therapy

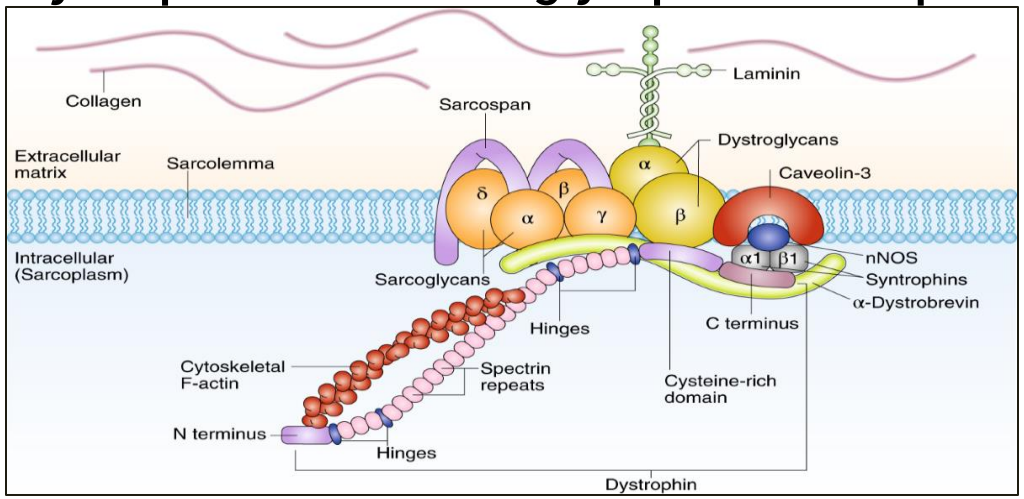
- Suppressor tRNAs offer a paradigm shift from a gene-centric to a PTC-centric therapeutic approach
- Use native cellular machinery
- Restore full-length protein
- Avoid transgene overexpression
- Specific for nonsense mutations - no effect on native stop codons
- When delivered with AAVs this is a long-lived fix for nonsense mutations



Ignatova and Albers, Pharm & Ther. 2025

Full-length dystrophin is optimal for muscle function

Dystrophin-associated glycoprotein complex



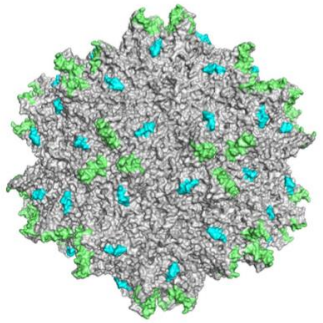
Jones. D, Nat. Biotechnol. 2019

- Dystrophin is a large cytoskeletal protein essential for the structural integrity of skeletal and cardiac muscle
- Nonsense mutations account for 12-15% of DMD cases
- Full-length dystrophin helps preserve critical protein-protein interactions required for optimal muscle function
- Existing products and product candidates deliver or create internally deleted proteins

Full-length dystrophin

Micro-dystrophins

Suppressor tRNAs restore translation of full-length Dystrophin protein in a mouse with a nonsense mutation

