FORCE™ Platform for Targeted Delivery of Oligonucleotide Therapeutics in Muscle Diseases

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Ravi, *living with DMD*

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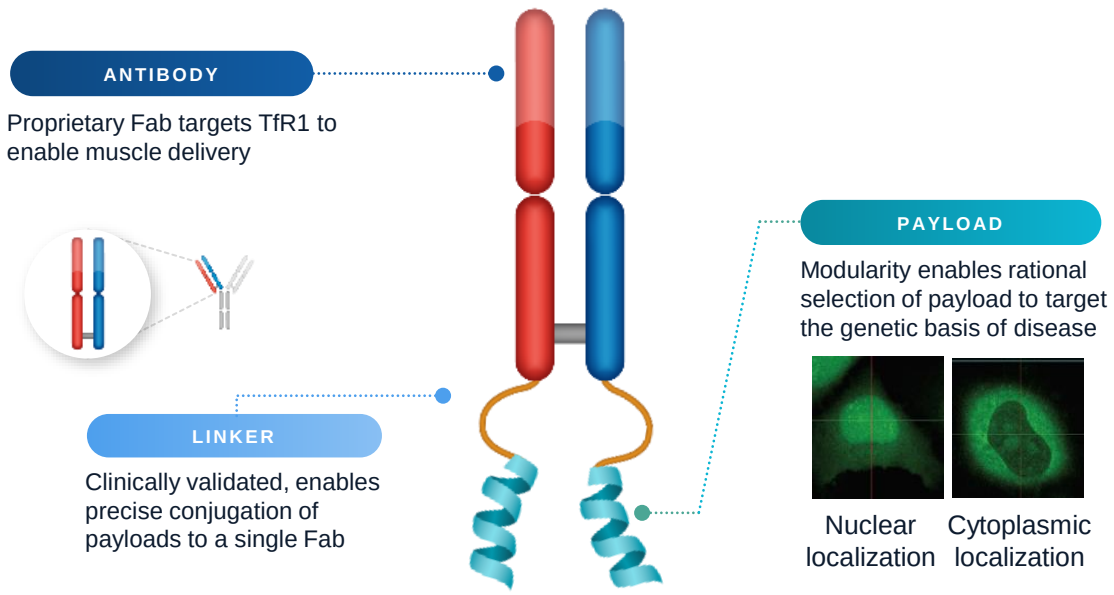
Dyne's Mission: Life-Transforming Therapies for Patients with Serious Muscle Diseases