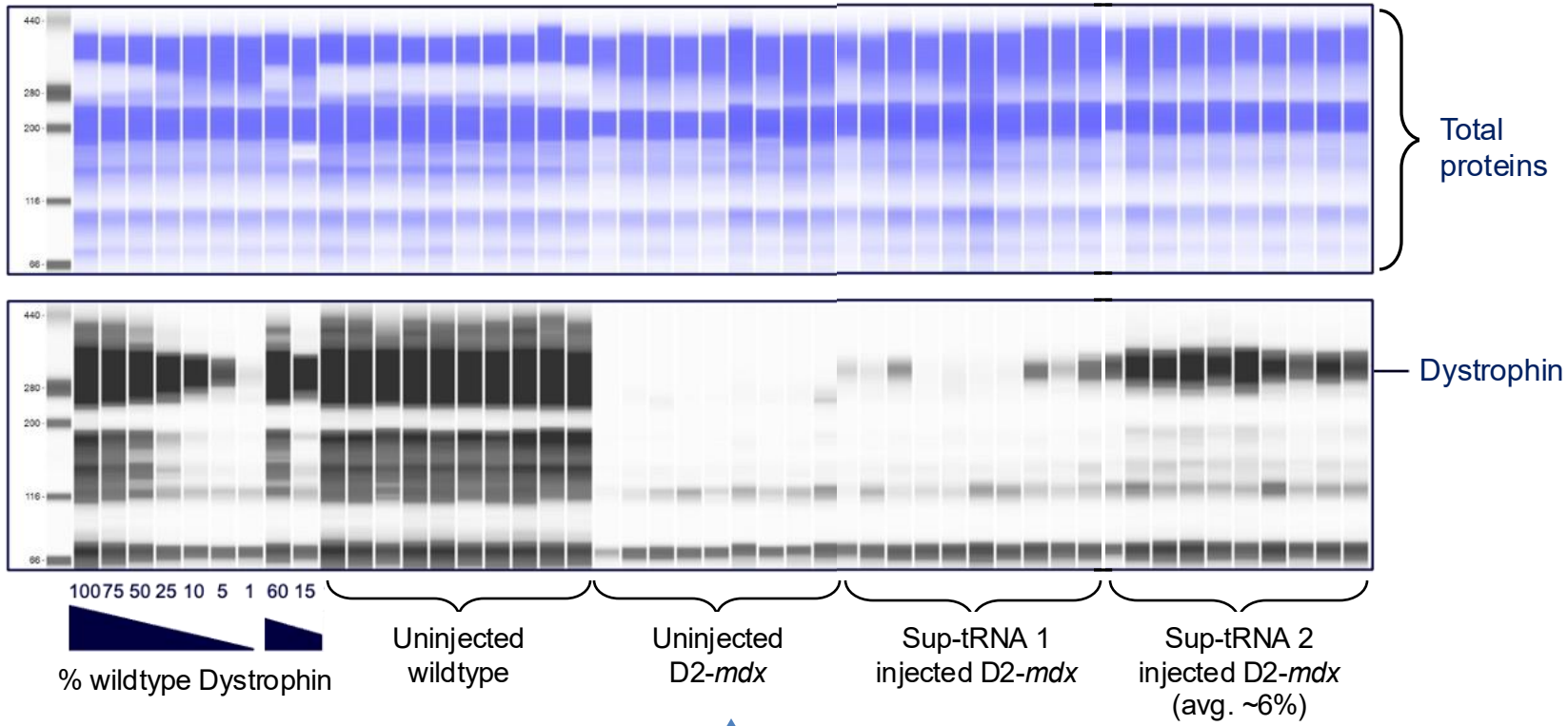


AAV with sup-tRNA

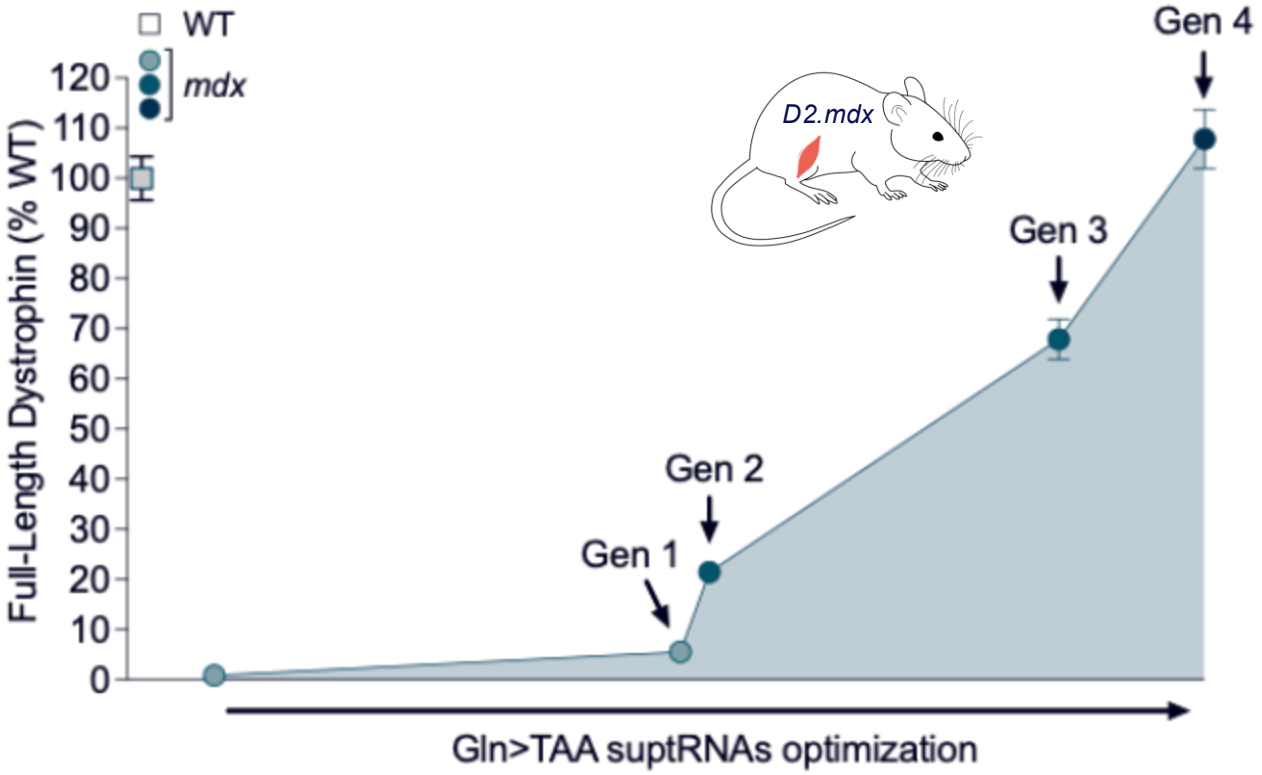
D2-*mdx* with TAA nonsense

Tibialis anterior muscle

Screening for sup-tRNA potency following intramuscular injection

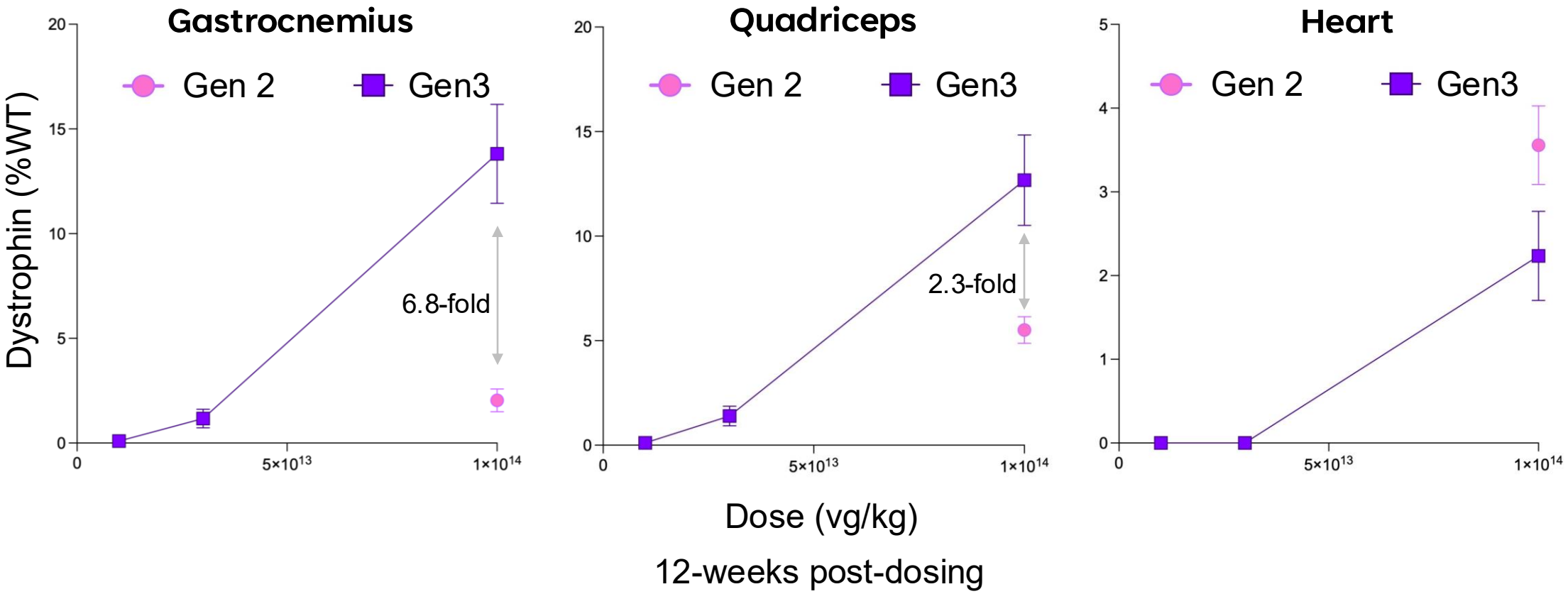


Tevard has screened >80,000 sup-tRNAs to identify lead tRNAs that are able to restore Dystrophin to wild-type levels in DMD-mice