Rare Muscle Disease Focus and Delivering for Patients

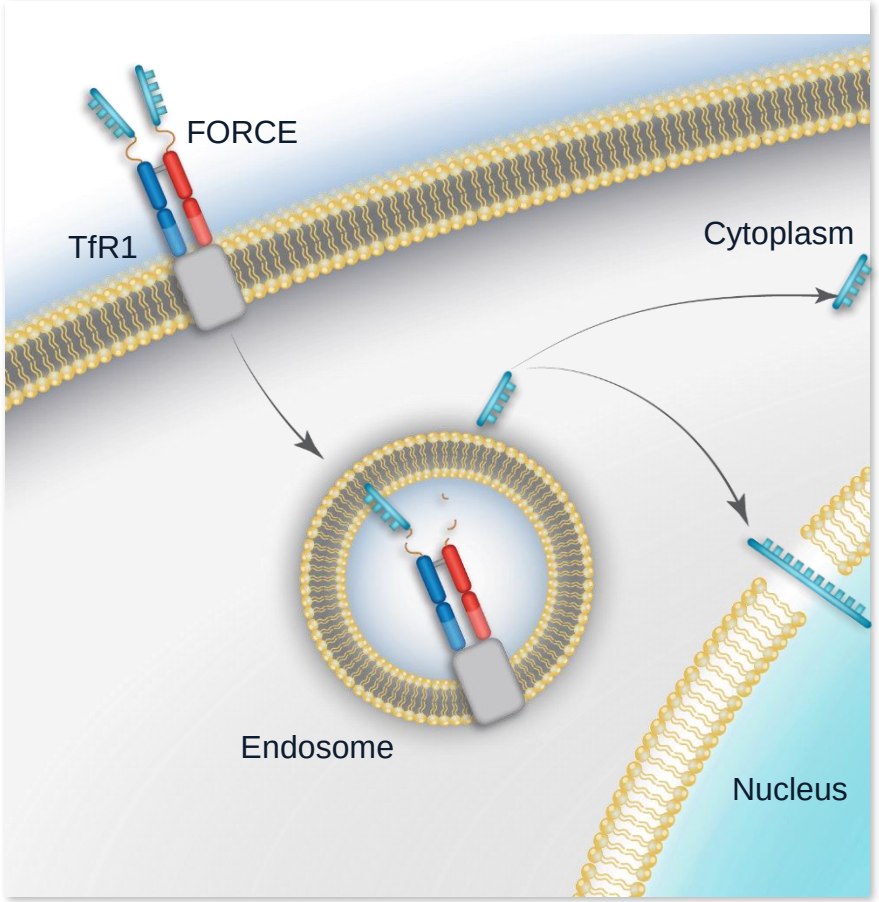
- Robust pipeline: DM1, DMD, and FSHD
- Developing multiple first-in-class or best-in-class therapies
- Precision medicine strategy
- Driving three programs to the clinic in 2022

Proprietary FORCE Platform

- Modern oligo therapeutics for muscle diseases
- Overcoming challenge of muscle delivery
- Plug-and-play therapeutics for multiple targets in skeletal, cardiac and smooth muscle diseases



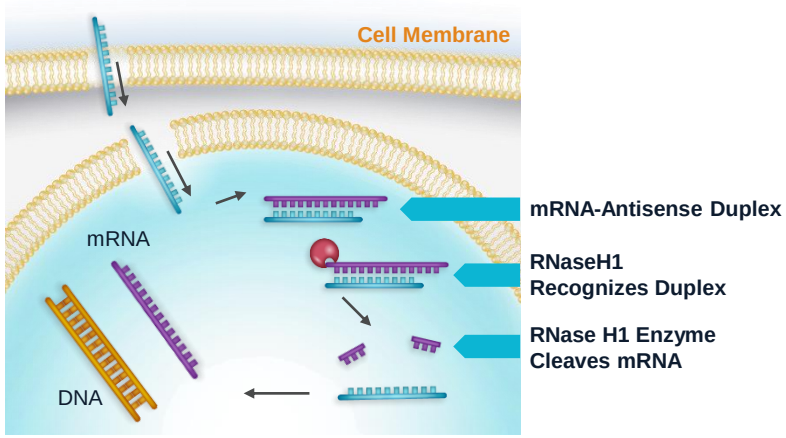
FORCE Platform Harnesses Cell Biology to Modify Disease



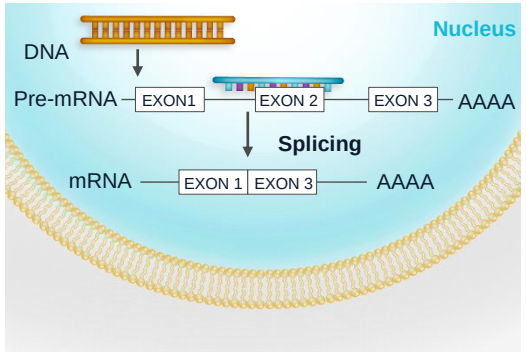
- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index