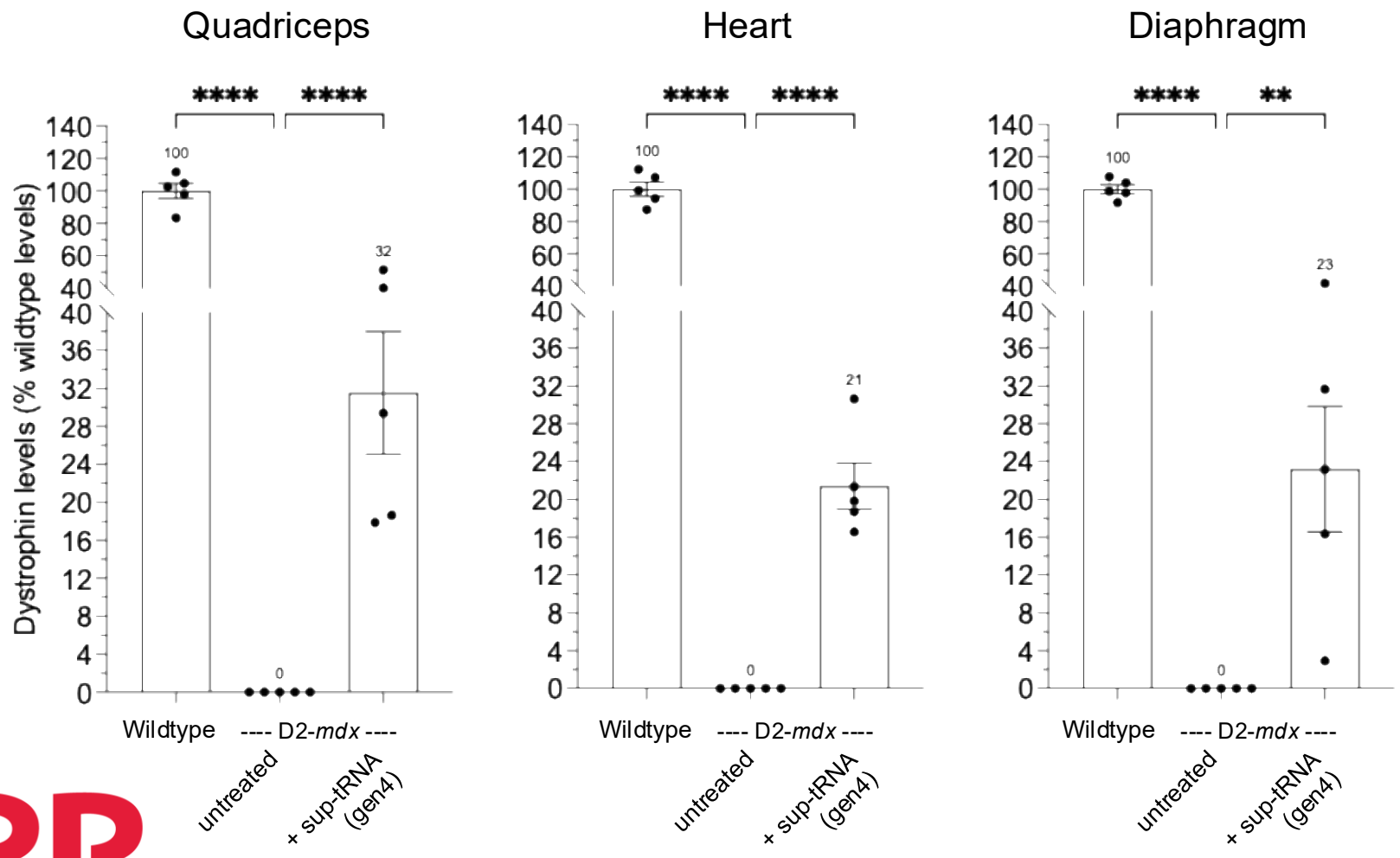


Generation	Screening (Cells)	Screening (Mice)	2nd Site Changes	HTS	Rational Design	Vector Optimization
Gen1	~20	10	No	No	No	No
Gen2	~60,000	5	Yes	Yes	No	No
Gen3		21	Yes	Yes	Yes	No
Gen4	~20,000	23	Yes	Yes	Yes	Yes