Rationally Select Payload to Target Genetic Basis of Disease

ASO acts in the nucleus and cytoplasm

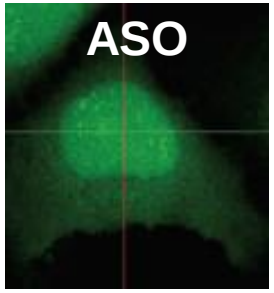


Splice-modulating ASO

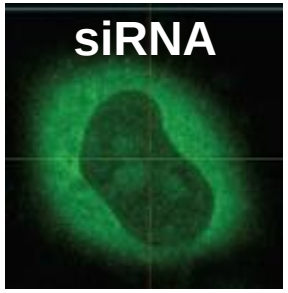


Single-Stranded Antisense

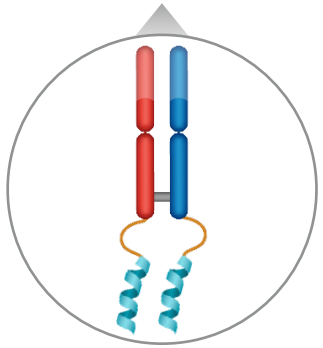
Subcellular distribution of ASO and siRNA



Nuclear localization

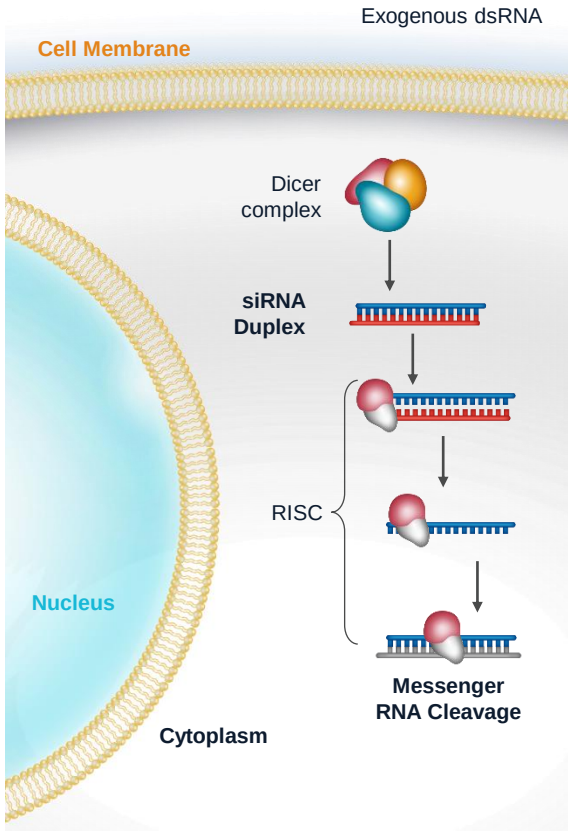


Cytoplasmic localization



FORCE delivers **ASO** payload for nuclear targets, **siRNA** payload for cytoplasmic targets

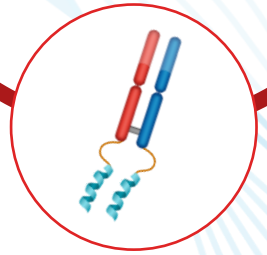
siRNA acts in the cytoplasm



Double-Stranded Antisense (siRNA)

FORCE Platform Designed to Deliver Significant Advantages

Stop or Reverse Disease Progression



Targeted Muscle Delivery

Leverages TfR1 expression on skeletal, cardiac and smooth muscle

Targets Genetic Basis of Disease

Rationally select payloads to match target biology

Redosable Administration

Potential for individualized patient titration and longer-term efficacy

Enhanced Tolerability

Targeted delivery limits systemic drug exposure

Extended Durability

Potential for prolonged disease-modifying effects, enabling less frequent dosing

Reduced Development and Manufacturing Costs

A single Fab and linker utilized across all programs

Robust Portfolio Focused on Muscle Diseases

DISEASE	TARGET	DISCOVERY / PRECLINICAL / PHASE 1/2	ESTIMATED PATIENTS
Myotonic Dystrophy Type 1 (DM1)	DMPK	**DYNE-101**	US: **>40,000** Europe: **>74,000**
Duchenne Muscular Dystrophy (DMD)	Exon 51	**DYNE-251**	US: **~12,000-15,000** Europe: **~25,000**
	Exon 53		
	Exon 45		
	Exon 44		
	Other Exons		
Facioscapulohumeral Muscular Dystrophy (FSHD)	DUX4	**DYNE-301**	US: **~16,000-38,000** Europe: **~35,000**

Pipeline Expansion Opportunities

Rare Skeletal

Cardiac

Metabolic

Notes: 1. Expects to submit regulatory filings in multiple countries for DYNE-101 in DM1 in Q2 2022. 2. Subject to FDA lifting clinical hold on DYNE-251 IND

Developing Transformative Therapies for People Living with DM1

Overview

- Mutation in the *DMPK* gene
- Onset at any point, depending on DM1 phenotype
- Life expectancy of 45 - 60 years

Clinical Presentation

- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

Population

- >40,000 (US)
- >74,000 (Europe)

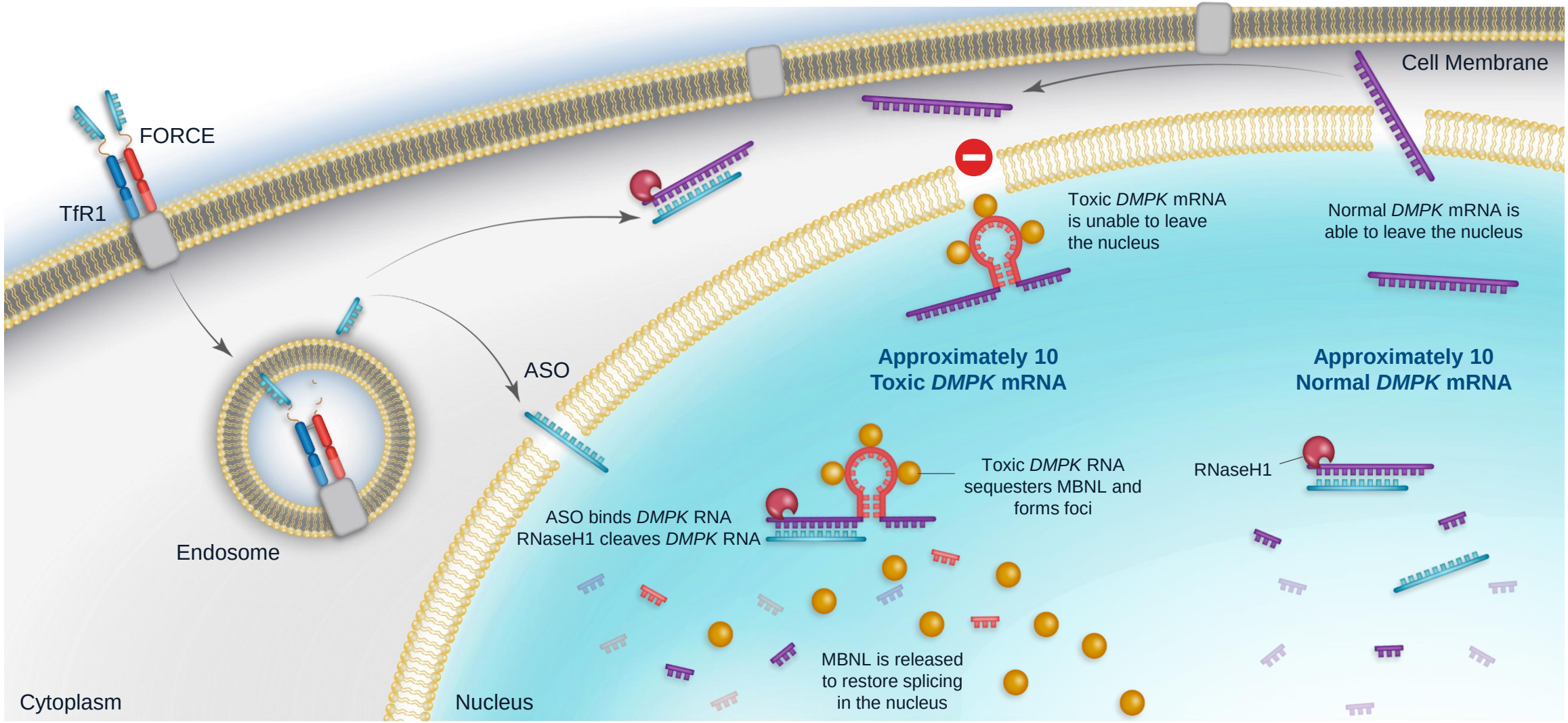
NO approved therapies

OUR APPROACH

Disease-Modifying Nuclear *DMPK* Knockdown

Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

FORCE Targets Toxic Nuclear *DMPK* RNA



DM1 Program Summary

Validating Data

- **Targeted** toxic *DMPK* in the nucleus in patient cells
- **Robust and durable toxic human *DMPK* KD** in novel hTfR1/DMSXL model
- **Reduced nuclear foci** *in vitro & in vivo*
- **Corrected splicing** changes *in vitro & in vivo*