Increasing sup-tRNA potency enables using a lower dose to achieve the same level of Dystrophin rescue



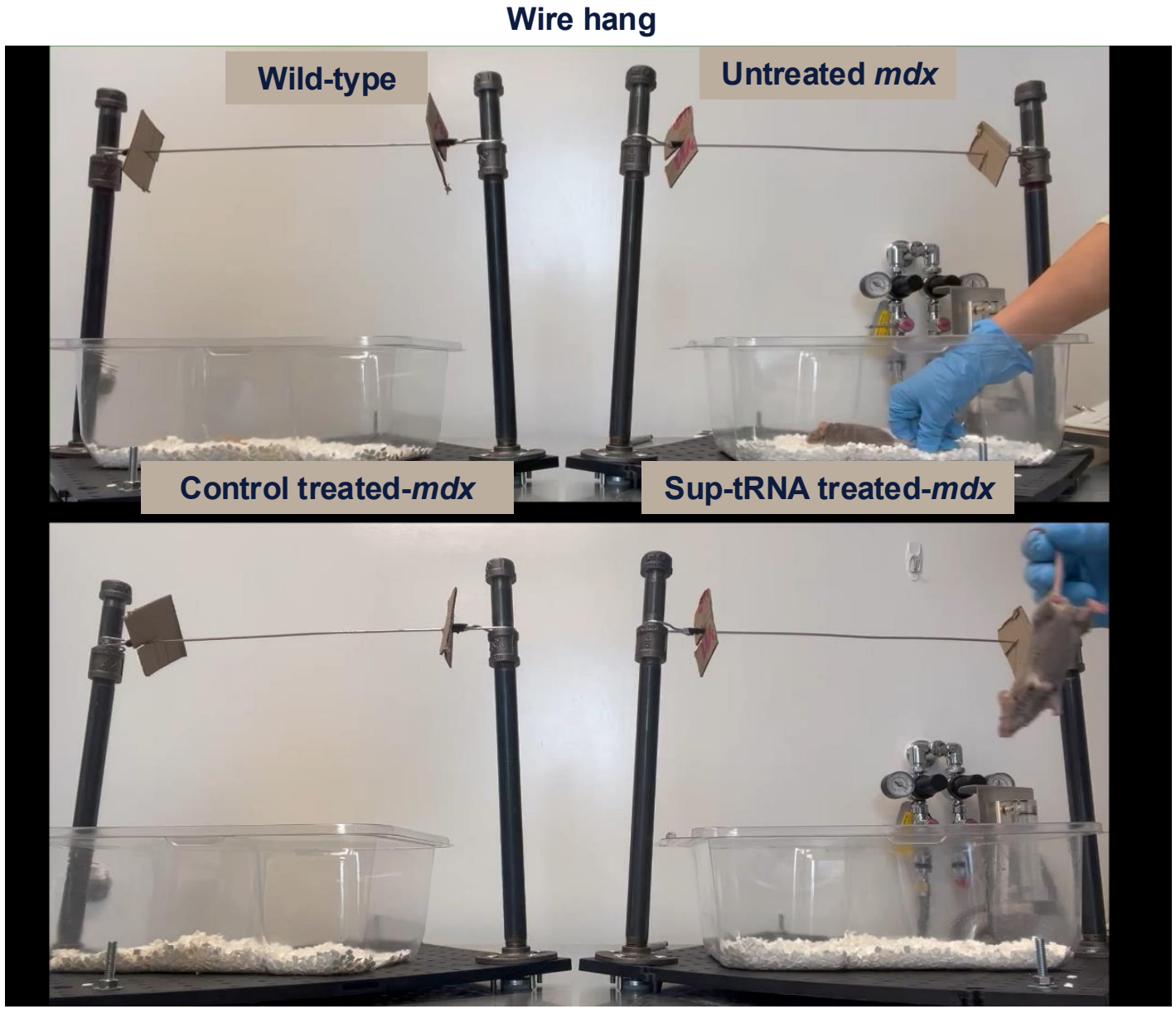
Tevard has achieved Dystrophin rescue to >30% of wild type levels in skeletal muscle and >20% of wild type levels in heart and diaphragm with intravenous dosing