- **Reversed myotonia** in HSA^{LR} model
- **Delivered** *DMPK* targeting ASO to mouse and NHP muscle tissues
- **Favorable safety profile in NHP GLP tox study**

Potential Advantages

- **Tractable development** with rapid path to human PoC
- **Efficient** commercial model, addressable with focused sales force

Multiple Regulatory Filings Planned in Q2 2022 [1]

Anticipate Dosing Patients in Mid-2022

Note: 1. Expects to submit regulatory filings in multiple countries for DYNE-101 in DM1 in Q2 2022

Building a Global DMD Franchise of Transformative Therapies

Overview

- Mutation in the *DMD* gene that encodes for dystrophin
- Onset in first few years of life
- Life expectancy ~30 years

Clinical Presentation

- Muscle weakness
- Progressive loss of function
- Loss of ambulation
- Respiratory/cardiac failure

Population

- ~12,000 - 15,000 (US)
- ~ 25,000 (Europe)

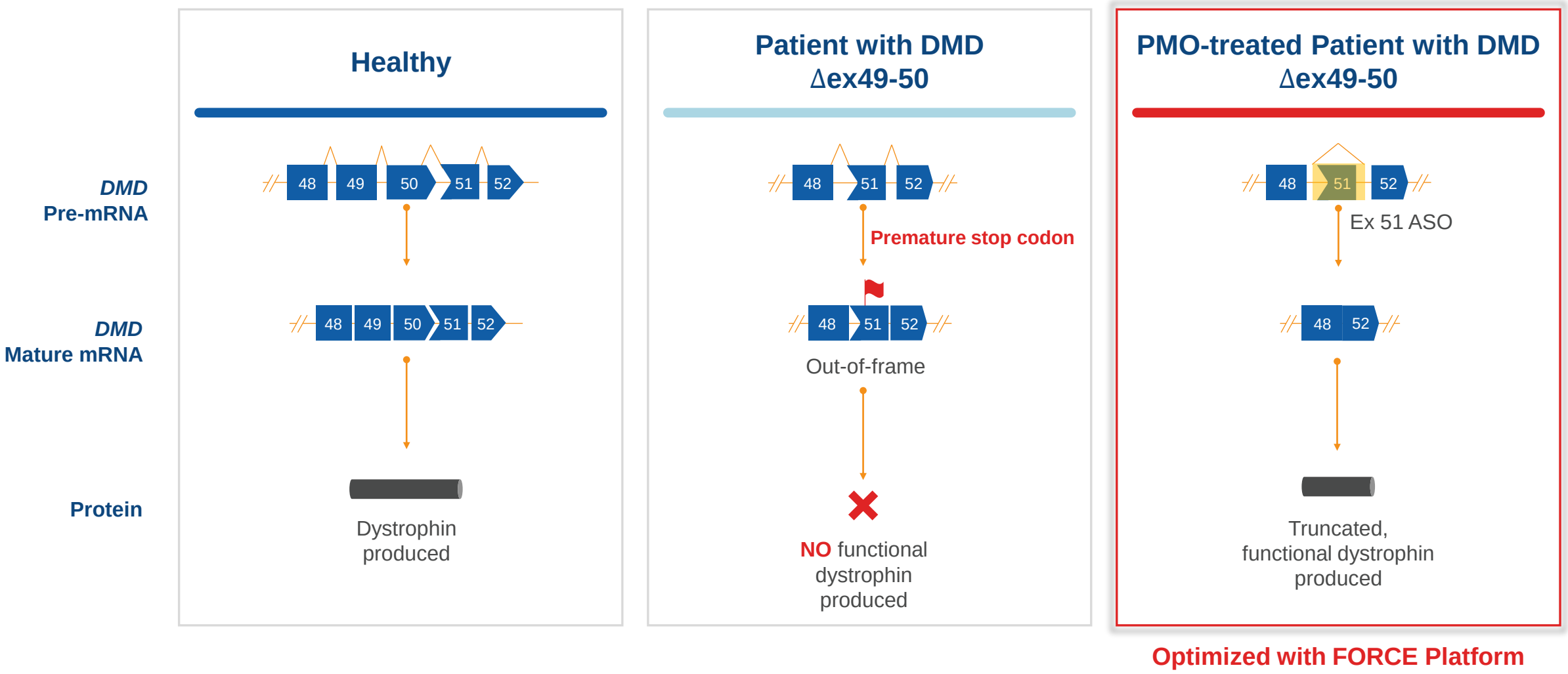
Current Approved Exon 51 Therapies Only Increased Dystrophin Production <1%

OUR APPROACH

Best-in-class Targeted Exon Skipping

Increase dystrophin expression and enable less frequent dosing to potentially **stop or reverse disease progression**

Targeting the Genetic Basis of DMD with a Proven Mechanism



Optimized with FORCE Platform

Adapted from Lim KRQ., et al. *Drug Des Devel Ther* 2017;11:533.

DMD Program Summary

Validating Data

mdx Model

- **Achieved robust and durable** exon skipping in skeletal and cardiac muscle
- **Dose-dependently increased dystrophin** expression up to 90% of WT based on western blot and ~80% dystrophin-positive fibers
- **Reduced serum CK levels**
- **Demonstrated functional benefit** in multiple standardized assessments

DYNE-251

- **Robust and dose-dependent exon skipping** in patient DMD patient myotubes (exon 51)
- **Transformative exon skipping in NHP** cardiac and skeletal muscles
- **Favorable safety profile in NHP GLP tox study**

Potential Advantages

- **Established** clinical and regulatory path
- **Opportunity to accelerate DMD franchise** expansion (exon 53, exon 45, exon 44) to reach additional patient populations

Anticipate Dosing Patients in Mid-2022[1]

Note: 1. Subject to FDA lifting clinical hold on DYNE-251 IND

FSHD Program

Overview

- Aberrant expression of DUX4
- Onset in teen years or young adulthood
- Normal life expectancy

Clinical Presentation

- Progressive wasting and skeletal muscle loss
- Significant physical limitations

Population

- ~16,000 - 38,000 (US)
- ~35,000 (Europe)

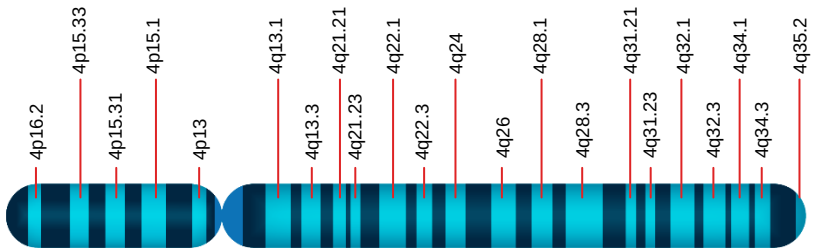
NO approved therapies

OUR APPROACH

Disease-Modifying DUX4 Knockdown

Targeting toxic *DUX4* mRNA expression to potentially **stop or reverse disease progression**