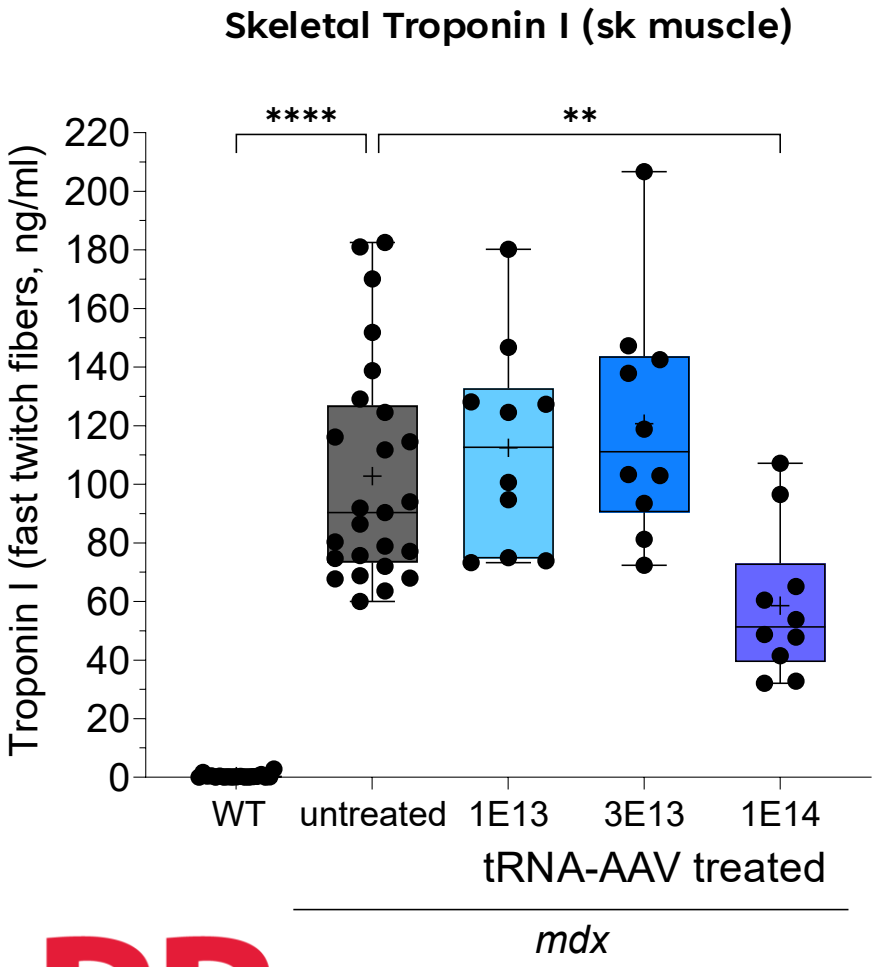
6-weeks post-dosing

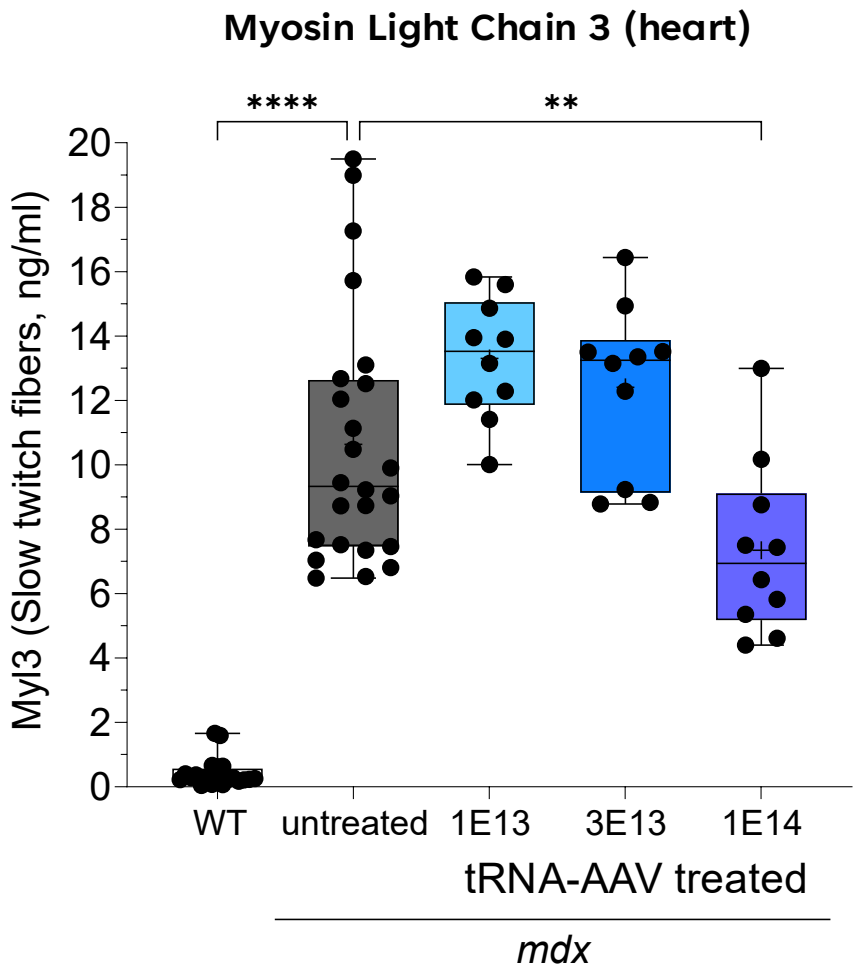
Intravenous delivery of sup-tRNAs restores motor function in D2-*mdx* mice