FORCE Targets the Genetic Basis of FSHD



Chromosome 4

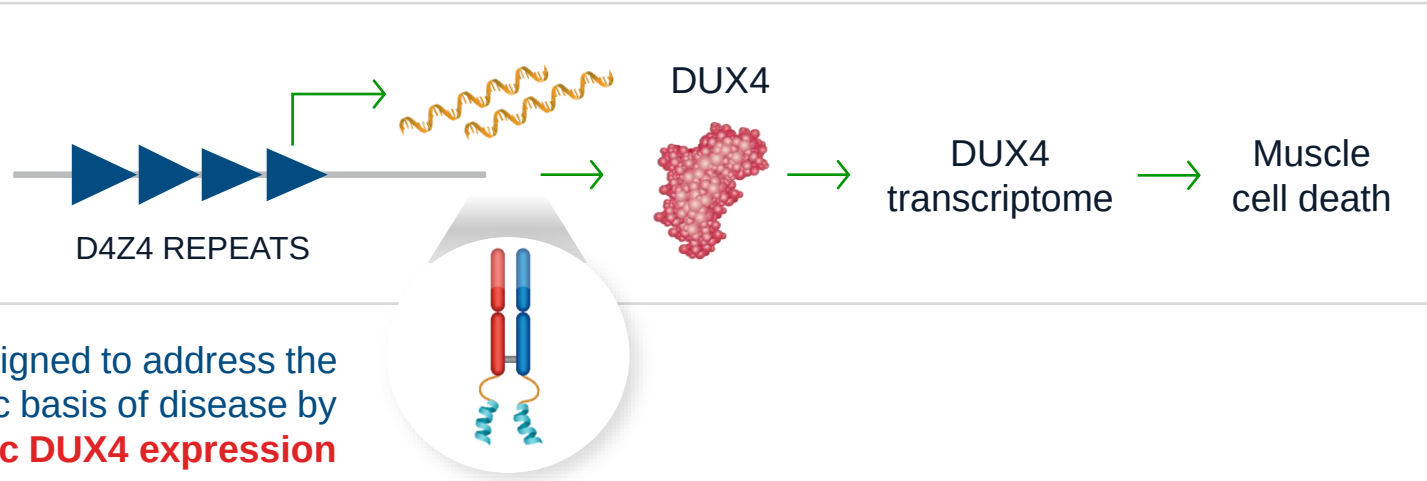
HEALTHY

11-120 D4Z4 Repeats

FSHD (Type 1)*

<10 D4Z4 Repeats (~95% of patients)

Epigenetic derepression



FORCE designed to address the genetic basis of disease by **targeting toxic DUX4 expression**

*FSHD Type 2 (~5% of patients) is caused by <20 D4Z4 repeats and concomitant mutations in *SMCHD1*, *DNMT3B* or *LRIF1* that also result in epigenetic derepression and aberrant expression of *DUX4*.

Banerji et al. *Hum Mol Genet*. 2019. Wang et al. *J Neuromusc Diseases*. 2021.

FSHD Program Summary

Validating Data

- **Reduced** toxic gain-of-function *DUX4* mRNA
- **Superior** suppression of DUX4 biomarkers observed over naked ASO
- **Enhanced** muscle distribution
- **Translatability** to primates expected; based on platform data in multiple NHP studies

Potential Advantages

- **Exclusive license** to potent *DUX4* targeting payloads
- **Tractable development** with rapid path to human PoC

Planned IND Submission in H2 2022

Dyne™ THERAPEUTICS

Targeting the genetic basis of serious muscle diseases to

STOP OR REVERSE DISEASE PROGRESSION

FORCE PLATFORM	**Robust** PIPELINE	**Delivering** FOR PATIENTS	**Exceptional** TEAM