Gen 3

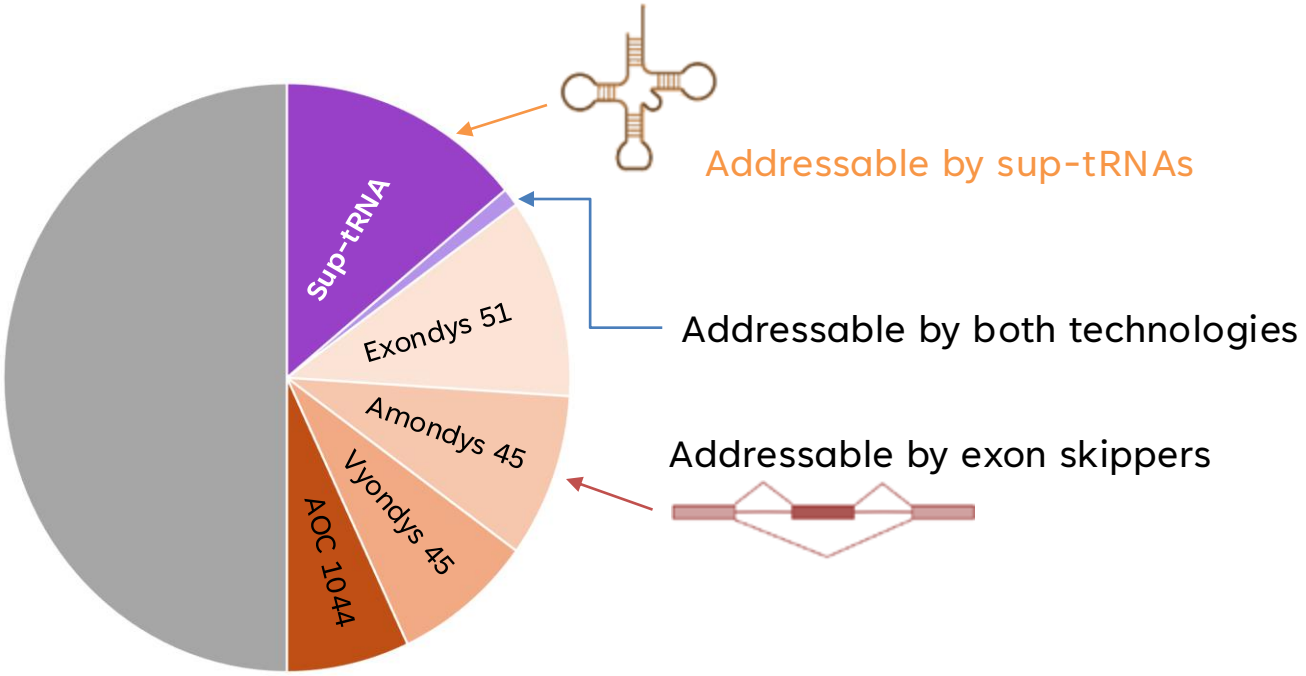


Gen 3 sup-tRNA treatment effectively mitigates muscle injury

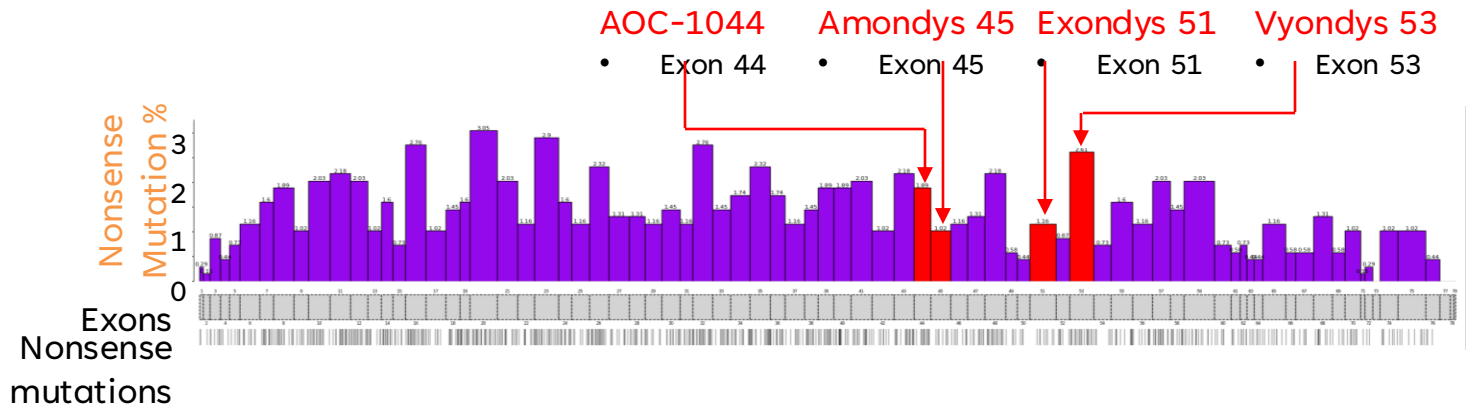




Suppressor tRNAs address a patient population with a high unmet need



- Most Dystrophin nonsense mutations are in regions of the protein that are not targeted by exon-skipping technology
- Patients that can respond to exon skipping technology and tRNA technology are minimally overlapping



Tevard is advancing sup-tRNAs toward the clinic with the objective of treating ~100% of patients with nonsense mutations

- ✓ A single intravenous administration of Gln-TAA sup-tRNA genes using a muscle specific AAV restores full-length Dystrophin protein & muscle function, and blocks muscle injury in a mouse with a TAA nonsense mutation in the DMD gene
- ✓ Tevard has additional data showing restoration of full-length Dystrophin protein and muscle function in mice with TGA or TAG nonsense mutations in the DMD gene
- ✓ The identification of 4th generation sup-tRNAs has led to significant AAV dose reductions
- ✓ Tevard's sup-tRNA technology is applicable to a range of diseases, including other muscular dystrophies, caused by nonsense mutations
- ✓ We are working to create a robust safety package to support clinical studies and starting discussions with FDA about our approach

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